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

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Background—Asymptomatic individuals account for the majority of sudden cardiac deaths (SCDs). Development of effective, low-cost, and noninvasive SCD risk stratification tools is necessary.

Methods and Results—Participants from the Atherosclerosis Risk in Communities study and Cardiovascular Health Study (n=20 177; age, 59.3±10.1 years; age range, 44–100 years; 56% female; 77% white) were followed up for 14.0 years (median). Five ECG markers of global electric heterogeneity (GEH; sum absolute QRST integral, spatial QRST angle, spatial ventricular gradient [SVG] magnitude, SVG elevation, and SVG azimuth) were measured on standard 12-lead ECGs. Cox proportional hazards and competing risks models evaluated associations between GEH electrocardiographic parameters and SCD. An SCD competing risks score was derived from demographics, comorbidities, and GEH parameters. SCD incidence was 1.86 per 1000 person-years. After multivariable adjustment, baseline GEH parameters and large increases in GEH parameters over time were independently associated with SCD. Final SCD risk scores included age, sex, race, diabetes mellitus, hypertension, coronary heart disease, stroke, and GEH parameters as continuous variables. When GEH parameters were added to clinical/demographic factors, the C statistic increased from 0.777 to 0.790 (P=0.008), the risk score classified 10-year SCD risk as high (>5%) in 7.2% of participants, 10% of SCD victims were appropriately reclassified into a high-risk category, and only 1.4% of SCD victims were inappropriately reclassified from high to intermediate risk. The net reclassification index was 18.3%.

Conclusions—Abnormal electrophysiological substrate quantified by GEH parameters is independently associated with SCD in the general population. The addition of GEH parameters to clinical characteristics improves SCD risk prediction. **(*Circulation*. 2016;133:2222-2234. DOI: 10.1161/CIRCULATIONAHA.116.021306.)**

Key Words: death, sudden, cardiac ■ electrocardiography ■ electrophysiology ■ risk assessment

Despite advances in the treatment and prevention of cardiovascular disease and a reduction in total cardiovascular mortality, the incidence of sudden cardiac death (SCD) remains high. In the United States, 180 000 to 450 000 people die suddenly each year,[1] and in up to half of SCDs, cardiac arrest is the first manifestation of cardiovascular disease.[2] Effective, low-cost, noninvasive, and readily available tools to identify individuals at increased SCD risk are therefore necessary to optimally target primary prevention interventions and to decrease SCD incidence.

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In the general population, SCD is related primarily to coronary heart disease (CHD)[2] and ventricular tachyarrhythmias.[3,4] Fundamental studies in electrophysiology have demonstrated that susceptibility to ventricular arrhythmias is characterized by heterogeneity in myocardial activation and recovery times[4,5] and action potential morphology,[6,7] which can be detected on QRST integral maps.[8,9] Noninvasive assessment of cardiac electric heterogeneity is therefore a promising method of assessing SCD risk.

In the 1930s, Wilson et al[10] developed the concept of an arithmetically summed area under the QRS complex and T wave as a measure of the net electric effect produced by local variations in the duration of the excited state. Wilson et al calculated the vectorial sum of the QRS and T vectors, defined as the spatial ventricular gradient (SVG), to determine the direction along which nonuniformity in excitation and repolarization was greatest[10] and the duration of the excited state was shortest.[11] Subsequent experimental and theoretical investigations demonstrated that the SVG is related to global heterogeneity of both action potential duration and morphology.[7] The concept underlying the SVG was extended to the spatial QRS-T angle, the 3-dimensional angle between the QRS and T vectors,[12] and the sum absolute QRST integral (SAI QRST), a scalar analog of the SVG calculated as the absolute value of the area under the QRS complex and T wave.[13–15] These electrocardiographic parameters have been associated with ventricular arrhythmia in high-risk individuals,[14,16] but their association with SCD in the general population and their utility in SCD risk stratification remain unclear.

We hypothesized that markers of myocardial global electric heterogeneity (GEH; SVG, spatial QRS-T angle, and SAI QRST) would be independently associated with SCD and that they would improve SCD risk prediction in the general population beyond clinical and demographic characteristics.

Methods

Study Populations

To obtain widely generalizable results, we merged 2 large, biracial, prospective, community-dwelling adult cohorts. The Atherosclerosis Risk in Communities (ARIC) study is an ongoing, prospective cohort study assessing risk factors, progression, and outcomes of atherosclerosis in 15 792 community participants (45% male, 74% white) 45 to 64 years of age recruited from 4 US communities between 1987 and 1989. Details of ARIC enrollment and study procedures have previously been given.[17] Black participants in the Washington and Minnesota cohorts (n=55) and participants with reported race other than white or black (n=48), uninterpretable ECGs (n=344), or missing covariates (n=736) were excluded. The final ARIC study population included 14 609 participants.

The Cardiovascular Health Study (CHS) is an ongoing, prospective cohort study assessing risk factors, progression, and outcomes of CHD and stroke in 5888 community participants 65 to 100 years of age (42% male, 85% white) recruited from 4 US communities. During 1989 to 1990, 5201 participants were enrolled, and in 1992 to 1993, a second cohort of 687 blacks was recruited. Details of CHS enrollment and study procedures have previously been published.[18] After the exclusion of participants with reported race other than white or black (n=39), uninterpretable ECGs (n=87), or missing covariates (n=194), the final CHS study population included 5568 participants.

Together, the 2 cohorts included 20 177 adults (mean age, 59.3±10.1 years; range, 44–100 years; 44.1% male; 77.3% white). Both studies were approved by the institutional review boards of all participating institutions, and all participants gave informed consent. Definitions of covariates and incident nonfatal cardiovascular events are provided in the Methods section of the online-only Data Supplement.

ECG Recording, Analysis, and Measurement of GEH Parameters

Recording and processing of 12-lead ECGs were identical in ARIC and CHS. Standard 10-second 12-lead ECGs were digitally acquired at a sampling rate of 500 Hz and amplitude resolution of 1μV with MAC personal computer electrocardiographs (Marquette Electronics, Milwaukee, WI) and were automatically processed with the GE Magellan research utility (GE Marquette, Milwaukee, WI) to measure amplitudes and intervals. The 12-lead ECGs were digitally recorded at study enrollment and during follow-up: yearly in the CHS cohort and triennially in the ARIC cohort. To evaluate longitudinal ECG changes, we analyzed ECGs at up to 10 visits in CHS participants and at up to 4 visits in ARIC participants.

A detailed description of GEH parameter measurement is provided in the Methods section of the online-only Data Supplement. SAI QRST was measured as the arithmetic sum of areas under the QRST curve as previously described[13,15] (Figure 1A). Spatial mean QRS-T angle was defined as the 3-dimensional angle between the mean QRS vector and the mean T vector (Figure 1B) as previously described.[12] SVG represents a vector in 3-dimensional space defined by the vectorial sum of the QRS vector and the T vector (Figure 1B). The magnitude, azimuth, and elevation of the SVG vector were measured (Figure 1C).

