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Global Electrocardiographic Measures and Cardiac Structure and Function: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background—Electrical excitation initiates myocardial mechanical contraction and coordinates myocardial pumping. We hypothesized that ECG global electrical heterogeneity (GEH) and its longitudinal changes are associated with cardiac structure and function.

Methods and Results—Participants from the Atherosclerosis Risk in Communities (ARIC) study (N=5,114; 58% female; 22% African Americans) with resting 12-lead ECGs (visits 1–5) and echocardiographic assessment of left ventricular ejection fraction (LVEF), LV global longitudinal strain, LV mass index (LVMi), LV end-diastolic (LVEDVi), and end-systolic volume index (LVESVi) at visit 5 were included. Longitudinal analysis included ARIC participants (N=14,609) with measured GEH at visits 1–4. GEH was quantified by spatial ventricular gradient, QRS-T angle, and sum absolute QRST integral (SAI QRST). Cross-sectional and longitudinal regressions were adjusted for manifest and subclinical cardiovascular disease (CVD). Having 4 abnormal GEH parameters was associated with a 6.4%(95% CI 5.5–7.3%) LVEF decline, a 24.2 (95%CI 21.5–26.9) g/m^2 increase in LVMi, a 10.3 (95%CI 8.9–11.7) mL/m^2 increase in LVEDVi, and a 7.8 (95%CI 6.9–8.6) mL/m^2 increase in LVESVi. Altogether, clinical and ECG parameters accounted for approximately 1/3rd of LV volume and 20% of systolic function variability. The

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associations were significantly stronger in CVD. SAI QRST increased by 20 mV*ms for each 3-year period in participants who demonstrated LV dilatation at visit 5. Sudden cardiac death victims demonstrated rapid GEH worsening, while those with LV dysfunction demonstrated slow GEH worsening. Healthy aging was associated with a distinct pattern of SVG azimuth decrement.

Conclusion—GEH is a marker of subclinical abnormalities in cardiac structure and function.

Journal Subject Terms

Electrocardiology (ECG); Epidemiology; Echocardiography; Electrophysiology; Aging

Keywords

electrocardiography; longitudinal cohort study; left ventricular hypertrophy; left ventricular systolic function; left ventricle geometry; global electrical heterogeneity; vectorcardiography

Introduction

The heart is an electrical generator and electromechanical pump[1]. Electrical excitation initiates mechanical contraction, orchestrates excitation-contraction coupling[1], and coordinates myocardial pumping. Changes in the frequency[2], regularity[3], and order[4] of cardiac electrical excitation can cause electrical heterogeneity, dyssynchrony, ventricular dysfunction, and ultimately clinical pump failure[2–4]. While the molecular biology of excitation-contraction coupling is well understood[1], and mechanisms of dyssynchrony-induced cardiomyopathy are recognized, its prognostic markers are not identified[5]. Additionally, there is no inexpensive and widely available method for monitoring the degree of or changes in electrical dyssynchrony over time.

Recently we described ECG parameters depicting global electrical heterogeneity (GEH)[6]. The GEH concept is based on the theory of Wilson's electrical gradient vector[7], which characterizes the degree of heterogeneity of total recovery time[8] across the ventricles, and points towards the area where the total recovery time is shortest. Five vectorcardiographic parameters (spatial QRS-T angle, sum absolute QRST integral (SAI QRST), spatial ventricular gradient (SVG) vector magnitude, azimuth, and elevation) characterize GEH[6]. We recently showed that GEH characterizes an electrophysiological substrate independently associated with the risk of sudden cardiac death (SCD)[6]. However, the relationships between GEH and cardiac structure and function have not been previously studied and have not been compared with traditional global ECG parameters (QRS and QTc intervals and electrocardiographic left ventricular hypertrophy (LVH) measures). We hypothesized that GEH is associated with echocardiographic measures of cardiac structure and function in the general community population with and without ventricular conduction abnormalities, LVH, and cardiovascular disease (CVD). We also hypothesized that longitudinal patterns of GEH changes over time differ in participants with different clinical outcomes (with vs. without left ventricular (LV) dysfunction, SCD, non-sudden cardiac death, and non-cardiac death).

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Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study sample

The Atherosclerosis Risk in Communities (ARIC) study is an ongoing, prospective cohort study evaluating risk factors, progression, and outcomes of atherosclerosis in 15,792 participants (45% male, 74% white) enrolled in four United States communities in 1987–1989. ARIC study design and protocol have been previously described[9]. Follow-up of ARIC participants included three triennial visits through 1998; each visit included a 12-lead ECG recording[10]. A fifth examination was conducted between June 1st, 2011, and August 30th, 2013. Out of 10,740 surviving participants, 6,538 participants (now aged 67–91 years) attended visit 5, and 6,118 underwent echocardiography, whereas 5,981 underwent 12-lead ECG recording at rest. The study protocol was approved by institutional review boards at each field center, and all participants signed informed consent.

Our cross-sectional study sample included ARIC cohort participants who underwent both echocardiography and 12-lead ECG during Visit 5 (on the same day) with echocardiographic images and ECG recordings of acceptable quality for analysis, and the ability to measure GEH. We excluded participants with reported race other than white or black (n=18), without echocardiographic examination (n=598), with atrial fibrillation at the time of echocardiography, with absent or uninterpretable ECGs (n=162), and those with missing covariates (n=272). The final study population included 5,114 participants with analyzable data on cardiac structure and function and ECG GEH. In addition, longitudinal analysis included all ARIC cohort participants (N=14,609) with measured GEH at visits 1–4, as reported previously[6].

Definition of clinical covariates

For cross-sectional analysis, demographic and clinical characteristics were assessed at the time of the 5th visit. Coronary heart disease (CHD) was defined as a history of myocardial infarction (MI), a history of angina pectoris, or a history of coronary revascularization (either via coronary artery bypass surgery or percutaneous coronary intervention). At baseline (visit 1) history of MI was defined by participant self-report. At subsequent visits, it was defined as baseline history plus adjudicated events between baseline and the visit of interest. Heart failure (HF)[11] was defined as evidence of symptomatic HF as defined by stage 3 of the Gothenburg criteria[12] which required the presence of specific cardiac and pulmonary symptoms in addition to medical treatment of HF, self-reported use of HF medications, an adjudicated HF hospitalization (since 2005), or HF hospitalization with International Classification of Diseases-9th Revision, code 428× (before 2005). Hypertension was defined as a systolic blood pressure (BP; average between second and third measures) of ≥140 mmHg, a diastolic BP ≥ 90 mmHg, or physician-reported history of hypertension and use of anti-hypertensive medications. Diabetes mellitus (DM) was defined as a non-fasting glucose level of at least 200 mg/dL, a fasting (≥8 hours) glucose level of

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≥126 mg/dL, a self-reported a physician diagnosis of DM, or the use of diabetic medications.

Concentrations of high sensitivity cardiac troponin T (hsTnT) and N-terminal pro–B-type natriuretic peptide (NT-proBNP) were measured as previously described[13] at the 4th (1996–1998) and 5th (2011–2013) study visits.

For longitudinal analyses, we used time-updated clinical covariates: incident CHD, HF, diabetes, and hypertension. Follow-up of the study participants included annual telephone calls, local hospital surveillance, three triennial visits through 1998, and the 5th study visit (2011–2013), as previously reported[10]. Incident HF was diagnosed as first HF hospitalization with *ICD-9* code 428.0–428.9 in any position of the hospital discharge list as well as characteristic signs and symptoms of congestion, characteristic chest X-ray findings, and/or assessment of left ventricular (LV) function[14]. Incident CHD was defined as a definite or probable MI, angina, or a coronary revascularization procedure[6]. Risk factors (BMI, smoking status, total cholesterol, high density lipoproteins (HDL), triglycerides, systolic and diastolic blood pressure) were assessed at each visit.

Assessment of global electrical heterogeneity and traditional ECG characteristics on ECG

GEH was quantified by five parameters, as previously described[6] (Supplemental Figure 1). Spatial mean QRS-T angle was measured as the three-dimensional angle between the mean QRS- and T-vectors[15]. The magnitude and direction (azimuth and elevation) of the mean SVG vector (vectorial sum of the mean QRS- and the mean T-vectors) were determined[6]. SAI QRST was computed as the arithmetic sum of areas under the QRST curve on XYZ leads, with baseline defined as the voltage at the end of the T-wave[16, 17]. As SVG magnitude is largely independent of the specific ventricular activation sequence[18], we did not exclude participants with ventricular conduction abnormalities. Sex- and race-specific thresholds were used to define abnormal GEH parameters, as previously described[6].

Heart rate, corrected QT interval (QTc), and QRS duration were measured on the median beat by the General Electric (GE) 12SL algorithm (GE Marquette, Milwaukee, WI). Prolonged QTc was defined as exceeding 450 ms in men and 470 ms in women[19]. Sex-specific Cornell product was calculated for assessment of ECG-LVH (> 2440 mm*ms)[20]. Presence of ventricular conduction abnormalities were defined by the Minnesota Code (MC)[21] (left bundle branch block MC 7.1, right bundle branch block MC 7.2 and 7.3, fascicular block MC 7.6–7.7, bi-fascicular block MC 7.8), or ventricular-paced rhythm.

