1.a. **Full Title**: Electrocardiographic Interatrial Block and Risk of Dementia: The Atherosclerosis Risk In Communities Study

b. **Abbreviated Title (Length 26 characters)**: Atrial block and dementia

2. **Writing Group**:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. WTO

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3. Timeline:

Analysis to begin after Publication Committee approval. Manuscript anticipated for initial P&P review 6 months after proposal approval.

4. Rationale:

Advanced interatrial block (aIAB) exists when atrial depolarization is delayed over Bachman’s bundle, and the left atrium is depolarized in a retrograde fashion by muscle connections near the coronary sinus. It manifests on the 12-lead electrocardiogram as a prolonged P-wave (≥120 ms) with biphasic morphology (±) in leads II, III, and AVF. This electrocardiographic phenotype is commonly observed in persons with underlying myocardial fibrosis and adverse remodeling of the left atrium. Accordingly, this marker is associated with an increased risk for atrial fibrillation (AF). A recent report also has linked aIAB with ischemic stroke and this relationship remained after accounting for incident AF, suggesting that aIAB is an independent risk factor for cardiac thromboembolism. The concept that AF-related complications are possible without clinical evidence of the arrhythmia (e.g., atrial cardiomyopathy) has emerged as an area of active exploration due to a potential to provide preventive therapies before AF occurrence.

Prior studies have demonstrated an association between AF and cognitive decline in stroke-free individuals. Explanations for this link have been related to the development of subclinical cerebral infarcts. Due to the known associations of aIAB with AF and stroke, it also is possible that this marker predisposes to development of dementia. A positive association between aIAB and incident dementia would further support that aIAB detects underlying left atrial pathology in which AF-related complications are later possible. Therefore, the purpose of this proposal is to examine the association between aIAB and incident dementia in the Atherosclerosis Risk In Communities (ARIC) Study.

5. Main Hypothesis/Study Questions:

The aims of this study are:

1) To examine the association of aIAB (at baseline and as a time-dependent variable) with incident dementia in ARIC.
2) To determine if AF mediates the association of aIAB with dementia.

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: Prospective cohort study.

Inclusion/Exclusion Criteria: We will include all participants with visit 1 ECG data. We will exclude participants with prevalent stroke or AF. The few ARIC participants with race other than black or white will also be excluded as well as the small number of black participants from Washington County and Minneapolis.
Outcomes: The outcome of interest will be incident dementia. A detailed summary of the adjudication of dementia has been previously reported. In ARIC, detailed in-person cognitive assessment was performed for participants of the ARIC Neurocognitive Study (ARIC-NCS) during visit 5. For those who were not able to be evaluated in person, cognitive status was assessed by telephone interview. For those evaluated by telephone, a telephonic instrument of cognitive status-modified (TICS-m) was used. Those not examined in person or unable/unwilling to participate in a phone interview, an informant interview was completed when there was suspicion of cognitive impairment or inability to rule it out: 1) follow-up interviewer suspected cognitive impairment; 2) follow-up interviewer reported hearing loss; 3) International Classification of Disease, Ninth Revision (ICD-9) dementia discharge code was present during surveillance; 4) self-report of dementia diagnosis; 5) participant’s proxy contacted in the most recent follow-up; or 6) the participant was part of an age comparable random sample of 100 participants not otherwise meeting the mentioned criteria. Incident dementia during follow-up will be defined based on information collected at visit 5, phone cognitive assessments, informant interviews, and hospital discharge diagnosis collected during follow-up.

Variables: Cases of aIAB will be identified during study visits 1-4 due to the small number of cases in the initial study visit. aIAB will be derived by the ARIC ECG Reading Center (EPICARE) and defined as a P-wave duration ≥120 ms and biphasic (positive negative) morphology in leads II, III, and AVF. Other variables needed from visit 1 will include the following: demographics (age, sex, race/ethnicity) stroke risk factors (systolic blood pressure, LDL cholesterol, body mass index, smoking, diabetes, coronary heart disease, heart failure), and baseline medication use (blood pressure lowering drugs, lipid-lowering therapies, and aspirin).

Statistics: Baseline characteristics will be examined by the presence or absence of aIAB. Categorical variables will be reported as frequency and percentage while continuous variables will be recorded as mean ± standard deviation. Follow-up will be defined as time between the baseline exam until the main outcome (incident dementia), loss to follow-up, or end of follow-up. For those with incident aIAB, time between baseline and aIAB diagnosis will be considered as non-aIAB follow-up. Kaplan-Meier estimates will be used to examine the cumulative incidence of dementia by the presence of aIAB as time-dependent variable. Cox regression will be used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association between aIAB and dementia. Multivariable models will be constructed as follows: Model 1 adjusted for age, sex, and race-center; Model 2 adjusted for Model 1 covariates plus smoking, heart rate, systolic blood pressure, diabetes, body mass index, LDL cholesterol, antihypertensive medication use, coronary heart disease, and heart failure. The variables included in the multivariable models will be from the initial study visit (visit 1), regardless of when aIAB was detected. To determine if the relationship between aIAB and dementia is mediated by AF development, an additional analysis will be performed with adjustment for incident AF. A sensitivity analysis will be performed with the outcome of interest limited to dementia ascertained for participants of ARIC-NCS who underwent detailed cognitive assessment during study visit 5. Additionally, among participants with etiologic diagnoses assigned by expert panel during visit 5, we will determine if aIAB is more strongly associated with dementia cases with primary or secondary etiologies due to Alzheimer’s disease or vascular disease, by limiting our outcome to each dementia type. A secondary analysis also will be performed that examines the
association between P-wave duration and dementia to determine if moderate levels of interatrial block are associated with dementia.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  _x_ 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 ICTDER 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  _x_ 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.cscc.unc.edu/ARIC/search.php  ____x___ 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)?

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

11.b. If yes, is the proposal
    _x__  A. primarily the result of an ancillary study (list number* __________)

2008.06  Prediction of cognitive impairment from mid-life vascular risk factors and markers: The ARIC Neurocognitive Study (ARIC-NCS) (PI: Coresh J)

    ___  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.cscc.unc.edu/aric/forms/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload

References