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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

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Objectives The aim of the study was to examine the predictive value of QRS duration and morphology during watchful waiting in asymptomatic patients with aortic stenosis (AS).

Background QRS duration and morphology are associated with poor prognosis in many different populations, but the predictive value, particularly of the risk of sudden cardiac death (SCD), in asymptomatic patients with AS has not been well studied.

Methods Data were obtained in asymptomatic AS patients randomized to simvastatin/ezetimibe combination versus placebo in the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study. The impact of QRS duration, evaluated as a categorical variable of <85 ms versus 85 to 99 ms and ≥100 ms (excluding bundle branch block [BBB]) and QRS morphology in those with BBB, on cardiovascular morbidity and mortality was assessed by adjusting for clinical and echocardiographic covariates.

Results QRS data were available in 1,542 patients who were followed for a mean of 4.3 ± 0.8 years (6,631 patient-years of follow-up). There were 68 cardiovascular deaths (4.6%), including 27 SCDs (1.8%). QRS duration was <85 ms in 900 patients (58.4%), 85 to 99 ms in 396 (25.7%), ≥100 ms in those without BBB in 144 (9.3%), and 102 (6.6%) in those with BBB. In multivariable analyses, those with QRS duration ≥100 ms had, compared with those with QRS duration <85 ms, a 5-fold higher risk of SCD (95% confidence interval: 1.8 to 13.7, p = 0.002) and a 2.5-fold higher risk of cardiovascular death (95% confidence interval: 1.2 to 5.1, p = 0.01).

Conclusions QRS duration and morphology in asymptomatic patients with AS are independently associated with a poor prognosis, particularly the risk of SCD. (Simvastatin Ezetimibe in Aortic Stenosis [SEAS]; NCT00092677)
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The increased afterload associated with aortic stenosis (AS) initially induces compensatory left ventricular (LV) hypertrophy and ultimately results in impaired LV systolic function as well as symptoms of heart failure (1). The onset of symptoms or LV systolic dysfunction is generally accepted as adverse signs in initially asymptomatic patients with AS and represents guideline criteria for aortic valve replacement (AVR) (2). The annual risk of sudden cardiac death (SCD)

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is ~0.4% per year in patients who have not yet met current criteria for AVR (3). Therefore, predictors of adverse outcome, and in particular SCD, are of special interest in asymptomatic AS because they may lead to a better selection of patients for AVR, perhaps reducing the risk of adverse outcome and prevention of SCD. In this regard, increased QRS duration is appealing because it has been shown to be associated with LV hypertrophy and the risk of congestive heart failure in the general population as well as the risk of SCD in patients with increased afterload due to hypertension or with impaired LV ejection fraction (4–7). Moreover, it is a low-cost, easily obtainable, and reproducible parameter. Several studies have suggested differing etiologies of left bundle branch block (LBBB), which is associated with LV dysfunction, right bundle branch block (RBBB), often in the absence of overt heart disease, and prolonged QRS duration not meeting the criteria for bundle branch block (BBB) (8). However, the association of QRS duration, especially lesser degrees of QRS prolongation (<120 ms), with the risk of adverse outcome, particularly SCD, and the additive value of QRS morphology, in those with BBB, have not been well studied in asymptomatic patients with AS. Thus, the present study investigated whether: 1) QRS duration in patients without BBB is related to the risk of cardiovascular morbidity and mortality, particularly of SCD; and 2) QRS morphology in those with BBB added prognostic information during long-term follow-up in asymptomatic patients with mild to moderate AS and preserved LV systolic function.

Methods

Study population. The SEAS (Simvastatin Ezetimibe in Aortic Stenosis) study was a multicenter, randomized, double-blind, placebo-controlled study investigating whether intensive lipid-lowering with simvastatin/ezetimibe combination compared with placebo could reduce the need for AVR and the risk of cardiovascular morbidity and mortality in 1,873 patients from ages 45 to 85 years with asymptomatic mild to moderate AS (defined as echocardiographic aortic valve thickening accompanied by a Doppler-measured aortic peak flow velocity ≥2.5 and ≤4.0 m/s and normal systolic LV function). The main outcome including study design, organization, clinical measures, exclusion criteria (most important systolic heart failure, diabetes, and known ischemic heart disease), baseline characteristics, and main outcome were published previously (9,10). This study uses pre-specified analyses of prospectively collected data from the SEAS and the SEAS electrocardiographic substudy to investigate whether QRS duration is independently associated with the risk of SCD, overall cardiovascular death, cardiovascular morbidity, AVR, and all-cause mortality in asymptomatic patients with AS. This study complies with the Declaration of Helsinki, and locally appointed ethics committees approved the research protocol, and informed consent was obtained from all participants.

Abbreviations and Acronyms

- **AS** = aortic stenosis
- **AVR** = aortic valve replacement
- **BBB** = bundle branch block
- **CI** = confidence interval
- **HR** = hazard ratio
- **LBBB** = left bundle branch block
- **LV** = left ventricular
- **RBBB** = right bundle branch block
- **SCD** = sudden cardiac death

Electrocardiography. Electrocardiographic study protocol, reading procedures, and reproducibility were published (11). In short, electrocardiograms were recorded at the local study centers at a paper speed of 25 or 50 mm/s, after which they were sent to the central electrocardiogram core laboratory at The Heart Center, Rigshospitalet, Copenhagen, Denmark. A physician, blinded to the randomization and all clinical data, read and transferred all electrocardiograms directly to an electrocardiogram database, using Minnesota codes, in agreement with recent recommendations (12). QRS duration was measured in the lead with the greatest QRS width. Patients were grouped according to: 1) QRS duration <85 ms; 2) QRS duration 85 to 99 ms; 3) QRS duration ≥100 ms (excluding patients with BBB); 4) LBBB; and 5) RBBB with and without left anterior fascicular block.

Echocardiography. The echocardiographic study protocol, reading procedures, and reproducibility were published (13). In short, transthoracic echocardiograms were read blinded at the SEAS echocardiography core laboratory at Haukeland University Hospital in Bergen, Norway. The aortic valve area was calculated using the continuity equation, in accordance with recent recommendations (14). Quantitative echocardiography was performed according to American Society of Echocardiography guidelines (15).

Endpoints. All endpoints were classified by an endpoint committee blinded to a randomization group with a pre-specified endpoint manual prepared by the SEAS steering committee (9). Specific endpoints were: 1) SCD (defined as either witnessed instantaneous unexpected death occurring without preceding symptoms or nonwitnessed unexpected death, if other causes of death were excluded with reasonable certainty [i.e., patients who had known signs, symptoms, or other fatal disease when last observed] or cardiac death occurring <24 h after onset of cardiac symptoms [e.g., acute pulmonary edema or cardiogenic shock]); 2) cardiovascular death (defined as death caused by complications of myocardial infarction, progressive heart failure, cerebrovascular disease, complications of cardiac surgery or intervention, other cardiac or cardiovascular diseases including SCD as defined previously); 3) AVR (defined as AVR as a single operative procedure or performed in combination with other procedures); 4) hospitalization for incident congestive heart failure (excluding patients after AVR, known heart failure, aortic valve area >1.0 cm^2, and/or known heart disease, aside from AS, that could have contributed to the development of heart failure); 5) nonfatal and fatal myocardial infarction (defined as a typical increase and decrease in troponin or creatine kinase–myocardial band