ARIC Manuscript Proposal # 2894

PC Reviewed: 11/08/16 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:
Infection as a trigger for CVD in the ARIC cohort

b. Abbreviated Title (Length 26 characters):
Infection and CVD

2. Writing Group:
Writing group members:
Logan Cowan
Pamela Lutsey
Kunihiro Matsushita
Junuchi Ishigami
Kamakshi Lakshminarayan
James Pankow

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

First author: Logan Cowan
Address:

Div. Epidemiology & Community Health
1300 S. 2nd Street, Suite 300
Minneapolis MN 55454 United States

Phone: 612-624-5238 Fax: 612-624-0315
E-mail: cowan046@umn.edu

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: James Pankow
Address:

Div. Epidemiology & Community Health
1300 S. 2nd Street, Suite 300
Minneapolis MN 55454 United States

Phone: 612-624-2883 Fax: 612-624-0315
E-mail: panko001@umn.edu

3. Timeline:

Obtain data set: Fall 2016
Complete statistical analysis: Winter 2016/2017
Complete manuscript: Summer 2017

4. Rationale:
Population-based cohort studies have identified many long-term risk factors for cardiovascular disease (CVD) that are both modifiable, like high blood pressure, elevated serum cholesterol, and smoking, and non-modifiable, like male sex, non-white race, family history, and greater age.[1, 2] Short-term risk factors—or triggers—of CVD have received less research attention. Identifying and understanding CVD triggers offer potential strategies for CVD prevention during periods of vulnerability.

A number of previous studies have shown that infection triggers acute CVD events including MI[3-5], stroke[3, 6, 7], and VTE.[8] While the results of these studies are informative, most previous studies only included hospitalized infections as their exposure of interest. Further, the magnitude and duration of increased cardiovascular risk has varied greatly between studies and remains under debate.

We propose to use the longitudinal data from ARIC and the corresponding participant outpatient CMS data to examine the relationship between infection, both inpatient and outpatient and CVD.

5. Main Hypothesis/Study Questions:
We hypothesize that there is an independent association between infection and CVD risk.

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:
We will use a case-crossover study design in which ARIC participants with CVD outcomes will serve as their own controls. The occurrence of infection immediately prior to CVD events will be compared with preceding time intervals of 1 year and 2 years prior to the event.

Inclusion/Exclusion:
All ARIC participants with each outcome during follow-up will be included. We will use CMS data to identify outpatient infections in ARIC study participants. Outpatient infections identified through CMS claims for outpatient services are available since 1991. We will exclude individuals who are younger than 65 years of age at the time of the CVD event or the matched control periods since they are not Medicare eligible for both the case and control periods. We will also exclude participants whose CVD events occurred prior to 1993 to ensure that CMS data are available for both case and control periods.

Exposure/Outcome:
The exposure of interest is infection determined using ICD-9 codes. Inpatient hospitalization codes and outpatient visit codes will be used to identify infections. The following codes for infection will be included:

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

The outcomes of interest are incident CHD, ischemic stroke, and VTE. The methods used for ascertainment of outcomes included: (1) participants were contacted annually by phone and interviewed about interim hospitalizations; (2) local hospitals provided lists of hospital discharges with cardiovascular diagnoses, and these were reviewed to identify cohort hospitalizations; and (3) health department death certificate files were continuously surveyed. All discharge codes for cohort hospitalizations and listed causes of death from death certificates were recorded.

Incident CHD is identified as a confirmed CHD death and fatal and nonfatal myocardial infarction.[9]

Incident ischemic stroke was identified and classified as thrombotic or cardioembolic stroke based on discharge codes, signs, symptoms, neuroimaging (computerized tomography/magnetic resonance imaging), and other diagnostic reports.[10]

Incident VTE was defined as all PEs and DVTs occurring in the legs and was identified using diagnosis codes, hospital records, physician and consultant reports, discharge summaries, and vascular and radiologic imaging, and was validated according to LITE study protocol.[11]

Each outcome will be analyzed separately. Separate manuscripts may be pursued based on the results of the analyses.

Analysis:
The prevalence of infection 14, 30, 42, and 90 days before CVD events will be compared with the corresponding time periods exactly 1 year and 2 years before the event. Conditional logistic regression will be used to estimate odds ratios (OR) of CVD events and 95% confidence intervals (CIs) for each time period (14, 30, 42, and 90 days).

Separate models will be run using all infections (both inpatient and outpatient) and outpatient infections only to see if the magnitude of the association differs between infection type. We will further explore the association between different types of infection (eg, pneumonia) and our CVD outcomes to see if the association differs by infection type.

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)?
#2391 - Hospitalized infection as a trigger for acute ischemic stroke in the ARIC study
#2663 - Hospitalization with Infection and Incident Venous Thromboembolism: The ARIC Study

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

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study (list number* ___1996.01_____)
___ 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, approved manuscripts using 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.

1. Arnold AM, Psaty BM, Kuller LH, Burke GL, Manolio TA, Fried LP, et al. Incidence of cardiovascular disease in older americans: The cardiovascular health study. *Journal of the American Geriatrics Society*. 2005;53:211-218
2. Wattanakit K, Folsom AR, Chambless LE, Nieto FJ. Risk factors for cardiovascular event recurrence in the atherosclerosis risk in communities (aric) study. *American heart journal*. 2005;149:606-612
3. Dalager-Pedersen M, Sogaard M, Schonheyder HC, Nielsen H, Thomsen RW. Risk for myocardial infarction and stroke after community-acquired bacteremia: A 20-year population-based cohort study. *Circulation*. 2014;129:1387-1396
4. Warren-Gash C, Hayward AC, Hemingway H, Denaxas S, Thomas SL, Timmis AD, et al. Influenza infection and risk of acute myocardial infarction in england and wales: A caliber self-controlled case series study. *The Journal of infectious diseases*. 2012;206:1652-1659
5. Nawrot TS, Perez L, Kunzli N, Munters E, Nemery B. Public health importance of triggers of myocardial infarction: A comparative risk assessment. *Lancet*. 2011;377:732-740
6. Cowan LT, Alonso A, Pankow JS, Folsom AR, Rosamond WD, Gottesman RF, et al. Hospitalized infection as a trigger for acute ischemic stroke: The atherosclerosis risk in communities study. *Stroke; a journal of cerebral circulation*. 2016;47:1612-1617
7. Elkind MS, Carty CL, O'Meara ES, Lumley T, Lefkowitz D, Kronmal RA, et al. Hospitalization for infection and risk of acute ischemic stroke: The cardiovascular health study. *Stroke; a journal of cerebral circulation*. 2011;42:1851-1856
8. Rogers MA, Levine DA, Blumberg N, Flanders SA, Chopra V, Langa KM. Triggers of hospitalization for venous thromboembolism. *Circulation*. 2012;125:2092-2099
9. Hardy DS, Hoelscher DM, Aragaki C, Stevens J, Steffen LM, Pankow JS, et al. Association of glycemic index and glycemic load with risk of incident coronary heart disease among whites and african americans with and without type 2 diabetes: The atherosclerosis risk in communities study. *Annals of epidemiology*. 2010;20:610-616
10. Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G, et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the atherosclerosis risk in communities (aric) cohort. *Stroke; a journal of cerebral circulation*. 1999;30:736-743
11. Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: The longitudinal investigation of thromboembolism etiology. *The American journal of medicine*. 2004;117:19-25