ARIC Manuscript Proposal # 3082

PC Reviewed: 11/14/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Severe Hypoglycemia and Risk of Falls in Type 2 Diabetes: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Hypoglycemia and Falls

2. Writing Group:

Writing group members: Alexandra K. Lee, Stephen P. Juraschek, B. Gwen Windham, Clare J. Lee, 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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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:

Falls and fractures have a high burden of morbidity and mortality among older adults (CDC 2008). It is estimated that of adults over age 65, one-third fall each year (Gill 2005), and falls are the leading cause of injury-related death among older adults in the US (Hu 2009). Falls resulting in serious fractures can also lead to a downward spiral in health: following a hospitalization for hip fracture, one year cumulative mortality is over 20% in older adults (Brauer 2009).

Falls are of particular concern to individuals with diabetes since prolonged exposure to hyperglycemia is thought to impair bone health. In type 2 diabetes, while bone mass remains normal or is even greater than those without diabetes, poor bone quality increases the risk of fracture with falling (Hamann 2012). Additionally, thiazolidinediones (TZDs) are known to interfere with osteogenesis and increase the risk of fracture, particularly in post-menopausal women, and thus are generally not recommended in this group (Colhoun 2012, Inzucchi 2015). SLGT2s may also cause bone loss; increased fracture risk has been observed in clinical trials (Meier 2016, Taylor 2015). Long-term complications of diabetes, such as retinopathy and peripheral neuropathy, have also been associated with decreased bone mass and increased risk of falls (Hamann 2012, Agrawal 2010).

Hypoglycemia may also pose a risk for falling. Autonomic symptoms of hypoglycemia, such as tremor, palpitations, and arousal are the earliest warning signs of hypoglycemia, but these symptoms may be reduced in older compared to younger adults (Cryer 2005, Zammit 2005, Bremer 2009). These symptoms of mild hypoglycemia could increase the risk of falling. More severe symptoms resulting from neuroglycopenia, or lack glucose to the brain, include cognitive impairment, ataxia, and loss of consciousness, which could directly lead to a fall (Johnston 2012, Cryer 2005). Both hypoglycemia and hyperglycemia can also cause blurred vision through an osmotic effect on lenses, which could contribute to fall risk (Malabu 2014). Thus, hypoglycemia, either mild or severe, could lead to increased risk of falls. It is also possible that a fall is either indicative of or causes declining health status, which could in turn lead to hypoglycemia. Given that hypoglycemia is common in older age and falls have more serious consequences for older adults, it is important to fully understand the possible danger of falling associated with hypoglycemia.

There have been few studies of hypoglycemia and falls in persons with diabetes. Two cross-sectional studies showed strong associations, but one included only 77 participants (Tilling 2006, Johnston 2012). Two prospective studies also found a fairly strong association, but they relied exclusively on claims data to capture comorbidities, meaning that they could not account for glycemic control or other lab-based markers of health (Lu 2015, Signorovitch 2013). One of these prospective studies also excluded insulin users, the highest-risk group for severe hypoglycemia. Thus, there is need for prospective studies with well-characterized participants and long follow-up to better address this important question.

We propose to evaluate the potential association of severe hypoglycemia with risk of falls in the ARIC cohort. Using the ARIC hospitalizations as well as the CMS claims, we can ascertain both hypoglycemia and falls in the ARIC cohort using ICD-9 codes, which are likely highly specific but may have low to moderate sensitivity (Ginde 2008,

McKenzie 2009). Our study will also benefit from rigorous measurements of kidney function, glycemic control, and other important clinical characteristics which are important confounding variables.

5. Main Hypothesis/Study Questions:

Aim: To determine if a history of severe hypoglycemia is associated with subsequent falls among black and white adults with diagnosed diabetes in the ARIC study.

> Hypothesis: Severe hypoglycemia will be associated with increased risk of falls, but the association will be substantially attenuated after adjusting for baseline functional abilities, such as ADLs, IADLs, and cognitive performance.

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), falls prior to Visit 4 (baseline).

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 through 2013. 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, 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 but is modified slightly to exclude 270.3 (leucine-induced hypoglycemia), 775.0 (hypoglycemia in infants), and 775.6 (neonatal hypoglycemia), codes that are unlikely to be present for ARIC participants and do not represent hypoglycemia in diabetes (Ginde 2008).

Outcome: The primary outcome will be any type of fall (see list below), defined by ICD-9 codes, from both ARIC hospitalizations and CMS inpatient and outpatient claims, through 2013. Individuals with falls prior to Visit 4 will be excluded from analysis.

Fall Grouping	ICD-9 codes
Falls unspecified	E888.0 E888.1, E888.8, E888.9
Falls on the same level	E885.0-E885.4, E885.9, E886.0, E886.9

Falls from a different level	E880.0, E880.1, E880.9, E881.0, E881.1, E882.0, E883.0-E883.2, E883.9, E884.0-E884.6, E884.9

The secondary outcome will be syncope events, identified by ICD-9 code 780.2, from Visit 4 to 2013. While syncope symptoms are more likely to be vasovagal or arrhythmic in origin, an ICD-9 code for syncope may be less specific to this etiology and relate to general loss of balance, which could have been caused by unrecognized mild hypoglycemia.

