ARIC Manuscript Proposal #2871

PC Reviewed: 10/11/2016 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:
Cardiac Markers and Risk for Hospitalization with Infection: The Atherosclerosis Risk in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters):
Cardiac markers & infection

2. Writing Group:
Writing group members:
Junichi Ishigami, Aaron Folsom, Josef Coresh, Elizabeth Selvin, Kunihiro Matsushita, others welcome

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

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3. Timeline:
Data ascertainment for the present study has been already completed. Data analysis and manuscript preparation will be done in the next 6 months.

4. Rationale:

Infectious disease is a major cause of hospitalization[1] and poses a significant social and economic burden.[2] Cardiac disease is highly prevalent (>50%) among patients hospitalized with infection.[3] Epidemiological studies have shown that risk of infection was significantly increased among persons with history of coronary heart disease[4,5] and heart failure.[5,6] However, patients with clinical cardiac diseases are under intensive clinical managements (e.g., invasive procedures, implantation of stent and pacemaker, and polypharmacy), which may confound this association. To better understand this pathophysiological link, therefore, it would be of value to explore whether subclinical cardiac abnormality is associated with future risk of infection.

Thus, we will explore the association of cardiac troponin T (cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) with risk of hospitalization with infection in a bi-ethnic community-based cohort, the Atherosclerosis Risk in Communities (ARIC) study. Since inflammation plays an important role in the pathogenesis of cardiovascular disease (CVD) [7,8] and may contribute to the link between cardiac abnormality and infection, we will account for high sensitivity C-reactive protein (hsCRP) in our analysis and contrast cTnT, NT-proBNP, and hsCRP regarding their associations with infection.

5. Main Hypothesis/Study Questions:

Elevated levels of cardiac markers are associated with risk for hospitalization with infection

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).

Inclusion criteria

- All ARIC study participants whose cTnT, NT-proBNP, and hsCRP levels were measured at visits 2 and/or 4
- White and black participants.

Exclusion criteria

- History of clinical cardiac disease (coronary heart disease or heart failure) or infection-related hospitalization prior to visit of interest.
- Non-black/non-white participants

Exposures

- Cardiovascular disease-related biomarkers
  - cTnT
  - NT-proBNP
  - hsCRP

Outcome

Primary outcome

- Incidence of all-cause hospitalization with infection,[9] defined as ICD-9 codes indicating any pathogen-, organ- symptom-based diagnoses of infectious

disease[10] (ICD codes: 001–139, 254.1, 320–326, 331.81, 372–372.39, 373.0–373.2, 382–382.4, 383, 386.33, 386.35, 388.60, 390–393,421–421.1, 422.0, 422.91–422.93, 460–466, 472–474.0,475–476.1, 478.21–478.24, 478.29, 480–490, 491.1, 494,510–511, 513.0, 518.6, 519.01, 522.5, 522.7, 527.3, 528.3,540–542, 566–567.9, 569.5, 572–572.1, 573.1–573.3,575–575.12, 590–590.9, 595–595.4, 597–597.89, 598.0,599.0, 601–601.9, 604–604.9, 607.1, 607.2, 608.0, 608.4,611.0, 614–616.1, 616.3–616.4, 616.8, 670, 680–686.9,706.0, 711–711.9, 730–730.3, 730.8–730.9, 790.7–790.8,996.60–996.69, 997.62, 998.5, and 999.3 [details in Supplemental table 1 on pages 7-8])

- A priori determined four major causes of infection
  - Pneumonia (ICD9, 480-486)
  - Kidney and urinary tract infections (590, 590.0-4, 597, 598, 599.0, 601, 604, 607, and 608)
  - Septicemia and bacteremia (038 and 790.7)
  - Cellulitis (681 and 682)

Secondary outcome

- Incidence of hospitalization with systemic inflammatory response syndrome (ICD-9, 995.9X)
- Event rate ratio of infection-related hospitalization accounting for multiple events.
- Infection-related mortality, defined as in-hospital death or death within 30 days after discharge of infection-related hospitalization

Sensitivity analysis

- Outpatient infection events using the same ICD-9 codes from the CMS data in participants aged 65 years or older with relevant data.

Other variables of interest and covariates:

- Estimated glomerular filtration rate using serum creatinine and cystatin C
- Age
- Gender
- Race
- Body mass index (BMI)
- Sitting blood pressure (systolic and diastolic)
- Smoking status
- Alcohol consumption
- Years of education from visit 1
- Kidney measures
  - GFR as estimated by CKD-EPI equation using serum creatinine and cystatin C[11]
  - Urinary ACR (visit 4)
- Medication use
  - Anti-neoplastic agents
  - Steroids
- Medical history
  - Diabetes (DM)

- Hypertension (HTN)
- Chronic obstructive pulmonary disease (COPD)
- Cancer
- Prior stroke

- Incident clinical event during follow-up
  - Clinical coronary heart disease and heart failure

Statistical Analysis Plan:

- Baseline characteristics will be compared across quantile of CVD-related biomarkers using chi-square tests and analysis of variance.
- Incidence rate and its 95% confidence interval will be estimated using Poisson regression models
- Relative risk using Cox proportional hazards models
- Models will be adjusted for potential confounders
  -Age, sex, race, BMI, smoking status, alcohol consumption, education level, medication use of anti-neoplastic agents and steroids, and history of HTN, DM, COPD, cancer, and stroke, and eGFR/ACR.
- Sensitivity analyses
  - Subgroup analysis by age (60+ vs. <60 years), sex (men vs. women), race (white vs. black), reduced kidney function (eGFR 60+ vs. <60 ml/min/1.73m^2), DM (yes vs. no)
  - Restricting infection related hospitalization to the primary diagnosis
  - Additional adjustment for incident ESRD as a time-varying exposure
  - Risk for non-infection related hospitalization according to bone-mineral metabolism markers (to evaluate whether their associations are unique to infection-related hospitalizations)
  - Including outpatient infection events using CMS data

Limitations

- Outcome ascertainment relying on ICD-9 codes may lead to misclassification
- Mild cases of infection not requiring hospitalization may not be captured
  - CMS data could be used to include outpatient infection events in a subset of persons aged 65+, although the number of individuals aged 65+ years at visit 2 may be limited
- Possibility of residual confounding may not be excluded.

