

ARIC Manuscript Proposal # 1539

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Priority: 2
Priority: _____

1.a. Full Title: Hemoglobin A1c (HbA1c) Cut-points and Risk of Kidney Disease and Prevalent Retinopathy

b. Abbreviated Title (Length 26 characters): HbA1c and microvascular disease

2. Writing Group:

Writing group members: Elizabeth Selvin, Mike Steffes, Brad Astor, Lori Bash, Ronald Klein, Tien Wong, Josef Coresh, Richey Sharrett, Frederick L. Brancati, others welcome

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

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3. Timeline: All HbA1c assays were completed in 2008. In light of recent recommendations for the use of HbA1c for the diagnosis of diabetes and the clinical relevance of these data, we aim to have this manuscript submitted to the ARIC publications committee in <1 year from the approval date.

4. Rationale:

In June 2009, an International Expert Committee appointed by the American Diabetes Association recommended the use of HbA1c for the diagnosis of diabetes (1). The clinical cut-points recommended in the report—HbA1c of 6.5% for diagnosis and 6- <6.5% for receipt of “demonstrably effective interventions”—are controversial. The Expert Committee justified the new diagnostic cut-point for diabetes of 6.5% based on microvascular risk, specifically “the substantial increase in prevalence of moderate retinopathy at A1c levels $\geq 6.5\%$.” Nonetheless, population-based studies of HbA1c levels in persons without a history of diabetes for the prediction of microvascular outcomes—typically retinopathy and kidney disease—are sparse. The overarching objective of this manuscript is to examine the association of a single baseline HbA1c measurement in persons without a prior history of diabetes with risk of microvascular outcomes (retinopathy and kidney disease) in the ARIC Study.

5. Main Hypothesis/Study Questions:

Aim: To determine the association of fasting glucose concentrations and HbA1c levels at baseline and the development of kidney disease and prevalent retinal disease. We will employ state-of-the-art statistical techniques to evaluate thresholds in any observed associations.

Hypothesis 1: fasting glucose and HbA1c will be independently associated with incident kidney disease and prevalent retinopathy after adjustment for known risk factors

Hypothesis 2: HbA1c will be superior to fasting glucose with steeper slopes and significantly improved risk discrimination in models of retinopathy and kidney disease

In light of recent recommendations for the use HbA1c for diagnosis of diabetes, a goal of these analyses will be to compare clinically relevant categories of HbA1c and fasting glucose (alone and in combination) in persons without a prior history of diabetes for the identification of persons at high risk for clinical outcomes.

In testing these hypotheses, we will also pay particular attention to possible differences by race/ethnicity. Race/ethnic disparities in HbA1c levels are well documented (2-6), with blacks having significantly higher HbA1c levels compared to whites even in the normal range. The clinical implications of racial differences in HbA1c are unknown and limited data exist on HbA1c and microvascular disease among African Americans.

Design & Methods

Study design: We will examine the associations between baseline (Visit 2) HbA_{1c} and fasting glucose levels—separately and in combination—and chronic kidney disease and

retinal findings. Visit 2 (1990-1992)—the only visit for which stored whole blood samples were available for measurement for HbA_{1c}—will be the baseline for all analyses. Glucose measurements are available on all participants at each ARIC examination.

Exposures: HbA_{1c}, glucose

Covariates: Age, sex, race/center, waist circumference, BMI, total, LDL- and HDL-cholesterol, systolic and diastolic blood pressures, blood pressure medication use, triglycerides, smoking, family history of diabetes, Baecke physical activity score (Visit 1), education level (Visit 1)

Outcomes:

1) Kidney disease

We will define incident kidney disease based on an glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² estimated from serum creatinine measured at Visit 4, an incident hospitalization (discharge or death) coded for chronic renal disease (ICD-9 codes 581-583 or 585-588), hypertensive renal disease (ICD-9 code 403), hypertensive heart and renal disease (ICD-9 code 404), unspecified disorder of kidney and ureter (ICD-9 code 593.9), diabetes with renal manifestations (ICD-9 code 250.4), kidney transplantation, renal dialysis, or adjustment/fitting of catheter (ICD-9 codes V42.0, V45.1, or V56), hemodialysis (ICD-9 code 39.95) or peritoneal dialysis (ICD-9 code 54.98), without acute renal failure (ICD-9 codes 584, 586, 788.9, or 958.5) as the primary or secondary hospitalization code with follow-up to 2005 or most recent hospitalization files available. We will also examine the visit-based GFR and hospitalization-based definitions separately to assess whether any observed associations are similar and compare MDRD and CKD-EPI equations for estimation of GFR. At ARIC Visit 4 we also have information on urinary albumin, urinary creatinine, and serum cystatin C that will be used in sensitivity analyses to identify additional cases of kidney disease.

