ORIGINAL RESEARCH

Electrocardiographic Deep Terminal Negativity of the P Wave in V_1 and Risk of Sudden Cardiac Death: The Atherosclerosis Risk in Communities (ARIC) Study

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***Background*—**Identifying individuals at risk for sudden cardiac death (SCD) is of critical importance. Electrocardiographic (ECG) deep terminal negativity of P wave in V_1 (DTNPV1), a marker of left atrial abnormality, has been associated with increased risk of all-cause and cardiovascular mortality. We hypothesized that DTNPV1 is associated with increased risk of sudden cardiac death (SCD).

***Methods and Results*—**This analysis included 15 375 participants (54.1±5.8 years, 45% men, 73% whites) from the Atherosclerosis Risk in Communities (ARIC) study. DTNPV1 was defined from the resting 12-lead ECG as presence of biphasic P wave (positive/negative) in V_1 with the amplitude of the terminal negative phase >100 μV, or one small box on ECG scale. After a median of 14 years of follow-up, 311 cases of SCD occurred. In unadjusted Cox regression, DTNPV1 was associated with an 8-fold increased risk of SCD (HR 8.21; [95%CI 5.27 to 12.79]). Stratified by race and study center, and adjusted for age, sex, coronary heart disease (CHD), and ECG risk factors, as well as atrial fibrillation (AF), stroke, CHD, and heart failure (HF) as time-updated variables, the risk of SCD associated with DTNPV1 remained significant (2.49, [1.51–4.10]). DTNPV1 improved reclassification: additional 3.4% of individuals were appropriately reclassified into a higher SCD risk group, as compared with traditional CHD risk factors alone. In fully adjusted models DTNPV1 was associated with increased risk of non-fatal events: AF (5.02[3.23–7.80]), CHD (2.24[1.43–3.53]), HF (1.90[1.19–3.04]), and trended towards increased risk of stroke (1.88[0.99–3.57]).

***Conclusion*—**DTNPV1 is predictive of SCD suggesting its potential utility in risk stratification in the general population. **(*J Am Heart Assoc*. 2014;3:e001387 doi: 10.1161/JAHA.114.001387)**

Key Words: electrocardiogram • risk stratification • sudden cardiac death

In spite of declining overall cardiovascular mortality,[1] the incidence of sudden cardiac arrest (SCA) remains high.[2] Only a minority of the out-of-hospital SCA victims achieved meaningful survival.[3,4] In more than half of the cases, SCA is the first manifestation of the cardiovascular disease (CVD).[5] Therefore, identifying individuals at risk of sudden death, and subsequently implementing prevention strategies are of critical importance.[6] Ventricular fibrillation remains the main cause of SCA.[3,7,8] While the electrophysiological substrate of SCA has been extensively studied during the last 3 decades, knowledge of cardiac arrhythmia mechanisms has not been adequately translated into risk stratification for SCA.

Electrocardiographic abnormal P terminal force in V_1 (PTF_{V1}) is a measure of compromised inter-atrial conduction[9] due to LA abnormalities.[10,11] Previous studies have shown that the presence of abnormal PTF_{v1} is predictive of AF[12] and stroke.[13] In addition to associations with the diseases of the upper chambers of the heart and their consequences, left ventricular hypertrophy (LVH)[14] is known to be associated with abnormal PTF_{V1}. Recently we showed that diffuse

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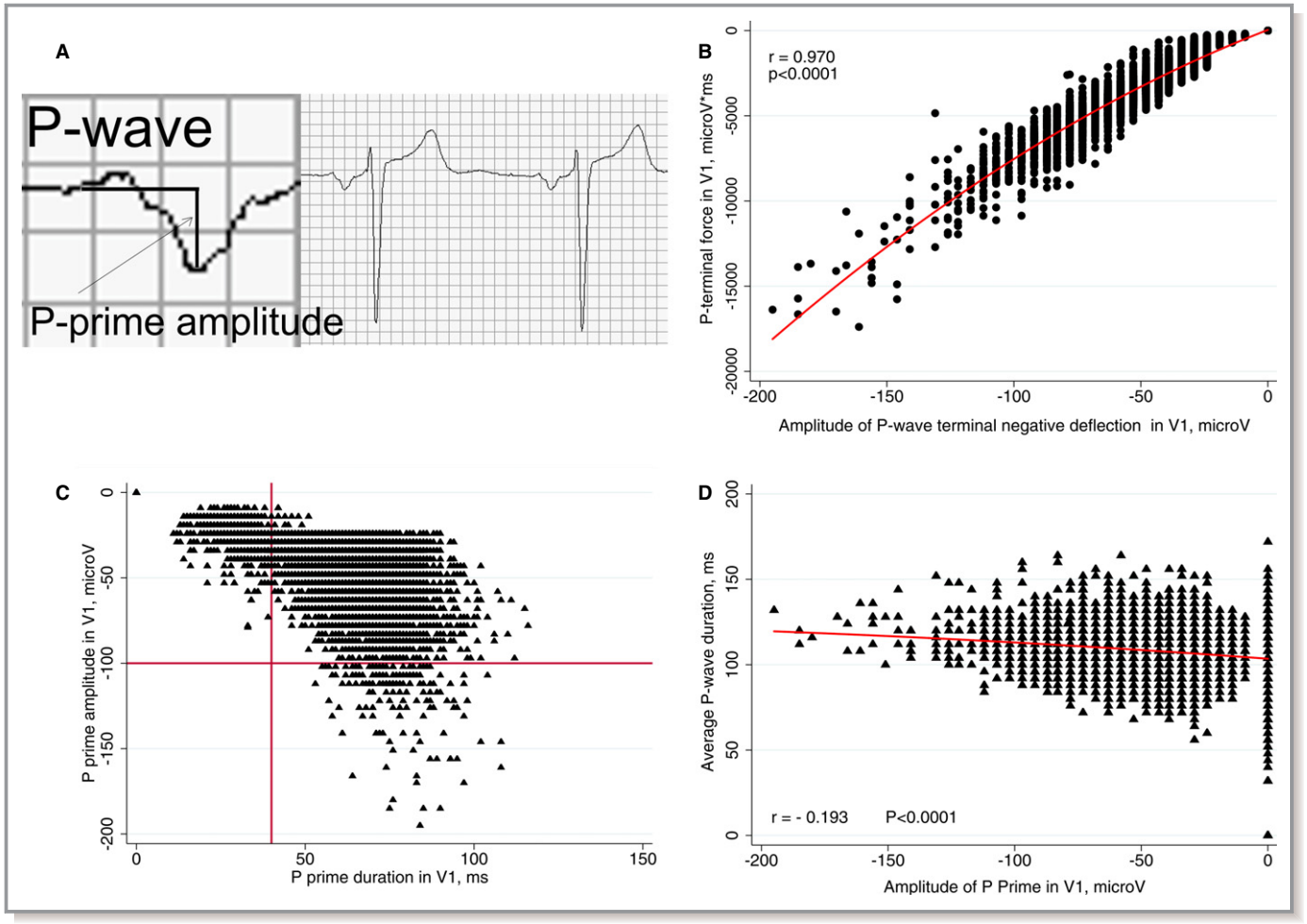

