ARIC Manuscript Proposal #3501

1.a. Full Title: Subclinical and Clinical Cardiovascular Disease and Physical Function in Older Adult Participants of the Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): Subclinical Cardiovascular Disease and Physical Function in ARIC

2. Writing Group:
   Writing group members: Stephen P Juraschek, Natalie Daya, Kunihiro Matsushita, Pamela Lutsey, B. Gwen Windham, Christie M. Ballantyne, Elizabeth Selvin, others welcome

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

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3. Timeline: Data analysis to begin after approval of this manuscript proposal. First draft should be available March, 2020.
4. **Rationale:**

Falls represent a significant, preventable cause of morbidity and mortality among older adults. Nearly one third of persons aged 65 or older falls yearly and the death rate from falls in the United States is rising.\(^1\)–\(^3\) Falls are a major reason for emergency room visits,\(^9\) and cost the US health system over $23 billion yearly.\(^5\) Older adults frequently do not recover from falls, resulting in persistent disability and premature death.\(^1\),\(^2\) Given the aging US population, identifying mechanisms by which falls occur and interventions to prevent falls represents a significant public health priority.

**CVD is itself an important, albeit controversial, risk factor for falls.** Multiple observational studies have demonstrated that CVD is associated with a higher risk of falls\(^16\),\(^17\) and fall risk factors.\(^18\) However, this has not been observed in all studies.\(^19\) One potential reason for these inconsistencies could be the classification of CVD as the presence or absence of clinical, self-reported CVD (prior diagnoses or events) rather than as a continuum of disease.\(^20\) This leads to misclassification, particularly among the group “without CVD.”

**There is a dearth of studies delineating how CVD might contribute to the pathogenesis of falls.** Despite many studies demonstrating an association between CVD and falls,\(^21\) insights on how CVD might cause falls are lacking. Several studies attribute the association between CVD and falls to syncope, as syncope is related to CVD and is often considered equivalent to falls in clinical settings.\(^20\) However, CVD influences multiple pathways that are related to falls. The cardiovascular system is responsible for augmenting cardiac output in the process of standing, increasing blood flow to peripheral muscle, sustaining adequate blood supply throughout physical activity, and stabilizing BP for cerebral perfusion, necessary for balance.\(^22\) CVD adversely affects these processes,\(^23\) which are critical for maintaining stable posture and preventing falls.

**High sensitivity cardiac troponin T and N-terminal pro b-type natriuretic peptide are novel markers of subclinical cardiac damage and strain, and highly effective means of characterizing subclinical CVD.** Subclinical CVD is highly prevalent in older adults and self-reported history of CVD misclassifies undetected CVD in older populations. Novel markers of cardiac injury and strain can help characterize cardiac disease in adults with both known and unknown CVD.

**High sensitivity cardiac troponin T** (hs-cTnT) is a biomarker of myocardial damage that measures structural proteins contained in cardiac muscle cells (myocytes), which increase in blood after cell death.\(^24\) As a specific marker of myocyte necrosis, the newest generation of highly sensitive assays can more quickly and accurately diagnose disease activity in adults with known CVD than standard assays.\(^25\),\(^26\) Furthermore, in asymptomatic populations without known atherosclerotic CVD, hs-cTnT is a strong predictor of incident heart failure, fatal CVD, and all-cause mortality, independent of other CVD risk factors.\(^27\)–\(^29\)

**N-terminal pro b-type natriuretic peptide** (NT-proBNP) is an important marker of cardiac wall strain, considered the “gold standard” biomarker in heart failure.\(^30\) NT-
proBNP is a hormonal byproduct secreted by the atrium in response to cardiac wall stretch, inflammation, and hypertrophy. Levels rise with greater ventricular volume as well as acute myocardial infarction, heart failure, diastolic dysfunction, and asymptomatic left ventricular systolic dysfunction. Beyond its utility among adults with known CVD, long-term observational studies have demonstrated strong associations between NT-proBNP and CVD risk in asymptomatic adults without heart failure.

We have recently shown a strong relationship between hs-cTNT and NT-proBNP and falls (manuscript under review, see Figure). However, pathways that might mediate the relationship between subclinical CVD and falls are unknown.

