ARIC Manuscript Proposal #2707

PC Reviewed: 2/9/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Hypoglycemia and Subclinical Myocardial Damage in Older Adults with Diabetes

b. Abbreviated Title (Length 26 characters): **Hypoglycemia & hs-troponin**

2. Writing Group:

Writing group members: Alexandra K. Lee, John W. McEvoy, Ron C. Hoogeveen, Christie M. Ballantyne, Elizabeth Selvin; others welcome

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

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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: All data are available. From time of approval of manuscript proposal, we expect to have a manuscript ready for submission in 6 months. We anticipate this will be a short research letter rather than a full-length article.

4. Rationale:

Hypoglycemia is an acute complication of diabetes that, when severe, can result in coma, seizures, or even death and requires emergency medical treatment. Previous research has demonstrated that persons with diabetes mellitus who have a history of severe hypoglycemia are at increased risk of cardiovascular disease (Goto 2013, Yeh 2015). However, it remains unclear whether hypoglycemia is causally linked to cardiovascular events or is merely a proxy of vulnerability. It has been posited that hypoglycemia and the immediately subsequent chain of biological reactions could be a trigger in already vulnerable individuals to make them more susceptible to future cardiovascular events (Pistrosch 2015, Leong 2012). It is also possible that hypoglycemia may directly cause microvascular damage to the heart; the activation of the sympathetic nervous system promotes coagulation and impairs endothelial function, which could lead to blockages in the microvasculature and thus micro-ischemia (Frier 2011).

Cardiac troponin T (cTnT) is a biomarker of cardiac necrosis and has been used for many years to diagnose myocardial infarction. Recently, highly-sensitive (hs) assays have been developed, enabling detection of extremely low levels of circulating troponin in the general population. These minute elevations on hs-cTnT are thought to reflect chronic myocardial damage (Jeremias 2005). Indeed, prior studies have demonstrated that hs-cTnT strongly and independently predicts future cardiovascular events and mortality in asymptomatic populations with no history of cardiovascular disease (Saunders 2011).

It is unknown whether hypoglycemia is associated with hs-cTnT in adults with diabetes. The ARIC study has information on both hypoglycemia and rigorous measurements of hs-cTnT allowing us to investigate the observed association in a community-based setting. If the association is present, it could suggest that subclinical myocardial injury is at least a partial mediator of the observed association between hypoglycemia and elevated risk of cardiovascular disease and mortality. Improved understanding of the risks of hypoglycemia will help inform ongoing debates on appropriate glucose targets for older adults with diabetes.

5. Main Hypothesis/Study Questions:

Research Question: Among older adults with diabetes, is a history of severe hypoglycemia associated with a greater prevalence of elevated high-sensitivity cardiac troponin T?

> Hypothesis: Among older adults with diabetes, compared to those who have not experienced severe hypoglycemia, individuals with prior severe hypoglycemia will be more likely to have elevated cardiac troponin T, a measure of chronic myocardial damage.

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: Cross-sectional analysis at visit 5

Inclusion criteria: Diagnosed diabetes by visit 5, by self-report or use of glucose-lowering medications

Exclusion criteria: Missing troponin measurements or other covariates.

Exposure: Severe hypoglycemia prior to visit 5, assessed with ICD-9 codes from ARIC/CMS hospitalizations and from linked CMS data on emergency department visits and observational hospital stays. Hypoglycemia will be identified by ICD-9 diagnosis codes 251.0 (hypoglycemic coma), 251.1 (other specified hypoglycemia), 252.2 (hypoglycemia, unspecified), 962.3 (poisoning by insulins and antidiabetic agents) in first position with 250.x (diabetes) in any other position, and by 250.8 in first position (in the absence of 681.xx, 682.xx, 686.90, 707.xx, 730.27, and 731.8). This follows a validated algorithm by Ginde et al., but is modified slightly to exclude 270.3 (leucine-induced hypoglycemia), 775.0 (hypoglycemia in infants), and 775.6 (neonatal hypoglycemia).

Outcome: Elevated troponin, defined as high-sensitivity cardiac troponin T (hs-cTnT) >14ng/L at Visit 5. We will also conduct sensitivity analyses to examine other possible cutpoints to define elevated hs-cTnT.

Statistical Analysis: As prior coronary heart disease and heart failure are important for the interpretation of hs-cTnT in an asymptomatic population, we will conduct all analyses either stratified by a history of these diseases or with an interaction term with hypoglycemia, as appropriate.

First, we will assess the crude prevalence of elevated troponin in individuals with and without prior hypoglycemia. Second, we will conduct logistic regression to examine whether the odds of elevated troponin are higher in individuals with a prior episode of severe hypoglycemia. Due to limited sample size of individuals with a prior hypoglycemic event (we anticipate approximately 60 of the roughly 2000 individuals with diagnosed diabetes will have a history of severe hypoglycemia), we will try to keep our models parsimonious after adjusting for the most important confounders of age, sex, race, and diabetes duration. We will evaluate other covariates, including diabetes medication use, BMI and smoking as potential confounders and eGFR and blood pressure and/or hypertension as potential mediators.

Limitations: A primary limitation will be the low number of severe hypoglycemia events detected in ARIC and correspondingly low statistical power to detect small to moderate associations. There are few individuals with diabetes who attended visit 5 and had a positive history of severe hypoglycemia (~60 events total). Power will be even more limited to examine associations stratified by history of clinical cardiovascular disease. Selection bias is another concern, since a high proportion of participants who had hypoglycemic episodes did not attend visit 5. Those who did not attend are likely to be

sicker and to have elevated troponin compared to those who attended, which could result in a strongly conservative bias (bias towards the null) in our data. Finally, residual confounding is always possible, and in this case, it is likely that adjusting for the duration of diabetes (which is substantially different between those with and without hypoglycemia) is not fully capturing the difference in diabetes severity and duration between the two groups. This could make hypoglycemia appear to be more strongly associated with elevated troponin, when in fact hypoglycemia is merely a proxy for more severe diabetes or a marker of vulnerability.

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 _____ 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)?

MP#2630: Hypoglycemia and Cognitive Function in Older Adults with Diabetes. Alexandra Lee, Andreea Rawlings, Andrea Schneider, Elbert Huang, A. Richey Sharrett, Elizabeth Selvin

Selvin E, Lazo M, Chen Y et al. Diabetes Mellitus, Prediabetes, and Incidence of Subclinical Myocardial Damage. Circulation 2014;130:1374-1382.

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

_X_ A. primarily the result of an ancillary study (list number* 2008.06)

___ 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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript __X__ Yes ____ No.

REFERENCES

Frier BM, Schernthaner G, Heller SR. Hypoglycemia and Cardiovascular Risks. *Diab Care*. 2011: 34; Supp2: S132-S137.

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Leong A, Berkowitz SA, Triant VA et al. Hypoglycemia in diabetes mellitus as a coronary artery disease risk factor in patients at elevated vascular risk. *J Clin Endocrinol Metab.* 2015; jc-2015.

Pistrosch F, Hanefeld M. Hypoglycemia and Cardiovascular Disease: Lessons from Outcome Studies. *Curr Diab Rep* 2015;15:117.

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Yeh JS, Sung SH, Huang HM et al. Hypoglycemia and risk of vascular events and mortality: a systematic review and meta-analysis. *Acta Diabetol* 2015;1-16.