ARIC Manuscript Proposal #3029

PC Reviewed: 8/8/17          Status: _____          Priority: 2
SC Reviewed: ________          Status: _____          Priority: _____

1.a. Full Title: Glycemia and short-term outcomes in older adults with diabetes

b. Abbreviated Title (Length 26 characters): Diabetes overtreatment


I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.  MJ [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:
   - We expect to have a full draft of the manuscript within one year of the proposal approval.
4. **Rationale:**

There is uncertainty regarding the balance of risks and benefits of tight glycemic control in older adults with type 2 diabetes. The American Diabetes Association (ADA) and the American Geriatric Society (AGS) jointly developed a framework using the number of comorbidities, cognitive status, functional status, and life expectancy to define a three-tiered health status indicator for stratifying glycemic targets in adults aged 65 years and older (1). Under this rubric, healthy older adults are defined as those with intact cognitive and functional status and fewer than three chronic conditions requiring medications or lifestyle management. Persons with complex health are defined as those with three or more chronic conditions, mild-to-moderate cognitive impairment, or impairments in two or more basic and instrumental activities of daily living. Very complex health status is used to refer to persons with an end-stage chronic illness that reduces life expectancy and may cause significant functional impairments. Both the ADA and AGS recommend higher glycemic targets for persons with complex or very complex health status (2,3). Citing concerns for hypoglycemia and mortality, the AGS and other organizations including the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes recommends not targeting HbA1c below 7% for any older adults with diabetes (3,4). ADA guidelines do not provide a lower limit for HbA1c targets in older adults.

There is a growing body of literature suggesting a high prevalence of potential overtreatment of diabetes in older adults and the lack of individualized treatment plans. In the Veteran’s Health Administration, 50% of older adults on antidiabetic medication that are associated with hypoglycemia (i.e., insulin and sulfonylureas) had HbA1c <7.0% (5). The prevalence was similar in subgroup analyses that stratified by dementia and end-stage disease status. Using data from the National Health and Nutrition Examination Survey, Lipska et al observed that over 60% of older adults with diabetes had HbA1c <7% and that the prevalence was not different by health status (6). Additionally, in people with HbA1c <7%, the use of antidiabetic medication that are associated with hypoglycemia was similar across health status groups, thus suggesting a lack of medication adjustment to reduce hypoglycemia risk and to de-intensify glycemic control in persons meeting their glycemic target. Furthermore, these results suggest a high proportion of older adults with complex health status may be inappropriately treated.

While HbA1c values <7% have been widely documented in older adults with diabetes, the mortality implications of HbA1c values below this threshold in older adults with diabetes are unclear. The objective of our study is to evaluate the determinants of HbA1c values <6% and <7% in older adults and investigate the association of glycemia with short-term cardiovascular risk and mortality. A focus of the study will be to evaluate possible differences in the associations of glycemia with cardiovascular risk and mortality by health status and the number and type of diabetes medications. Our results should help inform the ongoing debate concerning tight glycemic control in older adults with diabetes.
5. Main Hypothesis/Study Questions:

Aim 1: To identify determinants of low HbA1c (<6% or 6-7%) in older adults with diagnosed diabetes who attended visit 5 (2011-2013) of the community-based ARIC Study.

Hypothesis 1: We hypothesize that persons with diabetes and a low HbA1c will be a mix of healthy and unhealthy older adults. Healthy older adults with a low HbA1c will have had a more recent diagnosis of diabetes, fewer number of glucose-lowering medications, and higher proportion of meeting blood pressure and statin-use recommendations compared to unhealthy older adults with tight glycemic control.

Aim 2: To investigate the associations of glycemia with short-term (~3-year) cardiovascular risk and mortality in persons with diagnosed diabetes. We will also examine the continuous association of HbA1c with cardiovascular risk and mortality. We will evaluate potential differences in the associations (effect modification) by health status (healthy, complex, or very complex), which accounts for pre-existing history of cardiovascular disease, and number and type of glucose-lowering medications.

