Does Sex Modify an Association of Electrophysiological Substrate with Sudden Cardiac Death? The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background—Sex is a well-recognized risk factor for sudden cardiac death (SCD). Sex differences in electrophysiological (EP) substrate of SCD are known. However, it remains unknown whether sex can modify an association of EP substrate with SCD.

Methods—Participants from the Atherosclerosis Risk in Communities study with analyzable ECGs (n=14,725; age, 54.2±5.8 yrs; 55% female, 74% white) were included. EP substrate was characterized by traditional 12-lead ECG (heart rate, QRS, QTc, Cornell voltage), spatial ventricular gradient (SVG) and sum absolute QRST integral (SAI QRST) metrics. Two competing outcomes were adjudicated SCD and nonSCD. Cox proportional hazards and Fine-Gray competing risk models were constructed. Relative hazard ration (RHR) and relative sub-hazard ratio (RSHR) with 95% confidence interval for SCD and nonSCD risk for women relative to men was calculated. Model 1 was adjusted for prevalent cardiovascular disease (CVD) and risk factors. Time-updated model 2 was in addition adjusted for incident non-fatal CVD events.

Results—Over a median follow-up of 24.4 years, there were 530 SCDs (incidence 1.72 (1.58-1.88)/1000 person-years). Women experienced a greater than men risk of SCD associated with QRS duration (RHR 1.24(1.07-1.44); P=0.004) and QTc (RSHR 1.15(1.02-1.30); P=0.025), which was explained by incident CVD. Furthermore, Cornell voltage (RHR 1.18(1.06-1.32); P=0.003), SAI QRST (RHR 1.16(1.04-1.30); P=0.007), area SVG magnitude (RHR 1.24(1.05-1.45); P=0.009), and peak SVG magnitude (RHR 1.22(1.04-1.44); P=0.018) were associated with higher risk of SCD in women than in men, independently from incident CVD.

Conclusions—Sex modifies an association of EP substrate with SCD. In women, global EP substrate is associated with up to 27% greater competing risk of SCD than in men. Development of sex-specific risk scores of SCD is necessary.

Key words: sudden cardiac death, women, sex, ECG, global electrical heterogeneity, SAI QRST, spatial ventricular gradient, QRS-T angle

Introduction

Sudden cardiac death (SCD) is a leading cause of death in the United States with one in approximately every seven people in the United States dying of SCD.[1] Sex is a well-recognized risk factor for SCD. SCD more commonly occurs in men as compared to women.[2] Women have a lower prevalence of obstructive coronary heart disease (CHD) and systolic dysfunction preceding SCD.[3] Women are also less likely than men to receive implantable cardioverter defibrillators (ICD) for primary and secondary prevention of SCD.[4] Women were underrepresented in ICD trials, and, in result, randomized controlled trials (RCTs) did not have sufficient statistical power to detect a significant survival benefit of ICD therapy in women.[5] Moreover, regardless of underlying etiology of heart disease,[6] women with ICDs are less likely to experience ventricular tachyarrhythmias,[6] and receive appropriate ICD therapies,[7, 8] and are more likely to suffer device-related complications.[9] Therefore, SCD risk stratification is especially important for women.

Risk stratification of SCD for both sexes is inadequate and current practice relies on degree of left ventricular (LV) dysfunction.[10] While sex differences in cardiac electrophysiology have been recognized,[11] sex is not routinely considered a potential effect modifier of the association between electrophysiological (EP) substrate and SCD. As women develop CHD approximately 10 years later than men, women are commonly viewed as "younger men".

Widely available routine surface 12-lead electrocardiogram (ECG) describes global characteristics of the EP substrate of SCD.[12] Sex differences in EP substrate are known: women have faster heart rate, narrower QRS and longer QT interval than men.[11] However, it remains unknown whether sex can modify an association of EP substrate with SCD. Recently, we expanded the armamentarium for global ECG measures of EP substrate by adding global

electrical heterogeneity (GEH).[13] GEH is quantified by spatial ventricular gradient (SVG) magnitude and direction (elevation and azimuth), its scalar value sum absolute QRST integral (SAI QRST), and spatial QRS-T angle. The addition of GEH to demographic (age, sex, race) and clinical (diabetes, hypertension, CHD, stroke) risk factors improves reclassification of SCD[13]. However, it remains unknown whether GEH as a measure of independent EP substrate is different in men and women, and whether sex can modify the association of GEH and traditional global ECG measures with SCD. We hypothesized that (1) there are sex differences in GEH, and (2) sex modifies association of traditional and novel global ECG measures of EP substrate with SCD.

Methods

Study population

The Atherosclerosis Risk in Communities (ARIC) study is a prospective cohort that recruited 15,792 men and women, age 45-64 years, selected as a probability sample from four United States communities. Participants were recruited in 1987-1989. Standardized examinations were conducted as previously described.[14] Included in the analysis were ARIC cohort participants with recorded resting 12-lead ECG and measured global electrical heterogeneity (GEH); n=15,777. Excluded were participants self-identifying as non-white or non-black race (n=48), or as black at the Washington County, and Minneapolis field centers (n=55), those with missing covariates (n=903), and non-sinus median beat (n=46). The final sample of participants with normal sinus median beat included 14,725 participants.

Exposures of sex and electrocardiographic global electrical heterogeneity

Resting 12-lead ECGs of the first five study visits were analyzed. Visit 1 was conducted in 1987-1989, visit 2 in 1990-1992, visit 3 in 1993-1995, visit 4 in 1996-1998, and visit 5 in 2011-2013. Traditional ECG amplitudes and intervals were measured by the 12 SL algorithm (GE Marquette Electronics, Milwaukee, WI). Sex-specific Cornell product was calculated to define ECG-left ventricular hypertrophy (LVH)[15].

GEH was measured as previously described,[16] by spatial QRS-T angle, SVG magnitude, azimuth, and elevation, and SAI QRST. The MATLAB (MathWorks, Natick, MA, USA) software code for GEH measurement is provided at Physionet (https://physionet.org/physiotools/geh). Both area and peak SVG vectors[16] and QRS-T angles were included in analysis. Previously reported[13] area-based GEH metrics were used in this study. To measure peak-vector-based GEH metrics, we constructed time-coherent median beat and defined isoelectric heart vector origin point, as described.[17] The MATLAB (MathWorks, Natick, MA, USA) software code for the heart vector origin definition is provided at https://github.com/Tereshchenkolab/Origin. In this study we included only participants with a normal sinus median beat.

Primary outcome: sudden cardiac death

Follow-up of ARIC participants[18] and adjudication of SCD was previously described.[19] Physician-adjudicated SCD was defined as a sudden pulseless condition in a previously stable individual without evidence of a non-cardiac cause of cardiac arrest if the cardiac arrest occurred out of the hospital or in the emergency room. Definite, probable, or possible SCD was included in this study as a primary outcome.

Competing mortality outcome: non-sudden cardiac death

Non-sudden cardiac death (nonSCD) was defined as a composite of fatal CHD, heart failure (HF) death, death in a participant with baseline HF, or incident hospitalized HF. Cases of fatal CHD were adjudicated by the ARIC Morbidity and Mortality Classification Committee.[18, 20] Baseline prevalent HF was defined as a symptomatic HF (stage 3 by the Gothenburg criteria, requiring manifestation of HF cardiac and pulmonary symptoms in addition to medical treatment[21]), or self-reported use of HF medication. Incident HF was defined based on the HF codes in a death certificate or an International Classification of Diseases (*ICD*-9) discharge code, in any position, as previously described.[22] All other deaths comprised the noncardiac death outcome.

Baseline clinical characteristics

Body mass index (BMI) was categorized as underweight (<18.5 kg/m^2), normal weight (18.5 to <25.0 kg/m^2), overweight (25.0 to <30.0 kg/m^2) or obese (≥30.0 kg/m^2). Hypertension was defined as a blood pressure (BP) of ≥140/90 mm Hg, or report of taking antihypertensive medication at visit 1. Diabetes was defined as nonfasting blood glucose ≥200 mg/dL, fasting blood glucose ≥126 mg/dL, self-reported physician diagnosis of diabetes, or reporting taking medication for diabetes or high blood sugar at visit 1. Stages of chronic kidney disease (CKD) were based on estimated glomerular filtration rate (eGFR) calculated using the CKD Epidemiology Collaboration equation (CKD-EPI).[23] Stage 1 CKD included participants with normal or increased kidney function ($eGFR_{CKD\text{-}EPI}$ ≥90 mL/min/1.73 m^2). Stage 2 CKD included mild decreased kidney function ($eGFR_{CKD\text{-}EPI}$ 60 to <90 mL/min/1.73 m^2). Stage 3 CKD included moderate decreased kidney function ($eGFR_{CKD\text{-}EPI}$ 30 to <60 mL/min/1.73 m^2). Stage 4 CKD participants had severe decreased kidney function ($eGFR_{CKD\text{-}EPI}$ 15 to <30 mL/min/1.73 m^2), and

stage 5 CKD was established kidney failure ($eGFR_{CKD\text{-}EPI}$ <15 mL/min/1.73 m^2). Physical activity during leisure time was assessed using the Baecke questionnaire.[24] Postmenopausal status was determined by questionnaire[25] and was defined as either surgical or natural postmenopause, or primary amenorrhea. Prevalent stroke was diagnosed by a stroke and transient ischemic attack diagnostic algorithm, as previously reported[26]. Prevalent CHD was defined as a self-reported physician diagnosis of myocardial infarction (MI), or baseline ECG evidence of MI by the Minnesota code[27], a history of angina pectoris, or a history of coronary revascularization (either via coronary artery bypass surgery or percutaneous coronary intervention). Use of antiarrhythmic drugs included self-reported and validated by medications inventory use of class I, II (beta-blockers), III, IV (phenylalkylamines and benzothiazepines calcium channel blockers), or V (digoxin) antiarrhythmic agents.

Incident non-fatal cardiovascular events

Incident atrial fibrillation (AF) was defined as either detected on follow-up 12-lead ECG, or on hospital discharge records (*ICD-9* code 427.3).[28] Incident stroke was physician-adjudicated, as previously described.[29] Definite or probable incident strokes are included in this study. Expert-adjudicated incident CHD was defined as a definite or probable MI, angina, or a coronary revascularization procedure.[18, 20] Incident HF was defined above.[22]

Statistical analyses

Cross-sectional analyses at the baseline

Normally distributed continuous variables were compared using *t*-test and presented as means ± standard deviation (SD). Chi-square test was used to compare categorical variables.

To determine differences in GEH between men and women, we constructed two linear regression models with sex as a predictor and normally distributed GEH variables (one-by-one)

as an outcome. Model 1 was adjusted for age and combinations of race and study center. To determine whether sex differences in GEH can be explained by sex differences in clinical and traditional ECG characteristics, Model 2 was additionally adjusted for prevalent cardiovascular (CV) disease (HF, CHD, stroke), known CV risk factors (diabetes, hypertension, postmenopausal state in women, current smoking and alcohol intake, leisure physical activity level, levels of total cholesterol, high density lipoprotein, and triglycerides, BMI), use of antihypertensive and antiarrhythmic medications, serum concentrations of sodium, potassium, calcium, magnesium, phosphorus, and uric acid, total protein and albumin, blood urea nitrogen, CKD stage classified by $eGFR_{CKD\text{-}EPI}$, education level, and traditional ECG characteristics [mean heart rate, QRS duration, Bazett-corrected QT interval, Cornell voltage, and sex-specific ECG – LVH].

Analysis of circular variables

Spatial QRS-T angle, SVG azimuth, and SVG elevation are circular variables. By convention, QRS-T and SVG elevation angles can be only positive, ranging from 0 to 180 degrees. Distributions of QRS-T angle and SVG elevation angle were normal or nearly normal. Thus, QRS-T and SVG elevation angles were included in all conventional statistical analyses without transformation. SVG azimuth angle is expressed as an axial variable, ranging from -180º to +180º. As recommended for the circular statistics[30], we transformed SVG azimuth by doubling its value, and then adding 360º. Then we analyzed the SVG azimuth using a conventional statistical approach, and for interpretation we transformed it back.

Survival analyses

For adequate comparison of separate GEH measurements, we assessed the hazard of SCD per 1 SD of continuous GEH variables, one-by-one. Similar models were constructed for traditional global ECG variables, one-by-one: heart rate, QRS duration, QTc, and Cornell voltage. Cox

proportional hazards and Fine-Gray competing risks models were constructed. The proportional-hazards assumption was tested on the basis of Schoenfeld residuals, using *stcox PH-assumptions* suite of tests implemented in STATA (StataCorp LP, College Station, TX). To adjust for possible confounders we constructed 3 models, performed statistical test for interaction with sex in each model, and constructed sex-stratified Cox models for men and women. The proportional-hazards assumption was confirmed for all predictors of interest in most models. Exception were reported. Relative hazard ratio (RHR) with 95% confidence interval (CI) of SCD risk for women relative to men was reported, assuming HR for men is a reference (equal to 1).

Model 1 was adjusted for: age and combinations of race and study center, prevalent HF, CHD, stroke, diabetes, hypertension, postmenopausal state, education level, current smoking, alcohol intake, leisure physical activity level, BMI category, use of antihypertensive and antiarrhythmic medications, levels of total cholesterol, high density lipoprotein (HDL), and triglycerides, serum concentrations of sodium, potassium, calcium, magnesium, phosphorus, and uric acid, total protein and albumin, blood urea nitrogen, CKD stage classified by $eGFR_{CKD\text{-}EPI,}$ and sex-specific ECG-LVH. To avoid collinearity, models for Cornell voltage were not adjusted for ECG-LVH. Associations of continuous ECG variables with SCD were also evaluated using adjusted (model 1) Cox regression models incorporating cubic splines with 4 knots. The positions of the 4 knots in the cubic spline models are reported in Table 1.

To determine whether global ECG measures associate with SCD independently from the dynamic substrate of structural heart disease, time-updated model 2 included time-updated ECG predictors (one-by-one), all baseline covariates included in model 1, and time-updated incident nonfatal CV events (AF, HF, CHD, and stroke).

In addition, to determine whether GEH is associated with SCD independently from time-updated traditional ECG measures, time-updated ECG-adjusted model 3 included time-updated GEH metrics (one-by-one), all four time-updated traditional ECG measurements (heart rate, QTc, QRS, and Cornell voltage), baseline clinical covariates, and time-updated incident nonfatal CV events included in model 2.

To compare competing risk of SCD with competing risk of nonSCD, we constructed two Fine and Gray's competing risks models[31] for SCD and nonSCD outcomes, using the same covariates as described above for Cox models 1 and 2. Relative sub-hazard ratio (RSHR) with 95% CI of SCD risk for women relative to men was reported, assuming SHR for men is a reference.

Statistical analyses were performed using STATA MP 15.1 (StataCorp LP, College Station, TX). Considering the many multivariate analyses performed, statistical significance at the 0.05 level should be interpreted cautiously.

Results

Study population

Women comprised more than half of the study population (Table 2). Greater than a half of the women were postmenopausal. At baseline, women had a lower prevalence of CV disease as compared to men. Men had less favorable lipid profiles, were more likely current smokers and alcohol users, and were less physically active. However, there was similar prevalence of diabetes and hypertension in men and women. There were significant differences in electrolytes and kidney function between men and women (Table 2). Women had a faster heart rate, longer QTc, and a narrower QRS.

Differences in GEH between men and women

In both unadjusted and adjusted analyses, peak QRS-T angle, area QRS-T angle, and SAI QRST were significantly wider in men as compared to women. (Figure 1 and Table 3). In contrast, fully adjusted peak SVG magnitude was significantly larger in women as compared to men (Figure 1G). Sex differences in SVG magnitude were explained by covariates (Figure 1H). SVG vector pointed more upward and forward in men, and the difference in SVG direction not only remained significant after full adjustment but increased up to 15-17 degrees.

EP substrate of sudden cardiac death in men and women in Cox regression analysis

Over a median follow-up of 24.4 years, there were 530 SCDs (incidence 1.72; 95% CI 1.58-1.88 per 1000 person-years), 2,178 nonSCDs (incidence 7.09; 95% CI 6.80-7.39 per 1000 person-years), and 2,535 noncardiac deaths (incidence 8.25; 95%CI 7.93-8.58 per 1000 person-years). Incidence of SCD was higher in men (2.56; 95%CI 2.30-2.84 per 1000 person-years) than in women (1.10; 95%CI 0.95-1.26 per 1000 person-years). Incidence of nonSCD was also higher in men (8.51; 95%CI 8.03-9.03 per 1000 person-years) than in women (6.01; 95%CI 5.66-6.38 per 1000 person-years). Similarly, noncardiac death was also more frequent in men (incidence 10.51; 95% CI 9.97-11.08 per 1000 person-years) than in women (incidence 6.54; 95% CI 6.17-6.93 per 1000 person-years).

In Cox model 1, which adjusted for potential baseline confounders, QRS-T angle, SVG direction, heart rate, and Cornell voltage were associated with SCD (Table 4). Further adjustment for time-updated CHD, HF, AF, and stroke strengthened the association of nearly all ECG metrics with SCD. In Cox model 2, all studied ECG metrics, except SVG magnitude, were associated with SCD (Figure 2).

We observed a statistically significant interaction of sex with SAI QRST, SVG magnitude, and QRS duration (Table 4). In model 1, there was a 19-27% higher risk of SCD in women compared to men, per one SD of SVG magnitude, SAI QRST, and QRS duration (Figure 3). Adjustment for incident nonfatal CV events in model 2 further strengthened the interaction of sex with SVG magnitude and revealed significant interaction with Cornell voltage. However, model 2 attenuated the interaction with SAI QRST and wiped out the interaction with QRS duration.

