Long-term visit-to-visit variability in hemoglobin A1c and kidney-related outcomes in persons with diabetes

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Long-term Visit-to-Visit Variability in Hemoglobin A_{1c} and Kidney-Related Outcomes in Persons With Diabetes

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Rationale & Objective: To characterize associations between long-term visit-to-visit variability of hemoglobin A_{1c} (HbA_{1c}) and risk of adverse kidney outcomes in patients with diabetes.

Study Design: Observational study.

Setting & Participants: 93,598 adults with diabetes undergoing routine care in Stockholm, Sweden.

Exposures and Predictors: Categories of baseline and time-varying HbA_{1c} variability score (HVS, the percentage of total HbA_{1c} measures that vary by >0.5% [5.5 mmol/mol] during a 3-year window): 0-20%, 21%-40%, 41%-60%, 61%-80%, and 81%-100%, with 0-20% as the reference group.

Outcome: Chronic kidney disease (CKD) progression (composite of >50% estimated glomerular filtration rate [eGFR] decline and kidney failure), acute kidney disease (AKI by clinical diagnosis or transient creatinine elevations according to KDIGO criteria), and worsening of albuminuria.

Analytical Approach: Multivariable Cox proportional hazards regression.

Results: Compared with persons showing low HbA_{1c} variability (HVS 0-20%), any increase in variability was associated with a higher risk of adverse kidney outcomes beyond mean HbA_{1c}. For example, for patients with a baseline HbA_{1c} variability of 81%-100%, the adjusted HR was 1.6 (95% CI, 1.47-1.74) for CKD progression, 1.23 [1.16-1.3] for AKI, and 1.28 [1.21-1.36] for worsening of albuminuria. The results were consistent across subgroups (diabetes subtypes, baseline eGFR, or albuminuria categories), in time-varying analyses and in sensitivity analyses including time-weighted average HbA_{1c} or alternative metrics of variability.

Limitations: Observational study, limitations of claims data, lack of information on diet, body mass index, medication changes, and diabetes duration.

Conclusions: Higher long-term visit-to-visit HbA_{1c} variability is consistently associated with the risks of CKD progression, AKI, and worsening of albuminuria.

Complete author and article information provided before references.

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Glycated hemoglobin (HbA_{1c}) is routinely monitored for glycemic control in persons with diabetes, and intensive glycemic control is beneficial to both macro- and microvascular complications.[1-3] There are 2 different components of glycemic variability: short-term over days to weeks, and long-term, which may be ascertained by calculating visit-to-visit fluctuations of HbA_{1c} over months to years. The latter is closer to the standard monitoring procedures for patients in routine clinical care and may inform clinical decisions. Guidelines focus on keeping HbA_{1c} levels below target thresholds; however, there is growing awareness that variability in HbA_{1c} may be an independent risk factor for diabetes complications.[4-7]

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Between 20% and 40% of patients with diabetes develop chronic kidney disease (CKD).[8-10] Some but not all previous studies have observed an association between HbA_{1c} variability and the risk of developing CKD or worsening of albuminuria.[11-20] The identified limitations were, in general, low sample sizes and use of nonstandard outcome definitions. Further, they were mostly performed in clinical trials or prospective research cohorts, which may not be generalizable to the heterogeneous general population seeking health care. Acute kidney injury (AKI) is also common in patients with diabetes,[21,22] leading to poor outcomes and high health care costs.[23] We recently showed that single high HbA_{1c} levels were associated with the risk of developing AKI.[24] Whether long-term HbA_{1c} fluctuations are also associated with the risk of AKI is unknown.

Rigorous ascertainment of long-term glycemic variability may provide additional value in considering the likelihood of future kidney complications. If variability is important above and beyond the average levels of HbA_{1c}, this could suggest that specific lifestyle modifications or pharmacological preventative strategies are warranted. In this study, we used routine care data from the region of Stockholm, Sweden, to examine the associations between long-term visit-to-visit variability of HbA_{1c} with adverse kidney outcomes.

Methods

Data Source and Study Population

The study population consisted of individuals included in the Stockholm Creatinine Measurements (SCREAM) project, a health care utilization cohort including all residents

PLAIN-LANGUAGE SUMMARY

The evidence for current guideline recommendations derives from clinical trials that focus on a single HbA_{1c} as the definitive measure of efficacy of an intervention. However, long-term visit-to-visit fluctuations of HbA_{1c} may provide additional value in the prediction of future kidney complications. We evaluated the long-term fluctuations in glycemic control in almost 100,000 persons with diabetes undergoing routine care in Stockholm, Sweden. We observed that higher long-term HbA_{1c} fluctuation is consistently associated with the risks of chronic kidney disease progression, worsening of albuminuria and acute kidney injury. This finding supports a role for long-term glycemic variability in the development of kidney complications and illustrates the potential usefulness of this metric for risk stratification at the bedside beyond a single HbA_{1c} test.

from Stockholm, Sweden.[25] The region of Stockholm had a population of 2.3 million citizens in 2019 and has a universal tax-funded health care access. Using the personal identification number of each citizen, laboratory values were linked with (1) regional administrative databases with complete information on demographic data, migration procedures, health care use, and diagnoses; (2) national databases run by the Swedish National Board of Welfare with complete information on vital status and filled prescriptions at Swedish pharmacies; and (3) the Swedish Renal Registry (https://www.medscinet.net/snr/), a nationwide quality registry with validated cases of kidney replacement therapy (KRT). All linked registries are considered of high quality with no or minimal loss to follow-up.[26] The study was approved by the regional ethics review boards and the Swedish National Board of Health and Welfare, who deemed that informed consent was not needed and provided deidentified data to the authors.

