Visit-to-Visit Hemoglobin A_{1c} Variability Is Associated With the Risk of Lower-Extremity Amputation in Patients With Type 2 Diabetes

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Patients with diabetes have a 10-fold higher risk of lower-extremity amputation (LEA) than people without diabetes (1). LEA is associated with the greatest reduction in quality of life and the greatest increase in mortality and medical costs in all diabetes complications. Previous studies suggested that the mean hemoglobin A_{1c} (HbA_{1c}) level was associated with an increased LEA risk among patients with type 2 diabetes (2). However, emerging evidence indicates that long-term glycemic variability evaluated by clinical visit-to-visit HbA_{1c} variability may be a better predictor of diabetes complications (3). So far, the definitions of long-term HbA_{1c} variability are inconsistent. In most studies, standard deviation of serial HbA_{1c} measurements (HbA_{1c} SD) and the intrapersonal coefficient of variation of HbA_{1c} (HbA_{1c} CV) are often used to represent HbA_{1c} variability. In the current study, we added a new marker—HbA_{1c} variability score (HVS) (4)—which is more easily applied to clinical practice.

We collected data from electronic health records for patients with type 2 diabetes between 2013 and 2019 in the Louisiana Experiment Assessing Diabetes outcomes (LEAD) cohort study (5). We excluded patients who had LEA diagnosis before entry and within 2 years after the first date of diabetes diagnosis, those with incomplete baseline data, those who did not have at least four HbA_{1c} tests within 2 years after their first diagnosis of diabetes, and those who did not have at least five HbA_{1c} measures between the date of diagnosis of diabetes and the date of diagnosis of the outcome. HbA_{1c} SD was calculated within 2 years following the first date of type 2 diabetes diagnosis. HbA_{1c} CV was calculated as the HbA_{1c} SD divided by the mean value of HbA_{1c} and then converted to a percentage. HVS was calculated as the percentage of the number of changes (increase or decrease) in HbA_{1c} >0.5% (5.5 mmol/mol) from the value prior among all HbA_{1c} measurements between the diagnosis of diabetes and LEA for each individual. We defined type 2 diabetes, LEA, and some other outcomes according to codes from ICD-9 or ICD-10, Clinical Modification, and Current Procedural Terminology (CPT) codes.

The present analysis included 30,039 patients after excluding ineligible patients. During a mean follow-up of 5.64 years, 286 participants had LEA. Multivariable-adjusted (age, sex, race, BMI, systolic blood pressure, LDL cholesterol, estimated glomerular filtration rate, smoking, mean value of HbA_{1c}, peripheral arterial disease, foot deformity, and use of antihypertensive drugs, diabetes medications, lipid-lowering agents, and aspirin) hazard ratios (HRs) for LEA based on different levels of HVS (≤20%, >20% to ≤40%, >40% to ≤60%, >60% to ≤80%, and >80%) were 1.00, 1.00, 1.54, 1.70, and 3.31 ($P_{trend} < 0.001$), respectively (Table 1). Multivariable-adjusted HRs for LEA events were 1.00, 1.35, 1.81, and 2.15 across quartiles of HbA_{1c} SD ($P_{trend} = 0.012$) and 1.00, 1.21, 1.35, and 1.88 across quartiles of HbA_{1c} CV ($P_{trend} = 0.012$). After additional adjustment for foot ulcers, the positive association with LEA risk was still significant for HVS but was no longer significant for either HbA_{1c} SD or HbA_{1c} CV. This can be explained as a history of foot ulcers and LEA being extremely relevant. A total of 266 of 286 incident cases of LEA had a history of foot ulcers.