We will also explore using the self-reported falls data from the annual follow up interviews (forms GNB in 2012, GND in 2015, GNE in 2016), but it is likely that a large fraction of our study population (participants with diagnosed diabetes at Visit 4) will not have survived to 2012 or beyond.

Covariates:
For the Cox regression models with time-varying exposure. All covariates assessed at Visit 4 unless noted otherwise.

Model 1: age, sex, race-center
Model 2: Model 1 + indicators of diabetes severity: diabetes duration, diabetes medication use (none/oral only/any insulin), glycemic control (fructosamine tertiles)
Model 3: Model 2 + diabetes complications: eGFR, albuminuria, retinopathy (from Visit 3)
Model 4: Model 3 + other shared risk factors: DSST race-specific z-score, ADL disability, IADL disability, anti-depressant use, income (from Visit 1).

Statistical Analysis:

First, we will examine the incidence rate of falls, categorizing participants' person-time into "no prior episodes of severe hypoglycemia" and "any prior episodes of hypoglycemia." We will calculate both crude and age- and sex-adjusted incidence rates.

Next, we will use Cox proportional hazards regression to examine the association of severe hypoglycemia (as a time-varying exposure) with the primary and secondary outcomes. We will exclude individuals with a history of falls prior to Visit 4 for the analysis of falls. Models will be adjusted as described above (under Covariates). Since both diabetes severity and diabetes complications are associated with both severe hypoglycemia and falls, these factors are likely confounders that will be adjusted for in our models (Lee 2017, Lipska 2013, Leese 2003, Huang 2014, Agrawal 2010, Schwartz 2008). Additionally, there are several other factors, such as cognitive function, disability, anti-depressant use, and income that are also associated with both hypoglycemia and falls (Deandrea 2010, Leese 2003, Lee 2017, Thapa 1998). We will verify the proportional-hazards assumption is not violated by visually inspecting the negative log-log survival curves.

We will also examine if any severe hypoglycemia episodes also have codes for falls on the same medical claim, which would support the idea that hypoglycemia is an immediate, direct cause of a fall. An alternative possibility is that hypoglycemia and falls

both occur in vulnerable, frail adults, yet hypoglycemia itself does not cause falls, but it is not possible to directly test this hypothesis.

We will conduct several sensitivity analyses. First, we will restrict our study population to individuals with CMS Part B Fee-For-Service coverage at Visit 4. Second, we will include people with a history of falls at Visit 4, since these are likely the highest-risk individuals.

Limitations:

A primary limitation will be potentially limited power due to the small number of severe hypoglycemia events detected in ARIC. Secondly, for both hypoglycemia and falls, we are limited to cases that have been reported in the medical records and while this likely has high specificity, sensitivity is likely low to moderate. Third, we are using fructosamine rather than HbA1c to characterize glycemic control. Finally, while we are able to control for a number of potential confounders, we only have assessments at our study baseline (visit 4), and are unable to account for factors (such as diabetes medication and kidney function) that are likely to change over the 15-year follow-up period.

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)?

Juraschek SP, Daya N, Appel LJ, Miller III ER, Windham BG, Pompeii L, Griswold ME, Kucharska-Newton A, Selvin E. Orthostatic Hypotension in Middle-Age and Risk of Falls. Am J Hypert 2017;30(2):188-195.

Juraschek SP, Daya N, Rawlings AM, Appel LJ, Miller III ER, Windham BG, Griswold ME, Heiss G, Selvin E. Association of History of Dizziness and Long-term Adverse Outcomes with Early vs. Later Orthostatic Hypotension Assessment Times in Middle-aged Adults. JAMA Intern Med. 2017;177(9):1316-1323.

Deal JA, Sharrett AR, Bandeen-Roche K, Kritchevsky SB, Pompeii LA, Windham BG, Lin FR. Hearing Impairment and Physical Function and Falls in the Atherosclerosis Risk in Communities (ARIC) Hearing Pilot Study. J Am Geriatr Soc 2016;64(4):906-908.

Lee AK, Lee CJ, Huang ES, Sharrett AR, Coresh J, Selvin E. Risk Factors for Severe Hypoglycemia in Black and White Adults with Diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. Diabetes Care; 2017 Sept: dc170819.

Lee AK, Warren BW, Lee CJ, McEvoy JW, Matsushita K, Huang ES, Sharrett AR, Coresh J, Selvin E. The Association of Severe Hypoglycemia with Incident Cardiovascular Events and Mortality in Adults with Type 2 Diabetes (in press, *Diabetes Care*)

Schneider ALC, Williams EK, Brancati FL, Blecker S, Coresh J, Selvin E. Diabetes and risk of fracture-related hospitalization: the Atherosclerosis Risk in Communities Study. Diabetes Care. 2013;36(5):1153-1158.

MP #2381: Falls Prevalence in Older Black and White ARIC Participants. Lisa Pompeii, Kelley Gabriel, Gwen Windham, Anna Kucharska-Newton, Wanmei Wong, Michael Griswold, Kenneth Butler, Elizabeth Selvin, Tom Mosley.

MP#2589: Trajectories of physical activity in mid-life and risk of functional decline and falls in later life. Kelley Pettee Gabriel, Lisa Pompeii, Michael Griswold, B Gwen Windham, Wanmei Wang, Tom Mosley, Anna Kucharska-Newton, Priya Palta.

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.

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