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Lipid Lowering Treatment in Mild to Moderate Aortic Stenosis

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Paper II

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ABBREVIATIONS

AS	- aortic stenosis
AR	- aortic regurgitation
AVA	- aortic valve area
AVE	- aortic valve events
AVR	- aortic valve replacement
BAV	- bicuspid aortic valve
BMI	- body mass index
CABG	- coronar artery bypass grafting
CAD	- coronary artery disease
CV	- cardiovascular
ECG	- electrocardiogram
EF	- ejection fraction
LDL-C	- low density lipoprotein – cholesterol
ICE	- ischemic cardiovascular events
LV	- left ventricle/ventricular
LVH	- left ventricular hypertrophy
LVM	- left ventricular mass
LVMi	- left ventricular mass index
MCE	- major cardiovacsular events
PCI	- percutaneous coronary intervention
RCT	- randomized clinical trial
SCD	- sudden cardiac death
TAV	- tricuspid aortic valve
TEE	- transesophagal echocardiography

TTE	- transthoracal echocardiography
VHD	- valvular heart disease
Vmax	- peak aortic jet velocity
VTI	- velocity time integral
2-D	- 2-dimensional

INTRODUCTION

Calcification of the aortic valve was first described in 1672 by Carl Rayger, Germany. Later it was described in 1679 by Bonet, France, by Wilks and Moxon in 1875 and in 1904 by Mönckeberg[1, 2]. Aortic stenosis (AS) denotes the narrowing of the aortic valve. It can be classified as congenital or acquired; or according to the localization of the stenotic segment within the aortic root namely as subvalvular, supravalvular or valvular. The first and second entities are separate diseases different from the pure valvular disease, and they are therefore not further discussed in this work. Instead, the focus of the current work is solely on degenerative valvular AS. Rheumatic AS is also not included in the present work.

Various denominations have been used for valvular AS over the decades since its first description. These different denominations merely reflect the changing conceptions of explanation models of this disease over time; e.g. calcific aortic stenosis, degenerative aortic stenosis, aortic valve stenosis; all of these will here be handled as one entity and named AS in the continued discussions.

Valvular AS can be further subdivided into bicuspid or tricuspid aortic valve (TAV) stenosis, or very rarely other congenital valve malformations that increase the probability of valve degeneration during lifetime. The bicuspid aortic valve (BAV) is the most common congenital cardiac disease with a prevalence in all live births of 0.5-2%[2-4]. Patients with bicuspid valves tend to develop valve calcification at an earlier stage than patients with tricuspid aortic valve[3], and about 25% require valve surgery during a 20 year follow-up, however, with a 20 year survival similar to an age-matched control population if adequate follow-up and timely surgery is ensured[3, 5, 6]. In addition to the risk of valvular dysfunction and need for valve surgery, BAV is linked with thoracal aortic aneurisms due to a genetically determined loss of elastic fibres in the elastic lamina, and therefore patients with BAV are at higher risk for aortic dissection compared to patients with a normal aortic valve. With timely valvular and vascular surgery however survival

on a lifetime basis is comparable to the general population of similar age[3, 5]. Patients with BAV have been shown byRoberts et al to constitute about 50% of all patients undergoing valve surgery, however, with an age-related correlation so that in the younger ages, bicuspid valves dominate, and in older patients, tricuspid valves dominate[7]. Still, data suggest that even for bicuspid valves, the same risk factors as in patients with tricuspid valves increase the risk for developing AS[8].

The acquired AS developing from an anatomically normal tricuspid aortic valve can be caused by both calcific AS and rheumatic AS, the incidence of which is declining in developed countries. The latter was previously the commonest cause of acquired AS. Subramanian et al studied a population of 374 patients operated for pure AS at the Mayo Clinic in the period 1965 to 1980, registering bicuspid valves in 46% of the cases, degenerative AS in 10%, and rheumatic AS in about 35% of the cases[9]. In a later similar study from the Mayo Clinic analysing 646 patients operated with aortic valve replacement (AVR) during 1981-1985, degenerative AS represented 46% of all operated AS, an increase from 30% as compared to the previous period[10]. During the same period the frequency of rheumatic AS decreased further from 30% to 18%. Bicuspid valve decreased from 37 to 33%. As expected, the differences were especially obvious in the population above 70 years. In an age-mixed population of AS patients in developed countries in Western Europe, one would from the previous prevalence studies assume that the patients displayed a mixture of TAV and BAV, the mean age of the population influencing the main form of valve morphology. Indeed, in a later material published by Davies et al in 1996, 465 consecutive patients undergoing AVR for dominant AS were examined. Of these 63.7% had calcific bicuspid valves, 26.9% had calcific tricuspid valves, 5.4% had rheumatic disease, 2.6% had mixed etiology and 1.5% had unicommisural valve[11].

In this context the finding of an unicommisural valve in an adult population is indeed rare, with an incidence of about 0.02% in patients referred for echocardiography, up to 4-5% in patients

referred for aortic valve replacement, where aortic stenosis being the main dysfunction[12]. As previously mentioned Roberts et al described 932 patients undergoing AVR, finding tricuspid valves in 417 (45%) of the cases and congenital malformation in 504 (54%) – 9.1% of the congenital cases were unicuspid[7]. The frequency of tricuspid valves increased when comparing excised valves (n=1,849) from the first 3 decades of valve surgery (1961-1990) and the latter 3 years 1991-2004[13], and the relative prevalence of bicuspid versus tricuspid AS at time of surgery is again related to patient age, supporting the theory that malformed valves tend to calcify earlier than normal tricuspid valves[7, 14-17]. Other congenitial aortic valve malformations such as quadricuspid aortic valve[18] are rare, the reported incidence in literature being around 0.003-0.047%. They are usually detected as an incidental finding at surgery or necropsy, and are mainly associated with aortic regurgitation as the predominant hemodynamic dysfunction[19, 20]. In the Euro Heart Survey from 2001, the investigators found degenerative valve stenosis to be the cause of AS in 81.9% of cases with native AS, confirming that degenerative or calcific valve deformation is to date the main cause of native AS in developed countries[21].

The following parts of this thesis will focus on the previously termed "degenerative", or calcific, aortic valve stenosis, including both TAV and BAV; while other more rare malformations or rheumatic valve disease will not be handled further.

Aortic valve disease is a prevalent valvular heart disease in persons above 50 years of age. Calcific AS is a common disease in the elderly, with a prevalence of 3 to 5% of the population over 75 years, [22, 23]. The Helsinki Ageing Study found a prevalence of 2.9% of critical aortic stenosis (AVA$\leq$ 0.8 cm^2) in the age group 75-86 years, and a prevalence of 4.8% of at least moderate aortic stenosis (AVA$\leq$1.2 cm^2) in the same age group. Slight cusp calcification without hemodynamic obstruction, also denoted aortic sclerosis, is even more frequent and can be found in about 25% of the population above 65 years. In the total age group 55-86 years, 53% of the population had some calcification. There was a marked increase with age. Within the age group

55-71 years, 27% compared to 75% in subjects aged 85-86 years, had some degree of calcification[22]. The Cardiovascular Health Study found similar prevalence data: among their 5,201 patients, 1,417 (27%) had aortic sclerosis[23]. In the Euro Heart Survey on Valvular Heart Disease, studying 5,001 persons with native valvular heart disease (VHD), AS was the most common native single valve pathology, present in 1,197 (43.1%) cases. Among these the majority, 81.9%, were deemed degenerative AS; and only 11.2% rheumatic[21]. Data from a necropsy study of 48 unselected, consecutive patients in Finland[24] likewise indicate that atherosclerosis-like lesions are prevalent in adults of all ages, including young adults aged 20-40 years, suggesting that the disease process leading eventually to AS is common and probably starts in early adulthood.

The natural history of AS encompasses a long latent stage between initiation of the disease and symptom onset[25-29], where the degree of AS usually increases slowly. Patients need to be followed with regular visits including echocardiography to evaluate the progression rate and to assess the onset of cardiac symptoms, being an indication for aortic valve replacement surgery according to current guidelines[30, 31]. Progression rate shows, however, marked inter-individual variations[29, 32-36]. The baseline peak jet velocity is a robust and well-validated prognostic determinant of outcome, convincingly demonstrated in the prospective landmark study by CM Otto and co-workers[29]. In addition currently accepted risk factors for reduced event-free survival in AS are age>50 years, extensive calcification of the valve, annual progression >0.3 m/s/y and the presence of coronary artery disease as a co-morbidity[37, 38].

Etiology

Risk factors

During previous decades AS was considered to be a mere result of "wear and tear", passive calcification of the valves, or a result of normal ageing. This may, indeed, be part of the truth. It may at least play a role in the very early initiation process, where mechanical stress, shear stress or damage to the endothelium might be involved, similar to the development of atherosclerotic

vascular plaques[28]. This bio-mechanical aspect might also explain part of the reason why bicuspid valves become stenotic 10-20 years prior to tricuspid valves[39]. However, early clinical observations of increased risk of AS in familial hypercholesterolemia lead to the suspicion that lipid levels could be involved in the disease process[40-45]. The 'early lesion' demonstrated to be present in aortic valves has been found to contain LDL-cholesterol, and lipoprotein(a), and even oxidized LDL-cholesterol suggestive of a similar inflammatory process as in vascular atherosclerotic lesions[28, 46].

It has been established that several cardiovascular risk factors predispose for development of subsequent AS , particularly diabetes mellitus, hypertension, smoking and hyperlipidemia[28, 47-61], however some studies failed to demonstrate the same relationship with atherosclerotic risk factors to AS as to vascular disease[62-64]. The progression of the valve calcification shows close similarities to known inflammatory pathways demonstrated in atherosclerotic diseases, however, notably with some differences. Ortlepp et al did not find any association between any cardiovascular risk factors such as hypertension, smoking, male sex, diabetes mellitus or hypercholesterolemia with AS in 523 AS patients compared to nearly 4000 coronary patients, however such risk factors predicted coronary artery disease in patients with AS[62]. In addition, APO E alleles were not associated with AS[65]. Main published risk factors associated with AS are summarized in Table 1. In itself, the presence of atherosclerotic changes in the aortic valve bear considerably increased cardiovascular risk, even without hemodynamically significant changes of the valve. In a study by Otto et al the relative risk for cardiovascular mortality, acute myocardial infarction and congestive heart failure was increased by 66%, 46% and 33%, respectively in persons with aortic sclerosis compared to persons with normal valves[52].

Different risk factors previously known to be associated with other atherosclerotic diseases like coronary heart disease and cerebrovascular disease were investigated for AS, both for tricuspid AS, but also bicuspid AS[51, 54, 63, 66-69]. In the Cardiovascular Health Study Stewart et al. demonstrated correlation between age, male gender, smoking and history of hypertension, and

height (inverse relation), high lipoprotein(a) and high LDL-cholesterol levels and AS[23]. Lindroos et al demonstrated increased age, lower body mass index (BMI), hypertension, calcium and parathyroid hormone to be associated with increased risk of incident valve calcification[50]. Similar results were found in aprospective study investigating the prevalence of calcified or thickened aortic cusps or root in an unselected population of 578 persons older than 62 years[70]. A recent, small study from U.K. found significant correlation between hypercholesterolemia and calcific, tricuspid aortic stenosis, but not with bicuspid AS[68]. However, Chan et al. demonstrated the same risk factors to be significant also in patients with bicuspid valves[8]. This is plausible since studies related to risk factors have included both tricuspid and bicuspid valve in many cases, partly due to the known difficulty in separating the two entities by echocardiography once the valve becomes heavily calcified. In the aforementioned study by Davies et al the mean age for surgery was 64.9 years in patients with bicuspid AS, as compared to 73.4 years for those with tricuspid valves[8, 11]. The same study also demonstrated a higher risk for combined AVR and CABG in patients with tricuspid AS, 44.8%, as compared to 22.3% in patients with bicuspid AS, pointing to the increased risk for cusp calcification due to risk factors for atherosclerosis in these patients. There is increased risk for development of atherosclerotic changes in aortic valve cusps related to long term exposure to atherosclerotic risk factors. In a randomly selected group of 953 healthy individuals aged 24-75 years in the general population this was demonstrated by the MONICA/KORA investigators. In this study age (OR 2.0 [1.7-2.3] per 10 year, $p<0.001$), elevated total cholesterol (OR 1.2 [1.1-1.3] per increase of 20 mg/dL, $p<0.001$) and active smoking (OR 1.7 [1.1-2.4], $p=0.009$), in contrast to hypertension and obesity, were associated with development of aortic valve disease over a 10 year period[71]. Table 1 summarizes some main risk factors associated with development of AS.

Table 1: Published risk factors for AS:

RISK FACTOR	AUTHOR	REFERENCES	RESULTS
Age	*Mohler et al*[51]	*Clin Cardiol* 1991; 14: 995–99	*Age (for BAV)*
	Stewart et al Cardiovascular Health Study[23]	*JACC* 1997;29:630-34	*Doubled risk per 10 year*
	Lindroos et al Helsinki Ageing Study[50]	*Eur Heart J* 1994; 15: 865–70	*Increased age (p=0.000) associated with valve calcification. Independent predictor (p=0.000) for incident valve calcification and (p=0.022) for AS. OR 1.89 10 year increased age for valve calcification*
	Thanassoulis (Framingham Offspring study)[72]	*JACC 2010;55:2491-98*	*Early adulthood exposure to CV risk factors (TC>6.9 and smoking) increases risk of presence of AV and MV calcifications by CT 27 years later.*
	Ngo et al[73]	*JACC Imaging 2009;2:919-927*	*Reduced platelet NO responsiveness, increased age and lower BMI associated with aortic valve calcifications by backscatter score*
	Stritzke (KORA/MONICA study)[71]	*Eur Heart J 2009;16:2044-53*	*Age OR 2.0 [1.7-2.3] per 10 years, p < 0.001*
Male sex	*Mohler et al*[51]	*Clin Cardiol* 1991; 14: 995–99	*Younger males (p<0.01) both BAV and TAV*
	Stewart et al Cardiovascular Health Study[23]	*JACC* 1997;29:630-34	*Doubled risk*
Smoking	*Mohler et al*[51]	*Clin Cardiol* 1991; 14: 995–99	*p=0.03 for smoking (TAV)*
	Stewart et al Cardiovascular Health Study[23]	*JACC* 1997;29:630-34	*35% increased risk*
	Thanassoulis (Framingham Offspring study)[72]	*JACC 2010;55:2491-98*	*Early adulthood exposure to CV risk factors (TC >6.9 and smoking) increases risk of presence of AV and MV calcifications by CT 27 years later.*
	Ngo et al[74]	*Am J Geriatr Cardiol 2001;10:86-90*	*History of smoking (relative risk [RR]= 3.06; 95% CI 1.09-8.61; p = 0.034) and body mass index (BMI)(RR = 1.16; 95% CI = 1.03-1.30; p = 0.013) assoc. with increased progression (>5 mmHg/ year). Hypertension, diabetes, cholesterol, age, gender, and coronary artery disease (CAD) not independently associated with progression.*
	Stritzke (KORA/MONICA study)[71]	*Eur Heart J 2009;16:2044-53*	*Active smoking OR 1.7 [1.1-2.4], p = 0.009*
Diabetes mellitus	*Deutscher et al*[56]	*J Chronic Dis* 1994; 37: 407–15	*Increased risk of valve calcification*
	Aronow et al[57]	*Am J Cardiol* 1987; 59: 998–99	*Increased risk*

	Katz et al MESA study[75, 76]	*Circulation 2006;113:2113-19*	*MS and DM associated increased risk of AV calcification, women HR 1.45 and 2.12, and in man HR 1.70 and 1.73 for MS and DM respectively. Linear relationship related to number of MS components*
		Diabetes 2009;58:813-19	*MS, but not DM related to new AVS (initiation of AS)*
Metabolic syndrome	*Katz et al MESA study*[75, 76]	*Circulation 2006;113:2113-19*	*MS and DM associated increased risk of AV calcification, women HR 1.45 and 2.12, and in man HR 1.70 and 1.73 for MS and DM respectively. Linear relationship related to number of MS components MS, but not DM related to new AVS (initiation of AS)*
		Diabetes 2009;58:813-19	*MS, but not DM related to new AVS (initiation of AS)*
	Briand et al[77]	*JACC 2006;47:2229-2236*	*Faster progression (gradient) and reduced 3 y-survival 44 vs 69%(OR 3.85, p<0.001)*
	Page et al ASTRONOMER study[78]	*JACC 2010;55:1867-1874*	*Impaired LV geometry and function*
Hypertension	*Aronow et al*[67]	*Am J Cardiol* 1987; 59: 998–99	*Increased risk*
	Stewart et al Cardiovascular Health Study[23]	*JACC* 1997;29:630-34	*20% increased risk (history HT)*
	Lindroos et al Helsinki Ageing Study[50]	*Eur Heart J* 1994; 15: 865–70	*p=0.005 for valve calcification*
	Linefsky et al MESA study[79]	*Am J Cardiol 2011;107:47-51*	*Stage I/II hypertension and higher systolic BP and pulse pressure were associated with prevalent AVC strongest < 65 years of age*
	Ngo et al[74]	*Am J Geriatr Cardiol 2001;10:86-90*	*History of smoking (RR= 3.06; 95% CI 1.09-8.61; p = 0.034) and BMI (RR = 1.16; 95% CI = 1.03-1.30; p = 0.013) assoc. with increased progression (>5 mmHg/year). Hypertension, diabetes, cholesterol, age, gender, and CAD not independently associated with progression.*
Paget's disease	*Strickberger SA,Schulman SP,Hutchins GM*[80]	*Am J Med* 1987;82:953–56	*p<0.05*
Hyperparathyroidism	*Lindroos et al Helsinki Ageing Study*[50]	*Eur Heart J* 1994; 15: 865–70	*S-PTH (p=0.015)*
	Linhartova et al[81]	*Abstr3033 Circulation 2007;116*	*Increased PTH and reduced vit D associated with AV calcification*
Total cholesterol	*Sprecher et al*[84]	*Am J Cardiol* 1984; 54: 20–30	*Increased risk of AS in FH patients*
	Palta S,Pai AM,Gill KS,Pai RG[82]	*Circulation* 2000;101:2497–502	*p=0.04 for faster reduction AVA (chol>200 mg/dL)*
	Deutscher et al[66]	*J Chronic Dis* 1994; 37: 407–15	*Increased risk of valve calcification*
	Aronow et al[67]	*Am J Cardiol* 1987; 59: 998–99	*Increased risk*

	Thanassoulis (Framingham Offspring study)[72]	*JACC 2010;55:2491-98*	*Early adulthood exposure to CV risk factors (TC>6.9 and smoking) increases risk of presence of AV and MV calcifications by CT 27 years later.*
	Stritzke (KORA/MONICA study)[71]	*Eur Heart J 2009;16:2044-53*	*Elevated total cholesterol OR 1.2 [1.1-1.3] per increase of 20 mg/dL, p < 0.001*
LDL-cholesterol	*Stewart et al Cardiovascular Health Study*[23]	*JACC* 1997;29:630-34	*Increased risk*
Low HDL-cholesterol	*Aronow et al*[87]	*Am J Cardiol* 1987; 59: 998–99	*Increased risk*
Triglycerides	*Mohler et al*[51]	*Clin Cardiol* 1991; 14: 995–99	*Triglycerides p=0.0004*
Raised Lp(a)	*Gotoh et al JMS Cardiac Echo study*[83]	*Am J Cardiol* 1995;76:928–32	*Lp(a)≥30 mg/ml (p<0.001)*
	Stewart et al Cardiovascular Health Study[23]	*JACC* 1997;29:630-34	*Increased risk*
Uremia	*Maher ER,Pazianas M,Curtis JR*[84]	*Nephron* 1987; 47: 119–22	*Increased risk with HD(p=0.0004), increased with age, duration*
Raised serum creatinine	*Palta S,Pai AM,Gill KS,Pai RG*[82]	*Circulation* 2000;101:2497–502	*p=0.04 for faster reduction AVA*
Raised serum calcium	*Palta S,Pai AM,Gill KS,Pai RG*[82]	*Circulation* 2000;101:2497–502	*p=0.08 (ns) for faster reduction AVA*
	Aronow et al[87]	*Am J Cardiol* 1987; 59: 998–99	*Increased risk*
	Lindroos et al Helsinki AgeingStudy[50]	*Eur Heart J* 1994; 15: 865–70	*Serum ionized calcium (p=0.037) vs. valve stenosis*
Serum phosphorous	*Aronow et al*[87]	*Am J Cardiol* 1987; 59: 998–99	*Increased risk*
	Linefsky et al Cardiovascular Health Study[85]	*Abstr:Circulation 2009;120:S307*	*Higher phosphate levels, but not vitD or PTH associated with increased risk*
Body Mass Index	*Lindroos et al Helsinki Ageing Study*[50]	*Eur Heart J* 1994; 15: 865–70	*Low BMI associated valve calcification (p=0.005). 5 kg/m² decrease in BMI OR 1,39 for valve calcification*
	Ngo et al[74]	*Am J Geriatr Cardiol 2001;10:86-90*	*History of smoking (RR= 3.06; 95% CI 1.09-8.61; p = 0.034) and BMI (RR = 1.16; 95% CI = 1.03-1.30; p = 0.013) assoc. with increased progression (>5 mmHg/year). Hypertension, diabetes, cholesterol, age, gender, and CAD were not independently associated with progression.*
	Ngo et al[73]	*JACC Imaging 2009;2:919-927*	*Reduced platelet NO responsiveness, increased age and lower BMI associated with aortic valve calcifications by backscatter score*
	Rogge et al[86]	*JACC 2013;62:1683-90*	*Overweight and obesity do not influence AS progr or rate of AS-related or ischemic*

			CV events. Increased all cause mortality 46% and for BMI 25-29.9 kg/ m² and 67% for BMI≥30 kg/ m².
	Stritzke (KORA/MONICA study)[71]	*Eur Heart J 2009;16:2044-53*	*Hypertension and obesity no detectable relationship with long-term changes of aortic valve structure.*
Height	*Stewart et al Cardiovascular Health Study*[23]	*JACC* 1997;29:630-34	*Inverse association. OR 0.84 per 10 cm increase.*
Platelet responsiveness	*Ngo et al*[73]	*JACC Imaging 2009;2:919-927*	*Reduced platelet NO responsiveness, increased age and lower BMI associated with aortic valve calcifications by backscatter score*

Histopathology

Histopathological studies have demonstrated a chronic inflammatory infiltrate both in the "early lesion" in the valve, as well as in the clinically stenotic stage, with basement membrane disruption, lipid deposition and accumulation of calcium and inflammatory cells, similar to changes known from studies of coronary artery disease[28, 55-57, 87]. Later the numerous signalling pathways involved in the AS progression towards end-stage disease have been explored in the further search for potentially modifiable mechanisms that could impact upon treatment of the disease. There is now general acknowledgement of AS as a chronic inflammatory disease with many similarities with other atherosclerotic diseases. Expression of matrix metalloproteinases (MMPs) is involved and an altered balance towards their inhibitors[88-92], as well as their association to tenascin C, fetuin A, osteoprotegrin and other signalling substances[90, 93-102]. These signalling pathways are important in inducing the phenotypic transformation of the valvular smooth muscle myofibroblasts into osteoblast-like cells with the ability to stimulate to bone matrix formation, leading on to the end-stage AS[58, 59, 90, 91, 97, 103-107].