Figure 1. A. Measurement of P prime amplitude in V_1. B, Scatterplot of P terminal force in V_1 (Y) against P prime amplitude in V_1 (X). C, Scatterplot of P prime amplitude in V_1 (Y) against P prime duration in V_1 (X). D, Scatterplot of P duration (Y) against P prime amplitude in V_1 (X).

interstitial LV fibrosis (likely via associated LA fibrosis[15]) can affect and impair interatrial conduction, leading to characteristically abnormal PTF_{V1}.[16] PTF_{V1} is associated with heart failure (HF) hospitalizations and death.[17] Development of fibrosis in both upper and lower chambers of the heart could be a unifying mechanism, characterizing the structural heart disease continuum. We recently found that a simplified ECG metric of abnormal PTF_{V1}, namely deep terminal negativity of P wave in V_1 ($DTNPV_1$), was independently associated with increased risk of all cause and CVD mortality, as well as death due to ischemic heart disease.[18] We hypothesized that $DTNPV_1$ would also predict risk of SCD.

Methods

Study Population

The Atherosclerosis Risk in Communities (ARIC) study is a prospective cohort study designed to identify risk factors, progression, and outcomes of atherosclerosis in the community. From 1987 to 1989, 15 792 male and female participants aged 45 to 64 were recruited by probability sampling from 4 US communities (Forsyth County, NC; suburban Minneapolis, MN; Washington County, MD; and Jackson, MS). Details of the enrollment process and study procedures are fully described elsewhere.[19] We excluded participants with reported race other than white or black, blacks in the Minnesota and Washington County cohorts (for appropriate stratification by race and study center) (n=47), prevalent AF or flutter (n=37), atrial pacing, unreadable ECGs, and missing clinical covariates relevant to the current analysis (n=333). A final study population consisted of 15 375 participants. The study was approved by the institutional review boards of all participating institutions, and all participants gave informed consent.

Definition of Prevalent Cardiovascular Disease and Diabetes Mellitus

Prevalent CHD at baseline was defined as a history of intermittent claudication, angina, or myocardial infarction

(MI), diagnosed by Rose questionnaire,[20] a physician diagnosis of myocardial infarction or stroke, history of coronary revascularization, ECG evidence of MI as defined by Minnesota code.[21] Prevalent HF was defined as a self-reported current intake of HF medication or evidence of manifest HF as defined by the Gothenburg criteria[22] stage 3, which require the presence of specific cardiac and pulmonary symptoms, as well as medical treatment of HF. Prevalent MI was defined as self-reported MI, or ECG evidence of MI as defined by Minnesota code.[21] Prevalent stroke was diagnosed by the ARIC stroke and transient ischemic attack (TIA) diagnostic algorithm.[23] Prevalent diabetes mellitus was defined as a non-fasting glucose level of at least 140 mg/dL, a history of diabetes, or the current use of diabetes medications.

ECG Recording and Measurement of Deep Terminal Negativity of P Wave in V1

Standard 12-lead ECGs were digitally acquired using MAC Personal Computer electrocardiograph (Marquette Electronics, Milwaukee, WI) at Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Winston Salem, NC. All ECGs were initially inspected visually for technical errors and inadequate quality, then automatically processed with the GE Marquette 12-SL program 2001 version (GE Marquette, Milwaukee, WI). $DTNPV_1$ was defined as the presence of biphasic P wave (positive/negative) in V1 with the amplitude of the terminal negative phase >100 μV, or one small box on ECG scale (Figure 1A). Third-degree interatrial conduction block (IACB III) was diagnosed[11] if (1) P duration was ≥120 ms and (2) biphasic (+/−) P wave morphology in any 2 out of 3 inferior leads (II, III, aVF) with negative P prime deflection of any amplitude (<0 μV) was present. The sex-adjusted Cornell product (QRS duration times the Cornell voltage) was calculated (Cornell voltage=RaVL+SV3, with 6 mm [0.6 mV] added in women) to estimate ECG left ventricular hypertrophy (LVH).[24,25]

Incident CVD Events During Follow-Up

Participants were followed up with annual telephone calls, surveillance of hospitals in the community, National Death Index, and 3 triennial field visits through 2002; details have been previously reported.[26] Incident events (AF, stroke, CHD, HF) occurring through December 31, 2002 were included in the analysis as time-dependent covariates. Incident AF was diagnosed from 3 sources[27]: (1) 12-lead ECG performed during follow-up exams; (2) hospital discharge records (ICD-9 code 427.3 or ICD-10 code I-48); (3) death certificates. AF occurring during the cardiac surgery hospitalization event was not considered an incident AF event and follow-up was continued beyond cardiac surgery-related AF event. Incident stroke included definite or probable cases, defined as sudden or rapid onset of neurological symptoms that lasted for 24 hours in the absence of another cause.[28] Incident HF event was diagnosed as first HF hospitalization with *ICD-9* code 428 or *ICD-10* code I50 in any position of the hospital discharge list,[29] and included fatal HF cases. Incident CHD was defined as a definite or probable MI, silent ECG evidence of MI as defined by Minnesota code,[21] or coronary revascularization procedure (bypass surgery or coronary angioplasty), including fatal CHD cases. All potential clinical CHD events were validated by the ARIC Morbidity and Mortality Classification Committee.[26]

Outcomes Definition

SCD served as the primary outcome in this study. SCD was adjudicated in a 2-step process involving 2 independent death adjudication committees.[30] First all deaths were reviewed and adjudicated by the ARIC Morbidity and Mortality Classification Committee using established criteria to determine whether or not the death was attributed to CHD.[26] Then, both definite and possible CHD deaths were reviewed by an independent SCD Adjudication Committee to determine if the death was a sudden, presumably arrhythmic SCD, as previously described.[31] Secondary outcomes included non-sudden fatal CHD, non-CHD death, all-cause mortality, and non-fatal events (incident AF, incident HF, incident stroke, incident non-fatal CHD) as defined above.