We measured GEH and traditional ECG parameters on all ECGs recorded during visits 1–5.

Assessment of cardiac structure and function on echocardiogram

Details of the echocardiographic imaging and analysis protocol have been thoroughly described previously[22]. All echocardiograms were acquired during Visit 5 with a dedicated machine (Phillips iE33 Ultrasound systems with Vision 2011) per a detailed acquisition protocol that included comprehensive two-dimensional, Doppler, tissue Doppler, and speckle-tracking echocardiography[22]. Heart rate and systolic and diastolic blood pressure were measured at the time of echocardiography. Dedicated and blinded analysts at the

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Brigham and Women's Hospital Cardiac Imaging Core Laboratory performed quantitative measures on all echocardiograms according to American Society of Echocardiography (ASE) recommendations and standards[23, 24]. LV volumes and the LVEF were assessed using the modified Simpson rule.

Cardiac structure measurements included left-ventricular (LV) end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV mass index (LVMi). LV dimensions and mass were indexed to body surface area (BSA) as per ASE guidelines[23, 24]. As recommended, LVEDV index (LVEDVi) > 74 mL/m^2 for men and > 61 mL/m^2 for women and LVESV index (LVESVi) > 31 mL/m^2 for men and > 24 mL/m^2 for women were considered abnormal[24]. Echo-LVH was defined if LVMi exceeded 115 g/m^2 in men and 95 g/m^2 in women.[24]

Systolic LV function measurements included LV ejection fraction (LVEF) and global longitudinal LV strain (GLS) derived from speckle-tracking echocardiography. Speckle-tracking analysis was performed using Tom-Tec Cardiac Performance Analysis package (TomTec, Unterschleissheim, Germany). GLS was obtained from apical 4- and 2-chamber views, as previously described[22]. LVEF of less than 52% for men and less than 54% for women was defined as abnormal[24]. Peak GLS > −14% was considered abnormal[24, 25].

Statistical analysis

All continuous variables are presented as means ± standard deviation (SD). Square root transformed SVG elevation and square root transformed absolute SVG azimuth were used in all adjusted analyses to normalize distribution of these two circular variables. Due to a U-shaped association between SVG magnitude and echocardiographic parameters, we squared SVG magnitude for its entry as a predictor in linear regression models.

Comparison of Visit 5 responders to alive Visit 5 nonresponders—To determine how ARIC study participants who participated in visit 5 ("Visit 5 responders") are similar to alive ARIC study participants who did not participate in Visit 5 ("Visit 5 nonresponders"), we compared baseline (Visit 1) clinical characteristics of Visit 5 responders vs. Visit 5 nonresponders, using *t*-test and chi-squared test, as appropriate.

Cross-sectional analyses—ANOVA was used for unadjusted comparisons of LV structure and function in participants with abnormal GEH parameters. To assess continuous relationships between electrocardiographic and echocardiographic measures, we used multivariable linear regression models. Each ECG predictor variable was entered into a separate regression model. To answer whether cross-sectional associations between ECG and LV structure and function were mostly due to prevalent or subclinical CVD, we constructed multiple models. Model 1 was minimally adjusted for age, gender, and race. Model 2 was additionally adjusted for known confounders of cardiac structure and function[26, 27]: CHD, HF, hypertension, diabetes, BMI, smoking, presence of ventricular conduction abnormalities, as well as heart rate and systolic and diastolic blood pressure measured at the time of echocardiography. Model 3 was additionally adjusted for QRS duration. Standardized beta coefficients were used to compare the strength of the association across ECG predictors, reflecting the change of outcome variable per 1 SD of each ECG

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predictor variable increase. Subgroup analysis was performed in Model 2 to determine significant interactions between ECG parameters and clinical characteristics in their effect on LV structure and function. In addition, associations between ECG and echocardiographic parameters were also evaluated using fully adjusted (Model 2) multivariable linear regression models incorporating cubic splines with 4 knots.

Longitudinal analysis I: comparison of longitudinal ECG changes in participants who did vs. did not develop LVH, LV dilatation, and systolic dysfunction—To determine whether longitudinal changes in ECG parameters were associated with LV structure and function, we performed several longitudinal analyses. First, a *t*-test was used to compare differences in baseline (measured at visit 1) ECG parameters in participants with vs. without LV systolic dysfunction, dilatation, or hypertrophy, as diagnosed by echocardiography at visit 5 (median 24 years later). Next, we compared patterns of visit-to-visit changes in ECG parameters over time (from visit 1 to visit 5) in participants who did vs. did not develop LVH, LV dilatation, and systolic dysfunction. Generalized estimating equations (GEE) were used to fit population-averaged generalized linear models. Within-participant correlation structure was estimated as autoregressive of order 1. The canonical link function for the Gaussian family was used. Robust standard error was reported. Time-updated ECG variables served as continuous time-updated outcomes. Separate models were constructed for each ECG variable.

To answer the question of whether LVH, LV dilatation, and LV systolic dysfunction were associated with different patterns of ECG changes over time, these binary echocardiographic variables were entered in the models one-by-one. The pattern of dynamic ECG changes was described in each subgroup: in participants with and without LVH, LV dilatation, and systolic dysfunction. All linear GEE models were rigorously adjusted for time-updated confounders representing known pathways of myocardial injury. Model 1 was adjusted by gender and race. Model 2 was in addition adjusted for prevalent and incident HF and CHD. Model 3 was further adjusted for all time-updated covariates (diabetes, hypertension, BMI, current smoking status, levels of total cholesterol, HDL, triglycerides, systolic and diastolic blood pressure, heart rate, presence of ventricular conduction abnormalities, hsTnT and NTpro-BNP, age), and exact time interval (in days) between each ECG recording.

Longitudinal analysis II: comparison of ECG change patterns in healthy aging participants vs. those who developed LVH, LV dilatation, LV systolic dysfunction, or died due to SCD, non-sudden cardiac death, or non-cardiac death—We performed a comparison of longitudinal ECG changes in ARIC study participants who died due to SCD, non-sudden cardiac death, and non-cardiac death before the 5^{th} visit, and those who survived and were diagnosed with LV systolic dysfunction, LVH, and LV dilatation on the 5^{th} visit echocardiogram. For appropriate comparison, in survivors we used patterns of changes in ECG parameters from visit 1 to visit 4 (median 12 years). Linear GEE models were constructed in 3 subgroups of competing death outcomes[6], and 5 LV dysfunction subgroups. All models were adjusted for sex and race.

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Statistical analyses were performed using STATA MP 15.0 (StataCorp LP, College Station, TX). We applied the Bonferroni correction for multiple testing. As we tested 8 predictors and 5 outcomes, a P-value < 0.00125 (0.05/40) was considered statistically significant.

Results

Study population

Clinical characteristics of the study participants (obtained at visit 5) are shown in Table 1. Prevalent CHD and HF were infrequent, whereas CHD risk factors were common. LV systolic function and LV volumes were within the normal range in most participants. Approximately 10% of participants had ECG LVH. Abnormal GEH was observed more frequently than traditional ECG abnormalities: two thirds of participants had at least one abnormal GEH parameter, and 38% of participants had at least two abnormal GEH parameters. No participants had abnormal SVG magnitude.

Comparison of Visit 5 responders to alive Visit 5 nonresponders

Visit 5 nonresponders as compared to responders were older, were more likely to be female and black, and had higher rates of prevalent CVD and CVD risk factors (Table 1). Nevertheless, there were no significant differences in most baseline ECG GEH parameters between these two groups, with a few exceptions. SVG magnitude and SAI QRST were significantly smaller in Visit 5 nonresponders in spite of significantly longer QTc and larger Cornell product (Table 1).

Cross-sectional association of global ECG measures with LV structure and systolic function at study visit 5

In unadjusted analyses, the number of abnormal GEH parameters was associated with LV systolic function, LV volumes and LV mass indices (Figure 1). In adjusted regression analyses, all ECG metrics at visit 5 were robustly associated with echocardiographic measures of cardiac structure and systolic function at visit 5, except SVG magnitude, which did not associate with LVEF (Figure 2). All GEH ECG variables were monotonically associated with echocardiographic metrics (Figure 3 and Supplemental Figures 2–5). Adjustment for prevalent and subclinical CVD only slightly attenuated the strength of these associations, suggesting an independent cross-sectional association between ECG GEH characteristics and LV structure and function, although the strength of associations ranged from negligible to weak (Figure 2). Further adjustment for QRS duration confirmed an independent association between GEH and LV structure and function, and revealed differences between the 5 GEH parameters. QRS duration fully explained the associations of SVG elevation with GLS and of SVG azimuth with LV volumes (Figure 2).