Heart rate, corrected QT interval, and QRS duration were measured by the GE 12SL algorithm (GE Marquette). Sex-specific Cornell product was calculated for the assessment of ECG left ventricular hypertrophy.[19]

Patient Follow-Up and SCD Adjudication

Follow-up of ARIC participants included annual telephone calls, local hospital surveillance, 3 triennial visits through 1998, and a search of the Social Security Death Index; details of follow-up have previously been reported.[20] CHS follow-up included semiannual alternating phone calls and clinic visits through 1999 with twice-yearly phone calls thereafter, review of Medicare hospitalization records, and a search of the Social Security Death Index; details of follow-up have previously been reported.[21]

The primary outcome of this analysis was SCD, which was similarly adjudicated in ARIC and CHS. SCD was defined as a sudden pulseless condition presumed to be attributable to a ventricular tachyarrhythmia in a previously stable individual without evidence of a noncardiac cause of cardiac arrest. We a priori sought to exclude patients with nonarrhythmic characteristics, including those with evidence of progressive hypotension or advanced decompensated heart failure (HF) before death. All SCD events in this analysis occurred out of the hospital or in a hospital emergency department. A detailed description of SCD adjudication is provided in the Methods section in the online-only Data Supplement.

Participants were censored at time of loss to follow-up or death if the cause of death was not SCD. Administrative censoring occurred on July 31, 2006, for CHS and December 31, 2001, for ARIC.

Statistical Analysis

A detailed description of our statistical methods is provided in the online-only Data Supplement. In brief, we conducted the following analyses.

Association Between GEH Parameters and Baseline Characteristics

Minimally adjusted linear regression was used to determine associations between baseline demographic, clinical, and traditional ECG characteristics and GEH parameters. Circular variables (SVG azimuth and elevation) were analyzed with circular statistics.

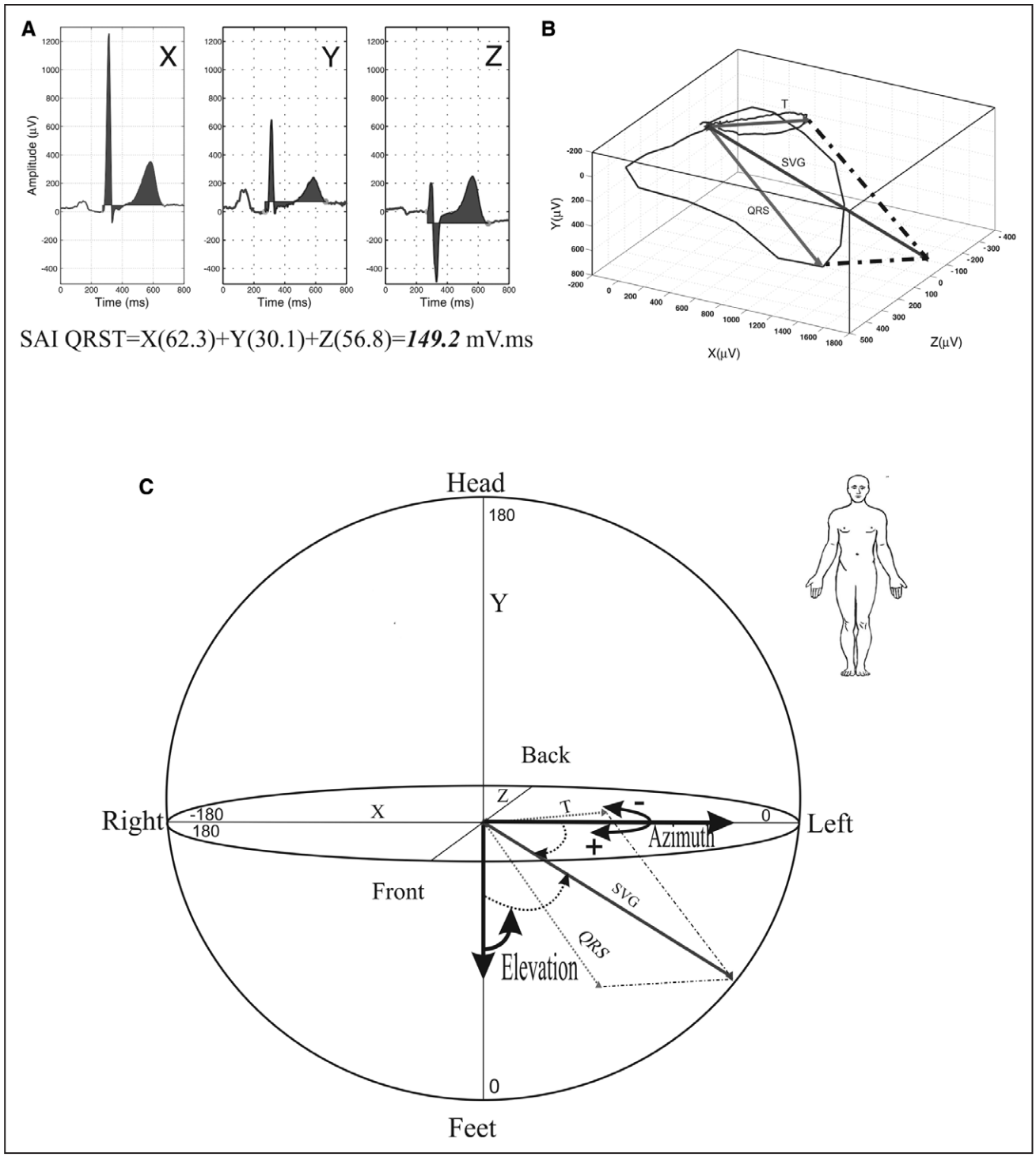

Figure 1. Measurement of global electric heterogeneity (GEH) parameters. **A**, Sum absolute QRST integral (SAI QRST) represents the sum of the area under the QRS complex and T wave with the isoelectric line used as the reference (shaded area). *x*-, *y*-, and *z*-lead QRS-T complexes and their calculated SAI QRST results are shown. **B**, Spatial QRS-T angle represents the angle between the QRS vector and T vector in 3-dimensional space. **C**, Spatial ventricular gradient (SVG) is a vector defined as the vectorial sum of the QRS vector and the T vector. SVG magnitude is the length of the SVG vector. SVG azimuth is the angle of the SVG vector projected onto the *xy* (horizontal) plane, and SVG elevation is the angle of the SVG-vector projected in the *xz* (vertical) plane.

Association Between GEH Parameters and SCD

Cox proportional hazards and competing risks models quantified associations between individual GEH parameters treated as continuous variables and SCD. Given that there are no prior data demonstrating the association between GEH parameters and SCD in the general population, we constructed 4 models designed to assess the magnitude and significance of association between each GEH parameter and SCD as additional potential confounders were sequentially added. Model 1 adjusted for demographic characteristics (age, sex, race, and study cohort/center). Model 2 additionally adjusted for

prevalent cardiovascular disease and traditional cardiovascular risk factors (CHD, HF, stroke, atrial fibrillation, β-blockers, creatinine, body mass index, hypertension, antihypertensive medications, diabetes mellitus, smoking status, alcohol intake, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and physical activity index). Model 3 further adjusted for electrocardiographic parameters associated with SCD (heart rate, corrected QT, QRS duration, sex-specific Cornell product, and bundle-branch block, or intraventricular conduction delay). Model 4 evaluated whether the association of GEH parameters with SCD remained significant over time and included all baseline covariates included in model 3, time-updated GEH parameters, time-updated traditional electrocardiographic measurements, and time-updated incident nonfatal cardiovascular events (atrial fibrillation, HF, CHD, and stroke). Because information on baseline left ventricular ejection fraction (LVEF) was not available for ARIC participants, sensitivity analyses evaluated the effect of adding LVEF into fully adjusted and time-updated models in 4954 CHS participants. Subgroup analysis was performed in model 3 to determine significant interactions between GEH parameters and clinical characteristics.

