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Association of P-Wave Abnormalities with Sudden Cardiac and Cardiovascular Death: The Atherosclerosis Risk (ARIC) in Communities Study

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Electrocardiographic assessment of cardiovascular (CV) risk has primarily relied on analysis of ventricular depolarization and repolarization.1 Atrial cardiomyopathy is increasingly recognized as an independent contributor to poor CV outcomes. It is characterized by adverse structural, architectural, contractile, and/or electrophysiological atrial remodeling,2 which manifests electrocardiographically3 as abnormal P-wave indices (aPWIs). We aimed to determine whether aPWIs are associated with sudden cardiac death (SCD) and CV death independent of clinical CV risk factors from the American College of Cardiology/American Heart Association (ACC/AHA) pooled cohort equation4 and established electrocardiographic1 CV risk markers. We also aimed to determine whether use of multiple electrocardiographic markers could improve prediction models for SCD and CV death.

We utilized Atherosclerosis Risk in Communities (ARIC) Study data. Details on study protocols including covariate and outcome adjudication have been previously reported3,5 and are included in supplemental methods. Informed participant consent and institutional review board approval from each participating institution was obtained. ARIC study participant consent does not allow for public release of data. Data, with some restriction, can be accessed by contacting the ARIC coordinating center (www2.cscc.unc.edu/aric/). We...
evaluated 13,580 participants at baseline without prevalent CV disease (stroke, heart failure (HF), coronary heart disease (CHD), atrial fibrillation (AF)) or missing electrocardiogram (ECG)/covariate data.

ECGs variables were obtained during the first four study visits (1987–1998). We evaluated abnormal P-wave axis (aPWA, <0°, >75°), prolonged P-wave duration (PPWD, >120ms), and abnormal P-wave terminal force in lead V1 (aPTFV1, ≤−4000 μV*ms) as well as previously reported electrocardiographic SCD and CV risk markers1– resting heart rate>75 bpm, prolonged QTc interval, QRS-T angle>90°, QRS transition zone>V4, left ventricular hypertrophy (LVH, sex specific Cornell product), Tpeak to Tend>89 ms, and QRS duration>100 ms. Clinical 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 and incident HF, CHD, and AF.

All fatal CHD events through 2012 were reviewed by a panel of physicians to adjudicate SCDs. CV deaths were defined as deaths associated with ICD-10 ‘I’ codes or ICD9 codes 401–459.

We used Cox proportional hazard models (Models 1–4’) to estimate hazard ratios of each aPWI for SCD and CV death. All PWIs and covariates were time-varying. To account for mediation by development of CV diseases associated with SCD and CV death, selected covariates (AF, CHD, and HF) were updated to the end of follow up (Table 1A).

Benchmark models predicting 10-year SCD and CV death risk were built using baseline variables from the ACC/AHA pooled cohort equation (Model A4) and previously established SCD risk scores (Models B1, C5).

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).

We identified 386 SCDs and 1,296 CV deaths in our cohort of 13,580 participants over a mean follow up period of 21.1 years. Baseline demographic data are displayed in supplemental Table 1.

All PWIs were independently associated with SCD and CV death after adjustment for age, sex, and race/study center (Model 1). These associations were attenuated but remained significant after adjustment for clinical risk factors from the ACC/AHA pooled cohort equation (Model 2), electrocardiographic CV risk factors (Model 3), CV diseases (Model 4), and CV diseases updated to the end of follow up (Model 4’).

For prediction of 10-year SCD and CV death risk, the addition of ECG markers to our benchmarks resulted in an improvement in model discrimination measured by C-statistic for SCD and CV death. This corresponded to accurate reclassification of risk measured by rIDI and NRI for SCD and CV death. All models were well calibrated for SCD and CV death.
aPWIs have been linked with atrial remodeling/enlargement and reduced atrial contractility. These elements of atrial cardiomyopathy can have diverse consequences including impaired ventricular filling/hemodynamics and arrhythmia such as atrial fibrillation. Ultimately, development of increased cardiac remodeling, pulmonary hypertension, heart failure, and myocardial ischemia can occur. In fact, aPWIs have been independently associated with increased left ventricular (LV) end diastolic diameter, lower LV systolic function, and increased LV fibrosis. By rigorously characterizing the association of aPWIs with CV death and SCD, this paper expands current understanding of the impact of atrial cardiomyopathy on CV disease. Since the majority of SCDs occur in people with subclinical CHD disease and normal LVEF, identifying novel predictors and improving general CV risk assessment is paramount. This is especially true as multi-variable SCD prediction models have not been able to meaningfully discriminate between SCD and non-SCD. Our findings illustrate the potential of improvement in CV risk prediction with multi-marker ECG analysis. Further validation and evaluation of clinical utility is needed.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments:**

