

ARIC Manuscript Proposal # 3329

PC Reviewed: 1/8/2019
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title:

Hypoglycemia, Clinical and Subclinical Cardiovascular Outcomes among Older Adults: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):

Hypoglycemia and adverse events

2. Writing Group:

Writing group members: Justin B. Echouffo-Tcheugui, Natalie Daya, Alexandra K. Lee, Olive Tang, Amil Shah, B. Gwen Windham, Elizabeth Selvin; others welcome

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

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3. Timeline:

Analysis to begin immediately after the approval of the proposal, and submission of a draft of the manuscript for review to ARIC for review within 6 months.

4. Rationale:

Hypoglycemia among individuals with diabetes has been related to a variety of clinical outcomes. Accruing evidence indicates that hypoglycemia is strongly linked to incident cardiovascular disease (CVD). Indeed, our group has previously shown that severe hypoglycemic was associated with increased CVD and mortality risks among the Atherosclerosis Risk in Communities (ARIC) study participants who attended visit 4 (1996-1998).¹ However, since then, there have been subsequent ARIC follow-up examinations, including much older individuals. Hypoglycemia tends to be more common in older adults with diabetes,² with a doubling of its frequency for each additional decade of life after age 60 years.³ Age-related physiological changes in the pharmacokinetics of oral medications and insulin makes older individuals more vulnerable to hypoglycemia.⁴ Furthermore, the adaptive response to hypoglycemia is critically lost in elderly patients with diabetes.¹ Given the age-related changes to the endocrine, neurologic and cardiovascular systems among older individuals, it is possible that the association of hypoglycemia with CVD may be of particular importance in an older population of individuals with diabetes. The mechanistic pathways through which hypoglycemia leads to CVD remains unclear.^{5,6} We have previously shown a strong link between hypoglycemia and subclinical cardiac damage in older adults in ARIC;⁵ however, it is unclear whether subclinical cardiac damage related to hypoglycemia translates into subclinical cardiac dysfunction and ultimately overt heart failure. Hypoglycemia may also contribute to cardiac dysfunction through autonomic dysfunction, a key component of heart failure pathogenesis.⁷ Indeed, hypoglycemia may coexist with or trigger autonomic dysfunction, with the latter related to hypoglycemia-associated autonomic failure.⁸ Hypoglycemia also carries a potential for arrhythmias,⁹ and it is therefore possible that older individuals experiencing hypoglycemia are at high risk of sudden cardiac death, especially given the high prevalence of coronary heart disease, systolic dysfunction, and heart failure in this population.

Using data from visit 5 of the Atherosclerosis Risk in Communities (ARIC) study, we aim to assess the association of severe hypoglycemia with subclinical CVD and CVD (new onset events and recurrent CVD events), and mortality among older individuals with diabetes.

5. Main Hypothesis/Study Questions:

Among older individuals, severe hypoglycemia will be positively associated with:

- 1) subclinical CVD, specifically alterations in cardiac structure and/or function;
- 2) a higher incidence of global CVD (coronary heart disease [CHD], stroke, heart failure, or atrial fibrillation);
- 3) a higher incidence of all-cause mortality.

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/Exclusion criteria

Individuals will be participants of the ARIC study, with a diagnosis of diabetes based on either self-report or diabetes medication use at visit 5 (2011–2013). The cross-sectional analyses will include those who underwent an echocardiographic assessment at visit 5. To assess the influence of hypoglycemia on incident outcomes (prospective analysis), we will include participants that attended visit 5. We will exclude individuals without data on the relevant covariates.

Exposure

Our exposure will be severe hypoglycemia prior to visit 5. The identification of severe hypoglycemia was done using the relevant International Classification of Disease (ICD)-9 code in primary position, derived from records of hospitalizations, emergency department visits and ambulance calls.

Outcomes

The outcomes will be of two types:

- Cross-sectional outcomes, which include cardiac indices assessed at visit 5 (2011–2013): left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), left ventricular (LV) mass, relative wall thickness (RWT), LV ejection fraction (LVEF), right ventricular fractional area change (RV FAC), left atrial volume (LA), E-A ratio, and septal E/E'.
- Incident outcomes (new or recurrent outcomes) after visit 5: cardiovascular disease (composite of CHD, stroke, heart failure, and atrial fibrillation), heart failure, and all-cause mortality.

Covariates

The covariates include age, sex, race-center, income, smoking status, duration of diabetes, degree of blood glucose control (as assessed by glycosylated hemoglobin [HbA_{1C}]), use of diabetes medications (oral medications or insulin), estimated glomerular filtration rate (eGFR), albuminuria, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), use of hypertension medication, hypertension status, LDL-cholesterol, HDL-cholesterol, cholesterol-lowering medication use, history of coronary artery disease/myocardial infarction, history of heart failure, and history of atrial fibrillation.

