

Development and Validation of a Sudden Cardiac Death Prediction Model for the General Population

BACKGROUND: Most sudden cardiac death (SCD) events occur in the general population among persons who do not have any prior history of clinical heart disease. We sought to develop a predictive model of SCD among US adults.

METHODS: We evaluated a series of demographic, clinical, laboratory, electrocardiographic, and echocardiographic measures in participants in the ARIC study (Atherosclerosis Risk in Communities) (n=13677) and the CHS (Cardiovascular Health Study) (n=4207) who were free of baseline cardiovascular disease. Our initial objective was to derive a SCD prediction model using the ARIC cohort and validate it in CHS. Independent risk factors for SCD were first identified in the ARIC cohort to derive a 10-year risk model of SCD. We compared the prediction of SCD with non-SCD and all-cause mortality in both the derivation and validation cohorts. Furthermore, we evaluated whether the SCD prediction equation was better at predicting SCD than the 2013 American College of Cardiology/American Heart Association Cardiovascular Disease Pooled Cohort risk equation.

RESULTS: There were a total of 345 adjudicated SCD events in our analyses, and the 12 independent risk factors in the ARIC study included age, male sex, black race, current smoking, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, serum potassium, serum albumin, high-density lipoprotein, estimated glomerular filtration rate, and QT_c interval. During a 10-year follow-up period, a model combining these risk factors showed good to excellent discrimination for SCD risk (c-statistic 0.820 in ARIC and 0.745 in CHS). The SCD prediction model was slightly better in predicting SCD than the 2013 American College of Cardiology/American Heart Association Pooled Cohort risk equations (c-statistic 0.808 in ARIC and 0.743 in CHS). Only the SCD prediction model, however, demonstrated similar and accurate prediction for SCD using both the original, uncalibrated score and the recalibrated equation. Finally, in the echocardiographic subcohort, a left ventricular ejection fraction <50% was present in only 1.1% of participants and did not enhance SCD prediction.

CONCLUSIONS: Our study is the first to derive and validate a generalizable risk score that provides well-calibrated, absolute risk estimates across different risk strata in an adult population of white and black participants without a clinical diagnosis of cardiovascular disease.

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Clinical Perspective

What Is New?

- This project provides the first, generalizable risk score for sudden cardiac death in adults without a history of cardiovascular disease.
- Using 17 884 adults ≥ 45 years of age without a history of cardiovascular disease across 2 large population-based studies, we derived and validated a SCD prediction model that outperformed the 2013 American College of Cardiology/American Heart Association Pooled Cohort risk equations for the prediction of SCD.
- The SCD prediction model included the following risk factors: age, male sex, black race, current smoking, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, serum potassium, serum albumin, high-density lipoprotein, estimated glomerular filtration rate, and QT_c interval.

What Are the Clinical Implications?

- Our findings provide a strong step toward distinguishing SCD risk across the general population and can help target future strategies aimed at SCD prevention for the highest risk subgroups of the general population.
- A low left ventricular ejection fraction was present in only 1% of participants and did not enhance SCD prediction.

Sudden cardiac death (SCD) is defined as an unexpected, pulseless condition attributable to a cardiac arrhythmia.¹ Most cardiac arrests present without warning symptoms and are nearly always fatal despite resuscitation attempts.^{2,3} As a result, preventive strategies have focused on using implantable cardioverter-defibrillators in the highest risk subgroups of the population, such as those with an advanced cardiomyopathy and depressed left ventricular ejection fraction (LVEF).⁴ Most SCD cases, however, occur in the general population,^{5–7} and the majority have no clinically recognized heart disease prior to the event.^{8–10} Therefore, when SCD occurs in the general population, it is typically the initial manifestation of cardiovascular disease.

The Institute of Medicine recently published “Strategies to Improve Cardiac Arrest Survival: A Time To Act” and emphasized the need for more effective prevention and resuscitation programs.¹¹ Expert panels have highlighted the lack of a baseline model that estimates a participant’s risk for SCD as a major obstacle to primary prevention efforts that target SCD risk stratification among the general population.^{12,13} Multiple population-based studies have demonstrated independent associations between specific risk factors and biomarkers of inflammation, myocyte injury, and

neurohormonal activation with risk for SCD.^{2,14–16} However, there is no widely accepted model of individual risk estimation for SCD.^{12,13,17} We sought to develop and evaluate a SCD prediction model among US adults without a history of cardiovascular disease (CVD). As part of this approach, we evaluated a comprehensive panel of traditional and novel cardiovascular risk factors in 2 large, biracial, population-based cohorts. We also compared SCD prediction using the current, 2013 American College of Cardiology/American Heart Association (ACC/AHA) CVD Pooled Cohort risk equations, which were developed to calculate the 10-year risk of a first cardiovascular event including nonfatal myocardial infarction, coronary heart disease death, or fatal or nonfatal stroke.¹⁸

METHODS

The ARIC study (Atherosclerosis Risk in Communities) and the CHS (Cardiovascular Health Study) are population-based, prospective cohorts designed to improve understanding of cardiovascular disease risk. The ARIC study included 15 792 participants who were 45 to 64 years of age at baseline (1987–1989). These participants were chosen from 4 communities in Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis suburbs, Minnesota; and Washington County, Maryland.¹⁹ The CHS included 5888 participants >65 years of age identified from Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA by use of Medicare eligibility lists. The original CHS cohort included 5201 participants recruited in 1989 and 1990. An additional 687 black participants were recruited in 1992 to 1993.²⁰ The ARIC and CHS protocols were approved by the institutional review board at each participating center, and informed consent was obtained from each study participant.

