

ARIC Manuscript Proposal #2741

PC Reviewed: 4/12/16
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1a. Full Title: Medication Utilization Patterns and Chronic Kidney Disease in the Atherosclerosis Risk in Communities (ARIC) Cohort Study

1b. Abbreviated Title: Medication use and CKD

2. Writing Group:

Alex Secora, MPH, Morgan Grams, MD, PhD; Josef Coresh MD, PhD, Others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. AS

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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:

Data analysis will start immediately. A manuscript is expected to be prepared within 10 months.

4. Rationale:

Chronic kidney disease (CKD) is an important public health issue. It has been estimated that CKD affects 13.6% of US adults and contributed to roughly 353 incident cases of end stage renal disease (ESRD) per million people in 2012 alone.¹ CKD is a complex condition that generally refers to a heterogeneous spectrum of disorders. It is characterized by persistent kidney damage (i.e. albuminuria) and/or decreased function (i.e. decreased eGFR) for 3 months or more.

Dose adjustments of medications used in patients with compromised renal function or chronic kidney disease (CKD) are imperative, yet many patients are not properly dosed and subsequently experience adverse effects of their medications.² The US Food and Drug Administration requests that sponsors submit pharmacokinetic data in patients with CKD in new drug applications, but many times these data are insufficient to fully characterize the PK profile in these patients.³ This presents a

major public health problem as prescribers and pharmacists may not have all the information they need to properly advise these patients on what dose to take. Although some medications have no information on dosing in CKD, many common medications have established dosing criteria in CKD.

Polypharmacy in CKD is also important, yet little is known about how many medications this population takes and what classes of medications are commonly used. This issue is particularly important in the context of drug-drug interactions.

At present, there is not a clear understanding of the prevalence of polypharmacy and dosing in CKD patients, as well as the rates of complications among patients on different medication regimens. It is important to fully characterize how individuals with CKD take medications in order to understand risk factors associated with polypharmacy or dose. This type of investigation is critical given the growing public health burden associated with CKD.

5. Main Hypothesis / Study Questions:

1. To characterize the medication utilization of CKD patients at various stages of disease
 - a. Polypharmacy
 - b. Medication class/indication
 - c. Medication dose
 - d. Specific drug classes of interest include, but are not limited to: ACE inhibitors, beta blockers, diuretics, hypoglycemic agents, antibiotics, statins, analgesics, antidepressants, anticoagulants, and proton pump inhibitors
2. To assess the association between polypharmacy and/or inadequate dosing in patients with CKD and complications/outcomes, in particular those relevant to CKD
 - a. Specific outcomes of interest include, but are not limited to: hyperkalemia, hypokalemia, lactic acidosis, bleeding, hypoglycemia

From Saheb et al, 2014⁴

Table 1. Medication most commonly implicated in causing the ADRs.

Drug category	No. (%) ^a	Implicated medicines (n)	Adverse reaction
Cardiovascular agents			
	2 (3)	ACEI/ARB	Hyperkalemia
	2 (3)	Furosemide	Hypokalemia
	1 (2)	Propranolol	Dermatitis
Analgesics			
	1 (2)	Acetaminophen	Vasovagal attack
Psychotropics			
	2 (3)	Benzodiazepine	Drowsiness
Anti-diabetic agents			
	4 (6)	Sulfonylurea	Hypoglycemia
Anticoagulants			
	8 (13)	Warfarin	Bleeding
	16 (26)	Enoxaparin	Bleeding
	11 (17)	Heparin	Bleeding
	7 (11)	Heparin	Thrombocytopenia
	2 (3)	Foundaparinux	Bleeding
Antithrombotics			
	1 (2)	Alteplase	Skin bruise
Antiplatelets			
	3 (4)	Antiplatelets	Bleeding
Others			
	1 (2)	Mycophenolate mofetil	Bone marrow suppression
	1 (2)	Darbepoetin	Gastrointestinal disorders

Abbreviations: ACEI/ARB, Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.
^aThe total number of definite or probable ADRs, n = 62.

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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: Serial cross-sectional analyses and prospective cohort analyses for the associations of medication use and adverse outcomes

Inclusion/exclusion: This study will include ARIC participants at all available visits that have information on medication usage

Outcome: Outcomes will only be explored in the prospective cohort analyses. All ICD9 or ICD10 (cause of death) codes will be explored. Specific outcomes of interest include, but are not limited to: hyperkalemia, hypokalemia, lactic acidosis, bleeding, hypoglycemia. These outcomes will be assessed through hospitalization data collected during the annual follow-up, and through ARIC hospital surveillance. We will also explore diagnostic codes from CMS files for those who have Medicare.

Covariates: The key variable of interest is eGFR. We will look at this continuously and also within stages of CKD. In addition, for visits after ARIC visit 4, we will also look at strata of albuminuria (CKD stages A1-3). Other covariates we may examine included age, sex, race, diabetes (lab evidence or history), hypertension (clinical evidence or history), coronary heart disease, BMI, and tobacco smoking status at baseline. Medication use will be assessed as a function of medication class (categorical variable), number of medications (ordinal and binary variable), and medication dose (ordinal and binary variable). Medication variables will be “outcomes” in the cross-sectional analyses, and covariates in the prospective analyses.

Data analysis: The cross-sectional analyses will be generally exploratory in nature, assessing proportions, distributions, frequencies and associations between variables. This exploratory analysis will inform the prospective analyses assessing clinical outcomes. Prospective analyses will ideally be performed with mixed effects models (random intercept) using generalized estimating equations; however, depending on the nature of the exposure, cox proportional hazard analyses may also be used. There may be a need to use propensity score matching as a means to control for confounding by indication in the prospective analyses, and viability of this approach will be explored.

Limitations:

1. We only have information on medication use at scheduled study visits and annual telephone survey starting in 2006. Also, because medication use is self-reported, the accuracy of these data may be problematic in some contexts.
2. There may be other unknown and unmeasured confounding factors that are independently associated with both medication use in those with CKD and the development complications/clinical outcomes (using diagnostic codes).
3. Medication indication is unknown in these data.
4. Most ICD9 codes are not validated and may be incorrectly coded as a result

7a. Will the data be used for non-CVD analysis in this manuscript?

No

8a. Will the DNA data be used in this manuscript?

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.

Yes

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)?

- 1) Lazarus/Grams: Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease (2015)
- 2) Miedema: Eligibility for statin therapy according to new cholesterol guidelines and prevalent use of medication to lower lipid levels in an older US Cohort: the Atherosclerosis Risk in Communities Study Cohort (2015)
- 3) O'Brien: Medication, reperfusion therapy and survival in a community-based setting of hospitalised myocardial infarction (2013)

11a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

No

11b. If yes, is the proposal

- A. Primarily the result of an ancillary study (list study number)? No**
- B. Primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____)?**

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.csc.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

1. United States Renal Data System. 2014 USRDS Annual Data Report: An overview of the epidemiology of kidney disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, **2014**.
2. Munar MY, Singh H. (2007) Drug dosing adjustments in patients with chronic kidney disease. *Am Fam Phys*, 75: 1487-96
3. Draft Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study design, data analysis, and impact on dosing and labeling. U.S. Food and Drug Administration, Center for Drug Evaluation and Research, March 2010.
4. Saheb SAF, Syed SAS, Saheb SAN, Al Sayed HA (2014) Development of an adverse drug reaction risk assessment score among hospitalized patients with chronic kidney disease. *PLoS ONE*, 9(4): e95991.