Definition of Abnormal GEH Parameters

Sex- and race-specific thresholds defining abnormal GEH parameter values were selected with the use of the Youden index[22] to maximize the sum of sensitivity and specificity. A competing risks model was constructed to determine the incremental SCD risk associated with multiple "abnormal" GEH parameters.

Longitudinal Changes in GEH Parameters Over Time and SCD Risk

Mixed-effect multilevel models (adjusted by age, sex, and race with participants nested within study center nested within cohort) were constructed to determine whether GEH parameters changed over time. To investigate whether longitudinal changes in GEH parameters were independently associated with SCD, the interaction with time was assessed in time-updated Cox models to test the assumption of proportionality for the hazard of time-updated variables over time. In addition, separate Cox proportional hazards models were used to determine whether large increases in GEH parameters between study visits 1 and 3 were associated with SCD.

Schoenfeld residuals confirmed that the proportional hazards assumption was valid in all Cox proportional hazards models.

Risk Score Development

We constructed 2 SCD risk scores using the Fine and Gray competing risks model to test the incremental predictive value of adding GEH parameters as continuous variables to clinical characteristics. A combination of clinical guidance and backward selection was used to select covariates for inclusion in the final risk score models. To allow wider applicability of the risk score, we initially assessed clinically important covariates from model 3 (see Methods in the online-only Data Supplement). The final clinical-only SCD risk score included known SCD risk factors: age, sex, race, CHD, stroke, diabetes mellitus, and hypertension.

The combined clinical+GEH score was initially developed with covariates from the clinical-only score, all 5 GEH parameters, and all significant interaction terms. Backward selection was then performed with a cutoff value of P=0.10. The final model included age, sex, race, CHD, stroke, diabetes mellitus, hypertension, SAI QRST, spatial QRS-T angle, SVG elevation, and interaction terms (SAI QRST×age, QRS-T angle×age, QRS-T angle×race, QRS-T angle×diabetes mellitus, QRS-T angle×hypertension, and SVG azimuth×sex). Weighting of the contribution of each variable to SCD risk was determined by the relative size of effect estimates. A cumulative incidence function was used to assign 10-year SCD risk to each participant on the basis of their individual clinical-only and clinical+GEH risk scores.

All statistical analyses were performed with STATA 14 (StataCorp LP, College Station, TX) and Oriana-Circular Statistics version 4 (Kovach Computing Services, Pentraeth, Wales, UK).

Results

Associations of Baseline Clinical and Traditional ECG Characteristics With GEH Parameters

Baseline characteristics and incident nonfatal cardiovascular events are shown in Table 1. Associations between baseline clinical and ECG characteristics and the 5 measures of GEH are shown in Tables I through III in the online-only Data Supplement. Abnormal LVEF was positively associated with all GEH parameters. Prevalent CHD was positively associated with all GEH parameters except SVG magnitude, for which a strong inverse association was observed.

Association Between GEH Parameters and SCD

Among ARIC participants, over a median follow-up of 14.1 years, 291 SCDs occurred (incidence, 1.48 [95% confidence interval, 1.32–1.66] per 1000 person-years). Among CHS participants, over median follow-up of 13.1 years, 195 SCDs occurred (incidence, 3.00 [95% confidence interval, 2.61–3.45] per 1000 person-years). In the combined cohort, over median follow-up of 14.0 years, 486 SCDs occurred (incidence, 1.86 [95% confidence interval, 1.70–2.03] per 1000 person-years). SCD accounted for 7.56% of all deaths in the combined cohort.

Table 2 shows the associations between GEH parameters and SCD risk in Cox proportional hazards models 1 through 4. In model 2, all 5 GEH parameters were associated with SCD. Figure 2 shows the hazard of SCD over the range of GEH parameter values, relative to the mean value, when quadratic splines were used to characterize the relationship between GEH parameters and SCD risk. In adjusted analyses, there was a dose-response relationship between GEH parameters and SCD. Further adjustment for baseline electrocardiographic parameters (model 3) and time-updated ECG/GEH measurements and incident nonfatal cardiovascular outcomes (model 4) revealed minimal change in the magnitude of association between SAI QRST, QRS-T angle, and SVG magnitude and SCD, although the associations between SVG elevation/azimuth and SCD were attenuated. In sensitivity analyses exploring the importance of adding LVEF to fully adjusted models (Table 2), the addition of baseline LVEF did not substantially change the magnitude or significance of association between any GEH parameter and SCD. Competing risks models revealed similar associations between GEH parameters and SCD (Table IV in the online-only Data Supplement).

Longitudinal Changes in GEH Parameters and SCD Risk

Mixed effects models revealed that over time values of SAI QRST, QRS-T angle, SVG elevation, and SVG azimuth increased and values of SVG magnitude decreased in a statistically significant manner (Table V in the online-only Data Supplement). Importantly, the overall magnitude of changes in GEH parameters, however, was small: for example, <1° of the QRS-T angle and <1 mV·ms of SAI QRST between 2 visits (median, 2.8 years). In time-updated Cox models, there were no significant interactions between time and time-updated SAI QRST (P=0.436), QRS-T angle (P=0.189), SVG magnitude (P=0.083), SVG elevation (P=0.982), and

Table 1. Baseline Characteristics and Incident Nonfatal Cardiovascular Events

Characteristic	Combined (n=20 177)	ARIC (n=14 609)	CHS (n=5568)
Characteristic			
Age, y	59.3±10.1	54.1±5.76	72.8±5.6
Female, n (%)	11 274 (55.9)	8067 (55.2)	3207 (57.6)
White, n (%)	15 590 (77.3)	10 873 (74.4)	4717 (84.72)
Diabetes mellitus, n (%)	2613 (13.0)	1693 (11.6)	920 (16.5)
Hypertension, n (%)	8250 (40.9)	4985 (34.1)	3265 (58.6)
Antihypertensive medications, n (%)	7030 (34.8)	4388 (30.0)	2642 (47.5)
CHD, n (%)	1762 (8.73)	674 (4.61)	1088 (19.5)
HF, n (%)	914 (4.5)	662 (4.5)	252 (4.5)
Stroke, n (%)	469 (2.32)	243 (1.7)	226 (4.1)
Atrial fibrillation, n (%)	183 (0.9)	32 (0.2)	151 (2.71)
Current smoking, n (%)	4452 (22.1)	3789 (25.9)	663 (11.9)
Body mass index, kg/m^2	27.4±5.2	27.7±5.3	26.7±4.7
Total cholesterol, mg/dL	213.8±41.1	214.8±41.8	211.3±39.3
HDL cholesterol, mg/dL	52.4±16.8	51.7±17.2	54.2±15.8
Triglycerides, mg/dL	133.6±86.8	131.6±90.5	139.0±75.8
β-Blockers, n (%)	1987 (9.9)	1269 (8.7)	718 (12.9)
Alcohol consumption, g/wk	40.8±114.5	42.4±95.3	36.7±153.7
Creatinine, g/dL	1.10±0.42	1.11±0.43	1.06±0.40
Abnormal LVEF*, n (%)	183 (3.4)	N/A	183 (3.4)
Heart rate, bpm	66±11	66±10	65±11
Corrected QT, ms	418.2±20.7	416.2±19.0	423.5±23.8
QRS duration, ms	92.7±14.6	92.2±12.3	92.5±12.8
BBB/IVCD, n (%)	2328 (11.5)	1672 (11.4)	656 (11.8)
Sex-adjusted Cornell product, mV·ms	1514±705	1457±619	1664±874
Ventricular pacing, n (%)	47 (0.2)	2 (0.01)	45 (0.81)
Incident nonfatal events, per 1000 person-y (95%CI)			
Incident HF	11.22 (10.82–11.64)	5.73 (5.40–6.08)	28.03 (26.76–29.37)
Incident atrial fibrillation	9.34 (8.97–9.72)	4.72 (4.42–5.04)	24.53 (23.29–25.83)
Incident stroke	6.44 (6.14–6.75)	3.26 (3.02–3.53)	15.76 (14.83–16.74)
Incident CHD	14.87 (14.39–15.37)	10.18 (9.73–10.65)	31.62 (30.14–33.19)