7.a. Will the data be used for non-CVD analysis in this manuscript? _X_ 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? __ X __ 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)?
To our knowledge, there is no other ARIC proposal focusing on the association between CVD-related biomarkers and infection.

MP 1837 proposed in 2011 "Clinical Risk Factors and Biomarkers to Predict Risk of Hospitalization With Pneumonia: Analyses of Three Multicenter Cohorts" explored the prediction model for hospitalization with pneumonia, and assessed the association of CRP with risk of pneumonia. The primary exposures in the present proposal will be cardiac biomarkers (cTnT and NTprBNP). The author of MP2837, Aaron Folsom, is included in the present proposal.

MP 1960 proposed in 2012 "Association between pneumonia hospitalization and acute cardiovascular events" assessed the association of pneumonia hospitalization with subsequent risk of cardiovascular events. The present proposal will focus on the association of cardiac biomarkers with risk of hospitalization with infection. In addition, the author of MP 1960, Aaron Folsom, is included in the present proposal.

MP 2624 proposed in 2015 "Chronic Kidney Disease and Risk for Infection-Related Hospitalization: The Atherosclerosis Risk in Communities (ARIC) Study" assessed the association of CKD with risk for infection. The primary exposures of interest in the present study will be CVD-related biomarkers though we will adjust for eGFR and ACR. Most of the authors of MP2624 including the first author are included in 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

_X_ A. primarily the result of an ancillary study (list number* _ 2002.02, 2009.17 __)

__ 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.

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Supplemental table 1: Cause of the infection and ICD-9-CM codes

ICD-9	Referred disease description
001–139	Infectious and parasitic diseases
254.1	Abscess of thymus
320–326	Diseases of the nervous system
331.81	Rye's syndrome
372–372.39	Conjunctivitis
373.0–373.2	Inflammation of eyelids (Blepharitis, Chalazion)
382–382.4	Suppurative and unspecified otitis media
383	Mastoiditis
386.33	Suppurative labyrinthitis
386.35	Viral labyrinthitis
388.6	Otorrhea
390–393	Rheumatic Fever
421–421.1	Acute and subacute endocarditis
422	Acute myocarditis
422.91–422.93	Acute myocarditis, idiopathic
460–466	Acute respiratory infections
472–474.0	Chronic pharyngitis and nasopharyingitis
475–476.1	Peritonsillar abscess
478.21–478.24	Other diseases of upper respiratory tract
478.29	Other diseases of upper respiratory tract
480–490	Pneumonia and influenza (480–488), Bronchitis, not specified as acute or chronic (490)
491.1	Mucopurulent chronic bronchitis
494	Bronchiectasis
510–511	Empyema (510) and pleurisy (511)
513	Abscess of lung and mediastinum
518.6	Allergic bronchopulmonary aspergillosis
519.01	Infection of tracheostomy stoma
522.5	Periapical abscess without sinus
522.7	Periapical abscess with sinus
527.3	Abscess of salivary gland
528.3	Cellulitis and abscess of oral soft tissues
540–542	Appendicitis
566–567.9	Abscess of anal and rectal regions
569.5	Abscess of intestine
572–572.1	Liver abscess and sequelae of chronic liver disease
573.1–573.3	Hepatitis, toxic

575–575.12	Other disorders of gallbladder
590–590.9	Infections of kidney
595–595.4	Cystitis
597–597.89	Urethritis, not sexually transmitted, and urethral syndrome
598	Stricture, urethral, unspecified infection
599	Urinary tract infection, unspecified/pyuria
601–601.9	Inflammatory diseases of prostate
604–604.9	Orchitis and epididymitis
607.1	Balanitis
607.2	Other inflammatory disorders of penis
608	Seminal vesiculitis
608.4	Other inflammatory disorders of male genital organs
611	Inflammatory disease of breast
614–616.1	Inflammatory disease of ovary fallopian tube pelvic cellular tissue and peritoneum
616.3–616.4	Abscess of Bartholin's gland, Other abscess of vulva
616.8	Other specified inflammatory diseases of cervix vagina and vulva
670	Major puerperal infection
680–686.9	Infections of skin and subcutaneous tissue
706	Acne varioliformis
711–711.9	Arthropathy associated with infections
730–730.3	Osteomyelitis, periostitis, and other infections involving bone
730.8–730.9	Osteomyelitis, periostitis, and other infections involving bone
790.7–790.8	Bacteremia (not septicemia), Viremia, unspecified
996.60–996.69	Infection and inflammatory reaction due to internal prosthetic device implant and graft
997.62	Infection of amputation stump, unspecified extremity
998.5	Postoperative infection not elsewhere classified
999.3.	Other infection due to medical care not elsewhere classified