Statistical Analysis

Data were analyzed using STATA 13 (StataCorp LP) statistical software and a 2-tailed $P<0.05$ was considered statistically significant. We used *t* test and chi-square test, as appropriate, to compare clinical and demographic characteristics of study participants with and without $DTNPV_1$. Pairwise correlations between P wave parameters were measured by Pearson's correlation coefficient r. Linear regression models were built to study associations between amplitude of P prime deflection in V1, and (1) P prime duration in V1, (2) P terminal force in V1, (3) amplitude of P prime in II, III, aVF. Association between amplitude of terminal negative P wave deflection in V1 and SCD was evaluated through the use of fully adjusted Cox regression model incorporating quadratic splines with 4 knots (at P $prime_{V1}$ amplitude of −0.073, −0.039, −0.024, and 0 mV). Cox proportional-hazards models were used to quantify the association between the $DTNPV_1$ and SCD. We constructed 4 models to adjust for covariates. Model 1 was stratified by race and study center, and adjusted by age and sex. Model 2 was further adjusted for prevalent CVD (CHD, MI, HF, stroke), and traditional cardiovascular risk factors (systolic

Table 1. Comparison of Clinical, Demographic, and ECG Characteristics of ARIC Participants With and Without Deep Terminal Negativity of P Wave in V_1 (Negative Amplitude >0.1 mV)

	No $DTNPV_1$ (n=15 209)	Yes $DTNPV_1$ (n=167)	*P* Value
Men, n (%)	6779 (44.6)	86 (51.5)	0.73
Whites, n (%)	11 167 (73.4)	81 (48.5)	<0.0001
Age (SD), y	54.1 (5.8)	56.3 (5.6)	<0.0001
Systolic blood pressure (SD). mmHg	121.1 (18.7)	132.0 (25.3)	<0.0001
Total cholesterol (SD), mmol/L	5.58 (1.08)	5.42 (1.18)	0.159
High density lipoprotein (SD), mmol/L	1.34 (0.44)	1.29 (0.46)	0.195
Triglycerides (SD), mmol/L	1.48 (1.02)	1.64 (1.57)	0.208
Body mass index (SD), kg/m^2	27.7 (5.4)	27.2 (5.5)	0.257
Diabetes mellitus, n (%)	1457 (9.7)	37 (22.7)	<0.0001
Prevalent coronary heart disease, n (%)	669 (4.5)	43 (26.4)	<0.0001
Prevalent heart failure, n (%)	673 (4.5)	32 (19.5)	<0.0001
Prevalent myocardial infarction, n (%)	567 (3.8)	41 (25.0)	<0.0001
Prevalent stroke, n (%)	250 (1.7)	12 (7.3)	<0.0001
Hypertension, n (%)	3781 (25.0)	80 (47.9)	<0.0001
Use of QT-prolonging drugs, n (%)	1407 (9.3)	32 (19.2)	<0.0001
Use of beta-blockers, n (%)	1316 (8.7)	28 (16.8)	<0.0001
Leisure activity index, mean (SD)	2.36 (0.57)	2.19 (0.59)	0.195
Current smoker, n (%)	3941 (25.9)	60 (36.1)	0.003
Mean heart rate (SD), bpm	66.2 (10.2)	72.6 (12.3)	<0.0001
P duration (SD), ms	106.4 (13.2)	115.0 (12.5)	<0.0001
PR interval (SD), ms	163.2 (25.5)	169.1 (29.6)	0.011
P axis (SD), deg	48.0 (21.6)	53.9 (19.5)	0.0001
Interatrial block III, n (%)	78 (0.51)	7 (4.19)	<0.0001
QRS-axis (SD), deg	29.8 (33.3)	23.8 (43.2)	0.076
T-axis (SD), deg	39.0 (31.2)	59.7 (52.9)	<0.0001
QRS-T angle (SD), deg	56.5 (33.2)	80.0 (43.9)	<0.0001
QRS duration (SD), ms	91.7 (12.5)	94.1 (15.7)	0.055
Cornell $product_{sex}$, (SD), mV×ms	1458 (619)	1885 (1011)	<0.0001
QTc (SD), ms	421.1 (20.5)	435.2 (28.4)	<0.0001

$DTNPV_1$ indicates deep terminal negativity of P wave in V_1.

blood pressure, antihypertensive medication, diabetes mellitus, smoking status (current vs. never/former), total cholesterol, high-density lipoprotein cholesterol (HDL), triglycerides, body mass index, leisure activity index), as well as use of QT-prolonging drugs and beta-blockers. Model 3 incorporated all variables in Model 2 plus ECG characteristics: heart rate, QRS duration, P duration, P axis, QTc, spatial QRS-T angle, sex-specific Cornell product, and third-degree inter-atrial conduction block. Model 4 was further adjusted for AF, stroke, CHD, and HF entered as time-updated covariates. Schoenfeld residuals were evaluated to test the assumption of the hazards proportionality. In addition, the multivariate (model 3) Fine and Gray's subhazards analyses[32] were performed for 3 competing outcomes: SCD, non-sudden fatal CHD, non-CHD death.

To evaluate whether the association was consistent across the subgroups, we examined the association of $DTNPV_1$ with SCD in subgroups defined by baseline age (cut-point 55 years), sex, race, CVD status (defined as CHD, MI, HF, stroke, QRS duration ≥120 ms), ECG-LVH by Cornell product (defined as sex-specific Cornell product >2440 mm×ms), hypertension, diabetes, ECG-left atrial enlargement per ROMICAT[33] criteria (defined as P duration >110 ms), third-degree intratrial conduction block. We evaluated interactions of