In Sweden, patients with type 1 diabetes are generally followed in specialist care and type 2 diabetes in primary care. Patients are recurrently offered culturally adapted education programs on lifestyle modifications and how to self-monitor blood glucose. Patients with type 2 diabetes are provided with self-monitoring finger prick devices. Patients with type 1 diabetes or with type 2 diabetes who have repeated episodes of hypo- or hyperglycemia are provided with subcutaneous glucose sensors.[27] LIBRE-type glucose monitoring is almost exclusively used by patients with type 1 diabetes. If HbA_{1c} is stable, the standard monitoring recommendations include 1 annual visit to a general practitioner (for type 2 diabetes) or endocrinologist/diabetologist (for type 1 diabetes), and 1-4 visits per year to a specialized diabetes nurse.[28] Before these visits, the usual laboratory tests and clinical examinations are performed (such as HbA_{1c}, lipids, albuminuria, glomerular filtration rate, or blood pressure). The cost of all prescribed medications is covered by the Swedish government.

We identified all adult (>18 years old) patients in SCREAM between January 1, 2006, to December 31, 2019, with a diagnosis of type 1 or 2 diabetes. Patients with at least 1 annual outpatient HbA_{1c} test in 3 consecutive years were included; all HbA_{1c} tests performed during those 3 years were used to calculate HbA_{1c} variability. The index date where follow-up started for each included patient was set at January 1 of the year after the HbA_{1c} variability calculation period. Patients with missing information on age, sex, and estimated glomerular filtration rate (eGFR) or with kidney failure (initiation of dialysis or kidney transplantation or eGFR < 15 mL/min/1.73 m^2) were excluded. A flow chart of the patient selection is illustrated in Figure S1.

Exposure: HbA_{1c} Variability

The study exposure was HbA_{1c} variability, investigated as a time-fixed and time-varying exposure. In the time-fixed design, baseline HbA_{1c} variability was calculated from all outpatient HbA_{1c} tests during the 3-year eligibility window that preceded baseline. In the time-varying design, 3-year HbA_{1c} variability was recalculated at each new outpatient HbA_{1c} test during follow-up (Fig S2). The variability of HbA_{1c} was calculated as the HbA_{1c} variability score (HVS). HVS ranges from 0 to 100% and is defined as the percentage of total HbA_{1c} measures that differed by 0.5% (5.5 mmol/mol) or more compared with the previous HbA_{1c} measurement.[6] For example, if a person had the following sequence of HbA_{1c} values of 7.1%, 6.4%, 6.6%, 7.2%, 7.5%, and 6.9%, the number of measures that differed by ≥0.5% was 3 and the HVS would be 60% [3/5 × 100]. We used increments of 0.5% (5.5 mmol/mol) in HbA_{1c} as an accepted indicator of a clinically significant difference in glucose exposure. HVS was grouped into 5 categories: 0-20%, 21%-40%, 41%-60%, 61%-80%, and 81%-100%, with 0-20% as the reference group.

Assessment of Covariates

In the time-fixed analyses, covariates were assessed at index date. In time-varying analyses, all covariates except age and sex were updated at each subsequent measure of HbA_{1c}. Covariates included age, sex, calendar year, diabetes type, diabetes complications, comorbidities, ongoing medications, laboratory measurements, and health care utilization in the year prior as a measure of overall disease burden. Detailed definitions are shown in Tables S1 and S2.

Baseline HbA_{1c} was defined as the average of outpatient HbA_{1c} values during the 3-year eligibility window that preceded baseline, whereas albuminuria, eGFR, and blood lipids were defined as the most recent value during the 3-year eligibility window that preceded baseline. At each subsequent HbA_{1c} measurement, these covariates were time-updated in the same manner. The eGFR stages were

defined according to KDIGO categories as G1 (≥90 mL/min/1.73 m^2), G2 (60-89 mL/min/1.73 m^2), G3a (45-59 mL/min/1.73 m^2), G3b (30-44 mL/min/1.73 m^2), G4 (15-29 mL/min/1.73 m^2), and G5 (<15 mL/min/1.73 m^2).[12] For albuminuria, we used all available measurements of both dipstick and albumin-creatinine ratio, and categorized them according to KDIGO stages: A1 (ie, mildly increased albuminuria <30 mg/g), A2 (ie, moderately increased albuminuria 30-300 mg/g), and A3 (ie, severely increased albuminuria >300 mg/g).[29]

Outcomes

Our primary study outcomes were kidney related: CKD progression was defined as the composite of kidney failure (initiation of dialysis or transplantation, sustained eGFR < 15 mL/min/1.73 m^2) and a sustained decline of eGFR relative to baseline of more than 50%.[30] To reduce outcome misclassification bias owing to intrinsic eGFR variability and to confirm whether eGFR declines were sustained over time, we used a linear interpolation method, fitting one linear regression model per patient to all the patient's outpatient eGFR measurements.[31]

We also modeled these single outcomes separately. Worsening of albuminuria was defined by the presence during follow-up of at least 2 consecutive albuminuria tests denoting a KDIGO A category worse than baseline. Thus, patients who were classified as KDIGO A1 at baseline were followed for the occurrence of 2 consecutive albuminuria tests denoting KDIGO A2 or A3; patients were classified as KDIGO A2 for the occurrence of 2 consecutive albuminuria tests denoting KDIGO A3; and patients classified as KDIGO A3 at baseline were not considered for this outcome. Acute kidney injury (AKI) was defined as the composite of clinical diagnoses or transient creatinine elevations according to KDIGO criteria[32] following the algorithm developed by Hapca et al.[33] Patients with a history of AKI were not excluded, but their comorbidity history of AKI was adjusted for in our models. These outcomes were calculated at baseline and recalculated at each measure of HbA_{1c} variability. Follow-up ended on the date of reaching end points, death, emigration, or December 31, 2018, whichever came first.

Secondary outcomes are those already evaluated in previous studies and here explored as a measure of internal validity.[4,7] These included all-cause mortality, major adverse cardiac events (MACE), and microvascular complications. MACE was defined as a composite of cardiovascular death, nonfatal myocardial infarction, heart failure, and stroke; patients with a history of these conditions were not excluded, but their comorbidity history was adjusted for in our models. Microvascular complications were defined as the composite of diabetic retinopathy, diabetic peripheral neuropathy, and diabetic foot ulcer; patients with any of these conditions at baseline were not excluded from the study, but we evaluated the risk of developing any of the other microvascular complications during follow-up. For these outcomes, follow-up ended on the occurrence of an event, death, emigration or December 31, 2019, whichever came first.

