Electric cardiothe PR Interval and Adverse Outcomes in Older Adults

The Health, Aging, and Body Composition Study

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Background—The electric cardio the PR interval increases with aging, differs by race, and is associated with atrial fibrillation (AF), pacemaker implantation, and all-cause mortality. We sought to determine the associations between PR interval and heart failure, AF, and mortality in a biracial cohort of older adults.

Methods and Results—The Health, Aging, and Body Composition (Health ABC) Study is a prospective, biracial cohort. We used multivariable Cox proportional hazards models to examine PR interval (hazard ratios expressed per SD increase) and 10-year risks of heart failure, AF, and all-cause mortality. Multivariable models included demographic, anthropometric, and clinical variables in addition to established cardiovascular risk factors. We examined 2722 Health ABC participants (aged 74±8 years, 51.9% women, and 41% black). We did not identify significant effect modification by race for the outcomes studied. After multivariable adjustment, every SD increase (29 ms) in PR interval was associated with a 13% greater 10-year risk of heart failure (95% confidence interval, 1.02–1.25) and a 13% increased risk of incident AF (95% confidence interval, 1.04–1.23). PR interval >200 ms was associated with a 46% increased risk of incident heart failure (95% confidence interval, 1.11–1.93). PR interval was not associated with increased all-cause mortality.

Conclusions—We identified significant relationships of PR interval to heart failure and AF in older adults. Our findings extend prior investigations by examining PR interval and associations with adverse outcomes in a biracial cohort of older men and women. (Circ Arrhythm Electrophysiol. 2013;6:84-90.)

Key Words: atrial fibrillation ■ ECG ■ epidemiology ■ heart failure ■ risk factors

The PR interval, accessible from the ECG, measures the duration of atrial and atrioventricular nodal conduction. Automated software routinely quantifies the median PR interval in clinical settings. As established by large-sized cohorts, PR interval increases progressively with age.1,2

Clinical Perspective on p 90

Previously, PR interval ≥200 ms was considered benign.3 More recently, PR interval prolongation has been associated with adverse outcomes, including a 1.4-fold to 2-fold increased risk of atrial fibrillation (AF). The association with mortality has varied in follow-up for several decades, and increased PR interval duration in a community-based cohort was associated with a 1.4-fold increased risk of all-cause mortality.5 In contrast, a National Health and Nutrition Examination Survey analysis found no association with all-cause or cardiovascular mortality.6 Studies examining racial differences have had varied results. Whereas a cross-sectional multiethnic study identified no significant ethnic differences in PR interval duration,7 a large community-based study reported significantly prolonged PR interval duration in blacks compared with whites.4

Heart failure, AF, and mortality are common in older age groups. We examined PR interval in the Health, Aging, and

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Body Composition (Health ABC) Study, a prospective, biracial cohort of older adults. We hypothesized that PR interval would be significantly associated with heart failure, AF, and all-cause mortality in a cohort of older adults after accounting for established clinical risk factors. We sought to identify racial differences in PR interval as an exposure, especially because blacks have been reported to have less incident AF than whites, despite observed differences in PR duration.

Methods

Study Cohort

Health ABC is a longitudinal cohort study examining the association of body composition with health outcomes. Participants were recruited from a random sampling of white Medicare beneficiaries in areas surrounding Pittsburgh, PA, and Memphis, TN, and all age-eligible blacks in the same zip codes. Enrollment criteria included age 70 to 79 years, white or black race, capacity to perform mobility-related activities of daily living, and absence of functional disability. The initial examination included a standardized physical, anthropometric assessment, laboratory, motor, and cognitive assessments, body imaging, and medications. Health ABC’s baseline examination (1997–1998) consisted of 3075 participants (52% women and 42% black) who have been followed with telephone contacts at 6-month intervals and clinic examinations in years 1 to 6, 8, 10, and 11. The study completed its 14th year, 2010 to 2011.

The present analysis excluded participants with missing ECG data or PR intervals <80 ms (n=81); atrial or other supraventricular arrhythmias including AF, ventricular preexcitation (Wolff–Parkinson–White), second-degree or higher heart block, or paced rhythm (n=136); absence of the examined covariates (n=133); and lacking outcome data (n=3). Participants with prevalent heart failure (n=64) were excluded from the analysis examining heart failure as an outcome. Participants with prevalent AF (n=126) or lacking Center for Medicare and Medicaid data (n=23) were excluded from analysis examining incident AF. The study protocols of Health ABC were approved by the Institutional Review Boards at the University of Pittsburgh and the University of Tennessee. All participants provided written informed consent.