Hypothesis 2: We hypothesize that low HbA1c (<6% or 6-7%) will be associated with a higher risk of mortality and cardiovascular risk compared to persons with moderate glycemia (HbA1c 7-8.5%). The associations will be stronger in persons with complex or very complex health status and those persons on glucose-lower medications (especially sulfonylureas and/or insulin). We also hypothesize that there will be a U-shaped association of HbA1c with cardiovascular risk and mortality (highest risk at the lowest and highest levels of HbA1c) in this population of older adults with diagnosed diabetes.

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 methodological limitations or challenges if present).

Design: Prospective cohort analysis.

Inclusion/exclusion: We will include participants with diagnosed diabetes at visit 5. Diagnosed diabetes will be defined as those participants who self-report a physician diagnosis or who are currently taking glucose-lowering medications. Due to small numbers, we will additionally exclude the following participants: 1) those who do not self-identify as white or black, 2) blacks from Washington County, and 3) blacks from Minnesota field centers.

Exposure: HbA1c levels at visit 5 (HbA1c <6, 6-7%, 7-8.5%, and >8.5%).

Possible determinants of HbA1c for Aim 1:

- Demographic characteristics: age, sex, race-center (white-Minnesota, white-Maryland, white-North Carolina, black-Mississippi, or black-North Carolina), and highest educational attainment (less than high school, high school or equivalent, and greater than high school).
- Diabetes-related variables: diabetes duration (years between first report of diagnosed diabetes and date of exam at visit 5), number of diabetes medication use (count), type of diabetes medication use (none, orals only, insulin only, both orals and insulin), sulfonylurea use, and insulin use.
- Meeting cardiovascular disease management guidelines: The ADA recommends monitoring and management of hypertension, dyslipidemia, and smoking status in
persons with diabetes to reduce cardiovascular disease risk in older adults with diabetes. We will define hypertension control according to the ADA 2017 guidelines as systolic blood pressure less than 140 mm Hg and diastolic blood pressure less than 90 mm Hg; dyslipidemia management should include statin use according to clinical guidelines; and participants who are never or former smokers will be categorized as meeting smoking guidelines (7). These variables will be assessed as a binary variable (yes or no) in analyses.

- Participant health status. We will define health status as a three-level variable (healthy, complex health, and very complex health) using the ADA and AGS jointly developed framework for stratifying glycemic targets in older adults (2). The chronic conditions that require medication or lifestyle management are arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, chronic kidney disease, myocardial infarction, and stroke. End-stage diseases are congestive heart failure, oxygen-dependent lung disease, chronic kidney disease requiring dialysis, and metastatic cancer. Details on how each variable will be identified and operationalized in the analysis is available on the next page. Healthy older adults are those with fewer than three coexisting chronic illnesses (listed below), intact cognitive status, and intact functional status. Complex health refers to those with three or more coexisting chronic illnesses and two or more basic and instrumental activities of daily living impairments, or mild-to-moderate cognitive impairment. Very complex health refers to older adults who require long-term care or with end-stage chronic illness. We will additionally consider how the presence or absence of the individual components are associated with glycemia in older adults with diabetes.

Possible effect measure modifiers in Aim 2:

- Health status
- Number of antidiabetic medications
- Type of antidiabetic medications

Outcome: We will examine associations with adjudicated cardiovascular events (fatal or non-fatal CHD, stroke, or heart failure) and all-cause mortality using the most recent follow-up data available. Cardiovascular endpoints are identified by ongoing community surveillance (8,9), with events validated by a physician review of medical records using standardized criteria. Vital status of ARIC participants is monitored using annual phone follow-up, community-wide hospital surveillance, and linkage to local and national death registries. Date of death is ascertained by death certificate review.

Statistical Methods

We will identify determinants of HbA1c levels by comparing the distributions of demographic characteristics, diabetes related variables, and other health variables by HbA1c level (<6%, 6-7%, 7-8.5%, or >8.5%). We will test for differences in the distribution using X² tests. In order to identify the independently associated determinants of tight glycemic control, we will fit multivariable polynomial logistic regression models with HbA1c 7-8.5% as the reference group.

