ARIC Manuscript Proposal # 3221

PC Reviewed: 08/14/18   **Status: _____**   **Priority: 2**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title: Subclinical Cardiovascular Disease, Falls, and Syncope in the Atherosclerosis Risk in Communities Study (ARIC)

  b. Abbreviated Title (Length 26 characters): Subclinical Cardiovascular Disease, Falls, and Syncope in ARIC

2.   Writing Group:
Writing group members: Stephen P Juraschek, Natalie Daya, Lawrence Appel, Edgar Miller, Kunihiro Matsushita, Erin D Michos, 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 December, 2018.

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,[4] 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.

Concern about fall risk complicates cardiovascular disease (CVD) treatment for older adults. CVD is highly prevalent among older adults.[6] Some CVD treatments are believed to contribute to falls and fall severity, including treatment with antihypertensive drugs for hypertension and blood thinning agents for thromboembolic conditions.[7–10] Concerns about falling have led to pronounced disagreements in blood pressure (BP) treatment guidelines.[11] Similarly, prior falls or higher perceived risk of falling influences views on blood thinning agents (anti-platelet therapy, anticoagulation) in older adults, due to bleeding risk.[12,13] In fact, concern about fall risk has been one of the most cited reasons for clinicians not to prescribe blood thinning agents in the setting of a cardiovascular indication such as stroke from atrial fibrillation.[14,15] Clinical decisions to curtail CVD treatment based on fall risk might have important consequences, including an increased risk of falls if the cause of falls is CVD.

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 reasons for inconsistencies in the literature is due to CVD being characterized based on 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.

Novel markers of subclinical cardiac damage, strain, and inflammation, high sensitivity cardiac troponin T and N-terminal pro b-type natriuretic peptide are 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.[30,31] Levels rise with greater ventricular volume as well as acute myocardial infarction,[32] heart failure,[33] diastolic dysfunction,[34] and asymptomatic left ventricular systolic dysfunction.[35] 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.[36]

Study objectives
Thus, the objective of this study is to study the relationship between 3 markers of subclinical cardiovascular disease, hs-cTnT and NTproBNP with incident falls in middle-aged participants of the ARIC study. We will secondarily evaluate the association of these markers with syncope, given that the clinical billing overlap between these conditions.

The ARIC population is ideal to address this question because of the availability of all three of these markers at visit 2, its long-term follow-up, and linkage with CMS claims, which included multiple fall and syncope 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 2 associated with incident falls in ARIC?
2. Are NTproBNP concentrations measured at visit 2 associated with incident falls in ARIC?

Secondary study questions:
1. Are hs-cTnT concentrations measured at visit 2 associated with incident syncope in ARIC?
2. Are NTproBNP concentrations measured at visit 2 associated with incident syncope in ARIC?

Hypotheses:
1. Higher concentrations of markers of subclinical cardiovascular injury, strain, and inflammation will be associated with higher risk of falls.
2. Higher concentrations of markers of subclinical cardiovascular injury, strain, and inflammation will be associated with higher risk of syncope.

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: Prospective cohort study with visit 2 as baseline

Exclusions:
- ARIC participants without hs-cTnT or NTproBNP measured at visit 2
- Missing covariates of interest
- Persons of ethnicity other than African American or white
- African-Americans from Washington County or Minnesota

Exposure assessment:
High sensitivity troponin T (hs-cTnT) and N-terminal pro b-type natriuretic peptide (NTproBNP) concentrations were measured in stored serum specimens from ARIC visit 2 (1990-1992) using a Roche Elecsys 2010 Analyzer (Roche Diagnostics Corp) at the University of Minnesota. The troponin assay has a measurement range of 3 ng/L to 100,000 ng/mL. Inter-assay CVs were 6.0% at a mean hs-cTnT concentration of 25 ng/L and 3.7% at 1,940 ng/L. A detectable hs-cTnT will be defined as a value ≥5 ng/L. With regards to NTproBNP, the measurement range was 5 to 35,000 pg/mL with CVs of 3.5% to 4.7%. We will define an elevated NTproBNP as ≥100 pg/mL. We will use a detectable hs-cTnT and elevated NTproBNP based on prior literature suggesting that detectable hs-cTnT is associated with underlying cardiac damage while elevated NT-proBNP is associated with cardiac wall strain.[37–39]

Concentrations will also be modeled as continuous values with an intermediary value imputed for values that were undetectable (e.g. 2.5 ng/L for hs-cTnT).

Primary and secondary outcome: Falls and Syncope
Falls or syncope 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.[40,41] 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 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. Syncope was defined by code: 780.2.

