

# Risk Stratifying Asymptomatic Aortic Stenosis: Role of the Resting 12-lead ECG

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## The three original papers are:

1. Differences in cardiovascular risk profile between electrocardiographic hypertrophy versus strain in asymptomatic patients with aortic stenosis (from SEAS data).” Greve AM, Gerds E, Boman K, Gohlke-Baerwolf C, Rossebø AB, Hammer-Hansen S, Køber L, Willenheimer R, Wachtell K. *Am J Cardiol.* 2011;108:541-7.
2. Clinical implications of electrocardiographic left ventricular strain and hypertrophy in asymptomatic patients with aortic stenosis: the Simvastatin and Ezetimibe in Aortic Stenosis study.” Greve AM, Boman K, Gohlke-Baerwolf C, Kesäniemi YA, Nienaber C, Ray S, Egstrup K, Rossebø AB, Devereux RB, Køber L, Willenheimer R, Wachtell K. *Circulation.* 2012;125:346-53.
3. Impact of QRS duration and morphology on the risk of sudden cardiac death in asymptomatic patients with aortic stenosis: the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) Study.” Greve AM, Gerds E, Boman K, Gohlke-Baerwolf C, Rossebø AB, Devereux RB, Køber L, Ray S, Willenheimer R, Wachtell K. *J Am Coll Cardiol.* 2012;59:1142-9.

## Introduction

AS is the most prevalent valvular heart disease in the industrialized world.<sup>1</sup> The primary form presents as an advancing calcification of the aortic valve, and affects 2-3% of the population aged over 65 years.<sup>2</sup> Calcific AS is now recognized as the result of an active process sharing several etiological- and histopathological findings with vascular atherosclerosis.<sup>3</sup> In clinical practice, AS is regarded as mild, moderate or severe based on cardiac imaging estimates of valve orifice and hemodynamics.<sup>4</sup> The progression from asymptomatic to symptomatic (dyspnea, angina and/or syncope) AS is an important prognostic hallmark.<sup>5</sup> Standard of care once severe AS becomes symptomatic and/or left ventricular (LV) ejection fraction falls below 50% is surgical aortic valve re-

placement (AVR) or transcatheter aortic valve implantation (TAVI) in patients not suitable for surgery.<sup>4,6,7</sup> There is a lack of randomized controlled trials (RCT) investigating the effect of AVR in earlier stages of AS. AVR is therefore, despite a marked improvement in post-operative survival, still restricted to severe AS with symptoms or signs of end-stage disease.<sup>4</sup> Identification of high-risk patients is nevertheless of critical importance, as data suggest a real (0.4-1%/year) risk of sudden cardiac death (SCD) during ‘watchful waiting’.<sup>8,9</sup>

## Asymptomatic Aortic Stenosis: Guideline Approach

Projections of the natural history of asymptomatic AS are based on extrapolation of data from decades of observational studies. Generally, prognosis is considered fair in mild-to-moderate stages and risks of symptoms and death is expected to correlate with the hemodynamic degree of AS severity.<sup>10</sup> However, due to wide variability in clinical- and hemodynamic progression, patients are generally recommended annual or biannual clinical and echocardiographic follow-up to monitor disease status. Timely intervention is therefore dependent upon early detection, reproducible and true estimates of disease severity. Most cases of AS are first detected by cardiac auscultation and subsequently referred for cardiologic evaluation. Left heart catheterization was the first technique that allowed reliable estimation of AS severity, replacing earlier indirect measures able to detect but not quantify AS.<sup>11,12</sup> The current non-invasive approach to grading asymptomatic AS began in the 1970s with the clinical introduction of ultrasound Doppler.<sup>13,14</sup> Since then, echocardiography has surpassed invasive measures as the primary tool for assessing AS severity.<sup>4,15,16</sup> Standard risk stratification of asymptomatic AS now entails careful questioning for symptoms and transthoracic echocardiography to determine; 1) the degree LV outflow obstruction; 2) the extent of valve calcification; 3) LV structure and function; and 4) the presence of other associated valve disease and/or aortic pathology.<sup>4</sup> In unclear cases, exercise echocardiography may be further helpful for appropriate classification of asymptomatic AS severity.<sup>17</sup>

## Asymptomatic Aortic Stenosis: Discrepancies in outcome

Despite improvements in epidemiological models and in the ability to image the aortic valve as well as the LV structure and function, asymptomatic AS remains a significant contributor to excess morbidity and mortality.<sup>18</sup> This is true for undiagnosed as well as properly and seemingly incorrectly risk classified AS.<sup>19,20</sup> This argues that; 1) there is an undetected disease burden; 2) lack of or delayed referral for AVR remains a concern; 3) comorbidities are common and drive, alone or in combination with AS, end-points for which AVR is not necessarily the remedy; and 4) some

parts of AS pathogenesis are not fully elucidated in current guidelines (Table 1).

