# Association of Long-term Change and Variability in Glycemia With Risk of Incident Heart Failure Among Patients With Type 2 Diabetes: A Secondary Analysis of the ACCORD Trial

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## OBJECTIVE

**To evaluate the associations between long-term change and variability in glycemia with risk of heart failure (HF) among patients with type 2 diabetes mellitus (T2DM).**

## RESEARCH DESIGN AND METHODS

**Among participants with T2DM enrolled in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, variability in $HbA_{1c}$ was assessed from stabilization of $HbA_{1c}$ following enrollment (8 months) to 3 years of follow-up as follows: average successive variability (ASV) (average absolute difference between successive values), coefficient of variation (SD/mean), and SD. Participants with HF at baseline or within 3 years of enrollment were excluded. Adjusted Cox models were used to evaluate the association of percent change (from baseline to 3 years of follow-up) and variability in $HbA_{1c}$ over the first 3 years of enrollment and subsequent risk of HF.**

## RESULTS

**The study included 8,576 patients. Over a median follow-up of 6.4 years from the end of variability measurements at year 3, 388 patients had an incident HF hospitalization. Substantial changes in $HbA_{1c}$ were significantly associated with higher risk of HF (hazard ratio [HR] for ≥10% decrease 1.32 [95% CI 1.08–1.75] and for ≥10% increase 1.55 [1.19–2.04]; reference <10% change in $HbA_{1c}$). Greater long-term variability in $HbA_{1c}$ was significantly associated with higher risk of HF (HR per 1 SD of ASV 1.34 [95% CI 1.17–1.54]) independent of baseline risk factors and interval changes in cardiometabolic parameters. Consistent patterns of association were observed with use of alternative measures of glycemic variability.**

## CONCLUSIONS

**Substantial long-term changes and variability in $HbA_{1c}$ were independently associated with risk of HF among patients with T2DM.**


Heart failure (HF) is common and associated with high morbidity and mortality among adults with type 2 diabetes mellitus (T2DM) (1–3). Risk factors for HF among patients with T2DM include high blood pressure (BP), coronary artery disease, abnormal kidney function, obesity, and low cardiorespiratory fitness levels (4,5). Moreover,

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epidemiologic studies have also demonstrated that chronic hyperglycemia in T2DM is associated with higher risk of HF (6–8). However, large-scale randomized controlled trials of intensive glycemic control among patients with T2DM did not lower the risk of HF (9–11). The null effect of strict glucose control on cardiovascular outcomes has been attributed in part to hypoglycemia, though such a causal link has not been proven (12,13). A single measurement of glycemia may not reflect chronic glucose exposure and its attendant cardiovascular risk. Fluctuation in glycemia has been proposed as an alternative prognostic marker in T2DM. Long-term glycemic variability is a measure of changes in glucose over time and is associated with adverse cardiovascular events, renal disease, and mortality in patients with T2DM (14,15). Whether long-term change and variability in glycemia are each associated with risk of HF among patients with T2DM is not well established.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was a multicenter clinical trial that examined the effects of intensive glycemic control on cardiovascular outcomes among adults with T2DM (9). In ACCORD, glycated hemoglobin ($HbA_{1c}$) and fasting plasma glucose (FPG) were measured at regular intervals and HF hospitalization events were adjudicated as a secondary outcome (9,16). The purpose of the current study was to examine the associations of long-term changes and variability in glycemic markers, specifically $HbA_{1c}$ and FPG, with risk of HF among participants of ACCORD. We hypothesized that substantial changes in $HbA_{1c}$ as well as greater long-term glycemic variability in $HbA_{1c}$ on follow-up would be associated with higher risk of HF.

## RESEARCH DESIGN AND METHODS

### Study Population

The current study was performed as a post hoc analysis of ACCORD and the subsequent ACCORD Follow-on (ACCORDION) study. The study design and results have previously been reported and are described in Supplementary Material (9,17,18). The present analysis included participants from the intensive and standard glycemic control arms of the trial with no history of HF who had at least three repeated measurements of glycemia ($HbA_{1c}$ or FPG) after stabilization of the values (8-month visit) following randomization up to 3 years from enrollment (Supplementary Fig. 1). Patients with an incident HF event within 3 years from enrollment were excluded from the present analysis.