Sex-stratified Cox models confirmed significant association of traditional and novel global ECG and VCG metrics with SCD (Table 4 and Figure 4). Larger SVG magnitude pointed towards higher risk of SCD in women. In contrast, a larger SVG magnitude trended towards lower risk of SCD in men. The strength of association of SVG magnitude with SCD did not reach statistical significance, but opposite trends were clearly seen (Figures 2H and 4). After full adjustment for incident nonfatal CV disease, there was a 24% increase SCD risk in women versus 10% in men with one SD increase in Cornell voltage. Similarly, there was a 19% increase in SCD risk in women versus 9% in men with one SD of SAI QRST.

Interaction of SVG magnitude and SAI QRST with sex remained significant after further adjustment for time-updated traditional ECG metrics (heart rate, QTc, QRS, and Cornell voltage) in model 3. In women, greater SVG magnitude was associated with higher risk of SCD, whereas in men, bigger SVG magnitude and SAI QRST tended to be protective (Table 4).

Competing risks of SCD and nonSCD

In a competing risk model 1, which adjusted for baseline confounders, one SD increase in spatial QRS-T angle or SVG direction (azimuth and elevation) was associated with a 10-19%

increase in competing risk of SCD (Table 5 and Figures 5-6). Traditional ECG metrics were not associated with SCD in the competing risks analysis.

Competing risk model 2, which adjusted for dynamic substrate of structural heart disease (incident CHD, HF, stroke, AF) only slightly attenuated the association of QRS-T angle, SVG elevation and SVG azimuth with competing risk of SCD. In addition, model 2 revealed a significant association between QRS duration with competing risk of SCD, suggesting interaction of QRS duration with structural heart disease substrate.

In competing risk model 1, heart rate and QTc demonstrated the strongest association with nonSCD (18-20% per one SD), whereas Cornell voltage was associated with increased competing risk of nonSCD by 10%. For QRS-T angle, the strength of association with competing risk of nonSCD was weaker (12-15%) than the association with SCD (17-19%). SVG magnitude was significantly inversely associated with competing risk of nonSCD: greater SVG magnitude was associated with lower competing risk of nonSCD (Table 6 and Figure 6).

Incident nonfatal CV events explained the association of QTc and Cornell voltage with competing risk of nonSCD, whereas heart rate remained independently associated with nonSCD even after adjustment in model 2. Of note, association of QRS-T angle with nonSCD reversed after adjustment in model 2, suggesting possible interaction of dynamic CV disease substrate with QRS-T angle. Similarly, model 2 revealed inverse associations between SAI QRST and QRS duration with nonSCD: greater SAI QRST and QRS duration were associated with lower competing risk of nonSCD (Table 6 and Figure 6).

Relative competing risk of SCD and nonSCD in women as compared to men

In competing risk model 1, a statistically significant interaction of sex with competing risk of SCD was observed for QTc, QRS duration, and SAI QRST. Women experienced greater

competing risk of SCD as compared to men: by 27% per SD of QRS duration, 16% per SD of SAI QRST, and 15% per SD of QTc interval.

Adjustment for dynamic CV disease substrate eliminated the interaction with QTc and QRS duration, suggesting that sex differences in SCD risk conveyed by QTc and QRS duration were explained by sex differences in structural heart disease substrate. Model 2, however, revealed significant interaction of sex with SVG magnitude and Cornell voltage, in addition to interaction with SAI QRST. After full adjustment for incident CV events, SVG magnitude, SAI QRST, and Cornell voltage were associated with 16-23% higher competing risk of SCD in women as compared to men (Table 5 and Figure 5).

Interaction was also observed for competing risk of nonSCD, albeit it to a lesser magnitude. In model 1, one SD of SVG magnitude, SAI QRST and Cornell voltage was associated with 11-16% greater competing risk of nonSCD in women as compared to men. Of note, in women, QTc was associated with a smaller risk of nonSCD than in men. However, further adjustment for incident CV events eliminated interaction for QTc, SVG magnitude, SAI QRST and Cornell voltage. This suggests that sex differences in the risk of nonSCD as conveyed by voltage-based ECG metrics and QTc were explained by incident nonfatal CV disease events. In addition, model 2 revealed that peak QRS-T angle was associated with 10% greater competing risk of nonSCD for women than for men, which was independent of incident CV events.

In sex-stratified analyses (Figure 6), in adjusted for baseline confounders model 1, QTc, QRS, and SAI QRST were associated with increased competing risk of SCD by 18-26% in women only. In men only, QTc was associated with increased competing risk of nonSCD, by 22% per one SD. In men, but not in women, smaller peak SVG magnitude was associated with increased competing risk of nonSCD.

When adjusted for dynamic CV disease substrate in model 2, women with larger SAI QRST, QRS duration, SVG magnitude, and Cornell voltage were associated with increased competing risk of SCD. Conversely, smaller SAI QRST, QRS duration, SVG magnitude, and Cornell voltage were associated with increased competing risk of nonSCD (Table 6 and Figure 6). In women, spatial QRS-T angle was associated with competing risk of SCD, but not nonSCD. In men, wider QRS-T angle was associated with increased competing risk of SCD, but narrower QRS-T angle was associated with increased competing risk of nonSCD.

Across all comparisons and models, peak-based and area-based GEH metrics displayed consistent results, reassuring robustness of analyses.

Discussion

Our study of a large, community-based prospective cohort of over 14,000 participants with greater than 24 years median follow up showed that sex is a significant modifier with respect to the association of EP substrate with SCD. In women, global EP substrate (heart rate, QTc, QRS duration, Cornell voltage, SAI QRST, and SVG magnitude) was associated with up to 27% greater competing risk of SCD than in men. Our findings have important clinical implications: development of sex-specific risk score of SCD is necessary and the addition of global EP substrate metrics in the risk prediction model for women is warranted. Further studies of mechanisms behind global EP substrate in men and women are needed for the development of sex-specific prevention of SCD. Theoretically, there are two major groups of mechanisms behind the observed effect modification: differences in the cardiac electrophysiologic substrate between men and women, and differences in structural heart disease substrate.

Why EP substrate is associated with greater risk of SCD in women? EP hypothesis.

Our study showed that after rigorous adjustment for baseline demographic and clinical risk factors of SCD, including prevalent CV disease and its risk factors, postmenopausal state, serum concentrations of electrolytes and degree of CKD, several traditional ECG metrics (heart rate, QTc and QRS duration), Cornell voltage, and voltage-based GEH metrics (SAI QRST and SVG magnitude) were associated with competing risk of SCD in women, but not in men. We observed that in men, EP substrate was explained by an underlying CV disease, whereas in women, EP substrate conveyed the additional risk of SCD, beyond the risk carried by the prevalent CV disease and its risk factors.

Our study showed that in women, QTc is associated with competing risk of SCD, whereas in men, QTc is associated with competing risk of nonSCD (Figure 6). While QT prolongation is a known risk marker of torsades de pointes (TdP) in congenital long QT syndrome,[32] in other populations, the association of QT interval with SCD was shown in some, [33, 34] but not other studies.[35, 36] One possible reason for controversy around the association of QTc with SCD can be explained by differences in the proportion and clinical characteristics of women enrolled in previous studies. No prior studies tested statistical interaction of sex with QTc after extensive adjustment for confounders. Consistently with our findings, the Rotterdam study showed an association of QT prolongation with SCD only in the absence of cardiac dysfunction (defined as prevalent symptomatic HF or left ventricular ejection fraction (LVEF) < 40%), whereas, in patients with systolic HF, risk of SCD was independent of QT prolongation.[33] Similarly, OregonSUDS study reported the stronger association of QTc prolongation with SCD in diabetes-free individuals as compared to those with diabetes.[37] Women have a longer QT interval due to reduced expression of potassium channels, resulting in decreased rapid and slow delayed rectifier

K^+ currents, inward rectifier current, and transient outward current.[38, 39] Estrogens inhibit the rapid delayed rectifier current, increase the L-type calcium current, the sodium calcium exchange current, and calcium release mediated by the ryanodine receptor, which can predispose to triggered activity.[40, 41] Two-thirds of the drug-induced TdP cases occur in women.[42] Thus, in women, QTc carries additional risk of SCD due to sex-specific EP mechanisms, independent of common for men and women CV disease substrate.

Similarly to QTc, we showed that in women, QRS duration is associated with competing risk of SCD, whereas in men, QRS duration is associated with competing risk of nonSCD (Figure 6). Existing literature on the association between QRS duration and SCD is inconsistent, likely owing at least in part to the study populations having very few women (1-16%) and majority of analyses lacking stratification by sex.[43-45] Our study showed that sex differences in SCD risk conveyed by QRS duration were largely explained by sex differences in dynamic structural heart disease substrate (incident CV events). Possibly similar mechanisms are responsible for greater benefit of cardiac resynchronization therapy in women, which remain incompletely understood.[11]

In this study, resting heart rate was associated with competing risk of SCD in women, but not in men (Figure 6). Association of a resting heart rate with SCD in women was independent of incident CV events, supporting previous OregonSUDS findings.[46] Women have faster resting heart rate[11] mostly because of smaller LV mass and volume, resulting in lesser exercise capacity in women than in men.[47] Exercise capacity is associated with cardiac arrhythmias.[48] Our results suggest that lesser exercise capacity in women, manifesting by faster resting heart rate, translates into the stronger association of heart rate with SCD in women, which is independent of the development of CV disease.

The most remarkable difference in the risk of SCD between men and women was conveyed by amplitude-based ECG metrics: Cornell voltage, SAI QRST, and SVG magnitude. Importantly, the interaction of sex with amplitude-based ECG metrics was independent not only from baseline CV disease and risk factors but also from incident CV events. Equally importantly, such interaction with sex was observed only for competing risk of SCD, but not for a nonSCD. We observed that Cornell voltage was associated with 23% higher competing risk of SCD in women as compared to men. Our finding is consistent with a recent autopsy SCD study in the Finnish population, which observed ECG-LVH more commonly in female than male SCD victims.[49]

We observed that the magnitude of SVG (expressed either as SVG vector magnitude, or SVG's scalar, SAI QRST) was associated with 16-21% higher competing risk of SCD in women as compared to men. A recent Finnish study demonstrated results consistent with our findings of sex differences in SAI QRST and its association with fatal CV disease,[50] although it did not specifically include SCD. The magnitude of SVG and SAI QRST are global measures of the dispersion of total recovery time in the heart, encompassing dispersion of activation and refractoriness.[51] Women have greater asymmetry in potassium channel expression between left and right ventricles, which can explain greater dispersion of global recovery time in women than in men.[52, 53] In a recent genome-wide association study, SAI QRST and SVG magnitude were associated with genetic polymorphisms tagging *HAND1* and *TBX3* genes, involving mechanisms of left to right asymmetry in the heart.[54] Therefore, SVG magnitude and SAI QRST can reflect inherited differences in cardiac electrophysiology between men and women, which are responsible for greater degree of the dispersion of activation and recovery in female heart,

manifesting by stronger association of SAI QRST and SVG magnitude with SCD in women than in men.

Sex differences in structural heart disease substrate.

In this study, incident non-fatal CV events explained the stronger association of QTc and QRS duration with competing risk of SCD in women, as compared to men. On another hand, sex did not modify the association of studied ECG features with nonSCD. This finding is in accord with known differences in structural heart disease between men and women. In spite of less frequent obstructive CHD, women with angina or myocardial infarction have greater cardiac mortality than men.[55, 56] Women have different coronary microvasculature and greater arteriolar wall thickness than men.[57] On the other hand, men are more likely to develop cardiac amyloidosis (manifesting by small ECG voltage), and subsequently HF.[58] Thus, in women, QTc and QRS duration reflect an underlying structural heart disease with greater than in men risk of proarrhythmia, whereas, in men, QTc and QRS duration reflect an underlying structural heart disease leading to pump failure and eventually, more likely to nonSCD.

Differences in GEH between men and women

Consistently with previous studies in healthy young individuals[59, 60] and young athletes[16], we observed wider QRS-T angle, larger SAI QRST, and SVG vector pointing more upward and forward in middle-aged men than in middle-aged women. Of note, our study for the first time revealed that differences in SVG magnitude between men and women are explained by differences in body size, and other clinical characteristics, both cardiac and non-cardiac. This finding suggests that fundamentally, there is no difference in the magnitude of ventricular gradient, or the difference between the longest and the shortest action potential duration between male and female heart.

Clinical implications of greater risk of SCD associated with global EP substrate in women

We observed the significantly stronger association of several ECG metrics of underlying EP substrate (heart rate, QTc, QRS duration, Cornell voltage, SAI QRST, and SVG magnitude) with SCD in women than in men. Therefore, the addition of these ECG metrics in the risk prediction model for women is warranted, for the development of sex-specific risk score of SCD in women. Our results indicate that significant improvement in SCD risk prediction in women can be made. Improvement of SCD risk stratification is especially important for women considering primary prevention ICD.[5] Further studies of sex-specific EP substrate in men and women are needed for the development of future therapies.

Strengths and Limitations

This is a large community-based prospective cohort study with long-term follow-up, well-adjudicated SCD, and approximately equal representation of men and women, providing unique opportunity to study sex exposure as an effect modifier. The well-characterized population of the ARIC study allowed us to perform comprehensive adjustment for confounders, including post-menopausal state, electrolytes, and kidney function, accounting for important non-cardiac differences between men and women. However, limitations of the study have to be taken into account. The study population was predominantly white; only 26% of the study participants were black. Validation of the study finding in a multiracial population is needed. Due to the lack of information on LVEF for most of the study participants, we did not adjust our analyses for LVEF. Nevertheless, as our previous analyses results[13] did not change after adjustment for LVEF, the probability of different study results after LVEF adjustment in this study is very low.

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Disclosures

None.

References

1. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS, Virani SS, American Heart Association Council on Epidemiology, Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation*. 2019;139:e56-e528.

2. Chugh SS, Jui J, Gunson K, Stecker EC, John BT, Thompson B, Ilias N, Vickers C, Dogra V, Daya M, Kron J, Zheng ZJ, Mensah G and McAnulty J. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. *J Am Coll Cardiol*. 2004;44:1268-75.

3. Chugh SS, Uy-Evanado A, Teodorescu C, Reinier K, Mariani R, Gunson K and Jui J. Women have a lower prevalence of structural heart disease as a precursor to sudden cardiac arrest: The Ore-SUDS (Oregon Sudden Unexpected Death Study). *J Am Coll Cardiol*. 2009;54:2006-11.

4. Curtis LH, Al-Khatib SM, Shea AM, Hammill BG, Hernandez AF and Schulman KA. Sex differences in the use of implantable cardioverter-defibrillators for primary and secondary prevention of sudden cardiac death. *JAMA*. 2007;298:1517-24.

5. Ghanbari H, Dalloul G, Hasan R, Daccarett M, Saba S, David S and Machado C. Effectiveness of implantable cardioverter-defibrillators for the primary prevention of sudden cardiac death in women with advanced heart failure: a meta-analysis of randomized controlled trials. *ArchInternMed*. 2009;169:1500-1506.

6. Tompkins CM, Kutyifa V, Arshad A, McNitt S, Polonsky B, Wang PJ, Moss AJ and Zareba W. Sex Differences in Device Therapies for Ventricular Arrhythmias or Death in the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) Trial. *J Cardiovasc Electrophysiol*. 2015;26:862-871.

7. MacFadden DR, Crystal E, Krahn AD, Mangat I, Healey JS, Dorian P, Birnie D, Simpson CS, Khaykin Y, Pinter A, Nanthakumar K, Calzavara AJ, Austin PC, Tu JV and Lee DS. Sex differences in implantable cardioverter-defibrillator outcomes: findings from a prospective defibrillator database. *Ann Intern Med*. 2012;156:195-203.

8. Conen D, Arendacka B, Rover C, Bergau L, Munoz P, Wijers S, Sticherling C, Zabel M and Friede T. Gender Differences in Appropriate Shocks and Mortality among Patients with Primary Prophylactic Implantable Cardioverter-Defibrillators: Systematic Review and Meta-Analysis. *PLoS One*. 2016;11:e0162756.

9. Russo AM, Daugherty SL, Masoudi FA, Wang Y, Curtis J and Lampert R. Gender and outcomes after primary prevention implantable cardioverter-defibrillator implantation: Findings from the National Cardiovascular Data Registry (NCDR). *American Heart Journal*. 2015;170:330-338.

10. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Granger CB, Hammill SC, Hlatky MA, Joglar JA, Kay GN, Matlock DD, Myerburg RJ and Page RL. 2017 AHA/ACC/HRS guideline

for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Executive summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm*. 2018;15:e190-e252.

11. Gillis AM. Atrial Fibrillation and Ventricular Arrhythmias: Sex Differences in Electrophysiology, Epidemiology, Clinical Presentation, and Clinical Outcomes. *Circulation*. 2017;135:593-608.

12. Tereshchenko LG. Electrocardiogram as a screening tool in the general population: A strategic review. *Journal of Electrocardiology*. 2013;46:553-556.

13. Waks JW, Sitlani CM, Soliman EZ, Kabir M, Ghafoori E, Biggs ML, Henrikson CA, Sotoodehnia N, Biering-Sorensen T, Agarwal SK, Siscovick DS, Post WS, Solomon SD, Buxton AE, Josephson ME and Tereshchenko LG. Global Electric Heterogeneity Risk Score for Prediction of Sudden Cardiac Death in the General Population: The Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) Studies. *Circulation*. 2016;133:2222-34.

14. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol*. 1989;129:687-702.

15. Molloy TJ, Okin PM, Devereux RB and Kligfield P. Electrocardiographic detection of left ventricular hypertrophy by the simple QRS voltage-duration product. *Journal of the American College of Cardiology*. 1992;20:1180-6.

16. Thomas JA, E AP-A, Junell A, Newton K, Hamilton C, Li-Pershing Y, German D, Bender A and Tereshchenko LG. Vectorcardiogram in athletes: The Sun Valley Ski Study. *Ann Noninvasive Electrocardiol*. 2019;24:e12614.

17. Perez-Alday EA, Li-Pershing Y, Bender A, Hamilton C, Thomas JA, Johnson K, Lee TL, Gonzales R, Li A, Newton K and Tereshchenko LG. Importance of the heart vector origin point definition for an ECG analysis: The Atherosclerosis Risk in Communities (ARIC) study. *Comput Biol Med*. 2019;104:127-138.

18. White AD, Folsom AR, Chambless LE, Sharret AR, Yang K, Conwill D, Higgins M, Williams OD and Tyroler HA. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. *Journal of clinical epidemiology*. 1996;49:223-33.

19. O'Neal WT, Singleton MJ, Roberts JD, Tereshchenko LG, Sotoodehnia N, Chen LY, Marcus GM and Soliman EZ. Association Between QT-Interval Components and Sudden Cardiac Death: The ARIC Study (Atherosclerosis Risk in Communities). *Circ Arrhythm Electrophysiol*. 2017;10.

20. Luepker RV, Apple FS, Christenson RH, Crow RS, Fortmann SP, Goff D, Goldberg RJ, Hand MM, Jaffe AS, Julian DG, Levy D, Manolio T, Mendis S, Mensah G, Pajak A, Prineas RJ, Reddy KS, Roger VL, Rosamond WD, Shahar E, Sharrett AR, Sorlie P and Tunstall-Pedoe H. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation*. 2003;108:2543-2549.

21. Eriksson H, Caidahl K, Larsson B, Ohlson LO, Welin L, Wilhelmsen L and Svardsudd K. Cardiac and pulmonary causes of dyspnoea--validation of a scoring test for clinical-epidemiological use: the Study of Men Born in 1913. *Eur Heart J*. 1987;8:1007-14.

22. Loehr LR, Rosamond WD, Chang PP, Folsom AR and Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). *Am J Cardiol*. 2008;101:1016-1022.

23. Matsushita K, Selvin E, Bash LD, Astor BC and Coresh J. Risk implications of the new CKD Epidemiology Collaboration (CKD-EPI) equation compared with the MDRD Study equation for estimated GFR: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis*. 2010;55:648-659.

24. Richardson MT, Ainsworth BE, Wu HC, Jacobs DR, Jr. and Leon AS. Ability of the Atherosclerosis Risk in Communities (ARIC)/Baecke Questionnaire to assess leisure-time physical activity. *Int J Epidemiol*. 1995;24:685-93.

25. Nabulsi AA, Folsom AR, Szklo M, White A, Higgins M and Heiss G. No association of menopause and hormone replacement therapy with carotid artery intima-media thickness. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Circulation*. 1996;94:1857-63.

26. Toole JF, Chambless LE, Heiss G, Tyroler HA and Paton CC. Prevalence of stroke and transient ischemic attacks in the atherosclerosis risk in communities (ARIC) study. *Annals of Epidemiology*. 1993;3:500-503.

27. Blackburn H, Keys A, Simonson E, Rautaharju P and Punsar S. The electrocardiogram in population studies. A classification system. *Circulation*. 1960;21:1160-1175.

28. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ and Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J*. 2009;158:111-7.

29. Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G, Copper LS and Shahar E. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. *Stroke*. 1999;30:736-743.

30. Cox NJ. Speaking Stata: In Praise of Trigonometric Predictors. *The Stata Journal*. 2006;6:561-579.

31. Fine JP and Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association*. 1999;94:496-509.

32. Jervell A and Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval and sudden death. *Am Heart J*. 1957;54:59-68.

33. Algra A, Tijssen JG, Roelandt JR, Pool J and Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. *Circulation*. 1991;83:1888-94.

34. Straus SM, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, Deckers JW, Kingma JH, Sturkenboom MC, Stricker BH and Witteman JC. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol*. 2006;47:362-7.

35. Surawicz B and Knoebel SB. Long QT: good, bad or indifferent? *J Am Coll Cardiol*. 1984;4:398-413.

36. Goldberg RJ, Bengtson J, Chen ZY, Anderson KM, Locati E and Levy D. Duration of the QT interval and total and cardiovascular mortality in healthy persons (The Framingham Heart Study experience). *Am J Cardiol*. 1991;67:55-8.

37. Chugh SS, Reinier K, Singh T, Uy-Evanado A, Socoteanu C, Peters D, Mariani R, Gunson K and Jui J. Determinants of prolonged QT interval and their contribution to sudden

death risk in coronary artery disease: the Oregon Sudden Unexpected Death Study. *Circulation*. 2009;119:663-670.

38. Gaborit N, Varro A, Le Bouter S, Szuts V, Escande D, Nattel S and Demolombe S. Gender-related differences in ion-channel and transporter subunit expression in non-diseased human hearts. *J Mol Cell Cardiol*. 2010;49:639-46.

39. Tadros R, Ton A-T, Fiset C and Nattel S. Sex Differences in Cardiac Electrophysiology and Clinical Arrhythmias: Epidemiology, Therapeutics, and Mechanisms. *Canadian Journal of Cardiology*. 2014;30:783-792.

40. Kurokawa J, Kodama M, Clancy CE and Furukawa T. Sex hormonal regulation of cardiac ion channels in drug-induced QT syndromes. *Pharmacol Ther*. 2016;168:23-28.

41. Odening KE and Koren G. How do sex hormones modify arrhythmogenesis in long QT syndrome? Sex hormone effects on arrhythmogenic substrate and triggered activity. *Heart Rhythm*. 2014;11:2107-15.

42. Drici MD and Clement N. Is gender a risk factor for adverse drug reactions? The example of drug-induced long QT syndrome. *Drug Saf*. 2001;24:575-85.

43. Dhar R, Alsheikh-Ali AA, Estes NA, 3rd, Moss AJ, Zareba W, Daubert JP, Greenberg H, Case RB and Kent DM. Association of prolonged QRS duration with ventricular tachyarrhythmias and sudden cardiac death in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II). *Heart Rhythm*. 2008;5:807-13.

44. Zimetbaum PJ, Buxton AE, Batsford W, Fisher JD, Hafley GE, Lee KL, O'Toole MF, Page RL, Reynolds M and Josephson ME. Electrocardiographic predictors of arrhythmic death and total mortality in the multicenter unsustained tachycardia trial. *Circulation*. 2004;110:766-9.

45. Iuliano S, Fisher SG, Karasik PE, Fletcher RD and Singh SN. QRS duration and mortality in patients with congestive heart failure. *Am Heart J*. 2002;143:1085-91.

46. Teodorescu C, Reinier K, Uy-Evanado A, Gunson K, Jui J and Chugh SS. Resting heart rate and risk of sudden cardiac death in the general population: influence of left ventricular systolic dysfunction and heart rate-modulating drugs. *Heart Rhythm*. 2013;10:1153-8.

47. Burke JH, Goldberger JJ, Ehlert FA, Kruse JT, Parker MA and Kadish AH. Gender differences in heart rate before and after autonomic blockade: Evidence against an intrinsic gender effect. *The American Journal of Medicine*. 1996;100:537-543.

48. Andersen K, Rasmussen F, Held C, Neovius M, Tynelius P and Sundstrom J. Exercise capacity and muscle strength and risk of vascular disease and arrhythmia in 1.1 million young Swedish men: cohort study. *Bmj*. 2015;351:h4543.

49. Haukilahti MAE, Holmstrom L, Vahatalo J, Kentta T, Tikkanen J, Pakanen L, Kortelainen ML, Perkiomaki J, Huikuri H, Myerburg RJ and Junttila MJ. Sudden Cardiac Death in Women. *Circulation*. 2019;139:1012-1021.

50. Lipponen JA, Kurl S and Laukkanen JA. Global electrical heterogeneity as a predictor of cardiovascular mortality in men and women. *Europace*. 2018;20:1841-1848.

51. Waks JW and Tereshchenko LG. Global electrical heterogeneity: A review of the spatial ventricular gradient. *J Electrocardiol*. 2016;49:824-830.

52. Kelly RG, Lemonnier M, Zaffran S, Munk A and Buckingham ME. Cell history determines the maintenance of transcriptional differences between left and right ventricular cardiomyocytes in the developing mouse heart. *Journal of cell science*. 2003;116:5005-13.

53. Schram G, Pourrier M, Melnyk P and Nattel S. Differential distribution of cardiac ion channel expression as a basis for regional specialization in electrical function. *Circ Res*. 2002;90:939-50.

54. Tereshchenko LG, Sotoodehnia N, Sitlani CM, Ashar FN, Kabir M, Biggs ML, Morley MP, Waks JW, Soliman EZ, Buxton AE, Biering-Sorensen T, Solomon SD, Post WS, Cappola TP, Siscovick DS and Arking DE. Genome-Wide Associations of Global Electrical Heterogeneity ECG Phenotype: The ARIC (Atherosclerosis Risk in Communities) Study and CHS (Cardiovascular Health Study). *J Am Heart Assoc*. 2018;7:e008160.

55. Hemingway H, McCallum A, Shipley M, Manderbacka K, Martikainen P and Keskimaki I. Incidence and prognostic implications of stable angina pectoris among women and men. *JAMA*. 2006;295:1404-11.

56. Simon T, Mary-Krause M, Cambou JP, Hanania G, Gueret P, Lablanche JM, Blanchard D, Genes N, Danchin N and Investigators U. Impact of age and gender on in-hospital and late mortality after acute myocardial infarction: increased early risk in younger women: results from the French nation-wide USIC registries. *Eur Heart J*. 2006;27:1282-8.

57. Campbell DJ, Somaratne JB, Jenkins AJ, Prior DL, Yii M, Kenny JF, Newcomb AE, Kelly DJ and Black MJ. Differences in myocardial structure and coronary microvasculature between men and women with coronary artery disease. *Hypertension*. 2011;57:186-92.

58. Connors LH, Sam F, Skinner M, Salinaro F, Sun F, Ruberg FL, Berk JL and Seldin DC. Heart Failure Resulting From Age-Related Cardiac Amyloid Disease Associated With Wild-Type Transthyretin: A Prospective, Observational Cohort Study. *Circulation*. 2016;133:282-290.

59. Sur S, Han L and Tereshchenko LG. Comparison of sum absolute QRST integral, and temporal variability in depolarization and repolarization, measured by dynamic vectorcardiography approach, in healthy men and women. *PLoS One*. 2013;8:e57175.

60. Scherptong RW, Henkens IR, Man SC, Le Cessie S, Vliegen HW, Draisma HH, Maan AC, Schalij MJ and Swenne CA. Normal limits of the spatial QRS-T angle and ventricular gradient in 12-lead electrocardiograms of young adults: dependence on sex and heart rate. *J Electrocardiol*. 2008;41:648-55.

Table 1. The positions of knots in the cubic spline models

	Men (n=6,601)				Women(n=8,124)			
ECG metric	Knot #1	Knot#2	Knot#3	Knot#4	Knot #1	Knot#2	Knot#3	Knot#4
Peak QRS-T angle, º	12.5	33.4	53.2	138.0	8.9	25.6	40.7	110.2
Area QRS-T angle, º	28.0	57.2	77.8	122.3	18.1	42.3	60.5	102.3
Peak SVG elevation, º	41.7	61.4	71.5	92.3	38.3	55.8	65.7	82.4
Area SVG elevation, º	44.1	62.3	74.5	104.9	42.5	58.6	69.7	93.2
Peak SVG azimuth, º	-55.7	-11.4	1.8	69.8	-19.6	-1.6	9.6	42.3
Area SVG azimuth, º	-18.8	12.6	30.6	65.1	-6.2	18.4	33.9	61.8
SAI QRST, mV*ms	92.2	135.4	171.0	257.5	79.2	110.8	135.5	195.2
Peak SVG magnitude, µV	919	1432	1764	2404	957	1407	1723	2332
SVG magnitude, µV	988	1517	1898	2676	1012	1484	1820	2473

Table 2. Comparison of baseline clinical characteristics in men and women

Characteristics	Men (n=6,601)	Women(n=8,124)	P-value
Age(SD), y	54.6(5.8)	53.8(5.7)	<0.0001
White, n(%)	5,229(78.1)	5,886(71.4)	<0.0001
Postmenopause, n(% of women)	n/a	4,834(59.5)	n/a
Heart Failure, n(%)	204(3.1)	475(5.9)	<0.0001
Coronary heart disease, n(%)	528(8.0)	169(2.1)	<0.0001
Stroke, n(%)	142(2.2)	107(1.3)	<0.0001
Body mass index(SD), kg/m^2	27.5(4.2)	27.8(6.1)	0.0002
Diabetes, n(%)	784(12.0)	948(11.7)	0.697
Hypertension, n(%)	2,227(33.7)	2,811(34.6)	0.272
Antihypertensive drugs, n(%)	1,782(27.0)	2,664(32.8)	<0.0001
Current tobacco smoker, n(%)	1,809(27.4)	2,020(24.9)	<0.0001
Current alcohol drinker, n(%)	4,282(64.9)	4,010(49.4)	<0.0001
Leasure physical activity score(SD)	2.34(0.56)	2.38(0.59)	0.0001
Education less than high school, n(%)	1,543(23.4)	1,863(22.9)	0.526
Total cholesterol(SD), mmol/L	5.46(1.03)	5.64(1.12)	<0.0001
HDL cholesterol(SD), mg/dL	44.3(13.8)	57.6(17.3)	<0.0001
Triglycerides(SD), mmol/L	1.60(1.13)	1.39(0.92)	<0.0001
Sodium(SD), mmol/L	140.8(2.4)	141.0(2.5)	<0.0001
Potassium(SD), mmol/L	4.49(0.46)	4.37(0.49)	<0.0001
Calcium(SD), mg/dL	9.76(0.42)	9.81(0.44)	<0.0001
Magnesium(SD), mEq/L	1.64(0.16)	1.63(0.16)	<0.0001
Phosphorus(SD), mg/dL	3.26(0.46)	3.57(0.48)	<0.0001
Total protein(SD), mg/dL	7.27(0.44)	7.28(0.46)	0.024
Albumin(SD), mg/dL	3.92(0.26)	3.83(0.27)	<0.0001
Blood urea nitrogen(SD), mg/dL	16.1(4.3)	14.5(4.3)	<0.0001
Chronic kidney disease stage≥2, n(%)	2,310(35.0)	2,2474(27.7)	<0.0001
Uric acid(SD), mg/dL	6.73(1.42)	5.48(1.43)	<0.0001
Use of antiarrhythmic drugs, n(%)	1,006(15.2)	1,043(12.8)	<0.0001
Heart rate(SD), bpm	64.6(10.2)	67.5(10.0)	<0.0001
QRS duration(SD), ms	96.9(12.5)	88.4(10.7)	<0.0001
QTc(SD), ms	411.6(17.0)	420.0(20.0)	<0.0001
Cornell voltage(SD), μV	1,403(588)	1,103(495)	<0.0001
Sex-specific ECG-LVH, n(%)	423(6.4)	419(5.2)	0.001

HDL=High-density lipoprotein; SD=standard deviation

Table 3. Difference in GEH variables in women as compared to men

GEH characteristic	Model 1		Model 2	
	Difference (95%CI)	P-value	Difference (95%CI)	P-value
Peak QRS-T angle, º	-12.1(-13.1 to -11.0)	<0.0001	-8.2(-10.7 to -5.7)	<0.0001
Area QRS-T angle, º	-15.5(-16.4 to -14.6)	<0.0001	-9.5(-11.6 to -7.5)	<0.0001
Peak SVG elevation, º	-5.95(-6.43 to -5.46)	<0.0001	-2.33(-3.43 to -1.22)	<0.0001
Area SVG elevation, º	-5.01(-5.56 to -4.46)	<0.0001	-3.42(-4.74 to -2.10)	<0.0001
Peak SVG azimuth, º	+11.27(+9.65to +12.88)	<0.0001	+13.58(+9.72 to +17.44)	<0.0001
Area SVG azimuth, º	+8.94(+7.32 to +10.57)	<0.0001	+11.95(+8.16 to+15.74)	<0.0001
SAI QRST, mV*ms	-33.6(-35.1 to -32.0)	<0.0001	-12.1(-15.4 to -8.8)	<0.0001
Peak SVG magnitude, µV	-51.6(-65.3 to -37.8)	<0.0001	+47.6(+12.9 to+ 82.3)	0.007
SVG magnitude, µV	-92.7(-107.9 to -77.5)	<0.0001	-14.8(-52.2 to -22.7)	0.439

Model 1 was adjusted for age and combination of race and study center. **Model 2** was in addition adjusted for prevalent heart failure, coronary heart disease, stroke, diabetes, hypertension, body mass index, postmenopause state, education level, current smoking, current alcohol intake, leisure physical activity level, use of antihypertensive and antiarrhythmic medications, levels of total cholesterol, high density lipoprotein, and triglycerides, serum concentrations of sodium, potassium, calcium, magnesium, phosphorus, and uric acid, level total protein and albumin, blood urea nitrogen, chronic kidney disease stage classified by $eGFR_{CKD-EPI}$, mean heart rate, QRS duration, corrected QT interval, Cornell voltage, and sex-specific ECG – left ventricular hypertrophy.

