Usefulness of the Electrocardiogram in Predicting Cardiovascular Mortality in Asymptomatic Adults With Aortic Stenosis (from the Simvastatin and Ezetimibe in Aortic Stenosis Study)

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Hypertension and coronary heart disease are common in aortic stenosis (AS) and may impair prognosis for similar AS severity. Different changes in the electrocardiogram may be reflective of the separate impacts of AS, hypertension, and coronary heart disease, which could lead to enhanced risk stratification in AS. The aim of this study was therefore to examine if combining prognostically relevant electrocardiographic (ECG) findings improves prediction of cardiovascular mortality in asymptomatic AS. All patients with baseline electrocardiograms in the SEAS study were included. The primary end point was cardiovascular death. Backward elimination ($p > 0.01$) identified heart rate, Q waves, and Cornell voltage-duration product as independently associated with cardiovascular death. Multivariate logistic and Cox regression models were used to evaluate if these 3 ECG variables improved prediction of cardiovascular death. In 1,473 patients followed for a mean of 4.3 years (6,362 patient-years of follow-up), 70 cardiovascular deaths (5%) occurred. In multivariate analysis, heart rate (hazard ratio [HR] 1.5 per 11.2 minute^{-1} [1 SD], 95% confidence interval [CI] 1.2 to 1.8), sum of Q-wave amplitude (HR 1.3 per 2.0 mm [1 SD], 95% CI 1.1 to 1.6), and Cornell voltage-duration product (HR 1.4 per 763 mm × ms [1 SD], 95% CI 1.2 to 1.7) remained independently associated with cardiovascular death. Combining the prognostic information contained in each of the 3 ECG variables improved integrated discrimination for prediction of cardiovascular death by 2.5%, net reclassification by 14.3%, and area under the curve by 0.06 (all $p \leq 0.04$) beyond other important risk factors. ECG findings add incremental predictive information for cardiovascular mortality in asymptomatic patients with AS. **(Am J Cardiol 2014;114:751−756)**

The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study demonstrated that individual 12-lead electrocardiographic (ECG) findings, such as ECG left ventricular (LV) hypertrophy with ST-T repolarization abnormalities, are independently associated with poor prognosis in asymptomatic aortic stenosis (AS).[1] On the population level, an "abnormal" ECG finding in asymptomatic patients with AS is likely to reflect a composite of AS and frequently coexisting hypertension and/or coronary heart disease, which may or may not be clinically recognized.[2,3] We hypothesized that the separate impacts of AS, hypertension, and coronary heart disease would be conveyed through different changes on the electrocardiogram and that combining prognostically relevant ECG variables may therefore further improve risk stratification of cardiovascular (CV) mortality in asymptomatic AS. The aim of this study was therefore to examine if the combined information contained in separate ECG variables, relating independently to CV mortality, added predictive information of CV mortality beyond that obtained from the individual ECG findings during follow-up of asymptomatic patients with mild-to-moderate AS and preserved LV systolic function.

Methods

The SEAS study (NCT00092677) was a multicenter, randomized, double-blind, placebo-controlled study,

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See page 756 for disclosure information.

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Table 1
Baseline characteristics in relation to observed cardiovascular mortality