Study objectives
Thus, the objective of this study is to study the associations of 2 markers of subclinical cardiovascular disease, hs-cTnT and NTproBNP, with measures of physical functioning in participants who attended ARIC visit 5. Physical functioning will be characterized using measures of grip strength, 4-meter usual gait speed, balance, and SPPB score (a summary of gait speed, balance, and chair stand maneuvers). We will examine the cross-sectional associations between subclinical CVD markers with these measures of physical functioning and determine whether subclinical cardiovascular disease is associated with falls independently of these characteristics of physical function.

The ARIC population is ideal to address this question because of the availability of these two markers at visit 5, the physical function measures, and linkage with CMS claims, which included fall events. Furthermore, the comprehensive assessments in ARIC afford the opportunity to address numerous confounding variables that may be related to both CVD and falls.

5. Main Hypothesis/Study Questions:

Primary study questions:
1. Are hs-cTnT concentrations measured at visit 5 associated with measures of physical function in ARIC?
2. Are NTproBNP concentrations measured at visit 5 associated with measures of physical function in ARIC?
3. Are hs-cTnT and NTproBNP concentrations measured at visit 5 associated with measures of physical function in ARIC independently of each other?
4. Are markers of subclinical CVD relationships with falls mediated by measures of physical function?

Hypotheses:
1. Higher concentrations of markers of subclinical cardiovascular injury, strain, and inflammation will be associated with reduced grip strength, slower gait speed, and poor balance.
2. The association between subclinical markers of cardiovascular disease with falls will be attenuated by adjustment for physical function as these mediate the relationship between subclinical CVD and falls.

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).

Study design: Cross-sectional study and prospective cohort study with visit 5 as baseline

Exclusions:
- ARIC participants without hs-cTnT or NTproBNP measured at visit 5
- Missing covariates of interest
- Persons of ethnicity other than African American or white
- African-Americans from Washington County or Minnesota
- Persons with prevalent CHD, CHF, or stroke

Exposure assessment:
Hs-cTnT concentrations were measured in plasma specimens from ARIC visit 5 (2011-2013) with a detection limit of 6 ng/L (Elecsys Troponin T; Roche Diagnostics, Indianapolis, IN). Hs-cTnT will be categorized, approximating quartiles, as follows: <8, 8-10, 11-16, ≥17 ng/L. NT-proBNP was measured using electrochemiluminescent immunoassay (Roche Diagnostics) with a detection limit of 5 pg/mL. NT-proBNP was categorized in the following manner, also approximating quartiles: <75, 75-124.9, 125-274.9, and ≥275 pg/mL. The interassay coefficient of variance for hs-cTnT was 6.4% (at a mean control of 29 ng/L). The interassay coefficient of variance for NT-proBNP was 7.4% (at a mean control of 134 pg/mL).

Primary and secondary outcome: Falls and Syncope
Falls will be defined at the first occurrence of any related hospitalization or claim for inpatient or outpatient services after the baseline visit. These outcomes were identified via two sources: 1) active surveillance of all hospitalizations for all ARIC participants; and 2) linkage to Centers for Medicare and Medicaid Services (CMS) claims data from 1991-2013.40,41
The ARIC Study obtains hospitalization information from annual telephone contact with study participants and through surveillance of hospitals in the study communities (inpatient hospitalization data currently available from January 1st, 1988, through December 31, 2015). In the original ARIC protocol, surveillance was primarily focused on coronary heart disease, stroke, and heart failure outcomes, but thereafter included other diagnostic codes for hospitalized events, including those attributed to fall, fracture, syncope, and motor vehicle accidents.

Participant data were also linked to CMS claims data using a finder file that included participants’ social security numbers, sex, and date of birth through a matching process described previously. These claims were available for eligible persons derived from two forms of coverage: (1) fee-for-service (FFS) or (2) managed care organizations. CMS data included inpatient and outpatient claims for participants enrolled in FFS continuously after reaching CMS Medicare eligibility and those with intermittent FFS enrollment during the period of observation. While no outpatient claims were available for cohort participants enrolled in managed care programs, inpatient claims were available for all participants with Medicare on a selective basis from the year 2008 onward.

MedPar files were used to identify inpatient CMS records for hospital encounters related to falls, fractures, syncope, and motor vehicle accidents. Outpatient falls and motor vehicle accidents were identified using the Clinical Classification System (CCS) category 2603, E codes, which were based on International Classification of Diseases, 9th revision (ICD-9) external cause of injury codes. Falls were identified using the following ICD9 codes: E880.X-E888.X.