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 use in the past 2 weeks, estimated glomerular filtration rate, alcohol use, education, leisure activity, smoking status, previous CHD, previous stroke, previous heart failure, 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 hs-TnT with falls or syncope (**Table 2**)
  - Absolute risk: age/sex/race adjusted cumulative incidences
  - Relative risk:
    - Cox Proportional Hazard Models:
      - Unadjusted
      - Minimally adjusted: age/sex/race adjusted
      - Fully adjusted (details above)
      - Exposure will be characterized as a dichotomous (detectable hs-TNT) and continuous variable
    - Characterization of risk between hs-TnT with falls or syncope using 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

- Association of NTproBNP with falls or syncope (**Table 3**)
  - o Absolute risk: age/sex/race adjusted cumulative incidences
  - o Relative risk:
    - Cox Proportional Hazard Models:
      - Unadjusted
      - Minimally adjusted: age/sex/race adjusted
      - Fully adjusted (details above)
      - Exposure will be characterized as a dichotomous (elevated NTproBNP) and continuous variable
    - Characterization of risk between NTproBNP with falls or syncope using fully adjusted restricted cubic splines (**Figure 2 A-B);** 4 knots will be selected via Harrell's method; histogram of values by outcome status will overlay each figure
- Stratified analysis of the 2 markers by the following: age, sex, race, visit 2 hypertension status, visit 2 CHD history, visit 2 diabetes status, obesity (**Supplement Table 1**)

Limitations:
- Insensitive event ascertainment (falls, syncope)
- Hs-TnT and proBNP are not available on all participants
- 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.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)?

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

00% Orthostatic Hypotension and Risk of Falls in the Atherosclerosis Risk in Communities Study (ARIC) Stephen P Juraschek
Hits_42 | Size_327k | 9/2/2015

98% Falls Prevalence in Older Black and White ARIC Participants Lisa A Pompeii
Hits_40 | Size_192k | 6/6/2014

93% Severe Hypoglycemia and Risk of Falls in Type 2 Diabetes: the Atherosclerosis Risk in Communities (ARIC) Study Alexandra Lee
Hits_42 | Size_344k | 2/1/2018

60% Trajectories of physical activity in mid-life and risk of functional decline and falls in later life Kelley Pettee Gabriel
Hits_18 | Size_104k | 7/22/2015

57% Association of Fasting Glucose and Diabetes with Orthostatic Hypotension, Falls, and Syncope in the ARIC Study Stephen Juraschek

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

Juraschek SP, Daya N, Appel LJ, et al. Orthostatic Hypotension in Middle-Age and Risk of Falls. *Am J Hypertens*. 2017;30(2):188-195. doi:10.1093/ajh/hpw108

Juraschek SP, Daya N, Appel LJ, et al. Orthostatic Hypotension and Risk of Clinical and Subclinical Cardiovascular Disease in Middle-Aged Adults. *Journal of the American Heart Association*. 2018;7(10):e008884. doi:10.1161/JAHA.118.008884

Liang M, McEvoy JW, Chen Y, Sharrett AR, Selvin E. Association of a Biomarker of Glucose Peaks, 1,5-Anhydroglucitol, With Subclinical Cardiovascular Disease. Diabetes Care. 2016;39(10):1752-1759. doi:10.2337/dc16-0840

McEvoy JW, Chen Y, Ndumele CE, et al. Six-Year Change in High-Sensitivity Cardiac Troponin T and Risk of Subsequent Coronary Heart Disease, Heart Failure, and Death. JAMA Cardiol. 2016;1(5):519-528. doi:10.1001/jamacardio.2016.0765

McEvoy JW, Chen Y, Rawlings A, et al. Diastolic Blood Pressure, Subclinical Myocardial Damage, and Cardiac Events: Implications for Blood Pressure Control. J Am Coll Cardiol. 2016;68(16):1713-1722. doi:10.1016/j.jacc.2016.07.754

Ndumele CE, Matsushita K, Sang Y, et al. N-Terminal Pro-Brain Natriuretic Peptide and Heart Failure Risk Among Individuals With and Without Obesity: The

Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2016;133(7):631-638. doi:10.1161/CIRCULATIONAHA.115.017298

Walker KA, Walston J, Gottesman RF, Kucharska-Newton A, Palta P, Windham BG. Midlife Systemic Inflammation is Associated with Frailty in Later Life: The ARIC Study. J Gerontol A Biol Sci Med Sci. 2018 Mar 9. doi: 10.1093/gerona/gly045

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.

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