Table 4: Sex interaction in association of GEH with SCD in Cox models

	Predictor, per 1 SD	All (n=14,725; 530 SCDs)		Men (n=6,601; 338 SCDs)		Women (n=8,124; 192 SCDs)	
		RHR for women vs. men (95%CI)	$P_{interaction}$	HR(95%CI)	P-value	HR(95%CI)	P-value
Model 1	Peak QRS-T angle	1.10(0.97-1.26)	0.146	**1.27(1.16-1.38)**	**<0.0001**	**1.38(1.23-1.56)**	**<0.0001**
	Area QRS-T angle	0.98(0.84-1.15)	0.788	**1.30(1.17-1.44)**	**<0.0001**	**1.25(1.09-1.44)**	**0.001**
	Peak SVG elevation	1.03(0.87-1.23)	0.694	**1.13(1.02-1.26)**	**0.018**	1.11(0.95-1.30)	0.173
	Area SVG elevation	1.02(0.87-1.21)	0.781	**1.16(1.06-1.28)**	**0.002**	1.12(0.96-1.30)	0.156
	Peak SVG azimuth	1.05(0.90-1.23)	0.501	**1.14(1.05-1.23)**	**0.002**	**1.19(1.03-1.38)**	**0.019**
	Area SVG azimuth	1.08(0.90-1.29)	0.423	1.04(0.95-1.14)	0.404	1.13(0.96-1.33)	0.153
	Peak SVG magnitude	**1.19(1.004-1.42)**	**0.044**	0.90(0.81-1.01)	0.084	1.00(0.86-1.16)	0.948
	Area SVG magnitude	**1.21(1.02-1.43)**	**0.028**	0.97(0.87-1.08)	0.580	1.10(0.94-1.28)	0.229
	SAI QRST	**1.27(1.11-1.44)**	**<0.0001**	1.07(0.97-1.17)	0.168#	**1.32(1.17-1.49)**	**<0.0001**
	Heart rate	1.08(0.92-1.28)	0.335	1.11(1.00-1.24)	0.057	**1.25(1.10-1.43)**	**0.001**
	Bazett's QTc	1.06(0.94-1.20)	0.352	**1.13(1.01-1.27)**	**0.034**	**1.18(1.09-1.26)**	**<0.0001**
	QRS duration	**1.24(1.07-1.44)**	**0.004**	0.99(0.89-1.10)	0.843	**1.24(1.08-1.42)**	**0.002**
	Cornell voltage	1.17(0.99-1.38)	0.063	**1.13(1.03-1.25)**	**0.014**	**1.22(1.05-1.42)**	**0.009**
Model 2	Peak QRS-T angle	1.10(0.96-1.26)	0.189	**1.26(1.15-1.37)**	**<0.0001#**	**1.27(1.12-1.44)**	**<0.0001**
	Area QRS-T angle	1.08(0.93-1.26)	0.287	**1.28(1.16-1.41)**	**<0.0001#**	**1.30(1.15-1.48)**	**<0.0001**
	Peak SVG elevation	1.02(0.86-1.21)	0.804	**1.15(1.04-1.26)**	**0.005**	1.09(0.95-1.26)	0.215
	Area SVG elevation	1.03(0.87-1.22)	0.738	**1.11(1.01-1.23)**	**0.026**	1.06(0.92-1.23)	0.426
	Peak SVG azimuth	1.11(0.96-1.30)	0.167	**1.17(1.08-1.26)**	**<0.0001#**	**1.26(1.10-1.46)**	**0.001**
	Area SVG azimuth	1.18(0.98-1.41)	0.081	**1.11(1.01-1.22)**	**0.024#**	**1.28(1.09-1.50)**	**0.002**
	Peak SVG magnitude	**1.22(1.04-1.44)**	**0.018**	0.93(0.83-1.04)	0.193	1.07(0.93-1.23)	0.355
	Area SVG magnitude	**1.24(1.05-1.45)**	**0.009**	0.97(0.87-1.08)	0.590	1.14(0.98-1.31)	0.080
	SAI QRST	**1.16(1.04-1.30)**	**0.007**	**1.09(1.03-1.16)**	**0.005**	**1.19(1.07-1.32)**	**0.001**
	Heart rate	1.13(0.97-1.32)	0.119	1.11(1.00-1.23)	0.057	**1.26(1.11-1.41)**	**<0.0001**
	Bazett's QTc	1.07(0.94-1.21)	0.305	**1.17(1.08-1.27)**	**<0.0001**	**1.19(1.08-1.31)**	**0.001**
	QRS duration	1.02(0.90-1.17)	0.728	**1.21(1.12-1.31)**	**<0.0001**	**1.16(1.04-1.30)**	**0.010**
	Cornell voltage	**1.18(1.06-1.32)**	**0.003**	**1.10(1.02-1.18)**	**0.012#**	**1.24(1.13-1.37)**	**<0.0001**
Model 3	Peak QRS-T angle	1.11(0.97-1.27)	0.138	**1.20(1.09-1.33)**	**<0.0001**	**1.17(1.02-1.34)**	**0.028**
	Area QRS-T angle	1.10(0.95-1.28)	0.204	**1.22(1.09-1.37)**	**<0.0001**	**1.18(1.02-1.37)**	**0.025**
	Peak SVG elevation	1.01(0.86-1.19)	0.883	1.08(0.98-1.20)	0.136	0.96(0.82-1.12)	0.595
	Area SVG elevation	1.02(0.87-1.20)	0.802	1.06(0.96-1.17)	0.240	0.98(0.84-1.15)	0.823
	Peak SVG azimuth	1.10(0.95-1.28)	0.205	**1.13(1.04-1.23)**	**0.005**	**1.16(0.99-1.36)**	**0.062**
	Area SVG azimuth	1.15(0.97-1.35)	0.099	**1.10(1.003-1.21)**	**0.042**	**1.19(1.02-1.40)**	**0.030**
	Peak SVG magnitud	**1.20(1.02-1.41)**	**0.029**	1.02(0.94-1.12)	0.599	**1.16(1.001-1.35)**	**0.049**
	Area SVG magnitude	**1.22(1.05-1.43)**	**0.011**	0.95(0.84-1.06)	0.354	1.04(0.91-1.20)	0.544
	SAI QRST	**1.14(1.02-1.27)**	**0.020**	0.97(0.87-1.09)	0.646	1.13(0.98-1.30)	0.100

#Proportionality hazards assumption not met; SVG=spatial ventricular gradient: RHR=relative hazard ratio. Model 1 was adjusted for age, combination of race and study center, prevalent HF, CHD, stroke, diabetes, hypertension, postmenopause state, education level, current smoking, alcohol intake, leisure physical activity level, BMI category, use of antihypertensive and antiarrhythmic medications, levels of total cholesterol, high density lipoprotein (HDL), and triglycerides, serum concentrations of sodium, potassium, calcium, magnesium, phosphorus, and uric acid, total protein and albumin, blood urea nitrogen, CKD stage classified by $eGFR_{CKD\text{-}EPI,}$ and sex-specific ECG-LVH. Models for Cornell voltage were not adjusted for ECG-LVH. Time-updated model 2 was adjusted for all baseline covariates included in model 1, and time-updated incident nonfatal CV events (AF, HF, CHD, and stroke). Time-updated ECG-adjusted model 3 was adjusted for all four time-updated traditional ECG measurements (heart rate, QTc, QRS, and Cornell voltage), in addition to baseline covariates, and time-updated incident nonfatal CV events included in model 2.

Table 5. Sex interaction in association of GEH with SCD in competing risk models

	Predictor, per 1 SD	All SCD (n=14,725; 530 SCDs)		Men (n=6,601; 338 SCDs)		Women (n=8,124; 192 SCDs)	
		RSHR for women vs.men (95%CI)	$P_{interaction}$	SHR(95%CI)	P-value	SHR(95%CI)	P-value
Model 1	Peak QRS-T angle	**1.12(0.98-1.28)**	**0.084**	**1.19(1.08-1.31)**	**<0.0001**	**1.32(1.17-1.49)**	**<0.0001**
	Area QRS-T angle	0.98(0.85-1.14)	0.840	**1.21(1.09-1.33)**	**<0.0001**	**1.16(1.02-1.33)**	**0.026**
	Peak SVG elevation	1.07(0.90-1.28)	0.445	**1.12(1.004-1.24)**	**0.041**	1.15(0.97-1.37)	0.107
	Area SVG elevation	1.06(0.90-1.26)	0.484	**1.15(1.05-1.25)**	**0.004**	1.15(0.98-1.35)	0.093
	Peak SVG azimuth	1.07(0.92-1.24)	0.408	**1.11(1.02-1.21)**	**0.011**	**1.18(1.03-1.36)**	**0.020**
	Area SVG azimuth	1.07(0.86-1.32)	0.557	1.01(0.93-1.11)	0.747	1.09(0.86-1.37)	0.473
	Peak SVG magnitude	**1.16(0.98-1.36)**	**0.083**	0.91(0.81-1.02)	0.110	0.98(0.84-1.14)	0.774
	Area SVG magnitude	**1.16(0.99-1.37)**	**0.063**	0.96(0.86-1.07)	0.484	1.06(0.90-1.24)	0.483
	SAI QRST	**1.16(1.01-1.33)**	**0.033**	1.04(0.93-1.15)	0.495	**1.21(1.06-1.38)**	**0.004**
	Heart rate.	**1.16(0.97-1.37)**	**0.087**	1.01(0.90-1.13)	0.895	**1.18(1.04-1.35)**	**0.012**
	Bazett's QTc	**1.15(1.02-1.30)**	**0.025**	1.05(0.94-1.18)	0.408	**1.18(1.10-1.27)**	**<0.0001**
	QRS duration	**1.27(1.08-1.49)**	**0.004**	0.98(0.88-1.08)	0.663	**1.26(1.09-1.46)**	**0.002**
	Cornell voltage	1.14(0.97-1.34)	0.112	1.08(0.98-1.20)	0.101	1.14(0.97-1.33)	0.109
Model 2	Peak QRS-T angle	**1.13(0.98-1.31)**	**0.081**	**1.14(1.03-1.25)**	**0.008**	**1.20(1.05-1.36)**	**0.005**
	Area QRS-T angle	1.09(0.93-1.27)	0.296	**1.18(1.06-1.31)**	**0.002**	**1.22(1.07-1.39)**	**0.003**
	Peak SVG elevation	1.06(0.89-1.27)	0.480	**1.13(1.02-1.25)**	**0.020**	1.11(0.95-1.30)	0.190
	Area SVG elevation	1.10(0.93-1.30)	0.283	1.09(0.99-1.21)	0.071	1.09(0.94-1.27)	0.269
	Peak SVG azimuth	**1.16(0.99-1.35)**	**0.065**	**1.12(1.02-1.22)**	**0.012**	**1.24(1.08-1.42)**	**0.003**
	Area SVG azimuth	**1.21(0.99-1.48)**	**0.063**	1.05(0.95-1.16)	0.349	**1.25(1.04-1.49)**	**0.016**
	Peak SVG magnitude	**1.18(1.00-1.39)**	**0.057**	0.94(0.84-1.06)	0.337	1.06(0.92-1.22)	0.433
	Area SVG magnitude	**1.21(1.03-1.43)**	**0.021**	0.96(0.85-1.07)	0.428	1.12(0.96-1.31)	0.148
	SAI QRST	**1.16(1.02-1.31)**	**0.025**	1.07(0.99-1.15)	0.073	**1.18(1.05-1.33)**	**0.009**
	Heart rate.	**1.19(1.01-1.40)**	**0.036**	0.99(0.89-1.11)	0.911	**1.16(1.02-1.32)**	**0.026**
	Bazett's QTc	**1.11(0.99-1.26)**	**0.086**	**1.10(1.01-1.21)**	**0.033**	**1.17(1.07-1.29)**	**0.001**
	QRS duration	1.10(0.96-1.27)	0.176	**1.15(1.06-1.25)**	**<0.0001**	**1.18(1.04-1.34)**	**0.011**
	Cornell voltage	**1.23(1.10-1.38)**	**<0.0001**	1.06(0.98-1.14)	0.177	**1.22(1.11-1.35)**	**<0.0001**

RSHR=relative sub-hazard ratio

Table 6. Sex interaction in association of GEH with nonSCD in competing risk models

	Predictor, per 1 SD	All nonSCD (n=14,725; 2,178 nonSCDs)		Men (n=6,601; 1126 nonSCD)		Women (n=8,124; 1,052 nonSCDs)	
		RSHR for women vs.men (95%CI)	$P_{interaction}$	SHR(95%CI)	P-value	SHR(95%CI)	P-value
Model 1	Peak QRS-T angle	1.12(0.97-1.14)	0.207	**1.15(1.08-1.21)**	**<0.0001**	**1.15(1.08-1.23)**	**<0.0001**
	Area QRS-T angle	1.07(0.98-1.18)	0.120	**1.16(1.09-1.24)**	**<0.0001**	**1.22(1.14-1.31)**	**<0.0001**
	Peak SVG elevation	0.97(0.88-1.06)	0.474	1.03(0.97-1.09)	0.361	1.00(0.93-1.08)	0.946
	Area SVG elevation	0.99(0.91-1.08)	0.784	1.01(0.95-1.07)	0.736	1.00(0.93-1.07)	0.927
	Peak SVG azimuth	1.06(0.98-1.16)	0.144	**1.05(1.00-1.11)**	**0.046**	**1.09(1.01-1.17)**	**0.021**
	Area SVG azimuth	1.03(0.94-1.13)	0.533	**1.08(1.01-1.15)**	**0.017**	**1.09(1.01-1.17)**	**0.023**
	Peak SVG magnitude	**1.11(1.01-1.22)**	**0.027**	0.94(0.88-1.005)	0.068	1.00(0.93-1.08)	0.960
	Area SVG magnitude	**1.15(1.05-1.26)**	**0.003**	0.96(0.90-1.03)	0.218	1.04(0.96-1.12)	0.308
	SAI QRST	**1.16(1.06-1.27)**	**0.002**	1.01(0.94-1.08)	0.832	**1.13(1.04-1.22)**	**0.004**
	Heart rate.	0.98(0.89-1.07)	0.624	**1.20(1.12-1.27)**	**<0.0001**	**1.15(1.07-1.23)**	**<0.0001**
	Bazett's QTc	**0.87(0.81-0.94)**	**0.001**	**1.22(1.15-1.30)**	**<0.0001**	1.04(0.99-1.09)	0.121
	QRS duration	0.95(0.88-1.03)	0.197	1.06(1.00-1.13)	0.058	1.00(0.93-1.07)	0.934
	Cornell voltage	**1.11(1.01-1.22)**	**0.032**	**1.12(1.05-1.19)**	**<0.0001**	**1.20(1.11-1.30)**	**<0.0001**
Model 2	Peak QRS-T angle	**1.10(1.004-1.20)**	**0.040**	**0.92(0.86-0.98)**	**0.011**	0.97(0.90-1.05)	0.476
	Area QRS-T angle	1.09(0.99-1.20)	0.078	**0.92(0.86-0.98)**	**0.011**	0.95(0.87-1.04)	0.284
	Peak SVG elevation	0.99(0.89-1.10)	0.833	0.94(0.88-1.01)	0.085	0.94(0.86-1.02)	0.119
	Area SVG elevation	0.95(0.86-1.06)	0.366	0.97(0.90-1.04)	0.340	**0.92(0.85-1.00)**	**0.053**
	Peak SVG azimuth	1.05(0.95-1.15)	0.379	0.95(0.90-1.01)	0.087	0.97(0.89-1.06)	0.484
	Area SVG azimuth	1.02(0.93-1.12)	0.605	0.96(0.91-1.02)	0.165	0.95(0.88-1.02)	0.178
	Peak SVG magnitude	0.97(0.87-1.07)	0.524	1.02(0.95-1.11)	0.549	0.97(0.90-1.05)	0.460
	Area SVG magnitude	1.00(0.90-1.10)	0.933	1.01(0.94-1.10)	0.711	0.98(0.91-1.06)	0.653
	SAI QRST	1.01(0.93-1.10)	0.810	**0.95(0.91-1.00)**	**0.060**	**0.93(0.86-1.00)**	**0.054**
	Heart rate.	1.06(0.96-1.17)	0.230	**1.09(1.02-1.16)**	**0.012**	**1.13(1.05-1.22)**	**0.001**
	Bazett's QTc	1.02(0.94-1.12)	0.619	1.02(0.96-1.09)	0.449	1.03(0.92-1.10)	0.397
	QRS duration	0.94(0.85-1.03)	0.154	**0.95(0.90-1.00)**	**0.070**	**0.88(0.81-0.95)**	**0.001**
	Cornell voltage	0.97(0.90-1.06)	0.525	0.98(0.93-1.03)	0.420	0.94(0.87-1.01)	0.093

RSHR=relative sub-hazard ratio

Figure Legends

Figure 1. Estimated adjusted marginal (least-squares) means and 95% Confidence Intervals of GEH variables for men and women. **Model 1** was adjusted for age, race, and study center. **Model 2** was in addition adjusted for prevalent HF, CHD, stroke, diabetes, hypertension, BMI, postmenopause state, education level, current smoking, current alcohol intake, leisure physical activity level, BMI category, use of antihypertensive and antiarrhythmic medications, levels of total cholesterol, HDL, and triglycerides, serum concentrations of sodium, potassium, calcium, magnesium, phosphorus, and uric acid, total protein and albumin, blood urea nitrogen, CKD stage classified by $eGFR_{CKD\text{-}EPI}$, mean heart rate, QRS duration, QTc, Cornell voltage, and sex-specific ECG – LVH.