Characteristic	All Patients (n = 1,473)	No CV Death (n = 1,403)	CV Death (n = 70)	p-Value
Clinical and biochemistry				
Age (years)	67.3 ± 9.7	67.0 ± 9.6	73.4 ± 8.7	<0.001
Women	573 (39%)	546 (39%)	27 (39%)	0.95
Body mass index (kg/m^2)	27.0 ± 4.4	27.0 ± 4.4	26.7 ± 4.5	0.58
Systolic BP (mm Hg)	145.1 ± 20.1	144.7 ± 20.0	152.8 ± 20.8	<0.001
Diastolic BP (mm Hg)	82.1 ± 10.4	82.0 ± 10.3	84.2 ± 12.1	0.13
LDL cholesterol (mg/dl)	137.3 ± 34.1	137.5 ± 34.0	133.4 ± 35.6	0.33
LDL cholesterol (mmol/l)	3.6 ± 0.9	3.56 ± 0.88	3.45 ± 0.92	—
HDL cholesterol (mg/dl)	58.4 ± 16.8	58.4 ± 16.8	58.8 ± 16.8	0.80
HDL cholesterol (mmol/l)	1.5 ± 0.4	1.51 ± 0.43	1.52 ± 0.45	—
eGFR (ml/min/1.73 m^2)	68.2 ± 12.1	68.4 ± 12.0	64.2 ± 14.8	0.03
12-Lead ECG				
Baseline atrial fibrillation	50 (3%)	45 (3%)	5 (7%)	0.09
T-wave inversion $V_{4–6}$	336 (24%)	312 (23%)	24 (36%)	0.01
Sum T-wave inversion (mm)†	0 (−3.5 to 0)	0 (−3.5 to 0)	−1 (−5.5 to 0)	0.01
ST-depression $V_{4–6}$	241 (17%)	224 (16%)	17 (26%)	0.04
Sum ST-depression (mm)†	0 (0–0)	0 (0–0)	0 (−1.5 to 0)	0.04
Cornell product (mm × ms)†	1600 (1160–2070)	1575 (1160–2040)	1710 (1320–2320)	0.01
$S_{V1} + R_{V5–6}$ (mm)	26.6 ± 9.5	26.5 ± 9.4	27.5 ± 10.4	0.40
Q-wave precordial leads	351 (24%)	330 (24%)	21 (30%)	0.23
Sum Q-wave precordial (mm)†	0 (0–0)	0 (0–0)	0 (0–2)	0.18
Q-wave limb leads	438 (30%)	413 (29%)	25 (36%)	0.26
Sum Q-wave limb (mm)†	0 (0–2)	0 (0–2)	0 (0–3)	0.09
Heart rate (beats/min)	65.1 ± 11.2	64.9 ± 11.0	70.3 ± 12.7	<0.001
Echocardiography				
LVIDD (cm)	5.0 ± 0.6	5.03 ± 0.62	5.12 ± 0.79	0.40
LVIDS (cm)	3.20 ± 0.57	3.19 ± 0.56	3.35 ± 0.68	0.06
LA_S volume/BSA (ml/m^2)†	34.0 (26.2–42.8)	33.9 (26.0–42.4)	34.8 (29.5–54.7)	0.04
LA_D volume/BSA (ml/m^2)†	17.0 (11.6–23.8)	16.8 (11.6–23.7)	19.6 (13.1–31.3)	0.02
Peak aortic jet velocity (m/s)	3.1 ± 0.5	3.08 ± 0.54	3.19 ± 0.55	0.12
AVA/BSA (cm^2/m^2)	0.6 ± 0.2	0.61 ± 0.19	0.56 ± 0.19	0.04
Mean aortic gradient (mm Hg)	22.8 ± 8.8	22.7 ± 8.8	24.9 ± 9.2	0.05
Mitral regurgitation (grade ≥2)	146 (11%)	135 (10%)	11 (17%)	0.08
LV stroke volume (ml)	75.8 ± 17.4	76.1 ± 17.5	70.9 ± 15.0	0.02
LV mass index (g/m^2)	99.5 ± 30.0	98.9 ± 29.3	111.1 ± 40.2	0.02
LV ejection fraction (%)	65.8 ± 8.3	66.0 ± 8.2	63.2 ± 8.9	0.01
Medicine				
Simvastatin/ezetimibe	733 (50%)	701 (50%)	32 (46%)	0.49
RAS inhibitor	600 (41%)	570 (41%)	30 (43%)	0.71
Ca^{2+}-blocker	418 (28%)	394 (28%)	24 (34%)	0.26
β-blocker	738 (50%)	704 (50%)	34 (49%)	0.79
Diuretic	674 (46%)	630 (45%)	44 (63%)	0.003
Aspirin	386 (26%)	365 (26%)	22 (31%)	0.32

BP = blood pressure; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LA_{S-D} = left atrial volume in systole and diastole; LDL = low-density lipoprotein; LV = left ventricular; LVIDD = left ventricular internal end-diastolic diameter; LVIDS = left ventricular internal end-systolic diameter; NA = not applicable.

† Values reflect medians with twenty-fifth to seventy-fifth percentiles and the corresponding p-values results from the Wilcoxon test.

investigating whether intensive lipid lowering with simvastatin and ezetimibe combination versus placebo could reduce the need for aortic valve replacement (AVR) and risk of CV morbidity and mortality in 1,873 patients, aged 45 to 85 years, with asymptomatic mild-to-moderate AS (defined as echocardiographic aortic valve thickening accompanied by Doppler-measured aortic peak flow velocity ≥2.5 and ≤4.0 m/sec and normal systolic LV function). The primary outcome including study design, organization, clinical measurements, exclusion criteria, and baseline characteristics and the main outcome have been published previously.[4,5] This study uses post hoc analysis of SEAS data to test the usefulness of electrocardiography to predict CV mortality during follow-up of initially asymptomatic AS.

ECG study protocol, reading procedures, and reproducibility have been published.[3] In brief, all electrocardiograms were read blinded to the randomization and all clinical data at a central ECG core laboratory. All coded ECG findings (Supplementary Figure 1) on the baseline electrocardiogram (1 electrocardiogram per patient) were entered into a Cox regression model that used backward elimination ($p > 0.01$) to identify the variables that were independently associated with subsequent CV mortality (heart rate at rest; Cornell voltage-duration product; and summed Q-wave amplitude in