

ARIC Manuscript Proposal #2113

PC Reviewed: 4/9/13
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: The associations of fructosamine and glycated albumin with vascular outcomes

b. Abbreviated Title (Length 26 characters): FA and GA with vascular risk

2. Writing Group:

Writing group members: Elizabeth Selvin; Andreea Rawlings; Pamela Lutsey; James S. Pankow; Linda Kao; Frederick L Brancati; Michael Steffes; Josef Coresh; 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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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 aim to submit this paper for ARIC review <1 year from approval of the manuscript proposal

4. Rationale:

Hemoglobin A1c (HbA1c) results from the glycation of hemoglobin in erythrocytes and represents long-term (2-3 month) glycemia. For decades, HbA1c has long been the primary test used to monitor glycemic control and guide treatment of diabetes in clinical

practice. In a major change to clinical guidelines in 2010, HbA1c was recommended for use as a diagnostic test for diabetes (1, 2). Thus, in addition to its central role in monitoring glycemic control, HbA1c is now being widely adopted as the first-line test for screening and diagnosis of diabetes. The epidemiologic evidence supporting current recommendations for use of HbA1c for screening and diagnosis comes primarily from studies that have characterized the association of HbA1c with prevalent retinopathy (3-7). There is also strong evidence linking elevated HbA1c—even below the threshold for a diagnosis of diabetes—to cardiovascular outcomes (8-11).

Fructosamine and glycated hemoglobin are markers of short-term (2-4 week) glycemic control and independent of both erythrocyte and hemoglobin characteristics; they reflect the modification of serum proteins (mainly albumin), which have a faster turnover (~10-14 days) as compared to erythrocytes (~120 days). In our pilot study in ARIC, we found evidence that fructosamine and glycated albumin may contribute independent clinical information, above and beyond standard glycemic markers (HbA1c and fasting glucose) (12-15). We contend that fructosamine and glycated albumin may add complementary information to HbA1c for the identification of persons at risk for future cardiovascular outcomes.

5. Main Hypothesis/Study Questions:

The overarching objective of this study is to characterize the associations of fructosamine and glycated albumin with cardiovascular outcomes in the community-based ARIC Study. We will compare fructosamine and glycated albumin to HbA1c (and fasting glucose) for the identification of persons who are at high risk for cardiovascular disease.

Hypotheses:

Hypothesis 1: Fructosamine and glycated albumin will be positively associated with the risk of cardiovascular outcomes among persons with and without a history of diabetes before and after adjustment for potential confounding factors.

Hypothesis 2: Fructosamine and glycated albumin will add independent prognostic information to HbA1c and also fasting glucose as markers of cardiovascular risk in persons with and without 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 methodologic limitations or challenges if present).

Study design: Prospective cohort analysis with visit 2 (1990-1992) as baseline

Exposures: Glycated albumin and fructosamine measured in 2012-2013 at the University of Minnesota as part of Dr. Selvin's ancillary study from stored serum samples originally collected at visit 2 (1990-1992).

Exposures (for comparison): HbA1c and fasting glucose

Outcomes: The proposed study will focus on incident coronary heart disease, ischemic stroke, heart failure hospitalizations, and all-cause mortality. ARIC participants are contacted annually by telephone and reported hospitalizations and deaths are identified. ARIC investigators also survey lists of discharges from local hospitals and death certificates from state vital statistics offices for potential events. Hospital records are abstracted and potential coronary heart disease, ischemic stroke, and heart failure events (after 2004 only) are adjudicated by an end points committee.

Coronary heart disease: We will define incident coronary heart disease cases using the composite definition incorporating definite or probable myocardial infarction, cardiac procedures, and deaths from coronary heart disease identified during the follow-up visits (silent myocardial infarctions) and during active surveillance for all hospitalizations and deaths among ARIC participants.

Ischemic stroke: We define incident stroke as an adjudicated (definite or probable) incident ischemic stroke event identified during active surveillance.

Heart failure: We will identify incident hospitalizations and deaths related to heart failure using discharge codes (ICD-9 code 428 for hospitalizations and ICD-10 code I50 for deaths). Additionally, an expert panel has additionally adjudicated those heart failure events occurring after 2004.

Mortality: Death from any cause identified during active surveillance of all participants in the ARIC study.

Exclusions: Missing information on exposures or covariates of interest, a history of cardiovascular disease at or before baseline (visit 2), race other than white or black, and blacks in the Minneapolis and Washington County cohorts. Persons who are non-fasting will be excluded from comparative analyses of fasting glucose.