Electrocardiography and PR Interval Measurement

Twelve-lead ECGs for the present investigation were collected at the baseline examination (Marquette Electronics MAC PC) by standardized protocol. ECG tracings were submitted to the St. Louis University Core ECG Laboratory (St. Louis, MO) for analysis, where ECG analysis was blinded to participant demographics. Two independent coders analyzed each ECG for standard intervals (heart rate, PR, QRS, and QT intervals) and amplitudes (R, S, and T waves and J and ST segments) as described elsewhere. The PR interval was determined as beginning at the T-PJ junction at the start of the P wave to the initiation of the QRS segment. Measurements of the PR interval were made in lead II using a 7-power magnifying loupe on a grid with 0.1 mm calibration. The PR interval was determined as the average measurement from 3 consecutive beats or 2 at slower heart rates (<50 beats per minute). Interreader discrepancies were resolved by direct comparison and adjudication by a supervisor. The St. Louis University Core ECG Laboratory has reported excellent reliability assessments. Interreader reproducibility assessments for PR interval measurement found a coefficient of reliability of 0.997 and a Pearson correlation coefficient of 0.997. A paired t test comparing interreader PR measurements did not achieve statistical significance (P=0.22).

Study Measurements and Clinical Assessments

The year 1 visit comprised the baseline examination for the present analysis. Subsequent examinations included interim health history updates, hospitalizations, and current medications. Race (black or white), smoking (current/former or never), and alcohol use were determined by self-report. Moderate-to-heavy alcohol consumption was determined by self-report of ≥21 drinks for men and ≥7 drinks weekly for women. Systolic and diastolic blood pressure consisted of 2 measurements averaged with participants in a seated position. Body mass index was derived using weight divided by height squared (kg/m²). Diabetes mellitus was determined from self-reported history, use of oral hypoglycemics or insulin, or fasting glucose ≥126 mg/dL. Blood samples were obtained after an 8-hour fast. Serum total and high-density lipoprotein cholesterol measures were assayed according to standardized methods (Ortho-Clinical Diagnostics, Rochester, NY). Medications taken within 2 weeks were brought to each examination and classified according to the Iowa Drug Information System, thereby identifying antihypertensive, oral hypoglycemic, or insulin medications and medications with antiarrhythmic nodal blocking properties (amiodarone, oral β-blockers, cardiac glycosides, and calcium channel blockers). Prevalent heart failure was determined by self-reported history or use of vasodilator, cardiac glycoside, or diuretic therapies. Prevalent coronary heart disease was determined by self-reported history of coronary artery bypass graft surgery, coronary angioplasty, history of myocardial infarction, angina, or ECG evidence of myocardial infarction by identification of an ECG major Q-wave abnormality. ECG left ventricular hypertrophy was categorized using an automated measurement of the R-wave amplitude >26 mm in precordial lead V5 or V6; R-wave amplitude >20 mm in limb lead I, II, III, or aVF; or R-wave amplitude >12 mm in limb lead aVL.

Study Events and Outcomes

Outcomes occurred during 10-year follow-up after the baseline examination and consisted of heart failure, AF, and all-cause mortality. Medical history for interim events and incident disease were reviewed at annual examinations and 6-month telephone contacts. Incident heart failure was determined by a physician diagnosis of congestive heart failure and medical treatment for heart failure (ie, combination of a diuretic and cardiac glycoside or vasodilator) requiring overnight hospitalization. Further criteria included presence of cardiomegaly or pulmonary edema by chest radiograph or evidence of ventricular dilation by cardiac imaging when available. Records from hospitalizations were obtained and reviewed. Incident heart failure cases underwent adjudication by physicians at the local research site as described previously. Incident AF was obtained by linking unique Health ABC identifiers to the Center for Medicare and Medicaid database for International Classification of Diseases, Ninth Revision, codes 427.31 or 427.32 obtained from the ambulatory or inpatient setting through 2008. Health ABC investigators did not have access to hospital ECGs, and AF was not an adjudicated study end point. Use of International Classification of Diseases, Ninth Revision, coding for ascertainment of incident AF has been demonstrated to have 84% sensitivity and 98% specificity. Date of death was ascertained from participant proxy or other participant representative, hospital records, obituary, or search of the National Death Index. The Health ABC central Diagnosis and Disease Ascertainment Committee integrates data to review all identified deaths. Follow-up duration was determined from the baseline visit until the first event or the day of death or 10 years. Outcomes were considered independently, and participants were censored from the analysis at the date of the event or last known study contact.