Pharmacologic intervention for AS?

Effective lipid-lowering treatment with statins has been shown to reduce progression of atherosclerotic disease and thus reducing risk of clinical events, as demonstrated in studies in coronary heart disease, but also other atherosclerotic diseases[108-111]. Thus, the hypothesis of potential effect of lipid-lowering treatment for AS arose. Observations of high prevalence of AS in young patients with familiar hypercholesterolemia also indicated that cholesterol played some part in the development of AS[40, 41]; available lipid lowering treatment became a tentative option for medical intervention even in VHD. Animal studies later demonstrated that a diet high in cholesterol was able to induce valve calcifications similar to AS, and that treating the animals with statin induced regression of the valvular changes[104, 112-115]. Retrospective or small case-control

studies in humans supported these findings by indicating that individuals treated with statin had a slower progression rate of their AS deemed by either echocardiography or by CT scan of aortic valve calcium[116-119].

Left ventricle hypertrophy

Established AS has a natural long course of the disease with gradually increasing narrowing of the aortic valve, over time influencing the outflow from the left ventricle (LV) into the aorta. The hemodynamic response to the increasing narrowing of the aortic valve leads to an increasing pressure afterload and wall stress of the left ventricle, which eventually will lead to the development of myocardial hypertrophy[120, 121]. There is overwhelming evidence that left ventricular hypertrophy (LVH) in general and in hypertensive population worsens cardiovascular prognosis with increased risk of heart failure and cardiovascular death[122-124]. In AS, it was traditionally thought that LV hypertrophy was primarily compensating for increased hemodynamic load, reflecting the severity of valve stenosis. However, recent reports have demonstrated that LV response to AS varies according to presence of other CV risk factors imposing pressure (hypertension) or volume (obesity, metabolic syndrome, valve regurgitation) overload on the LV[125-127]. A maladaptive remodelling of the LV in response to a sustained pressure overload in AS could explain why LV mass (LVM) predicts myocardial dysfunction, heart failure and thus adverse outcome. Stress-corrected midwall shortening of the LV has been demonstrated to be independently associated with symptoms in AS[128]. Data from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study have previously demonstrated that hypertension predicts higher LVM independently of important covariates, especially severity of AS, LV ejection fraction and body mass index (BMI)(multiple R^2=0.30, $p<0.001$)[127]. Hypertension did not predict any increased rate of major cardiovascular events (the primary endpoint of SEAS), however a 56% higher rate of ischemic events ($p<0.01$) and doubled mortality risk ($p<0.01$)[129]. The main determinants of LVH in mild to moderate AS were male gender, severity of AS and

concomitant hypertension . The study also demonstrated that LV myocardial dysfunction is common even in asymptomatic mild to moderate AS despite normal ejection fraction. Low stress-corrected midwall shortening was found in up to 63% in the patients with the highest global LV load[130, 131]. Impaired LV systolic function was also seen in another small tissue Doppler substudy from the SEAS patients, demonstrating reduced peak systolic tissue velocity and strain as well as augmented LV filling pressure and impaired LV relaxation indicating diastolic dysfunction in these patients compared to healthy control patients[132]. Also, we found that LV mass and LVH increased with obesity (22% with normal BMI vs 54% in obese patients). LVH was significantly associated with higher BMI (OR 1.15, 95% CI 1.12-1.18), independent of history of hypertension, AS severity, age, systolic blood pressure or LV ejection fraction[133]. Cioffi and co-workers demonstrated that inappropriate LVH, defined as excessive LVM that exceeds that of the anticipated physiologic response to the narrowing valve was associated with significantly lower survival than in patients with appropriate LVM (78% vs 56% at 1-year, 68% vs 29% at 3-year and 56% vs 10% at 5-year follow-up, respectively, all $p<0.01$)[134]. Patients with inappropriate LVM had 4.5 fold higher risk of cardiovascular adverse events than patients with LVM deemed appropriate. Inappropriately increased LVM has been suggested to be a strong predictor of worsened clinical outcome even in patients without AS[135-137]

AIMS OF THE STUDY

Hypothesis

The hypothesis of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) Study was that hypercholesterolemia is one of several risk factors for AS, and that modification of this risk factor by lipid lowering therapy could reduce the risk of cardiovascular events and need for valve surgery and reduce the progression of AS, and that such treatment would be well tolerated in elderly patients.

General aims

The SEAS study aimed to evaluate whether intensive lipid lowering therapy by simvastatin 40 mg and ezetimibe 10 mg daily compared to placebo could reduce the risk of a combined composite endpoint of major cardiovascular events (MCE) consisting of cardiovascular death, aortic valve surgery, heart failure as a result of progression, nonfatal myocardial infarction, hospitalized unstable angina, CABG, PCI and nonhemorrhagic stroke. Secondarily the study aimed to investigate whether the study treatment could reduce the risk of valve related events (AVE) and ischemic cardiovascular events (ICE) and whether echocardiographic progression of AS would be reduced. Finally, the safety of long-term intensive lipid-lowering treatment in elderly would be assessed.

Specific aims

Paper 1-2: Main study.

The aim was to investigate in a large randomized interventional trial the lipid hypothesis in AS as suggested in case-control, animal and retrospective studies. We wanted to assess in a placebo-controlled clinical study whether effective lipid lowering treatment does affect the progression and clinical outcome of AS.

Paper 3:

Is the effect of lipid lowering related to baseline severity of aortic stenosis? One retrospective and one open label, prospective study reported possible effect from statin treatment in early stages of aortic valve disease, indicating an effect of statins in the very early, even pre-clinical stages of the disease[138, 139], in spite of three negative randomized clinical trials (RCTs). Post-hoc analysis was planned to analyze the effect of intensive lipid lowering treatment versus placebo on morbididy and mortality in tertiles of AS severity in a prospective study.

Paper 4:

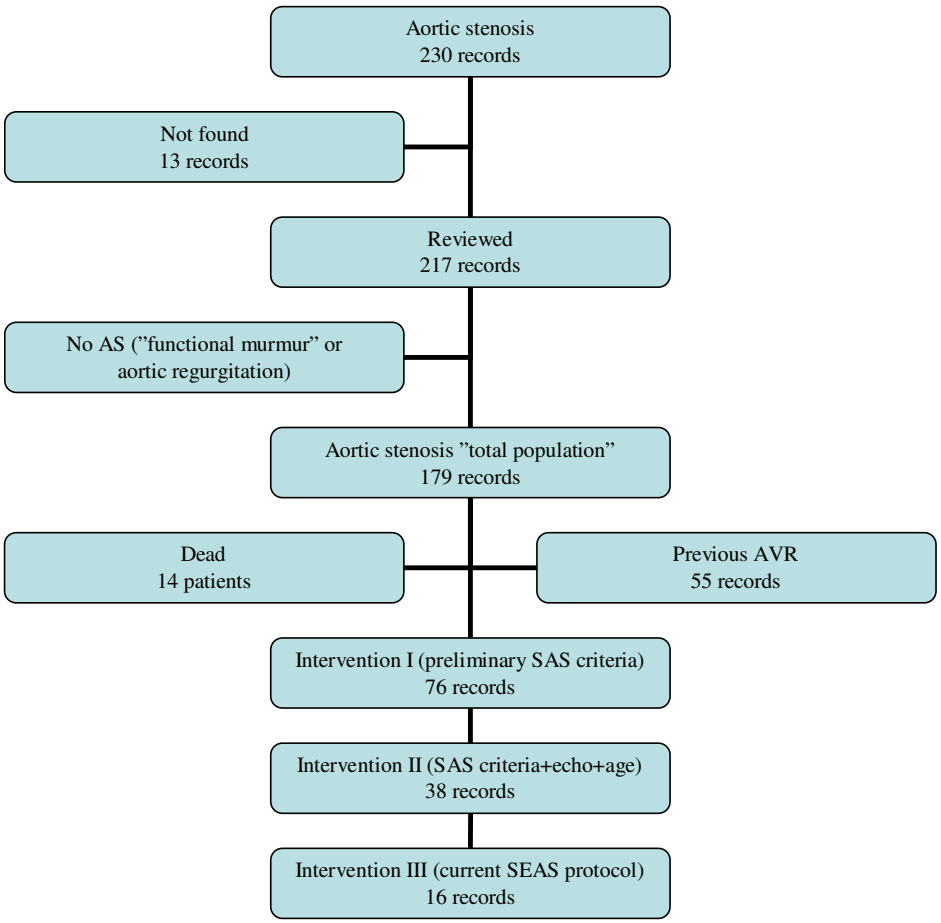
Left ventricular hypertrophy (LVH) is a well known marker of increased cardiovascular morbidity and mortality in hypertensive and general populations[122, 140, 141], and has been seen to add to adverse modulation of LVM in presence of other comorbidities as hypertension and obesity. The present analysis aimed to assess the prognostic importance of left ventricular mass in a large prospective study of patients with asymptomatic mild to moderate AS.

METHODS

Pilot study at Aker University Hospital 1995-97

The aim of this pilot study was to gain information to plan the current prospective study. Hospital records of 217 patients seen in the Cardiology Clinic, Aker University Hospital, Oslo, Norway, from Jan-1995 to Oct-1997 because of valvular AS, were examined retrospectively for the degree of obstruction, progression of AS, concomitant CHD, lipid profile, and conventional risk factors for CHD. This study was performed early spring 1998, as part of planning of the intended interventional study. Records of patients who died in the observation period were also examined, as were the records of patients undergoing aortic valve replacement (AVR) in the observation period or earlier. The hospital records were screened on the basis of patient lists of the diagnosis "aortic stenosis" at the cardiology outpatient clinic. This search was performed in the hospital's electronic diagnosis system (ICD9 at that time), by employing the diagnosis number "I35.9", resulting in a list of patients that had been seen at the clinic during this time span. The time span of 2 years was chosen, since most AS patients at that time were seen at yearly intervals and therefore most patients currently under regular follow-up would have been seen at the clinic during this time period. A total of 230 patients were given this diagnosis and their hospital records were collected for scrutinized review. All records at that time were in paper format, not electronic. Thirteen records (among them 2 dead patients) could not be found in the hospital's archive, so finally a total of 217 records were reviewed, see Figure 1. Of these 217 patients, 35 were discovered to have been miscoded as AS, but had by echocardiogram only a "functional murmur" and suspected AS was ruled out by the examination. Fifty-five patients had undergone AVR. Fourteen patients were dead. Some patients had predominantly or only aortic regurgitation, with an increase in peak aortic jet velocity due to higher flow. Such imprecisely coded patients were not included in the pilot study registry.

Figure 1:



The final register of AS patients at this institution, therefore, included 179 patients, including also dead and surgically-treated patients. In this register, the mean age was 69±15 years. The percentage of women was 55%. All records were reviewed for each patient's full history of valve disease, lipid levels, statin use and comorbidities, employing a preliminary set of inclusion and exclusion criteria intended for use in the later clinical study. Data from the first visit to the outpatient clinic, the follow-up visit (here named the intermediate visit) and the last recorded visit (here named the last visit) were collected. At the first recorded visit, the following values were measured (mean±standard deviation (SD)): peak aortic jet velocity 2.3±0.7 m/s, mean gradient 22±12 mmHg and aortic valve area (AVA) 1.42±0.34 cm^2. Forty-two percent had AS without

regurgitation. At the last visit, the peak aortic jet velocity was 3.1±1.2 m/s, mean gradient 39±26 mmHg, and AVA 0.95±0.52 cm^2. The data indicate progression of AS with an peak aortic jet velocity progression 0.4±2.8 m/s/year, mean gradient change 17±92 mmHg/year, and a mean reduction of AVA 0.95±3.64 cm^2/year. Of the 179 patients, 15% had previous myocardial infarction, 35% had clinical angina pectoris, 41% of the group had hypertension, 37% were smokers, and mean BMI was 25.2±3.7 kg/m^2. Cholesterol had not been measured in all patients, but among patients with available data there was a mean total serum cholesterol of 6.2±1.3 mmol/L, HDL-cholesterol 1.39±0.48 mmol/L, LDL-cholesterol 4.29±0.94 mmol/L, and triglycerides 1.61±1.14 mmol/L. Eighty percent of the group had total cholesterol >5.0 mmol/L, which at the time (1998) was the upper limit of risk defined by the European Atherosclerosis Society, in line with findings from a study from general practice in Norway by Svilaas and co-workers[142]. Ninety-one percent of the patients had LDL-cholesterol >2.6 mmol/L (defined as risk limit by the National Cholesterol Educational Program, U.S.[143, 144]), 67% had LDL-cholesterol >4.1 mmol/L (European Atherosclerosis Society guidelines in 1998), 19% had LDL-cholesterol >5.0 mmol/L and 9.5% had LDL-cholesterol >5.5 mmol/L. Only 10% of the patients had been prescribed statins for other indications than AS. Thirty eight patients (21% of all AS patients screened) remained eligible for possible study inclusion after excluding all deaths, previous AVRs as well as employing the preliminary echocardiographic criterion of maximum peak jet velocity 2.5-4.0 m/s according to the planned inclusion criteria for the future intervention study (Simvastatin in Aortic Stenosis Study - SAS). These 38 patients are denoted 'Intervention II' in Figure 1. However, almost 1/3 of these potential study patients had symptomatic angina pectoris and 10% had a history of myocardial infarction, and more than half of the eligible patients did not comply with the later determined age criterion, the majority being too old (>80 years). Among these 38 the mean age was 75.2±12.1 years (37.5 to 93.6 years). Average total cholesterol was 6.0±1.3 mmol/L (4.0 to 9.1 mmol/L), LDL-cholesterol 4.2±0.8

mmol/L (3.5 to 5.3 mmol/L), HDL-cholesterol 1.9±0.7 mmol/L (1.3 to 3.0 mmol/L), and triglycerides 0.91±0.28 mmol/L (0.4 to 1.3 mmol/L).

Furthermore; when employing the same limits of peak aortic jet velocity as well as other inclusion/exclusion criteria as in the later intervention study SEAS protocol, only 16 patients (about 10%) of the screened 179 AS patients from available hospital registers would remain eligible for inclusion according to the SEAS criteria per 2003; here denoted "intervention III" in Figure 1. These calculations from the pilot registry illustrate the challenging screening scenario our study was facing at a time when indications for statin treatment in the general population were dramatically changing according to recent publication of large statin trials[108, 145-151]. Diabetes mellitus and cerebrovascular disease are examples of new indications for statin treatment that in our study protocol revisions were necessary to include into our study protocol's exclusion criteria to allow for placebo treatment. Thus, these new scientific findings thereby made quite an impact upon the feasibility of including the planned study patients into the SAS/SEAS study.

Main study design and organization

A forerunner of the SEAS study called Simvastatin in Aortic Stenosis (SAS) Study was designed as an investigator initiated, multicenter, international clinical trial sponsored by the medical company MSD Norway AS, however otherwise managed by a scientific Steering Committee, and practically organized by the scientific coordinator (dr.Rossebø) and the chairman of the steering committee (prof.Pedersen) with assistance from 1-2 employees from the sponsor. Establishment of all study related material (patient binders, archive binders, brochures etc) into distribution to study sites and patients was organized from Aker University Hospital in Oslo. Approval of bottling and labeling of study drugs, as well as the distribution of study drugs through Norsk Medicinaldepot AS (NMD) was organized. Also established was agreement and set-up of all study blood sample analyses according to laboratory protocol at the chosen central laboratory for the SAS study, Medilab AB, located in Täby, Sweden, as well as routines for shipping all locally

drawn blood samples to the central laboratory. All study sites and study physicians were carefully chosen, based on their experience with aortic stenosis patients as well as their ability to recruit such patients into the study and follow them according to protocol.

However, due to the challenging recruitment scenario of patients because of rapidly expanding indications for statin treatment as described earlier, the estimated number of study sites quickly increased to more than double of the initially planned number of sites, in order to be able to randomize the needed number of patients to fulfill the study power calculations. This was further confirmed through a slow recruitment rate, only reaching 196 of the 760 needed number of study patients after the first two years of recruitment, starting early 2001. In agreement with the Aker pilot study, however, only up to 10-20% of all theoretically available and screened patients turned out to be eligible for the study. This challenging situation also called upon not only more collaborating hospitals, but even more manpower to ensure adequate scientific quality control for execution of the study and meet the aims. The Steering Committee therefore agreed upon an extension of the study.

The later transition into the larger Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study was approved by Ethics Committees and Medicines Agencies by September 2002. This expanded study was very similarly designed as a multicenter, double blind randomized placebo-controlled study led by a Steering Committee consisting of 1-2 persons from each participating country. The Steering Committee was lead by a chairman (prof.Pedersen) and coordinated by a scientific coordinator (dr.Rossebø). The same, independent, unblinded Data Safety Monitoring Board as in the SAS study performed interim analyses at pre-specified time points. The same Endpoint Classification Committee as already established in the SAS study classified all reported potential endpoints in accordance with an Endpoint Classification Manual drafted by the scientific coordinator (dr.Rossebø) and agreed upon by the Steering Committee. In case of disagreements in the classification between the two Endpoint Committee members, these cases were adjudicated in separate meetings. An Echocardiography Core Laboratory located at

Haukeland University Hospital received and analyzed in the revised SEAS study all echocardiograms in the study in accordance with a prespecified protocol approved by the Steering Committee. The responsibility for blood sample analyses was transferred from the previous central laboratory for the study Medilab AB, Sweden to the new central laboratory at PPD Global Central Labs, located in Zaventum, Belgium. All previously collected blood samples for storage were transferred to PPD Labs.

Study population

According to the feasibility study only about 10-20% of screened patients could be expected to be included in the study, as described earlier. In the SAS study the number of planned study sites was therefore increased from about 20 large hospitals to more than 40 study sites, however, still the progression of inclusion was slower than expected, and the number of participating hospitals was thereafter gradually increased to reach a total of 173. After 196 patients were included, the decision was made to transfer these into the SEAS study, as previously explained, and to continue inclusion into the revised SEAS study. The number of study sites was increased to 173 study sites in 7 Northern European countries (Norway, Sweden, Denmark, Finland, United Kingdom, Ireland and Germany). Management of these study sites was taken over by the sponsor Merck/Shering-Plough (MSP) staff. The recruitment of study sites was initiated already in 2000 and continued until patient recruitment into the SEAS study was closed end of March 2004 when N=1,873 patients was reached. Study sites were chosen based on their expertise in valvular heart disease as well as their ability to recruit patients into the study. Study sites and all investigators are listed in the report of the main outcome (Paper II)[152].