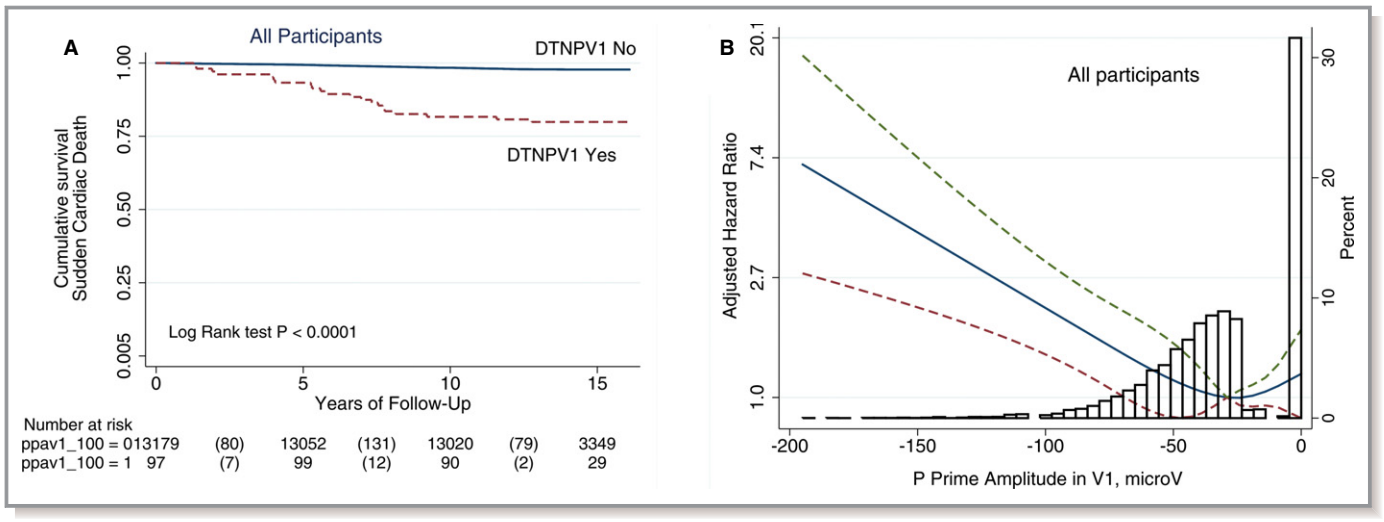

Figure 2. A. Unadjusted Kaplan–Meier curves for the probability of sudden cardiac death in patients with and without deep terminal negativity of P wave in V_1. B, Multivariate-adjusted Hazard Ratio with 95% confidence interval for sudden cardiac death, associated with P prime amplitude in V_1, modeled as a continuous variable using quadratic splines. $DTNPV_1$ indicates deep terminal negativity of P wave in V_1.

$DTNPV_1$ with these subgroups in model similar to the fully adjusted Cox model 4 used in the main analysis.

In CVD-free participants, we further investigated associations of $DTNPV_1$ with non-fatal events, known mediators of SCD: CHD, HF, AF, and stroke. Model 1 was adjusted for sex and age, stratified by race and study center. Model 2 in addition was adjusted by traditional risk factors: total cholesterol, triglycerides, high density lipoprotein (HDL), current smoking, diabetes mellitus, body mass index, leisure activity index, systolic blood pressure, use of blood-lowering medications, QT-prolonging drugs, beta-blockers. Model 3 in addition was adjusted by ECG characteristics: heart rate, QRS duration, P duration, P axis, QTc, QRS-T angle, sex-specific Cornell product, third-degree inter-atrial conduction block.

In CVD-free participants, we calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for SCD and combined endpoint of either death or non-fatal CVD event (MI, revascularization (PCI or CABG), stroke, HF hospitalization, AF). The predictive value of $DTNPV_1$ was evaluated by comparing the model with $DTNPV_1$ to the baseline SCD risk model. The baseline SCD risk model was created with the components of the CHD Framingham risk score: age, gender, systolic blood pressure, diabetes, HDL and total cholesterol, smoking, and blood pressure-lowering therapy. Calculated Framingham risk scores were not directly used due to possible issues of the applicability to different ethnic groups[34] and were adjusted for race. Net reclassification improvement (NRI) and integrated discrimination

Table 2. Deep Terminal Negativity of P Wave in V_1 and Risk of Sudden Cardiac Death, Fatal Coronary Heart Disease (CHD), Non-CHD Death, and All-Cause Mortality

	SCD (n=311)		Fatal CHD (n=370)		Non-CHD Death (=1753)		All-Cause Death (n=2197)	
	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value
Unadjusted	8.21 (5.27 to 12.79)	<0.0001	7.23 (4.70 to 11.13)	<0.0001	3.34 (2.25 to 4.44)	<0.0001	4.15 (3.30 to 5.22)	<0.0001
Cox model 1	5.12 (3.27 to 8.02)	<0.0001	4.62 (2.98 to 7.14)	<0.0001	2.35 (1.76 to 3.13)	<0.0001	2.85 (2.26 to 3.59)	<0.0001
Cox model 2	2.75 (1.72 to 4.38)	<0.0001	2.18 (1.39 to 3.42)	0.001	1.60 (1.17 to 2.18)	0.003	1.81 (1.41 to 2.31)	<0.0001
Cox model 3	2.37 (1.44 to 3.91)	0.001	1.74 (1.07 to 2.84)	0.026	1.31 (0.95 to 1.81)	0.100	1.44 (1.11 to 1.87)	0.006
Cox model 4	2.49 (1.51 to 4.10)	<0.0001	1.66 (1.09 to 2.55)	0.019	1.25 (0.93 to 1.69)	0.135	1.41 (1.11 to 1.79)	0.004
Competing risk model 3	2.45 (1.42 to 4.23)	0.002	1.69 (0.97 to 2.95)	0.066	1.15 (0.80 to 1.65)	0.453	—	—

Model 1 adjusted for sex and age, stratified by race and study center. Model 2 in addition adjusted by clinical characteristics: prevalent coronary heart disease, myocardial infarction, heart failure, stroke, total cholesterol, triglycerides, high density lipoprotein, current smoking, diabetes mellitus, body mass index, leisure activity index, systolic blood pressure, use of blood-lowering medications, QT-prolonging drugs, beta-blockers. Model 3 in addition adjusted by ECG characteristics: heart rate, QRS duration, P duration, P axis, QTc, QRS-T angle, sex-specific Cornell product, third degree inter-atrial conduction block. Model 4 in addition adjusted by time-dependent incidence of atrial fibrillation, stroke, heart failure, and CHD. Competing risk model included all variables as in model 3. CHD indicates coronary heart disease; SCD, sudden cardiac death.

