

## ARIC Manuscript Proposal #2936

PC Reviewed: 02/14/17  
SC Reviewed: \_\_\_\_\_

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Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Severe Hypoglycemia and Risk of Cardiovascular Disease and All-Cause Mortality

**b. Abbreviated Title (Length 26 characters):** Hypoglycemia, CVD & Mortality

### 2. Writing Group:

Writing group members: Alexandra K. Lee, Bethany Warren, Clare J. Lee, John W. McEvoy, Elbert S. Huang, A. Richey Sharrett, Josef Coresh, Elizabeth Selvin

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 8 months.

#### 4. Rationale:

There is increasing concern about the array of adverse outcomes associated with severe hypoglycemia, typically defined as an episode of low blood sugar requiring intervention by another person to correct blood glucose levels (Seaquist 2013, ADA 2017). Prior studies have shown that severe hypoglycemia is associated with increased risk of cardiovascular disease and all-cause mortality in type 2 diabetes (Zoungas 2010, Bonds 2010, Johnston 2011, Hsu 2013, Mellbin 2013, Khunti 2015). However, there is no clear biological mechanism tying severe hypoglycemia to long-term increased risk of cardiovascular events. While mechanistic studies have shown that severe hypoglycemia triggers inflammatory and pro-thrombotic responses, as well as ECG abnormalities and cardiac arrhythmias, once the hypoglycemia is resolved, these responses subside and seem unlikely to confer long-term risk (Chow 2014, Desouza 2003, Stahn 2014). However, in a recent Framingham study, investigators found that in participants who had atrial fibrillation secondary to other causes, such as surgery or infection, atrial fibrillation reoccurred in more than half of patients (Lubitz 2015). Thus, it is possible that single arrhythmic events triggered by other causes, such as hypoglycemia, could result in long-term risk. These patients could be a high-risk subgroup prone to similar adverse cardiovascular reactions to other subsequent stressors. Additionally, our previous work has tied severe hypoglycemia to greater subclinical myocardial damage assessed by high sensitivity cardiac troponin T, a potent indicator of poor prognosis (Lee 2015).

Others have posited that hypoglycemia may trigger cardiovascular events in individuals with existing cardiovascular disease, but not in those at low cardiovascular risk (Pistrosch 2015). This hypothesis is supported by one study that found no association between hypoglycemia and cardiovascular disease in individuals with low vascular risk, but a strong association in those with high vascular risk (Leong 2015). This hypothesis also seems to be borne out by largely null associations of hypoglycemia with cardiovascular disease in type 1 diabetes, who on average have lower cardiovascular risk than their type 2 counterparts (Khunti 2015, Gruden 2012). Residual confounding by diabetes severity is also a possible explanation for the observed associations. It remains unclear which particular cardiovascular risk factors may be altering the association of hypoglycemia with cardiovascular disease and death.

To our knowledge, this will be one of the first studies of hypoglycemia and cardiovascular disease, atrial fibrillation, and death in a community-based cohort. Most data on this topic comes from secondary analyses of randomized clinical trials, which are typically highly selective and often recruit high risk populations that may be far less representative of the general population of diabetes patients (Cruz-Jentoft 2013). Another source of evidence on this topic is from retrospective analyses of medical claims databases, which often lack information on important characteristics such as duration of diabetes and kidney function. The ARIC cohort is a well-characterized, representative cohort with adjudicated cardiovascular events over several decades. In the proposed study we will analyze hypoglycemia events that resulted in hospitalization and use linkage to CMS data to also capture those events treated in the emergency department or by ambulance. The combination of standardized, research-grade clinical characteristics, hospitalization surveillance and CMS data for hypoglycemia, adjudicated cardiovascular

events, and a cohort representative of the general population will result in an extremely high-quality study of hypoglycemia, cardiovascular disease and mortality.

## 5. Main Hypothesis/Study Questions:

Aim 1: To determine if severe hypoglycemia is associated with increased risk of cardiovascular disease, atrial fibrillation, all-cause mortality, CVD death, and non-CVD death.

Hypothesis 1: Overall, severe hypoglycemia will be associated with substantial (i.e. two-fold or greater) risk of cardiovascular disease (CVD), CVD death, all-cause mortality, and non-CVD death.

Aim 2: To assess whether the association between hypoglycemia and all-cause mortality is modified by baseline cardiovascular risk factors, including age, sex, race, blood pressure, cholesterol, kidney function, albuminuria, and hsCRP, or by time-updated characteristics, including hospitalizations for kidney disease.

Hypothesis 2a: There will be no substantial effect modification by cardiovascular risk factors.

## 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 with Visit 4 as baseline

Inclusion criteria: Diagnosed diabetes by visit 4, by self-report of diagnosis or use of glucose-lowering medications

Exclusion criteria: Missing covariates (see list of covariates below). For the analysis of CVD, we will exclude cases of prevalent CVD, and for the analysis of atrial fibrillation, we will exclude cases of prevalent atrial fibrillation.

Exposure: Severe hypoglycemia assessed with ICD-9 codes from ARIC/CMS hospitalizations and from linked CMS data on hospitalizations, emergency department visits and ambulance use from Visit 4 through December 31, 2013. Hypoglycemia will be identified by ICD-9 diagnosis codes following a validated algorithm that is modified slightly to exclude 270.3 (leucine-induced hypoglycemia), 775.0 (hypoglycemia in infants), and 775.6 (neonatal hypoglycemia) (Ginde 2008) (**Table 1**).