This analysis excluded participants who had prevalent cardiovascular disease defined by a previous history of coronary heart disease, heart failure, or stroke. Participants with missing covariates also were excluded. We performed an extensive review of the baseline data definitions and study sources so that only comparable clinical variables across the 2 cohorts were included. The final study sample consisted of 17 884 participants (13 677 from ARIC and 4207 from CHS; Figure 1).

Baseline variables from ARIC and CHS participants were assessed for these analyses. The baseline visit in each study consisted of a comprehensive examination including a thorough medical history, physical examination, laboratory testing, and a 12-lead electrocardiogram (ECG). In order to harmonize the baseline data between the 2 cohorts, each variable was defined similarly. Age, sex, race, education level, and income were determined by self-report. Education was dichotomized by whether or not participants had graduated from high school. Income groups were categorized into annual household earnings of $< \$8000$, $\$8000$ to $34\,999$, and $\geq \$35\,000$. Height and weight were measured by standard protocol, and body mass index was calculated as weight (in kilograms) divided by height (in meters) squared. Blood pressure (systolic and diastolic) was measured in seated participants after a 5-minute rest. Questionnaires assessed alcohol intake

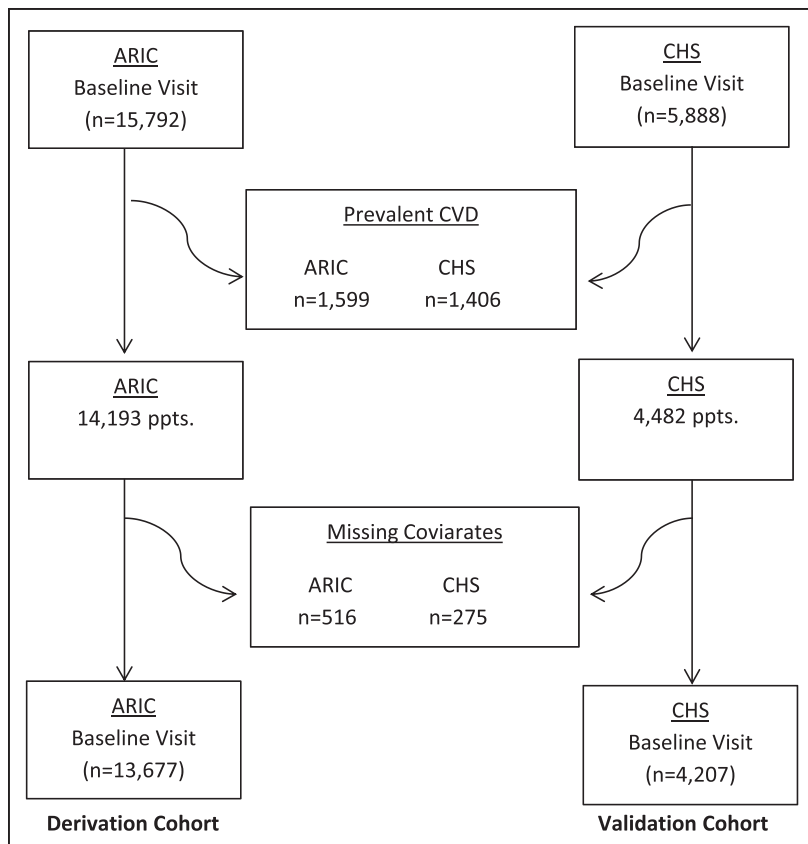


Figure 1. Study overview.

ARIC indicates Atherosclerosis Risk in Communities study; CHS, Cardiovascular Health Study; and CVD, cardiovascular disease.

and self-reported smoking status (current, former, never). Diabetes mellitus was defined as a fasting glucose ≥ 126 mg/dL, nonfasting glucose ≥ 200 mg/dL, or the use of hypoglycemic medications. A family history of coronary heart disease was defined as disease in a sibling among CHS participants or any immediate family member in the ARIC study. Physical activity was evaluated in the ARIC study and CHS using a questionnaire that assessed each participant's self-reported activity ([Methods in the online-only Data Supplement](#)). Estimated glomerular filtration rate was calculated from creatinine using the Chronic Kidney Disease Epidemiology Collaboration Equation.²¹ Total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, serum albumin (per 0.3 g/dL decrease), potassium (centered at 4.4, per 0.5 mmol/L increase), and hemoglobin (per 1 g/dL) were all modeled continuously. Twelve-lead ECGs were assessed in both cohorts for the following parameters: atrial fibrillation (ECG-defined), Cornell voltage, which evaluates left ventricular thickness and is calculated from the sum of the S-wave in V3 and R wave in aVL,^{22,23} corrected QT interval,²⁴ QRS duration,²⁵ heart rate, and left bundle-branch block status.

