Supplemental Material

Study Population

The Atherosclerosis Risk in Communities Study is a prospective cohort study designed to identify risk factors, etiology, and clinical manifestations of atherosclerotic CHD in the general population. Between 1987 and 1989, 15,792 men and women aged 45-64 years were recruited and enrolled from four United States communities (Washington County, MD; Forsyth County, NC; Jackson, MS; and suburban Minneapolis, MN). Participants have been evaluated by 7 clinical study visits, annual telephone interviews (semi-annual since 2012), and community surveillance. For this study, we analyzed data from the first 4 study visits: visit 1 (1987-89), visit 2 (1990-92), visit 3 (1993-95), visit 4 (1996-98) and participants were followed for events through the end of 2012. Approval for the study was obtained from the institutional review board on human research at each participating institution and all participants provided informed consent.

We considered all 15,792 participants at the baseline visit and excluded those with missing covariates (n=218), missing ECG data (n=242), prevalent atrial fibrillation (AF, n=37), missing ECG indices (n=81) and those who were not white or black from all study sites, and nonwhite from Minneapolis and Washington County (due to small sample size; n=103), prevalent cardiovascular disease – stroke, heart failure (HF), CHD – (n=1531) resulting in a final cohort of 13,580 participants.

Measurement of ECG Indices

ECGs obtained during the first four study visits (1987-1998) were recorded on MAC PC Personal Cardiographs (Marquette Electronics Inc. Milwaukee, WI) and processed at the

EPICARE Center (Wake Forest University, Winston-Salem, NC). ECGs were automatically processed with the GE Marquette 12-SL program version 2001.

We analyzed P-wave indices (PWI) – P-wave axis, P-wave duration, and P-wave terminal force, resting heart rate, QRS-T angle, QRS transition zone, left ventricular hypertrophy (LVH), and QRS duration. The automated GE 12SL algorithm (GE Marquette) was utilized to calculate heart rate, corrected QT interval (QTc), QRS duration, and P-wave axis. Abnormal P-wave axis (aPWA) was defined as any value outside 0-75°. P-wave duration was measured from the conclusion of the T-P segment (P wave onset) to return to baseline (PR interval). For biphasic P-waves, P-wave duration encompassed both positive and negative deflections from baseline. Prolonged P-wave duration (PPWD) was present if the maximum P-wave duration in any lead was >120 ms. P-wave terminal force in lead V1 was determined by multiplying the duration (ms) and the depth (μV) of the downward deflection (terminal portion) of the P-wave in lead V1. Abnormal P-wave terminal force in lead V1 (aPTFV1) was defined as ≤ -4000 μV*ms. The frontal QRS-T angle was calculated as the absolute value of the difference between QRS and T-wave frontal axis. ECG-based LVH was calculated using the sex-specific Cornell product. The QRS transition zone was defined as the precordial lead in which the R wave amplitude equaled or exceeded the S wave amplitude. Tpeak-Tend was defined as the time between the peak of the T-wave and the end of the T-wave. The median value in all 12 leads was utilized.

Measurement of Clinical Variables

Covariates were selected from the ACC/AHA pooled cohort equation including age, sex, systolic blood pressure, use of antihypertensive medications, smoking status, total cholesterol, high density lipoprotein. We also included race/study center. For mediation analysis, we

additionally included incident HF, CHD, and atrial fibrillation (AF) which were assessed until 2012. Demographic data (age, sex, race), smoking status (current smoker, non-current smoker), medication history, laboratory data, and blood pressure measurements were obtained by study staff from participants during study visits 1-4. Prevalent CHD at visit 1 was defined as a self-reported history of myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, or ECG signs of CHD. Heart failure (HF) at visit 1 was defined as stage 3 "manifest heart failure" by the Gothenburg criteria or self-reported diagnosis of heart failure. Incident CHD occurring after visit 1 was physician ahjudicated and defined as definite or probable myocardial infarction or definite CHD death. Incident HF occurring after visit 1 was defined by International Classification of Diseases, 9^{th} and 10^{th} revision (ICD-9, ICD-10) codes from hospitalization records (ICD-9 428) and death certificates (ICD-9 428, ICD-10 150). AF was ascertained from study visit ECGs, hospital discharge records, and death certificates.

