ARIC Manuscript Proposal # 3180

PC Reviewed: 6/12/18	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: **Hypomagnesemia, proton-pump inhibitor use and risk of cardiovascular diseases: the Atherosclerosis Risk in Communities (ARIC) study**

b. Abbreviated Title (Length 26 characters): **Mg, PPIs & CVD**

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

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3. Timeline:
Data analysis and manuscript preparation will begin immediately. We anticipate manuscript completion in summer 2019.

4. Rationale:

Proton pump inhibitors (PPIs) are medications used to treat gastroesophageal reflux disease (GERD) and other acid-related disorders, and may be prescribed or purchased over-the-counter.[1] PPIs are approved for short-term use, though are often misused.[2] This class of medication was first introduced to the U.S. marketplace in the late 1980s. Since then, PPI use has increased

dramatically. They are among the most widely used medications among American adults.[1] In 2009, an estimated 9% of outpatient visits involved patients who use PPIs.[3]

Since their introduction, there is growing concern over PPI-induced hypomagnesemia as evident by numerous case reports and studies regarding hypomagnesemia among long-term PPI users.[4-16] In 2011, the U.S. Food and Drug Administration released a warning regarding potential for PPI-induced hypomagnesemia.[17] The elderly and men are thought to have a higher risk of hypomagnesemia due to PPI use than their counterparts.[18] Additionally, drug interactions have been noted. Individuals who take diuretics may have a higher risk of hypomagnesemia compared to those only taking PPIs.[6] Elderly PPI users may also be at greater risk of hypomagnesemia than their younger counterpoints.[19]

Mechanisms and risk factors for PPI-induced hypomagnesemia is an ongoing area of research. Proposed mechanisms of PPI-induced hypomagnesemia are thought to arise due to reduced intestinal Mg absorption.[20,21] Much of the mechanistic research to date has focused on magnesium transports such as TRMP6. Case reports are largely based on patients who chronically used high-dose PPIs and presented at the hospital with clinical symptoms. Interestingly, a modeling study of PPI use indicates that even short-term PPI use can slightly reduce intestinal Mg absorption.[22]

PPIs have also been controversially associated with increased risk of CVD outcomes. Notably, the literature suggesting an association between PPIs and CVD is based on observational studies, which complicates causal inference. However, an intriguing possibility exists that hypomagnesemia may link PPI use to CVD outcomes. To our knowledge, only one cross-sectional study examined PPIs in relation to serum Mg and arrhythmias. In this study of 421 intensive care or critical care unit patients with a MI or unstable angina diagnosis, patients administered PPIs soon after hospital admission tended to have lower serum Mg concentrations and a greater prevalence of cardiac arrhythmias compared to those not exposed to PPIs. This study also did not collect data on diuretic use.[23] No studies have examined the association between PPI's and serum Mg in relation other CVD outcomes.

The primary aim of this paper is to evaluate whether low serum Mg mediates the association between PPIs and CVD risk using ~6 years of longitudinal data in the ARIC study. In exploratory analyses, we will also assess whether this association is stronger among diuretic users. Using a counterfactual mediation model which allows for exposure-mediator interaction,[24] we will also assess whether there is an interaction between PPI use and serum Mg on CVD risk. H_2-blockers are medications with similar indications as PPIs and no known cardiac toxicity. As a "negative control", we will repeat the analyses using H_2 blockers instead of PPIs.

5. Main Hypothesis/Study Questions:

- We hypothesize that low serum Mg will mediate the association between PPI use and elevated CVD risk.
- Use of H_2-blockers – medications with similar indications as PPIs and no known cardiac toxicity – will not be associated with risk of CVD outcomes. Likewise, serum Mg will not mediate the null relationship between H_2-blocker use and CVD risk.

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

Serum Mg was measured at visit 1 (1989-90), visit 2 (1990-92) and visit 5 (2011-13). Medication use was queried at all ARIC exams, and after 2006, participants were queried over the phone annually through 2011. Notably, PPIs were not introduced to the US market until 1990. Due the timing of serum Mg measurements and introduction of PPIs, Visit 5 will serve as baseline for this analysis.

Exclusions: Of the participants who attended visit 5, we will exclude participants (1) with a history of CVD, (2) those missing prevalent CVD information at visit 5, and (3) those missing visit 5 serum Mg measurement.

Variables

Exposures: PPI and H_2-blocker use

Outcomes: Incident coronary heart disease, heart failure, stroke, atrial fibrillation and CVD mortality (individual outcomes and as composite outcome) through most recent available follow-up

Potential Mediator: Serum Mg (visit 5)

Potential Effect Modifiers: diuretic use, race, sex

Covariates: Age, sex, race, study center, education, health insurance status, diabetes, baseline BMI, systolic blood pressure, antihypertension medication use, smoking status, drinking status, ethanol intake, physical activity, lipid medication use, HDL, LDL, total cholesterol, eGFR

Data Analysis

Visit 5 will serve as baseline. We will present baseline characteristics, including mean serum Mg concentrations, stratified by PPI use at visit 5. PPI use may be modeled a binary variable (yes/no) or based on cumulative exposure to PPIs (e.g. based on number of years) at visit 5.

Multivariable Cox proportional hazards regression will be used to examine the association between PPI use and incident CVD (composite and individual outcomes). Person-years will be calculated based on time from baseline to the outcome of interest, death, loss-to-follow-up, end of the most recent follow-up data, or whichever comes first. Serum Mg may be modeled continuously (per 1 SD) to preserve power or categorically (e.g. quartiles or using clinical cut-points[25]). After including serum Mg (the hypothesized mediator) in the model, we will initially qualitatively inspect for attenuation of the PPI-CVD association and will estimate controlled indirect effects.

- Model 1 = age, race, sex, center

- Model 2 = Model 1 + education, smoking status, ethanol intake, physical activity, diabetes, BMI, health insurance status
- Model 3 = Model 2 + systolic blood pressure, antihypertension medication use, lipid medication use, HDL, LDL, total cholesterol, eGFR
- Model 4 = Model 3 + serum Mg

We will test for multiplicative interactions with diuretic use, race and sex by including a cross-product term [e.g. PPI*diuretic] in the models (separately), and additive interactions by calculating the relative excess risk due to interaction (RERI).[26] As we may not have sufficient power to examine interactions, we will interpret these findings as exploratory in nature.

Sensitivity analyses: PPI users may inherently differ from non-users. Below we propose sensitivity analyses to test the robustness of our findings.

- Include H_2-blocker use as an active comparator to test the specificity of the association[27]
- Match PPI users and non-users using propensity scores to help balance potential confounding characteristics[28]
- Exclude diuretic users as diuretics are medications which can also influence circulating Mg concentrations

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 (some overlap; justification below) _____ No

There is some overlap of this proposal with MS proposal #2808 (Bell), however the lead author of that paper (Bell) is a coauthor on this paper. Additionally, the primary aim of this paper differs in that we seek to examine if the PPI-CVD association can be explained by

serum Mg concentrations. There are no publications which address this specific question, and ARIC is uniquely suited to do so.

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)?

#2808 PPI use and risk of CVD (Bell)
#2509: PPI use and risk of CKD (Lazarus)

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.

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