

ARIC Manuscript Proposal #3546

PC Reviewed: 1/14/20
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Status: _____
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Priority: 2
Priority: _____

1.a. Full Title: Mortality implications of comorbidities in older adults with diabetes

b. Abbreviated Title (Length 26 characters): Diabetes & health older adults

2. Writing Group:

Writing group members: Mary R Rooney, Olive Tang, Gwen Windham, Justin Echouffo Tcheugui, Pamela L Lutsey, Morgan Grams, Elizabeth Selvin. Others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. MRR [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:

Data analysis to begin immediately. Manuscript completion within 1 year.

4. Rationale:

The 2020 American Diabetes Association guidelines (1) provide a framework for treating older adults with diabetes (shown in the **Appendix** and referred to herein as “ADA Table of Comorbidities”). This framework recommends treatment goals based on the older patients’ comorbidity burden and functional status. The comorbidities include (but are not limited to): “arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke”, as well as the consideration of the cognitive function and activities of daily living dependencies, with three or more comorbidities reflecting a high burden (2). High comorbidity burden has been

associated with mortality (3; 4), however older adults are a heterogeneous population and using comorbidities to personalize treatment decisions is difficult to operationalize (5).

The ADA Table of Comorbidities sets forth a framework for setting different goals for glycemic control. The rationale for differing HbA1c goals by health status are driven by life expectancy and time to benefit principles, under the assumption that older adults with diabetes who have very complex or poor health status may be at highest risk for adverse effects of treatment and less likely to benefit from intensive glucose control. Yet, the prognosis of diabetes in older adults is poorly characterized (6). It is also unclear whether the health status categories set forth in the ADA guidelines, or specific combinations of conditions, provide discrimination for mortality risk (7). We will use data from the ARIC study to inform the current framework for treatment goals among older adults with diabetes.

5. Main Hypothesis/Study Questions:

Among older adults with diabetes, we aim to:

- 1) characterize the health status of older adults with diabetes according to the Table of Comorbidities,
- 2) describe the percent of participants according to ADA comorbidity categories and HbA1c treatment goals,
- 3) examine associations of health status categories with mortality and total hospitalizations during ~5 years of follow-up, overall and stratified by HbA1c categories.

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: We will restrict our analyses to participants with diagnosed diabetes (self-report physician diagnosis or use of diabetes medication).

- 1) Cross-sectional at visit 5 for characterizing comorbidity burden and percent meeting ADA HbA1c goals according to ADA Table of Comorbidities definitions
- 2) Prospective from visit 5 (baseline) for mortality and number of hospitalizations according to ADA Table of Comorbidities definitions

Exclusion: Of participants who attended visit 5, we will exclude those who:

- 1) are neither black nor white, blacks at the Maryland and Minnesota center,
- 2) missing information on diabetes status or HbA1c

Exposures: arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3+ chronic kidney disease, myocardial infarction, stroke, dementia, frailty, functional status

Summary Table of ADA Comorbidities

Comorbidity	Description
Arthritis	Self-reported at visit 4 (1996-1998)
Cancer	Ascertained via linkage to cancer registries, and via prospective follow-up since 2011

Congestive heart failure	Self-report at ARIC visit 1 (1987-1989) or subsequent adjudicated hospitalization prior to visit 5
Depression	Center for Epidemiological Studies Depression 12-item screening score of ≥ 16 or self-reported depression affecting daily life at visit 5.
Emphysema	(Emphysema or COPD) Self-reported at visit 5
Falls	Hospitalization code prior to visit 5
Hypertension	Measured visit 5 blood pressure $\geq 140/90$ (based on mean of second and third measurement) or hypertension medication use
Hypoglycemia	Ascertained through June 2, 2011 from hospitalization ICD-9 codes in the primary position based on records from ARIC surveillance of local community hospitals and medical record abstractions for hospitalizations outside the ARIC surveillance system. Additional events were identified with linkage to Medicare claims for hospitalizations, emergency department visits, and ambulance services are available for participants enrolled in Medicare fee-for-service part B.
Incontinence	Self-reported at visit 5
Chronic kidney disease	eGFR < 60 mL/min per 1.73 m^2 based on the CKD-EPI equation using cystatin c and creatinine at visit 5
Myocardial infarction	Self-report at ARIC visit 1 (1987-1989) or subsequent adjudicated hospitalization prior to visit 5
Stroke	Self-report at ARIC visit 1 (1987-1989) or subsequent adjudicated hospitalization diagnosis between visits 1 and 5

“High comorbidity burden” refers to 3 or more of the above coexisting illnesses per ADA definitions.