Higher GEH was significantly associated with worse LV systolic function (Figure 2). For every 10 ms increase in QRS duration, LVEF (Figure 3) decreased by 1% (95%CI 0.9–1.1%). Every 100 mV*ms increase in SAI QRST was associated with a 2% (95%CI 1.6–2.1%) LVEF drop. The presence of ECG-LVH was associated with a 3% (95% CI 2.4–3.6%) LVEF reduction, and having 4 abnormal GEH parameters was associated with a 6.4% (95% CI 5.5–7.3%) LVEF decline. SAI QRST had a strong association with GLS (Supplemental

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Figure 2). Although each ECG measure separately explained a relatively small proportion (approximately 10%) of population-level variability of LV systolic function parameters, altogether, electrocardiographic and clinical characteristics were responsible for about 20% of systolic function variability (Figure 2).

Cross-sectional associations between GEH and LVMi were stronger than those between GEH and LV systolic function (Figure 2 and Supplemental Figure 3). Having 4 abnormal GEH metrics was associated with 24.2 (95%CI 21.5–26.9) g/m^2 increase in LVMi, whereas having ECG-LVH was associated with only a 13.7 (95%CI 11.9–15.5) g/m^2 increase in LVMi. For every 10 ms increase in QRS duration, LVMi increased by 3.2 (95%CI 2.9–3.6) g/m^2. Altogether, ECG and clinical characteristics explained up to one quarter of LVMi variability.

SAI QRST strongly associated with LVEDVi, explaining 26% of LVEDVi variability (Figure 2). Altogether, clinical and ECG parameters accounted for approximately one third of LV volume variability (Supplemental Figures 4 and 5). Each 10 ms increase in QRS duration resulted in a 1.8 (95%CI 1.6–2.0) mL/m^2 increase in the LVEDVi. Having 4 abnormal GEH parameters was associated with a 10.3 (95%CI 8.9–11.7) mL/m^2 increase in LVEDVi, and a 7.8 (95%CI 6.9–8.6) mL/m^2 increase in LVESVi.

Subgroups analyses

We observed numerous interactions between ECG parameters and clinical characteristics in their effect on LV echocardiographic measures of cardiac structure and function (Supplemental Table 1). Overall, the associations between ECG parameters and LV structure and function were stronger in the subgroups of participants with prevalent and subclinical CVD (Figure 4 and Supplemental Figures 6–8), with few exceptions. SAI QRST was more strongly associated with LVEDVi and LVESVi in hypertension-free participants and individuals with normal conduction, as compared to hypertensive participants and those with conduction abnormalities (Supplemental Table 1). Cornell product was more strongly associated with LVEF in CHD-free participants as compared to those with CHD (Figure 4).

Association of longitudinal changes in ECG parameters over 24 years with LV structure and function

Measurement of visit 1 baseline ECG parameters was performed 23.6 ±1.0 years prior to the echocardiographic assessment of LV structure and function. Study participants with LV systolic dysfunction and abnormal LVESVi at visit 5 had wider (by 12 degrees) baseline QRS-T angles and larger (by 20 mV*ms) SAI QRST (Supplemental Table 2). SVG elevation (but not azimuth or magnitude) was also different ~24 years prior to the diagnosis of LV systolic dysfunction. Differences in QRS duration (3 ms) were statistically significant, but very small. Of note, baseline GEH parameters (especially SAI QRST) did not differ in individuals with vs. without echo-LVH which was diagnosed 24 years later. In contrast, baseline Cornell product was significantly larger in the subgroup with echo-LVH (Supplemental Table 2).

Unadjusted (Figure 5 and Supplemental Figures 9–12) and adjusted longitudinal analyses (Figure 6 and Supplemental Table 3) showed that patterns of longitudinal changes in all but

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one ECG parameter were significantly and dramatically different in participants with normal vs. abnormal LV structure and function. The pattern of temporal SVG magnitude changes, however, was an exception: it very slightly and monotonically decreased in all individuals. SAI QRST did not change in healthy aging participants. In contrast, SAI QRST increased on average by 20 mV*ms over each 3-year period in participants who demonstrated LV dilatation at visit 5. Similar patterns were confirmed for longitudinal changes of QRS-T angle (about 10 degrees/3-years), SVG azimuth and elevation, Cornell product (about 200 mm*ms/3-years), and QTc intervals (5–8 mm/3-years). Systolic dysfunction and LV dilatation were associated with larger longitudinal changes in GEH ECG parameters, whereas echo-LVH was associated with smaller longitudinal ECG parameter changes.

Longitudinal ECG changes in participants who developed LV systolic dysfunction, LVH, and LV dilatation were fully explained by clinically manifest and subclinical CVD and subclinical myocardial injury (Figure 6 and Supplemental Table 3). In contrast, after rigorous adjustment, uniform (across participants) and statistically significant longitudinal changes in all but one ECG parameter were observed in survivors with normal LV function. Healthy aging was characterized by a slight decrease in QRS-T angle (1º/3-years) and SVG azimuth, and a slight increase in SAI QRST (1–2 mV*ms/3-years), Cornell product (20 mm*ms/3-years), QTc (1.3 ms/3-years), and SVG elevation and magnitude. The degree of heterogeneity in ECG changes across healthy aging participants was very small. QRS duration was an exception, however; after full adjustment, there were no statistically significant longitudinal trends in QRS duration in healthy aging participants (Figure 6). Longitudinal changes in QRS duration were fully explained by subclinical myocardial injury not only in LV dysfunction, but also in a healthy aging group.

Comparison of longitudinal ECG trends in participants with different modes of death and LV dysfunction over 12-years of follow-up

Longitudinal changes in ECG parameters in ARIC cohort participants with different causes of death, in comparison to surviving participants, (Figure 7 and Supplemental Figure 13) showed that cardiac death victims experienced the fastest GEH worsening (Supplemental Table 4). The pattern of ECG changes in SCD victims and victims of non-sudden cardiac death was similar to that as described above for individuals with LV dysfunction (Figure 6). The major difference between these subgroups was in the speed of GEH worsening; while SCD victims were characterized by rapid worsening of GEH over time, those who developed LV dysfunction demonstrated slow progression of GEH worsening. One additional distinct feature of healthy aging was the opposite direction of SVG azimuth changes over time (decreasing sqrt-SVG azimuth; Figure 7D). Due to shorter follow-up (median 12 years vs. 24 years), longitudinal analysis II had less statistical power compared to longitudinal analysis I, which explains the wider confidence intervals in Figure 7. However, point estimates reported by both longitudinal analyses were consistent.

Discussion

In this large bi-racial community-based cohort of elderly individuals, we demonstrated, in both cross-sectional and longitudinal analyses, that GEH was associated with

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echocardiographic measures of cardiac structure and function. These findings confirm the concept that electrophysiological properties in general, and the GEH phenotype specifically, reflect subclinical abnormalities in cardiac structure and function, and represents one mechanism by which abnormal electrophysiological substrate may lead to an increased risk of LV dysfunction and/or SCD. Together with clinical characteristics, GEH ECG parameters explained up to one third of variability in LV structure and function, confirming the utility of assessing cardiac electrophysiological properties to better understand cardiac electromechanical pump physiology. Clear differences in GEH observed nearly 25 years prior to diagnosed LV dysfunction, and distinct patterns of gradually increasing GEH were independently associated with LV systolic dysfunction, dilatation, and hypertrophy. Slowly worsening GEH parameters were associated with subsequent LV dysfunction, whereas SCD victims were characterized by rapidly worsening GEH parameters. Observing longitudinal changes in GEH over time offers opportunities for preventive interventions, and this should be further explored in future prospective clinical trials. Longitudinal GEH changes in participants with LV dysfunction are likely explained by underlying CVD and subclinical myocardial injury. Importantly, our study described a distinct pattern of longitudinal changes in SVG azimuth in healthy aging participants. Altogether, our study provided evidence of a potential vicious cycle of abnormal GEH leading to LV dysfunction, which in turn further exacerbates GEH abnormalities.

Vicious cycle of GEH and LV dysfunction

We observed a distinct longitudinal association of SVG direction (SVG azimuth) with normal LV function over a median of 25 years of follow-up in spite of the presence of traditional risk factors[28]. This observation supports the hypothesis of a primary effect (either favorable or unfavorable) of SVG direction on electromechanical pump function. If favorable, it diminishes the influence of traditional risk factors and potentially counteracts subclinical myocardial injury, preserving LV function. In the case of abnormal GEH it may facilitate development of LV dysfunction, promote deleterious effects of traditional cardiovascular risk factors and subclinical injury, and facilitate progression of CVD substrate. In turn, this progressive CVD substrate may worsen GEH. As we observed, the degree of GEH abnormalities were significantly larger in participants with CVD, and the strength of correlation between LV function measures and GEH measures was stronger in participants with LV dysfunction. Further study of the mechanism of SVG direction effect on cardiac electrophysiology is warranted.

