1.a. Full Title:
Epidemiology of P Wave Indices: Clinical Associations and Long-term Outcomes

   b. Abbreviated Title (Length 26 characters):
Epidemiology of P Wave Indices

2. Writing Group:
Jared W Magnani, MD
Alonso Alvaro, MD, PhD
Ronald Prineas, MD
Richard Crow, PhD
Wayne D. Rosamond, PhD
Elsayed Z. Soliman, MD, MSc, MS
Other authors welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. JWM [please confirm with your initials electronically or in writing]

First author: Jared W Magnani
Address: Boston Medical Center
         88 E. Newton Street
         Boston, MA 02118

         Phone: 617 638 8714       Fax: 617 638 8969
         E-mail: jared.magnani@bmc.org

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Name: Alvaro Alonso, MD
Address: 1300 S 2nd St, Suite 300
         Division of Epidemiology and Community Health
         School of Public Health, University of Minnesota
         Minneapolis, MN 55454
         Phone: 612 626 8597       Fax: 612 624 0315
         E-mail: alonso@umn.edu

3. Timeline:
Assembly of preliminary data will be initiated immediately following proposal approval. Data cleaning and organization will occur over the subsequent 6 months. Analysis is anticipated to be completed in September 2010. Composition and submission of initial manuscript is anticipated by January 2011. Data analysis will be done at the University of Minnesota.

4. Rationale:

A recent National Heart Lung and Blood Institute’s Workshop on prevention of AF emphasized identification of non-invasive biomarkers and assessment of their contribution towards AF risk and its associated comorbidities. In this context, P wave indices constitute an electrocardiographic (ECG) intermediate phenotype which has been associated with AF and may have utility in characterizing risk for AF and its comorbidities. P wave indices include PR duration, P wave duration, amplitude, area, and terminal force.

The epidemiology, prognostic value and genetic determinants of P wave indices remain incompletely described. P wave indices have been assessed in subjects with paroxysmal AF, recurrent AF following cardioversion, AF following cardiothoracic surgery, and incident AF. Cross-sectional studies have demonstrated that subjects with risk factors for cardiovascular disease including hypertension, obesity, diabetes and sleep apnea have prolonged P wave indices compared to healthy controls. The majority of these reports have been limited by small sample sizes with poor statistical power, selection biases, lack of adjustment for potential confounders, cross-sectional study design, brief follow up, and deficits in measurement technique and reproducibility. As a result, our knowledge of clinical associations and correlates of P wave indices remains extremely limited. The largest identified study to date evaluating P wave indices occurred in the Atherosclerosis Risk in Communities (ARIC) study, and identified a significant association between prolonged P wave indices and AF and incident stroke.

The availability of P wave indices in ARIC provides a unique opportunity to expand our knowledge in this novel area of cardiovascular research. Therefore, we sought to expand the previous work in ARIC by examining the associations between P wave indices with incident adverse outcomes (heart failure, cardiovascular disease, and all-cause mortality) and how such associations, if exist, relate to incident AF. As P wave-indices is associated with a number of CVD risk factors, we hypothesize that abnormal P wave indices mark the accumulation of multifactorial insults and are associated with adverse events.

5. Main Hypothesis/Study Questions:

Primary hypothesis: We hypothesize P wave indices are associated with long-term adverse outcomes of heart failure, cardiovascular disease, and all-cause mortality. We further hypothesize associations with adverse outcomes will remain present following adjustment for established cardiovascular risk factors.

Secondary hypothesis 1:
We hypothesize P wave indices have significant associations with established cardiovascular risk factors, specifically hypertension, diabetes, dyslipidemia, and obesity.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

**Design:**
Longitudinal analysis utilizing baseline P-wave indices and adverse long-term outcomes in the follow-up visits of ARIC will be used to test our primary hypothesis. Cross sectional analysis will be used to examine associations and correlates of P-wave indices at the ARIC baseline visit to test the secondary hypothesis.