Statistical Analyses

Continuous variables were examined for their mean and SDs and categorical variables for their distributions. We examined the graphical and numerical distribution of the PR interval and determined that it did not depart from normality. The relationships of covariates to the PR interval were estimated using general linear models. Models were initially adjusted for demographic variables (age, sex, race, and site). A multivariable model was then adjusted for the demographic variables and the following clinical variables: smoking history, body mass index, systolic and diastolic blood pressure, heart rate, medications (amiodarone, cardiac glycosides, calcium channel blocker, and oral β-blocker), ratio of total to high-density lipoprotein cholesterol, ECG left ventricular hypertrophy, hypertension treatment, prevalent heart failure (for AF and mortality analyses), coronary heart disease,
and diabetes mellitus. The 10-year incident rates for the outcomes of heart failure, AF, and mortality were determined. Multivariable Cox proportional hazards regression models for each outcome examined PR interval per SD increase and dichotomized as ≤ or >200 ms.

We assessed for effect modification between PR interval and age, sex, and race in examining the association between PR and the outcomes of heart failure, AF, and mortality. We did not identify significant effect modification in the initial (age-, sex-, race- and site-adjusted) or the complete multivariable-adjusted Cox proportional hazards regression models. Survival curves based on stratified Cox regression models were constructed to examine differences between categorical PR and the associations with the outcomes of heart failure, AF, and mortality. We verified that the proportionality of hazards assumption was not violated.

Secondary analyses were conducted adjusting for interim heart failure before AF and for interim AF before heart failure and using medications as time-varying covariates during follow-up. The relationships of PR interval to the outcomes of AF and heart failure were examined further by constructing restricted cubic splines using the cohort mean PR as the reference and incorporating knots at 5, 27.5, 50, 72.5, and 95 quantiles as recommended by Harrell. All statistical analyses used SAS version 9.2 (SAS Institute, Cary, NC). A 2-sided P<0.05 was considered statistically significant.

Results

After exclusions, 2722 Health ABC participants comprised the present analysis. The cohort’s median PR interval was 168 (interquartile range, 152–188) ms and mean age was 74±3 years at baseline; 52.4% were women and 41.0% were black (Table 1). Race was not significantly correlated with PR interval in age-, sex- and site-adjusted analyses (P=0.28). The main significant clinical correlates of PR interval were age, sex, heart rate, body mass index, and hypertension treatment.

During the course of the 10-year follow-up, 369 participants were diagnosed with heart failure, 537 with incident AF, and 832 died. Table 2 presents the incidence rate per 1000 person-years for the outcomes. There was no significant interaction between race and PR interval with the outcome of heart failure (P=0.26), AF (P=0.89), or all-cause mortality (P=0.66). Incidence rates by race are given in the online-only Data Supplement Table SI.

In multivariable-adjusted analyses (Table 3), every SD increase (29 ms) of the baseline PR interval was associated with a 13% increased 10-year risk of heart failure (hazard ratio [HR], 1.13; 95% confidence interval [CI], 1.02–1.25) and a 13% increased 10-year risk of incident AF (HR, 1.13; 95% CI, 1.04–1.23). PR interval was not associated with all-cause mortality. Results for AF by race are particularly of interest, given prior findings that risk of AF varies by race. The HR per SD of PR interval adjusted for age, sex, and site was 1.14 (95% CI, 1.03–1.26; P=0.01) for whites and 1.17 (95% CI, 1.01–1.34; P=0.04) for blacks. Racially stratified results are summarized in the online-only Data Supplement Table SII.

Table 1. Baseline Characteristics and the Clinical Correlates of PR Interval in the Health, Aging, and Body Composition Cohort (N=2722)