Statistical Analyses

Baseline characteristics are presented as mean ± standard deviation (SD) or median (interquartile interval [IQI]) for continuous variables and as count (and proportion) for categorical variables.

We evaluated the association between baseline HVS groups and study outcomes using cause-specific Cox proportional hazards regression (with death considered as a competing event) and adjusted for the covariates listed earlier. Similarly, we evaluated outcomes associated with time-varying HVS through time-dependent Cox proportional hazards regression. To graphically depict the association between HVS (as a continuous variable) and study outcomes, we modeled HVS using natural cubic splines with 3 knots (at 25th, 50th, and 75th percentiles of the HVS distribution).

Study covariates had no missing values, to the extent that they were detected and measured in health care. The missing rate for albuminuria measurements was 18% at baseline and 9% during follow-up, for total cholesterol 3% at baseline and 2% during follow-up, and for low-density lipoprotein cholesterol 14% at baseline and 9% during follow-up. Because of the low proportion of missingness and current diabetes guideline recommendations to monitor these laboratory tests, we assumed missingness to be at random, and used chained equations by classification and regression trees (CART) to impute 10 complete datasets for each outcome separately.[34] The predictors included all covariates, the event indicator for the outcome, and the Nelson–Aalen estimator of the baseline and every updated HbA_{1c} variability cumulative hazard. Adjusted analyses were performed on the 10 imputed datasets, and then the results were combined using Rubin's rules.[35]

Subgroup analyses were performed to evaluate the consistency of the association across baseline categories of age (< 60 vs ≥60 years), sex (male vs female), eGFR categories, albuminuria categories, type 1/type 2 diabetes, baseline categories of HbA_{1c}, and presence/absence of CVD.

Supporting analyses evaluated (1) whether outcomes associated with HVS differed across patients whose HbA_{1c} was on target (≤53 mmol/mol) or not, and (2) whether outcomes differed according to increasing or decreasing HbA_{1c} variability trends. To that end, we calculated the linear regression slope of all HbA_{1c} measurements during the 3-year window and stratified analyses by negative (<0 mmol/mol/year) and positive (≥0 mmol/mol/year) slopes.

Sensitivity analyses were conducted to test the robustness of results: First, we used the coefficient of variation of HbA_{1c} (HbA_{1c}-CV) as an alternative study exposure. HbA_{1c}-CV is

the ratio of intraindividual HbA_{1c}-SD to intraindividual mean (HbA_{1c}-mean). HbA_{1c}-CV was categorized by using the 10th, 25th, 50th, 75th, and 90th percentiles as cutoff points, with the category of <10th percentile being the reference group. Second, we used attained age as the time scale instead of time-on-study to better capture the impact of age on study outcomes. Third, to avoid the impact of multiple HbA_{1c} measures in a short space of time, we allocated 1 HbA_{1c} measure for every 3-month period, using the median of all the outpatient HbA_{1c} measures within that time (18). We also calculated the binned HVS as exposure.

Fourth, we repeated our main analysis among incident diabetes patients, defined as patients with a first-ever recorded diabetes diagnosis within 4 years from baseline. To that end we inspected medical records up to January 1997, the time at which *International Classification of Diseases, Tenth Revision* (ICD-10) was implemented in Sweden. Finally, the HbA_{1c} variability calculation window was shortened and lengthened to 2 and 4 years, respectively, and the main analysis was repeated. Analyses were conducted in R software, version 3.4.3 (R Project for Statistical Computing).

Results

Baseline Characteristics

After applying inclusion and exclusion criteria, we evaluated 93,598 adults with diabetes who had at least 1 HbA_{1c} outpatient test during 3 consecutive years to define baseline HbA_{1c} variability (ie, baseline HVS; Fig S1). These patients underwent 527,015 outpatient HbA_{1c} tests during the preceding 3-years in total, with a median number of 5 HbA_{1c} tests per person.

Baseline characteristics are described in Table 1. The mean age of the participants was 65 ± 15 years, and 43.4% were women. The majority (87%) had type 2 diabetes; 19% had diabetic retinopathy, and 5% had diabetic peripheral neuropathy. Hypertension (68%) and psychiatric disorders (23%) were the most common comorbidities. Metformin (47%) and insulin (32%) were the most dispensed diabetes-controlling medications, and angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) (60%) were the most frequent nondiabetic medications.

A total of 17% of patients had CKD stages 3-5 at baseline, 23% had albuminuria stages A2/A3, and 1% had a history of diagnosed AKI. Patients with a higher HbA_{1c} variability (higher HVS categories) tended to be younger and more often were women. There was also a higher proportion of patients with type 1 diabetes and patients with diabetes complications or more severe albuminuria. Conversely, patients across higher HVS categories had higher eGFR. The proportion of patients with hypertension or receiving ACEI or ARBs decreased in higher HVS categories, and the proportion of patients on insulin increased.

HbA_{1c} Variability Score and Kidney Outcomes

During a median follow-up of 5.2 (IQI, 3.0-8.0) years, there were 891,536 subsequent outpatient HbA_{1c} tests, and at each test we recalculated HbA_{1c} variability (time-varying exposure). The median number of HbA_{1c} tests per person during the whole follow-up was 8, and the median number of HbA_{1c} tests per patient per year was 2 (IQI, 1-2).

Study outcomes are shown in Table 2. Compared with baseline HVS (0-20%), higher HVS categories were associated with higher CKD progression risk as well as a higher risk for each of its individual components. For example, those with HVS of 81%-100% had a 60% higher risk of CKD progression (HR, 1.60 [95% CI, 1.47-1.74]), attributed both to a higher risk of kidney failure (HR, 1.57 [95% CI, 1.39-1.77]), and of declining eGFR by more than 50% (HR, 1.60 [95% CI, 1.47-1.75]). The association between baseline HVS (continuous variable) and the risk of CKD progression is graphically depicted in Figure 1A and shows a monotonic risk increase with larger HVS. We observed similar associations and risks magnitudes in time-varying analyses (Table 2; Fig S3A).