Other variables of interest:
Models will be adjusted for age, sex, race-study center, body mass index, resting heart rate, high density lipoprotein cholesterol, total cholesterol, cholesterol lowering medications, hypertension, anti-hypertensive medication use in the past 2 weeks, estimated glomerular filtration rate, alcohol use, education, leisure activity, smoking status, antidepressant use, sedative use, hypnotic use, antipsychotic use, and anticholinergic use.

Data analysis:
Our primary analyses will be as follows:

- Cross-sectional examination of baseline characteristics (Table 1).
  - Means, proportions
- Association of quartiles of hs-TnT or NT-proBNP with grip strength, gait speed, balance, and SPPB score<7 (Table 2)
  - Models by outcome:
    - Linear regression: grip strength (kg), 4-meter walk speed (sec)
    - Logistic regression: poor balance (score <7)
Logistic regression: low overall SPPB score < 7 (dichotomous 0 or 1)
- Model covariates:
  - Unadjusted
  - Minimally adjusted: age/sex/race adjusted
  - Fully adjusted (details above)
- Characterization of association between hs-TnT or proBNP with falls fully adjusted restricted cubic splines (Figure 1 A-B); 4 knots will be selected via Harrell’s method; histogram of values by outcome status will overlay each figure; splines will be centered at the median values for hs-TnT or NT-proBNP
- Association of quartiles of hs-TnT or NT-proBNP with change in grip strength, gait speed, balance, and total SPPB score (Table 3) between visits 5 and 6
  - Linear regression
  - Fully adjusted models
  - Linear regression for change in grip strength, 4-m gait speed, change in SPPB total score
- Association of quartiles of hs-TnT or NT-proBNP with falls adjusted for physical function assessed at visit 5 (Table 4)
  - Absolute risk: age/sex/race adjusted cumulative incidences
  - Cox proportional hazard models:
    - Adjusted for each individual physical function component
    - Adjusted for all components
- Supplemental analysis: association of grip strength, 4-m gait speed, balance, low SPPB (and total score) with cardiovascular events using Cox models fully adjusted for covariates above (Supplement Table 1)
- Supplemental analysis: will examine change in hs-TnT or NT-proBNP between visits 5 and 6 as well; this analysis may be more principal if there is not too much attrition between visits

Limitations:
- Insensitive event ascertainment (falls)
- Hs-TnT and proBNP are not available on all participants
- Change in grip strength, gait speed, balance, and total SPPB score are not available in all people
- Residual confounding is always a concern with observational studies.

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.cscce.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)?

Here are the most relevant approved proposal related to our proposed study:

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Proposal Title</th>
<th>Author(s)</th>
<th>Hits</th>
<th>Size</th>
<th>Date</th>
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<tbody>
<tr>
<td>00%</td>
<td>Orthostatic Hypotension and Risk of Falls in the Atherosclerosis Risk in Communities Study (ARIC)</td>
<td>Stephen P Juraschek</td>
<td>42</td>
<td>327k</td>
<td>9/2/2015</td>
</tr>
<tr>
<td>98%</td>
<td>Falls Prevalence in Older Black and White ARIC Participants</td>
<td>Lisa A Pompeii</td>
<td>40</td>
<td>192k</td>
<td>6/6/2014</td>
</tr>
<tr>
<td>93%</td>
<td>Severe Hypoglycemia and Risk of Falls in Type 2 Diabetes: the Atherosclerosis Risk in Communities (ARIC) Study</td>
<td>Alexandra Lee</td>
<td>42</td>
<td>344k</td>
<td>2/1/2018</td>
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<tr>
<td>60%</td>
<td>Trajectories of physical activity in mid-life and risk of functional decline and falls in later life</td>
<td>Kelley Pettee Gabriel</td>
<td>18</td>
<td>104k</td>
<td>7/22/2015</td>
</tr>
<tr>
<td>57%</td>
<td>Association of Fasting Glucose and Diabetes with Orthostatic Hypotension, Falls, and Syncope in the ARIC Study</td>
<td>Stephen Juraschek</td>
<td>42</td>
<td>334k</td>
<td>7/1/2015</td>
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</table>

Here are recent ARIC manuscripts, relevant to the current proposal:


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
   ___  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.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 manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript __x__ Yes ____ No.
References