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Distribution</th>
<th>Change in PR±SD</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>Distribution</th>
<th>Change in PR±SD</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>74±3</td>
<td>1.7±0.6</td>
<td>0.003</td>
<td>1.19 (1.06–1.33)</td>
<td>0.003</td>
<td>1.7±0.5</td>
<td>0.002</td>
<td>1.19 (1.06–1.34)</td>
</tr>
<tr>
<td>Female</td>
<td>1427 (52.4)</td>
<td>−12.5±1.1</td>
<td>&lt;0.0001</td>
<td>0.36 (0.28–0.46)</td>
<td>&lt;0.0001</td>
<td>−12.4±1.2</td>
<td>&lt;0.0001</td>
<td>0.35 (0.26–0.46)</td>
</tr>
<tr>
<td>Memphis site</td>
<td>1373 (50.4)</td>
<td>−1.8±1.1</td>
<td>0.010</td>
<td>0.92 (0.73–1.15)</td>
<td>0.48</td>
<td>−0.4±1.1</td>
<td>0.75</td>
<td>1.03 (0.80–1.32)</td>
</tr>
<tr>
<td>Black</td>
<td>1115 (41.0%)</td>
<td>1.4±1.1</td>
<td>0.22</td>
<td>1.14 (0.90–1.44)</td>
<td>0.28</td>
<td>−0.2±1.2</td>
<td>0.84</td>
<td>1.03 (0.80–1.34)</td>
</tr>
<tr>
<td>Smoking (current and former)</td>
<td>1515 (55.7)</td>
<td>−3.1±1.2</td>
<td>0.007</td>
<td>0.88 (0.69–1.13)</td>
<td>0.33</td>
<td>−2.7±1.1</td>
<td>0.016</td>
<td>0.91 (0.71–1.16)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27±4±8</td>
<td>3.6±0.6</td>
<td>&lt;0.0001</td>
<td>1.26 (1.12–1.42)</td>
<td>0.0002</td>
<td>3.1±0.6</td>
<td>&lt;0.0001</td>
<td>1.22 (1.07–1.39)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>136±21</td>
<td>0.9±0.6</td>
<td>0.11</td>
<td>1.13 (1.01–1.27)</td>
<td>0.031</td>
<td>−0.2±0.7</td>
<td>0.82</td>
<td>1.05 (0.91–1.21)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>71±12</td>
<td>−0.3±0.6</td>
<td>0.61</td>
<td>1.02 (0.91–1.16)</td>
<td>0.71</td>
<td>0.2±0.7</td>
<td>0.78</td>
<td>1.02 (0.88–1.18)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>64 (2.4)</td>
<td>6.8±3.6</td>
<td>0.06</td>
<td>1.57 (0.83–2.96)</td>
<td>0.16</td>
<td>3.6±3.6</td>
<td>0.32</td>
<td>3.1 (0.67–2.55)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>565 (20.8)</td>
<td>5.2±1.4</td>
<td>0.0002</td>
<td>1.28 (0.98–1.66)</td>
<td>0.07</td>
<td>1.7±1.5</td>
<td>0.24</td>
<td>0.96 (0.71–1.29)</td>
</tr>
<tr>
<td>Stroke</td>
<td>214 (7.9)</td>
<td>0.8±2.1</td>
<td>0.70</td>
<td>1.09 (0.72–1.66)</td>
<td>0.68</td>
<td>−0.9±2.0</td>
<td>0.67</td>
<td>0.97 (0.63–1.50)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>400 (14.7)</td>
<td>2.4±1.6</td>
<td>0.13</td>
<td>1.22 (0.90–1.67)</td>
<td>0.20</td>
<td>1.7±1.6</td>
<td>0.27</td>
<td>1.17 (0.85–1.63)</td>
</tr>
<tr>
<td>Total/HDL cholesterol ratio</td>
<td>4.1±1.3</td>
<td>1.7±0.6</td>
<td>0.003</td>
<td>1.15 (1.03–1.28)</td>
<td>0.016</td>
<td>0.7±0.6</td>
<td>0.19</td>
<td>1.09 (0.97–1.22)</td>
</tr>
<tr>
<td>Hypertension treatment</td>
<td>1459 (53.6)</td>
<td>7.3±1.1</td>
<td>&lt;0.0001</td>
<td>1.70 (1.34–2.16)</td>
<td>&lt;0.0001</td>
<td>2.1±1.4</td>
<td>0.14</td>
<td>1.12 (0.80–1.56)</td>
</tr>
<tr>
<td>Selected medications</td>
<td>1126 (41.3%)</td>
<td>8.6±1.1</td>
<td>&lt;0.0001</td>
<td>1.91 (1.52–2.42)</td>
<td>&lt;0.0001</td>
<td>4.8±1.5</td>
<td>0.001</td>
<td>1.56 (1.12–2.18)</td>
</tr>
<tr>
<td>Heart rate, beats per min</td>
<td>65±11</td>
<td>−4.9±0.6</td>
<td>&lt;0.0001</td>
<td>0.73 (0.64–0.83)</td>
<td>&lt;0.0001</td>
<td>−4.9±0.6</td>
<td>&lt;0.0001</td>
<td>0.73 (0.64–0.83)</td>
</tr>
<tr>
<td>ECG left ventricular hypertrophy</td>
<td>237 (8.7)</td>
<td>5.2±2.0</td>
<td>0.009</td>
<td>1.58 (1.09–2.28)</td>
<td>0.015</td>
<td>4.6±1.9</td>
<td>0.016</td>
<td>1.47 (1.01–2.16)</td>
</tr>
</tbody>
</table>