Outcome Ascertainment

Incident cardiovascular events and deaths were identified through the end of 2012 by annual phone interviews with participants or proxy, community-wide surveillance of local hospitals, review of state death records, and review of National Death Index data.

All fatal CHD events through 2012 were reviewed by an independent panel of physicians to identify SCDs. Deaths were classified as definite SCD, possible SCD, not SCD, and unclassifiable. Definite SCD was defined as a sudden pulseless condition presumed to be of cardiac origin in a previously stable individual without evidence of non-cardiac cause of death. Possible SCD was defined as an unwitnessed death in a previously stable (<24 hours) individual without other evidence indicating non-cardiac origin for instantaneous death. All deaths

classified as SCD had to occur outside of the hospital or in the emergency room. For our analysis, SCD was defined as definite or possible SCD. CV deaths were defined as deaths associated with ICD-10 ‘I’ codes or ICD9 codes 401-459.

Evaluation of Risk Prediction Models

Improvement in risk prediction by the addition of ECG markers to benchmarks (Models A+, B+, and C+) was evaluated by calculating the C-statistic, categorical net reclassification improvement (NRI), and relative integrated discrimination improvement (rIDI).We used the Hosmer-Lemeshow chi-squared statistic to evaluate model calibration (Table 1B).

The C-statistic was used to evaluate model discrimination between events and non-events. NRI computes the proportions of participants moving up or down risk categories in cases and non-cases separately. The overall NRI reported is the sum of these proportions and is a measure risk reclassification. The rIDI measures the difference in discrimination slopes between two prediction models.

Table 1: Baseline Characteristics of Study Participants, Atherosclerosis Risk in Communities (ARIC) Study, 1987-1989

Characteristic*	SCD (n=386)	No SCD (n=13,194)	CV Death (n=1296)	No CV Death(n=12284)
Age, mean (SD), years	56.0 (5.7)†	53.9 (5.7)	56.8 (5.5)†	53.7 (5.7)
Female	150 (39%)†	7414 (56%)	604 (47%)†	6960 (57%)
Black race	167 (43%)†	3253 (25%)	502 (39%)†	2918 (24%)
Current smoker	151 (39%)†	3359 (25%)	468 (36%)†	3042 (25%)
Diabetes	103 (27%)†	1297 (10%)	322 (25%)†	1078 (9%)
Hypertension	222 (58%)†	4039 (31%)	717 (55%)†	3544 (29%)
Total Cholesterol>200 mg/dl	260 (67%)†	8019 (61%)	886 (68%)†	7393 (60%)
HDL<40 mg/dl	136 (35%)†	3291 (25%)	421 (32%)†	3006 (24%)
aPWA	29 (8%)	1035 (8%)	114 (9%)	950 (8%)
PPWD	88 (23%)†	1800 (14%)	289 (22%)†	1599 (13%)
aPTFV1	73 (19%)†	1205 (9%)	240 (19%)†	1038 (8%)
ECG LVH	21 (5%)†	236 (2%)	74 (6%)†	183 (1%)
Prolonged QTc (>450 ms male/460 ms female)	30 (8%)†	376 (3%)	83 (6%)†	323 (3%)
HR>75 bpm	84 (22%)†	2194 (17%)	313 (24%)†	1965 (16%)
QRS-T angle>90°	36 (9%)†	372 (3%)	101 (8%)†	307 (3%)
QRS >V4 transition	27 (7%)	812 (6%)	106 (8%)†	733 (6%)
QRS duration >100 ms	87 (23%)†	2190 (17%)	266 (21%)†	2011 (16%)

*Data are presented as no. (%) unless otherwise stated

† P value <0.01

‡Abbreviations: abnormal P-wave axis (aPWA), advanced interatrial block (aIAB), prolonged P-wave duration (PPWD), abnormal P-wave terminal force in V1 (aPTFV1), sudden cardiac death (SCD), cardiovascular (CV)