To examine the associations of HbA1c with short-term cardiovascular disease and all-cause mortality, we will fit Cox regression models with visit 5 as the time origin and years of follow-up as the time scale. We will consider HbA1c as a categorical (HbA1c <6%, 6-7%, 7-8.5%, or
>8.5%) and continuous variable. In analyses using HbA1c as a categorical variable, we will use HbA1c 7-8.5% as the reference group. When HbA1c is assessed as a continuous variable, we will use spline terms at HbA1c 6.0%, 7.0%, and 8.5% to account for possible non-linear associations between HbA1c and outcomes. We will fit a series of multivariable models to adjust for potential confounders to assess the independent association between HbA1c level and short-term cardiovascular disease and all-cause mortality.

Proposed adjustment models:
- Model 1: Unadjusted
- Model 2: Adjusted for age, sex, race, center, and highest educational attainment
- Model 3: Variables in Model 2 plus variables for meeting cardiovascular disease management guidelines for blood pressure, dyslipidemia, and smoking.

To evaluate differences in the association between HbA1c and short-term cardiovascular disease and mortality, we will stratify the by health status (healthy, complex, and very complex), number of glucose-lowering medications, and treatment modality (none, orals only, insulin only, or both orals and insulin). When sample size permits, we will stratify by age at visit 5 (less than 74 vs. 75 or older), sex (male vs. female), and race (black vs. white) to identify vulnerable populations.

A threshold of HbA1c 8.5% is high for healthy older adults with long life expectancy. In sensitivity analyses, we plan to consider a cut-point of HbA1c of 8.0% instead of 8.5%.

Potential limitations:
- We are limited to one HbA1c measure at visit 5 and cannot assess it as a time-varying exposure.
- Treatment preference by the physician and patient is unknown and cannot be evaluated.
- Adherence to medication use was not directly observed.
- Results will be limited to non-institutionalized older adults.

Appendix Table: Variables that will be considered for defining health status

<table>
<thead>
<tr>
<th>Variable</th>
<th>ARIC variable description</th>
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<tbody>
<tr>
<td>Chronic illness – The ADA/AGS framework defines chronic illness as a condition requiring medication or lifestyle management.</td>
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<tr>
<td>1. Arthritis</td>
<td>Arthritis status was evaluated in the inflammation questionnaire at visit 4 but not at visit 5. We will identify people as having arthritis if they reported arthritis at visit 4, having pain that limited their ability to perform the grip strength test at visit 5, or reported taking medications for arthritis, fever, or aches. A limitation of using medication use for arthritis, fever, or aches is that it is not specific to arthritis alone.</td>
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<tr>
<td>2. Cancer</td>
<td>Prevalent cancer will be defined for any participant with an adjudicated cancer event by visit 5.</td>
</tr>
<tr>
<td>3. Congestive heart failure</td>
<td>Prevalent heart failure will be defined for persons with a prior hospitalization classified as probably or chronic heart failure or heart failure reported on the Physician Heart Failure Survey or hospitalization with an ICD code for heart failure (ie, 428.x in first position before 1/1/2005).</td>
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</tbody>
</table>
4. Depression

Depression symptoms in the past week were evaluated in the 20-item Center for Epidemiologic Studies Depression scale (CES-D) (10). Each item is scored on a scale of 0-3; a higher value corresponds to more depressive symptoms. A cut-point of 16 is often used to identify persons with major depression (11). We will define depression if anti-depressant medication use was reported in the ARIC medication inventory or is a participant scored 16 or higher on the CES-D.

5. Emphysema

Prevalent emphysema will be defined if participants reported taking medication for chronic bronchitis or emphysema. A limitation of this variable is that it is not specific to emphysema alone.