**Table 1.** Factors suspected of contributing to continued adverse outcomes in asymptomatic AS.

Factors	
Insufficient pathophysiological understanding	True and 'pseudo' severe AS; <sup>21</sup> low-grade AS with preserved LV systolic function; <sup>22</sup> impact of vascular disease; <sup>23</sup> failing systolic function is a late marker of cardiac decompensation; <sup>24</sup> energy loss index; <sup>25</sup> reduced coronary flow reserve. <sup>26</sup>
Late or post-mortem detection of AS	There is no formal screening program for AS, and patients still die from undiagnosed AS. <sup>27</sup>
Misclassification of AS severity	Variability in LV outflow tract diameter; <sup>28</sup> flow- and angle dependent underestimations of AS severity; <sup>29</sup> method specific disagreements between invasive and non-invasive AS measures; <sup>30-32</sup> AS measures biased by high vascular resistance. <sup>23</sup>
Insufficient or late referral for AVR	There is still a significant doctor's delay in referring patients for AVR. <sup>19</sup>
Lack of current epidemiological data	AS cohort composition has changed dramatically since Braunwald's years - new epidemiological models is therefore needed to identify risk factors for AS and its outcome: e.g. obesity, hypertension, coronary- and peripheral vascular disease, diabetes mellitus type 2, kidney failure, smoking, atrial fibrillation, LVH.
Study designs	Paucity of RCTs in AS, prior studies are flawed by small sample sizes and the use of AVR as the main or only endpoint, the latter being partly tautological since the referral for AVR is based on the tested endpoint predictors. This compounds to make guidelines based on low-level evidence. <sup>33</sup>
Genes	Some patients have an accelerated disease process due to familial traits. <sup>34</sup>
AS is a marker of widespread disease	Comorbidities in a priori presumed 'benign' conditions, i.e. aortic sclerosis and mild-to-moderate AS, may drive endpoints not necessarily related to the need for AVR. <sup>35, 36</sup>
Inconsistent grading of AS	Unappreciated impact of LV outflow tract diameter; <sup>36</sup> pressure recovery. <sup>37</sup>

Abbreviations: AS: Aortic stenosis, LV: Left ventricular, AVR: Aortic valve replacement, LVH: Left ventricular hypertrophy.

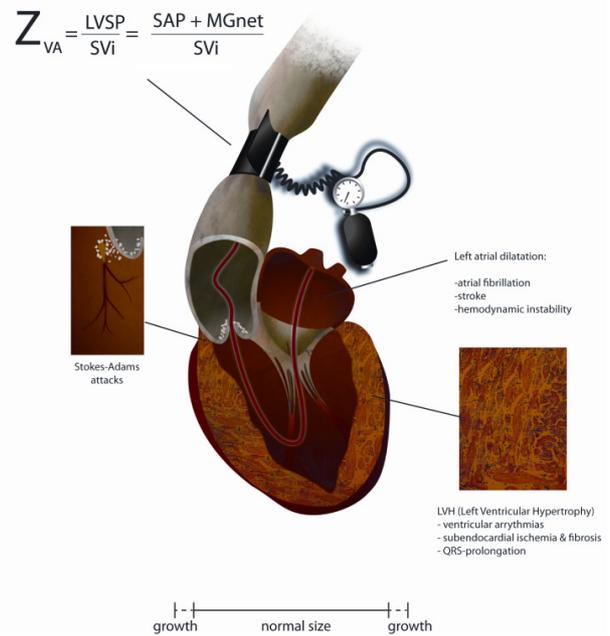
Application of novel therapeutic and diagnostic methods as well as a reexamination of current concepts in the setting of prospective observational and RCTs are therefore needed to blunt the detrimental impact of AS on public health. Recent work has highlighted the importance of preexisting myocardial damage on the hearts ability to cope with LV pressure load.<sup>38</sup> As such, is the performance of predictive models reported to improve when including B-type natriuretic peptides and patterns of LV relaxation and contraction as estimates of LV response to increased wall stress.<sup>24, 39, 40</sup> A grading system based on how the LV masters its global systolic load (Figure 1), prior to systolic function fails, could therefore be a novel approach to identify high-risk asymptomatic AS patients.

### Asymptomatic Aortic Stenosis: Rationale for the 12-lead ECG

The classic 12-lead ECG is very appealing in this concept, as it is a low-cost, easily repeatable and widely available tool, which is sensitive to changes in LV structure and function induced by valvular as well as vascular disease.<sup>41-43</sup> Examining the predictive value of 12-lead ECG findings in asymptomatic AS is therefore very pertinent for improved risk prediction in this rapidly growing patient population. The purpose of this PhD thesis was therefore to examine if the resting 12-lead ECG can provide incremental prognostic information in current patients with asymptomatic AS. This was evaluated by three individual postulates, each tested in separate peer-reviewed manuscripts:

1. Hypothesis Article #1: The resting 12-lead ECG can grade asymptomatic AS severity.
2. Hypothesis Article #2: ECG LV hypertrophy (LVH)/strain is an independent risk factor for poor prognosis in asymptomatic AS.
3. Hypothesis Article #3: QRS duration adds predictive information on the risk of SCD in asymptomatic AS.

**Figure 1.** Cardiac failure involves multiple mechanisms in the pressure-overloaded heart.



Abbreviations: Zva=global systolic load; LVSP=left ventricular systolic pressure; SVi=stroke volume index; SAP=systolic arterial pressure; MGnet=mean net pressure gradient. Figure adapted from Greve et.al. Cardiac Valvular Medicine 2012

### Methods

#### Patient Population

All data origin from the SEAS study (ClinicalTrials.gov, identifier: NCT00092677), a large multicenter randomized trial designed to investigate the effect of lipid lowering on clinical and echocardiographic outcomes in initially asymptomatic AS. Eligible patients had asymptomatic mild-to-moderate AS defined as echocardiographically determined aortic valve thickening and a Doppler measured peak aortic jet velocity  $\geq 2.5$  and  $\leq 4.0$  m/sec. Major exclusion criteria were prescribed or a perceived need for cholesterol-lowering therapy (e.g. diabetes and/or vascular atherosclerosis), systolic heart failure and/or other significant valvular disease (e.g., aortic- and/or mitral valve regurgitation, rheumatic-, supra- or subvalvular AS). From March 2001 through March 2004, the study enrolled 1,873 men and women aged 45-85 years from 173 study centers in northern Europe (Denmark, Finland, Germany, Great Britain, Ireland, Norway, and Sweden) and randomly assigned them (1:1) to either placebo or 40 mg simvastatin + 10 mg ezetimibe.<sup>44</sup> As part of the SEAS study, all patients were automatically enrolled in the SEAS ECG- and echocardiographic substudies, which involved visits at baseline, year 1-, 2- and 4 of follow-up. Data collection ended according to protocol in 2008 after all patients had been followed for  $\geq 4$  years.<sup>45</sup> The main study found that despite achieved lipid lowering and less ischemic cardiovascular events, treatment with simvastatin/ezetimibe combination had no detectable impact on the progression of AS or its outcome.<sup>45</sup>