PR interval, ms 168 (152–188)

Distributions are means (SD) or n (%) for anthropometric, clinical, and laboratory variables. Age-, sex-, site-, and race-adjusted models: each of age, sex, site, and race was adjusted for the other 3 variables. Comprehensive multivariable adjustment included adjustment for age, sex, site, race, and the remainder of the variables listed here. Selected medications are amiodarone, cardiac glycosides, calcium channel blockers, and β-blockers. Continuous variables are expressed per SD and categorical variables for the presence of variable. Estimates show the change in PR interval per SD change for continuous variables or for the presence of that variable for categorical variables. PR is expressed as median and interquartile range. BP indicates blood pressure; CI, confidence interval; HDL, high-density lipoprotein; and OR, odds ratio.
Incident heart failure 1.16 (1.05–1.28) 0.003 1.13 (1.02–1.25) 0.019

HR per 1-SD Increase

Table 2. Ten-Year Incidence Rate per 1000 Person-Years Follow-up

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total Sample (N=2722)</th>
<th>PR ≤200 ms (n=2383)</th>
<th>PR &gt;200 ms (n=339)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>369</td>
<td>16.7 (15.0–18.4)</td>
<td>15.4 (13.7–17.1)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>537</td>
<td>26.3 (24.1–28.5)</td>
<td>25.0 (22.7–27.3)</td>
</tr>
<tr>
<td>Mortality</td>
<td>832</td>
<td>35.6 (33.2–38.0)</td>
<td>34.5 (32.0–37.0)</td>
</tr>
</tbody>
</table>

The events column indicates the number of participants with the designated outcome out of the total eligible participants. Heart failure (white, n=201; black, n=168); atrial fibrillation (white, n=359; black, n=178); and mortality (white, n=435; black, n=397). CI indicates confidence interval.

The 339 Health ABC participants in our sample with PR >200 ms had 46% increased risk of incident heart failure (95% CI, 1.11–1.93; Table 3). In multivariable models, PR >200 ms was not significantly associated with 10-year risk of AF (HR, 1.26; 95% CI, 0.99–1.61) and was not associated with increased all-cause risk of death (HR, 1.16; 95% CI, 0.96–1.39). We present survival curves for the outcomes of heart failure, AF, and all-cause mortality adjusted for age, sex, race, and site in the Figure using PR stratified as ≤200 ms versus >200 ms.

We developed restricted cubic splines adjusting for sex, age, race, site, and clinical correlates and used the mean PR interval, 170 ms, as the reference value because of its proximity to the median value in our cohort. Online-only Data Supplement Figure SI shows the splines for heart failure, and online-only Data Supplement Figure SII shows the splines for AF. The restricted cubic splines use the median PR value as the referent to determine HRs. The splines (HR shown in red solid line and dashed line indicating the 95% CI) demonstrate a progressive increase in HRs, with the rise in PR interval beyond the reference value of 170 ms (Wald χ² overall association, 5.81; P=0.01 for heart failure and 5.81; P=0.005 for AF). We further note the limited rise in the HR for both heart failure and AF identified when considering PR values less than the referent. The wide CIs, however, indicate that the association is not significant. We report the HR estimates derived from the splines for heart failure and AF using a PR of 170 ms as the referent value in the online-only Data Supplement Table SIII.

Secondary analyses examined PR as a continuous measure using multivariable models and adjusting for interim events. After adjusting for interim AF, an incremental 1-SD increase in PR interval remained associated with a 13% increased risk of heart failure during 10-year follow-up (95% CI, 1.02–1.25; P=0.006). Similarly, a 1-SD increase in PR interval remained associated with AF after adjustment for interim heart failure (HR, 1.13; 95% CI, 1.04–1.23; P=0.02).