The inclusion criteria for the SAS study were men and women 45-80 years with asymptomatic valvular aortic stenosis defined by echocardiography as mild to moderate degree with a peak aortic jet velocity ≥ 2.5 and ≤ 4.0 m/s, with or without moderate aortic regurgitation,

with normal left ventricular function and serum LDL-cholesterol >2.5 mmol/L. Patients were excluded from randomization if they had hypercholesterolemia (LDL-cholesterol > 6 mmol/L) or other indication for lipid lowering treatment, importantly coronary artery disease, secondary hyperlipoproteinemia related to nephrotic syndrome or hypothyreosis, other significant valvular heart disease, heart failure, uncontrolled hypertension, renal or hepatic failure as well as other conditions precluding adequate compliance or ability to give informed consent. Notably in the SAS trial stable diabetes mellitus type I as well as cerebrovascular disease were not at that time indications for statin treatment according to available scientific evidence. The revised SEAS study employed the same criteria for inclusion into the study; however, it was decided according to reassessment of expected life-span of octogenarians, to expand the upper age limit to 85 years. In addition, during the time from planning of the prior SAS study till finalization of the revised SEAS protocol by end of 2002, new scientific data had confirmed the beneficial effect of statins in atherosclerotic disease; thus it would be unethical to include patients with any atherosclerotic disease, specifically diabetes mellitus, cerebrovascular disease as well as peripheral arterial disease. Except for these additions, the patient characteristics were the same in the revised SEAS study as in the smaller SAS study.

The study flow chart for both the initial study and the SEAS study are shown in Table 2 (A-B) to document the similarities of the two protocols with regard to timelines and planned examinations for the study patients.

Table 2a: Study Flow Chart: Simvastatin Aortic Stenosis (SAS) Study

* Appendix 1
** and last visit
*** in the case of early discontinuation

Study week (w)/year (y)	-8 w	-2 w	0	6 w	12 w	24 w	48 w	2 y	3 y	4 y	5 y**	D***
Study visit	0	1	2	3	4	5	6	7	8	9	10	
Consent form	X											
Medical history review	X		x									
Physical examination	X		x	x			x	x	x	x	x	x
Inclusion/exclusion criteria	X		x									
Complete laboratory*		x										x
Lipids				x	x	x	x	x	x	x	x	
ASAT ALAT CK				x	x	x	x	x	x	x	x	
12-lead ECG	X		x				x	x	x	x	x	x
Echocardiography	X						x●	x●	x	x●	x°	x
Randomization			x									
Dispensing of study drug			x	x		x	x	x	x	x	x	
Adverse Experience Form			x	x	x	x	x	x	x	x	x	x
Quality of Life (optional)			x				x	x	x	x	x	x
Diet advice	X						x	x	x	x		

● Not mandatory

●● Physical examination must be done before randomization

° Mandatory if final visit

Table 2b. Study Flow Chart – SEAS study

	Prerandomi-zation Period	Randomi-zation	Treatment Period											
Week/Year Number:	Week -4[†]	Week 0[§§] Day 1	Week 8	Week 24	1 Year	1 .5 Year	2 Year	2.5 Year	3 Year	3.5 Year	4 Year[‡‡‡]	Additional Visits (Every 6 months Thereafter)[##]	Discon-tinuation Visit[%%]	End of Study Visit[%%‡‡‡]
Clinic Visit I.D.:	Visit 1	Visit 2[#§§§]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11			
Informed consent[‡]	X													
Medical history	X													
Review inclusion/exclusion	X													
Review prior/concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Monitor for adverse experiences	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination		X					X				X		X	X
Cardiopulmonary exam[¶¶]	X		X	X	X	X		X	X	X		X		
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Echocardiography/Doppler[†††]	X				X		X		X		X	X[†††]	X	X
12-lead ECG[†††]	X				X		X				X	X[†††]	X	X
Lipids and lipoproteins[%¶]	X[%]	X[¶]	X[%]	X[¶]	X[¶]	X[%]	X[¶]	X[%]	X[¶]	X[%]	X[¶]	X[%]	X[¶]	X[¶]
High sensitivity C-reactive protein		X			X								X	
Serum β-hCG test[††]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Thyroid function (TSH, T_4)	X													
Sitosterol, campesterol		X			X								X	
Hematology		X					X				X		X	X
Blood chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis		X					X				X		X	X
Dietary advice	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X[‡‡]	X[‡‡]	X[‡‡]	X[‡‡]	X[‡‡]	X[‡‡]	X[‡‡]	X[‡‡]	X[‡‡]	X[‡‡]	X[‡‡]	X[‡‡]		
Monitor medication compliance		X	X	X	X	X	X	X	X	X	X	X	X	X
Archive plasma/serum sample		X			X						X		X	X
Genetic sample		X												

[†] Patients hospital records should be examined retrospectively to this visit.
[‡] Informed consent must be obtained before any protocol-related study procedures can be performed.
[%] Lipid panel at Visits 1, 3, 6, 8, 10, and an additional 6-month visit includes TC, LDL-C, HDL-C, non-HDL-C, TG.
[¶] Lipid panel at Visits 2, 4, 5, 7, 9, 11, discontinuation, and end-of-study visit includes TC, LDL-C, HDL-C, non-HDL-C, TG, apo B, (RLP-C. only at baseline, V5 and discontinuation)
[#] All inclusion/exclusion criteria will be evaluated at Visit 1.
[††] In women of childbearing potential as specified in the inclusion/exclusion criteria.
[‡‡] First dose of study drug should be taken the night of the visit; study drug should be taken daily in the evening.
[§§] Upon findings from Visit 1 screening evaluation, the site may contact patients qualifying for randomization immediately and schedule Visit 2.
[%%] Fourteen days following last dose of study medication, patients will be contacted by telephone.
[¶¶] Including auscultation of heart and lungs.
[##] If a patient completed Visit 11 before the study ends, then additional visits will be scheduled every 6 months thereafter until the study ends.
[†††] Echocardiography/Doppler and ECG should be done once per year and Echo performed before any planned aortic valve surgery
[‡‡‡] All patients currently enrolled at the time of study termination will need to return to complete an end-of-study visit.

	Prerandomi-zation Period	Randomi-zation	Treatment Period										Discon-tinuation Visit[%%]	End of Study Visit[%%‡‡‡]
Week/Year Number:	Week -4[†]	Week 0[§§] Day 1	Week 8	Week 24	1 Year	1 .5 Year	2 Year	2.5 Year	3 Year	3.5 Year	4 Year[‡‡‡]	Additional Visits (Every 6 months Thereafter)[###]		
Clinic Visit I.D.:	Visit 1	Visit 2[#§§§]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11			
§§§ Patients currently enrolled in Protocol 182-02 will have an unscheduled visit which follows their last scheduled visit in 182 and have all Visit 2 procedures completed.														

At annual visits the patients underwent clinical examination, including blood pressure, echocardiography and ECG, and were given dietary advice according to NCEP-III, as well as were interviewed about adverse events. Used bottles of study drug were replaced with a new bottle and the remaining number of tablets counted to assess compliance. Fasting blood samples were drawn at each visit; lipid levels annually and safety blood samples (including creatin kinase and liver enzymes) every 6 months.

Echocardiography

Echocardiograms were obtained at each local study site by an experienced cardiologist or by an echo technician. Echocardiography following a standardized protocol was performed at baseline and annually thereafter. All echocardiographic examinations were recorded and submitted to the Echocardiography Core Laboratory, where all echocardiographic analyses were performed according to international guidelines. All echocardiographic studies in the SEAS were first read by a junior reader, and thereafter proof read by a senior reader. All readers were blinded for study treatment and sequence. However, the decision to include the patient was made by the local study site according to measurements at baseline and not according to central reading. All clinical decisions regarding patients were taken on basis of local echocardiographic measurement. Thus, the study population included some patients with centrally deemed peak jet velocities slightly outside the inclusion criteria $\geq$ 2.5 and $\leq$ 4.0 m/s. Likewise the clinical management of the patients was based on local echocardiography interpretation.

In addition, at the time of planning the Simvastatin in Aortic Stenosis trial, the study administration was considerably smaller than after incorporation into the SEAS trial. The main outcome of the SAS study was the clinical events. Thus, in the early phase of the SAS study it was decided that echocardiographic measurements should be performed by each study physician and that the measurements be submitted to the study administration for analysis. Echocardiographic central reading was for organizational and financial reasons at that point decided to be regarded

as a substudy. However, the transition into the SEAS study increased manpower and financial support from the sponsor. It was then both practically feasible as well as from an academic point of view of great interest to have a centralized standardized reading of the echocardiograms. The Steering Committee for the SEAS study thus decided upon mandatory central reading of the echocardiograms at the Core Laboratory at Haukeland Hospital, Bergen.

All echocardiograms were recorded and sent to the Core Lab as VHS tapes, CD or MO discs, to be read by the Core Lab, even echocardiograms taped during the entry of the initial SAS study. The Echo Core Lab subset of the Steering Committee decided upon the reading protocol and which parameters to be included into the central database of the SEAS study. The echocardiographic protocol is described in detail in the addendum to the main SEAS protocol as well as in a substudy published from the Echo Core Lab.[130].

Study treatment

To test the hypothesis that lipid lowering treatment reduced the risk of cardiovascular events in patients with AS, it was seen as crucial to effectively lower the cholesterol, and the duration of treatment would need to last for at least 4-5 years in order for a difference to be detected, due to the prolonged natural history of AS and thus the expected relatively low rate of events in patients with mild to moderate AS. To test the hypothesis it was therefore in the first planned SAS trial chosen to treat patients with simvastatin 40-80 mg daily, compared to placebo. An uptitration algorithm was designed to ensure that patients with inadequate LDL-cholesterol lowering were given high dose statin treatment to lower LDL-cholesterol intensively. However, during the first year of inclusion of patients, new data regarding increased, dose-related risk of rhabdomyolysis were reported for the 80 mg dosage to the sponsor MSD, who therefore suggested that only the lowest dosage 40 mg daily would be used to avoid drug-related side-effects, in accordance with public advice regarding simvastatin dosing at the time. The risk of using a lower dose could lead to failure to detect any difference in risk between the treatment groups. So, when the new drug

ezetimibe became available through the sponsor, the Steering Committee decided to use a fixed combination of simvastatin 40 mg and ezetimibe 10 mg as the lipid intervention to provide the maximum difference in LDL-cholesterol between the two treatment groups.

Patients and study physicians as well as study Steering Committee were all blinded to study treatment throughout the study. The transition from the SAS to the expanded SEAS trial was performed in a way that ensured that study treatment group was undisturbed for the 196 patients already enrolled in the SAS trial. More specifically, all patients randomized to placebo treatment in the SAS trial were switched to the placebo arm of SEAS trial, and patients in the simvastatin 40 mg group in the SAS trial were switched to the ezetimibe 10 mg + simvastatin 40 mg arm of SEAS trial, without unblinding.

Simvastatin

Simvastatin is a hydroxymethylglutaryl co-enzyme A (HMG Co A)-reductase inhibitor, a potent inhibitor of LDL-cholesterol synthesis in the liver. Studies with simvastatin in various dosages have shown that the mean LDL-cholesterol reduction with 20 mg, 40 mg and 80 mg daily are 35, 41 and 47%, respectively. Simvastatin has been extensively investigated in atherosclerotic diseases and shown significant effects on mortality and morbidity in patients with coronary artery disease and other atherosclerotic diseases[108, 149, 153-155].

Ezetimibe

Ezetimibe belongs to a different class of cholesterol-lowering drugs, acting by inhibition of absorption of cholesterol and structurally related phytosterols from the small intestine, by selectively inhibiting the Niemann-Pick-C1 Like 1(NPC1L1) protein located on the brush border of the enterocyte in the small intestine. The drug thus acts primarily to reduce absorption of exogenous, dietary cholesterol and cholesterol from the enterohepatic circulation. It does not affect the absorption of other lipids or lipid derivatives. Ezetimibe and its active metabolite, a glucuronide conjugate, act mainly within the intestines, with little release into circulation. Studies

have demonstrated its ability to reduce LDL-cholesterol by 19% in two monotherapy multicenter studies; and in combination therapy with statin the combined LDL-lowering effects have been found to be an additional 19% compared to simvastatin 40 mg alone[156, 157]

Study treatment safety

Numerous studies on statins in general and simvastatin in particular have demonstrated the safety of simvastatin in doses up to 80 mg daily[154, 158, 159].Known adverse effects are myopathy and elevations of liver transaminases more than 3-fold of upper limit of normal, occurring in <1% and <2% of patients, respectively. The risk of the most feared side effect, rhabdomyolysis and myopathy, is reported to be 0.9% with the 80 mg dose[158]. The risk of side effects is, however, dose-related. The safety of statin treatment has been previously well described.[154]

Patients in the SEAS study were monitored throughout the duration of the study to detect any adverse effects of the study drugs. At all study visits patients were interviewed about adverse events. Laboratory adverse events were captured through the assessment of blood samples (creatin phosphokinase (CK) and liver enzymes) at every study visit (6 month intervals). Study physicians had reports of all laboratory results except lipid levels after the baseline visit. They were expected to react to any deviations outside the reference interval. In addition, all elevations of liver enzymes >3 times the upper limit of normal (ULN) or elevated CK >5 times ULN was in particular reported back from the laboratory to the monitors and study physicians. If two or more consecutive elevated values to such levels, the study drug was discontinued according to the study protocol, while study drug was allowed to continue if only single elevations.

Lipid levels were blinded to study physicians after the randomization visit, to avoid potential unblinding throughout the study course, and patients and general practitioners were encouraged not to have the lipids measured outside of the study. However, lipid levels were

monitored without unblinding by the Central Laboratory. Consistently high LDL-levels ≥6 mmol/L detected at the Central Laboratory at any time during the study would qualify for open-label statin treatment according to the local study physician's judgement at dosages equipotent to simvastatin 40 mg and ezetimibe 10 mg daily, as it in such cases was regarded unethical to continue placebo treatment. However, patients were still followed to study end for intention-to-treat-analysis for study endpoints as well as safety analyses.

Study endpoints

The primary endpoint of the SEAS study was a composite of major cardiovascular events including aortic valve events (AVE) and ischemic cardiovascular events (ICE). The secondary endpoints were AVE (a composite of cardiovascular death, aortic valve replacement (AVR) and heart failure caused by progression of aortic stenosis) and ICE (a composite of cardiovascular death, (coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), nonfatal myocardial infarction, hospitalized unstable angina and nonhemorrhagic stroke) analyzed separately, as well as echocardiographic progression of AS determined by change of peak aortic jet velocity from baseline to end of study. Other echocardiographic variables of AS progression were tertiary endpoints.

The rationale for selecting a composite endpoint instead of an endpoint consisting of pure valve related events was to allow for assessment of effect of intensive lipid lowering treatment not only on the risk of valve surgery or cardiovascular death, but also endpoints reflecting the entire burden of cardiovascular disease known to be related to AS in an elderly population[52]. Still, the study was powered also to assess the secondary composite valve related endpoint, as previously described in the statistics section. However, in AS patients with known atherosclerotic disease, the indication for lipid-lowering treatment would be driven by other

clinical indications and thus never be questioned. The role of statin treatment in AS patients with other indications for statin treatment would therefore be of little interest to study, even though this had not been evaluated in a randomized clinical trial of this large size before. Moreover, it was not previously known, due to the lack of prospective, controlled data in previous studies, whether such increased cardiovascular risk was related to coincident vascular disease or related to the progression of the valvular disease itself. High-risk individuals with clinical or symptoms of atherosclerotic diseases and all patients with symptomatic or known coronary or cerebrovascular disease were excluded from participation in the SEAS study. The study population thus consisted of 'pure' AS allowing for evaluation for the effect of the study treatment especially with regard to the valve related endpoints, but also whether such treatment could have a significant effect even on ischemic endpoints in patients with mild to moderate AS without clinical atherosclerotic disease. Even so, it was expected that a large elderly population would develop incident vascular disease or diabetes during the long term course of such a study, even if the patients were without symptoms of such disease at inclusion. Combining these clinically relevant valvular and vascular endpoints into a composite primary endpoint therefore seemed well justified. Although the direct effect of lipid lowering treatment on the AS progression was the primary area of interest to assess through the study, it was anticipated that the primary composite endpoint would still be dominated by the AVR endpoint. The second important clinically relevant issue would next be to clarify whether elderly AS patients without obvious indication for lipid-lowering treatment due to concomitant atherosclerotic diseases, would also benefit from such treatment even in non-valvular cardiovascular endpoints, as the global disease burden in these patients was regarded as the ultimate important issue.

Table 3. Study objectives SEAS study

PRIMARY	SECONDARY			
Major cardiovascular events (MCE)	**1. Aortic valve events (AVE)**	**2. Ischemic cardiovascular events (ICE)**	**3. Echocardiography**	**4. Safety**
Cardiovascular death	Cardiovascular death	Cardiovascular death	Retardation of AS progression based on echocardiographic measurements	Safety of ezetimibe 10 mg and simvastatin 40 mg
Aortic valve replacement surgery	Aortic valve replacement surgery			
Heart failure due to progression of AS	Heart failure due to progression of AS			
CABG		CABG		
PCI		PCI		
Hospitalized unstable angina		Hospitalized unstable angina		
Non-fatal myocardial infarction		Non-fatal myocardial infarction		
Non-hemorrhagic stroke		Non-hemorrhagic stroke		

Statistical analysis

Null hypothesis: there is no difference between active study treatment and placebo groups with regard to risk of the primary study endpoint (for SEAS study: composite of major cardiovascular endpoint events)

Alternative hypothesis: There is a difference between the treatment groups

A. SAS study sample size calculations

When designing the first SAS study, we made an estimate that in the placebo group the primary endpoint would occur at a rate of 30-40%, based on available prospective data[29]. For the

treatment group we conservatively assumed a risk reduction of 25-35% compared to the placebo group. Thus, for the original SAS trial the following sample size calculations were performed to assume a needed study sample size of 760 patients divided into two treatment groups:

Table 4a. Power calculation SAS study

SAMPLE SIZE CALCULATION

(1n = number of patients in each study group)

2alfa(2a)	0,01
1-beta(1-b)	0,80;0,90;0,95

p1=simva
p2=placebo

		% REDUCTION				1-beta
INCIDENCE CONTROL GROUP		**25 %**	**30 %**	**33 %**	**35 %**	
p2	**0,3**	799	542	442	389	0,8
		1018	691	563	495	0,9
		1216	826	673	592	0,95
p2	**0,35**	643	437	356	314	0,8
		819	557	454	400	0,9
		979	666	543	478	0,95
p2	**0,4**	526	358	292	258	0,8
		670	456	372	328	0,9
		801	519	445	392	0,95

B. New sample size calculation for the SEAS study:

After revision of the study into the larger SEAS study the revised sample size calculations made an initial estimation of an anticipated event rate over 4 years study duration of 40% in the placebo group, assuming a mean peak aortic jet velocity of 3.6 m/s in the study population, according to available prospective data in comparable range of AS severity[29]. The SEAS study was designed as an event-based trial, meaning that the trial was planned ongoing until the pre-estimated needed number of endpoint events was observed and in addition a minimum study duration of 4 years was observed in all randomized patients, to allow sufficient time for study treatment to impact on study endpoint, considering the natural very long history of AS. Based on

Lachin and Foulkes method, the needed number of patients with observed primary endpoint events was estimated to be 464, which would give 97% power to detect 25% reduction in the treatment group (estimated event rate of 30% compared to an estimated event rate of 40% in the placebo group[160]) and a two-tailed $p< 0.05$ regarded as level of significance (Table 4b). In the calculations the following assumptions were made: uniform recruitment over 1 year and constant hazard over time, 40% event rate in the placebo group. The sample size of 1400 was thus determined accordingly.

Table 4b. Initial power calculation SEAS study

Total number of patients needed to be randomized per group	Reduction in 4 year event rate for treatment group vs placebo group	Power	Number of patients with primary endpoint event needed
678 483	25% (HR 0.698)	**97%** **90%**	464 331
1051 749	20% (HR 0.755)	**97%** **90%**	747 532

Power calculations were then made for the key secondary endpoint consisting of valve related events (AVR, heart failure due to progression of AS, cardiovascular death) based on the same method and these assumtions: total sample size=1400, uniform inclusion of patients over about 1 year, exponential distributions of time to event, median study duration 4 years (of all patients), and in addition estimated event rate of 30% in the placebo group for AVR or cardiovascular death. With a two-sided significance level of 0.05 the chosen sample size was estimated to give a 98% power to detect a 33% reduction in 4 year event rate in the treatment group, 97% power for 30% reduction, 94% power for 27.5% reduction and 88% power for 25% reduction.

However, towards the end of the inclusion period preliminary blinded calculations of baseline variables in the randomized patients showed a lower mean peak aortic jet velocity of approximately 3.2 m/s in the study population. Study endpoints were anticipated to be dominated by valve replacement surgery, and a lower degree of AS at inclusion would lead to need for a longer observation period to detect the needed number of endpoints to be able to test the study hypothesis. This was based on further assumptions from the available comparable prospective study[29],where a mean increase in peak aortic jet velocity of 0.3 m/s/year gave a projected study duration in the SEAS study (based on the actual baseline peak aortic jet velocity) of more than 4.5 years. The Steering Committee therefore decided to increase the sample size to about 1800 patients in order to ensure that the necessary number of endpoint events could be expected within the planned study duration of about 53 months.

