ARIC Manuscript Proposal #3455

1.a. **Full Title**: Risk of incident chronic kidney disease after myocardial infarction presenting without chest pain in the Atherosclerosis Risk in Communities (ARIC) Study

b. **Abbreviated Title (Length 26 characters)**: CKD after MI

2. **Writing Group**:
   Writing group members:

   Bailey M. DeBarmore, Brad C. Astor, Wayne D. Rosamond, Kuni Matsushita, Gerardo Heiss, Nora Franceschini,

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

   **First author**: Bailey DeBarmore
   Address: 123 W. Franklin St Chapel Hill NC Suite 410

   Phone: 919-757-2266   Fax:
   E-mail: bdebarmo@live.unc.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: Nora Franceschini
   Address: 123 W. Franklin St Chapel Hill NC Suite 410

   Phone: 919-9661305   Fax:
   E-mail: noraf@unc.edu

3. **Timeline**:
   Identification of myocardial infarction with and without chest pain (sometimes called classic pain) has already been done in community surveillance data. This code can be adapted for the cohort in a timely manner. The data for this project is available and analysis will begin after approval is obtained.
4. **Rationale:**

Chronic kidney disease and cardiovascular disease share similar risk factors, such as diabetes, hypertension, and dyslipidemia. (Coresh et al 2004, Haroun et al 2003, Klag et al 1996). Markers of inflammation and hemostasis, including white blood cell count, fibrinogen, von Willebrand factor, factor VIIIc, C-reactive protein, and albumin, are associated with both chronic kidney disease and cardiovascular disease. (Fried et al 2004, Bleyer et al 2000, Bash et al 2008, Tin et al 2015, Chen et al 2015, Hiramoto et al 2012, Dubin et al 2011) A study of these markers in ARIC revealed an association between inflammatory factors and hemostatic factors with incident CKD among those with and without diabetes, though the association was stronger among those with diabetes. The authors hypothesized that increased advanced glycation products (AGEs) which stimulate cytokine production and are implicated in progression to diabetic nephropathy may drive the stronger association, particularly as further adjustment for body weight variables (BMI, waist-hip ratio) did not result in different findings (Bash et al 2008). Among those without diabetes, target organ damage leading to chronic kidney disease may be reflective of ongoing cardiovascular disease processes that ultimately led to the myocardial infarction.

Many studies have examined the risk of and management of myocardial infarction among persons with declining kidney function, and cardiovascular risk among those with ESRD on dialysis. (Bolad 2016, Bajaj et al 2017, Smilowitz et al 2017) A population-level study in Taiwan found that chronic kidney disease was associated with recurrent MI. (Chen et al 2017) The GRACE Study found that creatinine at the time of ACS is also associated with recurrent AMI. (Bolad 2016) The SMART study found that hs-CRP and eGFR was associated with recurrent vascular events. (Dorresteijn et al 2013) Many studies have also examined the risk of developing heart failure following myocardial infarction, but few if any studies have examined the risk of kidney function decline following myocardial infarction. Given the post-inflammatory state of the body following myocardial infarction and the increased risk of recurrent events, it is plausible that these same inflammatory processes may contribute to kidney function decline.

In addition, transitory hemodynamic changes during AMI, post-AMI heart failure and procedures that include contrast (such as PCI) are associated with acute kidney injury, a risk factor for CKD (Auer et al 2017).

Myocardial infarction (MI) presenting without classic pain (left arm, jaw, chest pain) – “chest pain” - is associated with higher case fatality, in-hospital complications such as congestive heart failure, pulmonary embolism, in-hospital stroke, and pulmonary embolism (MP2336, manuscript under review) as well delayed hospital arrival (Saczynski et al 2008, Ottesen et al 2004), lower likelihood of receiving medical therapies and invasive cardiac procedures, as well as higher in-hospital, thirty-day (MP2336), and one-year mortality (Canto et al 2012, Dorsch et al 2001). Women presenting with MI are more likely to present without chest pain compared to men, and presenting with MI without chest pain is more common in women, those with diabetes, and blacks compared to men, those without diabetes, and whites (MP2336).

We hypothesize that experiencing MI without chest pain (NSTEMI or STEMI) will be associated with a higher risk of incident CKD or CKD worsening (decline in eGFR). Classifying MI as with or without chest pain can be done in ARIC using the paindx and paindx2 variables as shown in Figure 1. This method has been used with ARIC community surveillance data to identify MI with and without chest pain, by NSTEMI and STEMI subtype (MP2336).
Figure 1. Pain and downgraded pain process for MI events in ARIC cohort and community surveillance.
5. Main Hypothesis/Study Questions:

Is MI without chest pain associated with higher risk of new-onset CKD, worsening CKD, or acute kidney injury compared to MI with chest pain?

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).