Values are n (percent total) for categorical variables and mean±SD for continuous variables. ARIC indicates Atherosclerosis Risk in Communities; BBB, bundle-branch block; CHD, coronary heart disease; CHS, Cardiovascular Health Study; CI, confidence interval; HDL, high-density lipoprotein; HF, heart failure; IVCD, intraventricular conduction delay; and LVEF, left ventricular ejection fraction;
*CHS only (n=4953).

SVG azimuth (P=0.534), and the assumption of proportional hazards was confirmed in all time-updated Cox regression models. Therefore, there was no evidence of change in the association between SCD risk and GEH parameters over time; small changes in GEH parameters over time were not associated with additional SCD risk.

However, large, sudden increases in GEH parameters (≥50% for SAI QRST and SVG magnitude, elevation, and azimuth; ≥3-fold for QRS-T angle) were independently associated with SCD after adjustment for all other covariates, incident nonfatal CVD events, and baseline GEH parameter values (Table VI and Figure I in the online-only Data Supplement). There was a dose-dependent increase in SCD proportional to the increase in GEH parameter values between baseline and study visit 2 or 3.

Subgroup Analyses

The strength of association between SAI QRST and spatial QRS-T angle and SCD decreased with increasing age (Table VII in the online-only Data Supplement). QRS-T angle had a stronger association with SCD in white participants and participants free of hypertension or diabetes mellitus. SAI QRST

Table 2. Associations of GEH Parameters With SCD per 1-SD Change in Parameter in Cox Regression Models

	SAI QRST		QRS-T Angle		SVG Magnitude		SVG Elevation		SVG Azimuth	
	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value
Merged										
Model 1	1.26 (1.20–1.33)	<0.0001	1.55 (1.43–1.68)	<0.0001	1.03 (0.95–1.13)	0.482	1.26 (1.15–1.37)	<0.0001	1.30 (1.20–1.42)	<0.0001
Model 2	1.21 (1.15–1.28)	<0.0001	1.30 (1.20–1.41)	<0.0001	1.10 (1.01–1.20)	0.032	1.19 (1.09–1.29)	<0.0001	1.14 (1.05–1.24)	0.002
Model 3	1.16 (1.07–1.25)	<0.0001	1.21 (1.10–1.32)	<0.0001	1.09 (1.00–1.19)	0.048	1.11 (1.02–1.22)	0.015	1.01 (0.92–1.11)	0.761
Model 4	1.16 (1.07–1.25)	<0.0001	1.29 (1.17–1.43)	<0.0001	1.15 (1.05–1.25)	0.002	1.01 (0.92–1.11)	0.807	1.05 (0.95–1.17)	0.309
ARIC										
Model 1	1.33 (1.24–1.43)	<0.0001	1.70 (1.54–1.88)	<0.0001	0.99 (0.88–1.11)	0.871	1.30 (1.17–1.44)	<0.0001	1.30 (1.16–1.46)	<0.0001
Model 2	1.23 (1.14–1.31)	<0.0001	1.39 (1.25–1.54)	<0.0001	1.08 (0.96–1.21)	0.200	1.18 (1.06–1.32)	0.002	1.11 (0.99–1.24)	0.065
Model 3	1.17 (1.07–1.29)	0.001	1.30 (1.16–1.46)	<0.0001	1.04 (0.93–1.17)	0.477	1.11 (1.00–1.24)	0.054	0.98 (0.87–1.11)	0.747
Model 4	1.06 (0.97–1.15)	0.180	1.37 (1.23–1.54)	<0.0001	1.08 (0.96–1.21)	0.210	1.05 (0.94–1.17)	0.390	1.09 (0.96–1.24)	0.207
CHS										
Model 1	1.27 (1.16–1.39)	<0.0001	1.40 (1.22–1.61)	<0.0001	1.10 (0.96–1.26)	0.157	1.20 (1.04–1.37)	0.011	1.34 (1.17–1.54)	<0.0001
Model 2	1.22 (1.10–1.34)	<0.0001	1.18 (1.03–1.36)	0.017	1.13 (0.99–1.29)	0.067	1.17 (1.02–1.34)	0.028	1.18 (1.03–1.35)	0.014
Model 3	1.13 (0.98–1.31)	0.098	1.05 (0.90–1.23)	0.534	1.14 (1.00–1.31)	0.050	1.08 (0.93–1.24)	0.308	1.02 (0.87–1.20)	0.777
Model 4	1.29 (1.13–1.49)	<0.0001	1.14 (0.97–1.33)	0.123	1.23 (1.08–1.41)	0.002	0.97 (0.85–1.12)	0.717	0.98 (0.83–1.16)	0.811
Sensitivity analysis to evaluate effect of LVEF on association with SCD in CHS participants*										
Model 4 without LVEF	1.34 (1.15–1.55)	<0.0001	1.15 (0.98–1.36)	0.109	1.24 (1.08–1.43)	0.002	0.98 (0.85–1.14)	0.800	0.97 (0.82–1.16)	0.773
Model 4 with LVEF	1.30 (1.12–1.51)	0.001	1.12 (0.95–1.32)	0.182	1.23 (1.07–1.42)	0.003	0.99 (0.85–1.14)	0.853	0.99 (0.83–1.18)	0.923

Model 1 was adjusted for age, sex, race, and study center/cohort. Model 2 was further adjusted for coronary heart disease, heart failure, stroke, atrial fibrillation, β-blockers, creatinine, body mass index, hypertension, antihypertensive medications, diabetes mellitus, smoking, alcohol intake, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and physical activity index. Model 3 was further adjusted for ECG characteristics: heart rate, corrected QT interval, QRS duration, Cornell product, and bundle-branch block or intraventricular conduction delay. Model 4 was further adjusted for time-updated electrocardiographic/GEH measurements and time-updated incident nonfatal cardiovascular outcomes (atrial fibrillation, heart failure, coronary heart disease, stroke). CI indicates confidence interval; GEH, global electric heterogeneity; HR, hazard ratio; LVEF, left ventricular ejection fraction; and SVG, spatial ventricular gradient.

*Restricted to 4,954 CHS participants with baseline LVEF available.

had a stronger association with SCD in women. There was no significant interaction with ventricular pacing or the presence bundle-branch block/intraventricular conduction delay.