Figure 2. Adjusted (for age, race, study center, prevalent at baseline HF, CHD, stroke, diabetes, hypertension, BMI, postmenopause state, education level, current smoking, current alcohol intake, leisure physical activity level, BMI category, use of antihypertensive and antiarrhythmic medications, levels of total cholesterol, HDL, and triglycerides, serum concentrations of sodium, potassium, calcium, magnesium, phosphorus, and uric acid, total protein and albumin, blood urea nitrogen, CKD stage classified by $eGFR_{CKD\text{-}EPI}$, mean heart rate, QRS duration, QTc, Cornell voltage, and sex-specific ECG – LVH.) risk of SCD associated with GEH variables in men and women. Restricted cubic spline with 95% CI shows change in hazard ratio (Y-axis) in response to GEH variable change (X-axis). 50th percentile of GEH variable is selected as reference.

Figure 3. Adjusted Cox proportional relative hazard ratio (RHR) and 95% confidence interval (CI) of SCD for GEH and traditional global ECG metrics in model 1 (green diamond)

and model 2 (orange triangle). Black lines correspond to 95% CI bounds. Forest plot shows RHR with 95%CI for women as compared to men, with HR for men equal 1.0.

Figure 4. Sex-stratified adjusted (models 1 and 2) Cox proportional hazard ratio (HR) and 95% confidence interval (CI) of SCD for GEH and traditional global ECG metrics in men (blue rectangle) and women (red oval). Black lines correspond to 95% CI bounds.

Figure 5. Adjusted competing risk relative sub-hazard ratio (RSHR) and 95% confidence interval (CI) of SCD and nonSCD for GEH and traditional global ECG metrics in model 1 (green diamond) and model 2 (orange triangle). Black lines correspond to 95% CI bounds. Forest plots show RSHR with 95%CI for women as compared to men, with SHR for men equal 1.0.

Figure 6. Sex-stratified adjusted (models 1 and 2) competing risk sub-hazard ratio (SHR) and 95% confidence interval (CI) of SCD and nonSCD for GEH and traditional global ECG metrics in men (blue rectangle) and women (red oval). Black lines correspond to 95% CI bounds.

Figure 1A: Spatial peak QRS-T angle in men and women:

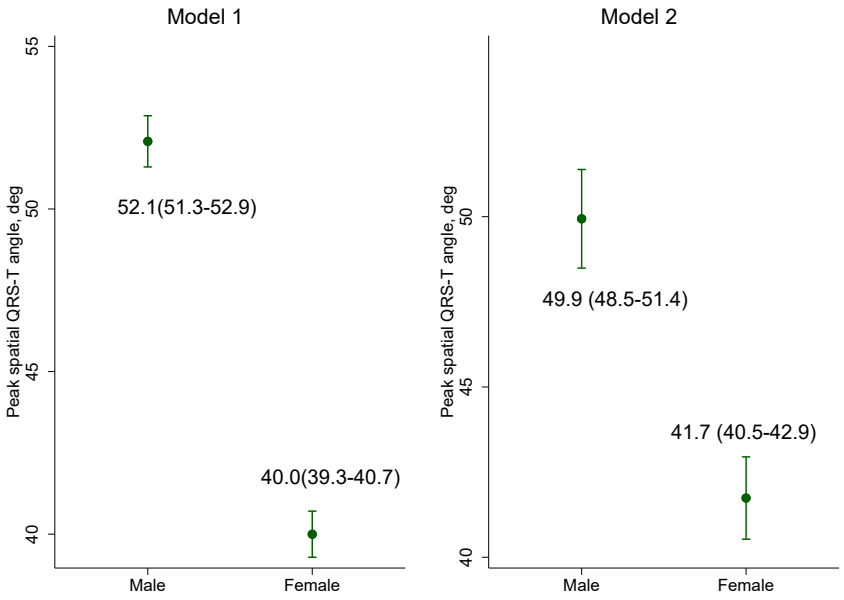


Figure 1B: Spatial area QRS-T angle in men and women:

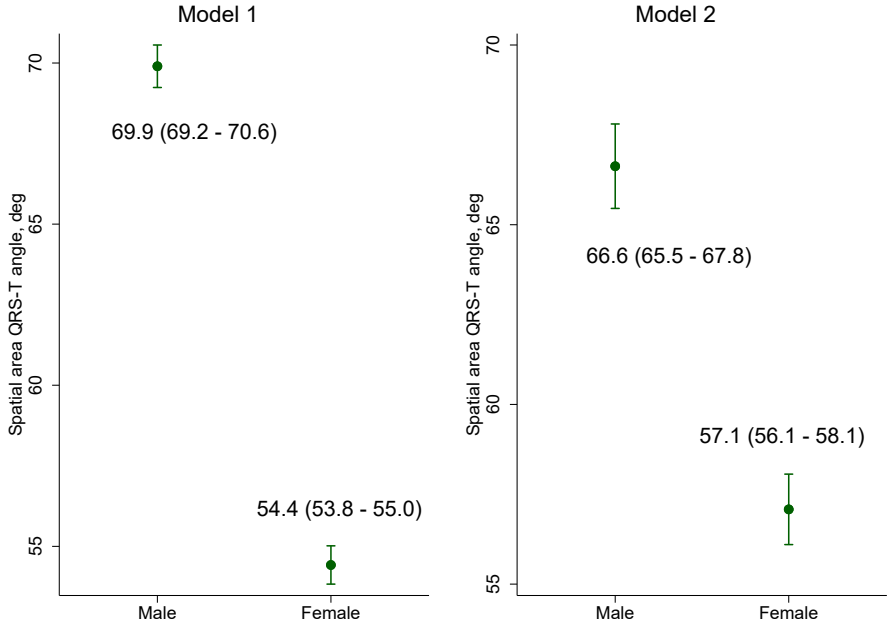


Figure 1C: Spatial peak SVG elevation in men and women:

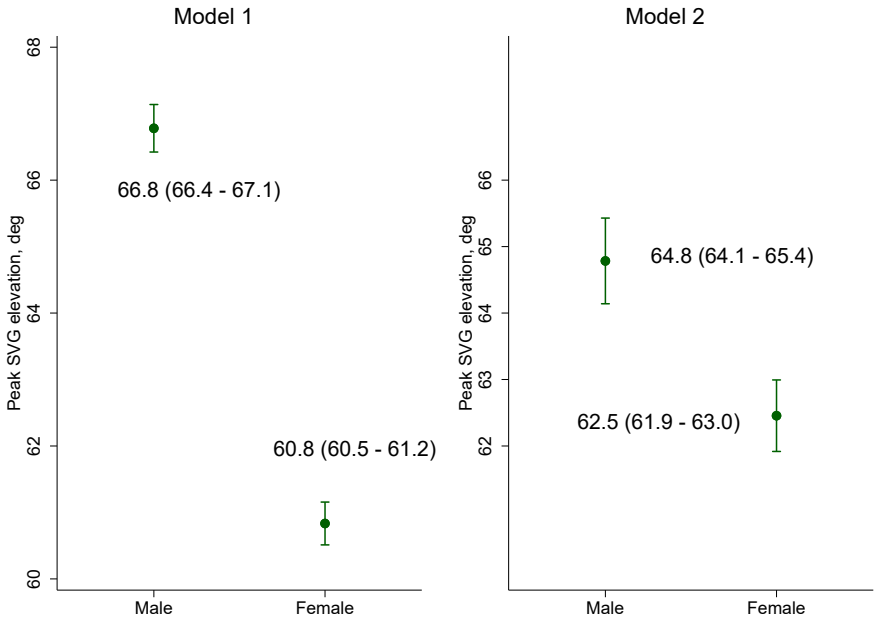


Figure 1D: Spatial area SVG elevation in men and women:

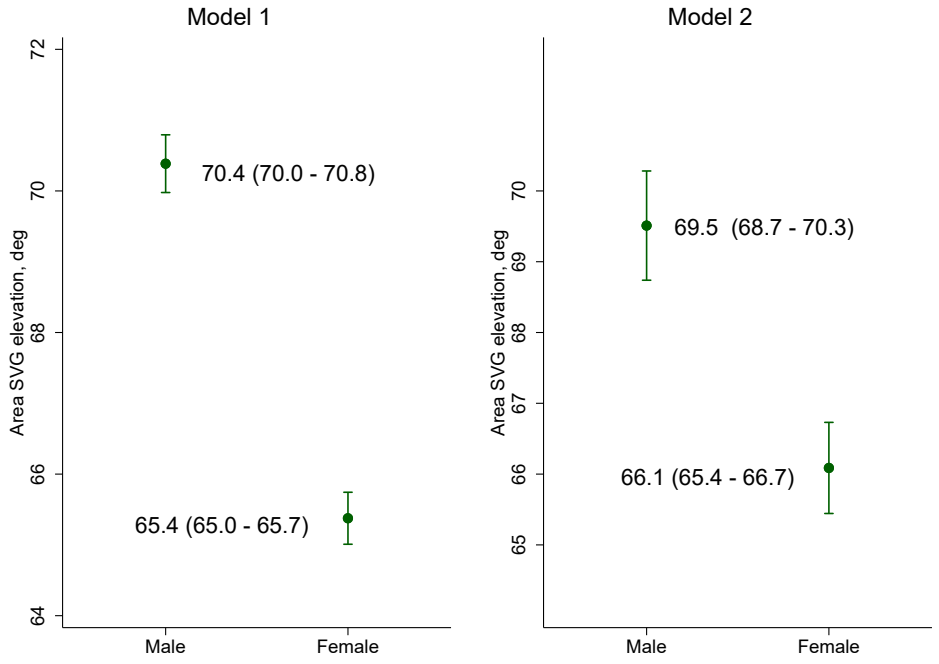


Figure 1E: Spatial peak SVG azimuth in men and women:

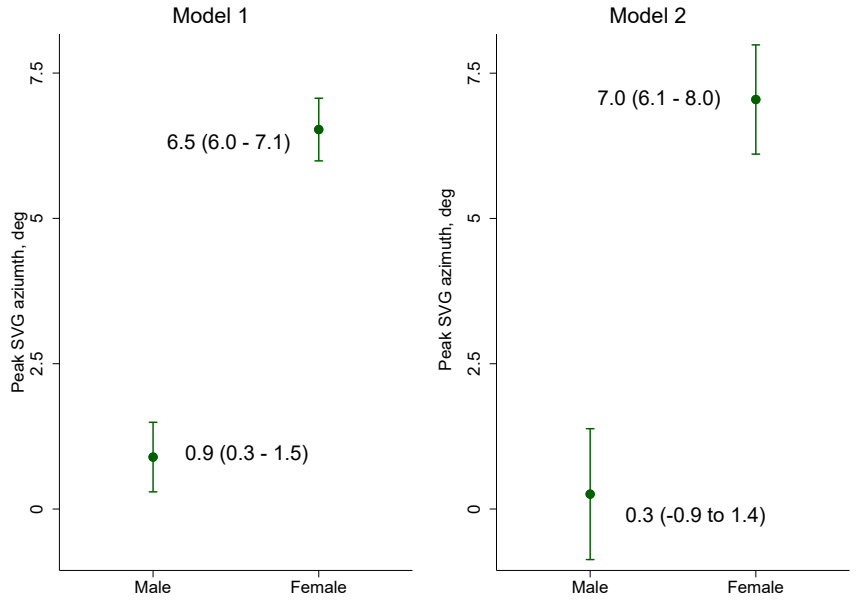


Figure 1F: Spatial area SVG azimuth in men and women:

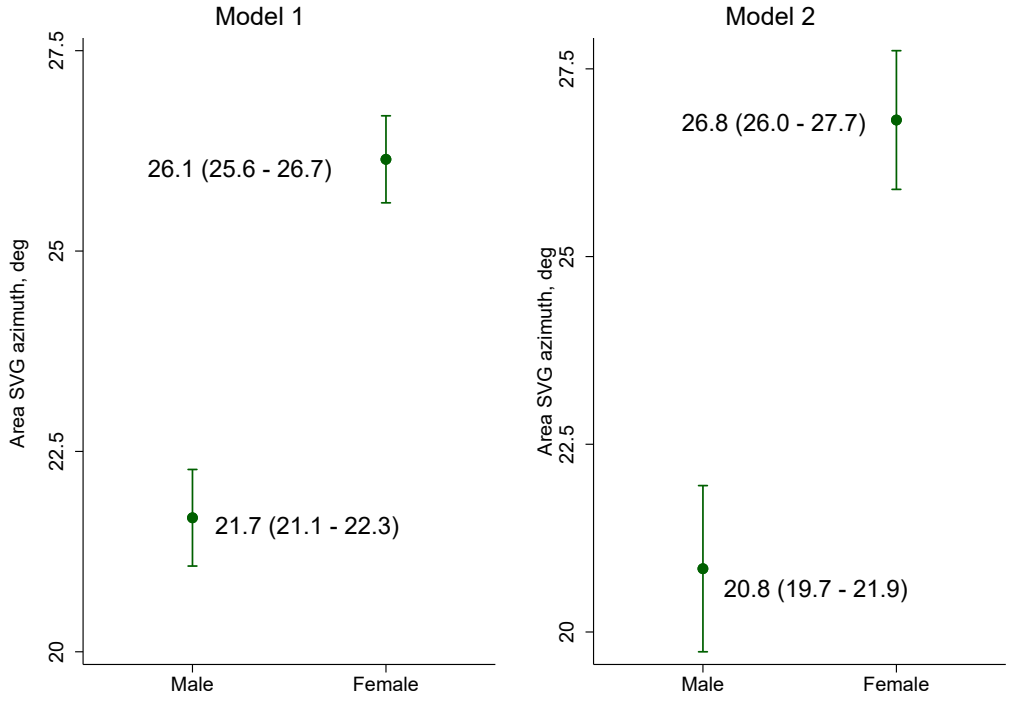


Figure 1G: Spatial peak SVG magnitude in men and women:

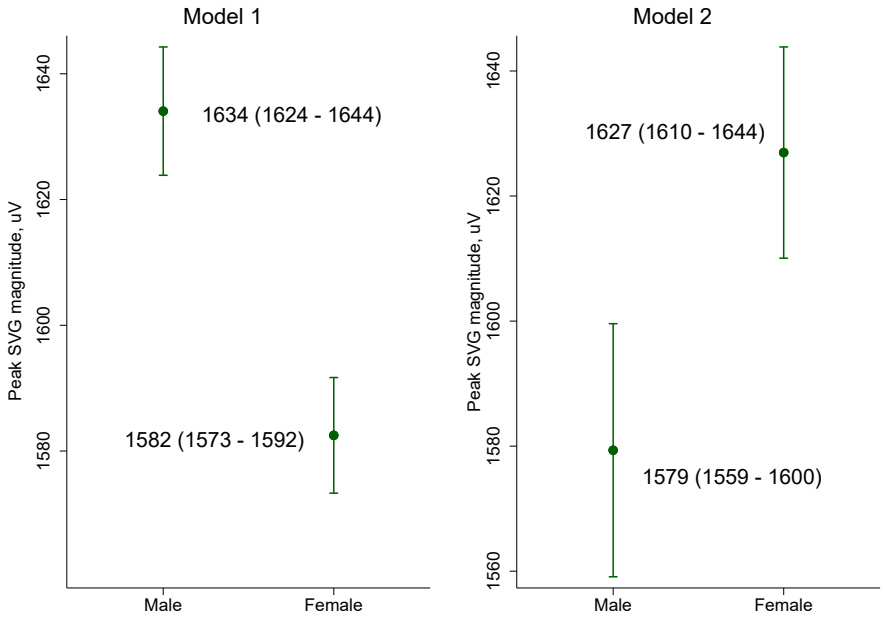


Figure 1H: Spatial SVG magnitude in men and women:

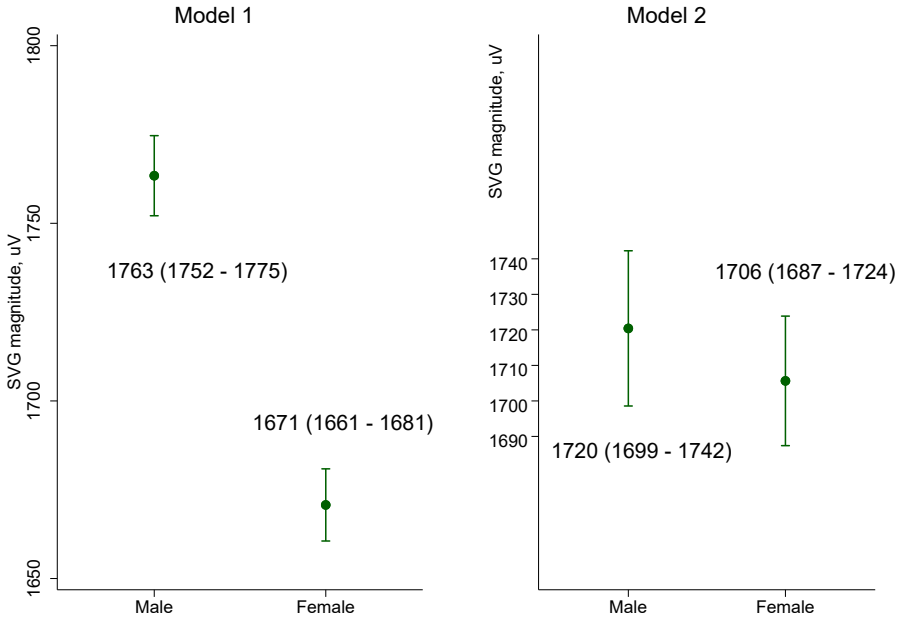


Figure 1I: SAI QRST in men and women:

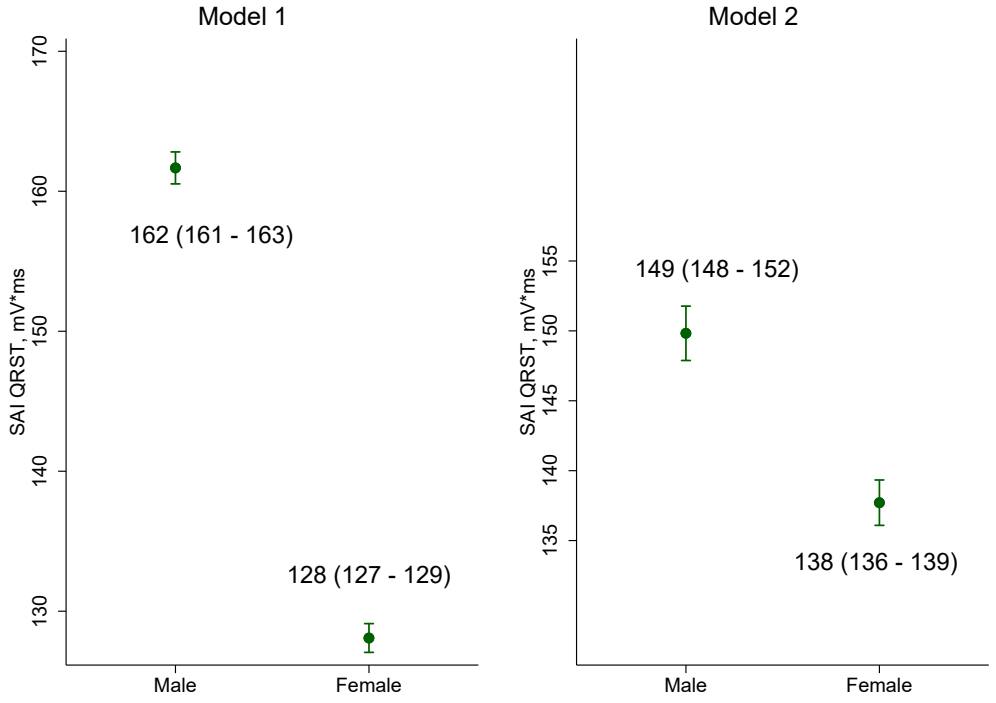


Figure 2A: Adjusted risk of SCD associated with peak QRS-T angle

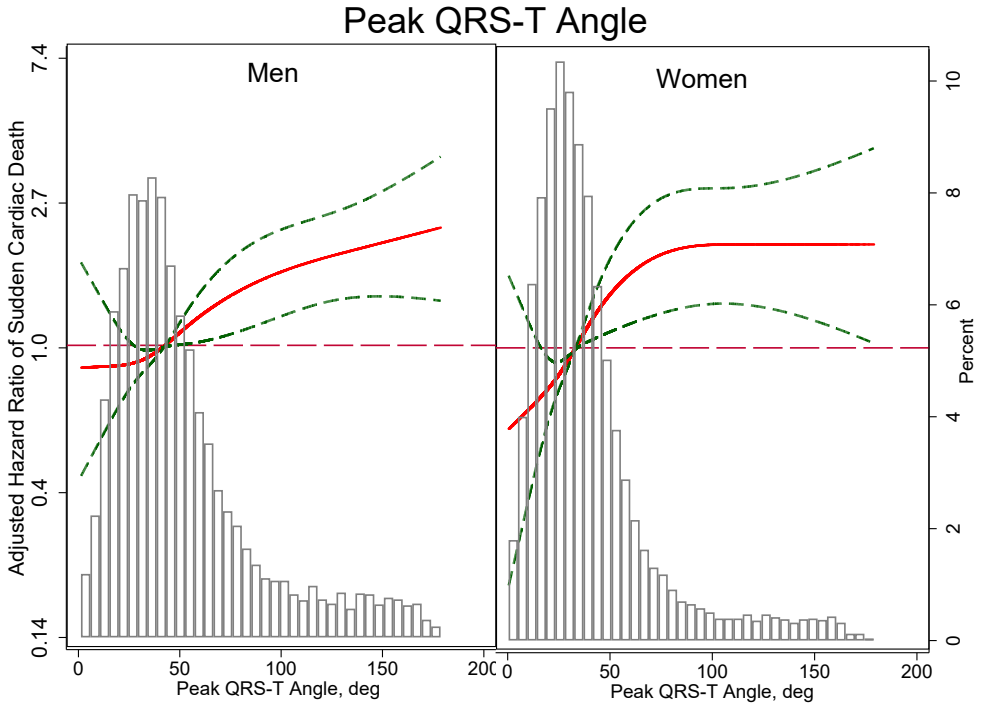


Figure 2B: Adjusted risk of SCD associated with area QRS-T angle

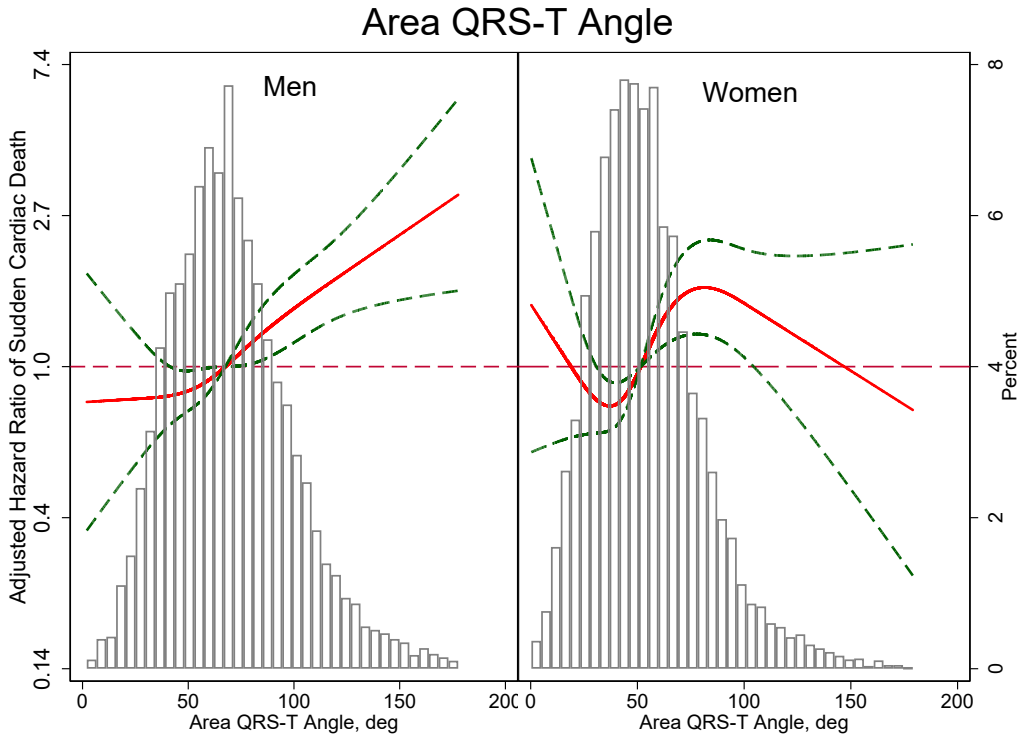


Figure 2C: Adjusted risk of SCD associated with peak SVG elevation

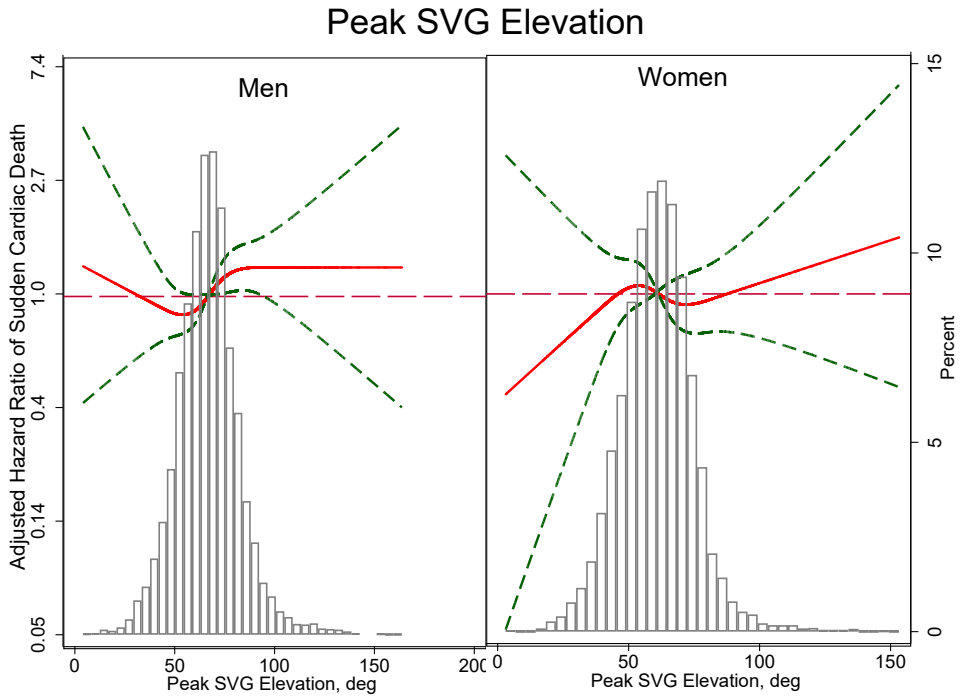


Figure 2D: Adjusted risk of SCD associated with area SVG elevation

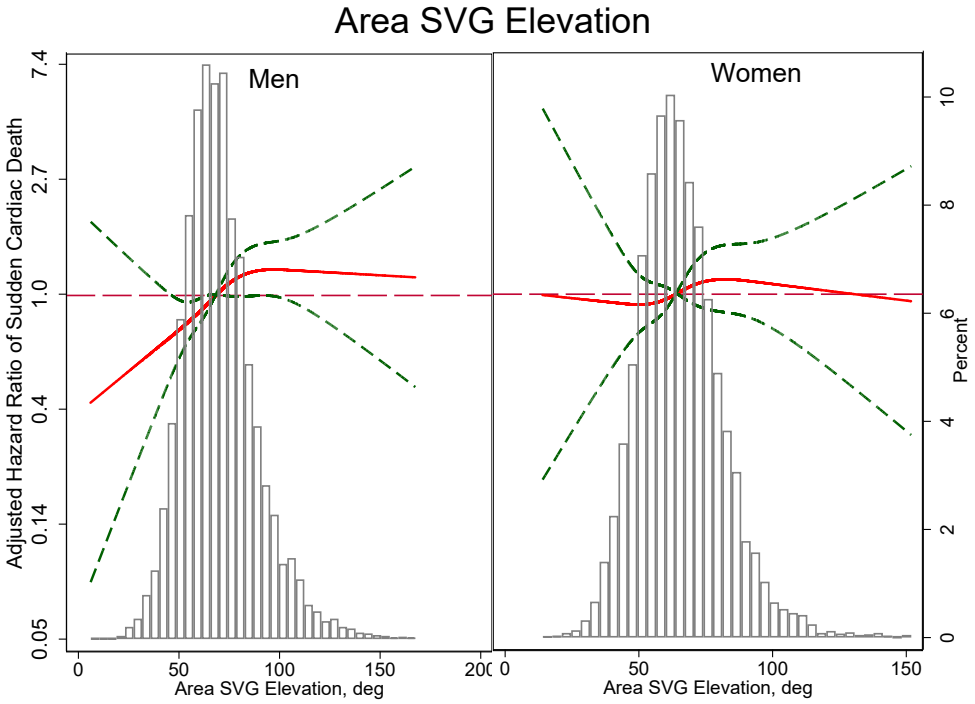


Figure 2E: Adjusted risk of SCD associated with peak SVG azimuth

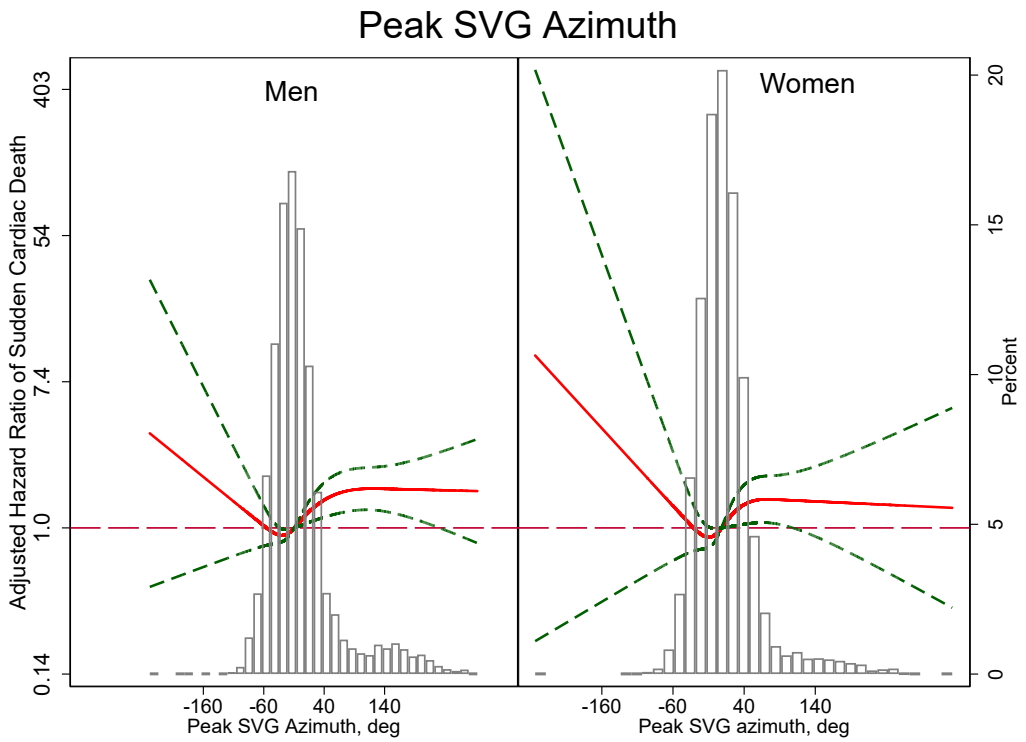


Figure 2F: Adjusted risk of SCD associated with area SVG azimuth

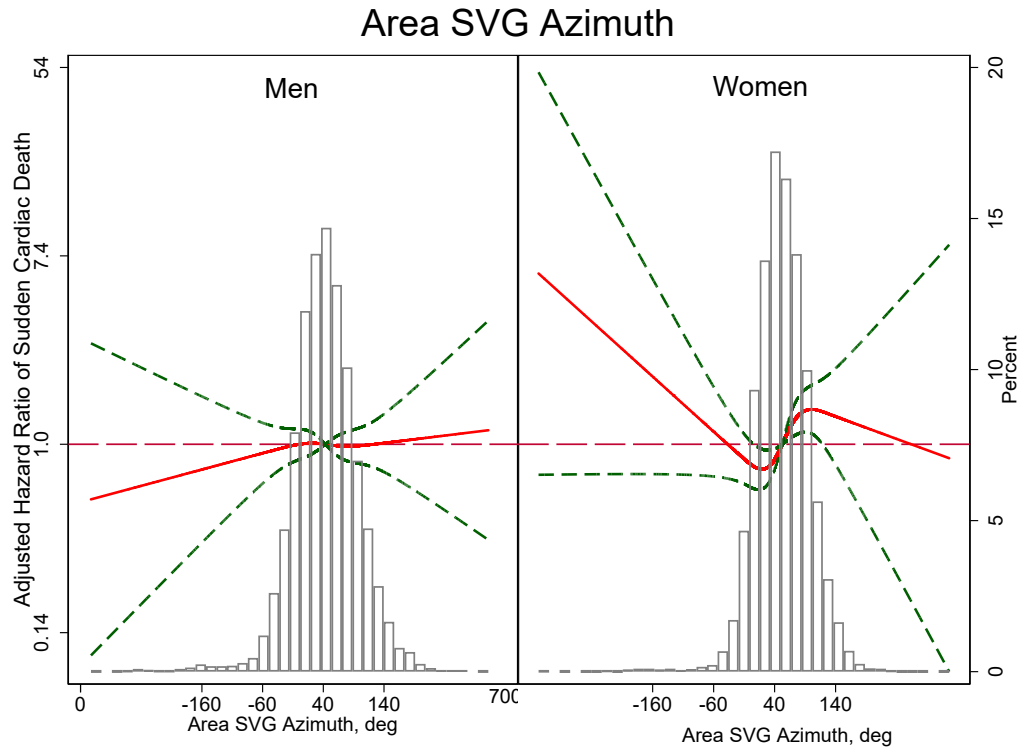


Figure 2G: Adjusted risk of SCD associated with peak SVG magnitude

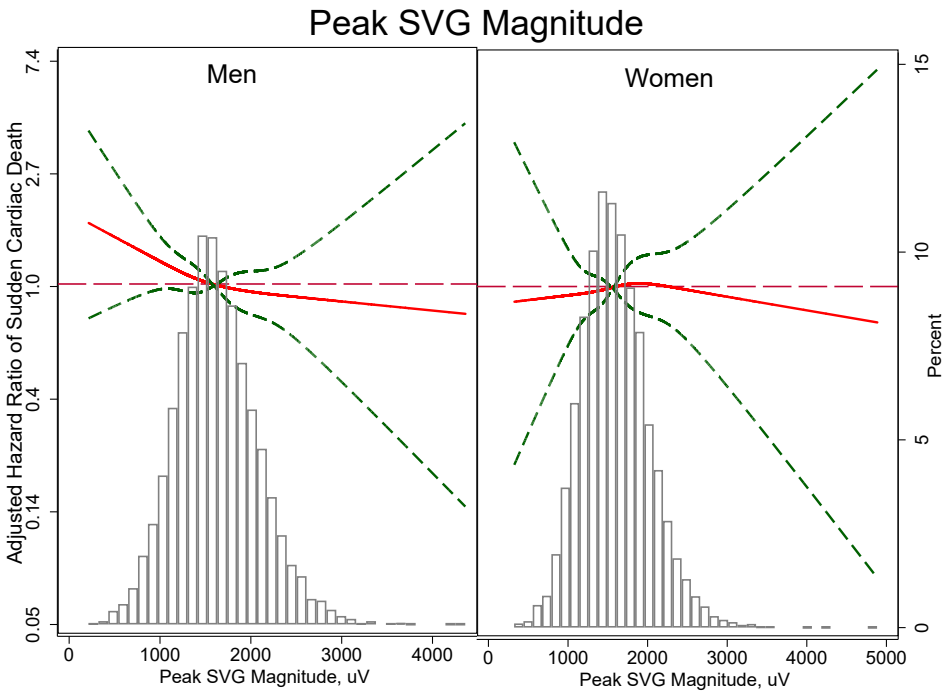


Figure 2H: Adjusted risk of SCD associated with SVG magnitude

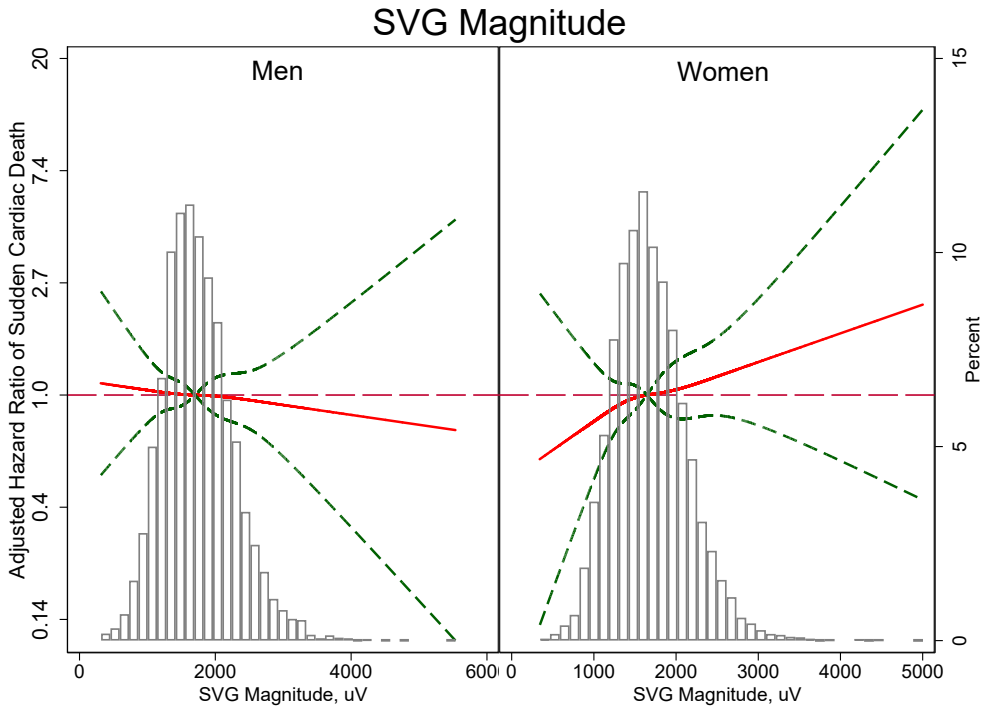


Figure 2I: Adjusted risk of SCD associated with SAI QRST

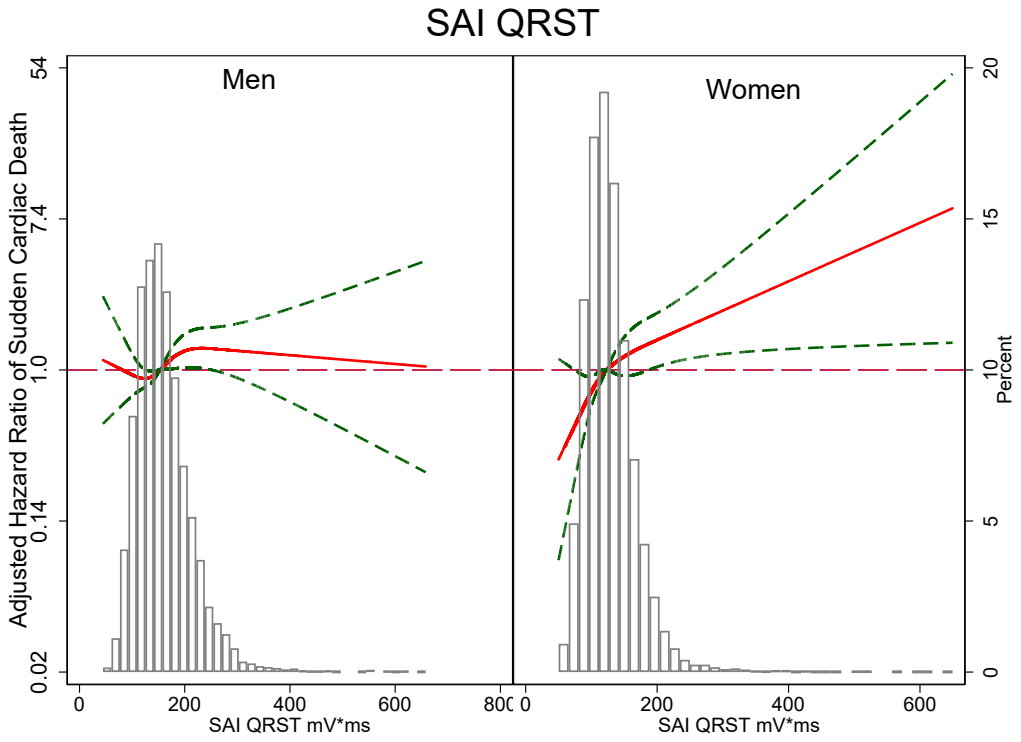


Figure 3:

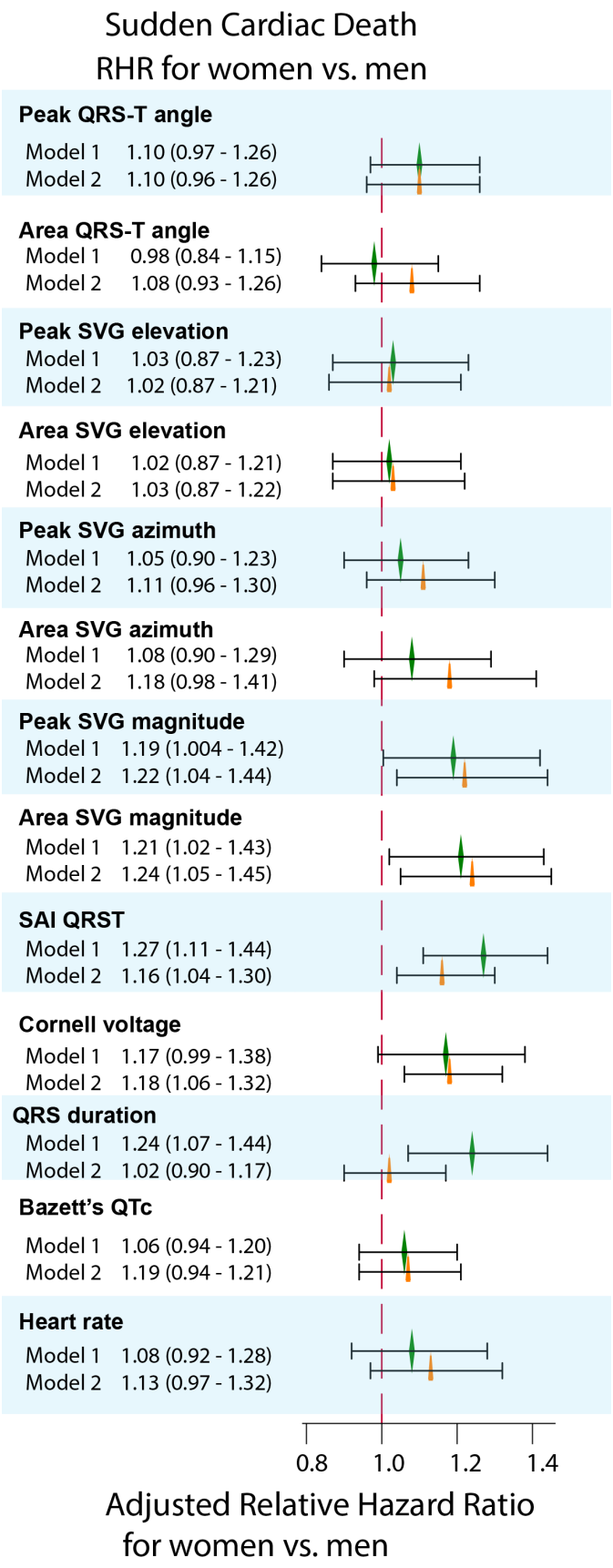

Sudden Cardiac Death
RHR for women vs. men
Peak QRS-T angle
Model 1 1.10 (0.97 - 1.26)
Model 2 1.10 (0.96 - 1.26)
Area QRS-T angle
Model 1 0.98 (0.84 - 1.15)
Model 2 1.08 (0.93 - 1.26)
Peak SVG elevation
Model 1 1.03 (0.87 - 1.23)
Model 2 1.02 (0.87 - 1.21)
Area SVG elevation
Model 1 1.02 (0.87 - 1.21)
Model 2 1.03 (0.87 - 1.22)
Peak SVG azimuth
Model 1 1.05 (0.90 - 1.23)
Model 2 1.11 (0.96 - 1.30)
Area SVG azimuth
Model 1 1.08 (0.90 - 1.29)
Model 2 1.18 (0.98 - 1.41)
Peak SVG magnitude
Model 1 1.19 (1.004 - 1.42)
Model 2 1.22 (1.04 - 1.44)
Area SVG magnitude
Model 1 1.21 (1.02 - 1.43)
Model 2 1.24 (1.05 - 1.45)
SAI QRST
Model 1 1.27 (1.11 - 1.44)
Model 2 1.16 (1.04 - 1.30)
Cornell voltage
Model 1 1.17 (0.99 - 1.38)