Echocardiography was performed on a subgroup of participants in both ARIC and CHS. Of the 13677 ARIC participants included in our analysis, echocardiographic studies were available in 1568 participants. In CHS, of the 4207 participants in our study, echocardiograms were completed on 3731 participants. In ARIC, echocardiography was performed using an Acuson XP 128/10c machine (Siemens Medical, Iselin, NJ) with both M-mode and pulsed Doppler examination following a standard protocol.²⁶ LVEF was determined semiquantitatively using visual assessment and a modified Quinones formula.²⁷

Left ventricular systolic dysfunction was defined as an ejection fraction $< 50\%$.^{28,29} In CHS, echocardiographic examinations included 2-dimensional and Doppler methods performed with the Toshiba SSH-160A sonographic units.³⁰ The CHS Echocardiography Reading Center classified the ejection fraction in qualitative terms as normal, borderline or abnormal.³¹

Outcome Ascertainment

In both ARIC and CHS, comprehensive data were gathered on cardiovascular events and deaths from hospital records; interviews with physicians, next of kin, and/or witnesses; death certificates; and autopsy reports when available. The causes of death were adjudicated by respective ARIC and CHS events' committees ([Methods in the online-only Data Supplement](#)). The primary outcome, SCD, was defined similarly in both ARIC and CHS: a sudden pulseless condition from a cardiac origin in a previously stable individual occurring out of the hospital or in the emergency department.³²⁻³⁵ For unwitnessed deaths, the participant must have been seen within 24 hours of the arrest in a stable condition and without evidence of a noncardiac cause of cardiac arrest. These definitions concur with those proposed by the National Heart, Lung, and Blood Institute working group on SCD.¹ For all cases, participants could not have life-threatening noncardiac comorbidities or be under hospice or nursing home care. Each event was independently adjudicated by 2 physicians. If there was a disagreement, a third investigator reviewed the event to provide final classification.^{32,33} A blinded second physician review of a random sample of 70 of these death records showed an 88% interviewer agreement and $\kappa = 0.74$ for SCD.

Statistical Analysis

Our initial objective was to derive a SCD prediction model using the ARIC cohort and validate it in CHS. We first harmonized 26 variables across both cohorts and calculated the mean and median values of relevant sociodemographic characteristics, cardiovascular risk factors, serum measures, and ECG variables across ARIC and CHS. When possible, each characteristic was modeled as a linear variable.

Model Building: Derivation Cohort

We evaluated the univariate association between each baseline variable in the ARIC study and SCD risk. Those variables associated with SCD at $P < 0.05$ were entered into a multivariable model. Backwards stepwise regression then was performed, and a retention criteria of $P < 0.1$ was used to identify candidate variables for our prediction model. Age and sex interactions were evaluated. Based on 10-years of follow-up, the β coefficients for each variable retained in the final multivariable model were evaluated.

Prediction Modeling

Model-based 10-year risks of SCD, nonsudden cardiac death, and all-cause mortality were calculated in both ARIC and CHS. The SCD prediction equations used the score calculated from the risk factors and corresponding regression coefficients obtained from the derivation cohort (ARIC). To determine if our SCD prediction equation was a better prediction tool than previously published risk scores, we calculated risk for each outcome using the 2013 ACC/AHA CVD Pooled Cohort risk equations. As part of this assessment, we calculated the discrimination (c-statistics) and quantified each prediction model's ability to separate those who experience a specific outcome from those who do not.³⁶ We also assessed calibration, which evaluates how closely the predicted outcome corresponds with the observed event. We utilized Nam and D'Agostino's modified Hosmer-Lemeshow χ^2 statistic.³⁷ The SCD prediction score and ACC/AHA CVD Pooled Cohort risk equation were used to divide subjects into deciles of risk for experiencing each outcome within 10 years. A χ^2 statistic was calculated to compare the differences between predicted and actual event rates. In addition, we recalibrated both the SCD prediction score and the ACC/AHA CVD Pooled Cohort risk equation for each outcome in each cohort. In this scenario, the average incidence rate is replaced by the mean risk in the cohort and the 10-year Kaplan-Meier event rate for each outcome. To do this, we multiplied the risk for each person by the ratio of the 10-year Kaplan-Meier over the mean of the risks to obtain the correct calibration. Recalibration does not affect discrimination. Given that CHS is comprised of elderly individuals, all prediction statistics in the validation cohort were assessed utilizing a competing risk approach.^{38,39} Finally, in the subgroup of participants who had an echocardiogram, we evaluated whether the addition of LVEF to the baseline model enhanced SCD prediction. The proportional hazards assumption was not violated in any of these analyses. SAS software version 9.2 (SAS Institute Inc., Cary, NC), R (version 3.0.2), and Stata (College Station, TX, version 13.1) were used for all analyses.