2) Retinal findings

Retinal photographic data are available for all participants at Visit 3 (1993-95) and a subsample of 1,034 participants at Visit 4 (1996-98). Trained graders evaluated retinal photographic slides for focal lesions, including signs typical of diabetic retinopathy, including both background and proliferative retinopathy (e.g., microaneurysms, retinal hemorrhages, hard exudates and/or cotton wool spots) according to a standardized protocol. The main retinal outcome of interest will be any retinopathy at Visit 3 in the absence of other retinal vascular causes, e.g., retinal vein occlusion. Secondary analyses will be conducted to examine the associations of HbA_{1c} with specific retinal findings and disease severity. We will also examine the relationship between HbA_{1c} and progression of retinopathy (defined at two steps or more along the ETDRS severity scale) in the N=981 participants who had retinal photographs at both Visits 3 and 4 (7).

Additional variables of interest: incident diagnosed diabetes during the follow-up period, detected during the annual follow-up (AFU) phone calls and incident cases of diabetes at Visits 3 and 4 detected by serum glucose concentration, medications, or self-report. We will conduct analyses to examine whether receiving a diagnosis of diabetes during follow-up partially or wholly explains any of the observed associations.

Exclusions: participants with diagnosed diabetes at baseline defined by a self-reported physician diagnosis or diabetes medication use at either Visits 1 or 2, participants missing HbA1c or covariates of interest, participants with estimated GFR <60 at either Visits 1 or 2, individuals with kidney-related hospitalizations prior to Visit 2 (i.e., between Visits 1 and 2), and participants with undiagnosed diabetes based on glucose levels at Visits 1 or 2 (for some analyses).

Statistical Analysis: Cox proportional hazards models will be used to estimate the adjusted hazard ratios and their 95% CIs to compare risk of incident kidney disease across categories of HbA1c (e.g., <5, 5-<5.5, 5.5-<6, 6-<6.5 \geq 6.5%) and fasting glucose (<100, 100-<126, \geq 126 mg/dl) after adjusting for covariates. Multivariable logistic regression models will be used to estimate odds ratios and their corresponding 95% CIs for the retinal outcomes at Visit 3 by categories of HbA1c and fasting glucose at Visit 2. Linear and restricted cubic spline models will be used to model and graphed to visually display the continuous associations between HbA1c, glucose and the outcomes of interest. We will test for interactions by race/ethnicity and also examine associations separately in black and white ARIC participants.

The overall predictive value of HbA1c added to glucose (nested models) will be assessed using Bayes information criterion, likelihood ratio and Wald's tests (global measures of model fit). For non-nested models (e.g. models with HbA1c vs glucose), model discrimination will be compared using Harrell's C-statistic (8) and risk classification will be assessed using net reclassification improvement (NRI) and integrated discrimination improvement (IDI) statistics (9).

We will formally assess the presence of thresholds in the observed associations and threshold locations using state-of-the-art smoothing methods for regression analysis when exposure variables are observed with error (10, 11). Specifically, we will use penalized spline smoothing (p-splines) for modeling the dose-response function using many knots placed at the quantiles of the measured HbA1c distribution and a roughness penalty designed to control for over-fitting. Thresholds are inflection points in the curve. We recognize that a continuous non-linear relationship may not have a sharp threshold. However, we hypothesize that the dose-response function will be relatively flat for low HbA1c levels (approximately the first two quintiles of the distribution) and then will become quite steep (as has been observed for microvascular outcomes in previous studies). In this context, the threshold can be defined as the maximum of the derivative of the dose-response function and its posterior distribution can be estimated using posterior distribution simulations (10, 11).

We recognize that measurement error is an inherent issue in examining the association of any blood analyte measured at a single point in time with long-term outcomes. We have previous experience working with measurement error expert, Dr. **Error! Reference source not found.** (Assistant Professor of Biostatistics, Johns Hopkins Bloomberg School of Public Health) to account for measurement error (short-term variability) using simulation extrapolation (SIMEX) methodology (10) implemented in the statistical package, R. In prior and ongoing projects, we have obtained the variance estimates for glucose and HbA1c from an external population; namely the Second Examination of the Third National Health and Nutrition Examination Survey (NHANES III), a repeat visit of N=2596 adults who participated in the original NHANES III study. These preliminary analyses have not substantively altered associations with HbA1c, likely because of the inherently low within-person variability in this measure (index of individuality = 0.16). In the present study, we anticipate emphasizing the more straightforward associations with the single value (without accounting for measurement error) as this most accurately replicates the clinical situation and guidelines in which health professionals make a decision based on a single measurement. Nonetheless, we have planned separate, more comprehensive studies formally comparing measurement error in different measures of glycemia (fasting glucose, HbA1c, 2-hour glucose, and several short-term markers of glycemia not yet assayed) to rigorously assess how measurement error might explain discrepancies in the associations of different glycemic markers with long-term outcomes in the diabetes literature.