**Discussion**

We examined the associations of the ECG PR interval with the 10-year risks of incident heart failure, AF, and mortality in a biracial cohort of older adults. We identified a significant association between baseline PR interval and incident heart failure and AF. Mainly, the analysis identified a 46% increased heart failure risk during the 10-year follow-up.

Our findings extend prior investigations of PR interval beyond younger or more racially homogenous cohorts. In the Framingham Heart Study, investigators identified an association between PR interval and AF highly consistent with our findings. In the Atherosclerosis Risk in Communities (ARIC) Study, Soliman et al found a 41% increase in AF risk with each SD increase in PR interval. However, only 10 black ARIC Study participants developed AF during the 7-year mean follow-up period, suggesting a lower risk of AF in blacks. The mean age of the ARIC participants (54 years) was younger, limiting comparison of the findings presented here. Our results validated these prior studies concerning the importance of PR prolongation as a marker of cardiovascular risk and extended their findings by identifying that PR was associated with heart failure and AF in a markedly older, biracial cohort.

We showed that baseline PR interval in this older cohort had no association with 10-year risk of all-cause mortality in contrast to prior studies. Our study participants were older, and hence likely had a higher burden of comorbidities with greater impact on prognosis than PR.

Several mechanisms may contribute toward the association of PR interval prolongation and incident heart failure. PR interval shares clinical correlates with established heart failure risk factors. Prolongation of the PR has been associated with obesity, increased waist circumference, and components of the metabolic syndrome, exposures that are associated
with incident heart failure.\textsuperscript{16–19} Metabolic syndrome has been previously associated with heart failure in Health ABC.\textsuperscript{20} Hypertension is similarly a main cause for heart failure with preserved and compromised systolic function\textsuperscript{21–23} and may promote elevated intracardiac pressures that alter atrial electric function.

PR interval progression is a marker of atrial electric and structural remodeling. Invasive electrophysiological studies have demonstrated severely altered atrial electric properties in the setting of left ventricular systolic dysfunction.\textsuperscript{24} Electrophysiological studies have quantified increased atrial refractoriness and conduction times accompanying aging.\textsuperscript{25,26} PR interval prolongation may consequently be consistent with generalized atrial aging or subclinical disease. Unaccounted for residual confounding may contribute toward the findings described here as well. Further study is needed to examine how modulation of risk factors may impact atrial and atrioventricular nodal conduction.

Potential mechanisms for the pathophysiological association between PR prolongation and AF mirror those proposed for heart failure. PR interval has been associated with AF in multiple longitudinal cohort studies, as has its constituent component, P wave duration.\textsuperscript{14,27,28} There has been discussion regarding the decreased prevalence of AF in blacks, despite both clinical risk factors and prolonged measures of atrial electric function, compared with whites.\textsuperscript{9,29} In this study of older white and black adults, we found no interaction by race between PR and the outcomes of heart failure and AF. Our findings suggest that racial differences in atrial electric function may be less relevant in older adults. PR interval reflects intra- and interatrial conduction (the P wave) through the atrioventricular node, and age-related changes in atrial conduction may not be related to race. Further studies are essential to evaluate racial differences in atrial electric function and their clinical relevance in relation to AF.

Our analysis has multiple strengths. The standardized protocol and examinations of Health ABC provide for comprehensive assessment of the covariates used here. Second, our cohort has a unique composition of community-dwelling whites and black older adults with preserved high-level baseline functional status. Our findings are relevant to the increasing number of independent older adults who are aging successfully with limited impairment. Third, electrocardiographic analyses were conducted by standardized reading and coding, thereby enhancing reliability and limiting misclassification. Fourth, heart failure and mortality are adjudicated outcomes in Health ABC.

Our study has multiple limitations. Health ABC enrolled highly functional, older adults of white and black race in the Memphis, TN, and Pittsburgh, PA, regions. Generalization to other races, ethnicities, and regions is uncertain, and generalization to less healthy older adults may also be limited. Second, the study was not designed to examine AF risk factors in older adults. Hence, AF was not an adjudicated outcome in Health ABC. The reliance on Center for Medicare and Medicaid coding for AF determination is another limitation because it may result in misclassification of AF. Third, heart failure events were determined by review of hospitalizations.
As recognized in an analysis of heart failure in Health ABC, this may underestimate heart failure cases and bias toward identification of more severe heart failure.12 We were not able to distinguish between heart failure with preserved or compromised ejection fractions, which may vary in their association with PR interval. Furthermore, Health ABC did not include baseline echocardiography. Inclusion of additional data not available here, such as echocardiographic diastolic indices, systolic function, chamber sizes, and left ventricular mass, may potentially eliminate the predictive value of the PR interval. Another limitation consisted in using a single determination of PR interval at the initial Health ABC examination. Residual confounding from PR interval variability is not accounted for in our analysis. However, we would expect the misclassification of PR interval to be nondifferential and bias our results toward the null. Finally, we cannot exclude residual confounding from other clinical variables that were not included in our multivariable adjustment.