#### Ethics

The SEAS study adheres to the declaration of Helsinki,<sup>46</sup> as reflected in approval by local ethics committees and enrollment based on informed consent. Each participant was assigned a random allocation number, which allowed for anonymous tracking and merging of biological information across datasets. Sepa-

rate consent was not needed for participation in the SEAS ECG or echocardiographic substudy as ethical considerations pertaining to the inclusion in the SEAS substudies were covered by the main study protocol. The recording of an ECG or echocardiogram is a non-invasive procedure that is not known to impose any risks. In theory, the ECG and echocardiogram could inadvertently reveal medical conditions without available treatment.

### Electrocardiography

The SEAS ECG substudy was conducted according to a pre-specified protocol; a detailed description of how ECG data were obtained and analyzed has been published.<sup>41</sup> In short, the ECGs were recorded at local study centers, labeled with date and the anonymous allocation number, after which they were sent to the SEAS ECG core laboratory, located at Rigshospitalet, Copenhagen, Denmark. A highly experienced reader blinded to the randomization, echocardiographic and clinical data, Minnesota coded the ECGs (total n=7,302) and transferred the score directly to a database for statistical analysis.<sup>47</sup> ECG left ventricular hypertrophy (LVH) was assessed by the Sokolow-Lyon voltage and Cornell voltage-duration criteria, and ECG strain by T-wave inversion in leads V<sub>4-6</sub> (Figure 2). Baseline ECGs were available for 1,563 (83.4%) patients. Age, peak aortic jet velocity and LV ejection fraction was not statistically significant different in subjects with and without ECG data (all p>0.05). Paired t-tests and kappa statistics showed excellent inter-observer reproducibility of key ECG findings on 20 randomly selected ECGs; kappa values for presence/absence of ST-segment depression and T-wave inversion were 0.88 and 1.0, respectively (both p>0.05).

### Echocardiography

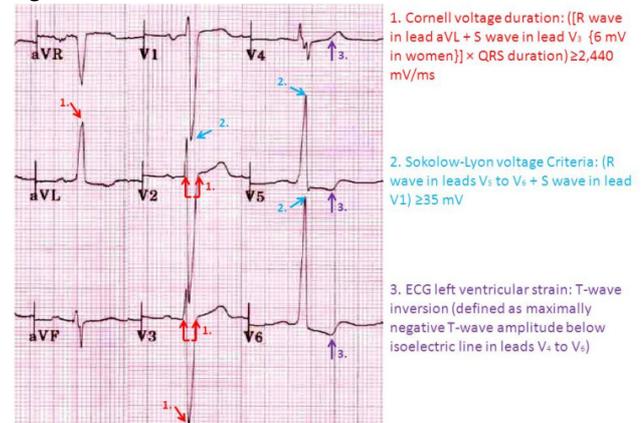
The SEAS echocardiographic substudy protocol, reading procedures and reproducibility have been published previously.<sup>48</sup> Briefly, transthoracic echocardiograms were read blinded to the randomization and study visits at the SEAS echocardiographic core laboratory, located at Haukeland University Hospital, Bergen, Norway. Aortic valve area was calculated with the use of the continuity equation, in accordance with recent recommendations.<sup>49</sup> Quantitative echocardiography was performed following the American Society of Echocardiography guidelines.<sup>50</sup> Among the 1,563 patients with available ECG data, 94.1% (n=1,471) also had recorded baseline echocardiographic data.

### Endpoint Definitions

All endpoints were classified by an Endpoint Classification Committee blinded to randomization according to a prespecified endpoint manual outlined by the SEAS Steering Committee.<sup>44</sup> Specific endpoints were: (1) SCD (defined as either witnessed instantaneous unexpected death occurring without any preceding symptoms, unwitnessed unexpected death, if other cause of death was excluded with reasonable certainty [i.e., patients with known signs, symptoms or other fatal disease when last observed], or cardiac death occurring <24 hours after onset of cardiac symptoms [e.g., acute pulmonary edema or cardiogenic shock]); (2) cardiovascular death (defined as death from complications of myocardial infarction, progressive heart failure, cerebrovascular disease, complications of cardiac surgery or intervention, other cardiac or cardiovascular diseases including sudden cardiac death as defined above); (3) AVR (defined as AVR as a single operative procedure or performed in combination with coronary artery bypass graft); (4) heart failure deemed to origin from AS progression (defined as date of hospitalization for congestive heart failure, excluding patients with AVR, known heart failure, aortic valve

area >1.0 cm<sup>2</sup>, and/or known heart disease, aside from AS, which could have contributed to the development of congestive heart failure); (5) non-hemorrhagic stroke (defined as a focal neurological deficit, lasting ≥24 hours, or until death [if death occurs <24 hours after onset of neurological symptoms], in the absence of signs of bleeding on computerized tomography, magnetic resonance imaging, or spinal fluid analysis); and (6) nonfatal- and fatal myocardial infarction (defined as typical rise and gradual fall of troponin or rapid rise and fall of creatine kinase-MB with the addition of at least 1 of the following: ischemic symptoms, ischemic ECG changes [development of pathological Q waves, ST-segment elevation, ST-segment depression, inversion of T waves in at least 2 leads], and/or percutaneous coronary intervention with significant coronary stenosis/thrombus). To increase clinical relevance, a separate combined endpoint (i.e., the first of nonfatal myocardial infarction, heart failure or cardiovascular death) was constructed post-hoc for article #2.