A final revision of the study duration about 2 years prior to study end ensured that all patients should be followed in the study for at least 4 years from randomization date in addition to the estimated needed number of endpoint events. A final set of power calculations was thus provided prior to end of study based on blinded evaluations of observed clinical endpoint rates suggesting that approximately 760 patients would be observed with primary endpoint events by study end:

Table 4c. Revised power calculation SEAS study

	Power		
	HR 30%	HR 25%	HR 20%
Primary EP (MCE)	99%	98%	86%
Secondary EP			
1.AVR	99%	97%	84%
2.ICE	94%	82%	61%

SUMMARY OF THE RESULTS

Paper I

The SAS and SEAS study design including selection of inclusion- and exclusion criteria, selection of endpoints and sample size calculations, as well as the study organization are described in the Methods-section.

The SEAS study randomized 1,873 patients aged 68±10 years, 39% women, with asymptomatic mild to moderate AS with echocardiographically determined peak-jet velocity 2.5-4.0 m/s (mean baseline peak-jet velocity 3.09±0.54) and normal left ventricular function (EF 66±7%) and no other major valvular disease. In some patients actual baseline degree of AS was slightly outside the inclusion limit, due to the fact that inclusion was made at local study site based upon locally measured peak aortic jet velocity, whereas the values employed in study analyses was done at the Echocardiographic Core Laboratory, thus an expected interobserver variation. Thus the study population included n=237 (13.5%) patients with peak aortic jet velocity ≤2.49 m/s and n=100 (5.7%) with peak jet velocity ≥4.0 m/s. Likewise n=27 patients (1.6%) was included with EF<50%, also explained by interobserver variation. 76.0% had no or grade I aortic regurgitations, according to inclusion criteria. The study population was overall slightly overweight, body mass index 26.9±4.3 kg/m^2, had a mean systolic blood pressure of 144.8±20.3 mmHg, mean diastolic blood pressure of 82.0±10.3 mmHg, 50.9% reported a history of hypertension and 27.9% had a family history of coronary artery disease. 19.2% and 36.1% were current and previous smokers, respectively. Mean total cholesterol was 5.74±1.02 mmol/L, mean LDL-cholesterol 3.60±0.92 mmol/L, mean HDL-cholesterol 1.49±0.92 mmol/L and triglycerides were 1.42±0.69 mmol/L.

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Paper II

1,873 patients with mild to moderate aortic stenosis were randomized after a placebo run-in period in a double-blind fashion to receive either simvastatin 40 mg and ezetimibe 10 mg or matching placebo daily. The study patients were followed with yearly clinical visits, safety blood samples and blinded lipid levels as well as echocardiograms for a median period of 52.2 months. All predefined endpoint events were reported to and adjudicated by a blinded endpoint committee. The study was planned to continue until all patients were followed until at least 464 patients experienced at least one endpoint event and until a minimum of 4 years of follow up for all study patients. An independent data safety and monitoring board performed interim analyses as well as safety analyses at prespecified time points.

After a median follow-up time of 52.2 months, the last patient finalized follow-up March 2008. At this point 688 patients had experienced an adjudicated endpoint event. Of these, 634 were aortic valve events (AVE), the dominating endpoint being valve replacement surgery that occurred in 545 patients. 335 events were ischemic events.

There were no differences between patients in treatment and placebo groups at baseline. The baseline data have been described previously under paper I.

As expected, LDL-cholesterol was lowered effectively by 61.3% to 1.36±0.60 mmol/l in the simvastatin-ezetimibe group compared to baseline level, the lowest level achieved at 8 weeks of treatment. In the placebo group the LDL-cholesterol was lowered by 0.5% at 8 weeks. The overall treatment difference in LDL-cholesterol was 50.0% lower in the treatment group compared to the placebo group (53.8% vs 3.8% reduction in the two groups overall). The corresponding overall treatment difference in percent change from baseline was for total serum cholesterol, serum triclycerides, HDL-cholesterol and non-HDL-cholesterol -32.1%, -20.0%, +4.0% and -45.2%, respectively. Study treatment was generally well tolerated.

The primary outcome events occurred in 333 patients (35.3%) in the simvastatin-ezetimibe group and in 355 patients (38.2%) in the placebo group, HR 0.96 95% confidence

interval (CI) 0.83-1.12. There was no significant difference between the treatment groups for the composite primary endpoint (p=0.59). There were no significant differences between treatment groups for cardiovascular or total death, p=0.80 and p=0.34 respectively. The main component of both the composite primary and of the main secondary endpoint, aortic valve replacement surgery, occurred equally often in both treatment groups, n=278 (29.9%) in placebo group and n=267 (28.3%) in simvastatin/ezetimibe group respectively, p=0.97. There was a significantly lower occurrence of the composite ischemic secondary endpoint in the simvastatin/ezetimibe group (p=0.02), mainly driven by the sub-component CABG (p=0.02) which in all cases except one was performed together with valve surgery.

A post hoc, non-published analysis of the AVR+CABG cases (n=169) from the SEAS study was undertaken to understand what was the primary reason for heart surgery, whether mainly a tight valve stenosis or coronary artery disease, since CABG was the dominating endpoint in the ICE group and since the decision to operate or not was left entirely to the local heart team according to current guidelines. This included case-by-case evaluation of endpoint narratives from study sites, most often citing heart team decisions and angiographic reports, however the latter not mandatory as study procedure and therefore not always available. In addition AVR endpoint desicions from the Endpoint Committee and preAVR echocardiographic data were reviewed, the latter, available for 159 of the 169 AVR+CABG cases. Serious AS was deemed the primary reason for surgery in 116 patients (69.6%), while ischemic heart disease was deemed the primary reason in 19 patients (11.2%). Two patients had surgery due to endocarditis, whereas the main cause for surgery was unclear (i.e. in many cases both a narrow valve, but also multivessel disease) in 32 cases (19.9%). Multivessel or 2-vessel disease was found in 24 patients (14.2%) and 39 patients (23.1%), respectively. Echocardiographic data supported the post hoc judgement that the AS was severe in the majority of cases as mean peak jet velocity in the group was 4.11±0.66 m/sec (measured locally 4.34±0.63 m/sec), and average mean gradient 43.5±13.7 mmHg (measured locally 45.6±12.3 mmHg).

For the other endpoint groups within the ischemic endpoint composite there was a trend towards more events in the placebo group even for hospitalized angina and PCIs, however, the number of cases were too small to allow calculations of p values. For myocardial infarction, nonhemorrhagic stroke and cardiovascular death there was no significant difference between treatment groups, p=0.15, p=0.65 and p=0.34, respectively.

In summary, long term intensive lipid lowering therapy had no effect compared to placebo on the course of mild to moderate AS, whether on rate of major cardiovascular events, valve surgery, CV death or echocardiographic progression rate. Lipid lowering therapy did lower the risk of ischemic events, especially CABG, in patients with no overt CAD

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Paper III

In spite of the negative results from three prospective clinical trials testing the effect of intensive lipid lowering effect demonstrating no effect on morbidity or mortality in patients with AS, a smaller retrospective study[138] still demonstrated an effect in delaying the progression of very mild aortic stenosis in patients treated with statins, which led to speculation that the lipid hypothesis in AS was maybe still valid in the very early stage of valve disease. Similar findings even for AS overall were found in retrospective studies before the randomized placebo controlled studies gave convincing evidence to the contrary[117]. To evaluate further this suggested effect of lipid lowering in different groups of AS severity in a controlled prospective setting the present study was designed as a posthoc analysis from the SEAS trial. The study population (n=1,763) was evaluated in equally sized tertiles based upon the baseline peak jet velocity ≤2.8 m/sec (n=588), >2.8 to ≤3.3 m/sec (n=597) and >3.3 m/sec (n=578). No statistically significant differences were found in other characteristics between the three groups at baseline. The annualized progression of AS was similar in all groups (0.16±0.28 m/s/year vs 0.19±0.28 m/s/year vs 0.19±0.27 m/s/year, p=0.113). Cox regression analysis demonstrated that intensive lipid

lowering treatment with simvastatin 40 mg plus ezetimibe 10 mg daily for a median follow-up of 4.3 years was not associated with statistically significant reduction in valve related endpoint events (cardiovascular death, valve surgery or hospitalization with heart failure) in any tertile of AS severity, as compared to placebo. However, in the lower tertile, there was significantly fewer ischemic cardiovascular events in the simvastatin and ezetimibe group than in the placebo group, HR 0.53, 95% CI 0.33-0.84, p=0.007, but not in the middle and upper tertiles. This was still valid after correcting for baseline degree of AS, LVM and smoking status -study treatment still gave reduced risk of ICE in whole study population HR 0.79, 95%CI 0.63-1.00, p=0.005, but not for AVE, HR 0.96 95%CI 0.81-1.13, p=0.519. Higher baseline severity of AS significantly predicted higher rate of cardiovascular events in all tertiles, valve related (AVE) and ischemic events (ICE), all $p<0.05$ in tertiles, and $p<0.001$ for the overall study population.

Paper IV

Several studies have demonstrated a negative prognostic importance of left ventricular hypertrophy on cardiovascular outcome, e.g. obstructive cardiomyopathy and hypertension. For AS this has not previously been evaluated in a prospective setting. The present study was planned within the SEAS analysis plan. The analysis included 1,656 patients with mild-to-moderate AS randomized in the SEAS study and followed for a median period of 4.3 years with randomized treatment of simvastatin 40 mg and ezetimibe 10 mg daily or placebo. Baseline and annual echocardiograms during follow-up and before planned valve surgery were recorded and patients were followed at regular intervals for endpoint events. Cox regression analysis demonstrated that 1 standard deviation (SD) (=15 $g/m^{2.7}$) higher baseline left ventricular mass indexed for body surface (LVMi) predicted increase in hazard of 12% for major cardiovascular events (AVE and ICE, as previously described under Methods) while it predicted increase in hazard of 28% for ischemic events, 34% for cardiovascular mortality and 23% for combined total mortality and

hospitalization for heart failure, all $p<0.01$. In addition, the study included time-varying Cox regression analysis to account for the expected in-study increase in LVH related to normal progression of AS. The latter analysis demonstrated that an increase of 1 SD higher LVMi was independently associated with 16% higher rate of AVEs, 13% higher rate of ICEs, 25% higher rate of ischemic cardiovascular events, 63% higher cardiovascular mortality and 44% higher mortality from a combination of death from any cause combined and hospitalization for heart failure, all $p<0.01$.

DISCUSSION

Mild to moderate aortic stenosis

Aortic stenosis (AS) represents a prevalent health problem for elderly patients. The disease has typically a very long natural course, with a long asymptomatic phase when the valve stenosis is mild to moderate, lasting perhaps 10-20 years before the onset of symptoms when the AS becomes severe[25]. Evaluation and follow-up of the disease is based upon echocardiographic measurements as well as development of symptoms. The grading of valve stenosis is defined according to echocardiographic parameters (Table 5):

	Mild	**Moderate**	**Severe**
V max m/s	2.5- 2.9	3.0 – 3.9	$\geq$ 4
Mean gradient mmHg	< 20	20 - 49	$\geq$ 50
AVA cm²	> 1.5	1.0 -1.5	$\leq$ 1.0
AVA / m² BSA	> 0.9	0.6 - 0.9	$\leq$ 0.6

Table 5 Grading of aortic stenosis.

Ref ESC guidelines on valvular heart disease[30]

In the Western world AS is the most common valve disease. 2-3 % of a general ageing population above 75 years has at least moderate, often severe AS that needs surgical intervention[22, 23]. With an increasing ageing population, the number of patients that need heart surgery is rising. In the US, the number of patients who are in need of undergoing aortic valve replacement (AVR) is rapidly increasing over the last decade, and is expected to increase further in the years to come[161]. The introduction of transcatheter aortic valve implantation (TAVI) will

probably increase these numbers further when comorbid elderly patients previously too frail for open heart surgery can have less invasive surgery to improve symptoms and survival.

The increase in severity from mild or moderate AS varies considerably. Baseline peak aortic jet velocity has been demonstrated in several studies to be a robust marker of prognosis[29, 37, 162]. Presence of heavy calcification in valve leaflets, associated coronary artery disease and age above 50 years have been associated with faster progression[38], as has metabolic syndrome[163, 164] The echocardiographic progression in the SEAS study was found to be slightly below that previously reported[29, 37, 165] (table 6):

Annual change	**Literature**	**SEAS**
Δ Vmax (m/s/y)	0.3	0.15
Δ mean gradient (mmHg/y)	7	2.7
Δ AVA (cm^2/y)	-0.1	-0.03

This is probably best explained by the fact that the SEAS patients excluded patients with coronary artery disease, diabetes mellitus, reduced renal function as well as other diagnosed atherosclerotic diseases. Even though the SEAS population was an elderly population with a high number of hypertensive patients as well as current and previous smokers, relatively high cholesterol levels and being slightly overweight, this absence of overt atherosclerotic disease at inclusion might explain the slightly lower progression rate. However, the progression rate in SEAS was comparable to the two other randomized clinical trials in AS patients, supporting the validity of our data[166, 167]

From the landmark study of Ross and Braunwald from 1968 we know that the onset of symptoms marks the onset of a worsened prognosis with high risk of cardiovascular events or death[25]. The prognosis of asymptomatic mild to moderate AS has been described in a number of studies, however, only a few studies performed prospectively[29, 37]. These studies included patients with more advanced disease than the patients in SEAS, and the 5 year event-free survival was

overall about 1/3 of patients. The SEAS study is still far the largest AS study yet performed, including more patients than all prior studies combined, as well as following the patients prospectively for a longer period than previous studies. This gives excellent opportunities to study the long term prognosis of patients with asymptomatic mild to moderate AS in a controlled fashion. As is demonstrated below; the event rate in SEAS was lower than in the previous studies, probably partly related to the milder degree of the AS at baseline as well as less comorbidities, mainly less CAD. Overall the prognosis of mild to moderate AS must be regarded as good when patients are followed according to state-of-the-art care in clinics experienced with such patients. About 1/3 of the SEAS patients had valve surgery during the 4.3 years of follow-up. One might argue that the lack of important comorbidities makes the SEAS study patients less representative for the general AS population. However, over a 4-5 year follow-up of patients with atherosclerotic risk factors, the rather high number of CV events indicates a significant risk of development of overt cardiovascular disease in 'healthy' elderly AS patients and underlines the need to follow even 'healthy' AS patients closely for cardiovascular risk factors according to general guidelines. These patients have not only a calcified valve and a murmur, but must be regarded as patients with increased risk of systemic atherosclerotic disease and followed accordingly.

The event rate is, as previously demonstrated, related to baseline degree of aortic stenosis. The majority of cardiovascular events in SEAS patients were valve related, mainly valve replacement surgery. The rate of events was clearly related to the baseline degree of valve obstruction. In the whole study population, 29.1% of patients experienced AVR during the course of the study.

Overall mortality was 11.1%. Half of the patients died from cardiovascular causes, sudden cardiac death (SCD) (n=40) being the dominating the mode of cardiovascular death. The risk of sudden death and potential risk factors for this feared complication is discussed in detail elsewhere. However, the overall rate of sudden death in the asymptomatic mild to moderate AS

patients in the SEAS study was comparable to what has been found in previous studies[29, 37, 165]. SCD is rare, but even in a controlled prospective setting there is still a non-negligible risk of AS patients for SCD.

Lipid lowering therapy in aortic stenosis

The SEAS trial was the largest randomized clinical trial to investigate the effect of lipid lowering therapy in AS. With a large study sample size, effective lipid-lowering treatment with LDL-lowering overall about 50%, the study had adequate power to answer the hypothesis of the study. In patients with mild to moderate AS and no known coronary artery disease, the SEAS study clearly showed that lowering lipids in patients without other indication for lipid lowering does not induce any reduced risk of clinical, cardiovascular events, including AVR, hospitalizations with heart failure secondary to AS or cardiovascular death, or more specifically the primary endpoint was not met, nor was the key secondary endpoint of valve related endpoints. Overall mortality was not reduced, in particular not cardiovascular death. The main study findings were comparable to the two other randomized clinical trials investigating intensive lipid lowering therapy in AS patients, the Scottish Aortic Stenosis and Lipid Lowering Trial Impact on Regression (SALTIRE)[167] and the Aortic Stenosis Progression Observation. Measuring Effects of Rosuvastatin (ASTRONOMER)[166] as summarized in table 7 below:

	RAAVE	**SALTIRE**	**ASTRONOMER**	**SEAS**
N	*121*	**155**	**272**	**1,873**
Age (yrs)	*74*	**68**	**58**	**68**
Design	*open-label*	double-blind, randomised, placebo-controlled	double-blind, randomised, placebo-controlled	double-blind, randomised, placebo-controlled
Treatment	*Rosuvastatin 20 mg vs. placebo*	**Atorvastatin 80 mg** vs. placebo	**Rosuvastatin 40 mg** vs. placebo	**Ezetimibe/ Simvastatin 10/40** vs. placebo
Follow up (yrs)	*1.5*	**2.1**	**4**	**≥4**
TC / LDL-C (mg/dL)	*218 / 138*	**219 / 135**	**207 / 168**	**222 / 139**
Peak velocity (m/s)	*3.63*	**3.42**	**3.2**	**3.09**
AVA (cm²)	*1.21*	**1.03**	**1.2**	**1.28**
Clinical Endpoint Results	*Co-1°: Echo (AV gradient & AVA changes) and LDL Both Positive*	1°: Echo (AV gradient & AVA changes), 2°: Composite clinical endpoint **No difference**	1°: Echo (AV gradient & AVA changes), 2°: CV death & AVR time **No difference**	1°: Composite clinical endpoint+ 2° AVE **No difference.** **2° ICE positive** p=0.02

Table 7: Randomized clinical trials – lipid lowering in AS

The inclusion criteria for all three randomized clinical trials were comparable, most importantly since patients with significant atherosclerotic comorbidity or diabetes were excluded from all studies. None of the studies included patients with established indication for lipid-lowering therapy, to allow for placebo control. All three studies obtained effective lipid lowering in the treatment group, in SALTIRE 53% and in ASTRONOMER 54.5% lowering of LDL-cholesterol compared to baseline. The SALTIRE study included n=155 patients with a slightly more advanced AS than did the other two, and the follow-up period was significantly shorter[167]. The ASTRONOMER study had as in the Scottish study a primary echocardiographic endpoint, which showed no significant difference in the progression of AS based upon aortic valve gradient or valve area[166]. A number of prespecified subgroup analyses did not show any significant differences in any subgroups. The other randomized trials observed no differences in their clinical secondary endpoints, however, only a smaller number of events were observed compared

to the much larger SEAS study that was primarily designed to detect differences in clinical endpoints. The secondary echocardiographic endpoint in SEAS was not met, however the large 'over-powering' of the SEAS study for echocardiographic data as well as the use of a blinded and uniform reading of the echocardiographic data in an Echo Core lab make the echocardiographic data from SEAS very robust. It could be argued that there was seen a statin effect in the early published, prospective, but open label Rosuvastatin Affecting Aortic Valve Endothelium (RAAVE) study. In this trial LDL-cholesterol lowering slowed echocardiographic AS progression in n=61 patients with elevated LDL-cholesterol compared to n=60 patients with normal LDL-cholesterol that received no statin, however without any data on clinical endpoints.[139]. However, the very solid and overall uniform results from all three randomized studies show convincingly that even state-of-the-art, intensive lipid lowering does not have any beneficial effect on the course of mild to moderate AS. Thus, one must conclude that lipid lowering therapy has no place in the management of pure AS, unless the patients have other indications for lipid lowering therapy.

Again, this underlines the importance of randomized clinical trials to test a hypothesized treatment effect, despite strong data from animal studies, histopathological data or retrospective data. However, how can one explain the difference in clinical data from lipid lowering and the pre-clinical data? What are future perspectives or current medical options for treatment of AS? Here one probably needs to differentiate between prevention of incident aortic valve calcification and prevention of progression of established AS. Data as described previously are quite convincing that LDL-cholesterol, as other atherosclerotic risk factors, are associated with later incident valve calcifications. This was confirmed by Thanassoulis et al from 27 years follow-up data from the Framingham study[72]as well as similar findings from the 10 year follow-up data from the MONIKA/KORA study[71], demonstrating that long term exposure to elevated cholesterol increases the risk of later incident valve calcification. Likewise, the authors of the MESA study demonstrated that metabolic syndrome and diabetes mellitus increases the risk of

incident valve lesions, however without any influence upon the progression of AS after the lesion has been established[75, 76]. This finding has been supported by recent substudy analyses from the SEAS trial, where overweight and obesity in patients with mild to moderate AS did not influence AS progression or rate of AVE or ICE, but were associated with 46% and 67% higher mortality in overweight and obese patients, respectively.[86] Taken together, the increased risk of valve calcification with atherosclerotic risk factors present, but lack of treatment effect from lipid lowering therapy, would support a thorough general follow-up of risk factors according to current guidelines on how to reduce atherosclerotic risk, even more in patients with AS than in the general population, but that no indication exist for statin treatment for pure AS.