### Measures of Long-term Glycemic Variability

Long-term glycemic variability was measured as the variability in $HbA_{1c}$ or FPG between visits for each participant and was calculated using repeated measures of $HbA_{1c}$ or FPG between 8 months and 3 years of follow-up. The variability assessment was landmarked at 8 months considering the study intervention directly influenced fluctuation in glycemic markers in the first few months following enrollment (Supplementary Fig. 2). Core laboratory measures of $HbA_{1c}$ and FPG were used for calculation of glycemic variability. The following three established measures of glycemic variability were used: average successive variability (ASV), SD, and coefficient of variation (CV) (15,19). The ASV was prespecified as the primary exposure variable of interest and was defined as the average absolute difference between successive values. The CV was calculated as the SD divided by the mean value.

### Clinical Covariates

Upon enrollment, patients underwent questionnaires, physical examination, and laboratory measures using a standardized protocol as previously described and detailed in Supplementary Material (9,17). $HbA_{1c}$ levels were measured at a core laboratory every 4 months. FPG levels were measured every 4 months for the first 2 years and subsequently every 12 months. Participants randomized to both trial arms achieved lower glucose levels soon after randomization with stabilization of glycemic levels at 8 months (Supplementary Fig. 2). In the current study, percent change ($\Delta$) in $HbA_{1c}$ ($\Delta HbA_{1c}$) and other cardiometabolic parameters was calculated with use of data collected from the baseline visit until up to 3 years of follow-up.

### Incident HF, Noncardiovascular Death, and Hypoglycemic Events

The primary outcome of interest for the present analysis was incident HF defined as the first hospitalization event for HF or death due to HF. In ACCORD, an independent committee adjudicated HF events as a prespecified secondary outcome (9,16). Hospitalization for HF was based on documented clinical and radiological evidence. Death due to HF was based on clinical, radiological, or postmortem evidence of HF with absence of an acute ischemic event according to clinical or postmortem evidence. The secondary outcome of interest was defined as an acute ischemic heart disease event, which was a prespecified secondary outcome in ACCORD defined as cardiovascular death, nonfatal myocardial infarction (MI), or unstable angina. Time to event was calculated as the number of months from year 3 of follow-up to occurrence of the first event. Long-term follow-up was recorded in all patients using data from ACCORD and ACCORDION (18). For analyses of all clinical outcomes, patients were censored at the time of their last follow-up.

Death events were adjudicated by a central committee, which was masked to treatment allocation and used predefined criteria. Hypoglycemic events were self-reported by the participant and defined as any episode requiring medical attention in which there was either a documented capillary glucose level $<$50 mg/dL ($<$2.8 mmol/L) or prompt recovery following administration of oral carbohydrate, intravenous glucose, or glucagon (20).

### Statistical Analysis

Patients were categorized into long-term $HbA_{1c}$ variability groups according to quintiles of ASV. Normality in distribution of patient characteristic variables was assessed by calculating the skewness and plotting a histogram for the vector of values with an overlying normal curve with the same mean and SD. Each continuous variable was confirmed as being normally distributed (skewness statistic between $-2$ and 2), and these variables were reported as mean (SD). Categorical variables were reported as percentages across the study groups. Differences between groups were tested using a $\chi^2$ test for categorical variables and one-way ANOVA for continuous variables. Baseline characteristics were compared across categories of baseline $HbA_{1c}$ and $\Delta HbA_{1c}$. Unadjusted rates of incident HF events were also compared across ASV categories in the overall cohort and across subgroups stratified by categories of baseline $HbA_{1c}$ ($<$7.0% [$<$53 mmol/mol],

