

ARIC Manuscript Proposal #2509

1a. Full Title: Association Between the Use of Proton Pump Inhibitors and Chronic Kidney Disease in the Atherosclerosis Risk In Communities (ARIC) Cohort Study

1b. Abbreviated Title: PPI use and risk of CKD

2. Writing Group:

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

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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) refers to a heterogeneous spectrum of disorders characterized by evidence of persistent kidney damage (i.e. albuminuria) and or decreased function (i.e. decreased eGFR) for 3 months or more. CKD can be categorized into stages, ranging from 1 to 5, according to the severity of this damage or functional deficit. There is little question that CKD is an enormous and growing public health problem, affecting 13.6% of US adults and resulting in 353 new cases of end stage renal disease per million per year in 2012 [1]. Globally, the estimated burden of death from CKD has risen by 82.3% over the last 2 decades, the third largest increase in major causes of death behind HIV/AIDs and diabetes [2]. In the US, the cost of CKD amongst patients older than 65 years in 2012 is approximately \$44.6 billion dollars, which has increased from the estimated cost of \$29.0 billion in 2008 [1].

Whilst risk factors for CKD, such as diabetes, hypertension, older age, race and low birth weight have been well described [3], identifying novel independent risk factors provides an

opportunity to prevent further cases and advances our understanding of the disease process, which could facilitate definitive therapies.

Proton pump inhibitors (PPI) are a commonly prescribed class of medication that inhibits gastric acid secretion. We hypothesize that PPIs may be an independent risk factor for CKD. Two mechanisms are postulated. Firstly, it has been recently discovered that PPIs may be a cause of acute interstitial nephritis, with multiple published case series and a large nested case control study demonstrating significantly elevated risk of acute interstitial nephritis amongst those currently on PPIs [4, 5]. Whilst the mechanism of PPI-induced AIN is unknown, the fact that PPIs can cause acute kidney injury leads us to believe that it may also cause a slower and more chronic degradation in kidney function and may thus be a risk factor for CKD.

Another potential mechanism by which PPI-use could independently increase risk of CKD is via its ability to cause hypomagnesemia, potentially due to impaired absorption of magnesium from inactivation of acid-dependent magnesium ion transporters [6-8]. Hypomagnesemia has recently been shown to be an independent risk factor for CKD [9].

Given the extensive prevalence of PPI use [10], demonstrating that it is a modifiable risk factor for CKD across a population could have substantial implications for public health. Thus, we propose to investigate whether the use of PPI medication is an independent risk factor for CKD and, if so, to quantify the magnitude of this risk.

5. Main Hypothesis / Study Questions:

1. Use of PPI at baseline is associated with incident CKD, independent of known CKD risk factors
2. Cumulative exposure to PPIs is associated with increased risk of kidney disease in a dose-dependent fashion.
3. Similar associations are present for PPI use and acute kidney injury as well as end-stage renal disease.

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: Prospective cohort study.

Inclusion/exclusion: This study will include ARIC participants at the fourth ARIC visit. This cohort was chosen as it contains information on both participant eGFR and albuminuria, two key risk factors for kidney outcomes. In addition, PPIs were not introduced to the US market until 1990. For the analysis of incident CKD, those with eGFR <60 ml/min/1.73 m² or microalbuminuria at visit 4 will be excluded; for the analysis of acute kidney injury (AKI), those with a history of AKI will be excluded; for the analysis of ESRD, those with ESRD at baseline will be excluded.

Outcome: An incident case of CKD is defined by either 1) a drop in eGFR to <60 mL/min/1.72m² and 25% decline in eGFR from baseline at visit 5 (between 13 years to

17 years follow up); 2) A hospitalization or death with diagnosis code indicating CKD (measured from discharge summaries or death certificates - see Figure 1 for diagnosis codes); or 3) Incident ESRD (identified through linkage with US Renal Data System). Acute kidney injury will be defined as a hospitalization with the diagnostic code 584.x in either the primary or subsequent position.

Figure 1. ICD-9-CM and ICD-10-CM diagnosis codes for CKD

ICD-9-CM code	ICD-10-CM code	Description
582	N03	Chronic glomerulonephritis
583	--	Nephritis and nephropathy
585, 585.x where x≥3	N18, N18.x where x≥3	Chronic kidney disease
586	N19	Renal failure
587	N26	Renal sclerosis
588	N25	Disorders resulting from impaired renal function
403	I12	Hypertensive chronic kidney disease
404	I13	Hypertensive heart and kidney disease
593.9	--	Unspecified disorder of the kidney and ureter
250.4	E10.2, E11.2, E13.2	Diabetes with renal complications
V42.0	Z94.0	Kidney replaced by transplant
55.6	--	Transplant of kidney
996.81	--	Complications of transplanted kidney
V45.1*	Z99.2*	Renal dialysis status
V56*	Z49*	Admission for dialysis treatment or session
39.95*	--	Hemodialysis
54.98*	--	Peritoneal dialysis
--	Z45.2*	Encounter for adjustment and management of vascular access device

*These codes are counted as incident CKD only if a concomitant AKI code (ICD-9: 584.x, ICD-10: N17) is not present.

Covariates: Age, sex, race, eGFR, diabetes (lab evidence or history), hypertension (clinical evidence or history), coronary heart disease, BMI, physical activity and tobacco smoking status at baseline. We will also consider magnesium level as a covariate in sensitivity analyses so we can evaluate whether there is evidence that magnesium is a contributing factor in the PPI - CKD causal pathway (if identified). PPI use will be determined at a binary variable at visit 4 as well as a count variable indicating years of exposure prior to visit 4. In sensitivity analysis, we will also assess cumulative exposure in a time-varying manner, and evaluate the impact of cumulative-exposure correction factors to account for patient-reported medication compliance.

Data analysis: Baseline characteristics of participants in PPI and non-PPI groups will be compared to assess for significant differences, which may indicate a possible source of selection bias or confounding. The association between PPI-use and renal outcomes will be analyzed in a multivariate Cox regression analysis. Adjustment for covariates will be performed as a means of controlling known potential confounders (risk factors for CKD that could be associated with PPI use). A propensity score that stratifies patients according to their likelihood of using PPI may also be used to control for potential bias. Analysis incorporating magnesium levels in the regression model will also be performed so as to assess the amount of an association between PPI use and CKD (if any) that can be explained by altered magnesium levels.

Limitations:

1. We only have information on PPI use at scheduled study visits and annual telephone survey. The use of serial data can introduce treatment by indication bias: it will be important to delineate between ongoing PPI use and NEW PPI use related to symptoms from CKD itself. In sensitivity analyses, we will exclude new PPI use within 1 year of CKD diagnosis.
2. There may be other unknown and unmeasured confounding factors that are independently associated with both PPI use and CKD development but are not themselves part of the casual pathway between the two. For example, people who use PPIs may have more overall comorbidities or be on more medications overall and the combination of these comorbidities and or medications may be a risk factor for CKD. We will attempt to deal with this particular idea in a sensitivity analysis using available data about comorbidity burden and extent of other medications.
3. In our definition of incident CKD, we have focused on eGFR levels and diagnostic codes. This definition would miss cases where a patient meets criteria based on urinary proteinuria. Similarly, this will miss cases among the non-hospitalized participants. In sensitivity analyses, we will evaluate eGFR trajectories using participants in Washington County, Maryland, where we have outpatient laboratory data linkage.

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)?

#1949 Validation of inter-visit kidney events
 #1944 Risk factors for acute kidney injury
 #2370 Risk factors for kidney function trajectories

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.

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