Figure 2. ECG criteria for LVH and strain



### Statistics

Data were analyzed using the statistical analytical software version 9.2 (SAS, Cary, NC). Distributions are expressed as percentages or mean±SD where appropriate. Continuous data were assessed for normality by visual inspection of histograms and transformations were performed when indicated. Pairwise comparisons in continuous variables were evaluated by Student's *t*-test and by chi-square analysis for categorical data. Differences in >2 groups were assessed by two-way ANOVA and trend tests as applicable. To reduce risk of type 1 error, pairwise comparisons with reference groups were in the two latter cases adjusted by Dunnett's test for multiple comparisons. Multivariable relations and likelihoods of a certain degree of AS by distinct ECG findings were assessed by generalized linear models and logistic regression, respectively. Goodness of fit was checked by residual plots and interaction-based testing of departure from linearity. A multi-state linear mixed model was used to investigate the effect of randomized treatment on in-study changes in QRS duration and ECG LVH/strain. Assumptions for Cox time-to-event analyses (proportional hazard and linear assumption) were checked by cumulative Martingale residuals (1,000 random resamplings were compared to the models functional form).<sup>51</sup> Due to competing risks (making the Kaplan-Meier estimator invalid), cumulative incidence plots were used to portray the probability of experiencing the event of interest using the SAS macro 'COMPRISK'.<sup>52</sup> In article #3, the log-rank test was used on the cumulative incidence plots of SCD and overall cardiovascular death due to no difference in the competing events (data not presented).<sup>53</sup> Cox cause-

specific hazards ratios with 95% confidence intervals (CI) were used to describe event rate ratios, as the Fine and Gray competing risk method has no direct clinical inference.<sup>54,55</sup> To take into account the effect of serial measurements and AVR, a multistate 'time-varying' Cox models was used.<sup>56</sup> The amount of predictive value added by the including the ECG findings, was evaluated by changes in the net reclassification index (NRI) and area under the receiver operator characteristics curve (C-statistics) using the SAS macro 'ROCPLUS'.<sup>57,58</sup> Due to the randomization therapy all models were checked for influence of active vs. placebo arm, but doing so did not significantly alter the correlates of ECG variables (data not presented). In models with ECG LV strain, an additional adjustment was made for concomitant digoxin therapy (n=41) to account for its potential influence on appearance of ST/T-segment (Cohn-effect). All other adjustments and interaction terms were based on clinical reasoning. To avoid overfitting (<10 events per covariate), article #3 used backwards elimination to reduce (alpha=0.05) the number of risk predictors. This method is, however, data driven and do not reduce the number of variables presented to the model. Due to multiple testing a two-tailed p<0.01 was the preset significance level for interactions. For all other models a two-tailed p<0.05 was required for statistical significance.

## Results and Clinical Inference

### Article #1

Baseline ECGs were available in 1,563 (83.4%) patients; consisting of 958 males (61.4%) and 605 females (38.7%) with a mean age of 67.4±9.6 years and a mean peak aortic jet velocity of 3.1±0.5 m/sec. ECG abnormalities were common (~60% had ≥1 finding); in large due to frequent ST/T repolarization abnormalities (~40% had T-wave changes). Of the ECG variables with a priori suspected predictive value of echocardiographic AS severity, prevalences of voltage LVH and ST/T changes did show significant relation to peak aortic jet velocity, whereas QRS duration displayed little association and atrial fibrillation a seemingly inverse propensity for severe AS (Table 2).

**Table 2.** ECG abnormalities differed in their relation to echocardiographic degree of AS severity\*

Variable	Mild (n=681)	Moderate (n=706)	Severe (n=84)	p
Sv1 + Rvs-6 voltage (mV)	25.6±9.2	27.2±9.4	29.6±11.1	<0.001
Cornell product (mV·msec)	1677.9±874.9	1801.0±885.0	1792.3±891.7	0.03
PR interval (msec)	174.3±28.4	176.4±32.6	179.5±25.7	0.22
QRS duration (msec)	87.9±14.4	88.2±13.6	90.1±16.5	0.41
QTc-interval (msec/√sec)	408.6±23.7	411.4±21.4	412.2±23.9	0.06
P-wave lead II (mm+msec)	95.6±13.9	96.4±13.1	96.8±11.3	0.72
Left bundle branch block	3.5%	2.1%	3.6%	0.23
Right bundle branch block	3.4%	4.3%	7.1%	0.12
ST-depression leads V4-6	12.5%	20.3%	27.3%	<0.001
T-inversion leads V4-6	18.5%	27.9%	39.4%	<0.001
ST-depression any lead	17.1%	25.5%	36.5%	<0.001
T-inversion any lead	32.6%	43.3%	52.2%	<0.001
Atrial fibrillation	3.7%	3.8%	2.4%	0.81
PVCs	1.6%	2.8%	2.4%	0.19
Normal ECG	49.4%	36.0%	40.6%	<0.001

Table adapted from Greve et al. Am J. Cardiol 2011. Abbreviations; PVC: premature ventricular contractions, \* Mild: peak aortic jet velocity >2.5 and <3.0 m/sec; Moderate: peak aortic jet velocity ≥3.0 and ≤4.0 m/sec; Severe: peak aortic jet velocity >4.0 m/sec. Abbreviations: NS: non-significant.