7.0%–8.5% [53–69 mmol/mol], and >8.5% [>69 mmol/mol]) and $\Delta HbA_{1c}$ (≥10% decrease, <10% decrease to <10% increase, and ≥10% increase). Separate multivariable Cox proportional hazards models were constructed to evaluate the association of categorical and continuous measures of baseline $HbA_{1c}$ and $\Delta HbA_{1c}$ with risk of HF. Validity of the proportionality assumption was verified using scaled Schoenfield residuals and by visually examining "log-log" plots. The models were sequentially adjusted with inclusion of the following covariates selected a priori based on biologic plausibility and prior published literature (21): model 1, demographic characteristics (age, sex, race, and level of education), intensive glycemic control treatment group, history of cardiovascular disease (CVD) (MI, stroke, or coronary revascularization), traditional cardiovascular risk factors (systolic BP, BMI, cigarette use, alcohol use, total cholesterol, serum creatinine, LDL cholesterol [LDL-c], and HDL cholesterol [HDL-c]), medication use (angiotensin receptor blocker, ACE inhibitor, β-blocker, loop diuretic, thiazide diuretic, calcium channel blocker, insulin, sulfonylurea, biguanide, meglitinide, and α-glucosidase inhibitor), and baseline $HbA_{1c}$, and model 2, adjustment for covariates in model 1 + $\Delta HbA_{1c}$, Δsystolic BP, ΔBMI, and Δcreatinine from enrollment baseline to year 3 + interval MI on follow-up as a time-dependent variable. The associations between measures of variability in $HbA_{1c}$ and risk of HF were also assessed using multivariable Cox models that included the covariates described above in models 1 and 2 along with measures of $HbA_{1c}$ variability (ASV, CV, and SD in separate models). Multiplicative interaction terms were included in the adjusted Cox models to evaluate whether the association between glycemic variability and risk of HF was modified by baseline $HbA_{1c}$ and $\Delta HbA_{1c}$. FPG, an alternative measure of glycemia, was also used to assess the independent associations of glycemic variability and risk of adverse events.

In the subset of the study population free of atherosclerotic CVD at baseline ($N$ = 5,822), the association between measures of glycemic variability with the risk of acute ischemic heart disease events was assessed using adjusted Cox models that included covariates described above in model 1 (except history of CVD) and model 2 (except interval MI).

Additional analyses were performed to evaluate the robustness of the association of $\Delta HbA_{1c}$ and variability in $HbA_{1c}$ with risk of HF. First, to account for the potential contribution of hypoglycemic events toward the observed association of $\Delta HbA_{1c}$ and variability in $HbA_{1c}$ with risk of HF, we performed sensitivity analysis excluding individuals with a hypoglycemic event on follow-up ($N$ = 1,159 with hypoglycemic events). Second, to account for seasonal changes in $HbA_{1c}$ and the effect of number of $HbA_{1c}$ measures used to estimate variability, we performed sensitivity analysis assessing $HbA_{1c}$ variability among individuals with higher minimum number of repeated $HbA_{1c}$ measures within the first 3 years of follow-up. Third, to account for the prognostic importance of variability in BP (22), BMI, and LDL-c, we additionally adjusted Cox models for variability in these parameters over the first 3 years (from 8 months to 3 years of follow-up). Finally, we performed stratified analyses examining the association of long-term variability in $HbA_{1c}$ with risk of HF across intensive glucose control versus standard control groups, across intensive BP control versus standard BP control groups, and among subgroups of participants with versus without history of atherosclerotic CVD. Analyses were performed using R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

Of the 10,251 patients enrolled in ACCORD, participants were excluded from the present analyses for the following reasons: 492 had a history of HF, 870 were missing at least three $HbA_{1c}$ measurements between month 8 and 3 years, and 223 developed HF and an additional 90 died within the first 3 years of enrollment (Supplementary Fig. 1). The current study included 8,576 patients (38.4% of whom were women and 18.3% of whom were black) with a mean ± SD baseline $HbA_{1c}$ of 8.3 ± 1.0% (mean 67 mmol/mol). The median number of $HbA_{1c}$ measurements between 8 months and 3 years of follow-up was eight (interquartile range 7–8). The mean $HbA_{1c}$ variability, as measured by ASV, was 0.6 ± 0.3%. Over a median follow-up of 6.4 (interquartile range 4.0–7.6) years from the end of variability measurements at year 3, there were 388 (cumulative rate: 4.5%) incident HF events.

The baseline characteristics of participants stratified by quintiles of long-term variability in $HbA_{1c}$ are shown in Table 1. The patients with greater long-term glycemic variability more commonly were black, younger, and randomized to standard therapy; used insulin; had a history of CVD; and had higher BMI, $HbA_{1c}$, and total cholesterol at baseline. These patients had more change in BMI and serum creatinine from baseline to 3 years of follow-up. Baseline characteristics of the patients stratified by baseline $HbA_{1c}$ and $\Delta HbA_{1c}$ from baseline to 3 years of follow-up are shown in Supplementary Tables 1 and 2.