Dichotomized GEH Parameters and SCD Risk

The optimal sex- and race-stratified cutoff points for GEH parameters, as calculated by the Youden index, are reported in Table VIII in the online-only Data Supplement. As the number of abnormal GEH parameters increased from 0 to 5, the rate of SCD increased from 0.5% to 12.0% (Figure 3), and the percent of all SCDs increased from 2.4% to 17.6% (Figure II in the online-only Data Supplement). In an unadjusted competing risks model, participants with 5 abnormal GEH parameters had a subhazard ratio for SCD of 25.4 (95% confidence interval, 14.6–44.1; $P<0.0001$) compared with those with 0 abnormal parameters.

Development of SCD Risk Scores

Table 3 describes the final SCD risk scores. Significant improvement in SCD risk prediction was seen with the addition of GEH parameters and appropriate interaction terms. The clinical-only risk score predicted 10-year cumulative SCD incidence between 0.44% and 42.14%, whereas the clinical+GEH risk score assigned participants to a wider range

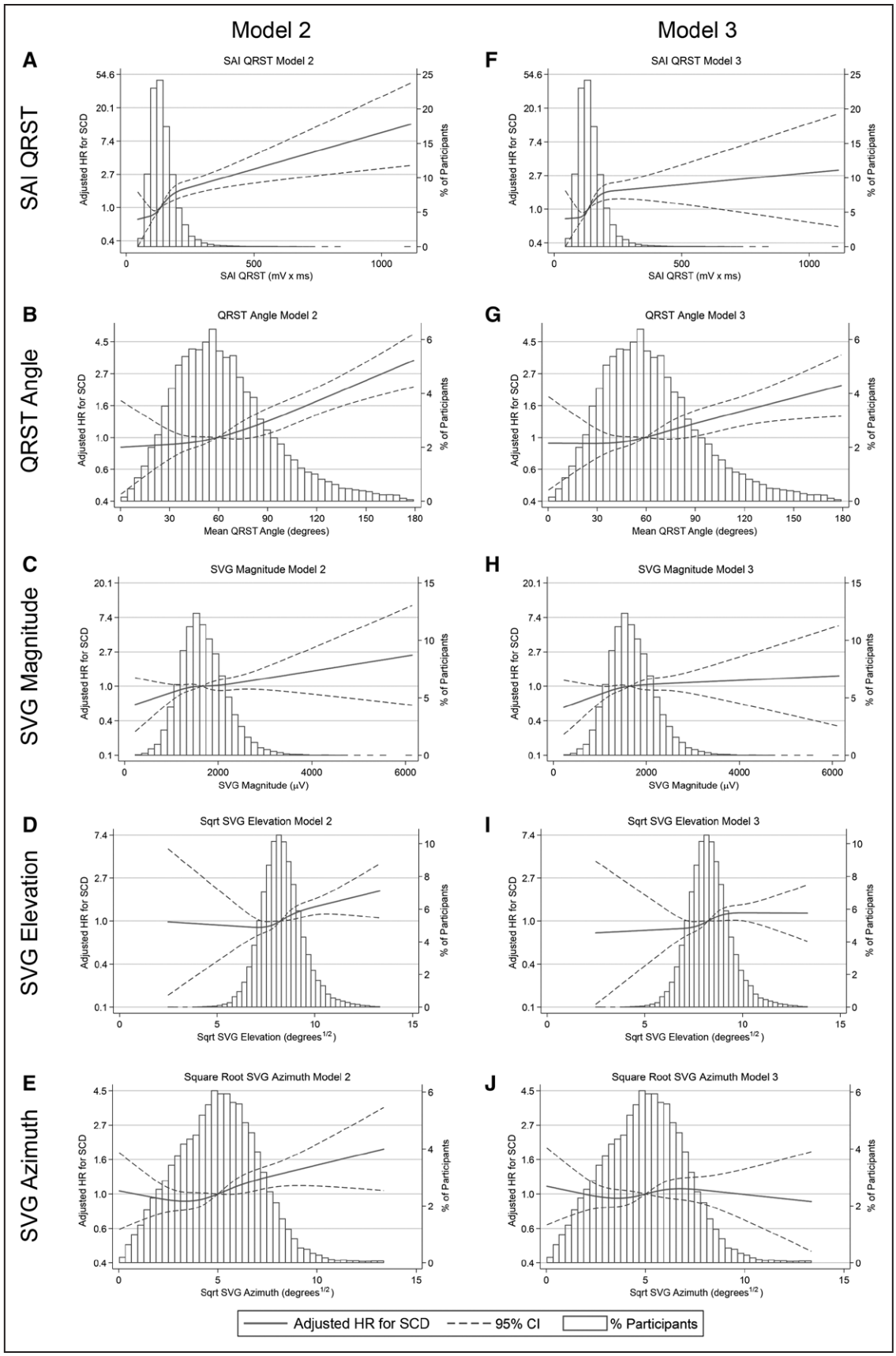

Figure 2. Multivariable adjusted hazard ratios with 95% confidence intervals for sudden cardiac death (SCD) associated with sum absolute QRST integral (SAI QRST; **A** and **F**), QRS-T angle (**B** and **G**), spatial ventricular gradient (SVG) magnitude (**C** and **H**), SVG elevation (**D** and **I**), and SVG azimuth (**E** and **J**), modeled as continuous variables with the quadratic splines in models 2 (**A**–**E**) and 3 (**F**–**J**). Plotted hazard ratios represent the hazard at a given value of the covariate relative to the hazard at the average value of the covariate.

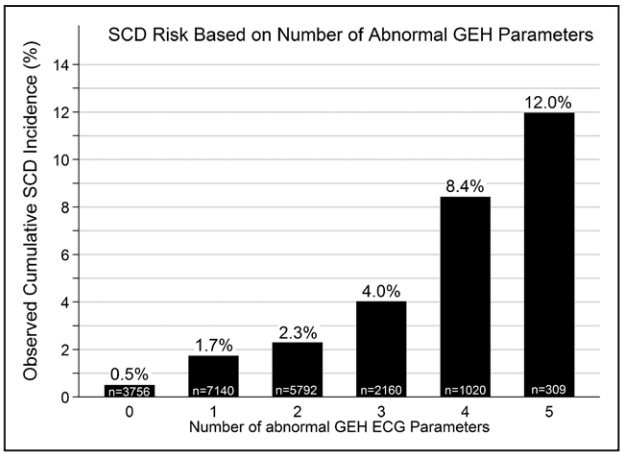

Figure 3. Sudden cardiac death (SCD) incidence based on the number of abnormal dichotomized global electric heterogeneity (GEH) parameters, with each parameter given equal weight.

of 10-year SCD risk (0.05%–55.12%). The clinical+GEH score C statistic was significantly higher than the clinical-only C statistic (0.790 versus 0.777; P=0.008), although the magnitude of the difference was small. Additionally, despite the increased complexity, goodness of fit of the clinical+GEH score was better than that of the clinical-only score, as shown by a smaller Akaike information criterion. The full clinical+GEH SCD risk score equation and an interactive risk calculator are available in the online-only Data Supplement and at http://www.ecgpredictscd.org/.

Performance of the Clinical+GEH SCD Risk Score

Internal Cross-Validation and Calibration

The clinical+GEH risk score was well calibrated for SCD events, with similar predicted and observed rates of SCD (Table IX in the online-only Data Supplement and Figure 4A).

No significant differences between C statistics in the 5 internal cross-validation partitions were observed for the clinical-only risk score (C statistic range, 0.746–0.806; P=0.29) or the clinical+GEH risk score (C statistic range, 0.762–0.811; P=0.53). Figure 4B shows results of cross-validation of the clinical+GEH score in 5 partitions of the study cohort.