Multivariable analyses demonstrated that increases in LV mass explained more of the observed ECG LVH/strain (model R<sup>2</sup>=0.20) than greater peak aortic jet velocity per se (model R<sup>2</sup>=0.07). This is line with prior evidence suggesting that mild-to-moderate AS has a minor impact on the LV as compared to frequently accompanying vascular disease, e.g. hypertensive heart disease.<sup>59</sup>

No ECG variable displayed sensitivity or specificity characteristics useful for screening or ruling out severe AS (Table 3). Although, the latter finding may be influenced by selection bias as well as the exclusion of symptomatic and sicker patients likely to have more prevalent ECG abnormalities.

**Table 3.** The 12-lead ECG could not be used to rule out severe AS\*

Variable	non-severe AS (n=1,387)	severe AS(n=84)	OR for severe AS (95% confidence interval)	P
Normal ECG	42.6%	40.6%	0.9 (0.56 – 1.51)	0.74
Atrial fibrillation	3.8%	2.4%	0.6 (0.15 – 2.61)	0.52
≥1 <sup>st</sup> degree of AV-block	5.5%	4.8%	0.9 (0.31 – 2.41)	0.78
Left bundle branch block	2.8%	3.6%	1.3 (0.39 – 4.23)	0.69
Right bundle branch block	3.8%	7.1%	1.9 (0.81 – 4.64)	0.14
Premature contractions	2.2%	2.4%	1.1 (0.25 – 4.53)	0.93
T-inversion leads v4-6	23.3%	39.4%	2.1 (1.31 – 3.52)	0.002
ST-depression leads v4-6	16.5%	27.3%	2.1 (1.29 – 3.46)	0.003
LVH by Cornell product	14.2%	17.5%	1.3 (0.71 – 2.32)	0.42
LVH by Sv1 + Rvs-6	16.3%	27.7%	2.0 (1.19 – 3.24)	0.008

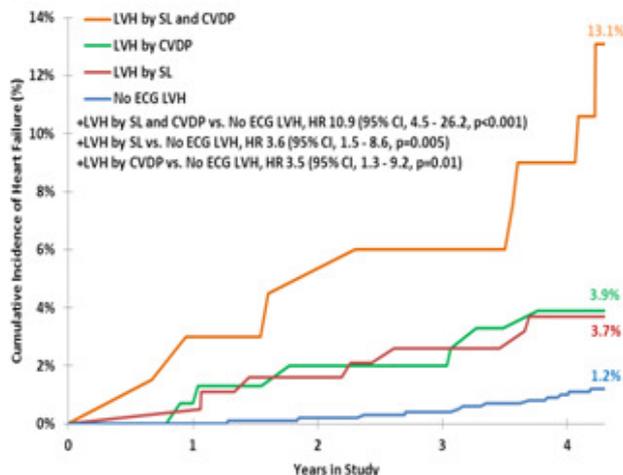
Table adapted from Greve et al. Am J. Cardiol 2011. Abbreviations; AV: atrio-ventricular, OR: odds ratio, \* Non-severe: peak aortic jet velocity ≤4.0 m/sec, Severe: peak aortic jet velocity >4.0 m/sec. Abbreviations: NS: non-significant.

### Article #2

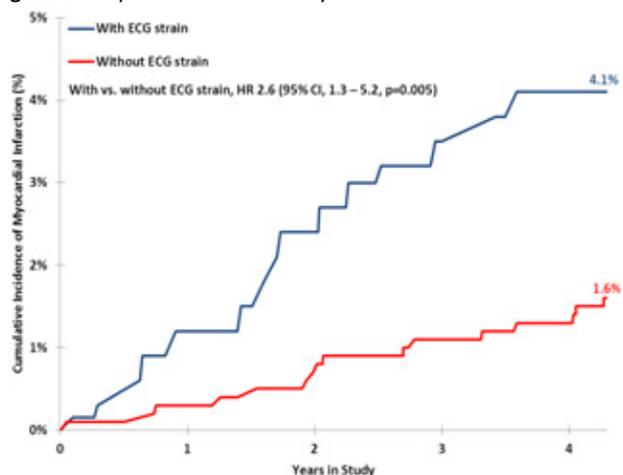
Baseline ECG criteria for LVH/strain could be assessed in 1,533 (Sokolow-Lyon voltage criterion in 1,518, Cornell voltage-duration criterion in 1,509 and T-wave inversion in 1,442). Altogether, the 1,533 patients with available data included 936 men (61.1%) and 597 women (38.9%) followed a mean of 4.3±0.8 years (6,592 patients-years of follow-up). As noted in article #1, ECG LVH/strain criteria related differently to coexisting hypertension, calculated myocardial oxygen consumption, and LV geometry and function (data not presented). Most patients fared well in non-surgical endpoints (averaged rates of heart failure, myocardial infarction and cardiovascular death were ~0.6%, ~0.5% and ~1% per year, respectively) but certain subgroups, such as those with ECG LVH/strain, tended to carry worse prognosis. For ECG LVH/strain, this was mainly driven by substantial increases in relative risks of late (~1.5 years post-enrollment) cardiac decompensation and myocardial infarction in subjects with baseline ECG LVH and strain, respectively (Figures 3A and 3B). These outcome differences remained significant in models adjusting for clinical- and echocardiographic covariates, baseline ECG LVH by both of the evaluated criteria was, as compared to no ECG LVH, independently predictive of 5.8-fold higher risk of heart failure (95% CI 2.0 to 16.8), and ECG strain, as compared to no ECG strain, of 3.1-fold higher risk of incident myocardial infarction (95% CI 1.4 to 6.8, both p<0.01).

These observations concur with data from hypertensive populations, indicating that ECG LVH contains separate prognostic information as compared to echocardiographic LVH in the pressure-overloaded heart.<sup>60</sup> The prevention or regression of ECG LVH/strain may therefore be potential therapeutic targets in AS. There was no detectable impact on randomized treatment to simvastatin/ezetimibe combination vs. placebo on annual measures of ECG LVH/strain (all p>0.05).