### Baseline $HbA_{1c}$, $\Delta HbA_{1c}$, and Risk of HF

Baseline $HbA_{1c}$ was significantly associated with risk of HF in multivariable-adjusted analysis such that 1 unit higher $HbA_{1c}$ was associated with 20% higher risk of incident HF after other baseline confounders were accounted for (hazard ratio [HR] 1.20 [95% CI 1.08–1.33]) (Supplementary Table 3). The association between $\Delta HbA_{1c}$ and risk of incident HF was nonlinear with a significantly higher risk noted at either extreme (Fig. 1). Individuals with ≥10% increase or ≥10% decrease in $HbA_{1c}$ during the first 3 years of follow-up had higher risk of HF compared with individuals with a more stable $HbA_{1c}$ (<10% decrease to <10% increase) (HR 1.55 [95% CI 1.19–2.04] and 1.32 [1.08–1.75], respectively) (Supplementary Table 3) after adjustment for baseline and longitudinal changes in risk factors on follow-up. In sensitivity analysis excluding individuals with a hypoglycemic event on follow-up, the risk of incident HF was significant among those with a >10% increase in $HbA_{1c}$ but not among those with >10% decrease in $HbA_{1c}$ on follow-up (Supplementary Table 4).

### Long-term Variability in $HbA_{1c}$ and Risk of HF

In unadjusted comparison, the risk of incident HF increased in a graded fashion across increasing quintiles of ASV (quintile 1 [Q1] 3.3% and Q5 6.2%) (Fig. 2). In adjusted analyses, higher measures of long-term variability in $HbA_{1c}$, as measured by ASV, were associated with significantly higher risk of HF independent of baseline risk factors, medication

