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ARIC Manuscript Proposal Form

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Publication Committee Review Date: 8/12/2025
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1.a. Full Title: Patterns of one-year change in HbA1c and Continuous Glucose Monitoring (CGM) Metrics in Older Adults with Type 2 Diabetes

b. Abbreviated Title (Length 26 characters): Changes in HbA1c and CGM

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
Writing group numbers: Tianyu Cao, Michael Fang, Amelia Wallace, Natalie Daya Malek, Arielle Valint, Dan Wang, Justin B. Echouffo-Tcheugui, Scott Zeger, Elizabeth Selvin; others welcome

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

First author [please provide a middle initial; EX: Adam L Williams]:

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ARIC sponsor to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located. The ARIC sponsor is responsible for **carefully reviewing the proposal and ensuring its soundness prior to submission to the ARIC Publications Committee.** (The ARIC sponsor should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

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3. Timeline: Data to be used in this proposal are available. Analyses and manuscript preparation will be performed over the next 6 months

4. Rationale: Hemoglobin A1c (HbA1c) reflects average blood glucose over the past two to three months, but does not provide information about glucose variability or real-time fluctuations, which are independently associated with risk of complications.[1,2] Continuous glucose monitoring (CGM) provides detailed information on glucose patterns throughout the day,[3] offering complimentary values to HbA1c in the management of diabetes.

HbA1c is an established surrogate outcome in clinical trials, used to evaluate the efficacy of glucose-lowering therapies.[4] While CGM is a relatively recent technology, it is now routinely used in clinical practice, recommended in guidelines, and has been shown to reduce hypoglycemia and improve health outcomes.[5-7] CGM trials have typically focused on time in target range (TIR)[8,9], a metric that is increasingly used in glycemic assessment but has not been recognized by the U.S. Food and Drug Administration (FDA) as a surrogate outcome. Understanding how changes in TIR and HbA1c track together over time has important implications for interpreting clinical trial results and the use of these metrics in clinical practice. Current evidence is limited, particularly in type 2 diabetes. Existing studies have primarily relied on cross-sectional measurements,[10,11] with limited longitudinal data from select populations in clinical trials (mostly type 1 diabetes trials).[12]

The prevalence of type 2 diabetes increases with age, affecting approximately 30% of adults aged 65 years and older, and is expected to increase substantially in the coming decades.[13] Optimal glycemic control among older adults is often challenging due to polypharmacy, heterogeneity in underlying comorbidities, and elevated risks of hypoglycemia.[13] In this context, relying solely on HbA1c for glycemic monitoring has clear limitations.[14] HbA1c alone is not a reliable marker for hypoglycemia as it does not capture the short-term glycemia fluctuations, which also limits its ability in assessing postprandial hyperglycemia. Additionally, conditions that alter red blood cell turnover can lead to discrepancies between HbA1c values and actual glycemic levels[15], and many of these conditions, such as advanced kidney disease and anemia, are prevalent in older adults with diabetes.[16,17] Evaluating how CGM metrics and HbA1c track together in older adults with diabetes may help identify discrepancies in glycemic assessment and guide treatment strategies.

We propose to examine the 1-year changes in CGM metrics and HbA1c using data from visits 9 (2021-2022) and 10 (2023) of the Atherosclerosis Risk in Communities (ARIC) study, which includes older adults with type 2 diabetes and repeated measurements of CGM and HbA1c.

5. Main Hypothesis/Study Aims: The aim of this study is to examine the concordance and discordance of 1-year changes in CGM metrics and HbA1c in older adults with type 2 diabetes

6. Design and analysis - please address the following aspects:

a) **Inclusion/exclusion**

We will include all participants with type 2 diabetes who attended ARIC visit 9 and visit 10, and had CGM and HbA1c measurements at both visits.

We will exclude participants without type 2 diabetes, those with missing CGM data or less than 5 days of analyzable CGM data, and those with missing HbA1c data at either ARIC visit 9 or visit 10.

b) **Study design**

Repeated measures study.

c) **Outcome and other variables of interest with specific reference to the time of their collection**

HbA1c:

Our key variable of interest is ~1-year change of HbA1c from ARIC visit 9 to visit 10, calculated as visit 10 levels minus visit 9 levels. The HbA1c levels were measured in whole blood with an automated high-performance liquid chromatography analyzer (Tosoh Bioscience), standardized to the Diabetes Control and Complications Trial assay.