In conclusion, we examined the association of PR interval with adverse outcomes. We found an association between PR interval and heart failure risk. We extended prior analyses of the relationship of PR interval to AF by examining AF risk in an older, biracial cohort. Contrary to our expectations based on prior literature, we found no interaction between race and PR interval in examining the association of PR interval with the outcomes we studied. The ECG is widely used in clinical practice, is of low cost, and includes automated determination of PR interval. Our analyses adjusted for anthropometric and clinical risk factors relevant to cardiovascular disease and related to incident heart failure and AF.12,26,27 Inclusion of such diverse covariates is meaningful: clinicians evaluate PR interval in the context of widely established risk factors and clinical history without considering PR interval in isolation. As the general population continues to age, further strategies for heart failure and AF risk stratification are essential for evaluating and treating those at increased risk. Our investigation suggests that PR interval may contribute toward identifying older adults at increased risk for the adverse outcomes examined here. Further investigation is necessary to incorporate PR interval into risk classification schemes for prevention strategies and to determine whether such treatment strategies will reduce risks of heart failure or AF.

Acknowledgments
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Disclosures
None.

References
CLINICAL PERSPECTIVE

The PR interval is regularly reported in routine electrocardiographic screening. Several studies have demonstrated that the PR interval is associated with adverse outcomes, including atrial fibrillation (AF), pacemaker implantation, and mortality. In the present study, we examined a cohort of healthy, well-functioning older adults (mean age, 74±3 years) and examined the prospective associations between baseline PR duration and risks of heart failure, AF, and mortality in a biracial cohort (the Health, Aging, and Body Composition Study). We demonstrated that prolongation of the PR interval in a cohort of older adults is significantly associated with a 13% subsequent increased risk for both heart failure and AF (P=0.019 for heart failure and P=0.005 for AF). Furthermore, when we compared individuals with PR ≤200 ms, a cut point routinely used in clinical practice to define first-degree atrioventricular block, and those with PR >200 ms, we found that PR >200 ms results in 46% increased risk of heart failure (P=0.006) and 26% increased risk of AF (P=0.059). Our results are important for addressing risk stratification in a progressively aging population. Our investigation suggests that PR interval may contribute toward identifying older adults at increased risk for adverse outcomes, such as heart failure and AF. Further investigation is necessary to incorporate PR interval into risk classification schemes for prevention strategies and to determine whether such treatment strategies will reduce risks of heart failure or AF.
Electrocardiographic PR Interval and Adverse Outcomes in Older Adults: The Health, Aging, and Body Composition Study

Jared W. Magnani, Na Wang, Kerrie P. Nelson, Stephanie Connelly, Rajat Deo, Nicolas Rodondi, Erik B. Schelbert, Melissa E. Garcia, Caroline L. Phillips, Michael G. Shlipak, Tamara B. Harris, Patrick T. Ellinor, Emelia J. Benjamin and for the Health, Aging, and Body Composition Study

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Supplemental Material
<table>
<thead>
<tr>
<th>Outcome</th>
<th>PR interval, continuous</th>
<th>PR interval, &gt;200 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PR interval, continuous</td>
<td>PR interval, &gt;200 ms</td>
</tr>
<tr>
<td></td>
<td>White race</td>
<td>Black race</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>Events*</td>
<td>Rate (95% CI)</td>
</tr>
<tr>
<td>359/1509</td>
<td>14.9 (12.9, 17.0)</td>
<td>168/1081</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>201/1577</td>
<td>29.8 (26.8, 32.9)</td>
</tr>
<tr>
<td>Mortality</td>
<td>435/1607</td>
<td>30.7 (27.9, 33.6)</td>
</tr>
</tbody>
</table>

Total sample (n=2722) examined for association of PR interval with incident heart failure, atrial fibrillation, and all-cause mortality during 10-year follow-up. Limited sample (n=422) examined for events associated with PR>200 ms during 10-year follow-up. Events indicates number of participants with the designated outcome over total eligible participants in race-stratified analysis.