Compared with baseline HVS (0-20%), higher HVS categories were associated with higher risk of AKI. For example, those with HVS of 81-100% had a 23% higher AKI (HR, 1.23 [95% CI, 1.16-1.3]) (Fig 1B; Table 2). Time-varying analyses showed similar findings (Table 2; Fig S3B).

The risk of albuminuria progression was evaluated in a subset of patients (n = 72,728) who had baseline measures of albuminuria detected and were in the range of A1/A2 severity. In this subset, and during 4 (IQI 2-7) years of follow-up, 19,693 individuals progressed to a worse albuminuria category. Again, larger HVS was associated with higher risk of worsening of albuminuria in both baseline and time-varying analyses (Fig 1C; Table 2; Fig S3C).

HbA_{1c} Variability Score (HVS) and Secondary Outcomes

During 6.0 (IQI, 3-10), 5.3 (IQI, 2.7-9), and 4.0 (IQI, 1.9-7.8) years of follow-up, we identified 22,475 deaths, 21,675 MACEs, and 31,943 microvascular complications events, respectively. Compared with reference HVS (0-20%), larger HVS were consistently associated with a higher risk of all 3 outcomes, both in baseline and time-varying analyses (Table 3). For instance, compared with baseline HVS 0-20%, patients with HVS of 81%-100% had a 26% higher risk of all-cause death (HR, 1.26 [95% CI, 1.19-1.33]), 17% higher risk of MACE (HR, 1.17 [95% CI, 1.11-1.24]), and 39% higher risk of microvascular complications (HR, 1.39 [95% CI, 1.34-1.45]).

Additional Analyses

Subgroup analyses generally showed similar results, both in direction and magnitude, except for some strata with limited sample size such as patients with CKD 4-5 or

Table 1. Baseline Characteristics of All Included Diabetic Patients, Overall and by Baseline Categories of HbA_{1c} Variability

		Categories of 3-Year Baseline HVS				
	Overall	**0-20%**	**20%-40%**	**40%-60%**	**60%-80%**	**80%-100%**
N	93,598	38,344	19,824	17,552	11,204	6,674
Age, y	65 ± 15	68 ± 13	65 ± 15	63 ± 15	63 ± 16	62 ± 16
Age categories						
<50 y	12,749 (13.6%)	3,494 (9.1%)	2,832 (14.3%)	3,025 (17.2%)	2,051 (18.3%)	1,347 (20.2%)
50-59 y	15,497 (16.6%)	5,115 (13.3%)	3,343 (16.9%)	3,307 (18.8%)	2,297 (20.5%)	1,435 (21.5%)
60-60 y	26,671 (28.5%)	11,211 (29.2%)	5,689 (28.7%)	4,958 (28.2%)	3,022 (27.0%)	1,791 (26.8%)
70-79 y	23,722 (25.3%)	11,627 (30.3%)	4,933 (24.9%)	3,737 (21.3%)	2,240 (20.0%)	1,185 (17.8%)
≥80 y	14,959 (16.0%)	6,897 (18.0%)	3,027 (15.3%)	2,525 (14.4%)	1,594 (14.2%)	916 (13.7%)
Female	40,646 (43.4%)	18,199 (47.5%)	8,474 (42.7%)	7,170 (40.9%)	4,360 (38.9%)	2,443 (36.6%)
Type 1 diabetes mellitus	11,831 (12.6%)	3,071 (8.0%)	2,736 (13.8%)	2,947 (16.8%)	1,850 (16.5%)	1,227 (18.4%)
Severity of Diabetes						
Diabetic retinopathy	17,653 (18.9%)	4,781 (12.5%)	4,031 (20.3%)	4,253 (24.2%)	2,841 (25.4%)	1,747 (26.2%)
Diabetic peripheral neuropathy	4,541 (4.9%)	1,248 (3.3%)	1,054 (5.3%)	1,132 (6.4%)	719 (6.4%)	388 (5.8%)
Hypoglycemia history	557 (0.6%)	112 (0.3%)	118 (0.6%)	136 (0.8%)	117 (1.0%)	74 (1.1%)
Laboratory Tests						
Mean HbA_{1c}, mmol/mol	52 [46-62]	46 [42-51]	54 [48-61]	58 [51-67]	63 [55-72]	65 [57-75]
eGFR, mL/min/1.73 m^2	86 [69-98]	83 [68-94]	86 [68-98]	88 [69-100]	89 [70-102]	90 [73-103]
eGFR categories						
G1	38,567 (41.2%)	13,354 (34.8%)	8,369 (42.2%)	8,006 (45.6%)	5,383 (48.0%)	3,455 (51.8%)
G2	39,565 (42.3%)	18,756 (48.9%)	8,048 (40.6%)	6,598 (37.6%)	3,941 (35.2%)	2,222 (33.3%)
G3a	9,353 (10.0%)	4,145 (10.8%)	1,995 (10.1%)	1,655 (9.4%)	1,015 (9.1%)	543 (8.1%)
G3b	4,622 (4.9%)	1,666 (4.3%)	1,034 (5.2%)	958 (5.5%)	634 (5.7%)	330 (4.9%)
G4-5	1,491 (1.6%)	423 (1.1%)	378 (1.9%)	335 (1.9%)	231 (2.1%)	124 (1.9%)
Albuminuria						
A1	55,394 (59.2%)	24,105 (62.9%)	11,718 (59.1%)	10,007 (57.0%)	6,023 (53.8%)	3,541 (53.1%)
A2	17,334 (18.5%)	6,029 (15.7%)	3,711 (18.7%)	3,547 (20.2%)	2,477 (22.1%)	1,570 (23.5%)
A3	3,587 (3.8%)	921 (2.4%)	802 (4.0%)	867 (4.9%)	645 (5.8%)	352 (5.3%)
Missing	17,283 (18.5%)	7,289 (19.0%)	3,593 (18.1%)	3,131 (17.8%)	2,059 (18.4%)	1,211 (18.1%)
Total cholesterol, mmol/L	4.7 [4.1-5.4]	4.7 [4.2-5.4]	4.7 [4.1-5.3]	4.7 [4.1-5.3]	4.7 [4.1-5.3]	4.7 [4.1-5.4]
LDL-cholesterol, mmol/L	2.7 [2.2-3.3]	2.7 [2.2-3.3]	2.6 [2.1-3.2]	2.6 [2.1-3.3]	2.7 [2.1-3.3]	2.7 [2.2-3.3]
Comorbidities						
Hypertension	63,155 (67.5%)	27,078 (70.6%)	13,354 (67.4%)	11,390 (64.9%)	7,236 (64.6%)	4,097 (61.4%)
Myocardial infarction	12,266 (13.1%)	4,913 (12.8%)	2,702 (13.6%)	2,310 (13.2%)	1,509 (13.5%)	832 (12.5%)
Heart failure	11,184 (11.9%)	4,015 (10.5%)	2,529 (12.8%)	2,218 (12.6%)	1,550 (13.8%)	872 (13.1%)
Cerebrovascular disease	10,816 (11.6%)	4,400 (11.5%)	2,245 (11.3%)	1,973 (11.2%)	1,418 (12.7%)	780 (11.7%)
Peripheral vascular disease	6,334 (6.8%)	2,407 (6.3%)	1,397 (7.0%)	1,230 (7.0%)	889 (7.9%)	411 (6.2%)
Cancer	12,010 (12.8%)	5,257 (13.7%)	2,589 (13.1%)	2,175 (12.4%)	1,284 (11.5%)	705 (10.6%)
COPD	14,489 (15.5%)	6,045 (15.8%)	3,162 (16.0%)	2,669 (15.2%)	1,688 (15.1%)	925 (13.9%)