GEH is a marker of early subclinical myocardial injury

We observed that adjustment for CVD, its risk factors, and subclinical myocardial injury (hs troponin T and proBNP) fully explained longitudinal trends in participants with developing LV dysfunction. Therefore, GEH can serve as a marker of subclinical myocardial injury. Previous studies have demonstrated a longitudinal association between hsTnI and SAI QRST[29] in HF patients, which is consistent with our findings.

Differences between SCD and LV dysfunction in longitudinal trend of GEH progression

Our findings help to explain differences in the risk of SCD and the risk of progressive LV dysfunction. Rapidly worsening GEH is associated with increased SCD risk, whereas slowly

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worsening GEH is associated with increased risk of developing LV dysfunction. We previously reported an increased risk of SCD associated with large GEH changes over time[6]. This finding underscored importance of serial GEH monitoring, as one single measure of GEH might not be sufficient for discrimination of the risk of SCD from non-SCD.

GEH and LV systolic function

In our study, QRS duration had the strongest cross-sectional association with LVEF, whereas SAI QRST had the strongest independent association with GLS. Altogether, GEH explained approximately 10% of systolic function variability in cross-sectional analysis. An inverse relationship between QRS duration and systolic function has been reported in the Framingham Heart Study[30]. GLS is more sensitive than LVEF for detection of myocardial dysfunction and prediction of adverse cardiovascular outcomes.[31, 32] Our findings confirm an association between global ECG measures (both traditional and novel) and LV systolic function. However, the weak-to-negligible strength of the association suggests that electrical and mechanical domains cannot be considered interchangeable, and should be viewed as complementary characteristics of cardiac electromechanical function. Longitudinally increasing QRS-T angle, SAI QRST, and changing SVG direction were strongly associated with LV systolic dysfunction. Early detection of subclinical cardiovascular disease is crucially important for successful prevention of overt CVD and adverse CV outcomes. Further studies are needed to assess how GEH changes in response to cardiovascular medications and life-style modifications. Additionally, in the future, automated GEH measurement can be easily implemented into routine clinical 12-lead ECG analysis, and this could enable widespread GEH monitoring for the early detection of abnormal electrophysiological substrate which might then trigger further testing or treatment.

GEH and cardiac structure

Several studies have shown a positive association between LV size (diameter, volumes, and length) and QRS duration[30, 33, 34]. In this study, SAI QRST, sex-specific Cornell product, and QRS duration had the strongest association with LV size and mass. Consistent with previous findings of QRS duration studies[30, 33, 34], the strength of association between LV structure and GEH was moderate. Agreement between electrocardiographic left ventricular hypertrophy (ECG-LVH) and LV mass has been extensively studied[35]. ECG-LVH predicts cardiovascular outcomes independent of LV mass[36–38]. Our observation of a moderate association between GEH and LV mass and size supports the concept of independent electrophysiological substrate[6], which only moderately correlates with LV size and mass.

Results of this study potentially explain previously reported discrepancies between ECG-LVH and LV mass[35]. We observed that the association between Cornell product and LVMi was significantly stronger in African Americans, as compared to whites, in younger participants, and in those with smaller BMI. These observed interactions should be considered in the interpretation of ECG-LVH. Of note, we observed that Cornell product was the strongest longitudinal predictor of LVMi, even if measured 25 years prior to observation of echo-LVH. Thus, a “false-positive” ECG-LVH could be considered as an early pre-clinical stage of LVMi increase. This hypothesis should be tested in a prospective study with longitudinal echocardiographic assessment.

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Comparison of ECG parameters

Few prior studies have evaluated associations between QRS-T angle and cardiac structure and function.[39, 40] This study is the first comprehensive cross-sectional and longitudinal evaluation of traditional and novel ECG parameters, uncovering differences between traditional ECG parameters and various GEH metrics.

Our study clarifies differences between SAI QRST and Cornell product. Both parameters incorporate QRS complex duration and voltage, and therefore, correlate with each other.[6] However, this study demonstrated that in longitudinal analysis SAI QRST did not predict echo-LVH, whereas Cornell product did. Consistently, SAI QRST was more strongly associated with LV volumes in hypertension-free participants compared to hypertensive participants, suggesting that LVH confounds SAI QRST interpretation. In our study, SAI QRST was the strongest longitudinal predictor of LV dilatation. Prospective longitudinal study of LV volumes is needed to study longitudinal relationships between SAI QRST and LV geometry. The strong association of SAI QRST with LV volumes (and geometry of the heart) could be explained by the solid angle theorem[41].

Across all studied ECG metrics, QRS duration stood out as the strongest cross-sectional marker of LV structure and systolic function (especially LVEF) in all participants, but especially in the subgroup with HF. At the same time, however, QRS duration, in contrast to all other studied ECG parameters, did not maintain an independent longitudinal trend over time. The patterns of longitudinal changes in QRS duration in both healthy aging and LV dysfunction subgroups was fully explained by CVD risk factors and subclinical myocardial injury. Therefore, QRS duration likely reflects the “end result” of the effect of myocardial injury on electrophysiological substrate, whereas, in contrast, GEH likely reflects the “cause” of myocardial injury. This hypothesis should be further tested in a longitudinal study of LV mechanical function. QRS duration and LVEF are excellent predictors of global and cardiac mortality, but the degree of increased risk for SCD in subjects with increased QRS duration and LVEF is similar to the magnitude of increased total cardiac mortality risk. If there were a mechanistic link between QRS duration/LVEF and SCD, patients with increased QRS duration/decreased LVEF should have risk for SCD increased out of proportion to their total cardiac mortality risk, which have not been shown[42–44].

Strengths and Limitations

Several limitations of the study should be noted. Due to the nature of observational analyses, we cannot rule out the possibility of residual confounding. Although we conducted longitudinal ECG analyses, we were not able to conduct longitudinal analysis of the cardiac structure and function, and therefore we cannot determine the exact timing of LV dysfunction onset. Nevertheless, robust longitudinal analyses of ECG changes over time allowed us to characterize differences in longitudinal trends in individuals who experienced different outcomes, and for the first time to describe SVG direction changes over time, likely contributing to the maintenance of cardiovascular health in spite of exposure to CVD risk factors. Baseline clinical characteristics of ARIC Visit 5 responders and nonresponders differed significantly, which could also reduce the generalizability of the study findings. However, in spite of greater exposure to CVD risk factors at baseline, visit 5 responders and

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nonresponders had similar GEH parameters except for SVG magnitude and SAI QRST. Racial and gender differences in visit 5 responders vs. nonresponders reinforce the importance of enriching future studies of GEH with women and African Americans.

In summary, in a large cohort of middle-aged and elderly men and women we observed that although most echocardiographic measures of cardiac structure and function are in the range of normal values, increasing GEH over time is associated with higher LV mass and volume, and worsening LV systolic function. These associations are independent of demographic characteristics and prevalent and subclinical CVD. GEH is a strong and more sensitive longitudinal predictor of cardiac structure and function as compared to traditional global ECG parameters. Increasing GEH represents a potential mechanism of LV dysfunction. Continuous, long-term monitoring of GEH using ECG patches[45] in the future may allow early identification of subclinical myocardial injury which potentially could assist in prompting timely interventions to improve patient outcomes. QRS duration stands out as the ECG marker having the strongest cross-sectional association with “today’s” LV structure and function, but it does not change over time in a clinically relevant way.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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What is Known?

- Myocardial global electrical heterogeneity (GEH) can be measured on a standard 12-lead ECG through vectorcardiographic parameters (spatial QRS-T angle, spatial ventricular gradient [SVG], and Sum-absolute QRST integral)
- Abnormal increases in GEH parameters are independently associated with sudden cardiac death (SCD) in an adult community-dwelling population

What the Study Adds?

- GEH reflects subclinical abnormalities in cardiac structure and function, and represents one mechanism by which abnormal electrophysiological substrate may lead to an increased risk of left ventricular (LV) dysfunction and SCD.
- Healthy aging in spite of a life-long cardiovascular disease risk factor exposure is characterized by longitudinal changes in SVG azimuth, manifest as posterior rotation of the SVG vector.
- Slow worsening of GEH over time is associated with subsequent LV dysfunction, whereas rapid worsening of GEH is associated with an increased risk of SCD.