For ischemic cardiovascular events, the second major composite endpoint including revascularizations, myocardial infarction, stroke and cardiovascular death, there was a significantly lower rate of events in the active study group compared to the placebo group (p=0.015). However, the dominant part of this composite was the CABG endpoint, being in all but one case (n=168) performed together with AVR. Post-hoc data from the SEAS study, exploring the ischemic endpoint in relation to the expected and achieved LDL-levels in the study demonstrated that in the lower tertile of the SEAS patients, based upon peak jet velocity, the significant reduction in ischemic events was in line with the expected 21% reduction in vascular events per 1 mmol/L lowering of LDL-cholesterol, as demonstrated in metaanalyses from the Cholesterol Treatment Trialists' Collaboration (CTT)[109, 110, 168]. However, in the upper tertile of more severe AS in the SEAS study, there was no significant reduction in ischemic event, even when correcting for the CABG subgroup. The post hoc discussion regarding the CABG endpoint has been described previously. Decision to operate, both for single AVR as well as need to do combined surgery was left to the local heart team to decide in accordance with current guidelines.

Role of left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is considered a physiologic adaptation of the left ventricle to the increasing narrowing of the aortic valve. It is usually not present until there is hemodynamically significant obstruction of outflow from left ventricle. Coexistence of hypertension, well known to be prevalent in elderly population with known atherosclerotic risk factors as was demonstrated in the baseline data from the SEAS population[169], would add to the risk of developing LVH.

In some AS patients LVH might develop in excessive amounts and have negative influence upon the function of the left ventricle. Such development of LVH might be regarded as a maladaptive respons that influences the left heart chamber in a negative way and thus affects the outcome of AS patients. Patients with LVH have been demonstrated in a large number of studies of different disease entities, to have a worse cardiovascular prognosis than patients without LVH, as previously described. The landmark Framingham study linked hypertrophy in a general population with increased risk of heart failure[122], and a number of ensuing studies have demonstrated LVH a marker of worsened prognosis in a number of cardiac conditions, among them hypertrophic obstructive cardiomyopathy[124] and hypertension[123].

LVH in AS has been demonstrated to increase the risk of midwall fibrosis, that has been linked to worsened outcome, even after AVR[170]. Substudy data from the SEAS population have already been discussed earlier. Recent studies, including data from the SEAS population have demonstrated a worsened overall prognosis for AS patients with LVH with regard to cardiovascular events [126, 127, 171]. Electrocardiographic (ECG) signs of LVH analysed in SEAS was demonstrated to be associated with increased risk of adverse cardiovascular events in general; and when compared to AS patients with normal ECGs patients with ECG LVH had 5.8-fold higher risk of heart failure (95% CI 2.0-16.8, p=0.001), 2-fold higher risk of AVR (95% CI, 1.3-3.1; p=0.001), and 2.5-fold higher risk of a combined end point of myocardial infarction, heart failure,

or cardiovascular death (95% CI, 1.3-4.9; p=0.008) [172, 173]. Also ECG LV strain was associated with 3.1-fold higher risk of myocardial infarction (95% CI, 1.4-6.8; p=0.004)[172]. This falls well into line with the findings from the Scottish researchers, demonstrating that LVH with signs of electrocardiographic strain also predicted LV midwall fibrosis confirmed by cardiovascular magnetic resonanse (CMR) and worse outcome in patients from the SALTIRE cohort compared to a second prospective AS cohort undergoingCMR[174]. The concept of inappropriate LV hypertrophy, denoting the recent understanding of an excessive LV response to global LV load in AS, associated with increased risk of adverse events, may be related to the risk of SCD in contemporary AS patients[134], although this remains to be evaluated further.

ACE inhibitors have been suggested to slow the progression of AS, however, a prospective non-randomized study of 211 patients could not confirm such an effect[118]. However, quite recently, a small, prospective, randomized controlled trial of ramipril in 100 patients with moderate or severe AS (RIAS) trial demonstrated by magnetic resonance imaging (MRI) a significant, however modest, reduction in LVM during the 1 year follow-up in the ramipril group compared to placebo[175]. The study hypothesizes that ramipril might benefit the course of AS that is related to the adverse LV remodeling. However, previous published post-hoc data from the SEAS study[176] did not find any reduction in cardiovascular, all-cause mortality or sudden death in 769 patients that were treated with renin-angiotensin system (RAS) inhibitors during the study follow-up, even though a significantly lower progression of LVM (p=0.040) was demonstrated in these patients compared to AS patients without RAS inhibitors.

The adverse CV outcome of patients with mild to moderate AS with LVH does not imply that patients with LVH should be receiving valvular intervention at an earlier stage. However, our data, as well as data from other studies, suggest that AS patients with LVH should be followed closely to detect and optimalize risk factors such as hypertension or coronary artery disease, and to detect possible onset of symptoms or comorbitities to prevent cardiovascular events in line with general cardiovascular guidelines.

Sudden cardiac death

Sudden cardiac death (SCD) is a feared complication in AS. The risk of SCD rises considerably with debut of symptoms of AS, and so new, valve related symptoms should prompt the need for valve surgery without delay to reduce risk of SCD. However, even in asymptomatic patients with AS, there is a small risk of SCD. Forty patients experienced SCD in the course of 4-7 years of the SEAS study, the to date largest prospective clinical study on asymptomtic mild to moderate AS with pre-defined evaluation of SCD as one of the endpoint events. These were asymptomatic patients with initially mild to moderate pure AS who had guideline oriented state-of-the-art follow up with clinical and echocardiographic evaluation. The SEAS study confirms that SCD in mild to moderate AS is rare with an annualized rate of 0.37%. Our data show a markedly lower risk of SCD than in the study by Pelikka et al who described 11 SCDs (4.1%) during 5 years follow-up of 622 patients without symptomatic coronary artery disease, with an annual risk of 1%/year compared to 0.37%/year in our study, probably reflecting the more severe AS at baseline in that study (a peak aortic-jet velocity ≥4 m/s)[165]. Otto et al[29] reported no SCD in 123 patients with moderate AS over 32 months, while Rosenhek et al detected one SCD in a true asymptomatic patient over 27 months in 126 patients with more severe AS (mean baseline peak aortic-jet velocity 5.0 m/s compared to 3.6 m/s in Otto's study)[38]. Thus, reflecting the different degree of AS in available studies, our data confirm the previously assumed low incidence if SCD in AS. However, in the clinical real world, the main challenge in detecting risk of SCD remain the debut of valve related symptoms, a most important sign of increased risk of SCD. This is often underreported from the patients themselves.

Data from the Framingham Study showed increased risk of ventricular arrhythmias associated with LVH determined by ECG, but with higher prevalence and better sensitivity for echocardiographic parameters[122]. Haider et al demonstrated in 3,661 otherwise healthy subjects ≥ 40 years of age enrolled in the Framingham Study that echocardiographically determined LVH was associated with increased risk of SCD (HR 2.16, p=0.008), and that increased LV mass was

associated with a HR 1.45 per 50 g increment of LV mass (p=0.008)[177]. Hypertrophic obstructive cardiomyopathy (HOCM) represents the extreme end of scale of LVH and is related to a high risk of SCD reported about 6%/year[178], although more recent community based data agree on a lower annual incidence of ≤1%[179, 180]. SCD in HOCM is partly thought to be related to a high prevalence of inducible ventricular arrhythmias 40-82%[181, 182]. Spirito et al further demonstrated in n=490 patients with HOCM that the degree of LV wall thickness was closely correlated to the risk of SCD in hypertrophic cardiomyopathy and a strong, independent predictor of prognosis[183], unrelated to heart failure. However, whether the same relationship can be applied to LVH regardless of cause, and to AS related LVH in particular, is not known. This needs to be evaluated further to understand better how this can be of clinical use in follow-up of such patients.

In summary, the adverse prognostic importance of increased LV mass and LVH even in mild to moderate AS strongly suggests the need to turn our focus from solely regarding the mechanical function of the narrowing valve itself as the only medical issue in these patients. Instead, we need to understand AS as a valvular disease with systemic importance, both in terms of general atherosclerotic risk factors that might need follow-up, as well as increased risk of adverse systemic outcome that should be detected.

Limitations

The most important limitiation of the SEAS study was the exclusion of high risk individuals with AS, including particularly patients with coronary artery disease, cerebrovascular disease or other indication for lipid-lowering treatment. The results from analysis in the SEAS database thus cannot be extended to all AS patients. This is further reflected in the challenges when recruiting for the study in the era of ongoing statin studies on various atherosclerotic populations in the years following the 4S-trial. Pilot studies prior to the start of the study demonstrated that the application of the inclusion- and exclusion criteria on available AS patients in a large city hospital

in Norway resulted in only about 10% of screened patients being included into the trial. It may be criticized that the exclusion of high risk patients with regard to established atherosclerotic disease may have resulted in a selected population not entirely representative for elderly AS patients in general. However, baseline data still showed that the population included a high percentage of hypertensive patients, current or previous smokers, as well as high mean levels of cholesterol. In contrast, the strict design of our study included a large number of patients, prolonged follow-up with state-of-the-art care, as well as statistical power to detect any differences both for cardiovascular and valve related endpoints. In addition standardized echocardiographical examination and core lab reading minimizes bias due to interindividual difference between many different echocardiographers. The latter would seem of great importance when analyzing and interpreting data on both valve and LV parameters.

Future perspectives

All three randomized clinical trials investigating lipid lowering therapy in AS have shown convincing and uniform clinical results that contradict the lipid hypothesis in AS generated from non-randomized trials. Even though one might argue that lipids might still play some role in initiating the very early stage, any lipid lowering therapy has no role in AS in the clinically detectable range of the disease. However, degenerative AS is a multifactorial disease associated with a high atherosclerotic burden of coronary artery disease, cerebrovascular disease and peripheral artery disease. Medical management should include careful diagnosis, risk assessment and treatment of associated diseases and risk factors. Lipid lowering therapy in patients with mild to moderat AS has no effect on the course of AS, yet a favourable affect on the risk of ischemic cardiovascular events can be expected, if otherwise indicated.

Clinical follow-up of AS patients will still need to be based on clinical risk factor assessment and treatment according to guidelines. Special attention should be given to patients

with increased left ventricular mass, which must be regarded not only as secondary to development of AS, but as a sign of maladaptive myocardial response to the valve disease that signals a worsened prognosis and thus need for closer follow-up.

CONCLUSIONS

1) AS is a progressive disease with about 1/3 of patients with mild to moderate AS requiring AVR during a 5-year follow-up
2) Intensive, long-term lipid-lowering treatment does not change the course of AS. It does not reduce echocardiographic progression rate or the rate of cardiovascular events or need for valve surgery as evaluated in a large double-blind randomized clinical trial.
3) Long term lipid lowering therapy reduces the development of coronary artery disease in AS patients, thereby reducing the risk of myocardial infarction and need for concomitant bypass surgery at the time of valve surgery. Thus, lipid-lowering treatment has no place in pure AS without other indication for such therapy.
4) Comorbidities increase the risk of more rapid progression, influencing outcome. Close follow-up of AS patients is required to identify those who need interventional treatment. Atherosclerotic risk factors do predict the risk of ischemic events in patients with AS, but not the risk of valve related events or valve surgery and not the risk of cardiovascular death. In addition, the rate of progression of AS cannot be predicted from such risk factors, although the initiation of valve sclerosis seems to be related to such factors, supporting the hypothesis that the initiation and progression of AS is regulated by different mechanisms. However, our data show that even a low-risk population of mild to moderate AS without concomitant atherosclerotic disease with slower mean progression than in previous studies, has a 30% risk of cardiovascular events over 4 years. Optimal management of comorbidities (hypertension, diabetes mellitus, overweight, CAD) according to guidelines is necessary to further improve overall outcome.
5) CV and sudden death rates are low in pure AS of mild to moderate degree. The risk of SCD in true asymptomatic AS is low, 0.37% per year or less.

6) Presence of increased LVM in mild to moderate AS is an indicator of worsened cardiovascular outcome and mortality.

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II

ORIGINAL ARTICLE

Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis

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ABSTRACT

BACKGROUND

Hyperlipidemia has been suggested as a risk factor for stenosis of the aortic valve, but lipid-lowering studies have had conflicting results.

METHODS

We conducted a randomized, double-blind trial involving 1873 patients with mild-to-moderate, asymptomatic aortic stenosis. The patients received either 40 mg of simvastatin plus 10 mg of ezetimibe or placebo daily. The primary outcome was a composite of major cardiovascular events, including death from cardiovascular causes, aortic-valve replacement, nonfatal myocardial infarction, hospitalization for unstable angina pectoris, heart failure, coronary-artery bypass grafting, percutaneous coronary intervention, and nonhemorrhagic stroke. Secondary outcomes were events related to aortic-valve stenosis and ischemic cardiovascular events.

RESULTS

During a median follow-up of 52.2 months, the primary outcome occurred in 333 patients (35.3%) in the simvastatin–ezetimibe group and in 355 patients (38.2%) in the placebo group (hazard ratio in the simvastatin–ezetimibe group, 0.96; 95% confidence interval [CI], 0.83 to 1.12; P=0.59). Aortic-valve replacement was performed in 267 patients (28.3%) in the simvastatin–ezetimibe group and in 278 patients (29.9%) in the placebo group (hazard ratio, 1.00; 95% CI, 0.84 to 1.18; P=0.97). Fewer patients had ischemic cardiovascular events in the simvastatin–ezetimibe group (148 patients) than in the placebo group (187 patients) (hazard ratio, 0.78; 95% CI, 0.63 to 0.97; P=0.02), mainly because of the smaller number of patients who underwent coronary-artery bypass grafting. Cancer occurred more frequently in the simvastatin–ezetimibe group (105 vs. 70, P=0.01).

CONCLUSIONS

Simvastatin and ezetimibe did not reduce the composite outcome of combined aortic-valve events and ischemic events in patients with aortic stenosis. Such therapy reduced the incidence of ischemic cardiovascular events but not events related to aortic-valve stenosis. (ClinicalTrials.gov number, NCT00092677.)

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Aortic-valve stenosis is common in elderly persons, with a prevalence of 3 to 5% in the population over 75 years of age.[1,2] The condition has been shown to be an inflammatory process associated with cardiovascular risk factors, with histopathological changes in the valve leaflets that are similar to those in other atherosclerotic diseases.[2-19] Changes in the aortic valve are associated with an increased risk of death from cardiovascular causes and myocardial infarction, even in the absence of hemodynamic obstruction and signs of coronary disease.[20-22] The standard treatment is surgical replacement when the valve becomes severely stenotic.[23,24]

Epidemiologic[2] and genetic[25,26] studies have identified risk factors for the development of aortic-valve stenosis, and experimental work has elucidated the cellular mechanisms involved in disease progression, many of which resemble atherosclerosis.[27-30] One interpretation of these findings is that lipid-lowering treatment might prevent progression of aortic-valve stenosis and thus reduce the need for aortic-valve replacement.

The effect of statin treatment on aortic-valve stenosis has been assessed in several retrospective or small case–control studies.[27,31-33] Most studies have suggested a beneficial effect of statins, whereas one prospective, randomized study did not find any effect of lipid-lowering therapy on the progression of aortic-valve stenosis.[34]

The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial was designed to study the effects of long-term, intensive cholesterol lowering with daily use of simvastatin and ezetimibe on clinical and echocardiographic outcomes in patients with asymptomatic, mild-to-moderate aortic-valve stenosis and no other indication for lipid-lowering treatment.

METHODS

PATIENT POPULATION

The study design and baseline characteristics of the patients have been reported previously.[35] Men and women between the ages of 45 and 85 years who had asymptomatic, mild-to-moderate aortic-valve stenosis, as assessed on echocardiography, with a peak aortic-jet velocity of 2.5 to 4 m per second, were eligible for the study. Patients were excluded if they had received a diagnosis or had symptoms of coronary artery disease, peripheral arterial disease, cerebrovascular disease, or diabetes mellitus or if they had any other condition requiring lipid-lowering therapy. The study was approved by all relevant institutional ethics committees or by ethics committees in each country, and all patients provided written informed consent.

STUDY PROTOCOL

The study was initiated by the investigators and was designed by the steering committee on the basis of a protocol developed for the Simvastatin in Aortic Stenosis (SAS) study,[35] which evaluated the effect of lipid-lowering therapy with simvastatin (at a dose of 40 to 80 mg) as compared with placebo on clinical and echocardiographic outcomes in patients with aortic stenosis. The SAS study was sponsored by Merck but was otherwise managed by the SAS study steering committee.

From March 2001 through December 2002, a total of 196 patients underwent randomization. To improve the lipid-lowering effect while decreasing the risk of myopathy, the steering committee decided to add ezetimibe (at a dose of 10 mg daily) to 40 mg of simvastatin in the larger SEAS trial, as suggested by the sponsor. The responsibility for the logistics of the SEAS trial was transferred to the sponsor, but the scientific responsibility remained with the independent steering committee, which included two nonvoting members of the sponsor.[35] The patients who were assigned to receive simvastatin in the SAS study remained in the active-treatment group in the SEAS trial, in which ezetimibe was added to simvastatin, and the patients in the SAS placebo group remained in the SEAS placebo group. During this process, neither the patients nor the investigators were aware of study-group assignments. After a 4-week run-in period in which all patients were given single-blind placebo tablets and were instructed to follow a lipid-lowering diet according to the recommendations of the National Cholesterol Education Program,[36] eligible patients underwent randomization in a 1:1 fashion in blocks of two to receive either simvastatin–ezetimibe or placebo (Fig. 1).

Open-label lipid-lowering therapy, which included up to 40 mg of simvastatin or an equipotent dose of another lipid-lowering drug, could be administered in addition to the study drug at the discretion of each treating physician, although patients and investigators remained unaware of study-group assignments. The numbers of patients receiving open-label therapy are shown in Figure 1.

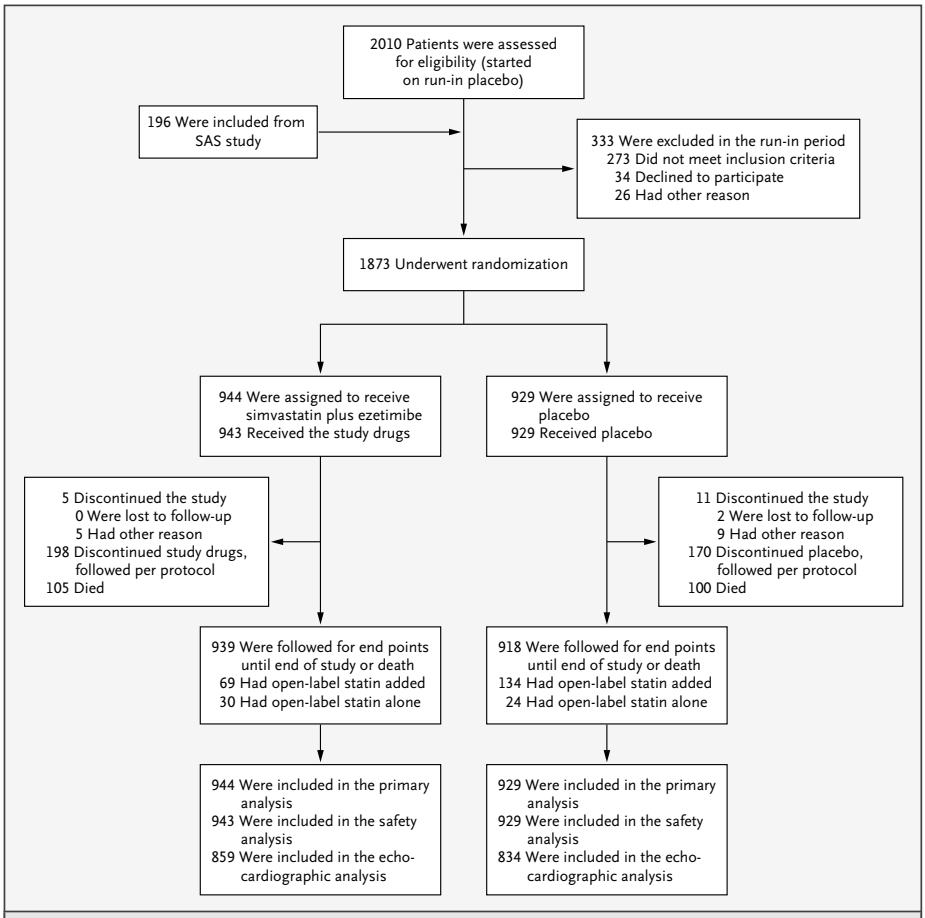

Figure 1. Enrollment and Outcomes.
SAS denotes the Simvastatin in Aortic Stenosis Study.

The study was completed according to the protocol when all patients had been followed for a minimum of 4 years after randomization, at which point the primary outcome had occurred in at least 464 patients.[35]

The SEAS steering committee designed the study and vouches for the accuracy and completeness of the data and the analysis. The sponsor gathered the data; the Echocardiography Core Laboratory read the locally recorded echocardiograms. The statistical analysis was performed by Merck, according to a predefined protocol. In addition, parallel statistical analysis with the use of SPSS software (version 15.0) was performed on raw data by an independent statistician, a process that generated identical results. The first draft of the manuscript was written by the lead academic author.