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**Nonstandard Abbreviations and Acronyms:**

- **CV** Cardiovascular
- **aPWI** Abnormal P-wave Indices
- **SCD** Sudden Cardiac Death
- **ACC** American College of Cardiology
- **AHA** American Heart Association
- **ARIC** Atherosclerosis Risk in Communities
- **HF** Heart Failure
- **CHD** Coronary Heart Disease
- **AF** Atrial Fibrillation
- **ECG** Electrocardiogram
- **aPWA** Abnormal P-wave Axis
- **PPWD** Prolonged P-wave Duration
aPTFV1 Abnormal P-wave Terminal Force in V1
LVH Left Ventricular Hypertrophy
LV Left Ventricular

References:
### Table 1.

Association of P-wave Indices with Sudden Cardiac Death and Cardiovascular Death

#### A. Hazard Ratios (95% CI) of SCD and CV death for Abnormal P-wave Indices

<table>
<thead>
<tr>
<th>P-Wave Index</th>
<th>Model</th>
<th>SCD</th>
<th>CV Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPW A (&lt;0°, &gt;75°)</td>
<td>1</td>
<td>4.27 (3.44–5.30)</td>
<td>3.99 (3.56–4.48)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3.94 (3.17–4.90)</td>
<td>3.80 (3.38–4.26)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3.77 (3.03–4.69)</td>
<td>3.61 (3.21–4.06)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>3.80 (3.05–4.73)</td>
<td>3.64 (3.23–4.10)</td>
</tr>
<tr>
<td></td>
<td>4'</td>
<td>2.84 (2.27–3.57)</td>
<td>2.79 (2.48–3.15)</td>
</tr>
<tr>
<td>PPWD (&gt;120 ms)</td>
<td>1</td>
<td>1.86 (1.51–2.30)</td>
<td>2.00 (1.78–2.25)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.78 (1.44–2.20)</td>
<td>1.90 (1.69–2.14)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.70 (1.37–2.11)</td>
<td>1.82 (1.62–2.05)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1.67 (1.34–2.07)</td>
<td>1.79 (1.59–2.02)</td>
</tr>
<tr>
<td></td>
<td>4'</td>
<td>1.32 (1.06–1.64)</td>
<td>1.38 (1.22–1.55)</td>
</tr>
<tr>
<td>aPTFV1 (≤ −4000 μV*ms)</td>
<td>1</td>
<td>2.46 (1.98–3.05)</td>
<td>2.35 (2.09–2.65)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.00 (1.60–2.48)</td>
<td>1.91 (1.69–2.15)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.82 (1.46–2.28)</td>
<td>1.73 (1.53–1.95)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1.79 (1.43–2.24)</td>
<td>1.69 (1.50–1.92)</td>
</tr>
<tr>
<td></td>
<td>4'</td>
<td>1.58 (1.26–1.99)</td>
<td>1.44 (1.27–1.62)</td>
</tr>
</tbody>
</table>