**Inclusion/exclusion:**
Participants with missing ECGs or with ECG conditions that interfere with calculation of P-wave indices will be excluded. This will yield a study sample 15,429 subjects, consistent with the prior analysis examining P wave indices in ARIC.18

**Variables of interest, including covariates and outcomes:**

<table>
<thead>
<tr>
<th>Clinical correlates (measured at baseline)</th>
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<tbody>
<tr>
<td>Age</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Race/Ethnicity</td>
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<tr>
<td>Site</td>
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<tr>
<td>Socioeconomic status (education, income)</td>
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<tr>
<td>Body mass index</td>
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<tr>
<td>Height</td>
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<tr>
<td>Cigarette smoking</td>
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<tr>
<td>Alcohol intake, moderate and heavy</td>
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<tr>
<td>Hypertension, use of antihypertensive medications</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Ratio of Total to HDL cholesterol</td>
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<tr>
<td>Systolic blood pressure</td>
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<tr>
<td>Diastolic blood pressure</td>
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<tr>
<td>Prior myocardial infarction</td>
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<tr>
<td>Prior stroke</td>
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<tr>
<td>Prior heart failure</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Electrocardiographic variables, including P wave indices (measured at baseline)</th>
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</thead>
<tbody>
<tr>
<td>Heart rate</td>
</tr>
<tr>
<td>PR interval</td>
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<tr>
<td>P wave duration, median</td>
</tr>
<tr>
<td>P wave amplitude (maximum)</td>
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<tr>
<td>P wave area</td>
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<tr>
<td>P wave terminal force</td>
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</tbody>
</table>
P wave dispersion (maximum - minimum)
QRS interval
Electrocardiographic LVH

Outcomes (ascertained during follow-up, using standard ARIC definitions)
Heart failure
Cardiovascular disease
Mortality

Summary of data analysis:
We will determine the distributions of P wave indices, verifying their consistency with previously published analyses using these data in ARIC. We will determine measures at baseline ECG acquisition and follow for events through the end of 2005. Multivariable Cox regression analyses will be used to assess the association of different P wave indices with the incidence of the outcomes. We will use restricted cubic splines to explore the shape of the association between different P wave indices and the different outcomes. Based on these analyses, we will categorize the P wave indices or consider them as linear exposures in the models. Initial models will adjust for age, sex, and race. In additional models, we will adjust for other potential confounders, including sociodemographic variables, cardiovascular risk factors, and other clinical variables (see table above). Sensitivity analyses will adjust for interim AF, as a potential mediator of the association between P wave indices and mortality and cardiovascular outcomes.

For the secondary hypothesis, we will be use linear regression analyses adjusted for sex, age, and standard clinical covariates to determine the association between P wave indices and clinical correlates.

In secondary analyses we will examine for effect modification by age, sex and race.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  ____ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used?  ____ Yes  ____ No
(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?  ____ Yes  ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?
 ____ Yes  ____ No
9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.csec.unc.edu/ARIC/search.php

   XXX Yes _______ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?
MS #1156 ECG prediction of atrial fibrillation and its impact on understanding the ethnic distribution of stroke in the ARIC study (Soliman). MS 1156 focused on P wave indices and the association with atrial fibrillation in ECG follow-ups and stroke incidence. The current proposal has a broader focus, including other cardiovascular outcomes in addition to stroke.

MS #1559 PR interval, P wave indices and the incidence of atrial fibrillation: the ARIC study (Alonso). MS1559 focuses specifically on the association of PR interval and P wave indices with atrial fibrillation, while the current proposal focuses on other cardiovascular outcomes, mortality and clinical correlates of P wave indices.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?   ____ Yes   XXX No

11.b. If yes, is the proposal

   ___ A. primarily the result of an ancillary study (list number* __________)

   ___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

*ancillary studies are listed by number at http://www.csec.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.
Reference List