**Table 1. ICD-9 Coding Algorithm for Identification of Severe Hypoglycemia**

ICD-9 codes in 1 <sup>st</sup> position	Other restrictions
251.0x: Hypoglycemic coma	(none)
251.1x: Other specified hypoglycemia	

251.2x: Hypoglycemia, unspecified 962.3x: Poisoning by insulins or other anti-diabetic agents	
250.8x: Diabetes with other specified manifestations	Must not have codes specifying other diabetes complications used for 250.8: 259.8: Secondary diabetic glycogenosis 272.7: Diabetic lipidosis 681.xx, 682.xx, 686.9x: Cellulitis 707.1 – 707.9: Ulcers of the lower extremity 709.3: Oppenheim-Urbach syndrome 730.0 – 730.2, 731.8: Osteomyelitis

Outcomes: Cardiovascular disease will be defined as fatal and non-fatal myocardial infarctions, fatal and non-fatal stroke, and fatal coronary heart disease. Atrial fibrillation will be defined by hospitalization for atrial fibrillation from the ARIC hospital surveillance (discharge code of 427.31 in the absence of procedure codes 35.x or 36.x). CVD death, non-CVD death, and all-cause death are also main outcomes for this analysis.

Covariates: We will evaluate progressively adjusted models to understand which factors are most influencing the hypoglycemia associations. Although we do not believe that most cardiovascular risk factors will be associated with hypoglycemia and thus not confounders, we will mention these results in the manuscript for completeness.

**Model 1:** Age, sex, race-center

**Model 2:** Model 1 + likely confounders (diabetes medications, diabetes duration, fructosamine, low eGFR, albuminuria, education (or other SES metrics) and Digit Symbol Substitution Test race-specific z-score)

**Model 3:** Model 2 + cardiovascular risk factors (blood pressure, cholesterol, antihypertensive medication, cholesterol-lowering medication, smoking (current/former/never))

Effect modifiers: Age, sex, race, systolic blood pressure, LDL cholesterol, HDL cholesterol, eGFR, albuminuria, and hs-CRP. We will categorize the continuous variables, using clinically relevant cut-points when available.

Statistical Analysis:

First, we will conduct exploratory analyses, using Kaplan-Meier curves to examine the association of hypoglycemia and each outcome. We will look at which hypoglycemia risk factors are associated with cardiovascular disease, and which cardiovascular risk factors are associated with hypoglycemia, to determine which factors are likely confounders that should be adjusted for.

We will calculate incidence rates of each outcome with and without hypoglycemia, and compare the incidence rates using Poisson regression. To examine unadjusted and

adjusted associations of hypoglycemia with each outcome, we will use Cox-proportional hazards models with severe hypoglycemia as a time-varying exposure. We will test the proportional hazards assumption by visually examining the negative log-log survival plots. We will progressively adjust models as described above. Additionally, if there are enough individuals with repeated severe hypoglycemia events, we will create a time-varying variable for the number of severe hypoglycemic events and the association with each outcome.

To look for potential effect modification of the hypoglycemia-mortality association, we will categorize the cardiovascular risk factors and create interaction terms between the risk factor and hypoglycemia. We will plot the hypoglycemia hazard ratio for each level of the risk factor and test for statistical significance using the likelihood ratio test.

We will conduct three sensitivity analyses. First, we will restrict our study population to individuals aged 65 years and older with CMS Part B Fee-For-Service coverage at Visit 4, to ensure that there is no obvious bias produced by having differential ascertainment of hypoglycemia that is dependent on insurance status. Second, we will exclude individuals who reported exclusive insulin use at all four study visits, as they may be type 1 diabetes cases. Third, we will stratify on current insulin use to examine differences in the characteristics of these diabetes patients and determine if the association of hypoglycemia with CVD differs by current insulin use.

#### Limitations:

Similar to other analyses of severe hypoglycemia and cardiovascular disease, we will be limited by the number of hypoglycemic events in our study, expected to be between 100 and 200 events. However, given the strength of the association of hypoglycemia with cardiovascular disease and death observed in many other studies, we are likely to have statistically significant results. Another limitation is the potential for residual confounding: hypoglycemia is modeled as time-varying but almost all other covariates are measured only at baseline, so other covariates could have changed over time to increase risk of both hypoglycemia and the outcome, but these changes would not be captured in our analysis. A third limitation is the lack of A1c data at Visit 4, but fructosamine, a measure of 2-4 week average glycemia, should be able to rank participants by level of glycemic control. Finally, we likely have under-ascertainment of hypoglycemic events that were treated in the emergency room or ambulance only, since these events would not be captured for participants who do not have CMS fee-for-service Part B insurance. A prior study has shown that individuals within ARIC with fee-for-service Part B coverage do not differ systematically from those without that coverage (Results from MS 2161, not yet published).

**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  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/search.php>

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)?

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 (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.csc.unc.edu/anic/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.csc.unc.edu/anic/index.php>, under

Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](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](mailto:pingping_wu@unc.edu). I will be using CMS data in my manuscript  Yes  No.

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