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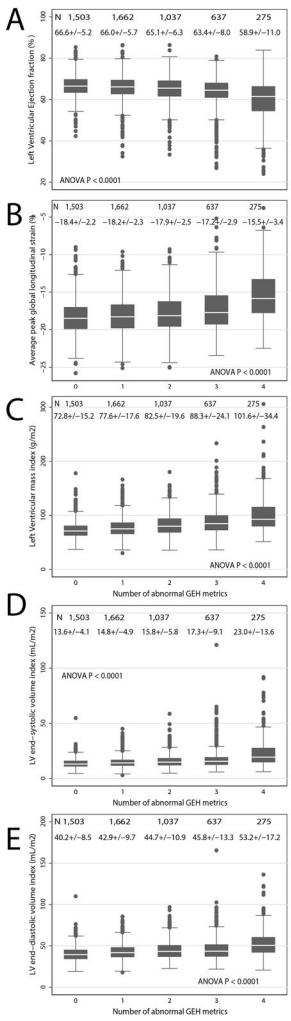

Figure 1. Cross-sectional analysis

Boxplot of left ventricular ejection fraction (**A**), global longitudinal strain (**B**), left ventricular mass index (**C**), left ventricular end-systolic volume index (**D**), and left ventricular end-diastolic index (**E**) in participants with increasing number of abnormal global electrical heterogeneity parameters. Median (white horizontal line crossing the box) and interquartile range (IQR) (box) of each echocardiographic parameter are shown. Whiskers specify the adjacent values, defined as the most extreme values within 1.5 IQR of the nearer quartile.

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Left Ventricular Ejection Fraction (LEVF)

Clinical only model R^2 0.13
GEH only model R^2 0.09

Per 1 SD↑ of:	Model 1 LVEF (95% CI), %		P-value	R^2	Model 2 LVEF (95% CI), %		P-value	R^2	Model 3 LVEF (95% CI), %		P-value
QRS-T angle	-1.52	-1.70 to -1.34	3.03E-59	0.1	-1.15	-1.34 to -1.00	5.83E-32	0.15	-0.68	-0.88 to -0.47	5.21E-11
SVG mag^2	-0.22	-0.39 to -0.04	0.017	0.05	-0.23	-0.40 to -0.06	0.009	0.13	-0.17	-0.34 to -0.006	0.043
SAI QRST	-1.18	-1.36 to -1.00	4.46E-38	0.08	-1.23	-1.42 to -1.04	1.25E-36	0.16	-0.63	-0.84 to -0.41	1.17E-08
Sqrt SVG az	-1.23	-1.40 to -1.05	1.43E-40	0.08	-0.91	-1.11 to -0.71	4.50E-19	0.14	-0.37	-0.58 to -0.16	5.39E-04
Sqrt SVG el	-0.86	-1.04 to -0.68	6.51E-21	0.07	-0.65	-0.83 to -0.46	4.14E-12	0.14	-0.48	-0.66 to -0.30	1.35E-07
QRS duration	-1.59	-1.77 to -1.41	2.62E-64	0.1	-2.11	-2.37 to -1.85	2.11E-56	0.17	-		
Cornell prod	-1.39	-1.57 to -1.1	1.06E-51	0.09	-1.25	-1.44 to -1.07	7.31E-39	0.16	-0.63	-0.85 to -0.41	1.24E-08
QTc interval	-1.45	-1.63 to -1.28	1.91E-58	0.1	-1.09	-1.29 to -0.90	4.76E-28	0.15	-0.54	-0.75 to -0.33	5.09E-07

Global Longitudinal Strain (GLS)

Clinical only model R^2 0.18
GEH only model R^2 0.1

Per 1 SD↑ of:	Model 1 GLS (95% CI), %		P-value	R^2	Model 2 GLS (95% CI), %		P-value	R^2	Model 3 GLS (95% CI), %		P-value
QRS-T angle	0.64	0.57-0.71	3.72E-70	0.1	0.43	0.36 – 0.51	1.19E-32	0.2	0.33	0.25-0.40	3.78E-17
SVG mag^2	0.14	0.07-0.21	9.22E-05	0.05	0.14	0.08-0.21	1.14E-05	0.18	0.13	0.07-0.19	6.44E-05
SAI QRST	0.5	0.43–0.57	2.62E-45	0.08	0.59	0.52-0.66	2.61E-59	0.22	0.51	0.43-0.59	6.38E-35
Sqrt SVG az	0.45	0.38-0.52	4.54E-37	0.07	0.29	0.22-0.37	2.19E-14	0.19	0.15	0.08-0.23	1.37E-04
Sqrt SVG el	0.25	0.18-0.32	5.76E-12	0.05	0.15	0.08-0.21	3.11E-05	0.18	0.1	0.03-0.17	0.003
QRS duration	0.48	0.41-0.55	2.03E-39	0.08	0.56	0.47-0.66	2.10E-29	0.2	-		
Cornell prod	0.58	0.51-0.65	2.95E-60	0.09	0.52	0.46-0.60	4.21E-49	0.21	0.43	0.35-0.52	2.43E-25
QTc interval	0.56	0.49 – 0.63	3.53E-58	0.09	0.35	0.28-0.42	3.99E-21	0.19	0.22	0.05-0.19	1.10E-07

Left Ventricular Mass Index (LVMi)

Clinical only model R^2 0.17
GEH only model R^2 0.17

Per 1 SD↑ of:	Model 1 LVMi (95% CI), g/m^2		P-value	R^2	Model 2 LVMi (95% CI), g/m^2		P-value	R^2	Model 3 LVMi (95% CI), g/m^2		P-value
QRS-T angle	6.04	5.48 – 6.59	2.41E-96	0.14	4.98	4.41 – 5.55	4.98E-63	0.22	3.63	3.02-4.24	2.77E-31
SVG mag^2	1.88	1.33-2.44	2.86E-11	0.07	1.87	1.35 – 2.40	2.62E-12	0.18	1.7	1.19-2.21	7.16E-11
SAI QRST	6.19	5.65-6.73	7.24E-107	0.15	5.42	4.85-5.99	5.42E-75	0.23	3.91	3.27-4.56	5.20E-32
Sqrt SVG az	5.58	5.03 – 6.12	8.24E-86	0.13	4.6	4.00 – 5.19	5.57E-50	0.21	3.1	2.47-3.74	1.60E-21
Sqrt SVG el	3.39	2.83 – 3.95	4.23E-32	0.09	2.29	1.74-2.85	8.55E-16	0.19	1.77	1.22-2.31	2.69E-10
QRS duration	6.26	5.70 - 6.82	8.24E-103	0.14	6.88	6.09 – 7.66	5.53E-64	0.22	-		
Cornell prod	7.97	7.45 – 8.50	1.91E-179	0.2	6.89	6.33 – 7.44	3.13E-126	0.26	5.93	5.29-6.57	8.27E-71
QTc interval	5.18	4.64 – 5.71	2.73E-76	0.12	4.19	3.60 – 4.78	2.86E-43	0.2	2.51	1.87-3.15	1.56E-14

Left Ventricular End Diastolic Volume Index (LVEDVi)

Clinical only model R^2 0.26
GEH only model R^2 0.16

Per 1 SD↑ of:	Model 1 LVEDVi (95% CI), mL/m^2		P-value	R^2	Model 2 LVEDVi (95% CI), mL/m^2		P-value	R^2	Model 3 LVEDVi (95% CI), mL/m^2		P-value
QRS-T angle	1.7	1.41 -1.98	5.96E-31	0.2	1.5	1.21 – 1.80	1.62E-23	0.28	0.55	0.24-0.85	4.88E-04
SVG mag^2	0.9	0.62 – 1.17	2.01E-10	0.18	0.68	0.42 – 0.95	3.95E-07	0.27	0.59	0.33-0.84	7.08E-06
SAI QRST	3.38	3.11 – 3.65	2.77E-129	0.26	2.71	2.42 – 2.99	1.41E-74	0.31	1.76	1.43-2.08	4.43E-26
Sqrt SVG az	1.16	0.88 – 1.44	8.17E-16	0.19	0.8	0.49 – 1.10	4.02E-07	0.27	-0.32	-0.64 to -0.0009	0.049
Sqrt SVG el	1.46	1.19 – 1.74	1.62E-24	0.19	1.27	0.99 – 1.55	8.92E-19	0.27	0.97	0.70-1.24	3.37E-12
QRS duration	2.88	2.60 – 3.16	4.11E-87	0.24	3.85	3.46 – 4.24	1.67E-79	0.31	-		
Cornell prod	2.57	2.30 – 2.84	4.42E-73	0.23	2.24	1.96 – 2.53	1.87E-52	0.3	1.1	0.77-1.43	8.45E-11
QTc interval	1.9	1.62 – 2.17	1.89E-41	0.2	1.97	1.67 – 2.26	6.89E-38	0.29	0.95	0.63-1.27	6.35E-09

Left Ventricular End Systolic Volume Index (LVESVi)

