ARIC Manuscript Proposal #2773

PC Reviewed: 6/2/16	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Risk of recurrent ischemic complications in myocardial infarction (MI) and peripheral arterial disease (PAD)

b. Abbreviated Title (Length 26 characters): Ischemic complications in MI and PAD

2. Writing Group:

Writing group members: Yejin Mok, Jingsha Chen, Shoshana Ballew, Lucia Kwak, Josef Coresh, Kunihiro Matsushita; others welcome

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

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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).
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3. Timeline: Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:

Antiplatelet drug therapy is a cornerstone in the management of coronary artery disease (CAD).[1] In the past five years, newer antiplatelet agents, e.g., prasugrel, have also become available and continue to refine the role of antiplatelet agents in the primary and secondary prevention of cardiovascular diseases.[2] Despite these advances in pharmacotherapy, the risk of recurrent ischemic complications among patients with CAD remains high. Therefore, the assessment of new platelet inhibitors continues to be important. In this context, of importance, vorapaxar, an antagonist of protease activator receptor-1 and an inhibitor of thrombin-induced platelet

aggregation, has demonstrated risk reduction of ischemic events in patients with a recent myocardial infarction (MI) and/or peripheral arterial disease (PAD) in the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA-2P)–Thrombolysis in Myocardial Infarction (TIMI) 50 Trial.[3] Recently, the TIMI Group demonstrated that an algorithm using nine readily available clinical parameters (TRA-2P-MI algorithm) can identify patients with recent MI in TRA-2P trial at particular high risk of ischemic events who may benefit from vorapaxar.[4] They are also developing another algorithm to identify PAD patients who would be particularly at risk of ischemic events (TRA-2P-PAD algorithm). However, both algorithms are based on data from selected patients in the TRA-2P Trial and their external validation is yet to be performed. Thus, we will try to validate those algorithm in several selected studies from the Chronic Kidney Disease Prognosis Consortium, including ARIC.

5. Main Hypothesis/Study Questions:

1. To estimate the risk of secondary events after MI or PAD diagnosis
    - To quantify and compare the risk of the secondary events from different regions
    - To assess whether these risks vary by patient demographic, clinical, and treatment characteristics
2. To assess the validity of RCT-based risk stratification algorithms
    - To assess the validity of TRA-2P-MI algorithm among those with a history of recent MI for identifying patients at high risk of secondary events
    - To assess the validity of TRA-2P-PAD algorithm among those with PAD for identifying patients at high risk of secondary events

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).

Inclusions:

- All black and white ARIC subjects who had MI or PAD

Exclusions:

- Ethnicity other than black or white
- Individuals with missing data on nine predictors (exposures) or outcomes described below.

Exposures:

1. Congestive heart failure (yes vs. no)
2. Prior Stroke (yes vs. no)
3. Hypertension (yes vs. no)
4. Diabetes mellitus (yes vs. no)
5. Current Smoking (yes vs. no)
6. Prior coronary artery bypass grafting (yes vs. no)
7. Age ($\geq$ vs. $<$75 years)
8. Peripheral arterial disease (yes vs. no)

9. Kidney function (eGFR < vs. ≥60 ml/min/1.73m^2)
10. Race
11. Gender
12. Dyslipidemia (yes [lipid lowering medications or total cholesterol >180 mg/dL] vs. no)

Outcomes:

1. CV mortality
2. Recurrent MI
3. Stroke
4. Gastrointestinal bleeding (based on ICD codes)
5. All-cause mortality

Statistical Analysis:

1. We will first identify and describe patients with a history of recent MI (adjudicated cases) and/or PAD (based on low ankle brachial index, self-reported leg revascularization, or ICD codes related to PAD). Then, we will summarize baseline characteristics overall as well as by subsequent ischemic event status. We will also describe the number of subsequent events and availability of the nine predictors of interest, other demographic and clinical variables as well as the patterns of antiplatelet use in detail.
2. To estimate the risk of secondary events after MI or PAD diagnosis, we will first quantify the risk of ischemic events defined as cardiovascular mortality, MI, and stroke among those with recent MI and PAD with Kaplan-Meier method overall and by the number of predictors (e.g., 0, 1-2, and 3-9). Then, we will run Cox proportional hazards models to identify major predictors of ischemic events among those with recent MI (we will repeat the analysis for those with PAD). Predictors with $p<0.10$ based on univariable analysis will be carried forward for multivariable analysis. Then, backward stepwise approach with a threshold of $p<0.01$ will be taken to select best predictors. Considering the validation test in study question 2, we will run a model restricting to the predictors proposed for the TRA-2P-MI algorithm.
3. To assess the validity of RCT-based risk stratification algorithms
   Calibration: Calibration describes how closely the predicted probabilities agree numerically with the observed outcomes. We will visually evaluate calibration in each of the selected studies, by plotting predicted levels of risk based on the TRA-2P-MI algorithm against observed risk. We will also quantify differences using a modified Hosmer-Lemeshow χ^2 statistic.[4,5] If the calibration is suboptimal, we will test whether recalibration (shifting baseline risk for each study) will solve the problem.[6]
   Discrimination: Discrimination refers to the ability of a model to correctly distinguish between 2 classes of outcomes. We will assess discrimination by computing Harrell's c-statistics, which allow for censoring.[7]
   Comparison of coefficients: When calibration and/or discrimination are suboptimal, we will also evaluate the impact of each predictor by comparing coefficients in the original TRA-2P-MI algorithm with those derived from "best fit" models developed within the four to six selected studies in this project. We will calculate differences, standard errors, and z-statistics.[8]

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)?
To the best of our knowledge, no proposals are specifically exploring predictors of those who had MI or PAD in ARIC.

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* _____)
___ 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 ____ Yes __x__ No.

References

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