Stratification: We will conduct analyses stratified by history of diagnosed diabetes based on self-reported physician diagnosis or diabetes medication use at or before visit 2.

Subgroups: We will specifically examine the performance of fructosamine and glycated albumin in the pre-diabetic range of A1c (5.7% to 6.4%) and fasting glucose (100 mg/dL to 125 mg/dL), among persons with anemia (hemoglobin <13 g/dL in men; hemoglobin <12 g/dL in women) since this is a population in which A1C values are thought to be particularly problematic, and also among persons with chronic kidney disease (estimated GFR <60) and among the small subgroups of persons with more severely reduced kidney function (recognizing the power will be quite low in this small subgroup).

Statistical analyses: We will estimate hazard ratios and their 95% confidence intervals using Cox proportional hazards models. The proportional hazards assumption will be examined using log(-log) plots and by testing risk factor-by-time interactions; if the

assumption is violated the interactions term(s) will be kept in the model and the time-dependent nature of the risk will be interpreted accordingly. We will consider the following core models:

Model 1: age, sex, race-center.

Model 2: age, sex, race-center, low-density and high-density cholesterol concentrations, triglyceride concentration, body mass index, waist-to-hip ratio, systolic blood pressure, hypertension medication use, family history of diabetes, education level (visit 1), alcohol use, physical activity (visit 1), and smoking status.

Model 3: all variables in Model 2 + HbA1c (per %-point)

Model 4: all variables in Model 2 + fasting glucose (per mg/dL)

We will model fructosamine and glycated albumin in diabetes-specific quartiles and also continuously. To characterize the continuous associations, we will generate piece-wise linear splines with knots corresponding to the cutoffs for the quartiles and we will also implement restricted cubic splines to obtain a smoother fit to the data. Model discrimination will be assessed using Harrell's C statistic. We will test for interactions by race. To evaluate the overall improvement in risk classification for the addition of fructosamine or glycated albumin to the fully adjusted model including HbA1c, we will calculate the net-reclassification improvement statistic (NRI) and the integrated-discrimination improvement statistic (IDI) (16). In subgroups (e.g., pre-diabetes) where we are examining the predictive performance of the markers in groups constrained by the range of A1C or fasting glucose, we will use a corrected NRI statistic to account for the bias introduced by sub-setting the data (17).

Because a J-shaped association has been previously observed for HbA1c with cardiovascular outcomes and all-cause mortality (8, 18-20), we are particularly interested in the shape of the associations of fructosamine and glycated albumin with each of the outcomes and whether a similar J-shape is observed. We will assess whether very low values of fructosamine and glycated albumin are associated with an increased risk of mortality or any of the other vascular outcomes.

Sensitivity analyses: There is ongoing debate regarding the need for correction of fructosamine assays for serum albumin concentrations (21, 22). Thus, we will also conduct additional analyses with further adjustment for total serum albumin. We will also conduct sensitivity analyses excluding persons with a history of diagnosed or undiagnosed diabetes (based on HbA1c $\geq 6.5\%$ or fasting glucose ≥ 126 mg/dL).

Limitations:

- Reliance on single measurements of fructosamine and glycated albumin at baseline.
- As with all observational studies, we will not be able to eliminate the possibility of residual confounding despite rigorous adjustment for known risk factors.

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes
 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)?

Associations of alternative markers of glycemia with hemoglobin A(1c) and fasting glucose. Juraschek SP, Steffes MW, Selvin E. Clin Chem. 2012 Dec;58(12):1648-55. doi: 10.1373/clinchem.2012.188367. Epub 2012 Sep 27. PMID: 23019309

Alternative markers of hyperglycemia and risk of diabetes. Juraschek SP, Steffes MW, Miller ER 3rd, Selvin E. Diabetes Care. 2012 Nov;35(11):2265-70. doi: 10.2337/dc12-0787. Epub 2012 Aug 8. PMID: 22875225

Racial differences in glycemc markers: a cross-sectional analysis of community-based data. Selvin E, Steffes MW, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL. Ann Intern Med. 2011 Mar 1;154(5):303-9. PMID: 21357907

Nontraditional markers of glycemia: associations with microvascular conditions. Selvin E, Francis LM, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL, Steffes MW. Diabetes Care. 2011 Apr;34(4):960-7. doi: 10.2337/dc10-1945. Epub 2011 Feb 18. PMID: 21335368

Glycated hemoglobin and the risk of kidney disease and retinopathy in adults with and without diabetes. Selvin E, Ning Y, Steffes MW, Bash LD, Klein R, Wong TY, Astor

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