Clinical only model R^2 0.19
GEH only model R^2 0.16

Per 1 SD↑ of:	Model 1 LVESVi (95% CI), mL/m^2		P-value	R^2	Model 2 LVESVi (95% CI), mL/m^2		P-value	R^2	Model 3 LVESVi (95% CI), mL/m^2		P-value
QRS-T angle	1.51	1.33-1.68	7.74E-63	0.17	1.2	1.02 – 1.38	3.47E-37	0.22	0.57	0.38-0.77	4.54E-09
SVG mag^2	0.44	0.27 – 0.61	3.97E-07	0.13	0.36	0.20 – 0.53	0.00001704	0.2	0.3	0.14-0.46	0.00026
SAI QRST	2	1.83 – 2.16	1.93E-117	0.21	1.76	1.58 – 1.94	1.43E-79	0.25	1.08	0.87-1.28	3.70E-25
Sqrt SVG az	1.16	0.99 – 1.33	4.27E-39	0.15	0.83	0.63 – 1.02	5.16E-17	0.2	0.11	-0.09 to 0.31	0.301
Sqrt SVG el	1.03	0.86 – 1.20	2.29E-31	0.15	0.83	0.65 – 1.00	4.49E-20	0.21	0.62	0.45-0.79	8.70E-13
QRS duration	2	1.83 – 2.17	7.13E-111	0.21	2.64	2.39 – 2.88	1.73E-94	0.26	-		
Cornell prod	1.79	1.62 – 2.00	3.18E-92	0.19	1.57	1.39 – 1.75	5.33E-65	0.24	0.8	0.59-1.00	3.23E-14
QTc interval	1.6	1.44 – 1.77	5.24E-77	0.18	1.43	1.24 – 1.61	5.56E-50	0.23	0.74	0.54-0.94	2.85E-13

Figure 2. Cross-sectional difference (95% CI) in left ventricular structure and function indices per 1 SD of ECG metric increase

Model 1 was adjusted for age, gender, and race. Model 2 was additionally adjusted for CHD, HF, hypertension, diabetes, BMI, smoking, presence of ventricular conduction abnormalities, as well as heart rate and systolic and diastolic blood pressure measured at the time of echocardiography. Model 3 in addition was adjusted for QRS duration. Heat map color coded the most significant findings (largest effect size and R^2, and smallest P-value) as red. Color transitioned to the least significant findings (smallest effect size and R^2, and the largest / less significant P-value) as green.

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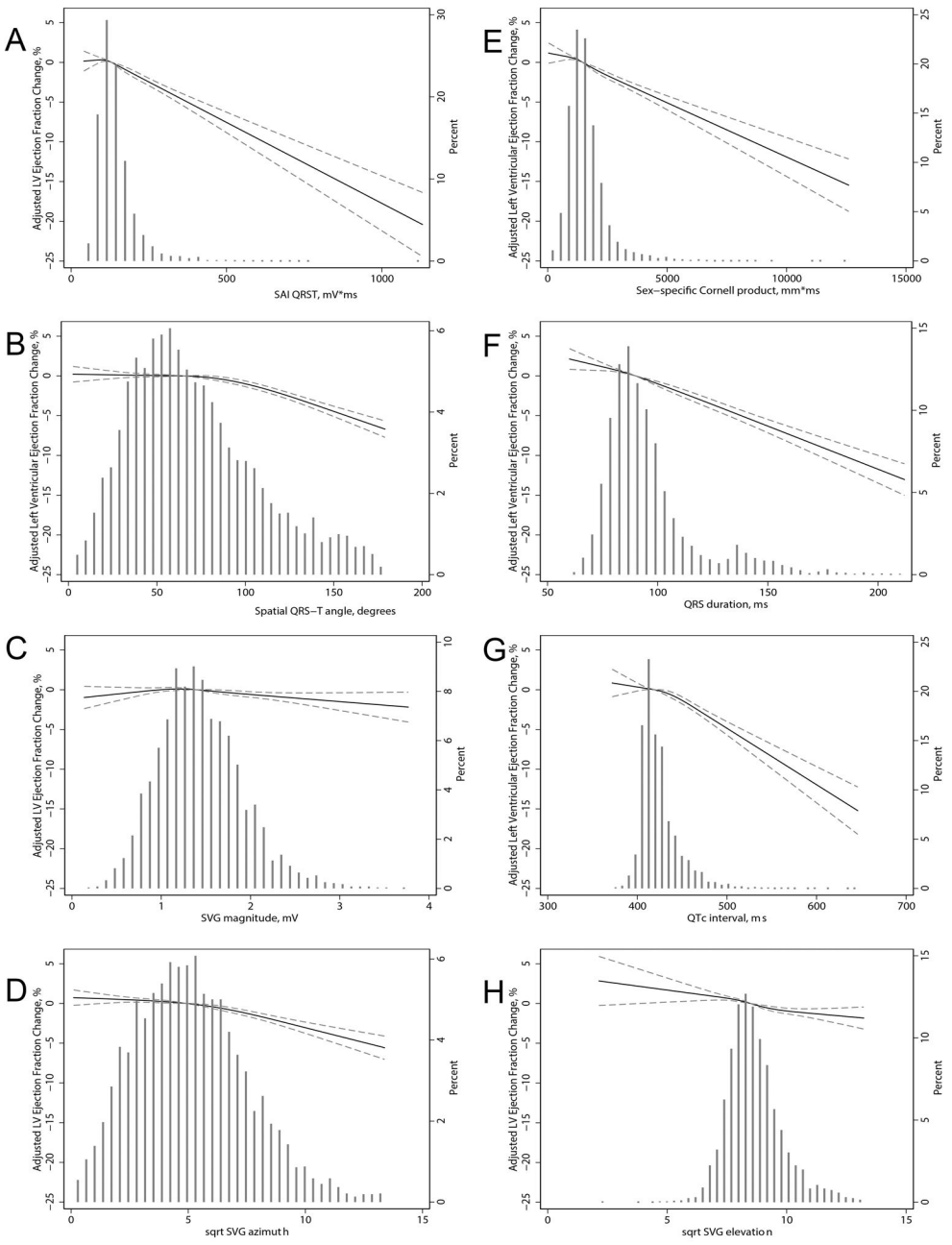

Figure 3. Cross-sectional analysis

Fully adjusted (by age, sex, race, CHD, HF, hypertension, diabetes, BMI, smoking, presence of ventricular conduction abnormalities, heart rate, systolic and diastolic blood pressure) association between (**A**) SAI QRST, (**B**) spatial QRS-T angle, (**C**) SVG magnitude, (**D**) sqrt-SVG azimuth, (**E**) Cornell product, (**F**) QRS duration, (**G**) QTc interval, (**H**) sqrt-SVG elevation and LV ejection fraction. The models adjusted for age, sex, race, BMI, CHD, HF, hypertension, diabetes, smoking, and blood pressure. Restricted cubic spline with 95% confidence interval shows change in LVEF (Y-axis) in response to ECG predictor (X-axis); 50th percentile of predictor variable is selected as the reference.

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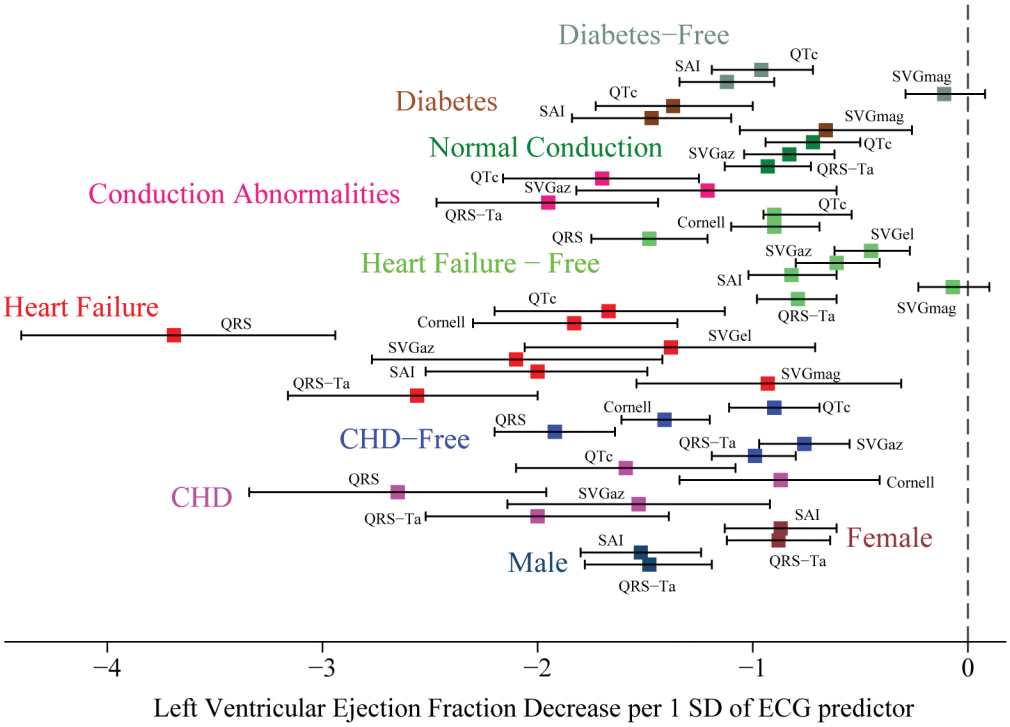

Figure 4. Cross-sectional analysis

Change (with 95% confidence interval) in LVEF per 1 standard deviation of ECG predictor in the study subgroups.