Design: prospective analysis

Exposure: myocardial infarction without chest pain versus with chest pain (See Figure 1)

Analysis:

Study Entry MI event
Follow-up time from MI event to incident CKD3+ or ESRD, non-CKD death, or administrative censoring (end of visit 6 or 7, depending on status of data availability)
Model Cox proportional hazards regression, accounting for competing risk of non-CKD death and attrition

Outcomes

(1) incident CKD as defined below (CKD stage 3 or higher, or ESRD based on USRDS registry/hospitalized ICD codes) using ARIC Kidney Definition 2 – individuals developing an eGFR-Cr < 60 mL and an eGFR-Cr decline from baseline visit of at least 25% or USRDS-identified ESRD events and those with hospitalizations or deaths with kidney disease related ICD-9-CM or ICD-10 codes in any position.

(2) incident acute kidney injury defined as defined as hospitalization or death with the ICD-9-CM code 584.X (ICD-10-CM code N17.x) in any position (From ARIC Derived and Incident Kidney Disease Documentation page 4 last updated January 18, 2019).

Hospital codes for incident CKD

<table>
<thead>
<tr>
<th>ICD-9-code</th>
<th>Description</th>
<th>ICD-10-code</th>
</tr>
</thead>
<tbody>
<tr>
<td>582</td>
<td>Chronic glomerulonephritis</td>
<td>N03</td>
</tr>
<tr>
<td>583</td>
<td>Nephritis and nephropathy</td>
<td></td>
</tr>
<tr>
<td>585, 585.x</td>
<td>Chronic kidney disease where x ≥ 3</td>
<td>N18, N18.x</td>
</tr>
<tr>
<td>586</td>
<td>Renal failure</td>
<td>N19</td>
</tr>
<tr>
<td>587</td>
<td>Renal sclerosis</td>
<td>N26</td>
</tr>
<tr>
<td>588</td>
<td>Disorders resulting from impaired renal function</td>
<td>N25</td>
</tr>
<tr>
<td>403</td>
<td>Hypertensive chronic kidney disease</td>
<td>I12</td>
</tr>
<tr>
<td>404</td>
<td>Hypertensive heart and kidney disease</td>
<td>I13</td>
</tr>
<tr>
<td>593.9</td>
<td>Unspecified disorder of the kidney and ureter</td>
<td></td>
</tr>
<tr>
<td>250.4</td>
<td>Diabetes with renal complications</td>
<td>E10.2, E11.2, E13.2</td>
</tr>
<tr>
<td>V42.0</td>
<td>Kidney replaced by transplant</td>
<td>Z94.0</td>
</tr>
<tr>
<td>55.6</td>
<td>Transplant of kidney</td>
<td></td>
</tr>
<tr>
<td>996.81</td>
<td>Complications of transplanted kidney</td>
<td></td>
</tr>
</tbody>
</table>
Adjustments for:

Model 1: age at MI, race, sex, education level

Model 2: Model 1 + in-hospital complications during MI

Model 3: Model 1 + diabetes, HDL-C, LDL-C, TG, TC, statin-med use, aspirin use, anticoagulant med use, hypertension med use (captured in hypertension def 5) or use of ACEI/ARB, lipid-lowering med use, alcohol intake, smoking status, BMI, waist circumference

Model 4: Model 2 + Model 3

Covariates measured within 1-2 years prior to MI event within 1-2 years
Stratify or control for prevalent CHD or previous MI, diabetes, hypertension

Effect Measure Modification

For analysis for outcome 1 (incident CKD), explore effect measure modification by AKI during MI event, with AKI defined as hospitalization or death with the ICD-9-CM code 584.X (ICD-10-CM code N17.x) in any position (From ARIC Derived and Incident Kidney Disease Documentation page 4 last updated January 18, 2019).

Sensitivity Analyses:

1) Adjustment for inflammation and hemostasis biomarkers, such as WBC, albumin, fibrinogen, factor VIIIc, von Willebrand factor, apoE variant when available
2) Time-varying diabetes status from MI event to incident CKD or eGFR worsening
3) Adjust for duration of diabetes at time of incident CKD
4) Repeat analyses using estimated GFR < 80 mL/min/1.73 m² at visit 1
5) Sensitivity analyses using incident CKD3+ Definition 1: individuals developing an eGFR-Cr < 60 mL and an eGFR-Cr decline from baseline visit of at least 25%

Hoogeveen 2017 demonstrates increased cardiovascular mortality with kidney function decline below eGFR 80, not the traditionally used 60 cut-point. Albuminuria was not measured in ARIC until visit 5, and thus using eGFR cut-point of <60 to define prevalent CKD stage 3-5 may leave some with “normal” eGFR but albuminuria, more likely to progress to kidney disease over time (Rifkin et al 2009). Using a sensitivity definition CKD of eGFR <90 or <80 may correctly exclude those with normal eGFR but possible albuminuria, controlling the confounding of inflammatory markers and albuminuria at baseline.
Exclusion:
- Those not white or black race/ethnicity
- Self-report black participants at Minnesota and Maryland sites
- estimated GFR < 60 mL/min/1.73 m² at visit 1
- Those missing any variables needed to define exposure or outcome

Inclusion: self-report white or black participants from cohort population

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

   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/mantrack/maintain/search/dtSearch.html

   _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)?

   abstract presented at AHA EPI Lifestyle 2019 and manuscript under review; lead author: Bailey
   DeBarmore

   We plan to prepare an abstract for AHA EPI Lifestyle 2020, with submissions due October 2019.

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

   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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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.

References