#### B. Prediction Model Performance for 10-Year SCD and CV Death Risk

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Model</th>
<th>C-statistic (95% CI)</th>
<th>Calibration $X^2$ (P-value)</th>
<th>Category-based NRI (95% CI)</th>
<th>rDI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCD</td>
<td>A</td>
<td>0.815 (0.781–0.848)</td>
<td>10.1 (0.34)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>A+</td>
<td>0.832 (0.798–0.865)</td>
<td>5.89 (0.75)</td>
<td>0.087 (0.013, 0.162)</td>
<td>0.338 (0.145, 0.559)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.814 (0.782–0.846)</td>
<td>8.44 (0.49)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>B+</td>
<td>0.822 (0.790–0.855)</td>
<td>14.3 (0.11)</td>
<td>0.079 (0.004 to 0.150)</td>
<td>0.100 (0.006 to 0.232)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>0.838 (0.807–0.868)</td>
<td>5.97 (0.74)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>C+</td>
<td>0.848 (0.818–0.879)</td>
<td>8.43 (0.49)</td>
<td>0.078 (0.018 to 0.143)</td>
<td>0.222 (0.069 to 0.412)</td>
</tr>
<tr>
<td>CV Death</td>
<td>A</td>
<td>0.816 (0.794–0.839)</td>
<td>7.81 (0.55)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>A+</td>
<td>0.830 (0.808–0.853)</td>
<td>9.51 (0.39)</td>
<td>0.072 (0.017, 0.128)</td>
<td>0.239 (0.097, 0.415)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.802 (0.778–0.825)</td>
<td>13.6 (0.14)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>B+</td>
<td>0.808 (0.784–0.832)</td>
<td>10.9 (0.28)</td>
<td>0.058 (0.011 to 0.101)</td>
<td>0.094 (0.032 to 0.171)</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>0.822 (0.799–0.845)</td>
<td>6.67 (0.67)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>C+</td>
<td>0.833 (0.811–0.856)</td>
<td>5.82 (0.76)</td>
<td>0.085 (0.037 to 0.133)</td>
<td>0.215 (0.088 to 0.375)</td>
</tr>
</tbody>
</table>

*P-wave indices and covariates (Models 1–4) are time varying.

†All P-values <0.01 for 1A

‡Model 1: Cox proportional hazard model adjusted for age, sex, and race/study center

Model 2: Model 1+ hypertension medications, systolic blood pressure, diabetes, smoking status, total cholesterol, high density lipoprotein (clinical covariates from the ACC/AHA pooled cohort equation)
Model 3: Model 2+ ECG left ventricular hypertrophy, QTc>450 ms (men)/460 ms (female), resting heart rate>75 bpm, Frontal QRS-T angle>90°, QRS transition >V4, QRS duration>100 ms, TpTe>89 ms (previously reported ECG markers of CV risk)

Model 4: Model 3+ atrial fibrillation, coronary heart disease, heart failure

Model 4': Model 4 with atrial fibrillation, coronary heart disease, heart failure updated to end of follow-up

Model A: Cox proportional hazard model adjusted for age, sex, race/study center, hypertension medications, systolic blood pressure, diabetes, smoking status, total cholesterol, high density lipoprotein (variables from the ACC/AHA pooled cohort equation)

Model A+: Model A + ECG variables (aPW A, aPTFV1, PPWD, ECG left ventricular hypertrophy, QTc>450 ms (men)/460 ms (female), resting heart rate>75 bpm, QRS-T angle>90°, QRS transition >V4, QRS duration>100 ms, TpTe>89 ms)

Model B: Cox proportional hazard model adjusted for age, sex, hypertension, diabetes, body mass index, smoking status, ECG left ventricular hypertrophy, QRS transition>V4, resting heart rate>75, frontal QRS-T angle>90, QTc>450 (men)/460 (female), TpTe>89 ms

Model B+: Model B + remaining ECG variables (aPWA, aPTFV1, PPWD, QRS duration>100 ms)

Model C: Cox proportional hazard model adjusted for age, sex, race, diabetes, smoking status, systolic blood pressure, hypertension medications, potassium, albumin, HDL, estimated glomerular filtration rate, QTc>450 (men)/460 (female)

Model C+: Model C + remaining ECG variables (aPWA, PPWD, aPTFV1, ECG left ventricular hypertrophy, QRS transition>V4, resting heart rate>75 bpm, Frontal QRS-T angle>90°, TpTe>89 ms, QRS duration>100ms)

\\* NRI categories:

SCD: <1%, 1–2%, >2%
CV Death: <2.5%, 2.5–5%, >5%

Abbreviations: ACC (American College of Cardiology), AHA (American Heart Association), abnormal P-wave indices (aPWIs), confidence interval (CI), sudden cardiac death (SCD), cardiovascular (CV), 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), categorical net reclassification improvement (NRI), relative integrated discrimination improvement (rIDI), TpTe (Tpeak-Tend)