**Table 1—Baseline characteristics of participants stratified by quintiles of variability in $HbA_{1c}$**

| | Quintile 1 ($n$ = 1,748) | Quintile 2 ($n$ = 1,700) | Quintile 3 ($n$ = 1,716) | Quintile 4 ($n$ = 1,702) | Quintile 5 ($n$ = 1,710) | $P$ |
|---|---|---|---|---|---|---|
| $HbA_{1c}$ ASV, % | 0.2 (0.05) | 0.3 (0.03) | 0.4 (0.04) | 0.6 (0.06) | 1.1 (0.44) | <0.001 |
| Age, years | 63.4 (6.4) | 63.1 (6.6) | 62.7 (6.5) | 62.5 (6.4) | 61.3 (6.4) | <0.001 |
| Female | 641 (36.7) | 659 (38.8) | 645 (37.6) | 661 (38.8) | 683 (39.9) | 0.33 |
| BMI, kg/m$^2$ | 31.9 (5.2) | 31.7 (5.3) | 32.0 (5.4) | 32.3 (5.4) | 32.8 (5.5) | <0.001 |
| Intensive glycemic control | 1,369 (78.3) | 1,077 (63.4) | 852 (49.7) | 553 (32.5) | 415 (24.3) | <0.001 |
| Race | | | | | | <0.001 |
| Black | 222 (12.7) | 272 (16.0) | 294 (17.1) | 350 (20.6) | 430 (25.1) | |
| Hispanic | 79 (4.5) | 115 (6.8) | 97 (5.7) | 117 (6.9) | 181 (10.6) | |
| Other | 223 (12.8) | 232 (13.6) | 197 (11.5) | 203 (11.9) | 169 (9.9) | |
| White | 1,224 (70.0) | 1,081 (63.6) | 1,128 (65.7) | 1,032 (60.6) | 930 (54.4) | |
| Education | | | | | | 0.003 |
| <High school | 224 (12.8) | 230 (13.5) | 215 (12.5) | 255 (15.0) | 283 (16.6) | |
| High school (or GED) | 465 (26.6) | 404 (23.8) | 483 (28.2) | 454 (26.7) | 429 (25.1) | |
| Some college | 552 (31.6) | 594 (35.0) | 564 (32.9) | 555 (32.6) | 565 (33.1) | |
| College | 506 (29.0) | 471 (27.7) | 453 (26.4) | 438 (25.7) | 431 (25.2) | |
| Established CVD | 499 (28.5) | 522 (30.7) | 572 (33.3) | 576 (33.8) | 585 (34.2) | 0.001 |
| Alcoholic drinks/week | 1.2 (3.0) | 1.0 (2.8) | 1.0 (2.7) | 1.0 (2.8) | 0.8 (2.4) | 0.001 |
| Current smoker | 219 (12.5) | 219 (12.9) | 227 (13.2) | 220 (12.9) | 285 (16.7) | 0.002 |
| Systolic BP, mmHg | 136 (16) | 137 (17) | 136 (16) | 136 (17) | 137 (17) | 0.46 |
| Serum creatinine, mg/dL | 0.90 (0.2) | 0.89 (0.2) | 0.91 (0.2) | 0.91 (0.2) | 0.91 (0.2) | 0.04 |
| $HbA_{1c}$, % [mmol/mol] | 8.0 (0.9) [64] | 8.1 (0.9) [65] | 8.3 (1.0) [67] | 8.4 (1.1) [68] | 8.6 (1.2) [70] | <0.001 |
| Total cholesterol, mg/dL | 183 (40) | 182 (41) | 184 (43) | 184 (43) | 186 (43) | 0.03 |
| LDL-c, mg/dL | 104 (33) | 103 (33) | 106 (34) | 106 (34) | 107 (35) | 0.12 |
| HDL-c, mg/dL | 42 (11) | 42 (12) | 42 (12) | 42 (12) | 42 (11) | 0.08 |
| Angiotensin receptor blocker | 281 (16.1) | 288 (17.0) | 320 (18.7) | 296 (17.4) | 250 (14.7) | 0.03 |
| ACE inhibitor | 904 (51.8) | 911 (53.7) | 933 (54.4) | 913 (53.8) | 963 (56.5) | 0.09 |
| β-Blocker | 450 (25.8) | 464 (27.4) | 479 (27.9) | 498 (29.3) | 507 (29.8) | 0.07 |
| Calcium channel blocker | 184 (10.5) | 206 (12.2) | 173 (10.1) | 209 (12.3) | 211 (12.4) | 0.09 |
| Loop diuretic | 94 (5.4) | 101 (6.0) | 121 (7.1) | 114 (6.7) | 140 (8.2) | 0.01 |
| Thiazide diuretic | 490 (28.1) | 470 (27.7) | 502 (29.3) | 479 (28.2) | 491 (28.8) | 0.86 |
| Insulin use | 245 (15.2) | 368 (23.7) | 432 (28.3) | 448 (29.5) | 448 (29.4) | <0.001 |
| Δ$HbA_{1c}$, % | −0.0 (6.6) | 0.3 (9.5) | 1.2 (11.5) | 1.5 (14.0) | 5.1 (22.1) | <0.01 |
| ΔSystolic BP, % | −5.4 (13.0) | −4.9 (13.4) | −4.8 (14.1) | −4.9 (13.7) | −4.5 (14.2) | 0.40 |
| ΔSerum creatinine, % | 10.4 (20.8) | 13.6 (28.8) | 13.4 (26.2) | 13.9 (24.3) | 16.2 (26.9) | <0.001 |
| ΔBMI, % | 2.0 (7.4) | 2.2 (7.3) | 2.3 (7.2) | 1.7 (7.2) | 2.8 (7.7) | <0.001 |

Data presented as mean (SD) for continuous variables or $n$ (%) for categorical variables. For $HbA_{1c}$, data in square brackets are means. Long-term variability in $HbA_{1c}$ was assessed by ASV from 8 months to 3 years of follow-up. Δ is the percent change in cardiometabolic parameters from enrollment baseline to 3 years of follow-up. GED, General Education Development.

use, and treatment arm (intensive vs. standard glucose control) (HR per 1-SD higher ASV 1.27 [95% CI 1.15–1.40]) (Fig. 3 [model 1]). This association was not attenuated and remained significant after further adjustment for Δ$HbA_{1c}$ and changes in other cardiometabolic factors as well as interval MI on follow-up (HR per 1 SD of ASV 1.34 [95% CI 1.17–1.54]) (Fig. 3 [model 2]). Further adjustment for variability in other cardiometabolic parameters (ASV for BP, LDL-c, and BMI) also did not attenuate the association between variability in $HbA_{1c}$ and risk of HF (HR per 1 SD higher ASV 1.24 [95% CI 1.12–1.37]) in the most adjusted model. Similar patterns of association were also observed using other measures of long-term variability in $HbA_{1c}$ (CV, SD) (Fig. 3).