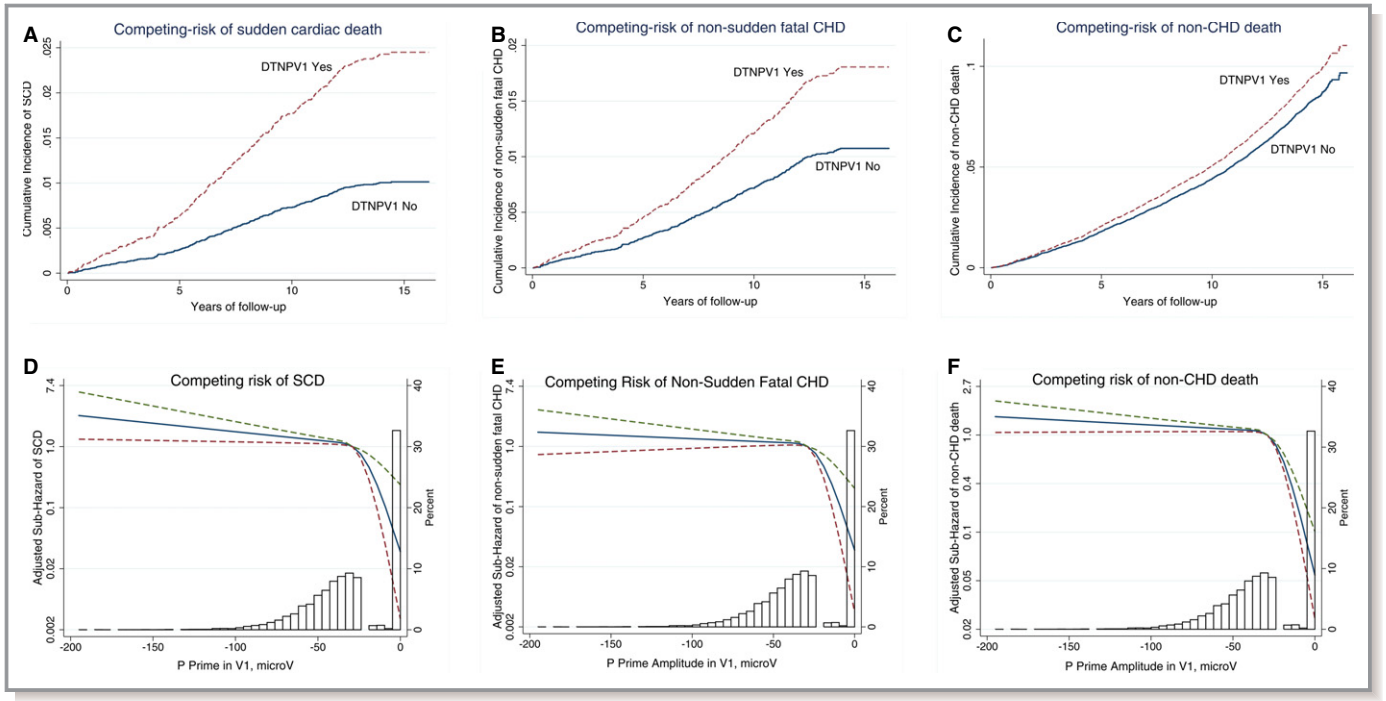

Figure 3. Competing risks. Multivariate-adjusted cumulative incidence functions for SCD (A), non-sudden fatal CHD (B), and non-CHD death (C), associated with deep terminal negativity of P wave in V_1 ($DTNPV_1$). Multivariate-adjusted sub-hazard ratios (SHRs) for SCD (D), non-sudden fatal CHD (E), and non-CHD death (F), associated with P prime amplitude in V_1, modeled as a continuous variable using 4 quadratic splines. CHD indicates coronary heart disease; $DTNPV_1$, deep terminal negativity of P wave in V_1; SCD, sudden cardiac death.

improvement (IDI) were calculated as described by Pencina et al.[35] NRI was calculated from the Framingham predicted risk cut points of 5% and 15% at 10 years. NRI and IDI were calculated by an STATA add-on developed by the Uppsala clinical research center.[36]

Nonparametric unadjusted receiver operating characteristic (ROC) analysis was performed for SCD in 4 subgroups: white men, white women, black men, and black women. Total area under the ROC curve (AUC) was estimated and AUCs of the following ECG parameters were compared: PTF_{V1}, P-prime amplitude in V_1, P duration, heart rate, QTc, and ECG LVH.

Results

Biphasic P wave with negative P prime was present in 67.4 % of the cohort (n=10 358). The median amplitude of terminal negative P wave deflection in V_1 was −39 μV (interquartile range [IQR] −53 to −29 μV). $DTNPV_1$ was observed in 167 individuals (1.09%). P prime amplitude in V_1 strongly correlated with P terminal force (Figure 1B) and P prime duration in V_1 (r=−0.840; $P<0.0001$; Figure 1C). In all cases of the terminal negative portion of P_{V1} amplitude ≥1.00 mm (100 μV) in depth, duration of that terminal negative P_{V1} portion exceed 0.04 s (Figure 1C). Third-degree interatrial block was observed more rarely (in 85 subjects; 0.55%) than $DTNPV_1$, and was more frequent in participants with $DTNPV_1$ (Table 1). There was no meaningful correlation between P prime amplitudes in leads II and V_1 (r=0.010), III and V_1 (r=0.078), aVF and V_1 (r=0.060). Correlation between P prime amplitude in V_1 and average P duration was minor (Figure 1D); it was smaller as compared with the correlation between P terminal force and average P duration (r=−0.272; P<0.0001).

Participants with $DTNPV_1$ were more likely to be older, black, to have CVD (CHD, HF, MI, stroke), to be on antihypertensive, QT-prolonging drugs and beta-blockers, with risk factors (hypertension, diabetes, smoking), and ECG abnormalities (faster heart rate, wider P wave, longer QTc, larger Cornell product, and QRS-T angle) than those without $DTNPV_1$ (Table 1).

During a median follow-up period of 14 years, there were 1998 cases of CHD, 687 cases of stroke, 1166 cases of incident HF, 958 cases of incident AF, and 311 SCD outcomes. Out of 167 participants with $DTNPV_1$ there were 21 cases of SCD (12.6%), whereas 290 SCD cases occurred in 15 209 participants without $DTNPV_1$ (1.9%). Cumulative unadjusted SCD was higher in participants with $DTNPV_1$ (Figure 2A). In adjusted analysis, there was a dose-response relationship between P prime amplitude in V_1 and SCD (Figure 2B).