Secondary Analysis

As part of a secondary analysis, we evaluated CHS for the association of the following biomarkers with SCD risk: C-reactive protein, N-terminal pro-brain natriuretic peptide, and troponin T measured with a high sensitivity assay. Biomarkers were evaluated both continuously (log-transformed variable per doubling) and categorically in the multivariable model for SCD in CHS. This step was repeated with each biomarker categorized into quintiles.

RESULTS

For these analyses, there were a total of 345 adjudicated SCD events. During a median [interquartile range] follow-up of 13.1 [interquartile range 2.3] years in the ARIC study, there were 171 SCD events; in CHS, during a median follow-up of 14.2 [interquartile range 8.2] years, there were 174 SCD cases. Baseline characteristics of eligible participants are presented in Table 1. The average age was 54 ± 6 years in ARIC and 72 ± 5 years in CHS. The majority of participants for these analyses were women: 56% of ARIC and 61% of CHS. Black participants comprised 26% of ARIC and 15% of CHS.

Using backwards selection to derive the prediction model, the following variables were retained as independent risk factors for SCD in the ARIC study: age, male sex, black race, current smoker, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, serum potassium, serum albumin, high-density lipoprotein, estimated glomerular filtration rate, and the corrected QT interval (Table 2). Serum potassium fit the model as a quadratic term, and estimated glomerular filtration rate fit the model best when it was divided into categories of <60 , 60 to 90, and >90 mL/min/1.73 m². Age and sex-based interactions were not significant, and we did not derive separate age and sex-based equations.

SCD Prediction

Based on 10 years of follow-up, the SCD prediction equation derived from the ARIC study is $1 - 0.99522^{\exp(\Sigma \beta x - 3.0702734)}$ where β is the regression coefficient and x is the level for each risk factor. The SCD prediction model resulted in moderate prediction of SCD (Table 3) and was slightly better than the ACC/AHA CVD Pooled Cohort risk equations in discriminating 10-year risks of SCD in ARIC and CHS. The SCD prediction model revealed a large gradient of risk in both ARIC and CHS with the highest decile having a 10-year SCD risk of $\approx 5\%$ in ARIC and $>10\%$ in CHS (Figures 2A and 2B). Furthermore, the overall prediction for SCD was similar and accurate using both the original, uncalibrated SCD prediction score (Table 3) and the recalibrated equation (Table I in the online-only Data Supplement). In addition,

Table 1. Baseline Characteristics of Atherosclerosis Risk in Communities Study and Cardiovascular Health Study Participants Without Prevalent Cardiovascular Disease

Variable, Mean (SD) or N (%)	ARIC (n=13677)	CHS (n=4207)
Demographics		
Age	54.0 (6)	72 (5)
Female	7606 (56%)	2566 (61%)
Black	3485 (26%)	610 (15%)
High school degree	10 647 (78%)	3457 (82%)
Income		
<\$8000	1862 (14%)	543 (13%)
\$8000–34 999	5886 (43%)	2451 (58%)
≥\$35 000	5929 (43%)	949 (23%)
CVD risk factors		
Current smoker	3521 (26%)	522 (12%)
Alcohol ≥3 drinks/wk	3477 (25%)	771 (18%)
BMI, kg/m ²	27.5 (5.2)	26.6 (4.7)
Physical activity, scale 0–5	2.4 (0.8)	
Physical activity (kcal/wk)		1100 [405,2374]
Systolic blood pressure, mm Hg	121 (19)	136 (21)
Diastolic blood pressure, mm Hg	74 (11)	71 (11)
Diabetes mellitus	1410 (10%)	578 (14%)
Family history of CHD/CVD	1121 (8%)	1416 (34%)
Serum measures		
Potassium, mmol/L	4.4 (0.5)	4.2 (0.4)
Albumin, g/dL	3.9 (0.3)	4.0 (0.3)
Hemoglobin, g/dL	13.9 (1.4)	14.0 (1.4)
Total cholesterol, md/dL	214 (42)	212 (39)
HDL, mg/dL	52 (17)	56 (16)
LDL, mg/dL	137 (39)	130 (35)
eGFR, mL/min/1.73 m ²	96 (15)	80 (19)
ECG		
Atrial fibrillation	19 (0.5%)	77(2%)
Cornell voltage, mm	12.1 (5.3)	15.4 (4.2)
QT _c interval, ms	416 (18)	428 (24)
QRS interval, ms	97 (12)	91 (16)
Heart rate, beats per minute	67 (10)	65(11)
Left bundle-branch block	6 (0.05%)	49 (1%)
Biomarkers, median [IQR]		
CRP, mg/L		2.38 [1.20, 4.25]

(Continued)

Table 1. Continued

Variable, Mean (SD) or N (%)	ARIC (n=13677)	CHS (n=4207)
NT-proBNP, ng/dL		103 [54, 197]
High sensitivity troponin T, ng/L		4.72 [2.99, 9.07]

ARIC indicates Atherosclerosis Risk in Communities study; BMI, body mass index; CHD, coronary heart disease; CHS, Cardiovascular Health Study; CRP, C-reactive protein; CVD, cardiovascular disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; and SD, standard deviation.

the ACC/AHA CVD Pooled Cohort risk equations were not well calibrated in CHS because the model's predicted risk of SCD was consistently greater than the observed one using both the original and recalibrated equation. Furthermore, the SCD prediction model re-