Model 2 1.18 (1.06 - 1.32)
QRS duration
Model 1 1.24 (1.07 - 1.44)
Model 2 1.02 (0.90 - 1.17)
Bazett's QTc
Model 1 1.06 (0.94 - 1.20)
Model 2 1.19 (0.94 - 1.21)
Heart rate
Model 1 1.08 (0.92 - 1.28)
Model 2 1.13 (0.97 - 1.32)
0.8
1.0
1.2
1.4
Adjusted Relative Hazard Ratio
for women vs. men

Figure 4:

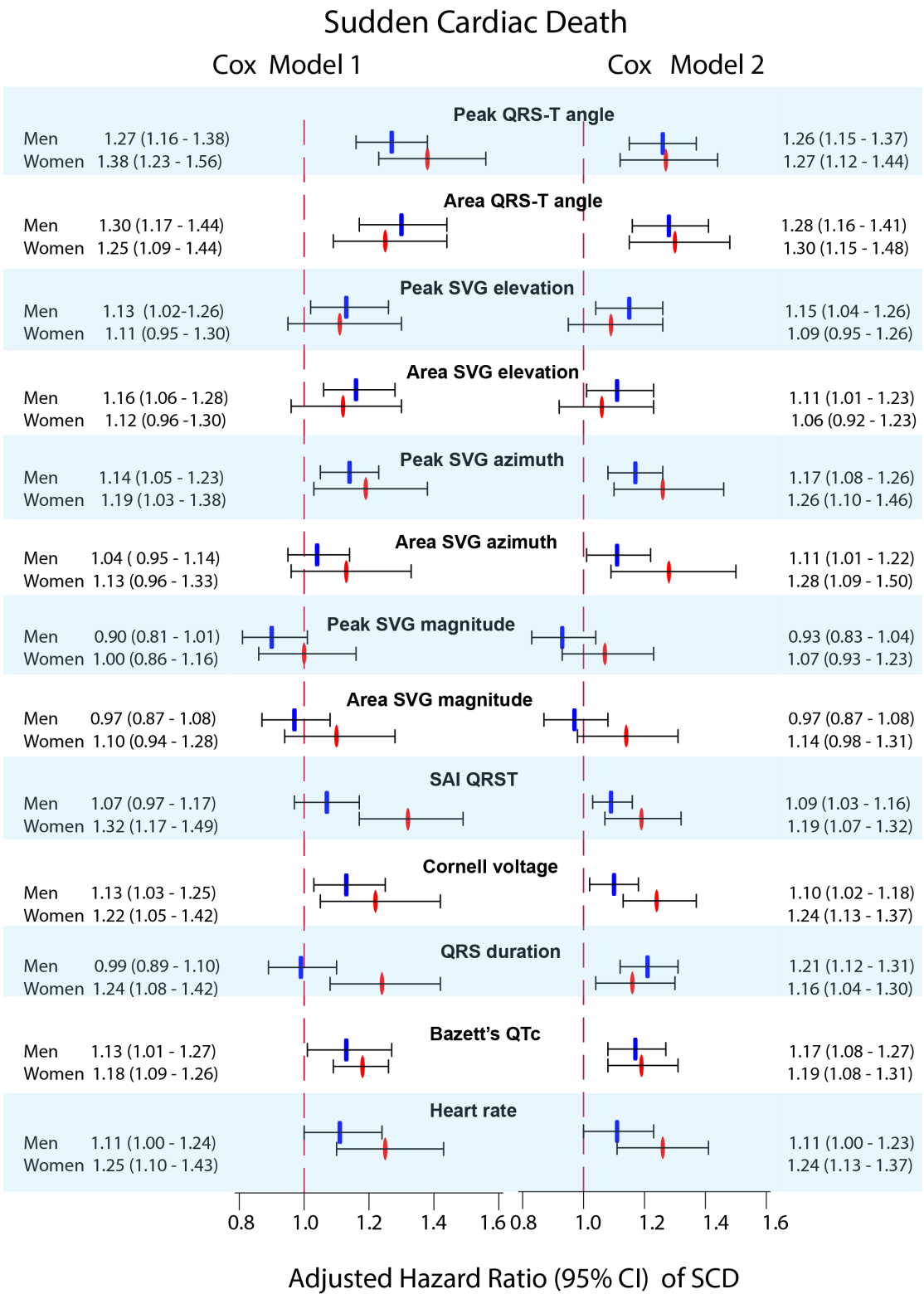

Sudden Cardiac Death
Cox Model 1
Cox Model 2
Peak QRS-T angle
Men 1.27 (1.16 - 1.38)
Women 1.38 (1.23 - 1.56)
1.26 (1.15 - 1.37)
1.27 (1.12 - 1.44)
Area QRS-T angle
Men 1.30 (1.17 - 1.44)
Women 1.25 (1.09 - 1.44)
1.28 (1.16 - 1.41)
1.30 (1.15 - 1.48)
Peak SVG elevation
Men 1.13 (1.02-1.26)
Women 1.11 (0.95 - 1.30)
1.15 (1.04 - 1.26)
1.09 (0.95 - 1.26)
Area SVG elevation
Men 1.16 (1.06 - 1.28)
Women 1.12 (0.96 -1.30)
1.11 (1.01 - 1.23)
1.06 (0.92 - 1.23)
Peak SVG azimuth
Men 1.14 (1.05 - 1.23)
Women 1.19 (1.03 - 1.38)
1.17 (1.08 - 1.26)
1.26 (1.10 - 1.46)
Area SVG azimuth
Men 1.04 (0.95 - 1.14)
Women 1.13 (0.96 - 1.33)
1.11 (1.01 - 1.22)
1.28 (1.09 - 1.50)
Peak SVG magnitude
Men 0.90 (0.81 - 1.01)
Women 1.00 (0.86 - 1.16)
0.93 (0.83 - 1.04)
1.07 (0.93 - 1.23)
Area SVG magnitude
Men 0.97 (0.87 - 1.08)
Women 1.10 (0.94 - 1.28)
0.97 (0.87 - 1.08)
1.14 (0.98 - 1.31)
SAI QRST
Men 1.07 (0.97 - 1.17)
Women 1.32 (1.17 - 1.49)
1.09 (1.03 - 1.16)
1.19 (1.07 - 1.32)
Cornell voltage
Men 1.13 (1.03 - 1.25)
Women 1.22 (1.05 - 1.42)
1.10 (1.02 - 1.18)
1.24 (1.13 - 1.37)
QRS duration
Men 0.99 (0.89 - 1.10)
Women 1.24 (1.08 - 1.42)
1.21 (1.12 - 1.31)
1.16 (1.04 - 1.30)
Bazett's QTc
Men 1.13 (1.01 - 1.27)
Women 1.18 (1.09 - 1.26)
1.17 (1.08 - 1.27)
1.19 (1.08 - 1.31)
Heart rate
Men 1.11 (1.00 - 1.24)
Women 1.25 (1.10 - 1.43)
1.11 (1.00 - 1.23)
1.24 (1.13 - 1.37)
0.8 1.0 1.2 1.4 1.6 0.8 1.0 1.2 1.4 1.6
Adjusted Hazard Ratio (95% CI) of SCD