Table 3. Risk of SCD, Adjusted by Demographic, Clinical and ECG Risk Factors (Model 3)

	All Participants (n=15 376)		CVD-Free Participants (n=13 278)		Prevalent CVD (n=2098)	
	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value	HR (95%CI)	P (95%CI)
$DTNPV_1$	2.37 (1.44 to 3.91)	0.001	3.51 (1.72 to 7.13)	0.001	2.05 (1.11 to 3.70)	0.022
Female	0.56 (0.41 to 0.77)	<0.0001	0.45 (0.32 to 0.68)	<0.0001	0.68 (0.41 to 1.11)	0.122
Age, y	1.006 (1.003 to 1.008)	<0.0001	1.07 (1.04 to 1.10)	<0.0001	1.04 (1.00 to 1.08)	0.057
CHD	0.30 (0.04 to 2.19)	0.234	—		0.82 (0.19 to 3.54)	0.417
MI	15.81 (2.17 to 114.96	0.006	—		6.22 (1.52 to 25.49)	0.011
HF	0.80 (0.53 to 1.23)	0.318	—		1.01 (0.63 to 1.60)	0.983
Stroke	1.80 (1.15 to 2.83)	0.010	—		2.22 (1.40 to 3.52)	0.001
BMI, kg/m^2	1.00 (0.97 to 1.02)	0.848	0.99 (0.96 to 1.02)	0.647	1.01 (0.97 to 1.05)	0.568
Total cholesterol, mmol/L	1.21 (1.09 to 1.34)	<0.0001	1.18 (1.04 to 1.35)	0.009	1.27 (1.08 to 1.50)	0.003
HDL, mmol/L	0.57 (0.39 to 0.84	0.005	0.56 (0.36 to 0.89)	0.014	0.68 (0.35 to 1.31)	0.258
Triglycerides, mmol/L	0.98 (0.88 to 1.08)	0.679	0.97 (0.85 to 1.11)	0.663	0.96 (0.80 to 1.14)	0.637
Leisure activity index	0.87 (0.69 to 1.08)	0.209	0.75 (0.57 to 0.99)	0.046	—	
Diabetes mellitus	2.24 (1.68 to 3.00)	<0.0001	2.82 (1.98 to 4.00)	<0.0001	1.56 (1.00 to 2.43)	0.048
Current smoking	2.00 (1.54 to 2.58)	<0.0001	2.13 (1.55 to 2.93)	<0.0001	1.68 (1.12 to 2.50)	0.011
Systolic blood pressure, mmHg	1.01 (1.01 to 1.02)	<0.0001	1.02 (1.01 to 1.02)	<0.0001	1.01 (1.01 to 1.02)	0.002
BP lowering drugs	1.35 (1.03 to 1.77)	0.029	1.74 (1.24 to 2.44)	0.001	0.95 (0.62 to 1.44)	0.794
QT-prolonging drugs	1.05 (0.72 to 1.53)	0.787	1.01 (0.61 to 1.69)	0.958	1.03 (0.62 to 1.73)	0.903
Beta-blockers	0.96 (0.67 to 1.53)	0.824	0.55 (0.30 to 1.01)	0.054	1.23 (0.78 to 1.94)	0.367
Cornell $product_{sex}$, mm×ms	1.00 (1.00 to 1.00)	0.519	1.00 (1.00 to 1.00)	0.361	—	
QRS duration, ms	1.00 (0.99 to 1.01)	0.411	0.98 (0.96 to 1.00)	0.098	1.02 (1.00 to 1.03)	0.004
Heart rate, bpm	1.01 (0.99 to 1.02)	0.367	1.00 (0.99 to 1.02)	0.621	1.02 (1.00 to 1.04)	0.027
QTc, ms	1.008 (1.003 to 1.014)	0.004	1.009 (1.001 to 1.017)	0.022	1.00 (0.99 to 1.01)	0.531
P duration, ms	1.00 (0.99 to 1.01)	0.462	0.99 (0.98 to 1.00)	0.131	1.01 (1.00 to 1.03)	0.046
P axis, deg	1.00 (0.99 to 1.00)	0.331	0.99 (0.99 to 1.00)	0.129	—	
QRS-T angle, deg	1.005 (1.002 to 1.009)	0.001	1.00 (1.00 to 1.01)	0.062	—	
Itraatrial block third degree	1.20 (0.43 to 3.37)	0.727	1.38 (0.33 to 5.78)	0.660	—	

CHD indicates coronary heart disease; $DTNPV_1$, deep terminal negativity of P wave in V_1; HF, heart failure; MI, myocardial infarction.

In unadjusted Cox regression, compared with participants without $DTNPV_1$, individuals with $DTNPV_1$ had 8-times higher risk of SCD (Table 2). Adjusted for age, sex, and stratified by race and study center, individuals with $DTNPV_1$ demonstrated a 5-fold increased risk of SCD. Further adjustment for potential confounders (prevalent CVD and clinical risk factors) substantially attenuated the association of $DTNPV_1$ with SCD, to a hazard ratio of 2.75. This association did not change appreciably after further adjustment for other ECG abnormalities or AF, stroke, CHD an HF as time-updated variables, (Table 2). Association of $DTNPV_1$ with all-cause mortality was similar to that of SCD, but weaker. In competing analyses (Table 2) $DTNPV_1$ was associated with SCD, but not with non-sudden fatal CHD, or non-CHD death (Figure 3A through 3C). Adjusted competing analysis showed consistent dose-response relationship between P prime amplitude in V_1 and SCD, but not other outcomes (Figure 3D through 3F).

Finally, we examined this association in various subgroups. Table 3 shows fully adjusted models for all study participants, as well as for patients with and without prevalent CVD at baseline. Table 4 shows that the results were largely consistent across different subgroups of ARIC participants (all *P* values for interaction >0.05). Importantly, $DTNPV_1$ was independently associated with SCD in participants without diagnosed CVD at baseline.

In CVD-free participants, in fully adjusted models $DTNPV_1$ was associated with a 5-fold increased risk of AF, and about 2-fold increased risk of non-fatal CHD and HF (Table 5). Trend towards increasing risk of non-fatal stroke was observed.