**Figure 3A.** Heart failure by ECG LVH



**Figure 3B.** Myocardial infarction by ECG strain



Figures adapted from Greve et al. Circulation 2012

Extending the models to include data from the annual ECG reexaminations, highly significant (all  $p < 0.01$ ) univariate risks of heart failure, need for AVR and cardiovascular death were noted for ECG strain as well as both of the ECG LVH criteria. Updating the analyses with information from in-study clinical- and echocardiographic reexaminations, the hazards remained significant (Table 4).

**Table 4.** Serial measures of ECG LVH/strain were independently predictive of poor prognosis\*

ECG finding	Heart failure	p	AVR	p	CVD	p
$S_{V1}+R_{V5-6}$ LVH	3.5 (1.6 - 7.7)	0.002	1.5 (1.2 - 1.9)	<0.001	1.9 (1.1 - 3.3)	0.02
Cornell product LVH	3.7 (1.6 - 8.6)	0.002	1.4 (1.1 - 1.8)	0.003	2.3 (1.3 - 3.9)	0.003
T-inversion leads $V4-6$	4.5 (1.8 - 11.3)	0.002	1.7 (1.3 - 2.1)	<0.001	2.1 (1.2 - 3.8)	0.008

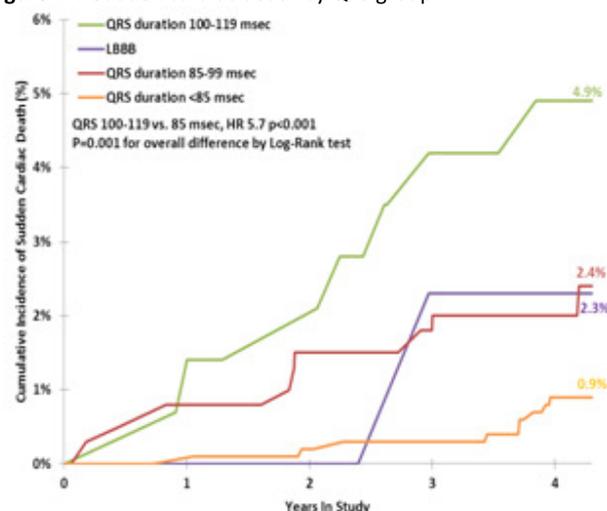
Table adapted from Greve et al. Circulation 2012. Abbreviations; AVR: aortic valve replacement, CVD: cardiovascular death, LVH: left ventricular hypertrophy, \* Hazard ratios for +/- ECG LVH/strain when adjusted for age, gender, echocardiographic peak aortic jet velocity, left ventricular ejection fraction and left ventricular mass, cholesterol levels, systolic- and diastolic blood pressure, estimated glomerular filtration rate, study drug and body mass index (based on annual reexamination) with 95% confidence limits in parentheses.

### Article #3

QRS duration could be assessed in 1,542 (98.7% of patients with available ECG data); consisting of 942 men (61.1%) and 600

women (38.9%) followed for a mean of  $4.3 \pm 0.8$  years, totaling 6,631 patient-years of follow-up. As noted in article #2, absolute event rates were low and SCD occurred in  $\sim 0.4\%$ /year, which is close to that expected in age matched background population ( $\sim 0.2\%$ /year).<sup>61</sup> At baseline, longer QRS duration was associated with worsening LV systolic function and increased LV mass. However, the group of patients with bundle branch block (BBB) was small and distinct, consisting mainly of older patients without significantly more AS. The explanation for this may be the exclusion of symptomatic and frailer patients from the SEAS study. Test of departure from linearity when assessing QRS duration as a continuous predictor of SCD was borderline significant ( $p=0.08$ ), largely due to poor model fit in  $QRS \geq 120$  msec. Goodness of fit was markedly improved by assigning indicator variables to QRS duration; 1)  $<85$  msec; 2) 85-99 msec; 3)  $\geq 100$  msec (excluding patients with BBB); 4) left BBB; and 5) right BBB with and without left anterior fascicular block,  $p=0.27$  for overall lack of proportional hazard. Using this clustering, highly significant differences in the probabilities of experiencing SCD were observed by QRS group (Figure 4A). Due to the limited number of SCDs, an additional test was performed to illustrate that the association with SCD also translated to an increased risk of overall cardiovascular death (Figure 4B).

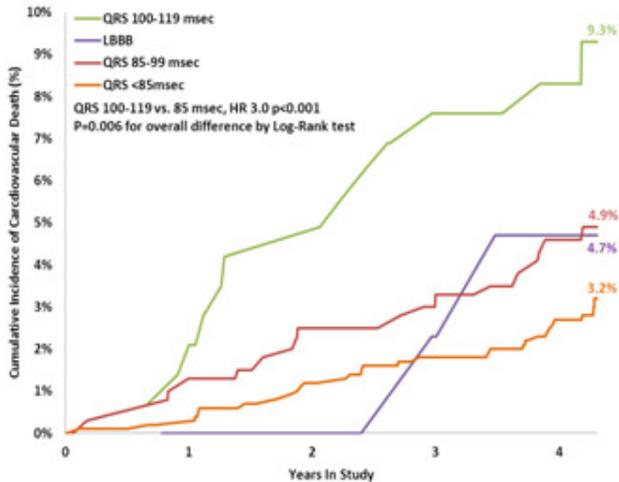
**Figure 4A.** Sudden cardiac death by QRS group