Table 2. Estimated β Coefficients in the Derived SCD Prediction Model

	Estimated β	Standard Error
Demographics		
Age (centered at 54, per 1 y increase)	0.043	0.014
Male	0.858	0.175
Black	0.597	0.179
CVD risk factors		
Current smoker	0.881	0.159
Systolic blood pressure (per 1 SD increase)	0.347	0.062
Antihypertensive medication use	0.322	0.171
Diabetes mellitus	0.792	0.181
Serum measures		
Potassium (centered at 4.4, per 0.5 mmol/L increase)	−0.004	0.007
Quadratic potassium term	0.0009	0.0003
Albumin (per 0.3 g/dL decrease)	0.253	0.081
HDL (per SD decrease)	0.202	0.097
eGFR 60–90 mL/min/1.73m ²	0.315	0.175
eGFR <60 mL/min/1.73m ²	0.849	0.348
QT _c interval (per SD increase)	0.158	0.052

CVD indicates cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; SCD, sudden cardiac death; and SD, standard deviation.

Based on 10 years of follow-up, the SCD prediction equation derived from the Atherosclerosis Risk in Communities study is $1 - 0.99522 \exp(\sum \beta x - 3.0702734)$, where β is the regression coefficient and x is the level for each risk factor.

Table 3. Model Discrimination and Calibration for SCD, Non-Sudden Cardiac Death, and All-Cause Mortality Using the 10-Year Risk Prediction Equation

	ARIC	CHS
Sudden cardiac death		
SCD prediction score		
C-statistic (95% CI)	0.820 (0.785, 0.854)	0.745 (0.701, 0.789)
Calibration χ^2 (P value)	11.46 (0.25)	13.74 (0.088)
ACC/AHA CVD risk equation		
C-statistic (95% CI)	0.808 (0.772, 0.844)	0.743 (0.700, 0.768)
Calibration χ^2 (P value)	851.0 (<0.001)	24.71 (0.003)
Non-sudden cardiac death		
SCD prediction score		
C-statistic (95% CI)	0.818 (0.784, 0.853)	0.720 (0.693, 0.747)
Calibration χ^2 (P value)	20.90 (0.01)	45.17 (<0.001)
ACC/AHA CVD risk equation		
C-statistic (95% CI)	0.823 (0.791, 0.856)	0.753 (0.728, 0.779)
Calibration χ^2 (P value)	800.6 (<0.001)	34.72 (<0.001)
All-cause mortality		
SCD prediction score		
C-statistic (95% CI)	0.731 (0.715, 0.747)	0.681 (0.666, 0.696)
Calibration χ^2 (P value)	6058 (<0.001)	91.40 (<0.001)
ACC/AHA CVD risk equation		
C-statistic (95% CI)	0.728 (0.712, 0.743)	0.692 (0.678, 0.707)
Calibration χ^2 (P value)	34.59 (<0.001)	68.32 (<0.001)

ACC indicates American College of Cardiology; AHA, American Heart Association; ARIC, Atherosclerosis Risk in Communities study; CHS, Cardiovascular Health Study; CI, confidence interval; CVD, cardiovascular disease; and SCD, sudden cardiac death.

sulted in slightly enhanced discrimination of SCD risk compared with non-SCD in both cohorts (Table 3). In comparison the ACC/AHA CVD Pooled Cohort risk equations were better at predicting non-SCD than SCD in both cohorts. Neither 1 of the 2 prediction models was well calibrated for the non-SCD outcome even after recalibrating using the baseline 10-year event rates of non-SCD in each cohort. Finally, the prediction of all-cause mortality using either one of these prediction equations was relatively weak.

The SCD prediction equation seemed to discriminate SCD risk similarly in blacks and whites (Figure 3). In ARIC, SCD prediction seemed stronger in women compared

with men; however, the limited number of events prevents a rigorous evaluation of differences across subgroups.

Left Ventricular Ejection Fraction Analysis

Of the 5299 participants with echocardiographic data available, only 57 (1.1%) had an ejection fraction <50% or described as abnormal. The mean duration of follow-up after the initial echocardiographic study was 13.0 years in ARIC and 9.3 years in CHS. The significant majority of participants in our study, both with and without SCD events, had a normal LVEF. The addition of LVEF to the baseline prediction model did not result in any significant enhancement of the c-statistic in either ARIC or CHS.

Biomarker Analysis

In CHS, N-terminal pro-brain natriuretic peptide and high sensitivity troponin T were associated with SCD risk in unadjusted analysis. However, when C-reactive protein, N-terminal pro-brain natriuretic peptide, and high sensitivity troponin T were added individually to the final multivariable model, none was significant in the adjusted analysis (Table 4).

