ARIC Manuscript Proposal #2480

PC Reviewed: 12/9/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Chronic kidney disease and risk for gastrointestinal bleeding in the community: The Atherosclerosis Risk in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters):
CKD and GI bleeding

2. Writing Group:
Writing group members:
Junichi Ishigami, Morgan Grams, Rakhi P. Naik, Josef Coresh, Kunihiro Matsushita, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __JI__ **[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:

Patients with chronic kidney disease (CKD), particularly at advanced stage, are known to have high risk for bleeding. Indeed, patients on dialysis are reported to have 5-fold higher risk of gastrointestinal (GI) bleeding as compared to matched cohort without CKD [1, 2]. Anticoagulant agents used for extracorporeal circulation during hemodialysis may increase the risk of GI bleeding; however, the risk is also higher in peritoneal dialysis patients [3] as well as transplant patients [4]. Anti-platelet agents are frequently prescribed to patients on end-stage renal disease [5] and may also contribute to the risk of bleeding in this population [6]. In addition, impairments in coagulation system such as platelet dysfunction are present among patients with end-stage renal disease as well as those with less severe CKD [7, 8],

Regarding non-dialysis CKD patients, a couple of studies explored whether the risk for the GI bleeding is higher in this clinical population compared to individuals without CKD and obtained conflicting results [1, 2, 9-11]. Most of these studies assessed dichotomy of having CKD based on various definitions of CKD, i.e., MDRD eGFR or Cockroft creatinine clearance < vs. ≥60 ml/min or ICD codes for CKD, making hard to quantify the impact of full-range kidney function on GI bleeding. The only study assessing bleeding risk across categories of creatinine clearance, was conducted in patients who underwent coronary artery bypass surgery, leaving uncertainty about CKD-bleeding relationship in the general population [12]. More importantly, to our knowledge, no studies have evaluated whether the other element of CKD, the presence of albuminuria, contributes to the risk of GI bleeding.

Therefore, the aim of the study is to comprehensively assess whether measures of CKD are associated with the risk for GI bleeding in a bi-ethnic community-based cohort, ARIC Study. The study will focus on 1) evaluating the risk for GI bleeding according to the degree of kidney function and damage; and 2) assessing other risk factors which may increase the risk for GI bleeding in persons with CKD.

5. Main Hypothesis/Study Questions:

CKD measures are independently associated with risk for GI bleeding

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 serum creatinine and urine albumin/creatinine ratio (ACR) are measured.
- White and black participants.

Exclusion criteria

- Participants whose serum creatinine are not available.
- Non-black/non-white participants.

Exposures

- CKD measures (Given the availability of albuminuria, visit 4 will be used for primary analysis but prior visits will be used for sensitivity analysis)
    - eGFR: calculated from CKD-EPI equations based on serum creatinine and/or cystatin C
        - eGFR will be modeled as continuous variable with its splines and also will be stratified to the following categories: ≥105, 90-104, 75-89, 60-74, 45-59, 30-44, 15-29, and <15 ml/min/1.73m^2 [13]
    - Novel filtration markers
        - beta-2 microglobulin (B2M), and beta trace protein (BTP)
    - Kidney damage marker
        - Urine ACR (will be treated as continuous and categorical [<10, 10-29, 30-299, and ≥300 mg/g] variables [13])

Outcome

- Hospitalizations for GI bleeding (ICD code: 532.xx, 531.xx, 535.01, 534.xx, 533.xx, 535.31, 537.83, 535.11, 532.xx, 531.xx, 534.xx, 535.61, 533.xx, 537.84, 530.82, 456.0, 456.20, 535.21, 530.7, 578.0, 535.41, 530.21, 535.51, 569.85, 569.86, 562.13, 562.03, 562.12, 562.02, 557.0, 569.3, 578.9, 792.1, 578.1)
- While we will primarily use hospitalization ICD codes for outcome ascertainment, we will also explore data from CMS for sensitivity analysis.