Other comorbidities we will consider, as they are highly relevant to this age group:

- Dementia based on detailed neurocognitive testing and adjudication (8).
- Frailty based on the Fried et al. criteria as previously described in ARIC (9; 10).
- Functional status based on SPPB < 7 as “poor function” or gait speed $< 0.8 \text{ m/s}$ (11).

Health status categories:

- Healthy: 0-2 ADA comorbidities, no dementia, no frailty, and good functional status
- Complex/intermediate: ≥ 3 ADA comorbidities, no dementia, no frailty, and good functional status
- Very complex/poor: dementia or frailty or poor functional status

Outcomes: all-cause mortality; cardiovascular mortality, number of hospitalizations

Other variables: age, sex, race, study center, current smoking, current drinking, BMI, systolic blood pressure, diastolic blood pressure, eGFR, anti-hypertensive medication use, total cholesterol, HDL-cholesterol, cholesterol-lowering medication use, HbA1c

Statistical Analysis

We will describe the proportion of individuals with each comorbidity listed above, and the proportion within each health status category [healthy, complex/intermediate, very complex/poor]. Further, we will describe the proportion meeting their respective HbA1c goals according to ADA health status-specific goals and by HbA1c categories (<7.0%, 7.0-<8.0%, ≥8.0%) for each comorbidity burden category. We will further describe the proportion with HbA1c below 7.0% and the proportion who were being treated with insulin and other glucose-lowering medications.

Multivariable Cox proportional hazards will be used to examine associations between health status categories (and individual comorbidities) with all-cause and cardiovascular mortality through the most recent follow-up available. We will further stratify these prospective associations by HbA1c categories. We may also explore shorter-term mortality risk (e.g. 1 year mortality). Poisson regression will be used to look at number of hospitalizations across health status categories. We will estimate life expectancy using an Accelerated Failure Time model with covariates.

- Model 1 = age, sex, race-center
- Model 2 = Model 1 + smoking status, drinking status, BMI, systolic blood pressure, antihypertension medication use, eGFR, HDL, total cholesterol, cholesterol-lowering medication use

Limitations

There may be small numbers when stratifying by comorbidity burden and HbA1c at visit 5, particularly as we are further restricting analyses to individuals with diagnosed diabetes (~30% of ARIC participants at visit 5). When examining the cumulative influence of the comorbidities (using the categories) on the outcomes, we are indirectly assuming that the comorbidities have equal weights, which may not be true. We will consider using alternative definitions of predictors such as combining groups that appear similar depending on results for exploratory data analyses.

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.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)?

- ARIC MS proposal #3033 (Selvin) - Short-term mortality and cardiovascular risk in older adults with diabetes or prediabetes
- ARIC MS proposal #3477 (Rooney) – Diabetes progression in older adults
- ARIC MS proposal #3454 (Rooney) – Hemoglobin A1c and outcomes in older adults

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* 2009.16)**
 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/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.csc.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.

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Appendix. ADA Table of Comorbidities

Table 12.1—Framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes (2)

Patient characteristics/ health status	Rationale	Reasonable A1C goal‡	Fasting or preprandial glucose	Bedtime glucose	Blood pressure	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.5% (58 mmol/mol)	90–130 mg/dL (5.0–7.2 mmol/L)	90–150 mg/dL (5.0–8.3 mmol/L)	<140/90 mmHg	Statin unless contraindicated or not tolerated
Complex/intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0% (64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)	<140/90 mmHg	Statin unless contraindicated or not tolerated
Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	<8.5%† (69 mmol/mol)	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)	<150/90 mmHg	Consider likelihood of benefit with statin (secondary prevention more so than primary)

This represents a consensus framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes. The patient characteristic categories are general concepts. Not every patient will clearly fall into a particular category. Consideration of patient and caregiver preferences is an important aspect of treatment individualization. Additionally, a patient's health status and preferences may change over time. ‡A lower A1C goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden. *Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. "Multiple" means at least three, but many patients may have five or more (54). **The presence of a single end-stage chronic illness, such as stage 3–4 congestive heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy. †A1C of 8.5% (69 mmol/mol) equates to an estimated average glucose of ~200 mg/dL (11.1 mmol/L). Looser A1C targets above 8.5% (69 mmol/mol) are not recommended as they may expose patients to more frequent higher glucose values and the acute risks from glycosuria, dehydration, hyperglycemic hyperosmolar syndrome, and poor wound healing. ADL, activities of daily living.