The higher risk of incident HF among individuals with greater variability in $HbA_{1c}$ (above vs. below median ASV) was consistent across all strata of different baseline $HbA_{1c}$ levels ($P_{interaction}$ for baseline $HbA_{1c}$ * ASV = 0.29) as well as Δ$HbA_{1c}$ categories ($P_{interaction}$ for Δ$HbA_{1c}$ * ASV = 0.38) (Supplementary Fig. 3*A* and *B*). The association between long-term variability in $HbA_{1c}$ and risk of HF was consistent across relevant subgroups including glucose treatment strategies (intensive vs. standard), BP treatment strategies (intensive vs. standard), and prior history of ischemic event (yes vs. no) (Supplementary Tables 5–7). In sensitivity analysis using a higher minimum number of $HbA_{1c}$ measures to estimate variability, the association between long-term variability in $HbA_{1c}$ with risk of incident HF was consistent with that observed in the primary analysis (Supplementary Fig. 4).

### Long-term Variability in FPG and Risk of HF

For further evaluation of the association between long-term glycemic variability and risk of incident HF, an alternative measure of glycemic variability based on

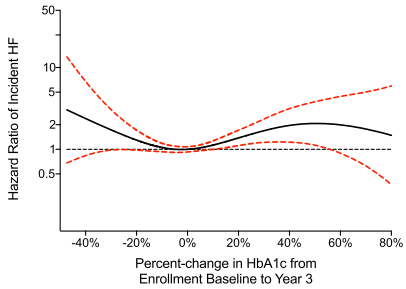


**Figure 1**—Cubic spline demonstrating multivariable-adjusted HRs (95% CI: red dotted line) for incident HF across $\Delta HbA_{1c}$ from baseline to 3 years of follow-up. HR refers to the association of $\Delta HbA_{1c}$ with risk of incident HF. Model included demographic characteristics (age, sex, race, and level of education), intensive glycemic control treatment group, history of CVD (MI, stroke, or coronary revascularization), risk factors (systolic BP, alcohol use, cigarette use, BMI, total cholesterol, serum creatinine, LDL-c, and HDL-c), medication use (angiotensin receptor blocker, ACE inhibitor, β-blocker, loop diuretic, thiazide diuretic, calcium channel blocker, insulin, sulfonylurea, biguanide, meglitinide, and α-glucosidase inhibitor), baseline $HbA_{1c}$, ΔHbA1c, Δsystolic BP, ΔBMI, Δcreatinine, and incident MI as a time-dependent variable.

FPG measurements was examined. The median number of FPG measurements from month 8 to year 3 of follow-up was four. The mean ± SD FPG at month 8 (study baseline) was 136 ± 32 mg/dL, and variability, as measured by ASV, was 36 ± 19 mg/dL. A significant graded association was observed between greater long-term variability in FPG and risk of HF such that participants in the highest quintile of ASV for FPG had approximately a twofold higher risk of HF compared with those in the lowest quintile (event rate 6.0% vs. 3.1%, respectively) (Fig. 2*B*). In adjusted analysis, higher measures of long-term variability in FPG were significantly associated with higher risk of HF (HR per 1-SD higher ASV 1.21 [95% CI 1.07–1.36]) independent of other potential confounders including ΔFPG and other cardiometabolic parameters as well as time-updated MI event on follow-up (Fig. 3). Consistent patterns of association were observed with alternative measures of long-term variability in FPG, including CV and SD (Fig. 3). There was no significant interaction between long-term variability in FPG (assessed by ASV) and either baseline FPG ($P_{interaction} = 0.72$) or ΔFPG ($P_{interaction} = 0.11$) for the risk of HF (Supplementary Fig. 3*C* and *D*).