(Continued)

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Table 1 (Cont'd). Baseline Characteristics of All Included Diabetic Patients, Overall and by Baseline Categories of HbA_{1c} Variability

		Categories of 3-Year Baseline HVS				
	Overall	0-20%	20%-40%	40%-60%	60%-80%	80%-100%
Dementia	2,558 (2.7%)	831 (2.2%)	534 (2.7%)	518 (3.0%)	397 (3.5%)	278 (4.2%)
Liver disease	2,960 (3.2%)	998 (2.6%)	688 (3.5%)	586 (3.3%)	440 (3.9%)	248 (3.7%)
Psychiatric disorder	21,937 (23.4%)	8,668 (22.6%)	4,631 (23.4%)	4,203 (23.9%)	2,786 (24.9%)	1,649 (24.7%)
AKI history	1,289 (1.4%)	363 (0.9%)	300 (1.5%)	262 (1.5%)	230 (2.1%)	134 (2.0%)
Ongoing Medication Use						
Metformin	44,150 (47.2%)	15,935 (41.6%)	10,116 (51.0%)	8,877 (50.6%)	5,883 (52.5%)	3,339 (50.0%)
Sulfonylurea	15,275 (16.3%)	4,236 (11.0%)	3,683 (18.6%)	3,587 (20.4%)	2,376 (21.2%)	1,393 (20.9%)
Thiazolidinedione	1,365 (1.5%)	585 (1.5%)	296 (1.5%)	270 (1.5%)	130 (1.2%)	84 (1.3%)
α-Glucosidase inhibitor	286 (0.3%)	109 (0.3%)	59 (0.3%)	57 (0.3%)	42 (0.4%)	19 (0.3%)
Glinide	1,613 (1.7%)	544 (1.4%)	405 (2.0%)	344 (2.0%)	188 (1.7%)	132 (2.0%)
GLP1-RA	1,161 (1.2%)	165 (0.4%)	241 (1.2%)	326 (1.9%)	284 (2.5%)	145 (2.2%)
DPP4 inhibitor	2,924 (3.1%)	715 (1.9%)	696 (3.5%)	739 (4.2%)	488 (4.4%)	286 (4.3%)
SGLT2 inhibitor	333 (0.4%)	60 (0.2%)	79 (0.4%)	93 (0.5%)	56 (0.5%)	45 (0.7%)
Insulin	30,061 (32.1%)	6,197 (16.2%)	6,964 (35.1%)	7,909 (45.1%)	5,577 (49.8%)	3,414 (51.2%)
ACEI/ARB	56,500 (60.4%)	23,545 (61.4%)	12,175 (61.4%)	10,471 (59.7%)	6,677 (59.6%)	3,632 (54.4%)
Loop diuretic	15,939 (17.0%)	5,608 (14.6%)	3,607 (18.2%)	3,322 (18.9%)	2,221 (19.8%)	1,181 (17.7%)
Other diuretic	14,326 (15.3%)	6,220 (16.2%)	3,105 (15.7%)	2,546 (14.5%)	1,570 (14.0%)	885 (13.3%)
Other hypertensive agents	48,572 (51.9%)	21,060 (54.9%)	10,387 (52.4%)	8,674 (49.4%)	5,464 (48.8%)	2,987 (44.8%)
Statin	2,520 (2.7%)	797 (2.1%)	589 (3.0%)	543 (3.1%)	350 (3.1%)	241 (3.6%)
Platelet inhibitor	33,935 (36.3%)	13,880 (36.2%)	7,342 (37.0%)	6,368 (36.3%)	4,069 (36.3%)	2,276 (34.1%)
Health Care Utilization in the 1 Year Prior						
Primary care visits	3 [2-7]	4 [2-7]	4 [2-7]	3 [1-7]	3 [1-7]	3 [1-6]
Outpatient visits	2 [0-5]	2 [0-4]	2 [0-5]	2 [0-5]	2 [0-5]	2 [0-5]
Inpatient visits	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]

Baseline characteristics are presented as mean ± SD or median [interquartile interval] for continuous variables and as count (and proportion) for categorical variables. Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; DPP4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GLP1-RA, glucagon-like peptide 1 receptor agonists; HbA_{1c}, hemoglobin A_{1c}; HVS, HbA_{1c} variability score; LDL, low-density lipoprotein; SGLT2, sodium-glucose cotransporter 2.