Stratification Capacity

Risk stratification capacity of the clinical+GEH score is shown in Table 4 and Tables X and XI in the online-only Data Supplement. Compared with the clinical-only score, the clinical+GEH score classified twice as many participants (24.1% versus 11.9%) as low risk (10-year SCD risk <0.5%), fewer participants (68.7% versus 82.0%) as intermediate risk (10-year SCD risk, 1%–5%), and more participants (7.2% versus 6.2%) as high risk (10-year SCD risk >5%). Overall, 35.8% of SCD victims were identified as high risk by the clinical+GEH risk score, whereas the clinical-only score identified only 27.4% of SCD victims as high risk. Only 6.5% of participants without SCD events were identified as high risk by the clinical+GEH score.

Reclassification Improvement

Table 4 also demonstrates that, with the addition of GEH parameters, 50 of 486 SCD victims (10.3%) were appropriately reclassified into a higher-risk category, and almost all of these participants (49 out of 50) were appropriately reclassified from intermediate risk to high risk. Overall, 14.9% of SCD-free participants were appropriately reclassified from intermediate risk to low risk. Only 8 of 486 SCD victims (1.7%) were inappropriately reclassified from high risk to intermediate risk, and no SCD victims were inappropriately reclassified from high risk to low risk. Net reclassification index was 18.3%, with an event net reclassification index of 6.6% and a nonevent net reclassification index of 11.7%.

The addition of GEH parameters also improved SCD-specific risk prediction (Table 4). The proportion of all SCDs decreased from 6.1% to 2.8% in the low-risk groups and increased from 14.7% to 16.4% in the high-risk groups. Among participants with a predicted 10-year SCD risk of >10%, 1 of every 4 deaths was an SCD (Table X in the online-only Data Supplement).

Classification Tests

A high-risk clinical+GEH score predicted SCD with 35.8% sensitivity, 93.6% specificity, 98.3% negative predictive value, and 12.1% positive predictive value. A combined high or intermediate risk score predicted SCD with improved sensitivity (96.9%) at the cost of reduced specificity (24.7%) and retained a very high negative predictive value (99.7%).

Clinical+GEH Risk Score Performance in Subgroups

As shown in Table XII in the online-only Data Supplement, the risk score also performed well in the subgroup of patients with abnormal intraventricular conduction (bundle-branch block/intraventricular conduction delay; n=2328). In this group, assessment of GEH appropriately reclassified 29.4% of SCD victims (all intermediate risk to high risk), and no patients with SCD were inappropriately reclassified into a lower-risk category. Importantly, 64.1% of SCD victims were appropriately identified as high risk. In a small subgroup of participants with ECGs analyzed during ventricular pacing (n=47), assessment of GEH appropriately reclassified 33% of SCD victims and identified 5 of 6 SCD victims (83%; Table XIII in the online-only Data Supplement).

Discussion

Analysis of this large, community-based, biracial prospective cohort of >20 100 participants with a wide age range revealed several important findings. First, we demonstrated an independent association of GEH with SCD. GEH electrocardiographic parameters remained independently associated with SCD after adjustment for multiple known SCD risk factors, time-updated ECG measurements, and time-updated incident nonfatal cardiovascular events. GEH parameters selectively predicted SCD over nonsudden fatal CHD and noncardiac death in competing risks models, suggesting that abnormal GEH parameters selectively identified participants with abnormal electrophysiological substrate rather than simply identifying a sicker population with structural heart disease. Moreover, each GEH parameter provided additive information on SCD risk. The complementary nature of SVG, QRS-T angle, and SAI QRST is expected because each of these measures represents distinct ways of quantifying GEH. Large increases in GEH parameters over short periods of time

Table 3. Competing Risks Scores for SCD

	Clinical-Only Score		Clinical+GEH Score	
	Sub-HR (95%CI)	β Coefficient	Sub-HR (95%CI)	β Coefficient
Age, per 10 y	1.131 (1.032–1.241)	0.1234	2.027 (1.644–2.500)	0.7066
Female	0.495 (0.411–0.596)	–0.7034	0.373 (0.228–0.612)	–0.9851
White	0.663 (0.544–0.809)	–0.4106	0.361 (0.226–0.577)	–1.0180
Diabetes mellitus	2.132 (1.739–2.615)	0.7572	3.233 (2.035–5.136)	1.1734
Hypertension	1.711 (1.397–2.096)	0.5370	2.329 (1.439–3.769)	0.8452
CHD	3.647 (2.930–4.540)	1.2939	3.095 (2.503–3.828)	1.1298
Stroke	2.070 (1.503–2.852)	0.7278	1.920 (1.397–2.641)	0.6525
SQRT SVG elevation	…	…	1.127 (1.036–1.227)	0.1199
QRS-T angle, per 10° increase	…	…	1.480 (1.273–1.722)	0.3923
SAI QRST, per 100-mV·ms increase	…	…	2.491 (1.433–4.328)	0.9126
SAI QRST×age	…	…	0.902 (0.833–0.977)	–0.1030
QRS-T angle×age	…	…	0.945 (0.923–0.968)	–0.0566
QRS-T angle×race	…	…	1.095 (1.034–1.159)	0.0908
QRS-T angle×diabetes mellitus	…	…	0.948 (0.902–0.997)	–0.0534
QRS-T angle×hypertension	…	…	0.953 (0.904–1.004)	–0.0481
SQRT SVG azimuth×female	…	…	1.092 (1.010–1.182)	0.0882
Akaike information criterion	9121		9028	
C statistic (95% CI); comparison *P*=0.008	0.777 (0.757–0.797)		0.790 (0.770–0.809)	
Partial ROC AUC for 2% false-positive fraction (95% CI); comparison *P*=0.006	0.0017 (0.0013–0.0021)		0.0022 (0.0017–0.0027)	
Predicted cumulative incidence/10 y, %	0.44–42.14		0.05–55.12	

AUC indicates area under the curve; CHD, coronary heart disease; CI, confidence interval; GEH, global electric heterogeneity; HR, hazard ratio; ROC, receiver-operating characteristic; SCD, sudden cardiac death; and SVG, spatial ventricular gradient.

were also associated with increased SCD risk. Decreases in GEH parameters were not associated with reduced SCD risk, but given that relatively few participants experienced large decreases in GEH parameters, this study may be underpowered to detect a reduction in SCD risk in these subgroups.

Importantly, there was no significant change in the magnitude or significance of association between GEH parameters and SCD when LVEF was included in the models, suggesting that, although GEH parameters are associated with LVEF, their association with SCD is independent of the degree of left ventricular dysfunction. The finding that GEH parameters are independently associated with SCD highlights the importance of including electrophysiological markers in SCD risk stratification models and future investigation of heritable genetic mechanisms underlying increased GEH.

Second, we developed a competing risks SCD risk score that combined clinical/demographic SCD risk factors with GEH parameters. The risk score identified a small subgroup of individuals with a high risk of SCD over 10 years of follow-up among a study population with an overall low SCD risk. The risk score was cross-validated internally. Our results open a new avenue for risk stratification and primary prevention of SCD, although validation in prospective studies is needed, and the optimal management/treatment of high-risk individuals requires further study.