Limitations: The timing of measurements of HbA1c, kidney function, and retinal assessments in the ARIC Study is a major limitation. We have only a single measurement of HbA1c at Visit 2, the baseline for this study. Serum creatinine is only available at Visits 1, 2, and 4, and the availability of urine measurements of albumin and creatinine only at Visit 4; thus, we cannot exclude prevalent cases of albuminuria at Visit 2. Retinal data are only available on all participants at Visit 3 and thus we also cannot exclude prevalent cases of retinopathy and we will have limited ability to draw conclusions regarding the temporality of any observed associations. There are also concerns regarding misclassification of the kidney and retinal outcomes, particularly a lack of sensitivity of our definitions (we may miss cases). Direct measurement of kidney function is not available and incident kidney disease defined by GFR will be estimated based on a single creatinine measurement. For identification of additional kidney disease cases, we are limited to hospitalized cases or deaths and the associated limitations of this un-adjudicated endpoint based on discharge codes from hospital records. The retinal photography data are only available from one eye for each participant and some participants are missing retinal data because the photographs were ungradeable (largely attributable to poor pupil dilation). And, ultimately, due to the observational nature of this investigation, we will also not be able to eliminate the possibility of residual confounding.

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).

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 ICTDER03 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

8.c. If yes, is the author aware that some DNA data is not allowed to be used by 'for profit' groups. Is this data being used by a 'for profit' organization? If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded?
____ 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>

____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)?

***** Please note that the present proposal has complete overlap with and supersedes approved ARIC manuscript proposal #1252 ("Non-Diabetic Glycemia (HbA1c) and Incident Chronic Kidney Disease: The Atherosclerosis Risk in Communities Study," B. Astor). Dr. Astor and I have spoken and we agree that the proposed analyses in MSP #1252 will be included in this new proposal. *****

ARIC 1011 Stability of haemoglobin A1c (HbA1c) measurements from frozen whole blood samples stored for over a decade. Selvin, E

ARIC 1024 Glycemic control and coronary heart disease risk in persons with and without diabetes: The Atherosclerosis Risk in Communities Study Selvin, E
 ARIC 1025 Glycemic control, Atherosclerosis, and risk factors for cardiovascular disease in individuals with diabetes: The ARIC Study Selvin, E
 ARIC 1056 HbA1c and peripheral arterial disease in diabetes Selvin, E
 ARIC 1067 Glycemia (haemoglobin A1c) and incident stroke: The ARIC Study Selvin, E
 ARIC 1164 Hemoglobin A1c as a Risk Factor for Heart Failure Hospitalization among Persons with Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study Pazin Filho, A
 ARIC 1418 Glycemic control (hemoglobin A1c), cognitive decline and dementia risk: The Atherosclerosis Risk in Communities (ARIC) Study Selvin, E
 ARIC 1431 Hemoglobin A1c, glucose, and incident diabetes: the Atherosclerosis Risk in Communities Study
 1496 Measurement of Hemoglobin A1c (HbA1c) from Stored Whole Blood Samples in the Atherosclerosis Risk in Communities Study Selvin, E
 ARIC 1488 The association of hemoglobin A1c with incident heart failure among persons without diabetes: The Atherosclerosis Risk in Communities (ARIC) Study Matsushita, KM
 1245 Glycemic Control (HbA1c) and Incident Chronic Kidney Disease in Diabetes: The Atherosclerosis Risk in Communities Study Bash, LD
 1440 Longitudinal predictors of retinal microvascular dysfunction: The Atherosclerosis Risk in Communities (ARIC) Carotid MRI Study Avery, C
 1432 Retinal Signs and Risk of Incident MRI Brain Abnormalities
 234 Retinal microvascular pathology associated with hypertension in blacks and whites: the ARIC study (A) Sharrett, AR
 401 (A) Retinal microvascular abnormalities and stroke/lacunar syndromes/ TIA- The ARIC Study Mo, J
 514 (J) Association of arterial stiffness and retinal microvascular Liao, D
 945 Neighborhood factors and the prevalence of age-related maculopathy, diabetic retinopathy and retinal arteriolar disease Wong, TY
 1057 Retinal Microvascular Abnormalities and Weight Gain Magliano, D
 1222 The association of microvascular retinal abnormalities with cognitive decline and cognitive status after 10 years. (ARIC study) Lesage, S
 1231 Retinal Arteriolar Caliber and 10-year incidence of Hypertension Wong, TY
 1234 10-year Incidence, Progression and Regression of Retinal Vascular Abnormalities and their Relationship with Vascular and Inflammatory Risk Markers. Wong, TY
 337A Retinopathy in persons without diabetes in the ARIC study Klein, R
 540 (A) Association of diabetic retinopathy with CHD Duncan, BB
 1123 Albuminuria and kidney function as predictors of cardiovascular events mortality Astor, BC

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