DISCUSSION

In this combined analysis from 2 large US-based cohorts with >17000 adults without a clinical history of cardiovascular disease, we derived and validated a SCD prediction model that identified a gradient of risk across the general population. In ARIC, approximately three-fourths of the participants had a 10-year SCD risk of <1%. The highest decile of risk, however, approached 5% throughout the 10 years, suggesting that this panel of risk factors can distinguish a large gradient in SCD risk among middle-aged adults. Similarly, a gradient of risk was observed in CHS with the lowest and highest deciles having predicted SCD risks of approximately 1.5 and 11%, respectively during a 10-year follow-up period. Our study is the first to derive and validate a generalizable risk score that provides well-calibrated, absolute risk estimates across different risk strata in an adult population without a clinical diagnosis of cardiovascular disease. It is important to delineate these risks as the significant majority of SCD cases arise from this subgroup of the population.^{8,9,40} Finally, the SCD rates identified in the highest decile are significantly lower than the current clinical thresholds for implantable cardioverter-defibrillator implantation in the primary prevention of SCD (annualized SCD rate approximately 3%).^{4,41} Our findings, however, provide a strong step toward distinguishing SCD risk across the general population and can help target future strategies aimed at SCD prevention for the highest risk subgroups in the community.

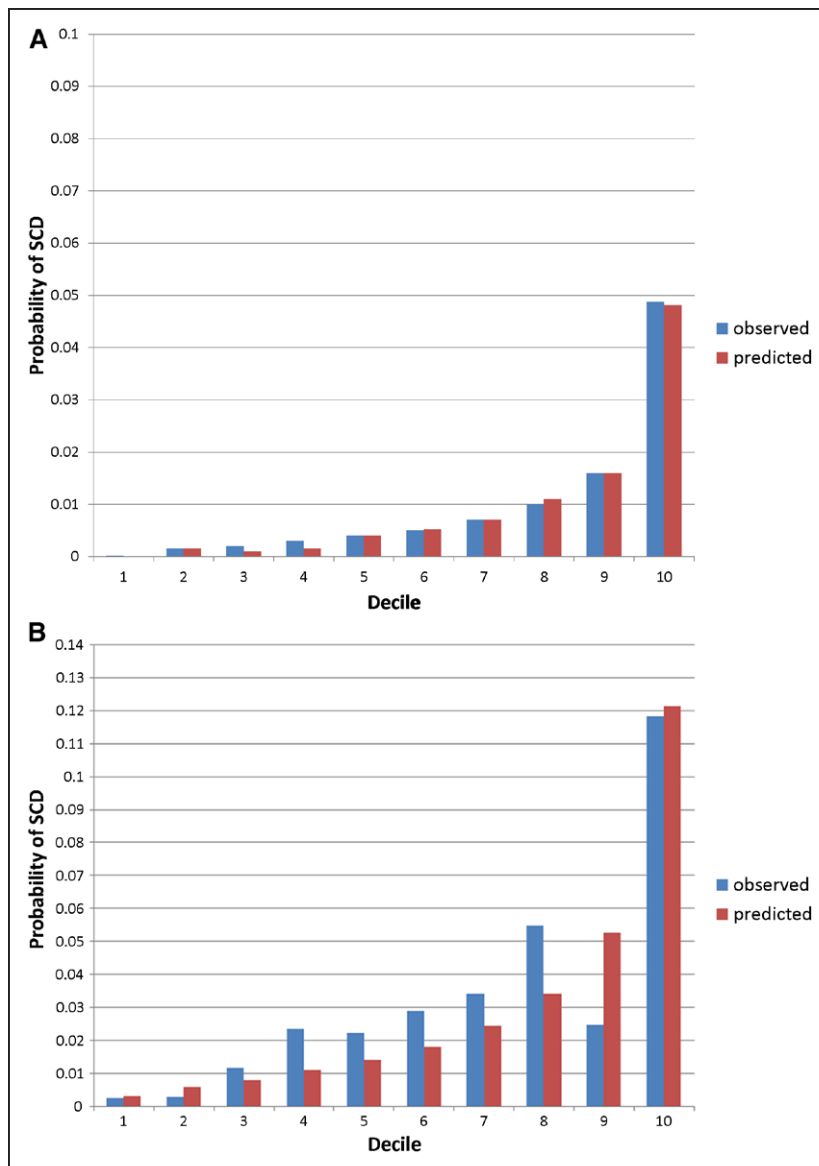


Figure 2. A, ARIC study (Atherosclerosis Risk in Communities) 10-year calibration plot using the sudden cardiac death (SCD) prediction model and B, Cardiovascular Health Study (CHS) 10-year calibration plot using the SCD prediction model.

The SCD prediction model outperformed the 2013 ACC/AHA CVD Pooled Cohort risk equations especially in providing calibrated predictions of SCD risk in both community-based cohorts. The newly derived prediction model contained nearly all the variables present in the 2013 ACC/AHA CVD Pooled Cohort risk equation plus additional, arrhythmia-specific variables. In particular, both potassium and the corrected QT interval were selected as risk markers for SCD prediction. In addition, estimated glomerular filtration rate, which has strong, independent associations with SCD also was selected as an independent risk factor.^{42–44} The 2013 ACC/AHA CVD Pooled Cohort risk equations were developed to provide 10-year risk estimates of developing a first cardiovascular event defined as a nonfatal MI or coronary heart disease death or fatal or nonfatal stroke among participants free from CVD at the beginning of the evaluation period. Although SCD events

comprised a portion of coronary heart disease deaths, there were other cardiovascular events, both fatal and nonfatal, present in the combined end point that were used to generate the 2013 ACC/AHA CVD Pooled Cohort risk equation and likely limit its performance for SCD prediction.