Table 2. Primary Outcome of Risk of Kidney Outcomes Across Categories of HbA_{1c} Variability

	Categories of 3-Year HVS				
	0-20%	20%-40%	40%-60%	60%-80%	80%-100%
CKD Progression					
Composite outcome					
No. of events/N[a]	2,693/38,344	1,963/19,824	1,905/17,552	1,367/11,204	783/6,674
Incidence rate/per 1,000 person-years[a]	12.27 (11.82-12.74)	17.08 (16.34-17.84)	18.63 (17.82-19.48)	21.72 (20.6-22.89)	20.86 (19.45-22.35)
Baseline HVS	1 (Ref)	1.25 (1.18-1.33)	1.31 (1.23-1.4)	1.45 (1.35-1.56)	1.6 (1.47-1.74)
Time-varying HVS	1 (Ref)	1.3 (1.21-1.39)	1.42 (1.32-1.52)	1.54 (1.42-1.66)	1.59 (1.45-1.74)
Kidney failure outcome					
No. of events/N[a]	1,225/38,344	1,047/19,824	1,043/17,552	733/11,204	421/6,674
Incidence rate/per 1,000 person-years[a]	5.54 (5.24-5.85)	9 (8.47-9.55)	10.07 (9.48-10.69)	11.47 (10.67-12.31)	11.03 (10.03-12.11)
Baseline HVS	1 (Ref)	1.31 (1.21-1.43)	1.34 (1.23-1.47)	1.43 (1.29-1.58)	1.57 (1.39-1.77)
Time-varying HVS	1 (Ref)	1.28 (1.18-1.4)	1.37 (1.25-1.5)	1.48 (1.34-1.63)	1.41 (1.25-1.59)
50% decline of eGFR outcome					
No. of events/N[a]	2,608/38,344	1,887/19,824	1,833/17,552	1,318/11,204	755/6,674
Incidence rate/per 1,000 person-years[a]	11.87 (11.43-12.33)	16.37 (15.65-17.12)	17.88 (17.08-18.71)	20.88 (19.78-22.02)	20.08 (18.7-21.54)
Baseline HVS	1 (Ref)	1.24 (1.17-1.32)	1.32 (1.23-1.4)	1.46 (1.36-1.57)	1.6 (1.47-1.75)
Time-varying HVS	1 (Ref)	1.31 (1.21-1.41)	1.48 (1.37-1.6)	1.65 (1.51-1.79)	1.72 (1.56-1.9)
AKI					
No. of events/N[a]	7,912/38,344	4,886/19,824	4,554/17,552	3,132/11,204	1,742/6,674
Incidence rate/per 1,000 person-years[a]	39.18 (38.33-40.05)	46.87 (45.57-48.19)	49.43 (48.02-50.88)	55.62 (53.7-57.58)	51.22 (48.88-53.66)
Baseline HVS	1 (Ref)	1.12 (1.08-1.16)	1.17 (1.13-1.22)	1.22 (1.17-1.27)	1.23 (1.16-1.3)
Time-varying HVS	1 (Ref)	1.16 (1.12-1.2)	1.23 (1.19-1.28)	1.28 (1.22-1.34)	1.33 (1.26-1.41)
Worsening of Albuminuria					
No. of events/N[a]	7,331/30,134	4,388/15,429	3,951/13,554	2,519/8,500	1,504/5,111
Incidence rate/per 1,000 person-years[a]	52.78 (51.59-54)	62.3 (60.49-64.16)	63.22 (61.28-65.21)	66.83 (64.27-69.47)	65.13 (61.92-68.46)
Baseline HVS	1 (Ref)	1.17 (1.13-1.22)	1.21 (1.16-1.26)	1.26 (1.2-1.32)	1.28 (1.21-1.36)
Time-varying HVS	1 (Ref)	1.21 (1.16-1.26)	1.26 (1.2-1.31)	1.31 (1.25-1.38)	1.31 (1.23-1.39)

Values are hazard ratios and 95% CI unless otherwise indicated. Models were adjusted for age, sex, diabetes type, diabetic retinopathy, diabetic peripheral neuropathy, history of hypoglycemia, hypertension, myocardial infarction, heart failure, cerebrovascular disease, peripheral vascular disease, cancer, chronic obstructive pulmonary disease, dementia, liver disease, psychiatric disorder, metformin, sulfonylurea, thiazolidinedione, alpha glucosidase inhibitor, glinide, glucagon-like peptide 1 receptor agonists, dipeptidyl peptidase 4 inhibitors, sodium-glucose cotransporter 2 inhibitors, insulin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, loop diuretics, other diuretics, other hypertensives, statins, platelet inhibitors, mean hemoglobin A_{1c}, eGFR, albuminuria category, total cholesterol, low-density lipoprotein, number of primary care visits, number of outpatient visits, number of hospitalizations. For the outcome of AKI, history of AKI was additionally included in the list of covariates; for the outcome of progression of albuminuria, persons with albuminuria A3 or untested were not included. Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HVS, hemoglobin A_{1c} variability score; Ref, reference value.

[a]Number of events, patients and incidence rate considered in time-fixed analyses.