In further analyses including classic risk factors for SCD, longer QRS duration ( $p=0.002$  for omnibus test of QRS groups, QRS duration 100-119 msec vs.  $<85$  msec; HR 6.4; 95% CI, 2.5 to 16.7,  $p < 0.001$ ) and older age (HR 1.06; 95% CI, 1.01 to 1.12,  $p=0.01$ ) remained as the only predictors of SCD. Adding QRS duration, as a group variable, to a model with SCD as outcome and age as well as LV mass indexed by body surface area as covariates, increased the C-index from 70.4 to 73.0% ( $p=0.02$ ) and improved NRI by 21.0% ( $p=0.03$ ). In models altering the time counting process to account for the effect of in-study events, AVR did not affect the predictive value of QRS duration or the risk of SCD in itself (both  $p=NS$ ). Similarly, using incident myocardial infarction as a time-dependent covariate, the predictive value of QRS duration was only marginally lower (QRS duration 100-119 msec vs.  $<85$  msec; HR, 5.9; 95% CI, 2.2 to 15.8,  $p < 0.001$ ). However, in this model, incident myocardial infarction was associated with a subsequent 4.6-fold higher risk of SCD (95% CI, 1.0 to 20.9,  $p < 0.05$ ). Thus, QRS duration and morphology as well as factors influencing these parameters add to the prediction of SCD in asymptomatic AS. To

the clinician, the low absolute event rates might suggest that in patients similar to the SEAS population, earlier AVR, at least in those with QRS duration <85 msec, is not likely to have a significant benefit on reducing non-ischemic SCD.

**Figure 4B.** Cardiovascular death by QRS group



Figures adapted from Greve et al. J Am Coll Cardiol 2012

## Discussion

This PhD thesis is, to the best of my knowledge, the first study to review the prognostic value of resting 12-lead ECGs in current patients with asymptomatic mild-to-moderate AS. Several findings add to current knowledge; 1) ECG LVH/strain is independently predictive of poor prognosis in asymptomatic AS; 2) QRS duration improves the performance of models trying to predict the risk of SCD in asymptomatic AS; and 3) ECG LVH/strain showed low/moderate concordance with LV mass and echocardiographic AS severity. Thus, the resting 12-lead ECG contains separate information and cannot substitute or screen for echocardiographic measures of AS severity.

### ECG Left Ventricular Hypertrophy and Strain

Prior studies have linked ECG LVH/strain to risks of poor prognosis and death in AS patients on the waiting list for AVR.<sup>62</sup> Moreover, ECG signs of LVH/strain have shown to be associated with a shorter asymptomatic period before onset of symptoms requiring AVR.<sup>8,63</sup> The lack of agreement between ECG and echocardiographic findings is not well understood. Recent evidence has focused on electrical remodeling in LVH, as a possible mechanism for explaining the differing diagnostic and prognostic implications of ECG LVH/strain as compared to anatomically determined LV mass.<sup>64</sup> In this study, observed incidences of myocardial infarction and relations to increased myocardial oxygen consumption, were consistent with ECG LV strain indicating subendocardial ischemia and reduced coronary flow reserve.<sup>65</sup> Similarly, ECG LVH as a marker of the individual response to increased afterload, identified patients with a more than 10-fold increase in the risk of heart failure.<sup>65</sup> Thus, low-cost and easily accessible ECG LV strain and LVH data provide valuable tools for risk stratification in AS. Whether or not these ECG abnormalities results from AS and thus correlates with the need for AVR is more uncertain, but merits further study.

### QRS Duration

Substantial evidence links QRS abnormalities to risks of cardiovascular morbidity and mortality in the general population and in

various cardiovascular diseases.<sup>66-68</sup> Notably, longer QRS duration has been shown to be predictive of SCD in the general population as well as in subjects with structural heart disease.<sup>69,70</sup> A pathophysiological mechanism may involve that longer QRS duration reflects abnormal myocardial depolarization and/or a higher threshold for termination of spontaneously occurring ventricular arrhythmia.<sup>71</sup> The predictive value of longer QRS duration of risk of SCD is very interesting in AS, since observational studies indicate a real risk of SCD in these patients.<sup>8,9</sup> However, there is limited mechanistic data on SCD in AS. Literature describes at least two pathways relating to whether or not cardiac arrhythmia is a primary or secondary phenomenon, i.e. subsequent to an abnormal Bezold-Jarisch reflex with hypotension and bradyarrhythmia.<sup>72</sup> In theory, secondary arrhythmias might be expected to have a relatively larger impact in later AS, where aortic pressures are likely to be more dependent upon LV outflow obstruction. Delayed cardiac activation, as a measure of pressure induced myocardial damage, is therefore probably related to the risk of primary arrhythmic death likely to have a relatively larger role in earlier asymptomatic AS.<sup>73</sup> In the clinical setting, there are, however, often comorbidities, such as hypertension, atrial fibrillation, ischemic heart disease and/or stroke, which could be an important etiology of SCD potentially unrelated to AS severity.<sup>35</sup> Furthermore, longer QRS duration might not only reflect AS induced myocardial damage, as similar correlates with SCD can be found in patients with increased afterload due to hypertension.<sup>74</sup> Finally, etiology of QRS durations of  $\geq 120$  msec may, especially in healthy older subjects, be isolated degenerative changes in conductive fibers (Lenégre syndrome).<sup>75,76</sup> This along with the exclusion of sicker patients might relate to the low number of patients with left BBB in the SEAS population and the observed modest event rates in these patients. The clinical message might therefore be that patients with short QRS durations have a lower risk of non-ischemic arrhythmic death during watchful waiting in asymptomatic AS.<sup>77</sup>

## Conclusion

Prognostication in AS involves a complex interplay between known and lesser studied factors.<sup>78</sup> Ideally every AS patient should therefore undergo a complete cardiovascular examination, genetic profiling combined with multiple tests for comorbidities. However, in the clinical setting it is not possible or cost-effective to submit all patients with aortic valve disease, ranging from early lesions to severe AS, to very expensive and frequent invasive testing. This PhD thesis demonstrated that resting 12-lead ECG findings, as detected by annual reexamination, were strong and independent predictors of poor prognosis during long term follow-up of initially asymptomatic mild-to-moderate AS. This suggests that ECG signs of myocardial damage contain a sum of biologic information, which could be helpful for elucidating the mechanisms of cardiac failure in the pressure overloaded heart as well as the development of pertinent risk stratification scores in asymptomatic AS.