The current guidelines from the American Diabetes Association recommend

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Table 1—HRs of LEA according to three different indicators of visit-to-visit HbA_{1c} variability as categorical or continuous variables among patients with type 2 diabetes

	No. of participants	No. of cases	HRs (95% CI)			
			Model 1	Model 2	Model 3	Model 4
HVS (%)						
≤20	11,189	42	1	1	1	1
>20 to ≤40	7,189	41	1.48 (0.96–2.28)	1.10 (0.71–1.70)	1.00 (0.64–1.54)	0.95 (0.61–1.48)
>40 to ≤60	5,817	71	3.04 (2.07–4.46)	1.94 (1.30–2.90)	1.54 (1.01–2.34)	1.33 (0.88–2.00)
>60 to ≤80	4,289	76	4.54 (3.09–6.67)	2.50 (1.67–3.76)	1.70 (1.08–2.67)	1.37 (0.90–2.13)
>80	1,555	56	10.0 (6.65–15.1)	5.41 (3.50–8.34)	3.31 (2.02–5.42)	2.21 (1.36–3.59)
P_{trend}			<0.001	<0.001	<0.001	0.004
As a continuous variable			1.03 (1.02–1.03)	1.02 (1.02–1.03)	1.01 (1.01–1.02)	1.01 (1.00–1.02)
HbA_{1c} SD						
Quartile 1	7,588	27	1	1	1	1
Quartile 2	7,531	43	1.81 (1.11–2.97)	1.42 (0.86–2.32)	1.35 (0.82–2.21)	1.33 (0.81–2.19)
Quartile 3	7,543	87	3.48 (2.22–5.46)	2.07 (1.30–3.28)	1.81 (1.13–2.89)	1.60 (1.00–2.56)
Quartile 4	7,377	129	5.42 (3.50–8.40)	2.94 (1.86–4.63)	2.15 (1.31–3.52)	1.85 (1.13–3.02)
P_{trend}			<0.001	<0.001	0.012	0.084
As a continuous variable			1.64 (1.45–1.85)	1.39 (1.21–1.60)	1.18 (1.00–1.39)	1.08 (0.92–1.28)
HbA_{1c} CV						
Quartile 1	7,561	32	1	1	1	1
Quartile 2	7,575	50	1.67 (1.06–2.64)	1.28 (0.81–2.02)	1.21 (0.76–1.92)	1.14 (0.72–1.81)
Quartile 3	7,556	81	2.68 (1.75–4.09)	1.55 (1.01–2.40)	1.35 (0.87–2.10)	1.25 (0.80–1.93)
Quartile 4	7,347	123	4.45 (2.96–6.70)	2.40 (1.58–3.67)	1.88 (1.21–2.92)	1.55 (1.00–2.39)
P_{trend}			<0.001	<0.001	0.012	0.157
As a continuous variable[a]			1.52 (1.33–1.74)	1.32 (1.12–1.55)	1.17 (1.00–1.40)	1.08 (0.91–1.28)

Model 1 adjusted for age, sex, and race. Model 2 adjusted for covariates in model 1 plus baseline BMI, systolic blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, estimated glomerular filtration rate, smoking, insurance type, use of antihypertensive drugs, use of antidiabetes medications, use of lipid-lowering agents, use of aspirin, peripheral arterial disease, and foot deformity. Model 3 adjusted for covariates in model 2 plus mean value of HbA_{1c}. Model 4 adjusted for covariates in model 3 plus foot ulcers. [a]Per 10 units increase for HbA_{1c} CV.

HbA_{1c} <7% (53 mmol/mol) as the treatment goal for patients with diabetes to prevent diabetes complications and that HbA_{1c} tests should be performed approximately every 3 months in all patients. Poor glucose control can lead to a higher risk of LEA. However, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial did not confirm the beneficial effect of intensive glycemic treatment compared with the standard therapy. Moreover, HbA_{1c} does not reflect glucose fluctuations over a long period, which may have better ability to predict diabetes complications. Oscillating glucose can have more deleterious effects on endothelial function and oxidative stress than constantly high glucose exposure. The rigorous inclusion and exclusion criteria of the current study were similar to several post hoc analyses of clinical trials, which would enhance the accuracy of our analysis to a large extent. To our knowledge, the study is the first to assess the association between HbA_{1c} variability, defined as HVS, HbA_{1c} SD, and HbA_{1c} CV, and LEA risk using electronic record data to generate real-world evidence.

In conclusion, we found long-term glycemic fluctuation was an independent indicator of LEA risk among patients with type 2 diabetes. Our findings indicated that HbA_{1c} variability could be considered as a supplementary glycemic control target in preventing LEA among patients with type 2 diabetes.

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Data Availability. Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will, on request, detail the restrictions and any conditions under which access to some data may be provided.

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