Table 4. Terminal Negativity of P Wave in V_1 and Fully Adjusted Risk of SCD Across Subgroups

	HR (95%CI)	*P* Value
Male (199 SCDs/6865)	2.36 (1.27 to 4.38)	0.007
Female (112 SCDs/8511)	3.37 (1.44 to 7.86)	0.005
Interaction		0.375
Age ≥55 y (207 SCDs/7244)	2.42 (1.28 to 4.57)	0.006
Age<55 y (104 SCDs/8132)	2.84 (1.21 to 6.67)	0.017
Interaction		0.929
White (177 SCDs/11248)	1.82 (0.87 to 3.80)	0.111
Black (134 SCDs/4128)	3.33 (1.67 to 6.65)	0.001
Interaction		0.716
CVD Yes (129 SCDs/2098)	2.06 (1.07 to 3.96)	0.030
CVD-Healthy (182 SCDs/13278)	3.59 (1.62 to 7.97)	0.002
Interaction		0.801
Diabetes Yes (102 SCDs/1494)	3.93 (1.57 to 9.82)	0.003
Diabetes No (208 SCDs/13766)	1.85 (0.99 to 3.46)	0.056
Interaction		0.659
Hypertension Yes (150 SCDs/3861)	2.71 (1.35 to 5.44)	0.005
Hypertension No (159 SCDs/11436)	2.67 (1.28 to 5.65)	0.010
Interaction		0.326
ECG LVH Yes (52 SCDs/863)	4.32 (1.56 to 11.92)	0.005
ECG LVH No (259 SCDs/14513)	2.10 (1.13 to 3.93)	0.019
Interaction		0.192
P duration >110 ms (155 SCDs/5955)	2.02 (1.06 to 3.84)	0.034
P duration ≤110 ms (156 SCDs/9421)	4.65 (2.10 to 10.28)	<0.0001
Interaction		0.064
IACB third degree Yes# (4 SCDs/85)	6.62 (0.62 to 70.42)	0.117
IACB third degree No (307 SCDs/15291)	2.95 (1.79 to 4.85)	<0.0001
Interaction		0.821

CVD is defined as a presence of either coronary heart disease, or heart failure, or stroke, or QRS duration ≥120 ms. Left ventricular hypertrophy defined as sex-specific Cornell product >2440 mm×ms. IACB, interatrial conduction block. # model was adjusted by sex, race, age, and CVD only. CHD indicates coronary heart disease; CVD, cardiovascular disease; LVH, left ventricular hypertrophy SCD, sudden cardiac death.

In CVD-free participants (Table 6), $DTNPV_1$ demonstrated 3.8% sensitivity, 99.3% specificity, 7.5% PPV, and 98.7% NPV for prediction of SCD. For the prediction of the combined endpoint (death, or non-fatal CHD, HF, stroke, or AF event), $DTNPV_1$ showed 1.6% sensitivity, 99.6% specificity, 55.9% PPV, and 74.5% NPV.

$DTNPV_1$ has shown borderline significant discrimination ability between 2 models (Table 7), with NRI estimate =0.028 (*P*=0.06). Notably, $DTNPV_1$ appropriately reclassified participants with SCD outcome into the higher risk categories: 3.4% of individuals were appropriately reclassified into a higher risk group, whereas only 0.3% was reclassified into a higher risk group inappropriately. In addition, in the subgroup of CVD-free at baseline participants we compared unadjusted AUCs of several ECG markers of SCD: P prime amplitude in V_1, PTF_{V1}, P duration, ECG LVH, heart rate, and QTc. AUCs of P prime amplitude in V_1, PTF_{V1}, ECG LVH, heart rate, and QTc were similar and significantly larger, as compared with AUC of P duration. There were no significant differences in AUCs ROCs in 4 race-sex subgroups.

Discussion

In this large bi-racial prospective cohort, ECG sign of $DTNPV_1$ was independently associated with SCD in individuals with and without prevalent at baseline CVD, even after adjustment for CHD risk factors, known ECG predictors of ventricular and atrial arrhythmias, and time-updated CHD, HF, AF, and stroke events. Associated with $DTNPV_1$ risk of SCD exceeded risk of non-fatal CHD, HF, and stroke; only risk of AF exceeded risk of SCD. This finding suggests that $DTNPV_1$ is an intermediate marker on the pathway linking cardiac fibrosis[16] (both in LA and LV) with atrial and ventricular arrhythmias and SCD. Our finding of an independent association between $DTNPV_1$ and SCD supports the unifying hypothesis of the key role of fibrosis[16] in arrhythmogenesis of both atrial and ventricular arrhythmias.[37,38] $DTNPV_1$ represents an epiphenomenon of advanced fibrotic disease process and damaged heart.

$DTNPV_1$ is an easily recognizable ECG sign. $DTNPV_1$ added incremental value to the traditional CHD risk factors for the prediction of SCD events. In CVD-free individuals, $DTNPV_1$ improved risk prediction over what was achieved by a model with Framingham CHD risk factors alone. Importantly, validation of our findings in another study is needed before $DTNPV_1$ could be considered as a component of a SCD risk score.

Deep Terminal Negativity of P Wave in V_1

Morris et al[14] in 1964 developed P terminal force metric as a product of amplitude and duration of a P prime deflection in V_1. They defined an abnormal P terminal force as "a terminal portion of the P wave at V_1 1 box in depth (−1.0 mm.) and 1 box in duration (0.04 sec.)," yielding a P terminal force of −0.04. Our study showed that in all cases of the terminal negative portion of P_{V1} amplitude ≥1.00 mm in depth, duration of that terminal negative P_{V1} portion always

Table 5. Risk of Non-Fatal CHD, HF, Stroke, AF Events in CVD-Healthy Participants With and Without $DTNPV_1$

	Non-Fatal CHD (N=1422)		Heart Failure (N=910)		Stroke (N=505)		Atrial Fibrillation (N=699)	
Model	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value
U	2.61 (1.68 to 4.05)	<0.0001	4.57 (2.99 to 6.98)	<0.0001	3.97 (2.18 to 7.21)	<0.0001	6.35 (4.15 to 9.71)	<0.0001
1	2.27 (1.45 to 3.54)	<0.0001	2.88 (1.88 to 4.40)	<0.0001	2.43 (1.33 to 4.44)	0.004	5.60 (3.64 to 8.61)	<0.0001
2	2.21 (1.41 to 3.46)	0.001	2.29 (1.46 to 3.62)	<0.0001	2.26 (1.23 to 4.14)	0.009	5.51 (3.58 to 8.50)	<0.0001
3	2.24 (1.43 to 3.53)	<0.0001	1.90 (1.19 to 3.04)	0.007	1.88 (0.99 to 3.57)	0.054	5.02 (3.23 to 7.80)	<0.0001

U, unadjusted; 1, Model 1 is adjusted for sex and age, stratified by race and study center. 2, Model 2 in addition adjusted by traditional risk factors: total cholesterol, triglycerides, high density lipoprotein, current smoking, diabetes mellitus, body mass index, leisure activity index, systolic blood pressure, use of blood-lowering medications, QT-prolonging drugs, beta-blockers. 3, Model 3 in addition adjusted by ECG characteristics: heart rate, QRS duration, P duration, P axis, QTc, QRS-T angle, sex-specific Cornell product, third degree inter-atrial conduction block. CHD indicates coronary heart disease; CVD, cardiovascular disease.