CGM:

CGM data was collected at ARIC visit 9 and visit 10 using Freestyle Libre Pro (Abbott Diabetes Care) CGM system, which records interstitial glucose level every 15 minutes for up to 14 days. All participants were masked to the glucose readings.

Mean CGM glucose and TIR will be our primary measures of interest.

We will consider the following CGM metrics:
Mean glucose: average of all available glucose measurements
Glycemic variability: coefficient of variation (CV) and standard deviation (SD)
Time in range (TIR): % of glucose levels between 70-180 mg/dL
Time above range (TAR): % of glucose levels >180 mg/dL
Time below range (TBR): % of glucose levels <70 mg/dL
Hypoglycemia: Episodes- sustained glucose <70 mg/dL for at least 15 minutes during the 2-week period [at least two consecutive readings]
Hyperglycemia: Episodes- sustained glucose >140 mg/dL (Level 1) or >180 mg/dL (Level 2) for at least 15 minutes during the 2-week period

d) **Summary of data analysis**

Continuous variables will be summarized by mean and standard deviation (SD) or median and interquartile range (IQR) depending on the distribution, and by percentages (%) for categorical variables according to study visits. Paired t-tests and McNemar's Chi-squared test will be used to compare continuous and categorical variables, respectively.

We will use Deming regression, Bland and Altman plots, and Pearson's correlations to compare the mean glucose, TIR, and HbA1c at visit 9 to visit 10. From the regressions, we will calculate the root mean squared errors (RMSEs). We will calculate within-person coefficient of variation (CV_w) using within-subject variance (δ^2_{ws}) obtained from a linear mixed effects model with CGM metrics or HbA1c as the dependent variable and participants as random effect.

We will visualize individual changes in HbA1c and mean glucose or TIR using water fall plot. In order to quantify the degree of discordance over time, we will define HbA1c change $\geq 0.5\%$ from visit 9 to visit 10 as clinically significant, and calculate the equivalent thresholds for mean glucose and TIR using a random effects model accounting for repeated measures. We will define concordant change as having the same direction and similar magnitude of change; discordance will be defined otherwise. We will calculate the degree of agreement, defined as # of concordant pairs divided by total pairs

Any anticipated methodologic limitations or challenges if present Strengths: This will be the first study to examine the 1-year change of CGM metrics and HbA1c in older adults with type 2 diabetes in a community-based population. Additionally, this study is greatly strengthened by the repeated and concurrently collected CGM and HbA1c data, obtained using the same device and standardized protocol.

Limitations: The data used in this study are relatively recent (latest follow-up: December 19, 2023), which currently limits our ability to link HbA1c–CGM discordance with health outcomes. This important question will be addressed in future research.

e) **Will the author need Limited data to complete the proposed manuscript?**

☐ Yes, Limited data is needed. (Provide a brief (2-3 sentences) justification for requesting PHF data)

☒ No, De-identified data will be sufficient.

Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7. Will the data be used by a for-profit organization in this manuscript? ☐ **Yes*** ☒ **No**

8. Will the DNA data be used in this manuscript? ☐ **Yes*** ☒ **No**

* Please carefully review the instructions and documentation on the ARIC website at: https://aric.cscc.unc.edu/aric9/researchers/Obtain_Submit_Data [ARIC website > Researchers > Obtain/Submit Data] for instructions on proper data use.

9. The lead author or the ARIC sponsor 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website >Publications >Proposal Search]

☒ 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 currently no manuscript proposals in ARIC that examine the longitudinal change of CGM and HbA1c. Manuscript proposal #4320 explores the relationship between HbA1c-glycated albumin and HbA1c-fructosamine and develops translation. Dr. Fang is the first author and Dr. Selvin is the senior investigator on that manuscript proposal as well as the current proposal. Manuscript proposal #1495 investigates the change in HbA1c levels, but does not include CGM data. Dr. Selvin is the first author.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)?

☐ Yes ☒ No→ **Skip to question 12**

11.b. If yes to 11.a., is the proposal

☐ A. primarily the result of an ancillary study
☐ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)

11.c. If yes to 11.a., list number*

*ancillary studies are listed by number
https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website >Ancillary Studies >Approved Ancillary Studies]

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. The NIH-NHLBI Public Access Brochure about the public access policy from http://publicaccess.nih.gov/ is posted in https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website > Publications >Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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