To the best of our knowledge, our study is one of the first to identify low albumin concentration as an independent SCD risk factor in both cohorts, suggesting that it is an important marker for arrhythmic mortality. Prior studies have demonstrated an association between low serum albumin and increased cardiovascular morbidity including coronary heart disease, myocardial infarction, and heart failure.^{43–46} Experimental models also have demonstrated that low serum albumin reflects the overall inflammatory burden.⁴⁶ In our study of >17 000 participants without coronary heart disease, prevalent heart failure, or stroke, low serum

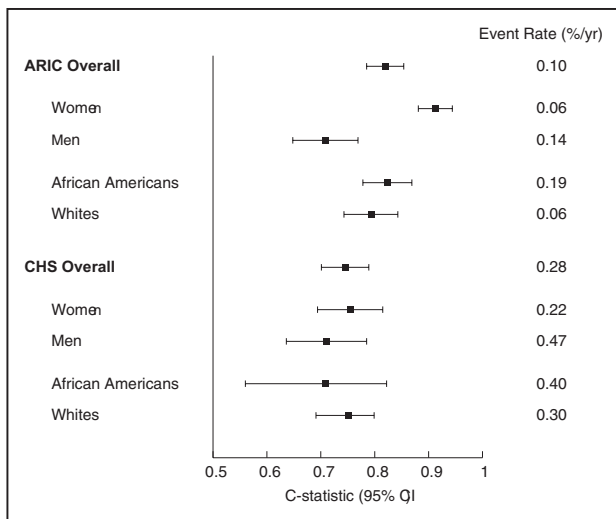


Figure 3. Sudden cardiac death prediction stratified by sex and race.

ARIC indicates Atherosclerosis Risk in Communities study; CHS, Cardiovascular Health Study; and CI, confidence interval.

albumin levels may be a marker of subclinical cardiac dysfunction that subsequently increases the risk for arrhythmias and SCD.

The overwhelming majority of participants in both cohorts had a normal LVEF. As such, an echocardiographic-based assessment of systolic function among individuals

in the general population provides limited insight from the standpoint of SCD risk stratification, largely because of the low prevalence of systolic dysfunction. In addition, the preserved LVEF group comprised the majority of the SCD cases that occurred during the approximately 10 years of follow-up after the echocardiogram. Recent data from the Oregon Sudden Unexpected Death Study also support that the majority of patients who died suddenly did not have a depressed LVEF documented prior to the cardiac arrest.⁴⁰

Our findings from these prospective cohort studies support previous community-based surveillance studies from the early 1990s conducted in Seattle and Chicago that demonstrated the presence of racial disparities in SCD risk after adjusting for service-related variables including cardiopulmonary resuscitation, response times of emergency medical services, and the likelihood of being hospitalized after the cardiac arrest.^{47,48} A recent autopsy-based study in San Francisco found a more than 3-fold higher incidence of SCD among blacks compared with whites.⁴⁹ In addition, the prediction model performed similarly in blacks and whites.

Several limitations should be considered when interpreting our findings. First, participants in the ARIC study were younger than CHS participants at the time of their initial assessment for baseline characteristics. Evaluation of potential risk factors at a later period in life may enhance SCD prediction in the elderly population. The variables assessed in our study were obtained at only one time point.

Table 4. Association of Biomarkers With Sudden Cardiac Death in CHS

	Biomarker Quintiles					Per Doubling	Linear Model P value
	1	2	3	4	5		
CRP							
CRP range (mg/L)	<1.05	1.05–1.99	2.00–3.18	3.19–5.68	>5.68		
Unadjusted; HR (95% CI)	1.00 (ref)	0.77 (0.45, 1.32)	1.08 (0.66, 1.78)	1.14 (0.69, 1.89)	1.50 (0.92, 2.46)	1.10 (0.93, 1.30)	0.275
Adjusted*; HR (95% CI)	1.00 (ref)	0.75 (0.44, 1.29)	1.04 (0.63, 1.72)	0.92 (0.54, 1.56)	1.19 (0.71, 1.99)	1.03 (0.87, 1.23)	0.712
NT-proBNP							
NT-proBNP range (pg/dL)	<51	51–91	92–156	157–298	>298		
Unadjusted; HR (95% CI)	1.00 (ref)	1.13 (0.63, 2.01)	1.62 (0.93, 2.81)	1.88 (1.09, 3.27)	2.96 (1.65, 5.33)	1.18 (1.00, 1.39)	0.045
Adjusted*; HR (95% CI)	1.00 (ref)	1.10 (0.61, 1.96)	1.51 (0.86, 2.66)	1.56 (0.87, 2.79)	1.83 (0.95, 3.50)	1.14 (0.90, 1.28)	0.418
High sensitivity troponin T							
High sensitivity troponin T range (pg/mL)	<3.00	3.00–5.44	5.45–8.16	8.17–12.94	>12.94		
Unadjusted; HR (95% CI)	1.00 (ref)	0.53 (0.25, 1.14)	1.51 (0.86, 2.64)	1.97 (1.16, 3.37)	3.75 (2.24, 6.26)	1.50 (1.25, 1.81)	<0.001
Adjusted*; HR (95% CI)	1.00 (ref)	0.41 (0.19, 0.89)	0.96 (0.54, 1.72)	1.03 (0.58, 1.83)	1.39 (0.76, 2.55)	1.14 (0.88, 1.49)	0.327

CHS indicates Cardiovascular Health Study; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; and NT-proBNP, N-terminal pro-brain natriuretic peptide.