CI, confidence interval; Health ABC, Health, Aging and Body Composition Study.
### Electronic Supplementary Table 2. Hazard ratio per 1-SD increase in PR for selected outcomes in Health ABC, stratified by race.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Adjusted for age, sex, site</th>
<th>White Race</th>
<th>Black Race</th>
<th>Adjusted for age, sex, site</th>
<th>Multivariable Adjusted**</th>
<th>Adjusted for age, sex, site</th>
<th>Multivariable Adjusted**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Incident HF</td>
<td>1.23 (1.08, 1.40)</td>
<td>0.002</td>
<td>1.20 (1.05, 1.38)</td>
<td>0.008</td>
<td>1.09 (0.93, 1.25)</td>
<td>0.31</td>
<td>1.05 (0.91, 1.21)</td>
</tr>
<tr>
<td>Incident AF</td>
<td>1.14 (1.03, 1.26)</td>
<td>0.012</td>
<td>1.11 (1.00, 1.23)</td>
<td>0.06</td>
<td>1.17 (1.01, 1.35)</td>
<td>0.036</td>
<td>1.17 (1.01, 1.34)</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>1.03 (0.94, 1.14)</td>
<td>0.53</td>
<td>1.07 (0.97, 1.18)</td>
<td>0.17</td>
<td>0.97 (0.88, 1.07)</td>
<td>0.55</td>
<td>1.01 (0.91, 1.12)</td>
</tr>
</tbody>
</table>

Stratified by Race, Multivariable models adjusted for age, sex, site, body mass index, heart rate, systolic and diastolic blood pressures, past or current smoking, diabetes, ratio of total to high density lipoprotein cholesterol, electrocardiographic left ventricular hypertrophy, hypertension treatment, selected medications (amiodarone, cardiac glycosides, calcium channel blockers, beta blockers), and prevalent cardiovascular disease as defined in the text.

SD, standard deviation; Health ABC, Health, Aging and Body Composition Study; HF, heart failure; AF, atrial fibrillation.
### Electronic Supplementary Table 3. 10-year hazard ratios (HR) and 95% confidence intervals from restricted cubic splines following multivariable adjustment.

<table>
<thead>
<tr>
<th>PR duration, ms</th>
<th>Atrial fibrillation</th>
<th>Heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>170</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>190</td>
<td>1.02 (0.90 to 1.15)</td>
<td>1.13 (1.04 to 1.22)</td>
</tr>
<tr>
<td>210</td>
<td>1.13 (1.06 to 1.21)</td>
<td>1.30 (1.09 to 1.53)</td>
</tr>
<tr>
<td>230</td>
<td>1.30 (1.12 to 1.50)</td>
<td>1.49 (1.14 to 1.93)</td>
</tr>
<tr>
<td>250</td>
<td>1.49 (1.19 to 1.86)</td>
<td>1.71 (1.20 to 2.43)</td>
</tr>
<tr>
<td>270</td>
<td>1.71 (1.26 to 2.31)</td>
<td>1.96 (1.26 to 3.06)</td>
</tr>
<tr>
<td>300</td>
<td>1.96 (1.34 to 2.87)</td>
<td>2.41 (1.35 to 4.32)</td>
</tr>
</tbody>
</table>

HRs adjusted for age, sex, race, site, smoking status, body mass index, systolic and diastolic blood pressures, treatment for hypertension, prevalent cardiovascular disease, diabetes, ratio of total to low density lipoprotein cholesterol, heart rate, electrocardiographic left ventricular hypertrophy, and selected medications (amiodarone, cardiac glycosides, calcium channel blockers, beta blockers).
Supplementary Figure 1.

The cubic restricted splines demonstrating the association between the PR interval and 10-year increased risk of incident heart failure as expressed by multivariable-adjusted hazard ratios. A PR interval of 170 ms is used as a reference because of its proximity to the median PR of the cohort, 168 ms. The solid red line demonstrates a progressively increased 10-year risk of incident heart failure risk with PR interval prolongation. The dashed black lines indicate the 95% confidence intervals.

Supplementary Figure 2.

The cubic restricted splines demonstrating the association between the PR interval and 10-year increased risk of incident atrial fibrillation as expressed by multivariable-adjusted hazard ratios. A PR interval of 170 ms is used as a reference because of its proximity to the median PR of the cohort, 168 ms. The solid red line demonstrates a progressively increased 10-year risk of incident atrial fibrillation associated with PR interval prolongation. The dashed black lines indicate the 95% confidence intervals.