EFFICACY OUTCOMES

The primary outcome of the study was major cardiovascular events, a composite consisting of death from cardiovascular causes, aortic-valve replacement, congestive heart failure as a result of progression of aortic-valve stenosis, nonfatal myocardial infarction, hospitalization for unstable angina, coronary-artery bypass grafting (CABG), percutaneous coronary intervention (PCI), or nonhemor-

rhagic stroke. The primary composite outcome included aortic-valve–related clinical events and ischemic events to account for possible cardiovascular symptoms and events occurring in patients with aortic-valve stenosis.[21]

Key secondary outcomes were aortic-valve events (which were defined as aortic-valve replacement surgery, congestive heart failure due to aortic stenosis, or death from cardiovascular causes) and ischemic events (which were defined as death from cardiovascular causes, nonfatal myocardial infarction, hospitalization for unstable angina, CABG, PCI, or nonhemorrhagic stroke). Other secondary objectives were progression of aortic stenosis, as seen on echocardiography, and the safety of the study drugs.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Placebo (N=929)	Simvastatin–Ezetimibe (N=944)	P Value†
Age — yr	67.4±9.7	67.7±9.4	0.46
Female sex — no. (%)	360 (38.8)	363 (38.5)	0.92
White race — no. (%)‡	928 (99.9)	940 (99.6)	NA
Blood pressure — mm Hg			
Systolic	144.0±20.0	145.6±20.4	0.08
Diastolic	82.0±10.0	82.0±10.6	0.98
Hypertension — no. (%)	476 (51.2)	489 (51.8)	0.82
Smoking status — no. (%)			0.59
Current	171 (18.4)	189 (20.0)	
Former	344 (37.0)	333 (35.3)	
Never	414 (44.6)	422 (44.7)	
Body-mass index	26.8±4.3	26.9±4.3	0.58
Atrial fibrillation — no. (%)§	90 (9.7)	87 (9.2)	0.75
Atrioventricular block — no. (%)	23 (2.5)	21 (2.2)	0.76
Benign prostatic hyperplasia — no. of men (%)	63 (11.1)	74 (12.7)	0.47
Neoplasm (benign, malignant, or unspecified) — no. (%)	103 (11.1)	79 (8.4)	0.05
Drug therapy — no. (%)			
Angiotensin-converting–enzyme inhibitor	149 (16.0)	139 (14.7)	0.44
Angiotensin-receptor blocker	98 (10.5)	95 (10.1)	0.76
Calcium antagonist	160 (17.2)	157 (16.6)	0.76
Beta-blocker	268 (28.8)	242 (25.6)	0.12
Aspirin or other platelet inhibitor	260 (28.0)	236 (25.0)	0.16
Anticoagulant agent	49 (5.3)	58 (6.1)	0.43
Diuretic (including spironolactone)	229 (24.7)	209 (22.1)	0.21
Digitalis glycoside	22 (2.4)	28 (3.0)	0.47
Laboratory values			
Glucose — mg/dl	96.2±15.5	96.3±14.7	0.95
Creatinine — mg/dl	1.06±0.17	1.06±0.18	0.82
Estimated glomerular filtration rate — ml/min per 1.73 m^2¶	68.2±12.0	68.5±12.6	0.54
High-sensitivity C-reactive protein — mg/liter			0.76
Median	2.20	2.10	
Interquartile range	0.90–4.90	0.90–4.10	

Table 1. **(Continued.)**

Characteristic	Placebo (N=929)	Simvastatin–Ezetimibe (N=944)	P Value†
Lipids			
Cholesterol			
Total — mg/dl	221±38	223±40	0.41
LDL — mg/dl	139±35	140±36	0.42
HDL — mg/dl	58±17	58±17	0.87
Ratio of total cholesterol to HDL cholesterol	4.13±1.39	4.12±1.22	0.81
Non-HDL cholesterol — mg/dl	164±38	165±39	0.46
Triglycerides — mg/dl	126±60	126±63	0.93
Apolipoprotein B — mg/dl	130±28	132±28	0.37
Echocardiographic measures			
Peak aortic-jet velocity — m/sec	3.10±0.54	3.09±0.55	0.67
Transaortic pressure gradient — mm Hg			
Peak	39.6±13.8	39.3±13.9	0.70
Mean	23.0±8.7	22.7±8.8	0.42
Aortic valve			
Area — cm^2	1.27±0.46	1.29±0.48	0.29
Area index — cm^2/m^2	0.67±0.23	0.68±0.24	0.35
Bicuspid valve — no. (%)	47 (6.3)	38 (5.0)	0.32
Left ventricular mass — g	194.5±69.4	194.1±66.8	0.92
Left ventricular ejection fraction — %	66±7	67±6	0.56

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for creatinine to micromoles per liter, multiply by 88.4. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and NA not applicable.

† P values for baseline comparisons were not included in the statistical analysis plan.

‡ Race was determined by the investigators.

§ Atrial fibrillation included past events and those that were intermittent, constant, or present at the baseline visit, as well as atrial flutter.

¶ The glomerular filtration rate was calculated with the formula used in the Modification of Diet in Renal Disease Study, which accounts for age, sex, race, and calibration of the serum creatinine level.

All outcomes were classified by an independent end-point classification committee whose members were unaware of study-group assignments. The data and safety monitoring board performed four preplanned interim analyses of efficacy and safety,[35] as well as two extra analyses of safety.

Echocardiography was performed at baseline and then annually and before valve surgery, according to a standardized echocardiographic protocol.[37] All images were recorded on Video Home System videotape or digitally in Digital Imaging and Communications in Medicine format on compact disk or magneto-optical disk and were forwarded to the SEAS Echocardiography Core Laboratory at Haukeland University Hospital in Bergen, Norway. All readings were performed according to the American Society of Echocardiography guidelines[38] with the use of an off-line digital computerized review system on workstations with Image Arena software (TomTec Imaging Systems). The readers were unaware of the sequence and site in order to minimize bias.

STATISTICAL ANALYSIS

The study outcomes were analyzed according to the intention-to-treat principle. The study had a power of 90% to detect a reduction of 22% in the relative risk of the primary outcome. For all time-

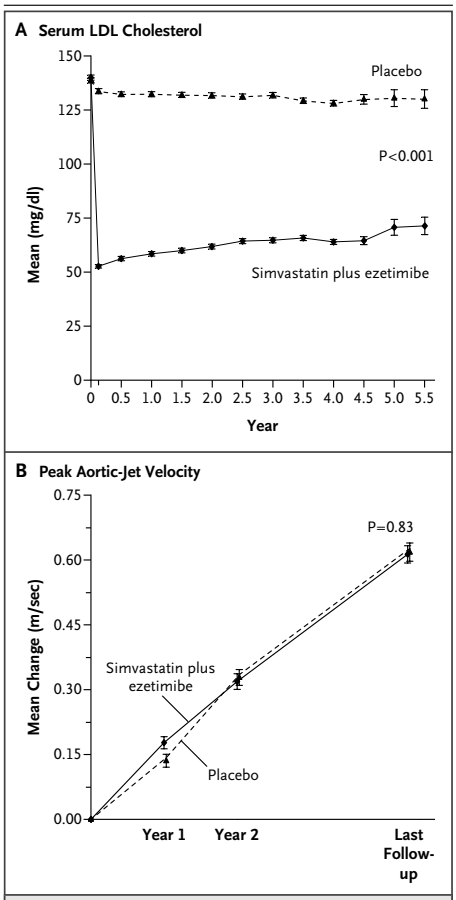

Figure 2. Serum Low-Density Lipoprotein (LDL) Cholesterol Levels (Panel A) and the Change from Baseline in Peak Aortic-Jet Velocity (Panel B).

The I bars represent standard errors. In Panel A, the first data points correspond to results at the 8-week visit.

to-event outcomes, survival analytic methods were used, with analyses based on a Cox proportional-hazards model.

Analyses were performed with the use of SAS software, version 8.2. For aortic-stenosis progression, the analysis included data from all patients with at least one baseline and one follow-up measurement. For analyses of adverse events, confidence intervals for differences in proportions of patients were computed with the method of Miettinen and Nurminen and with Fisher's exact test, when appropriate. Tests were generally performed at a two-sided significance level of 0.05, except that for the primary outcome, which was performed at a significance level of 0.0490 to account for interim analyses.

Data on adverse events were collected from all patients who underwent follow-up and analysis, with the exception of nonfatal events that did not require hospitalization and that occurred at least 15 days after the discontinuation of study drug or placebo, according to the protocol.

RESULTS

PATIENTS

A total of 1873 patients underwent randomization at 173 study sites in seven European countries.[35] Of these patients, 944 were assigned to receive 40 mg of simvastatin and 10 mg of ezetimibe daily, and 929 were assigned to receive placebo. Baseline demographic, laboratory, and echocardiographic data for the two study groups are shown in Table 1. The median follow-up period was 52.2 months.

LIPIDS

The mean serum level of low-density lipoprotein (LDL) cholesterol remained unchanged in the placebo group and decreased by 61.3%, to a mean (±SD) level of 53±23 mg per deciliter (1.36±0.60 mmol per liter) at 8 weeks, in the simvastatin–ezetimibe group. During the entire follow-up period, the mean percent reduction in LDL cholesterol was 53.8% in the simvastatin–ezetimibe group and 3.8% in the placebo group (Fig. 2A).

OUTCOME MEASURES

The primary composite outcome occurred in 333 patients (35.3%) in the simvastatin–ezetimibe group and in 355 patients (38.2%) in the placebo group (hazard ratio in the simvastatin–ezetimibe group, 0.96; 95% confidence interval [CI], 0.83 to 1.12; P=0.59) (Table 2 and Fig. 3A).

There was no significant difference between the two study groups in the secondary outcome of aortic-valve–related events, including aortic-valve replacement, death from cardiovascular causes, and hospitalization for heart failure as a consequence of progression of aortic stenosis (hazard ratio, 0.97; 95% CI, 0.83 to 1.14; P=0.73) (Fig. 3B). The principal component of this secondary composite outcome was aortic-valve replacement, which occurred in 267 patients (28.3%) in the simva-

Table 2. Prespecified Primary and Secondary Composite Outcomes and Death.*

Outcome	Placebo (N=929)	Simvastatin plus Ezetimibe (N=944)	Hazard Ratio (95% CI)†	P Value
	number (percent)			
Primary outcome				
Patients with any event‡	355 (38.2)	333 (35.3)	0.96 (0.83–1.12)	0.59
Death from cardiovascular causes	56 (6.0)	47 (5.0)	0.83 (0.56–1.22)	0.34
Aortic-valve replacement surgery	278 (29.9)	267 (28.3)	1.00 (0.84–1.18)	0.97
Congestive heart failure as a result of progression of aortic stenosis	23 (2.5)	25 (2.6)	1.09 (0.62–1.92)	0.77
Nonfatal myocardial infarction	26 (2.8)	17 (1.8)	0.64 (0.35–1.17)	0.15
Coronary-artery bypass grafting	100 (10.8)	69 (7.3)	0.68 (0.50–0.93)	0.02
Percutaneous coronary intervention	17 (1.8)	8 (0.8)	0.46 (0.20–1.06)	NA
Hospitalization for unstable angina	8 (0.9)	5 (0.5)	0.61 (0.20–1.86)	NA
Nonhemorrhagic stroke	29 (3.1)	33 (3.5)	1.12 (0.68–1.85)	0.65
Secondary outcomes				
Aortic-valve events	326 (35.1)	308 (32.6)	0.97 (0.83–1.14)	0.73
Aortic-valve replacement surgery	278 (29.9)	267 (28.3)	1.00 (0.84–1.18)	0.97
Congestive heart failure as a result of progression of aortic stenosis	23 (2.5)	25 (2.6)	1.09 (0.62–1.92)	0.77
Death from cardiovascular causes§	56 (6.0)	47 (5.0)	0.83 (0.56–1.22)	0.34
Ischemic events	187 (20.1)	148 (15.7)	0.78 (0.63– 0.97)	0.02
Nonfatal myocardial infarction	26 (2.8)	17 (1.8)	0.64 (0.35–1.17)	0.15
Coronary-artery bypass grafting	100 (10.8)	69 (7.3)	0.68 (0.50– 0.93)	0.02
Percutaneous coronary intervention	17 (1.8)	8 (0.8)	0.46 (0.20–1.06)	NA
Hospitalization for unstable angina	8 (0.9)	5 (0.5)	0.61 (0.20–1.86)	NA
Nonhemorrhagic stroke	29 (3.1)	33 (3.5)	1.12 (0.68–1.85)	0.65
Death from cardiovascular causes§	56 (6.0)	47 (5.0)	0.83 (0.56–1.22)	0.34
Death				
From any cause	100 (10.8)	105 (11.1)	1.04 (0.79–1.36)	0.80
From cardiovascular causes	56 (6.0)	47 (5.0)	0.83 (0.56–1.22)	0.34
Myocardial infarction	10 (1.1)	5 (0.5)	0.49 (0.17–1.42)	
Stroke	6 (0.6)	5 (0.5)	0.82 (0.25–2.70)	
Sudden death	20 (2.2)	20 (2.1)	0.99 (0.53–1.83)	
Related to cardiac surgery (perioperative)	7 (0.8)	7 (0.7)	0.99 (0.35–2.83)	
Heart failure	5 (0.5)	6 (0.6)	1.21 (0.37–3.95)	
Other	8 (0.9)	4 (0.4)	0.49 (0.15–1.63)	
From noncardiovascular causes	44 (4.7)	56 (5.9)	1.26 (0.85–1.86)	0.26
Cancer¶	23 (2.5)	39 (4.1)	1.67 (1.00–2.79)	0.05
Infection	14 (1.5)	7 (0.7)	0.50 (0.20–1.23)	
Violence or accident	1 (0.1)	3 (0.3)	2.95 (0.31–28.4)	
Other	6 (0.6)	7 (0.7)	1.15 (0.39–3.42)	
Could not be classified	0	2 (0.2)		

* NA denotes not applicable because of the small number of events.
† The hazard ratio is for the simvastatin–ezetimibe group versus the placebo group.
‡ Patients could have more than one event.
§ All deaths from cardiovascular causes were included in both secondary outcomes.
¶ Numbers include recurrent cancers in three patients in the placebo group and one patient in the simvastatin–ezetimibe group. One patient in the simvastatin–ezetimibe group died from cancer that was diagnosed in the SAS study before randomization in the SEAS study.

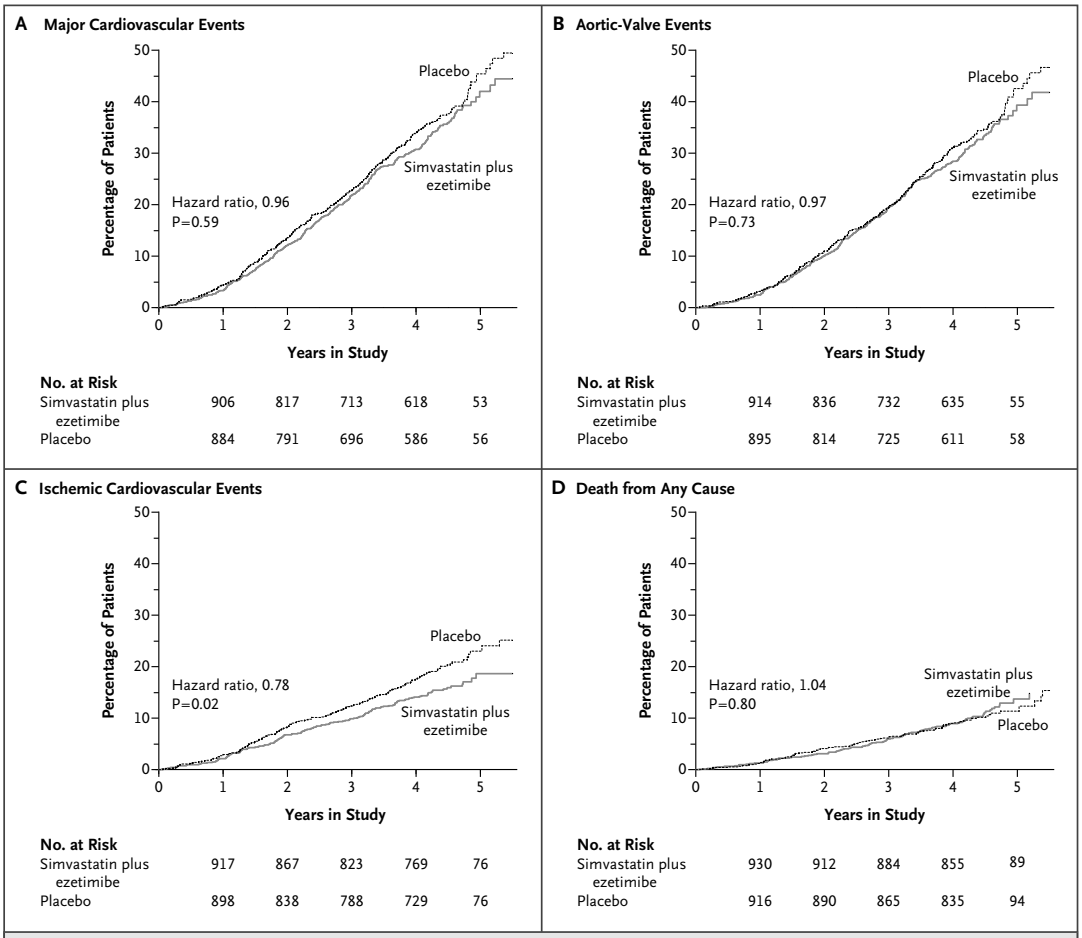

Figure 3. Kaplan–Meier Curves for Primary and Secondary Outcomes and Death.

The primary outcome was a composite of major cardiovascular events, including death from cardiovascular causes, aortic-valve replacement, nonfatal myocardial infarction, hospitalization for unstable angina pectoris, heart failure, coronary-artery bypass grafting, percutaneous coronary intervention, and nonhemorrhagic stroke (Panel A). Secondary outcomes were events related to aortic-valve stenosis (Panel B) and ischemic cardiovascular events (Panel C). There was no difference between the study groups in overall mortality (Panel D).

statin–ezetimibe group and in 278 patients (29.9%) in the placebo group (hazard ratio, 1.00; 95% CI, 0.84 to 1.18; P=0.97).

There were fewer patients with the secondary composite outcome of ischemic cardiovascular events in the simvastatin–ezetimibe group (148 patients, or 15.7%) than in the placebo group (187 patients, or 20.1%) (hazard ratio, 0.78; 95% CI, 0.63 to 0.97; P=0.02) (Table 2 and Fig. 3C). The treatment effect was dominated by a significant reduction in the need for CABG, with 69 patients (7.3%) in the simvastatin–ezetimibe group, as compared with 100 patients (10.8%) in the placebo group, undergoing the procedure (hazard ratio, 0.68; 95% CI, 0.50 to 0.93; P=0.02). All but one of the CABG procedures were performed together with aortic-valve replacement.

Effect on Progression

In the placebo group, the mean (±SD) peak aortic-jet velocity was 3.71±0.76 m per second at the end of the study, an increase of 0.62±0.61 m per second. This change was similar to that in the simvastatin–ezetimibe group, in which the velocity

was 3.69±0.78 m per second at the end of the study, an increase of 0.61±0.59 m per second (95% CI, −0.06 to 0.05; P=0.83) (Fig. 2B). This was the predefined key echocardiographic measure for the evaluation of progression of aortic stenosis. In the placebo group, the mean pressure gradient was 22.5±8.5 mm Hg at baseline and increased to 34.4±14.9 mm Hg at the end of the study, as compared with a value of 22.2±8.5 mm Hg at baseline with an increase to 34.0±15.1 mm Hg in the simvastatin–ezetimibe group. Neither the difference between the two groups at either time point nor the difference in the change from baseline in the aortic-valve area was significant. Annualized changes in the mean (±SE) peak aortic-jet velocity were 0.15±0.01 m per second per year in the simvastatin–ezetimibe group and 0.16±0.01 m per second per year in the placebo group. The mean transaortic pressure gradient increased by 2.7±0.1 mm Hg per year in the simvastatin–ezetimibe group and by 2.8±0.1 mm Hg per year in the placebo group. There was an annualized reduction in the aortic-valve area of 0.03±0.01 cm^2 per year in each of the two groups.

MORTALITY

There was no significant difference between the study groups in overall mortality (Table 2 and Fig. 3D). The composite outcome of death from cardiovascular causes and the components of this composite outcome also did not differ significantly between the two groups.

Deaths from noncardiovascular causes occurred in 56 patients (5.9%) in the simvastatin–ezetimibe group and in 44 patients (4.7%) in the placebo group (hazard ratio in the simvastatin–ezetimibe group, 1.26; 95% CI, 0.85 to 1.86; P=0.26). The numbers of fatal cancers were 39 (4.1%) in the simvastatin–ezetimibe group and 23 (2.5%) in the placebo group (hazard ratio, 1.67; 95% CI, 1.00 to 2.79; P=0.05 according to the prespecified data-analysis plan; P=0.06 with Yates' continuity correction) (Table 2). Of these patients, one in the simvastatin–ezetimibe group and three in the placebo group died from recurrent cancers, plus one patient in the simvastatin–ezetimibe group died from cancer that was diagnosed in the SAS trial, before entry into the SEAS trial.