SCD Risk Score Development and Performance

Development of an accurate and easily deployable SCD risk score is an important goal,[23] and no SCD risk scores are available for use in the general population. Several SCD risk scores have been proposed (including the Muerte Subita en Insuficiencia Cardiaca [MUSIC; Sudden Death in Heart Failure] score,[24] The Multicenter UnSustained Tachycardia Trial [MUSTT] score,[25] and Duke score[26]), yet none has performed well enough for widespread clinical application. Many SCD risk scores are specific for patients with reduced LVEF, and an important limitation is that factors associated with SCD are also associated with nonsudden death caused by progressive HF. Importantly, our SCD risk score considered competing risks of nonsudden fatal CHD and noncardiac death. This approach allowed us to demonstrate that our risk score is specific for SCD over other modes of death, likely as a result of our ability to identify abnormal electrophysiological substrate with inclusion of GEH parameters.

Our risk score performed well in identifying individuals with a high risk of SCD from an overall low-risk community population. Population screening tests are often designed to be highly sensitive at the expense of specificity; initial false-positive tests are accepted if specific confirmatory tests are available. In the case of SCD, however, no specific tests are available that could confirm the results of a highly sensitive and poorly specific screening test. Thus, for screening for and

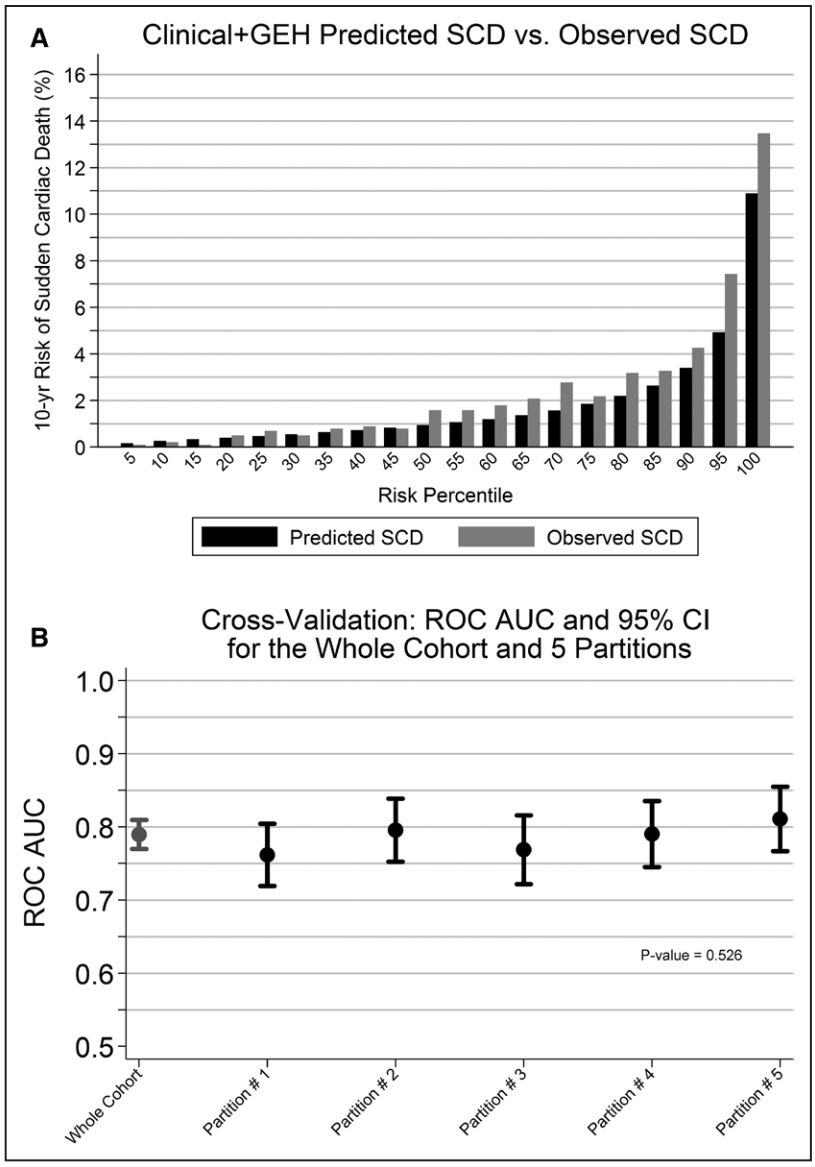

Figure 4. Clinical plus global electric heterogeneity (GEH) risk score performance. **A**, Clinical+GEH risk score calibration. Predicted and observed sudden cardiac death (SCD) incidences are shown. **B**, Clinical+GEH risk score internal cross-validation. AUC indicates area under the curve; CI, confidence interval; and ROC, receiver-operating characteristic.

risk stratification of SCD in the general population, a highly specific test is desirable.

It is important to consider that abnormal GEH by itself is not responsible for the onset of ventricular arrhythmias or SCD. Even with myocardial electrophysiological substrate favorable for ventricular arrhythmias, a triggering event is required. Thus, it is not surprising that there might be significant delay in the onset of SCD even in patients with significantly abnormal GEH parameters. This offers an opportunity for intervention.

Our finding of improved reclassification of SCD risk in a small subgroup of participants with ventricularly paced ECGs or bundle-branch block/intraventricular conduction delay supports the Wilson et al[10] hypothesis that variability in GEH can be detected independently of the ventricular activation sequence. The SVG reflects heterogeneity of activation (and secondary heterogeneity of repolarization) across the myocardium that is independent of the myocardial activation sequence. It is often assumed that ventricularly paced ECGs do not provide useful information beyond the presence of pacing. Our results, although limited by small numbers, tend to refute this assumption. Ventricular pacing introduces electric dyssynchrony and heterogeneity, which are reflected by larger GEH parameters compared with ECGs recorded during native ventricular activation. Despite the overall pacing-induced increase in GEH, however, assessment of GEH parameters during pacing still improved SCD reclassification in this subgroup. Further study of GEH in patients with ventricular pacing is warranted.

Clinical Application of the SCD Risk Score

Beyond treatment of cardiovascular risk factors, there are no accepted interventions specifically for the primary prevention of SCD in the general population. Prediction and prevention of SCD, however, are interconnected in that the development of effective SCD prevention requires the availability of effective SCD risk prediction tools. Although measurement of GEH parameters is not currently readily available, existing 12-lead ECG systems could easily report their values with minimal additional software modification. A 2-step strategy, however, may also be reasonable: The clinical-only SCD score could be easily evaluated without

Table 4. The 10-Year Competing Risks for SCD as Predicted by Clinical-Only and Clinical+GEH Models