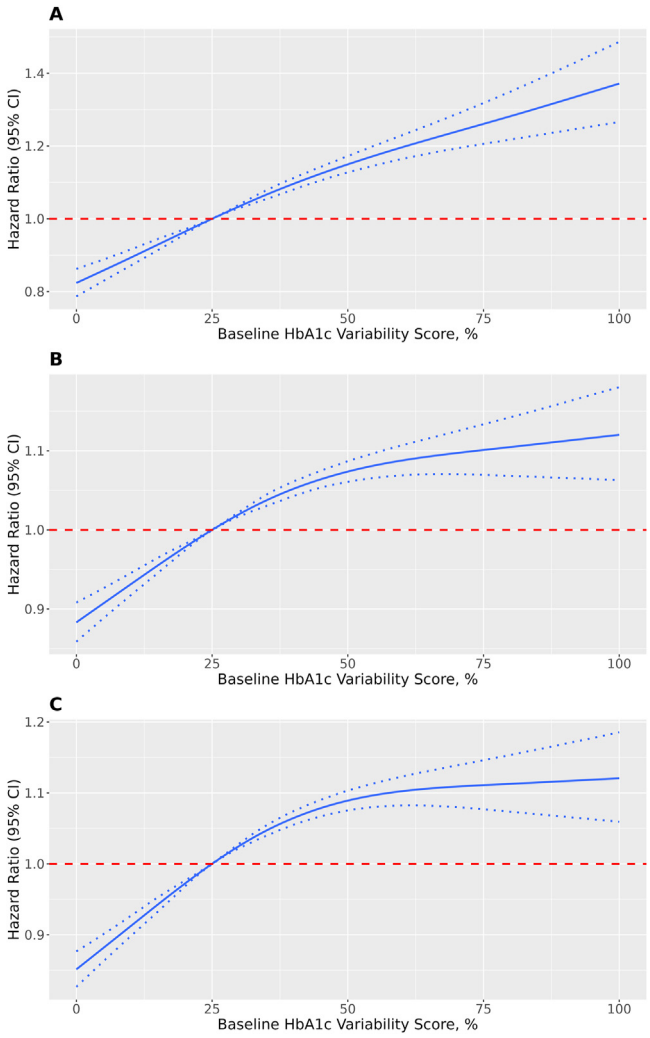

Figure 1. Associations between 3-year baseline HbA_{1c} variability score with kidney-related outcomes. A: CKD progression; B: AKI; C: Worsening of albuminuria. Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; HbA_{1c}, hemoglobin A_{1c}.

patients with albuminuria A3. Risk associations increased across higher HVS categories regardless of whether attained HbA_{1c} was on target or not, and whether variability was increasing or decreasing (Tables S3-S5). When HbA_{1c}-CV was used as an alternative metric of HbA_{1c} variability, we observed similar linear associations with study outcome (Tables S6-S7). Using attained age as the time scale produced similar results, as well as averaging HbA_{1c} in 3-month periods or using binned HVS as a measure of HbA_{1c} variability. Restricting the analysis to the >40.000 patients with an incident diabetes diagnosis or estimating the 2-year or 4-year HbA_{1c} variability produced results consistent with our main analysis (Tables S8-S12).

Discussion

Poor glycemic control is an established contributor to the occurrence and progression of CKD,[9] but whether long-term visit-to-visit variability in glycemic control is associated with kidney outcomes is not well studied. By evaluating the long-term trajectories of glycemic control in almost 100,000 persons with diabetes, we observed a consistent and linear association between high HbA_{1c} variability and the risks of CKD progression, worsening of albuminuria, and AKI. Results were robust to adjustment for mean HbA_{1c} and multiple covariates. We saw similar associations across a variety of subgroup and sensitivity analyses, including patients with and without manifest CKD.

Our finding of an association between HbA_{1c} variability and the risk of AKI is novel and is consistent with mechanistic evidence suggesting a role for hyperglycemia in increasing AKI susceptibility in diabetes.[36-38] Our finding of an association between HbA_{1c} variability and the risk of CKD progression or worsening of albuminuria is confirmatory, expanding the previous observations we will discuss. The strengths of our analysis include its large sample size (more than 10-fold larger than previous studies), inclusion of persons with type 1 and type 2 diabetes, and unique setting, involving real-world patients from a country with universal tax-funded health care, which minimizes selection bias from disparate access to health care.

Some previous studies have reported an association between HbA_{1c} variability and the risk of worsening albuminuria or developing incident CKD.[11-20] These studies typically evaluated a single baseline assessment of HbA_{1c} variability, and study outcomes were not harmonized, precluding comparisons. They were performed in predominantly smaller research cohorts and through post hoc analyses of clinical trials. In these settings, HbA_{1c} variability is lower compared with that of our study, which includes a more heterogeneous population of persons seeking health care. Whereas previous studies used the standard deviation of repeated HbA_{1c} tests as a measure of variability, we opted for the HVS as it accounts for the number of HbA_{1c} tests in its calculation. This method aligns with recent studies evaluating glycemic variability and other macro- and microvascular complications[4-7] and may be more relevant to routine care settings, given that sicker patients tend to have more frequent contact with the health care system and more frequent HbA_{1c} testing. The windows of ascertainment of HbA_{1c} variability for most previous studies was 1 or 2 years, which may underestimate the importance of HbA_{1c} variability, given that in the absence of complications contact with the health care system may be infrequent.

Our study has clinical implications. The evidence for current guideline recommendations derives from clinical trials that focus on HbA_{1c} as the definitive measure of efficacy of an intervention. For instance, intensive glycemic control with the goal of achieving near-normoglycemia delayed the onset and progression of albuminuria and reduced eGFR in patients with type 1[39] and type 2 diabetes,[2] supporting the conclusion that glycemic control

Table 3. Risk of Secondary Outcomes Across Categories of HbA_{1c} Variability

	Categories of 3-Year HVS				
	0-20%	20%-40%	40%-60%	60%-80%	80%-100%
All-cause death					
No. of events/N[a]	8,172/41,329	4,923/20,949	4,568/18,460	3,061/11,758	1,751/6,983
Incidence rate/per 1,000 person-years[a]	31.97 (31.28-32.67)	36.87 (35.85-37.91)	38.5 (37.4-39.63)	41.64 (40.19-43.12)	39.96 (38.13-41.85)
Baseline HVS	1 (Ref)	1.13 (1.09-1.17)	1.21 (1.16-1.26)	1.23 (1.18-1.28)	1.26 (1.19-1.33)
Time-varying HVS	1 (Ref)	1.23 (1.19-1.28)	1.33 (1.28-1.39)	1.45 (1.39-1.52)	1.63 (1.55-1.71)
MACE					
No. of events/N[a]	8,328/41,329	4,731/20,949	4,206/18,460	2,860/11,758	1,550/6,983
Incidence rate/per 1,000 person-years[a]	35.61 (34.85-36.38)	38.98 (37.89-40.1)	39.19 (38.02-40.38)	43.16 (41.61-44.76)	38.64 (36.76-40.59)
Baseline HVS	1 (Ref)	1.1 (1.06-1.14)	1.14 (1.1-1.19)	1.18 (1.13-1.24)	1.17 (1.11-1.24)
Time-varying HVS	1 (Ref)	1.14 (1.1-1.18)	1.19 (1.15-1.24)	1.19 (1.14-1.24)	1.31 (1.24-1.38)
Microvascular complications					
No. of events/N[a]	9,784/41,329	7,217/20,949	7,145/18,460	4,813/11,758	2,984/6,983
Incidence rate/per 1,000 person-years[a]	46.07 (45.17-46.99)	72.99 (71.33-74.68)	84.78 (82.84-86.76)	94.46 (91.83-97.15)	99.43 (95.92-103.02)
Baseline HVS	1 (Ref)	1.28 (1.24-1.32)	1.34 (1.29-1.38)	1.39 (1.34-1.44)	1.39 (1.34-1.45)
Time-varying HVS	1 (Ref)	1.26 (1.23-1.3)	1.36 (1.32-1.41)	1.35 (1.3-1.4)	1.39 (1.33-1.45)