Statistical analysis

Cross-sectional analyses

We will use multivariable linear regression models to assess the association between the history of severe hypoglycemia and each of the cardiac indices. We will also use logistic regression to assess the odds of having an abnormal cardiac index (left ventricular hypertrophy [LVH], LA enlargement, abnormal E-A ratio, abnormal septal E/E', or abnormal GLS) by history of hypoglycemia. All the cross sectional regression models (linear or logistic) will include the following adjustment variables: age, sex, race-center, smoking status, use of insulin, HbA_{1C}, BMI, hypertension status, and heart rate.

Prospective analyses

For the prospective analyses of the association of severe hypoglycemia with cardiovascular outcomes and all-cause mortality using Cox proportional hazard regression (negative binomial regression for analyses including recurrent events). We will adjust for the following potential confounders: age, sex, race-center, smoking status, use of diabetes medications, duration of diabetes, HbA_{1C}, eGFR, albuminuria, hypertension status, LDL cholesterol, HDL cholesterol, and cholesterol lowering medication use.

We will specifically assess whether severe hypoglycemia related to incident HF using Cox proportional hazards (negative binomial regression for analyses including recurrent events) models. The HF analysis will include the following adjustment variables: age, sex, race-center,

smoking status, heart rate, HbA_{1C}, eGFR, BMI, hypertension status. In a subsequent model, we will additionally adjust for prevalent CHD and a history of myocardial infarction.

For each of the Cox models, we will verify the proportional hazards assumption by inspecting negative log-log survival plots.

For the analyses including recurrent events, we will further perform a stratification by the prevalent disease status at baseline.

Limitations

The potential limitations of our study include a somewhat limited power to detect association for some of the outcomes, due to a small number of hypoglycemia events (possibly linked to the rigorous method of identification) on one hand, or a small number of outcome events on the other hand. In addition, we will not capture changes in covariates over time (including diabetes medications that may change).

7.a. Will the data be used for non-CVD analysis in this manuscript? 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 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 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.csc.unc.edu/aric/mantrack/maintain/search/dtSearch.html>

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)?

ARIC 2707: Hypoglycemia and Subclinical Myocardial Damage in Older Adults with Diabetes
ARIC 2936: Severe Hypoglycemia and Risk of Cardiovascular Disease and All- Cause Mortality

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes No

11.b. If yes, is the proposal

- A. primarily the result of an ancillary study (Study #2009.16 - PI: Selvin)**
 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 <https://www2.csc.c.unc.edu/aric/approved-ancillary-studies>

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.c.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. Meneilly GS, Cheung E, Tuokko H. Counterregulatory hormone responses to hypoglycemia in the elderly patient with diabetes. *Diabetes*. 1994;43:403–410.
2. Pathak R, Schroeder E, Seaquist E, Zeng C, Lafata J, Thomas A, Desai J, Waitzfelder B, Nichols G, Lawrence J, Karter A, Steiner J, Segal J, O'Connor P, Group for the S-DS. Severe Hypoglycemia Requiring Medical Intervention in a Large Cohort of Adults With Diabetes Receiving Care in U.S. Integrated Health Care Delivery Systems: 2005–2011. *Diabetes Care*. 2016; 39:363-70.
3. Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, Karter AJ. Rates of complications and mortality in older patients with diabetes mellitus : the diabetes and aging study. *JAMA Intern Med*. 2014;174:251–258.
4. Ligthelm RJ, Kaiser M, Vora J, Yale JF. Insulin use in elderly adults: Risk of hypoglycemia and strategies for care. *J Am Geriatr Soc*. 2012;60:1564–1570.
5. Lee AK, McEvoy JW, Hoogeveen RC, Ballantyne CM, Selvin E. Severe Hypoglycemia and Elevated High-Sensitivity Cardiac Troponin T in Older Adults With Diabetes: The ARIC Study. *J. Am. Coll. Cardiol*. 2016;68:1370–1371.
6. Rezende PC, Everett BM, Brooks MM, Vlachos H, Orchard TJ, Frye RL, Bhatt DL, Hlatky MA. Hypoglycemia and Elevated Troponin in Patients With Diabetes and Coronary Artery Disease. *J Am Coll Cardiol*. 2018;72:1778 LP-1786. t
7. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The Sympathetic Nervous System in Heart Failure. Physiology, Pathophysiology, and Clinical Implications. *J. Am. Coll. Cardiol*. 2009;54:1747–1762.
8. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med*. 2013;369:362–72.

9. Frier BM, Schernthaner G, Heller SR. Hypoglycemia and Cardiovascular Risks. *Diabetes Care*. 2011;34:S132–S137.