Table 6. Two-by-Two Tables for SCD and Combined Endpoint (Death or Non-Fatal CHD, HF, Stroke, AF Events) in CVD-Healthy at Baseline Participants

	Sudden Cardiac Death			Death or Non-Fatal Event (CHD, HF, Stroke, AF)			
	Yes	No	Total		Yes	No	Total
$DTNPV_1$ (+)	7	86	93	$DTNPV_1$ (+)	56	37	93
$DTNPV_1$ (−)	175	13 010	13 185	$DTNPV_1$ (−)	3368	9817	13 185
Total	182	13 096	13 278	Total	3424	9854	13 278

AF indicates atrial fibrillation CHD, coronary heart disease; CVD, cardiovascular disease; SCD, sudden cardiac death.

Table 7. Comparison of Proportions of Subjects in Low- (<5%), Medium- (5 to 20%), and High-(>20%) Risk Categories, Presented Separately for SCD Events and Nonevents (SCD-Free)

	Framingham CHD risk factors+ $DTNPV_1$			
	<5%	5 to 20%	≥20%	Total
Framingham CHD risk factors				
SCD events				
<5%	135	3 (2.2%)		138
5% to 20%	1 (2.6%)	34	3 (7.8%)	38
≥20%			3	3
Total	136	37	6	179
SCD non-events				
<5%	12 298	27 (0.22%)		12 325
5% to 20%	35 (6.64%)	485	7 (1.33%)	527
≥20%		1 (5.56%)	17	18
Total	12 333	513	24	12 870

CHD indicates coronary heart disease SDC, sudden cardiac death.

exceeded 1 box in duration, or 0.04 seconds (Figure 1). Therefore, one can ignore duration and measure only amplitude in order to derive $DTNPV_1$ metric. We confirmed strong correlation between P terminal force and amplitude of P prime in V_1. Moreover, virtually identical AUCs for P prime amplitude in V_1 and PTF_{V1} confirmed that the risk assessment by amplitude only is adequate.

Historically investigators considered several underlying mechanisms resulting in the appearance of $DTNPV_1$. Romhilt et al[39] regarded $DTNPV_1$ as a "sign of left atrium involvement" in patients with LVH. In the past abnormal $PTFV_1$ was considered a sign of LA enlargement, until Josephson et al established that abnormal PTF_{V1} represents an inter-atrial conduction defect that can be produced by a variety of factors.[9] Posteriorly directed LA depolarization vector is primarily responsible for the appearance of P wave terminal negative deflection in V_1. We speculate that intraatrial fat infiltration[40,41] and gradual development of atrial fibrosis could lead to the interruption of interatrial conduction over tiny (and therefore more susceptible) posterior interatrial connections, resulting in predominant conduction via the Bachmann's bundle, associated with the anterior-to-posterior direction of left atrial activation. Pulmonary vein isolation could modify P wave morphology in V_1.[42] Moreover, extensive ablation of septal areas could result in electrical isolation of LA.[43]

LVH and LV fibrosis characterize pathophysiological substrate for SCD due to VF in patients early in the continuum of structural heart disease. Development of fibrosis both in LA and LV is likely a main mechanism of $DTNPV_1$ manifestation

on ECG. Emerging experimental data showed[44] that fibrosis disrupts the normal electrical connectivity of cardiac tissue, alters source–sink relationships, facilitates the emergence of after depolarization-induced premature ventricular complexes and, therefore, increases the vulnerability to arrhythmias. In clinical studies, the presence and amount of LV fibrosis were associated with documented ventricular arrhythmias and SCD.[45] Gradually increasing risk of SCD, associated with the increasing amplitude of terminal negative P wave deflection in V_1 illustrates the continuum of structural heart disease development, consistent with gradual progression of LA and LV fibrosis.[16] In this study, we chose a threshold of P prime amplitude in V_1 (1 mm, or 0.1 mV) not only due to historical reasons, but also because of convenience and simplicity of its use. This threshold identified individuals at high risk of SCD. At the same time, we demonstrated the continuity of the risk (Figure 2B) and, therefore, future studies could explore other thresholds of P prime amplitude in V_1 to target desired sensitivity and specificity.

Resting 12-Lead ECG for Prediction of SCD

In this study $DTNPV_1$ predicted SCD, and demonstrated significant 60% precision for prediction of the combined endpoint (death, or non-fatal CHD, HF, stroke, or AF event). Importantly, $DTNPV_1$ improved discrimination of SCD above traditional CHD risk factors (Framingham CHD risk score). While there is no well-accepted risk score of SCD in the general population, SCD is included in the CHD classification as one of the manifestations of CHD. It is important to emphasize that while $DTNPV_1$ is suggestive of added value, it has to be validated prospectively before considering implementation of $DTNPV_1$ into clinical practice.

Strength and Weakness of the Study

Strengths of this study include standardized ECG recording procedures, automated central processing of ECG data, long-term follow-up data, and well-ascertained outcomes in a large population-based cohort. Nonetheless, there are several limitations that merit attention. As with any observational study, we cannot rule out the possibility of residual confounding despite rigorous adjustment for potential confounders. Identification of incident HF relied on International Classification of Diseases codes abstracted from hospital records. Reliance on hospital discharge codes could result in underestimation of HF incidence. Similarly, incident AF diagnosis was based on hospital records and 10-s, 12-lead ECGs, recorded during follow-up visits. Absence of long-term ECG monitoring likely resulted in an underestimation of AF incidence.[46] While adjudication of SCD was performed according to the rigorous protocol, ECG of the exact moment of SCD was not available, and, therefore, causative arrhythmia underlying the SCD event is unknown. This is the common limitation of the SCD investigation field. We reported ROC results for the race and sex subgroups, even if we did not find meaningful interaction with race and sex in this study.

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Disclosures

None.

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