ADVERSE EVENTS

There was a significant increase in the number of patients with elevated liver enzyme levels in the simvastatin–ezetimibe group, as compared with the placebo group, during the study period (Table 3). There were no differences in clinical, organ-related adverse events, except for significantly higher incident cancers in the simvastatin–ezetimibe group (Table 3).

CANCER

In the simvastatin–ezetimibe group, incident cancer was diagnosed in 105 patients (11.1%), as compared with 70 patients (7.5%) in the placebo group (P=0.01). Cancers that had been diagnosed before randomization recurred in eight of these patients (three in the simvastatin–ezetimibe group and five in the placebo group), and one patient had a cancer that developed during the SAS trial, before enrollment in the SEAS trial. The excess cancers in the simvastatin–ezetimibe group were not clustered at any particular site (Table 4). In addition, the risk of incident cancer was not associated with the degree of LDL-cholesterol lowering. Figure 4 shows Kaplan–Meier curves for cancer-related mortality in the two study groups.

DISCUSSION

The combination of simvastatin and ezetimibe resulted in an average reduction in LDL cholesterol of at least 50%, as compared with placebo. Despite this favorable effect over a minimum period of 4 years, there was no overall effect on aortic-valve stenosis and no significant overall effect on the composite primary outcome. The lack of any effect on the progression of aortic stenosis as seen on echocardiography supports the conclusion that the lack of effect on clinical valve-related events was real and not due to a lack of statistical power. The finding of increased numbers of incident and fatal cancers in the simvastatin–ezetimibe group, as compared with the placebo group, was unexpected and requires further exploration in trials of simvastatin and ezetimibe.

The lack of effect on aortic-valve stenosis is in agreement with the findings of the smaller Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) study, in which atorvastatin was used.[34] The results of the Rosuvastatin Affecting Aortic Valve Endothelium (RAAVE) study (ClinicalTrials.gov number, NCT00114491) indicated a favorable effect on aortic stenosis, but the study had a nonrandomized and open-label design, with comparisons of various categories of patients with aortic stenosis.[39]

Our study population did not represent all pa-

Table 3. Adverse Events (Safety Population).*

Event	Placebo (N=929)	Simvastatin plus Ezetimibe (N=943)	P Value†
	no./total no. (%)		
Clinical			
Any event	852 (91.7)	854 (90.6)	
Any serious event‡	463 (49.8)	468 (49.6)	
Incident cancer§	70 (7.5)	105 (11.1)	0.01
Recurrent cancer	5 (0.5)	3 (0.3)	
New cancer	65 (7.0)	102 (10.8)¶	0.01
New cancer after ezetimibe	65 (7.0)	101 (10.7)	0.01
Event attributed to study treatment‖			
Any	110 (11.8)	134 (14.2)	
Serious	3 (0.3)	5 (0.5)	
Event resulting in permanent discontinuation of study treatment			
Any	122 (13.1)	144 (15.3)	
Attributed to treatment	29 (3.1)	46 (4.9)	
Serious event resulting in permanent discontinuation of study treatment			
Any	79 (8.5)	77 (8.2)	
Attributed to treatment	1 (0.1)	2 (0.2)	
Musculoskeletal condition	181 (19.5)	165 (17.5)	0.28
Hepatitis	6 (0.6)	5 (0.5)	0.77
Gastrointestinal condition	281 (30.2)	308 (32.7)	0.27
Gallbladder-related condition	11 (1.2)	10 (1.1)	0.83
Allergic reaction or rash	102 (11.0)	104 (11.0)	1.00
Laboratory findings			
Creatine kinase			
>10 times ULN without muscle-related symptoms	2/915 (0.2)	2/925 (0.2)	1.00
>10 times ULN with muscle-related symptoms	0	0	NA
>10 times ULN with muscle-related symptoms and drug relationship	0	0	NA
Liver enzymes			
Alanine aminotransferase or aspartate aminotransferase ≥3 times ULN (consecutive)**	5/915 (0.5)	16/925 (1.7)	0.03

* Listed are the numbers of patients who had at least one event (or elevated value) during the study period, with each event counted only once within a category. Patients could have more than one event in different categories. The denominators are the numbers of patients who received at least one dose of study drug or placebo. One patient who underwent randomization was not included in the safety analyses because he did not receive study drug or placebo. NA denotes not applicable, and ULN upper limit of the normal range.

† P values were not calculated for comparisons between small numbers and for those for which there was no a priori hypothesis, with the exception of cancer.

‡ Serious adverse events included fatal or life-threatening conditions, those resulting in hospitalization or persistent disability, cancer, and any drug overdose.

§ This category includes 11 patients whose fatal cancers were diagnosed after the discontinuation of study drug or placebo and were therefore not reported as serious adverse events, according to the study protocol.

¶ This number includes one patient who had a newly diagnosed cancer before randomization in the SEAS study.

‖ Events attributed to study treatment were those that were determined by the investigator to be associated with study drug or placebo.

** This category includes patients with values that were three or more times the ULN at two or more consecutive visits, the single last visit, or at least one visit, with a subsequent value that was less than three times the ULN when measured more than 2 days after the last dose of study drug or placebo.

Table 4. Incident Cancer (Safety Population).

Site	Placebo (N=929)	Simvastatin plus Ezetimibe (N=943)	P Value*
	number (percent)		
Any cancer†	70 (7.5)	105 (11.1)	0.01
Any cancer excluding recurrent cancer	65 (7.0)	102 (10.8)‡	0.01
Lip, mouth, pharynx, or esophagus	1 (0.1)	1 (0.1)	1.0
Stomach	1 (0.1)	5 (0.5)	0.23
Large bowel or intestine	8 (0.9)	9 (1.0)	1.0
Pancreas	1 (0.1)	4 (0.4)	0.38
Liver, gallbladder, or bile ducts	3 (0.3)	2 (0.2)	1.0
Lung	10 (1.1)	7 (0.7)	0.60
Other respiratory organ	0	1 (0.1)	1.0
Skin	8 (0.9)	18 (1.9)	0.08
Breast	5 (0.5)	8 (0.8)	0.60
Prostate	13 (1.4)	21 (2.2)	0.24
Kidney	2 (0.2)	2 (0.2)	1.0
Bladder	7 (0.8)	7 (0.7)	1.0
Genital	4 (0.4)	4 (0.4)	1.0
Hematologic	5 (0.5)	7 (0.7)	0.79
Other known sites	1 (0.1)	3 (0.3)	0.63
Unspecified	6 (0.6)	9 (1.0)	0.63

* All P values were calculated with Yates' continuity correction because of small numbers.
† The numbers of patients include those with any cancers including recurrent cancer. One patient who underwent randomization was not included in the safety analyses because he did not receive study drug or placebo. Some patients had more than one site of cancer. The numbers per anatomical site exclude recurrent cancers.
‡ This number includes one patient whose cancer was diagnosed after entry in the SAS study but before randomization in the SEAS study.

tients with aortic-valve stenosis, since high-risk patients with severe hyperlipidemia requiring active lipid-lowering treatment, known atherosclerotic disease, or diabetes mellitus were not included in order to allow for placebo treatment. This factor may explain the relatively low rate of progression of aortic-valve stenosis in our study, as compared with that in other studies.[34,40] Otherwise, the patients in our study had characteristics that are typical of patients with aortic stenosis. It is possible that treatment in our study was initiated too late in the course of the disease to affect further progression, but it is also possible that high levels of LDL cholesterol are just a marker for progression of stenosis.

Therapy with simvastatin and ezetimibe resulted in a significant reduction in the risk of ischemic cardiovascular events, mainly through fewer CABG procedures. Since nearly all coronary surgery was performed as a combined procedure with aortic-valve replacement, the study-drug regimen may have had a substantial effect on atherosclerosis, as shown on coronary angiography. However, the reduction in the risk of other components of the secondary ischemic outcome was smaller than expected on the basis of the large reduction in LDL cholesterol levels.[41] There was a weaker relationship between baseline LDL cholesterol levels and any ischemic event in the placebo group than was seen in studies in high-risk populations, suggesting less potential for risk reduction with lipid-lowering therapy.

Long-term statin therapy has not been associated with an increased risk of cancer. Analysis of data from 14 statin trials involving approximately 90,000 patients showed no evidence of an increased incidence of or death from cancer.[41] However, ezetimibe has been studied less extensively than statins, and the finding of a significant difference between the two study groups in the num-

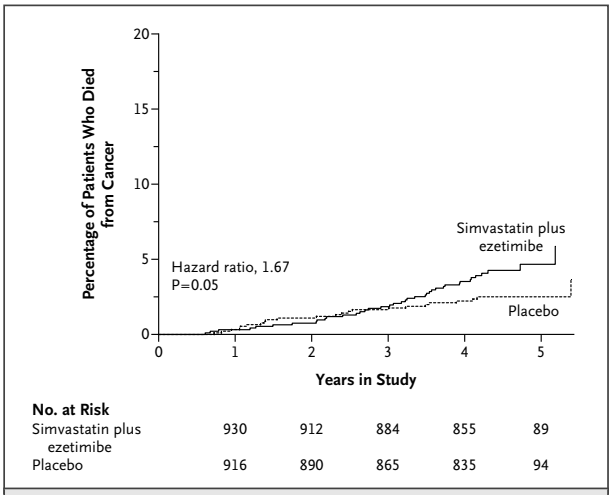

Figure 4. Kaplan–Meier Curves for Cancer-Related Mortality.
P=0.06 as calculated with log-rank continuity correction.

bers of patients with new and fatal cancers is a concern. In this issue of the *Journal*, Peto et al.[42] describe the results of an independent analysis of preliminary data on cancer from two large, ongoing studies, the Study of Heart and Renal Protection (SHARP) (NCT00125593) and the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) (NCT00202878).[42] Both trials tested the same study-drug combination that we used in our study, though in other patient populations and with a combined study population of nearly 20,000 patients. Cancer was one of a very large number of safety indicators analyzed in the SEAS trial, and the observed difference in cancer rates in the study may have been the result of chance, but this possibility requires further study.

We conclude that in patients with mild-to-moderate, asymptomatic aortic-valve stenosis and no traditional indications for lipid-lowering therapy at baseline, long-term, intensive lipid-lowering therapy with simvastatin and ezetimibe had no overall effect on the course of aortic-valve stenosis. However, lipid-lowering therapy reduced the risk of ischemic cardiovascular events, especially the need for CABG. The higher incidence of cancer in the simvastatin–ezetimibe group requires further exploration in ongoing and future trials.

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IV

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Relation of Left Ventricular Mass to Prognosis in Initially Asymptomatic Mild to Moderate Aortic Valve Stenosis

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Background—The prognostic importance of left ventricular (LV) mass in nonsevere asymptomatic aortic stenosis has not been documented in a large prospective study.

Methods and Results—Cox regression analysis was used to assess the impact of echocardiographic LV mass on rate of major cardiovascular events in 1656 patients (mean age, 67 years; 39.6% women) with mild-to-moderate asymptomatic aortic stenosis participating in the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study. Patients were followed during 4.3 years of randomized treatment with combined simvastatin 40 mg and ezetimibe 10 mg daily or placebo. At baseline, LV mass index was 45.9+14.9 g/m$^{2.7}$, and peak aortic jet velocity was 3.09+0.54 m/s. During follow-up, 558 major cardiovascular events occurred. In Cox regression analyses, 1 SD (15 g/m$^{2.7}$) higher baseline LV mass index predicted increases in hazards of 12% for major cardiovascular events, 28% for ischemic cardiovascular events, 34% for cardiovascular mortality, and 23% for combined total mortality and hospitalization for heart failure (all P<0.01), independent of confounders. In time-varying models, taking the progressive increase in LV mass index during follow-up into account, 1 SD higher in-study LV mass index was consistently associated with 13% to 61% higher hazard for cardiovascular events (all P<0.01), independent of age, sex, body mass index, valvuloarterial impedance, LV ejection fraction and concentricity, and the presence of concomitant hypertension.

Conclusions—Higher LV mass index is independently associated with increased cardiovascular morbidity and mortality during progression of aortic stenosis.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00092677.

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Key Words: aortic valve stenosis ■ echocardiography ■ hypertrophy, left ventricular ■ mortality ■ prognosis

It is well known that the presence of left ventricular (LV) hypertrophy by echocardiography predicts increased cardiovascular morbidity and mortality both in general and in hypertensive populations.[1–3] In patients with aortic valve stenosis (AS), LV hypertrophy is mainly considered an adaptive response that keeps LV wall stress close to normal, offsetting the hemodynamic load.[4] However, as recently demonstrated, the presence of concomitant hypertension, obesity, and metabolic syndrome significantly modulates LV mass and geometry in patients with asymptomatic AS independent of AS severity.[5–7]

See Clinical Perspective
See Editorial by Barasch and Reichek

Few studies in AS have focused on the prognostic impact of LV mass. In patients with severe symptomatic AS, concentric LV geometry and severe LV hypertrophy by echocardiography have been associated with increased mortality after aortic valve replacement.[8,9] Increased cardiovascular morbidity and mortality has also been demonstrated for asymptomatic patients with severe AS and excessive LV hypertrophy.[10] Recently, higher LV mass was associated with worse outcome after transcatheter aortic valve replacement for severe symptomatic AS.[11] However, the independent prognostic impact of LV mass by echocardiography in asymptomatic mild-to-moderate AS patients has not been reported from a large prospective study. Thus, the aim of this study was to test the

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hypothesis that higher LV mass is independently associated with higher rate of cardiovascular events in these patients.

Methods

Patient Population

The present analysis was prespecified within the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study analysis plan. Study design, baseline characteristics, and main outcome results of the SEAS study have previously been published.[12,13] In short, 1873 men and women aged 45 to 85 years with asymptomatic mild-to-moderate AS having a peak aortic jet velocity between 2.5 and 4.0 m/s by echocardiography were randomized to placebo or to combination treatment with simvastatin 40 mg and ezetimibe 10 mg daily. Patients with known coronary heart disease, heart failure, diabetes mellitus, history of stroke or peripheral vascular disease, clinically significant mitral valve disease, severe or predominant aortic regurgitation, rheumatic valvular disease, aortic valve prosthesis, or renal insufficiency and patients already on lipid-lowering therapy or with a guideline indication for lipid-lowering therapy were not included in the SEAS study. Core laboratory readings of peak aortic jet velocity and LV mass were available from baseline and at least 1 follow-up echocardiogram in 1656 patients (88% of the study population), who comprise the present study population. Hypertension was defined as history of hypertension, use of antihypertensive drug treatment, or elevated blood pressure at the baseline clinic visits. All patients gave written informed consent, and the study was approved by ethics committees in all participating countries.

Echocardiography

Echocardiograms were performed at baseline, annually and before planned aortic valve surgery following a standardized protocol at 173 study centers in 7 European countries. Echocardiographic images were stored on videotapes, compact discs, or magnetic optical discs and forwarded for blinded interpretation at the SEAS echocardiography core laboratory at Haukeland University Hospital, Bergen, Norway, as previously published.[5,12,14] Severity of AS and LV structure and function were measured following current guidelines.[15,16] LV mass was measured by an autopsy-validated method and indexed to body height in the allometric power of 2.7.[17] LV hypertrophy was defined using the prognostically validated cutoff values LV mass index >46.7 g/m$^{2.7}$ in women and >49.2 g/m$^{2.7}$ in men.[3] Relative wall thickness was assessed from 2×LV posterior wall thickness/LV end-diastolic diameter ratio and considered increased if >0.43 (concentric LV geometry).[15] Valvuloarterial impedance was calculated using a previously validated method.[18] Pressure recovery was assessed at the aortic sinotubular junction and used for calculation of energy loss index as prognostically validated.[19,20]

End Points

The prespecified primary end point of SEAS was major cardiovascular events, a composite end point, including aortic valve–related events (combined aortic valve replacement, hospitalization for heart failure because of aortic stenosis, and death from cardiovascular causes) and ischemic cardiovascular events (combined death from cardiovascular causes, nonfatal myocardial infarction, hospitalization for unstable angina, coronary revascularization, and nonhemorrhagic stroke).[12] The secondary end points were aortic valve events and ischemic cardiovascular events analyzed separately. Total mortality was a tertiary end point. All end points were classified by an independent end point classification committee whose members were unaware of study group assignments.[13] We also assessed the post hoc defined composite end point of total mortality and hospitalization for heart failure because of aortic stenosis.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 22.0 (IBM Corporation, Armonk, NY). Values are given as mean+SD for continuous variables and as percentages for categorical variables. Comparison between groups was performed by paired and unpaired t test, χ^2 test, and general linear model with post hoc test and Bonferroni adjustment as appropriate. Cumulative incidences of cardiovascular events during follow-up were estimated by Kaplan–Meier. Kaplan–Meier plots were used to compare event-free survival in groups of patients with and without LV hypertrophy at baseline. Correlates of the prespecified primary and secondary composite end points were identified by Cox regression analysis in univariable and multivariable models and presented as hazard ratio and 95% confidence intervals. In the primary analyses, LV mass index was used as the continuous variable. In secondary models, LV hypertrophy as a dichotomous variable was used. Age, sex, body mass index, peak aortic jet velocity, LV ejection fraction, concentric LV geometry, hypertension, and valvuloarterial impedance were included as covariates in all multivariable models. Aortic valve replacement was included as a time-varying covariate in models assessing cardiovascular death and total mortality. In subsequent models, concentric LV geometry was replaced by stress-corrected midwall shortening, and the presence of aortic regurgitation was added. To take the progressive increase in LV mass during progression of AS into account, time-varying Cox regression analysis was used. Two-tailed P<0.05 was regarded as statistically significant both in univariable and multivariable analyses.

Results

Compared with patients with normal LV mass index at baseline, the group with LV hypertrophy was older, had higher body mass index, lower LV midwall function, and included more patients with hypertension (all P<0.01; Tables 1 and 2). During a median of 4.3-year follow-up, LV mass indexed to height$^{2.7}$ (LV mass index) and concentricity increased, whereas LV endocardial and myocardial function declined (all P<0.001). The prevalence of LV hypertrophy increased from 36% at baseline to 60% at the last study visit (P<0.01). The annual AS progression rate did not differ between groups of patients with and without LV hypertrophy at baseline, whether calculated based on change in peak aortic jet velocity (0.21±0.39 versus 0.20±0.27 m/s per year), mean gradient (4±7 versus 4±5 mm Hg/y), or aortic valve area (−0.03±0.25 versus −0.03±0.29 cm^2/y, all P>0.3). The average time between the baseline and the last follow-up study was 3.6±1.2 years. The average time between the follow-up study and an aortic valve event, an ischemic cardiovascular event, and death from any cause was on average 0.59±0.03, 0.94±0.06, and 0.80±0.55 years, respectively.

During follow-up, each SD higher unindexed LV mass, LV mass/height$^{2.7}$, and LV mass/body surface area was associated with comparable 21%, 23%, and 25% higher rates of the primary study end point, respectively, in univariable analyses (all P<0.001). The rates of aortic valve events, ischemic cardiovascular events, cardiovascular death, and combined death from any cause and hospitalization for heart failure because of progression of AS all increased progressively with increasing quartile of baseline LV mass index and were 1.5, 1.8, 3.2, and 2.5 times higher in the upper LV mass index quartile than in the lowest quartile (Figure 1). In multivariable Cox regression, higher LV mass index was associated with higher rates of aortic valve events, ischemic cardiovascular events, cardiovascular death, and combined death from any cause and hospitalization for heart failure when adjusted for known prognosticators in AS patients like age, sex, body mass index, AS severity, LV ejection fraction,

Table 1. Clinical Patient Characteristics in the Total Population and in Patients With or Without LV Hypertrophy at Baseline

Variable	Total Population, n=1616	LV Hypertrophy, n=592	No LV Hypertrophy, n=1064
Age, y	67.4±9.6	68.2±9.2*	66.9±9.8
Women, %	39.4	38.3	40.0
Systolic blood pressure, mm Hg	146±20	149±20*	145±20
Diastolic blood pressure, mm Hg	82±10	83±10†	81±10
Heart rate, bpm	66±11	66±11	66±12
Body surface area, m^2	1.89±0.20	1.92±0.20*	1.88±0.20
Body mass index, kg/m^2	26.8±4.3	28.5±4.6*	25.9±3.9
Baseline hypertension, %	83.0	88.2*	80.2
Baseline current smoker, %	19.0	15.4*	21.1
Serum creatinine, mg/dL	1.06±0.18	1.06±0.18	1.06±0.17

LV indicates left ventricular.
*P<0.01 vs no LV hypertrophy group.
†P<0.05 vs no LV hypertrophy group.

concentric LV geometry, and concomitant hypertension (Table 3). Similar results were found in a second model, replacing concentric geometry by stress-corrected midwall shortening (hazard ratio, 1.13 for primary end point per 1 SD higher LV mass index [95% confidence interval, 1.02–1.24]; P=0.017). Adding the presence of aortic regurgitation or type of antihypertensive drug among the covariates did not influence results.