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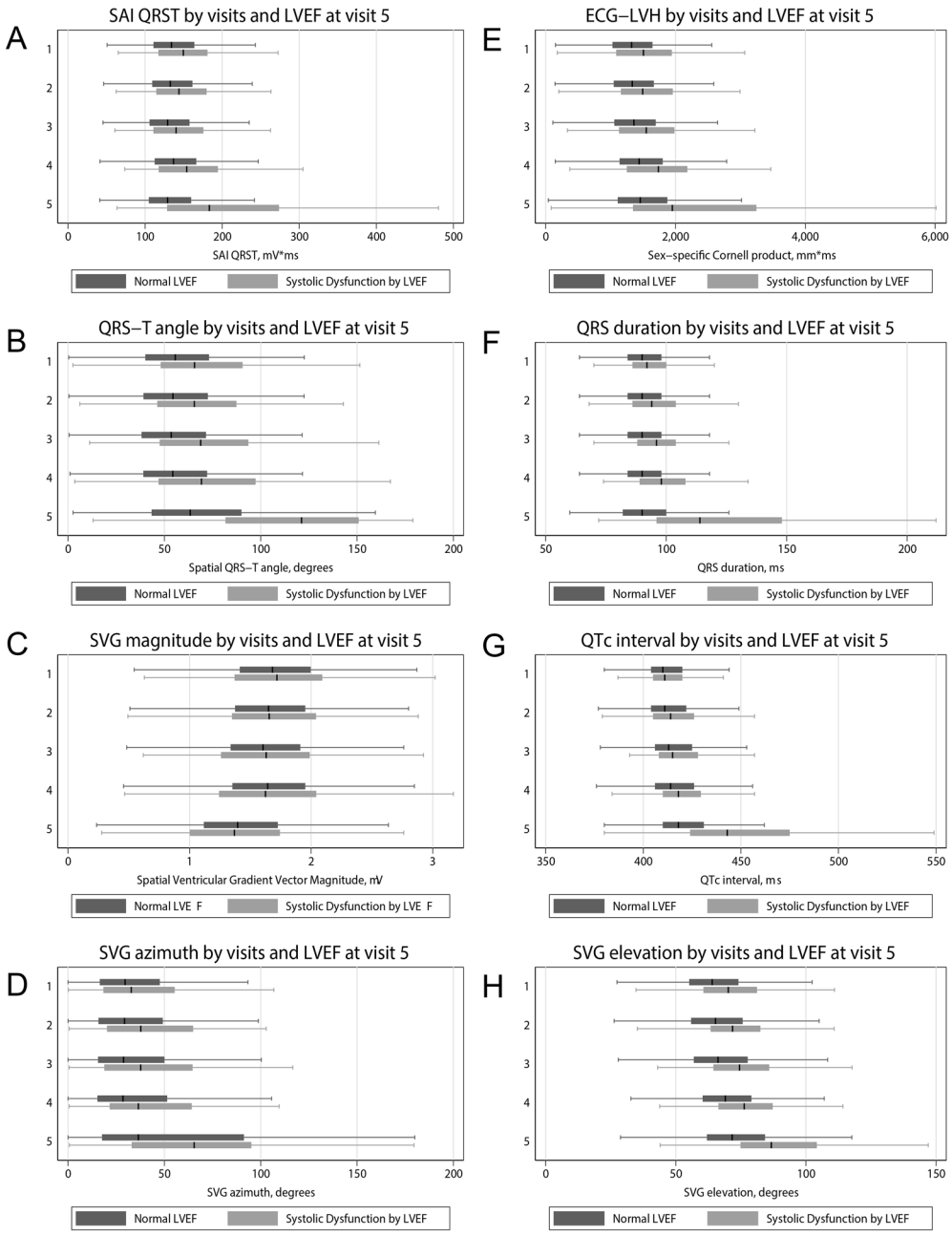

Figure 5. Longitudinal analysis

Boxplot of (**A**) SAI QRST, (**B**) spatial QRS-T angle, (**C**) SVG magnitude, (**D**) sqrt-SVG azimuth, (**E**) Cornell product, (**F**) QRS duration, (**G**) QTc interval, (**H**) sqrt-SVG elevation at each study visit (1–5) in participants with and without abnormal LVEF, measured at visit 5.

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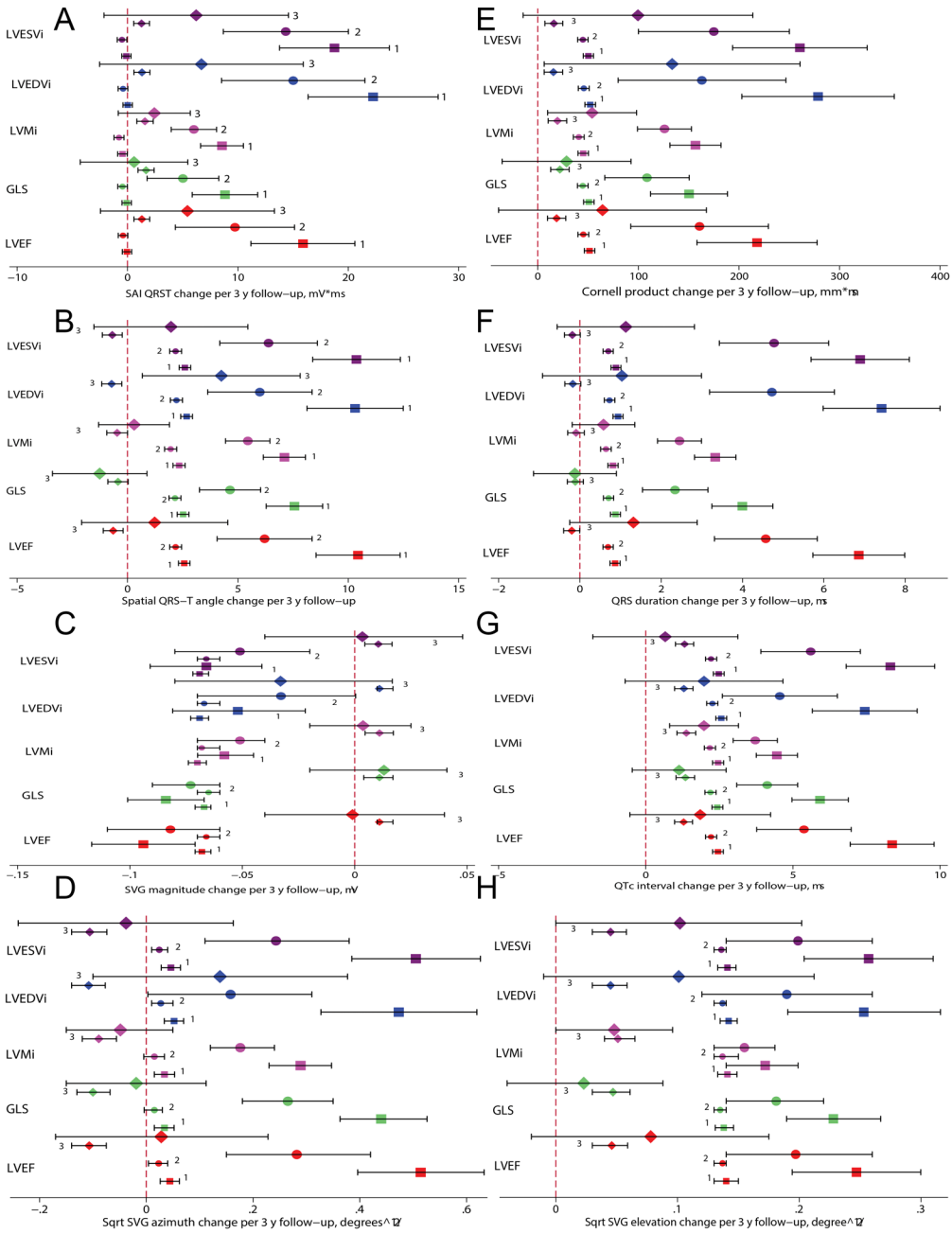

Figure 6. Longitudinal analysis I (24 years follow-up)

Change (with 95% confidence interval) in (**A**) SAI QRST, (**B**) spatial QRS-T angle, (**C**) SVG magnitude, (**D**) sqrt-SVG azimuth, (**E**) Cornell product, (**F**) QRS duration, (**G**) QTc interval, (**H**) sqrt-SVG elevation per median 3 years, over 24 years of follow-up (visits 1–5) in participants with (large size mark) vs. without (medium size mark) abnormal LVEF (red), abnormal GLS (mint), echo-LVH (magenta), abnormal LVEDVi (blue), and abnormal LVESVi (purple). Model 1 (square) was adjusted by gender and race. Model 2 (circle) was in addition adjusted for prevalent and incident HF and CHD. Model 3 (diamond) was further adjusted for all time-updated covariates (diabetes, hypertension, BMI, current smoking

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status, total cholesterol, HDL, triglycerides, systolic and diastolic blood pressure, heart rate, presence of ventricular conduction abnormalities, hsTnT and NTpro-BNP, age), and exact time interval (in days) between each ECG recording.