Values are hazard ratios and 95% CI unless otherwise indicated. Models were adjusted for age, sex, diabetes type, diabetic retinopathy, diabetic peripheral neuropathy, history of hypoglycemia, hypertension, myocardial infarction, heart failure, cerebrovascular disease, peripheral vascular disease, cancer, chronic obstructive pulmonary disease, dementia, liver disease, psychiatric disorder, metformin, sulfonylurea, thiazolidinedione, alpha glucosidase inhibitor, glinide, glucagon-like peptide 1 receptor agonists, dipeptidyl peptidase 4 inhibitors, sodium-glucose cotransporter 2 inhibitors, insulin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, loop diuretics, other diuretics, other hypertensives, statins, platelet inhibitors, mean hemoglobin A_{1c}, eGFR, albuminuria category, total cholesterol, low-density lipoprotein, number of primary care visits, number of outpatient visits, number of hospitalizations.
Abbreviations: AKI, acute kidney disease; HbA_{1c}, hemoglobin A_{1c}; HVS, hemoglobin A_{1c} variability score; MACE, major adverse cardiovascular events; Ref, reference value.
[a]Number of events, patients, and incidence rate considered in time-fixed analyses.

itself helps prevent CKD and its progression. Although target HbA_{1c} levels in people with CKD are still controversial,[9,40] the current guidelines emphasize individualized HbA_{1c} targets and possibly less intensive glycemic control for these persons. However, HbA_{1c} reflects average glycemia without regard to glycemic variability, which is associated with higher risk of hypoglycemia on average.[41] Thus, our work emphasizes the value of going "beyond HbA_{1c}": patients with greater HbA_{1c} variability should be considered high risk over and above their level of glycemic control.

Because HbA_{1c} variability is associated with the quality of patient care,[42] it is possible to reduce the HbA_{1c} variability in clinical practice. Interventions that reduce variability in HbA_{1c} may include education programs on diet and lifestyle, closer contact with a dietitian, and modifying antidiabetic medication regimes. Most people with high variability in our study were on insulin and might benefit from enhanced teaching in insulin administration and incorporation of emerging technologies that integrate continuous glucose monitoring, food intake, and insulin dose.[40]

Interestingly, contact with the health care system tended to be lower in patients with high HbA_{1c} variability, suggesting that this high-risk population might benefit from targeted monitoring strategies.[4-7] Although it was not feasible in our current analysis, it would be interesting to evaluate whether adherence or changes in antidiabetic treatments reduce HbA_{1c} variability and can explain the improved outcomes with some of these agents. Both glucagon-like peptide 1 (GLP-1) receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce HbA_{1c} variability compared with standard of care,[43] together with additional benefits to prevent kidney and cardiovascular complications.[44-46]

We acknowledge additional limitations. We lacked information on diet, body mass index, volume status, and diabetes duration; however, our sensitivity analysis among >40,000 patients with incident diabetes showed similar findings. Our definition of albuminuria worsening considers quantitatively large changes across KDIGO A thresholds and may underestimate risks. Our population was predominantly White, and additional studies in more diverse populations are needed. HbA_{1c} tests may be less reliable in persons with advanced CKD owing to the influence of CKD-related anemia and the life spans of red cells with subsequent alterations in hemoglobin glycation percentages,[47] or the interference from posttranslational protein carbamylation, which can increase in states of high urea burden such as CKD.[48] As recently suggested, the extent of both these abnormalities may impact on HbA_{1c}'s predictive abilities for the risk of CKD progression.[49] Finally, all limitations inherent to observational studies apply.

To conclude, the findings of this study support a role for long-term glycemic variability in the development of kidney complications and illustrates the potential usefulness of this metric for risk stratification at the bedside beyond a single HbA_{1c} test.

Supplementary Material

Supplementary File (PDF)

Figure S1: Flow chart of patient selection into the study.

Figure S2: Illustration of time-varying design.

Figure S3: Associations between 3-year time-varying HbA_{1c} variability score with kidney-related outcomes.

Table S1: Definition of study outcomes.

Table S2: Definition of study covariates.

Table S3: Subgroup analyses for the risk of CKD progression across categories of HbA_{1c} variability.

Table S4: Subgroup analyses for the risk of AKI across categories of HbA_{1c} variability.

Table S5: Subgroup analyses for the risk of worsening of albuminuria across categories of HbA_{1c} variability.

Table S6: Baseline characteristics of all included patients, overall and by categories of baseline HbA_{1c}-CV.

Table S7: HRs and 95% CI for the risk of different adverse clinical outcomes across categories of 3-year HbA_{1c}-CV.

Table S8: Sensitivity analysis 1: HRs and 95% CI for the risk of adverse clinical outcomes across categories of HbA_{1c} variability when age is used as the time scale.

Table S9: Sensitivity analysis 2: HRs and 95% CI for the risk of different adverse clinical outcomes across categories of HbA_{1c} variability averaging HbA_{1c} measurements every 3-months.

Table S10: Sensitivity analysis 3: HRs and 95% CI for the risk of adverse clinical outcomes across categories of HbA_{1c} variability among patients with incident diabetes.

Table S11: Sensitivity analysis 4: HRs and 95% CI for the risk of different adverse clinical outcomes across categories of HbA_{1c} variability (shortening the ascertainment window to 2 years).

Table S12: Sensitivity analysis 4: HRs and 95% CI for the risk of adverse clinical outcomes across categories of HbA_{1c} variability (enlarging the ascertainment window to 4 years).

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