Other variables of interest and covariates:

- Age
- Gender
- Race
- Body mass index (BMI)
- Smoking status (current smoker or not)
- Alcohol consumption
- Level of education as social economic status (SES)
- Hypertension
- Sitting blood pressure (systolic and diastolic)
- Diabetes
- Medications of interest (Variables will be treated as time-varying based on annual survey and regular visit)
    -Anticoagulant (e.g., warfarin)
    -Antiplatelet (e.g., aspirin)
    -H2 blocker, or proton pump inhibitor
- History of cardiovascular disease (at baseline and as time-varying covariate)
- Hemostatic markers (These variables are available at visit1, and will be used for sensitivity analysis.)
    - Fibrinogen (mg/dL)
    - von Willebrand factor (%)
    - Factor VIIc (%)
    - Factor VIIIc (%)
    - Protein C
    - Antithrombin III (AT-III)

Statistical Analysis Plan:

- Baseline characteristics will be compared across groups determined by CKD measures.
- Incidence rate will be calculated according to CKD measures and status.
- Cox proportional hazard models will be used to quantify the association of CKD measures with the risk of hospitalization for GI bleeding.
- Models will be adjusted by variables listed above.
- Several additional models will be analyzed for sensitivity analysis. First, we will repeat the analysis in key demographic and clinical subgroups to assess potential effect modifications. Second, we will explore whether the contribution of CKD to GI bleeding varies across different GI sites (e.g., stomach vs. colon), Finally, we will assess whether the association of CKD with GI bleeding, if any, remains significant even after accounting for cardiovascular events during follow-up (time-varying analysis).

Limitations

- Outcome ascertainments rely on ICD codes, although previous studies showed that there is good correlation between diagnostic code based diagnosis and endoscopy proved GI bleeding [14-16]. Another concern is that due to the nature of observational study, residual confounders might be remained even after adjustment for various confounders.

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? ____ Yes __X__ 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, there are no other ARIC proposals exploring the association between CKD and GI bleeding.

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* _____)
__X__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2006.16)

*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.

[References]

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

Upper GI bleeding	Acute duodenal ulcer with hemorrhage	532.xx
	Acute gastric ulcer with hemorrhage	531.xx
	Acute gastritis with hemorrhage	535.01
	Acute gastrojejunal ulcer with hemorrhage	534.xx
	Acute peptic ulcer with hemorrhage	533.xx
	Alcoholic gastritis with hemorrhage	535.31
	Angiodysplasia of stomach and duodenum with hemorrhage	537.83
	Atrophic gastritis with hemorrhage	535.11
	Chronic duodenal ulcer with hemorrhage	532.xx
	Chronic gastric ulcer with hemorrhage	531.xx
	Chronic or unspecified gastrojejunal ulcer with hemorrhage	534.xx
		535.61
	Chronic peptic ulcer with hemorrhage	533.xx
	Dieulafoy lesion (hemorrhagic) of stomach and duodenum	537.84
	Esophageal hemorrhage	530.82
	Esophageal varices with bleeding	456
	Esophageal varices with bleeding in diseases classified elsewhere	456.2
	Gastric mucosal hypertrophy with hemorrhage (hypertrophic gastritis)	535.21
	Gastroesophageal laceration-hemorrhage syndrome (Mallory-Weiss syndrome)	530.7
	Hematemesis	578
	Other specified gastritis with hemorrhage	535.41
	Ulcer of the esophagus with bleeding	530.21
	Unspecified gastritis and gastroduodenitis with hemorrhage	535.51
Lower GI bleeding	Angiodysplasia of intestine with hemorrhage	569.85
	Dieulafoy lesion (hemorrhagic) of intestine	569.86
	Diverticulitis of colon with hemorrhage	562.13
	Diverticulitis of small intestine with hemorrhage	562.03
	Diverticulosis of colon with hemorrhage	562.12
	Diverticulosis of small intestine with hemorrhage	562.02
	Acute vascular insufficiency of intestine	557
	Hemorrhage of rectum and anus	569.3
Unspecified source	Hemorrhage of gastrointestinal tract, unspecified	578.9
	Occult blood in stool	792.1
	Blood in stool	578.1