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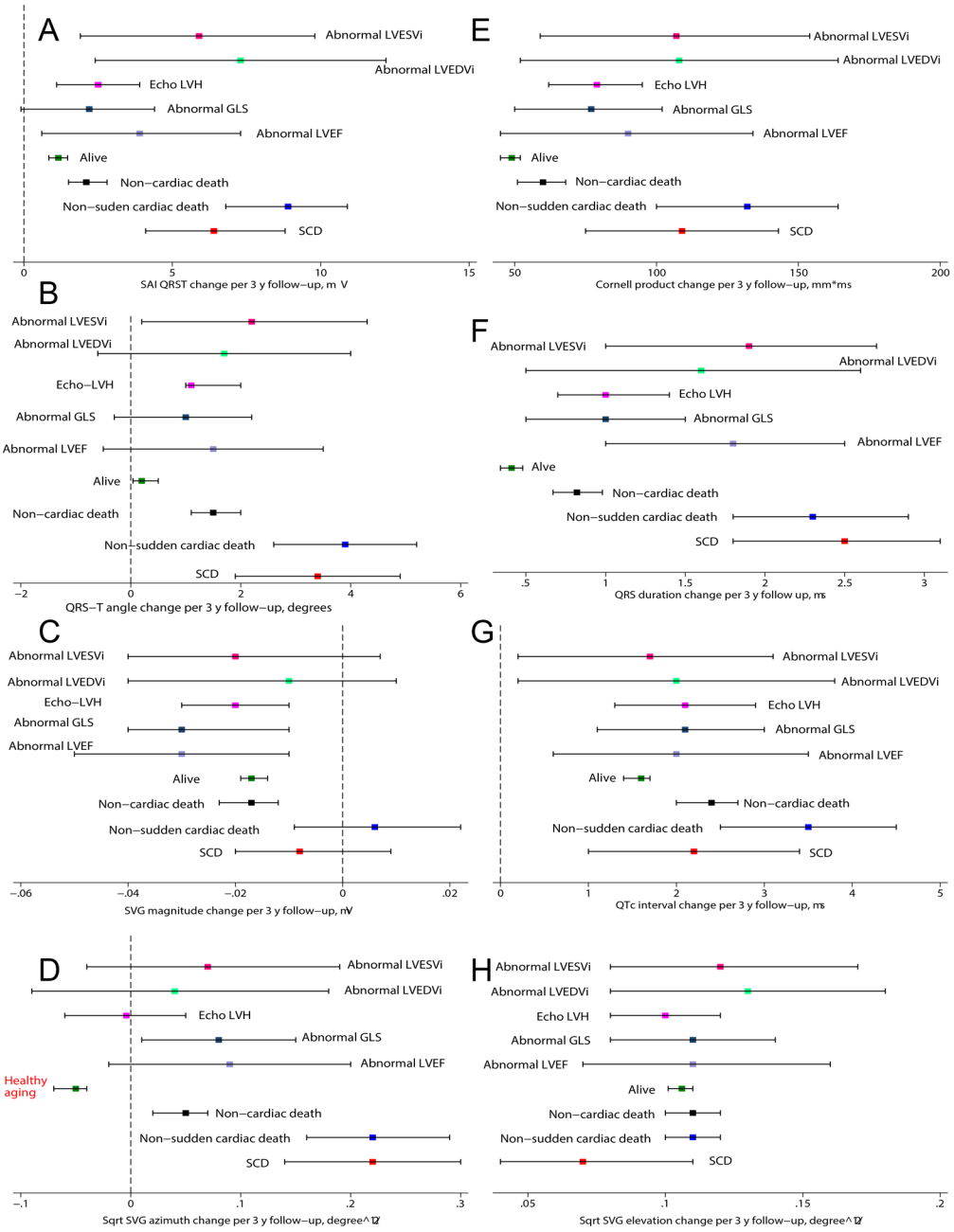

Figure 7. Longitudinal analysis II (12 years follow-up)

Change (with 95% confidence interval) in (**A**) SAI QRST, (**B**) spatial QRS-T angle, (**C**) SVG magnitude, (**D**) sqrt-SVG azimuth, (**E**) Cornell product, (**F**) QRS duration, (**G**) QTc interval, (**H**) sqrt-SVG elevation per median 3 year, over 12 years of follow-up (visits 1–4) in participants with different outcomes: sudden cardiac death (red), non-sudden cardiac death (blue), non-cardiac death (black), all alive (green), alive with abnormal LVEF (lavender), abnormal GLS (navy), echo-LVH (magenta), abnormal LVEDVi (mint), abnormal LVESVi (pink).

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Table 1

Clinical characteristics of study participants at visit 5, and comparison of baseline characteristics of visit 5 responders vs. alive visit 5 non-responders

	Visit 5 responders (n=5,114)		Alive Visit 5 nonresponders (n=4,200)	
Parameter	**Visit 5 characteristics**	**Visit 1 characteristics**	**Visit 1 characteristics**	**P-value**
Age (SD), y	75.9(5.1)	51.7(5.0)	54.1(5.7)	<0.0001
Female gender, n (%)	2,949(57.7%)	2,949(57.7)	2,562(61.0)	0.001
Black, n (%)	1,099(21.5%)	1,099(21.5)	1,060(25.2)	<0.0001
Body mass index (SD), kg/m^2	28.5(5.5)	26.9(4.6)	27.8(5.4)	<0.0001
Coronary heart disease, n (%)	729(14.3%)	87(1.7)	127(3.1)	<0.0001
Heart failure, n (%)	741(14.5%)	105(2.1)	168(4.1)	<0.0001
Hypertension, n (%)	3,762(73.6%)	1,180(23.2)	1,410(33.7)	<0.0001
Diabetes, n(%)	1,583(31.0%)	258(5.1)	381(9.2)	<0.0001
Current smoking, n (%)	291(5.7%)	895(17.5)	1,021(24.3)	<0.0001
Systolic blood pressure (SD), mmHg	130.3(17.8)	116.0(15.6)	121.1(17.9)	<0.0001
Diastolic blood pressure (SD), mmHg	66.5(10.5)	72.6(10.3)	73.5(11.0)	0.0001
Heart Rate (SD), bpm	62.3(10.3)	65.0(9.4)	66.3(9.8)	<0.0001
Spatial QRS-T angle (SD),°	71.2(36.5)	58.5(25.3)	58.1(26.8)	0.509
Abnormal[6] Spatial QRS-T angle, n (%)	1,940(37.9)	1,105(21.6)	971(23.1)	0.081
SVG magnitude (SD), mV	1.44(0.47)	1,725(458)	1,693(476)	0.002
Abnormal[6] SVG magnitude, n (%)	0	2,496(48.8)	1,875(44.6)	<0.0001
SAI QRST (SD), mV*ms	144.1(66.3)	141.8(45.5)	137.8(46.0)	<0.0001
Abnormal[6] SAI QRST, n (%)	970(19.0)	980(19.2)	741(17.6)	0.060
sqrtSVG azimuth (SD)	5.12(2.40)	4.83(1.88)	4.84(1.91)	0.749
Abnormal[6] sqrtSVG azimuth, n (%)	1,439(28.1)			
sqrtSVG elevation (SD)	8.64(1.16)	8.06(0.96)	8.11(0.99)	0.016
Abnormal[6] sqrtSVG elevation, n (%)	2,398(46.9)			
QRS duration (SD), ms	96.1(21.2)	91.6(10.9)	91.2(11.8)	0.105
Abnormal ventricular conduction, n (%)	696(13.6)	146(2.9)	156(3.7)	0.020
QTc (SD), ms	424.4(22.7)	413.2(16.4)	416.4(19.9)	<0.0001

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	Visit 5 responders (n=5,114)		Alive Visit 5 nonresponders (n=4,200)	
Parameter	**Visit 5 characteristics**	**Visit 1 characteristics**	**Visit 1 characteristics**	**P-value**
Prolonged QTc, n (%)	348(6.8)	97(1.9)	134(3.2)	<0.0001
Sex-specific Cornell product (SD), mm*ms	1625(895)	1385(538)	1443(565)	<0.0001
ECG-Left Ventricular Hypertrophy, n (%)	523(10.2)	178(3.5)	180(4.3)	0.040
LVEF (SD), %	65.3(6.6)			
Abnormal LVEF, n (%)	188(3.7)			
GLS (SD), %	−17.9(2.6)			
Abnormal GLS, n (%)	356(7.0)			
Left Ventrocuar Mass Index (SD), g/m^2	79.8(20.8)			
Echo- Left Ventricular Hypertrophy, n (%)	561(11.0)			
LVEDV index (SD), mL/m^2	43.4(11.1)			
Abnormal LVEDV index, n (%)	117(2.3)			
LVESV index (SD), mL/m^2	15.4(6.7)			
Abnormal LVESV index, n (%)	170(3.3)			