Figure 5:

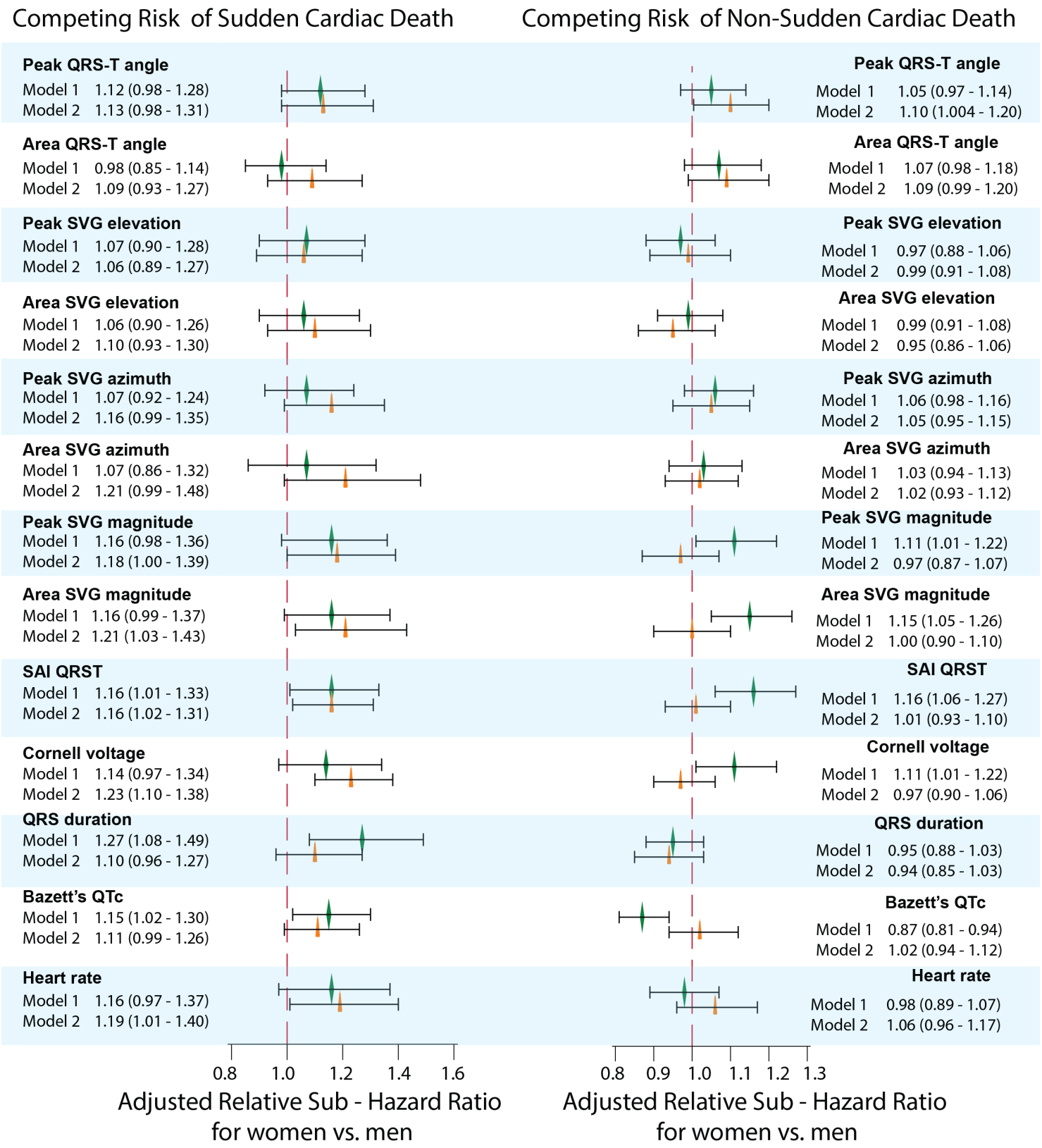
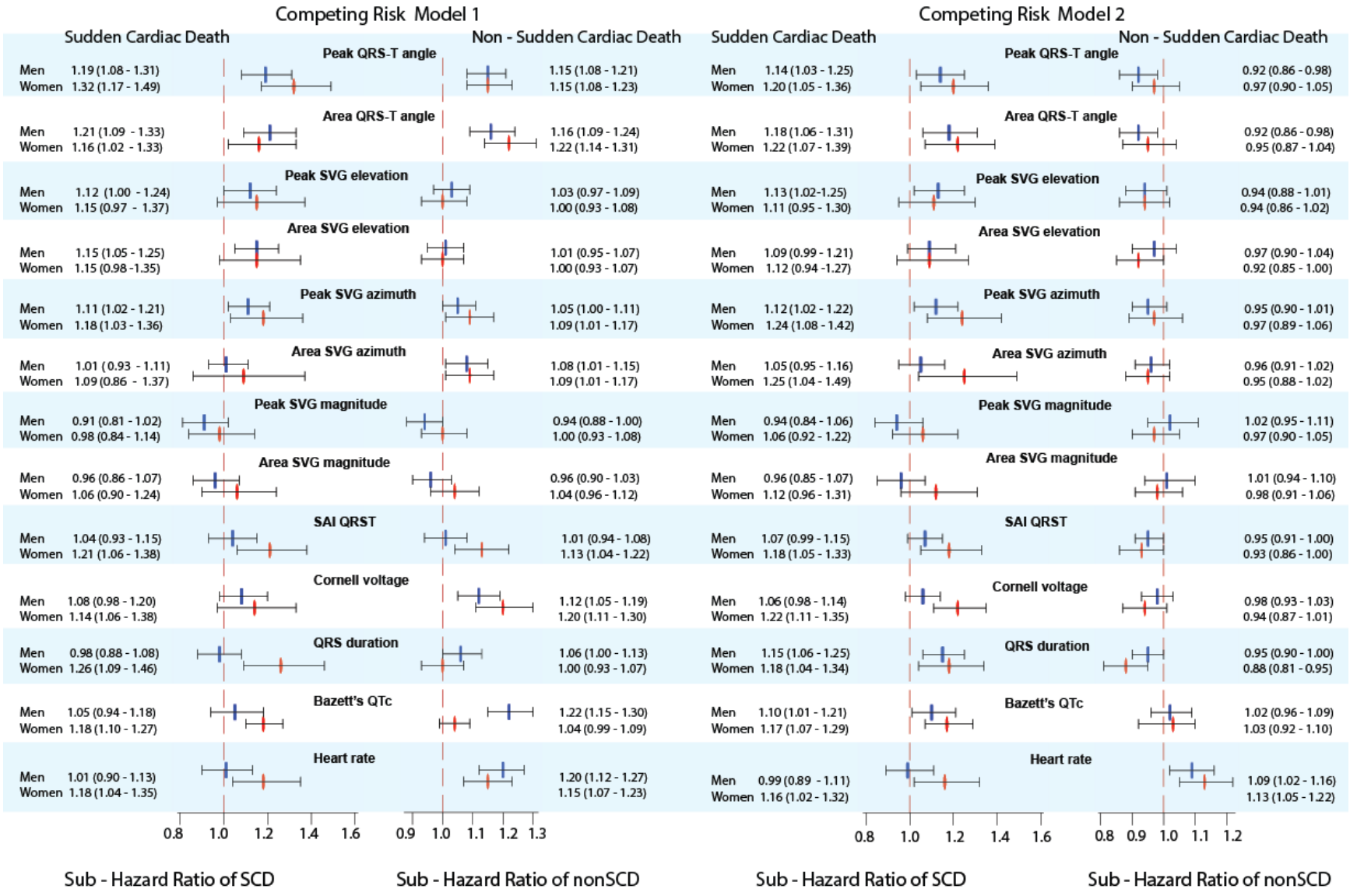

Competing Risk of Sudden Cardiac Death
Competing Risk of Non-Sudden Cardiac Death
Peak QRS-T angle
Model 1 1.12 (0.98 - 1.28)
Model 2 1.13 (0.98 - 1.31)
Area QRS-T angle
Model 1 0.98 (0.85 - 1.14)
Model 2 1.09 (0.93 - 1.27)
Peak SVG elevation
Model 1 1.07 (0.90 - 1.28)
Model 2 1.06 (0.89 - 1.27)
Area SVG elevation
Model 1 1.06 (0.90 - 1.26)
Model 2 1.10 (0.93 - 1.30)
Peak SVG azimuth
Model 1 1.07 (0.92 - 1.24)
Model 2 1.16 (0.99 - 1.35)
Area SVG azimuth
Model 1 1.07 (0.86 - 1.32)
Model 2 1.21 (0.99 - 1.48)
Peak SVG magnitude
Model 1 1.16 (0.98 - 1.36)
Model 2 1.18 (1.00 - 1.39)
Area SVG magnitude
Model 1 1.16 (0.99 - 1.37)
Model 2 1.21 (1.03 - 1.43)
SAI QRST
Model 1 1.16 (1.01 - 1.33)
Model 2 1.16 (1.02 - 1.31)
Cornell voltage
Model 1 1.14 (0.97 - 1.34)
Model 2 1.23 (1.10 - 1.38)
QRS duration
Model 1 1.27 (1.08 - 1.49)
Model 2 1.10 (0.96 - 1.27)
Bazett's QTc
Model 1 1.15 (1.02 - 1.30)
Model 2 1.11 (0.99 - 1.26)
Heart rate
Model 1 1.16 (0.97 - 1.37)
Model 2 1.19 (1.01 - 1.40)
0.8 1.0 1.2 1.4 1.6
Adjusted Relative Sub - Hazard Ratio for women vs. men
Peak QRS-T angle
Model 1 1.05 (0.97 - 1.14)
Model 2 1.10 (1.004 - 1.20)
Area QRS-T angle
Model 1 1.07 (0.98 - 1.18)
Model 2 1.09 (0.99 - 1.20)
Peak SVG elevation
Model 1 0.97 (0.88 - 1.06)
Model 2 0.99 (0.91 - 1.08)
Area SVG elevation
Model 1 0.99 (0.91 - 1.08)
Model 2 0.95 (0.86 - 1.06)
Peak SVG azimuth
Model 1 1.06 (0.98 - 1.16)
Model 2 1.05 (0.95 - 1.15)
Area SVG azimuth
Model 1 1.03 (0.94 - 1.13)
Model 2 1.02 (0.93 - 1.12)
Peak SVG magnitude
Model 1 1.11 (1.01 - 1.22)
Model 2 0.97 (0.87 - 1.07)
Area SVG magnitude
Model 1 1.15 (1.05 - 1.26)
Model 2 1.00 (0.90 - 1.10)
SAI QRST
Model 1 1.16 (1.06 - 1.27)
Model 2 1.01 (0.93 - 1.10)
Cornell voltage
Model 1 1.11 (1.01 - 1.22)
Model 2 0.97 (0.90 - 1.06)
QRS duration
Model 1 0.95 (0.88 - 1.03)
Model 2 0.94 (0.85 - 1.03)
Bazett's QTc
Model 1 0.87 (0.81 - 0.94)
Model 2 1.02 (0.94 - 1.12)
Heart rate
Model 1 0.98 (0.89 - 1.07)
Model 2 1.06 (0.96 - 1.17)
0.8 0.9 1.0 1.1 1.2 1.3
Adjusted Relative Sub - Hazard Ratio for women vs. men

Figure 6:


Competing Risk Model 1
Sudden Cardiac Death
Non - Sudden Cardiac Death
Peak QRS-T angle
Men 1.19 (1.08 - 1.31)
Women 1.32 (1.17 - 1.49)
1.15 (1.08 - 1.21)
1.15 (1.08 - 1.23)
Area QRS-T angle
Men 1.21 (1.09 - 1.33)
Women 1.16 (1.02 - 1.33)
1.16 (1.09 - 1.24)
1.22 (1.14 - 1.31)
Peak SVG elevation
Men 1.12 (1.00 - 1.24)
Women 1.15 (0.97 - 1.37)
1.03 (0.97 - 1.09)
1.00 (0.93 - 1.08)
Area SVG elevation
Men 1.15 (1.05 - 1.25)
Women 1.15 (0.98 -1.35)
1.01 (0.95 - 1.07)
1.00 (0.93 - 1.07)
Peak SVG azimuth
Men 1.11 (1.02 - 1.21)
Women 1.18 (1.03 - 1.36)
1.05 (1.00 - 1.11)
1.09 (1.01 - 1.17)
Area SVG azimuth
Men 1.01 (0.93 - 1.11)
Women 1.09 (0.86 - 1.37)
1.08 (1.01 - 1.15)
1.09 (1.01 - 1.17)
Peak SVG magnitude
Men 0.91 (0.81 - 1.02)
Women 0.98 (0.84 - 1.14)
0.94 (0.88 - 1.00)
1.00 (0.93 - 1.08)
Area SVG magnitude
Men 0.96 (0.86 - 1.07)
Women 1.06 (0.90 - 1.24)
0.96 (0.90 - 1.03)
1.04 (0.96 - 1.12)
SAI QRST
Men 1.04 (0.93 - 1.15)
Women 1.21 (1.06 - 1.38)
1.01 (0.94 - 1.08)
1.13 (1.04 - 1.22)
Cornell voltage
Men 1.08 (0.98 - 1.20)
Women 1.14 (1.06 - 1.38)
1.12 (1.05 - 1.19)
1.20 (1.11 - 1.30)
QRS duration
Men 0.98 (0.88 - 1.08)
Women 1.26 (1.09 - 1.46)
1.06 (1.00 - 1.13)
1.00 (0.93 - 1.07)
Bazett's QTc
Men 1.05 (0.94 - 1.18)
Women 1.18 (1.10 - 1.27)
1.22 (1.15 - 1.30)
1.04 (0.99 - 1.09)
Heart rate
Men 1.01 (0.90 - 1.13)
Women 1.18 (1.04 - 1.35)
1.20 (1.12 - 1.27)
1.15 (1.07 - 1.23)
0.8 1.0 1.2 1.4 1.6
0.9 1.0 1.1 1.2 1.3
Sub - Hazard Ratio of SCD
Sub - Hazard Ratio of nonSCD
Competing Risk Model 2
Sudden Cardiac Death
Non - Sudden Cardiac Death
Peak QRS-T angle
Men 1.14 (1.03 - 1.25)
Women 1.20 (1.05 - 1.36)
0.92 (0.86 - 0.98)
0.97 (0.90 - 1.05)
Area QRS-T angle
Men 1.18 (1.06 - 1.31)
Women 1.22 (1.07 - 1.39)
0.92 (0.86 - 0.98)
0.95 (0.87 - 1.04)
Peak SVG elevation
Men 1.13 (1.02-1.25)
Women 1.11 (0.95 - 1.30)
0.94 (0.88 - 1.01)
0.94 (0.86 - 1.02)
Area SVG elevation
Men 1.09 (0.99 - 1.21)
Women 1.12 (0.94 -1.27)
0.97 (0.90 - 1.04)
0.92 (0.85 - 1.00)
Peak SVG azimuth
Men 1.12 (1.02 - 1.22)
Women 1.24 (1.08 - 1.42)
0.95 (0.90 - 1.01)
0.97 (0.89 - 1.06)
Area SVG azimuth
Men 1.05 (0.95 - 1.16)
Women 1.25 (1.04 - 1.49)
0.96 (0.91 - 1.02)
0.95 (0.88 - 1.02)
Peak SVG magnitude
Men 0.94 (0.84 - 1.06)
Women 1.06 (0.92 - 1.22)
1.02 (0.95 - 1.11)
0.97 (0.90 - 1.05)
Area SVG magnitude
Men 0.96 (0.85 - 1.07)
Women 1.12 (0.96 - 1.31)
1.01 (0.94 - 1.10)
0.98 (0.91 - 1.06)
SAI QRST
Men 1.07 (0.99 - 1.15)
Women 1.18 (1.05 - 1.33)
0.95 (0.91 - 1.00)
0.93 (0.86 - 1.00)
Cornell voltage
Men 1.06 (0.98 - 1.14)
Women 1.22 (1.11 - 1.35)
0.98 (0.93 - 1.03)
0.94 (0.87 - 1.01)
QRS duration
Men 1.15 (1.06 - 1.25)
Women 1.18 (1.04 - 1.34)
0.95 (0.90 - 1.00)
0.88 (0.81 - 0.95)
Bazett's QTc
Men 1.10 (1.01 - 1.21)
Women 1.17 (1.07 - 1.29)
1.02 (0.96 - 1.09)
1.03 (0.92 - 1.10)
Heart rate
Men 0.99 (0.89 - 1.11)
Women 1.16 (1.02 - 1.32)
1.09 (1.02 - 1.16)
1.13 (1.05 - 1.22)
0.8 1.0 1.2 1.4 1.6
0.8 0.9 1.0 1.1 1.2
Sub - Hazard Ratio of SCD
Sub - Hazard Ratio of nonSCD