Table 2. Echocardiographic Findings in the Total Study Population and in Patients With or Without LV Hypertrophy at Baseline

Variable	Total Population, n=1616	LV Hypertrophy, n=592	No LV Hypertrophy, n=1064
LV end-diastolic diameter, cm	5.03±0.63	5.29±0.63*	4.89±0.57
LV end-systolic diameter, cm	3.19±0.55	3.42±0.57*	3.06±0.50
Interventricular septal thickness, cm	1.15±0.28	1.34±0.27*	1.05±0.22
Posterior wall thickness, cm	0.89±0.19	1.02±0.18*	0.81±0.14
LV fractional shortening, %	37±6	35±6*	37±6
LV ejection fraction, %	66±7	66±7*	67±6
Circumferential end-systolic stress, $dyne/cm^2$	112±32	111±32	113±31
Midwall fractional shortening, %	17.0±3.3	15.6±3.0*	17.9±3.2
Stress-corrected midwall shortening, %	98±19	89±18*	102±19
Relative wall thickness	0.36±0.09	0.39±0.10*	0.34±0.08
LV mass, g	193±67	252±66*	160±39
LV mass index, $g/m^{2.7}$	45.6±14.5	60.5±12.2*	37.3±7.1
Aortic valve velocity, m/s	3.08±0.54	3.18±0.56*	3.03±0.52
Aortic valve mean gradient, mm Hg	23±9	24±9*	22±8
Aortic valve area/body surface area, cm^2/m^2	0.67±0.23	0.66±0.22	0.68±0.24
Energy loss index, cm^2/m^2	0.90±0.46	0.86±0.43†	0.92±0.47
Stroke volume, mL	45±13	46±14†	44±13
Aortic regurgitation, %	60.2	62.2*	59.1
Grade 1, %	43.4	41.6	44.3
Grade 2, %	16.1	19.7	14.2
Grade 3, %	0.7	0.9	0.6

LV indicates left ventricular.
*P<0.01 vs no LV hypertrophy group.
†P<0.05 vs no LV hypertrophy group.

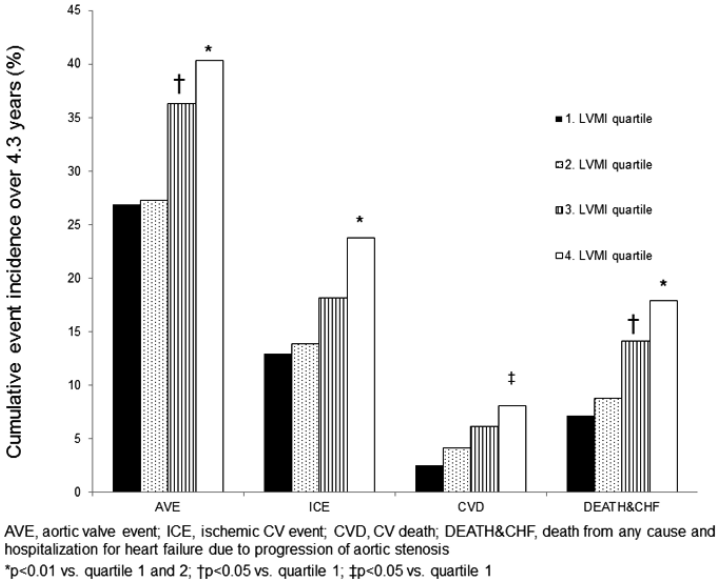

Figure 1. Cumulative incidences of aortic valve events (AVE), ischemic cardiovascular (CV) events (ICE), CV death (CVD), and combined death from any cause and hospitalization for heart failure because of progression of aortic stenosis (DEATH&CHF) during >4.3 years of follow-up in relation to quartile of baseline left ventricular (LV) mass index in mild-to-moderate asymptomatic aortic stenosis.

In a secondary set of models, having LV hypertrophy on the baseline echocardiogram was associated with higher rates of the primary and secondary composite study end points and combined all-cause death and hospitalization for heart failure, consistent with the outcome association demonstrated for LV mass index (Table 4; Figure 2).

In multivariable linear regression higher LV mass/height$^{2.7}$ at the last study echocardiogram was associated with male sex (β=0.06), and higher mean aortic gradient (β=0.15), systolic blood pressure (β=0.04), body mass index (β=0.14), initial LV mass/height$^{2.7}$ (β=0.54), and presence of normal midwall shortening (β=0.05, all P<0.05) at the baseline echocardiogram. To take into account the progressive increase in LV mass during progression of AS, a set of time-varying Cox regression models were used. Higher LV mass index during follow-up was associated with a 16% higher rate of the primary study end point, 13% higher rate of aortic valve events, 25% higher rate of ischemic cardiovascular events, 63% higher cardiovascular mortality, and 44% higher combined death from any cause and hospitalization

Table 3. Impact of Baseline Left Ventricular Mass Index (Per 1 SD [15 g/m$^{2.7}$] Higher) on the Rates of the Primary and Secondary Study End Points, Hospitalization for Heart Failure, Cardiovascular Death, All-Cause Death, and Combined All-Cause Death and Hospitalization for Heart Failure During >4.3 Years of Follow-Up in Patients With Initially Asymptomatic AS

Study End Point	No. of Events	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)*	*P* Value
Primary study end point	498	1.23 (1.14–1.37)	<0.001	1.12 (1.02–1.23)	0.020
Aortic valve events	468	1.19 (1.11–1.29)	<0.001	1.09 (0.99–1.19)	0.083
Aortic valve replacement	411	1.17 (1.07–1.27)	<0.001	1.03 (0.93–1.14)	0.562
Heart failure due to progression of AS	36	1.47 (1.16–1.61)	0.001	na	
Cardiovascular death	66	1.34 (1.12–1.70)	<0.001	1.34 (1.07–1.67)	0.011
Ischemic cardiovascular events	232	1.28 (1.15–1.43)	<0.001	1.28 (1.13–1.47)	<0.001
Total mortality	129	1.27 (1.11–1.46)	<0.001	1.19 (1.01–1.42)	0.048
Total mortality and hospitalization for heart failure	149	1.30 (1.15–1.47)	<0.001	1.23 (1.05–1.44)	0.011

Univariable and multivariable Cox regression analyses. AS indicates aortic stenosis; CI, confidence interval; HR, hazard ratio; and na, multivariable analysis not performed because of low number of events.

*Adjusted for aortic jet velocity, sex, age, left ventricular ejection fraction, body mass index, randomized study treatment, hypertension, concentric left ventricular geometry, and valvuloarterial impedance.

Table 4. Impact of Baseline Left Ventricular Hypertrophy on the Rates of the Primary and Secondary Study End Points, Hospitalization for Heart Failure, Cardiovascular Death, All-Cause Death, and Combined All-Cause Death and Hospitalization for Heart Failure During >4.3 Years of Follow-Up in Patients With Initial Asymptomatic AS

Study End Point	No. of Events	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)*	*P* Value
Primary study end point	498	1.53 (1.30–1.81)	<0.001	1.26 (1.03–1.54)	0.022
Aortic valve events	468	1.50 (1.27–1.79)	<0.001	1.25 (1.02–1.54)	0.035
Aortic valve replacement	411	1.46 (1.22–1.76)	<0.001	1.21 (0.97–1.52)	0.087
Heart failure due to progression of AS	36	2.08 (1.08–4.00)	0.028	na	…
Cardiovascular death	66	1.68 (1.06–2.65)	0.026	1.35 (0.79–2.11)	0.277
Ischemic cardiovascular events	232	1.55 (1.22–1.98)	<0.001	1.42 (1.06–1.89)	0.017
Total mortality	129	1.61 (1.17–2.23)	0.004	1.31 (0.89–1.94)	0.178
Total mortality and hospitalization for heart failure	149	1.67 (1.24–2.26)	0.001	1.35 (0.94–1.92)	0.110

Univariable and multivariable Cox regression analyses. AS indicates aortic stenosis; CI, confidence interval; HR, hazard ratio; and na, multivariable analysis not performed due to low number of events.

*Adjusted for aortic jet velocity, sex, age, left ventricular ejection fraction, body mass index, randomized study treatment, relative wall thickness, hypertension, and valvuloarterial impedance.

for heart failure (all $P<0.01$; Table 5). In subsequent models replacing energy loss index by peak aortic jet velocity, mean aortic valve gradient, or aortic valve area as measure of AS severity, or LV ejection fraction by midwall shortening or stress-corrected midwall shortening, the results did not change (data not shown).

Discussion

This is the first large prospective study to assess the prognostic impact of LV mass and hypertrophy assessed by echocardiography in patients with asymptomatic mild-to-moderate AS without known coronary heart disease or diabetes mellitus. As demonstrated by our results, higher LV mass at baseline or during follow-up was associated with higher rates of both the primary and secondary prespecified composite study end points in the SEAS study, resulting in a considerably increased overall cardiovascular morbidity and mortality. These findings were also independent of documented prognosticators in asymptomatic AS, including AS severity, hypertension, body mass index, sex, LV ejection fraction, and concentric LV geometry.[4,7,8,21–23] Of note, patients in the highest versus lowest quartile of LV mass index at baseline had a 13% higher 4.3-year cumulative incidence of aortic valve events and a 11% higher incidence of combined death from any cause and hospitalization for heart failure, corresponding to absolute differences of 3.0% and 2.6% per year, respectively.

Traditionally, development of LV hypertrophy in AS has been considered a physiological, compensatory process taking advantage of Laplace's law to sustain normal systolic function during chronically elevated systolic stress.[4,24] However, as recently demonstrated, concomitant hypertension, obesity, and the presence of the metabolic syndrome have been associated with increased LV mass in patients with asymptomatic nonsevere AS, suggesting that development of LV hypertrophy is multifactorial also in patients with AS.[5–7] The relatively larger impact of hypertension on LV wall volume in mild-to-moderate AS than of AS itself has also been demonstrated in experimental simulation models by Garcia et al.[25] However, having increased LV mass on the baseline echocardiogram was associated with increased event rates in the present study independent of the prognostic impact of concomitant hypertension and increased body mass index previously demonstrated in asymptomatic mild-to-moderate AS.[21–23]

Risk prediction in asymptomatic AS remains a challenge, including identification of AS patient with high risk for development of congestive heart failure, the most prognostically severe complication of AS.[26] Both American and European guidelines recommend aortic valve replacement in patients with severe AS irrespective of symptoms if LV dysfunction defined as LV ejection fraction <50% is present.[27,28] Population-based studies have demonstrated that increased LV mass was associated with incident heart failure independent of LV ejection fraction and independent of incident myocardial infarction.[29–31] The present findings expands this knowledge by demonstrating that also in patients with mild-to-moderate AS, increased LV mass index is associated with higher rate of combined death and heart failure independent of LV systolic function. Current European guidelines suggest excessive LV hypertrophy unless because of hypertension among indications for aortic valve replacement in AS,[28] as this has been associated with increased perioperative morbidity and mortality and may be less reversible after delayed surgery, precluding an optimal long-term prognosis.[8,32] The present results from the large SEAS study document the association of increased LV mass with increased cardiovascular morbidity and mortality also in patients with asymptomatic mild-to-moderate AS independent of the presence of concomitant hypertension. Our findings contrast with previous reports from smaller studies in patients with moderate to-severe AS. Stewart et al[33] following 183 patients with initially asymptomatic moderate or severe AS for a median of 31 months found that neither LV mass nor tissue Doppler measures of LV systolic and diastolic function predicted outcome independent of AS severity. Similar findings were reported by Monin et al[34] in a study of 107 patients

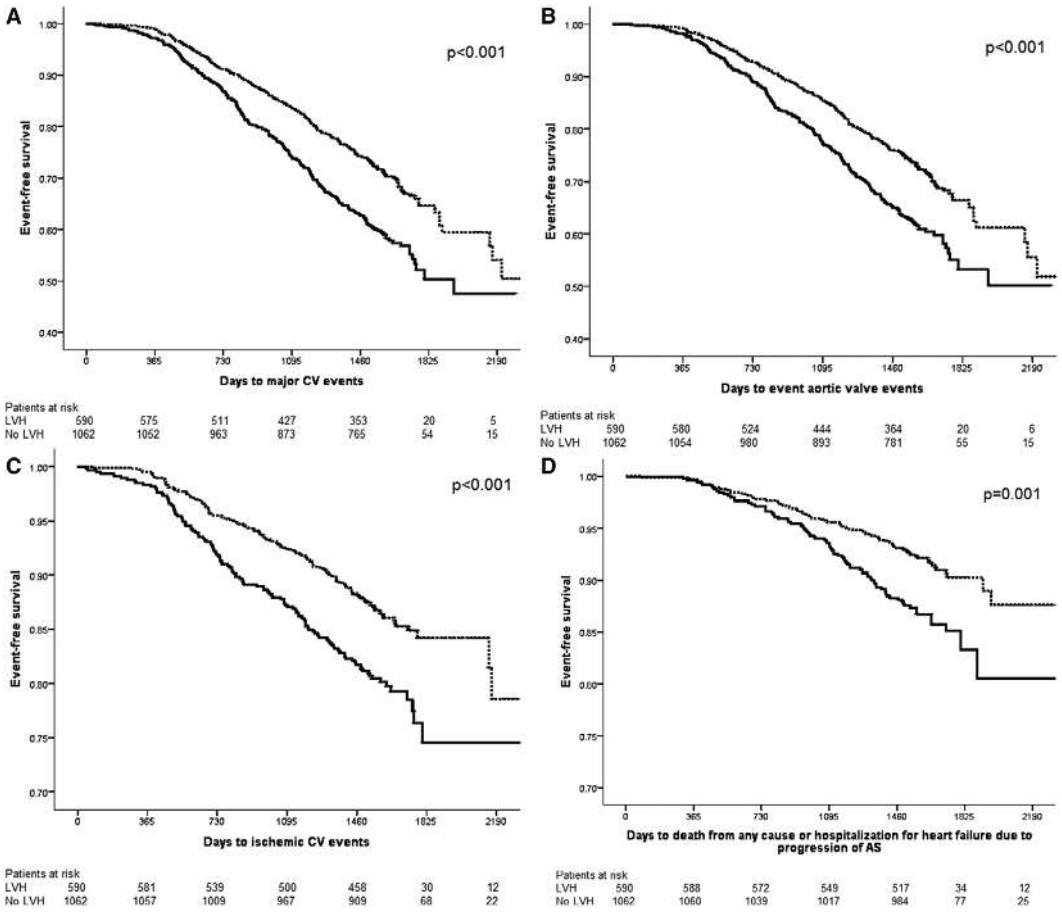

Figure 2. Survival free from major cardiovascular (CV) events (**A**), aortic valve events (**B**), ischemic CV events (**C**), and combined death from any cause and hospitalization for heart failure because of progression of aortic stenosis (AS; **D**) in groups of patients with (—) and without (---) left ventricular hypertrophy (LVH) on the baseline echocardiogram.

with moderate-to-severe AS, who therefore did not include LV mass in the suggested risk assessment score for asymptomatic patients with moderate-to-severe AS based on their findings. Electrocardiographic LV strain pattern was recently suggested as a strong correlate of mortality and hospitalization for heart failure by Greve et al[35] in a SEAS substudy. Of note, electrocardiographic strain pattern was not significantly associated with either cardiovascular death or all-cause mortality when mean aortic gradient was included as covariate in their multivariable models, in contrast to the strong independent association with echocardiographic LV mass and hypertrophy reported in the present article. However, Shah et al[36] documented that electrocardiographic strain pattern as a highly specific marker of midwall myocardial fibrosis, reflecting more advanced myocardial injury, LV decompensation, and impaired prognosis.[35–37]

Both LV mass and concentricity increased considerably during follow-up. Concentric LV geometric patterns have been demonstrated to carry individual risk of cardiovascular morbidity and mortality in hypertension.[38] Furthermore, an association with reduced coronary flow reserve as a substrate for reduced myocardial function in hypertensive subjects with LV concentric geometry free from coronary artery disease has been reported by Galderisi et al.[39] In patients operated for AS, both concentric LV geometry and excessive LV hypertrophy have been associated with higher postoperative mortality.[8,9] Cioffi et al[10] previously demonstrated that excessive LV hypertrophy was the strongest correlate of combined death, congestive heart failure, and nonfatal myocardial infarction in 218 patients with asymptomatic severe AS. Of note, these findings were independent of patient age, extent of aortic valve calcification, renal dysfunction, or the presence of concomitant diabetes mellitus, all factors that have been associated with worsened prognosis in previous studies in asymptomatic severe AS.[10,40,41] The present results expand this knowledge by demonstrating the independent prognostic importance of higher LV mass in a large prospective study of patients with initially asymptomatic mild-to-moderate AS.

Table 5. Impact of In-Study Left Ventricular Mass Index (Per 1 SD [15 g/m$^{2.7}$] Higher) on the Rates of Study End Points During >4.3 Years of Follow-Up in Patients With Initial Asymptomatic Aortic Stenosis

Study End Point	No. of Events	HR (95% CI)*	*P* Value
Primary study end point	466	1.16 (1.05–1.28)	0.004
Aortic valve events	435	1.13 (1.01–1.25)	0.027
Aortic valve replacement	381	1.05 (0.93–1.17)	0.455
Cardiovascular death	62	1.61 (1.29–2.00)	<0.001
Ischemic cardiovascular events	220	1.25 (1.08–1.43)	0.002
Total mortality	125	1.42 (1.20–1.68)	<0.001
Total mortality and hospitalization for heart failure	141	1.42 (1.21–1.66)	<0.001

Time-varying multivariable Cox regression analyses. CI indicates confidence interval; and HR, hazard ratio.

*Adjusted for time-varying aortic jet velocity, left ventricular ejection fraction, body mass index, concentric LV geometry and valvuloarterial impedance, baseline age, sex, hypertension, and randomized study treatment.

Limitations

Patients with known coronary heart disease, heart failure, diabetes mellitus, history of stroke or peripheral vascular disease, other clinically significant valve disease, rheumatic valve disease, or renal insufficiency and patients with a guideline indication for lipid-lowering therapy were not included in the SEAS study. Thus, projection of study results to these patient groups should be done with caution.

In the SEAS study, referral for aortic valve replacement was left to the decision of the attending cardiologist at the 173 participating centers, and the basis for referral of individual patients for surgery was not captured in the study database. We cannot exclude that presence of extreme LV hypertrophy may have influenced the decision to refer for surgery in individual cases. However, an independent impact of higher LV mass index was also found with the more objective end points cardiovascular and total mortality.

Several studies have found speckle strain imaging, in particular 2-dimensional (2D) global longitudinal strain, useful for detecting asymptomatic AS patients with more advanced LV injury despite normal LV ejection fraction.[41–43] Lower global longitudinal strain in these patients has been associated with higher LV mass, concentric LV geometry, more severe AS, concomitant hypertension,[41] and with impaired prognosis.[42] Recently, Nagata et al[43] reported the superior performance of 3D compared with 2D global longitudinal strain for risk prediction in such patients, also when adjusting for LV mass in multivariate analysis. However, speckle tracking echocardiography was not included in the large SEAS study, where the majority of echocardiogram were recorded on video tapes during the period 2002 to 2008.

Maréchaux et al[44] have demonstrated the usefulness of exercise stress echocardiography for risk stratification in asymptomatic patients with severe AS, and current European guidelines include exercise testing for additional risk assessment in patients with asymptomatic severe AS.[28] However, exercise testing was not included in the large SEAS study, which was undertaken in 173 study centers during the years 2002 to 2008.

Conclusions

In patients with asymptomatic AS, higher LV mass index is independently associated with increased cardiovascular morbidity and mortality during progression of valve stenosis.

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Disclosures

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CLINICAL PERSPECTIVE

It is well known that the presence of left ventricular (LV) hypertrophy by echocardiography predicts increased cardiovascular morbidity and mortality both in general and hypertensive populations. In patients with aortic valve stenosis (AS), LV hypertrophy has traditionally been considered as an adaptive response that keeps LV wall stress close to normal, offsetting the hemodynamic load. Recent publications have demonstrated that the presence of concomitant hypertension, obesity, and metabolic syndrome significantly modulates LV mass and geometry in patients with asymptomatic AS independent of AS severity. Furthermore, excessive LV hypertrophy in severe AS has been associated with incident heart failure and increased mortality. The present study is the first to demonstrate the prognostic impact of LV mass and hypertrophy in a large, prospective study in asymptomatic mild-to-moderate AS. Higher LV mass at baseline or during follow-up was associated with considerable increased overall cardiovascular morbidity and mortality. The findings were independent of other documented prognosticators in asymptomatic AS. Patients in the highest versus the lowest quartile of baseline LV mass index had 2.6% higher incidence per year of death and hospitalization for heart failure. Emerging data suggest that speckle strain echocardiography may be used for further identification of AS patients with more advanced LV injury. Whether asymptomatic AS patients with LV hypertrophy should undergo valve replacement at an earlier stage of disease remains unknown. However, LV hypertrophy in asymptomatic AS should not be regarded as purely compensatory, and referral to a heart valve center for further evaluation may be indicated.

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Relation of Left Ventricular Mass to Prognosis in Initially Asymptomatic Mild to Moderate Aortic Valve Stenosis

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