6. Falls

Prevalent fall by visit 5 will be defined for persons with any fall-related hospitalization using ICD9 discharge codes from hospital or Centers for Medicare and Medicaid Services (CMS) claims (12). Hospitalization data will be obtained from active surveillance on all ARIC participants and CMS data will be linked to ARIC participants.

7. Hypertension

Systolic blood pressure greater than or equal to 140 or diastolic blood pressure greater than or equal to 90 or hypertension medication use at visit 5.

8. Incontinence

We will exclude incontinence in the primary analysis since it is available in a subset of visit 5 participants (n=2,985) who had a Clinical Dementia Rating Informant interview.

9. Chronic kidney disease - stage 3 or worse

We will define using the KDIGO 2012 cut-points using estimated glomerular filtration rate categories alone, albuminuria categories alone, or both (13). The primary definition for CKD will be defined using estimated glomerular filtration rate with creatinine, cystatin C, age, sex, and race, and the albumin-to-creatinine ratio.

10. Myocardial infarction

Prevalent myocardial infarction will be defined for persons with an adjudicated event by visit 5.

11. Stroke

Prevalent stroke will be defined for persons with an adjudicated event by visit 5.

Cognitive impairment

The ADA and AGS framework considers persons with mild-to-moderate cognitive impairment as having complex health. We will define mild-to-moderate cognitive impairment as those having a visit 5 cognitive status diagnosis of mild cognitive impairment or dementia.

Activities of daily living (ADL)

Basic and instrumental ADL was assessed by asking participants if they had difficulty walking from one room to another on the same level, getting in or out of bed, eating, dressing, doing chores around the house, preparing own meals, and managing money in the annual and semi-annual telephone calls contemporaneous to visit 5. Possible responses were “no difficulty”, “some difficulty”, “much difficulty”, or “unable to do”. We will consider those who report “much difficulty” or “unable to do” as having an
impairment for the queried ADL task.

**Long-term or end-stage disease – the ADA/AGS framework considers conditions that significantly reduces functional status and life expectancy.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1. Congestive heart failure, stage 3-4</td>
<td>Congestive heart failure staging class I-IV refers to severity of their symptoms. HF symptom severity was not assessed at ARIC visit 5. As an alternative, we will use the American College of Cardiology (ACC)/American Heart Association (AHA) Heart Failure Staging as done by Dr. Shah using ARIC visit 5 data (14). The ACC/AHA Heart Failure Staging has six categories (Stage 0, A, B, C1, C2, and D) and is classified using information on prevalent cardiovascular disease, cardiac structural or functional abnormalities, and previous hospitalizations or treatment for heart failure (15). We will consider people with HF stage C2 as having long-term HF.</td>
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<tr>
<td>2. Oxygen-dependent lung disease</td>
<td>Persons who respond yes to both “Has a doctor ever told you that you have emphysema or chronic obstructive pulmonary disease” and “Do you still have it” will be considered to have current lung disease. A limitation of this method is that persons with lung disease may not be oxygen-dependent. We will use an alternative definition using spirometry data in a sensitivity analysis. A spirometry test was conducted during ARIC visit 5 but it is only available in approximately 67% of the participants. Individuals with very severe COPD defined using the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease have appreciably impaired quality of life and are recommended to receive long-term oxygen therapy (16). Persons with very severe COPD will have FEV1/FVC&lt;70% or FEV1&lt;30% predicted. We will not use the third definition for very severe COPD (FEV1&lt;50% predicted plus chronic respiratory failure) as chronic respiratory failure is not available in ARIC.</td>
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<tr>
<td>3. Chronic kidney disease requiring dialysis</td>
<td>We will link visit 5 data to the USRDS registry. Those in the registry will be considered to have permanent end-stage renal disease.</td>
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<td>4. Uncontrolled metastatic cancer</td>
<td>Not available.</td>
</tr>
</tbody>
</table>

References:

3. America Geriatrics Society Expert Panel. Guidelines abstracted from the American


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)?

There are no related manuscripts.

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

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

___ X__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)*: 2009.16)

*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, approved manuscripts using 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 _____ Yes ___X___ No.