	10-y Risk From Clinical+GEH Score			
10-y Risk From Clinical-Only Score	<0.5%	0.5%–5%	>5%	Total
<0.5%				
Participants in category, n (% total cohort)	1921 (9.52)	472 (2.34)	4 (0.02)	2397 (11.88)
SCD events, n (% of all SCDs)	5 (1.03)	1 (0.21)*	0 (0.00)*	6 (1.23)
Nonevents (non-SCD), n (% all non-SCDs)	1916 (9.73)	471 (2.39)†	4 (0.02)†	2397 (12.14)
All SCDs in category, %	6.67	4.35	0.00	6.12
Nonsudden fatal CHD, n (% all deaths in category)	10 (13.33)	5 (21.74)	0 (0.00)	15 (15.31)
Non-CHD death, n (% all deaths in category)	60 (80.00)	17 (73.91)	0 (0.00)	77 (78.57)
Proportion of all deaths not SCDs in category, %	93.33	95.65	0.00	93.88
All-cause death, n (% total in category)	75 (3.90)	23 (4.87)	0 (0.00)	98 (4.09)
0.5%–5%				
Participants in category, n (% total cohort)	2948 (14.61)	13 191 (65.38)	401 (1.99)	16 540 (81.97)
SCD events, n (% of all SCDs)	10 (2.06)†	288 (59.26)	49 (10.08)*	347 (71.40)
Nonevents (non-SCD), n (% all non-SCDs)	2938 (14.92)*	12 903 (65.53)	352 (1.79)†	16 193 (82.24)
All SCDs in this category, %	2.21	6.12	18.49	6.40
Nonsudden fatal CHD, n (% all deaths in category)	78 (17.22)	1403 (29.81)	108 (40.75)	1589 (29.29)
Non-CHD death, n (% all deaths in category)	365 (80.57)	3016 (64.07)	108 (40.75)	3489 (64.31)
All deaths not SCDs in category, %	97.79	93.88	81.51	93.60
All-cause death, n (% total in category)	453 (15.37)	4707 (35.68)	265 (66.08)	5425 (32.80)
>5%				
Participants in category, n (% total cohort)	0 (0.0)	201 (1.00)	1039 (5.15)	1240 (6.15)
SCD events, n (% of all SCDs)	0 (0.0)†	8 (1.65)†	125 (25.72)	133 (27.37)
Nonevents (non-SCD), n (% all non-SCDs)	0 (0.0)*	193 (0.98)*	914 (4.64)	1107 (5.62)
All SCDs in this category, %	0.0	7.27	15.72	14.70
Nonsudden fatal CHD, n (% all deaths in category)	0 (0.0)	47 (42.73)	326 (41.01)	373 (41.22)
Non-CHD death, n (% all deaths in category)	0 (0.0)	55 (50.00)	344 (43.27)	399 (44.09)
All deaths not SCDs in category, %	0.0	92.73	84.28	85.30
All-cause death, n (% total in category)	0 (0.0)	110 (54.73)	795 (76.52)	905 (72.98)
Total				
Participants in category n (% total cohort)	4869 (24.13)	13 864 (68.71)	1444 (7.16)	20 177 (100.00)
SCD events, n (% of all SCDs)	15 (3.09)	297 (61.11)	174 (35.80)	486 (100.00)
Nonevents (non-SCD), n (% all non-SCDs)	4854 (24.65)	13 567 (68.90)	1270 (6.45)	19 691 (100.00)
All SCDs in this category, %	2.84	6.14	16.42	7.56
Nonsudden fatal CHD, n (% all deaths in category)	88 (16.67)	1455 (30.06)	434 (40.94)	1977 (30.76)
Non-CHD death, n (% all deaths in category)	425 (80.49)	3088 (63.80)	452 (42.64)	3965 (61.68)
All deaths not SCDs in category, %	97.16	93.86	83.58	92.44
All-cause death, s (% total in category)	528 (10.84)	4840 (34.91)	1060 (73.41)	6428 (31.86)

CHD indicates coronary heart disease; GEH, global electric heterogeneity; and SCD, sudden cardiac death.
*Appropriate reclassification.
†Inappropriate reclassification.

the need for laboratory tests or an ECG, and individuals with elevated clinical-only SCD risk could then undergo further risk stratification via measurement of GEH electrocardiographic parameters.

Individuals identified as at extremely high risk for SCD (such as those with 10-year SCD risk >10%) might be appropriate candidates for future randomized, controlled trials investigating expanded indications for implantable

cardioverter-defibrillators. Those with more modest risk might be targeted for aggressive diagnosis and treatment of subclinical heart disease. Patients with large increases in GEH parameters in the short term might also be similarly targeted with aggressive cardiovascular risk modification.

There is growing recognition[27] that approximately half of sudden cardiac arrest victims have warning symptoms before their index event, but most symptoms are ignored, likely because only one third of sudden cardiac arrest victims have previously been diagnosed with cardiovascular disease. Implementation of our risk score would enable early identification of individuals at increased SCD risk, which, in turn, could also improve education and awareness of SCD risk factors and warning signs. Simply having high-risk individuals recognize their increased SCD risk could improve sudden cardiac arrest survival by increasing rates of seeking medical attention at the onset of cardiac symptoms.[27]

Strengths and Limitations

We developed our SCD risk score in 2 large, biracial, prospective cohorts encompassing a wide age range. Our risk score is therefore likely to be widely generalizable. However, the study does have limitations. The definition of covariates was slightly different in each cohort. We adjusted for multiple SCD confounders, but it is possible that residual confounding influenced the results. Information on LVEF, which has been associated with SCD, was available only in the CHS cohort and therefore could not be included in the final risk score. However, the addition of LVEF in time-updated models did not alter the association between GEH parameters and SCD. One possible reason for this observation is that LVEF is normal in the vast majority of the general population. Additionally, although HF was associated with SCD in minimally adjusted analyses, after multivariable adjustment, HF was not a significant predictor of SCD in the study population, and according to our procedure for backward selection, it was removed from the final risk score.

Patients who experienced sudden cardiac arrest but who were successfully resuscitated and survived to hospital discharge were not considered cases of SCD in this analysis. However, because survival of out-of-hospital cardiac arrest is rare,[27] it is unlikely that this significantly affected the results. Finally, although all deaths were thoroughly adjudicated, we cannot determine whether some SCDs were due primarily to bradyarrhythmias as opposed to ventricular tachyarrhythmias. However, because sudden cardiac arrest caused by bradyarrhythmia is frequently the result of pause-dependent polymorphic ventricular tachycardia, GEH might still be associated with SCD in these patients. This phenomenon requires further study.

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Disclosures

Johns Hopkins University (Dr Tereshchenko) holds the US patent "Methods for Determining Risk of Ventricular Arrhythmia," which was among the methods used to measure SAI QRST (not licensed).

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CLINICAL PERSPECTIVE

Despite advances in treatment and primary prevention of cardiovascular disease, sudden cardiac death (SCD) incidence remains high, and SCD is frequently the first manifestation of cardiovascular disease. Development of a noninvasive, inexpensive, and easy-to-use SCD risk score for use in the general population is an important goal. In this study, we assessed 5 ECG measures of myocardial global electric heterogeneity (GEH)—sum absolute QRST integral, spatial QRS-T angle, and spatial ventricular gradient (magnitude, azimuth, and elevation)—in 20 177 participants in the community-based Atherosclerosis Risk in Communities (ARIC) study and Cardiovascular Health Study (CHS). We demonstrated that baseline GEH electrocardiographic parameters and large increases in GEH parameters over time were independently associated with SCD and that assessment of multiple GEH electrocardiographic parameters provided additive/complementary information on SCD risk. We developed a novel SCD risk score that used readily available clinical characteristics (age, sex, race, hypertension, diabetes mellitus, stroke, and coronary heart disease) and GEH electrocardiographic parameters. We demonstrated that the risk score was highly specific for SCD and that the addition of GEH electrocardiographic parameters to clinical characteristics significantly improved SCD risk prediction, likely because GEH electrocardiographic parameters identified participants with myocardial electric substrate favorable for ventricular arrhythmias. Our study represents an important step forward in understanding SCD risk factors and identifying people in the general population with elevated SCD risk who might be targeted for future SCD risk reduction strategies. The genetic basis of abnormal myocardial electric heterogeneity, as expressed by abnormal GEH electrocardiographic parameters, also warrants further study.