### Study Limitations

This work has several limitations, which can be regarded as; 1) those inherent to the exploratory nature of the substudy design; and 2) those relating to the methods used to obtain and analyze data.

### Study Design

Even though the hypotheses for the SEAS ECG substudy were postulated a priori, the experiment-wise type 1 error rate in-

creases the likelihood of wrongly rejecting the null hypothesis. To reduce the risk of accepting false alternative hypotheses, the significance level was increased to 99% for interactions. For other hypotheses testing the significance level was kept at 95%, in an attempt to balance the risk of type II errors given that the power calculations and endpoints were not designed to detect an effect of ECG findings. Since the ECGs were read at a blinded corelab, it is not possible to ascertain whether clinical decision-making was influenced by the ECG findings, and therefore if acting differently would have altered the outcome. Similarly, several ECGs were recorded outside of the scheduled time points and it is uncertain whether these ECGs were recorded due to clinical worsening rather than forecasting an imminent deterioration. No baseline coronary artery data were available and it is therefore not possible to evaluate if the relations to incident myocardial infarction were caused by obstructive or non-obstructive coronary disease. Moreover, the SEAS study did not include measures of aortic valve calcification, e.g. computed tomography calculated aortic valve calcium score, which is shown to be predictive of the rate of AS progression.<sup>79, 80</sup> The event rates in the SEAS study population might not be representative of a normal AS population due to several exclusion criteria. As such, the exclusion of known vascular atherosclerosis is counterintuitive given our current understanding of calcific AS as a representation of atherosclerosis. The exclusion of sicker and/or symptomatic patients might have resulted in fewer patients with atrial fibrillation and the surprising finding of atrial fibrillation protecting against severe AS. Finally, the randomization to cholesterol-lowering therapy vs. placebo limits the generalization of our findings. However, we did perform several sensitivity analyses to detect an influence of the study drug; 1) models were adjusted for active- vs. control arm; 2) tests of interaction were performed between the ECG findings and randomization status; and 3) differences in evolution of ECG abnormalities during the course of the study were tested in patients treated with simvastatin/ezetimibe combination vs. placebo.

## Methods

Due to some unexpected findings involving use of the continuity equation, the external validity of the SEAS echocardiographic data has been questioned.<sup>81</sup> As such, the referral of a SEAS patient for AVR 22 days after enrollment for mild-to-moderate AS is a cause for concern. The given patient had a baseline peak aortic jet velocity of  $\sim 3.6$  m/s, indexed aortic valve area of  $\sim 0.4$  cm<sup>2</sup>, and a mean gradient of  $\sim 30$  mmHg. This suggests that either an orthogonal angle was not achieved or that the SEAS inclusion criteria overlapped with the entity of low-flow AS with preserved ejection fraction. Notwithstanding, that even though the echocardiograms were read by an expert, the image acquisition was not quality approved. The interpretations of the time-varying statistical models were limited by missing in-study values. This is important since the models in this PhD thesis necessitated available ECG data but carried forward last known values for missing non-ECG covariates, which could cause a false inflation of the ECG variables predictive effect.<sup>82</sup> Some endpoints were mutually exclusive in the SEAS study, and thereby violated the assumption of random censoring, as such is the large proportion of AVR likely to have influenced the observed risks of heart failure prior to AVR. Finally, C-statistics and NRI are limited in their ability to test if the improved discriminatory power is clinically useful.<sup>83, 84</sup> Most importantly, there were no pre-established risk-classes for SCD in asymptomatic AS and the use of slightly different arbitrary risk groups would have changed the interpretation of the NRI model.

## Clinical Implications

In the till date, largest prospectively followed cohort of asymptomatic mild-to-moderate AS, resting 12-lead ECG findings improved prediction of major cardiovascular outcomes. Most importantly, this PhD thesis demonstrated that; 1) adding QRS-duration to classic risk factors for SCD reclassified subjects into risk categories applicable for clinical decision making; 2) regression- and progression of ECG LVH/strain related independently to reduced- and increased risks of experiencing hard endpoints, respectively. The SEAS study population was not randomized to have therapy guided vs. not guided by resting 12-lead ECG findings. Future studies should therefore examine if and which resting 12-lead ECG abnormalities should elicit closer follow-up, earlier AVR, and/or other forms of therapy, e.g. antihypertensive treatment,<sup>85</sup> in order to improve prognosis in asymptomatic AS patients.

## Summary

Despite being routinely performed in the clinical follow-up of asymptomatic AS patients, little or no evidence describes the prognostic value of ECG findings in asymptomatic AS populations. This PhD thesis examined the correlates of resting 12-lead ECG variables with echocardiographic measures of AS severity and cardiovascular outcomes in the till date largest cohort (n=1,563) of asymptomatic patients with mild-to-moderate AS. Most importantly, this PhD thesis demonstrated that QRS-duration adds independent predictive value of sudden cardiac death and that the additional presence of ECG LVH/strain for fixed AS severity represents a lethal risk attribute. Finally, ECG abnormalities displayed low/moderate concordance with echocardiographic parameters. This argues that the ECG should be regarded as a separate tool for obtaining prognostically important information. Treatment was not randomized by ECG findings, future studies should therefore examine if and which ECG variables should elicit closer follow-up and/or earlier intervention to improve prognosis in asymptomatic AS populations.

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