*The final multivariable model selected based on the summary estimates from the derivation cohort: age, male sex, black race, current smoker, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, potassium, albumin, high-density lipoprotein, estimated glomerular filtration rate, and QT_c.

Our study does not evaluate how changes in risk factors affect SCD risk, nor can we discern whether they are modifiable risk factors. In addition, the events in our analyses are not contemporary as formal adjudication protocols for SCD ended in 2001 in the ARIC study and 2006 in CHS. As a result, ongoing adjudication protocols in these cohorts and a larger number of SCD cases will enhance the predictive accuracy of the SCD equation especially across the different deciles of risk. Furthermore, the echocardiograms were obtained in only 30% of participants, and a detailed assessment of different LVEF categories as predictors of SCD could not be performed. Finally, the 3 biomarkers in our analysis were not measured at baseline in ARIC participants. As a result, their lack of improvement for SCD prediction is based on CHS data only.

CONCLUSIONS

Our study is one of the first to develop and validate a prediction model for SCD risk across middle aged and elderly populations in the United States. After a systematic evaluation of demographic, clinical, laboratory, electrocardiographic, echocardiographic, and biological markers, we identified a substantially elevated 10-year risk of SCD among participants in the highest decile of predicted SCD risk. These findings allow identification of high-risk individuals appropriate for targeted interventions designed to reduce the burden of SCD.

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DISCLOSURES

None.

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FOOTNOTES

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Development and Validation of a Sudden Cardiac Death Prediction Model for the General Population

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SUPPLEMENTAL MATERIAL

Development and Validation of a Sudden Cardiac Death Prediction Model for the General Population

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Supplemental Methods

Physical Activity

In ARIC, the level of physical activity was assessed at baseline using the sport index of the Baecke Questionnaire.¹ Sport activity scores range in whole and half increments from 1 – 5, with values <2 indicative of physical inactivity.²

In CHS, questionnaires were administered at baseline to estimate each participants' self-reported walking pace, exercise intensity, number of blocks walked weekly and leisure-time activity levels. During the baseline examination, participants were asked they had engaged in any of the following 15 leisure time activities in the prior 2 weeks: swimming, hiking, aerobics, tennis, jogging, racquetball, walking, gardening, mowing, raking, golfing, bicycling, dancing, calisthenics, and riding an exercise cycle. The intensity of each activity has been established and validated by the Minnesota Heart Survey.³ Participant responses regarding each type of activity, frequency, and duration were used to calculate leisure time physical activity, expressed in kilocalories per week.

Outcome Definitions

Myocardial infarction was defined by a clinical history of cardiac symptoms, elevated cardiac enzymes, and electrocardiographic changes.^{4,5} In ARIC, incident heart failure was defined as the presence of an ICD code for heart failure (ICD 9 428, ICD 10 I50) in a hospitalization or death certificate.⁶ In CHS, adjudication by the Events Committee required symptoms, signs, chest radiographic findings, and treatment of heart failure.^{4,7} In both ARIC and CHS, cases of possible stroke were validated using established criteria and were based on interviews with patients, medical records, and brain imaging studies.^{4,8-10} Death from cardiovascular causes in both cohorts was defined as death caused by coronary heart disease,

heart failure, or cerebrovascular disease. Cardiovascular deaths that were not considered to be cases of SCD comprised the non-SCD endpoint. All-cause mortality in ARIC and CHS was identified by a review of obituaries, follow-up calls, medical records, death certificates, and linkage to the National Death Index.

Supplemental Table 1. Calibration metrics after recalibrating prediction models

	ARIC	CHS
<u>Sudden Cardiac Death</u>		
SCD Prediction Score		
Calibration chi-square (p-value)	N/A	14.89 (0.094)
ACC/AHA CVD risk equation		
Calibration chi-square (p-value)	11.47 (0.25)	17.98 (0.021)
<u>Non-Sudden Cardiac Death</u>		
SCD Prediction Score		
Calibration chi-square (p-value)	9.05 (0.43)	43.58 (<0.001)
ACC/AHA CVD risk equation		
Calibration chi-square (p-value)	28.20 (0.001)	21.69 (0.010)
<u>All-Cause Mortality</u>		
SCD Prediction Score		
Calibration chi-square (p-value)	90.16 (<0.001)	71.47 (<0.001)
ACC/AHA CVD risk equation		
Calibration chi-square (p-value)	34.54 (<0.001)	24.16 (0.0022)

Supplemental References

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