### Glycemic Variability, Hypoglycemic Events, and HF

The risk of clinical hypoglycemic events was evaluated across categories of long-term glycemic variability. Overall, 13.5% of study participants reported clinically significant hypoglycemic events in the study cohort. The reported rates of hypoglycemic events increased significantly across increasing quintiles of long-term variability in $HbA_{1c}$ (assessed by ASV) (Q1 10.8% vs. Q5 15.2%) as well as long-term variability in FPG (Q1 10.4% vs. Q5 19.5%). In adjusted analysis, greater variability in $HbA_{1c}$ was significantly associated with greater likelihood of a hypoglycemic event on follow-up (odds ratio 1.23 (95% CI 1.01–1.49]). Furthermore, individuals who developed hypoglycemia on follow-up had higher incidence of HF versus those without reported hypoglycemic event (6.9% [80 of 1,159] vs. 4.2% [308 of 7,417], *P* value <0.001). In sensitivity analysis excluding individuals with hypoglycemic events on follow-up ($N = 7,417$), the association between long-term variability in $HbA_{1c}$ (assessed by ASV) with higher risk of HF was significant and consistent with that observed in the primary analysis (HR per 1 SD higher ASV 1.35 [95% CI 1.16–1.56]) in the most adjusted model. Consistent patterns of associations were also observed between long-term variability in FPG and risk of HF in sensitivity analysis excluding individuals with hypoglycemic events on follow-up (HR per 1-SD higher ASV 1.27 [95% CI 1.11–1.45]).

### Long-term Glycemic Variability and Risk of Acute Coronary Ischemic Events

Among the subset of study participants free of atherosclerotic CVD at baseline, there were 664 (cumulative rate 11.4%) incident acute coronary ischemic events during the study period. In unadjusted comparison, the risk of acute coronary ischemic events increased in a graded fashion across increasing quintiles of $HbA_{1c}$ ASV (Q1 8.7% and Q5 15.5%) (Supplementary Fig. 5). In adjusted analyses, higher measures of long-term variability in $HbA_{1c}$, as measured by ASV, were associated with significantly higher risk of acute coronary ischemic events independent of baseline risk factors, $\Delta HbA_{1c}$, and other cardiometabolic parameters (HR per 1 SD higher ASV 1.25 [95% CI 1.13–1.39]) (Supplementary Fig. 6). Similar patterns of association were also observed using alternative parameters of $HbA_{1c}$ variability (CV, SD) as well as using FPG in measures of glycemic variability (Supplementary Fig. 6).

## CONCLUSIONS

In this post hoc secondary analysis of data from ACCORD, several important findings were observed. First, there was a nonlinear relationship between changes in $HbA_{1c}$ during the trial and risk of HF. Individuals with a substantial decrease as well as increase in $HbA_{1c}$ had significantly higher risk of HF compared with those with stable $HbA_{1c}$ values, independent of other risk factors. Furthermore, the higher risk of HF observed among individuals with a substantial decrease in $HbA_{1c}$ on follow-up was largely related to downstream hypoglycemic events. Second, greater long-term variability in $HbA_{1c}$ was also significantly associated with higher risk of HF, independent of other risk factors, changes in $HbA_{1c}$ and other cardiometabolic parameters, and interval occurrence of MI event. Third, greater long-term variability in FPG,

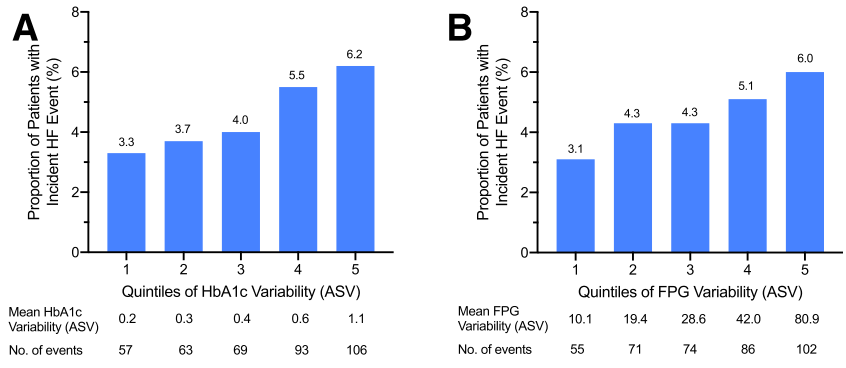


**Figure 2**—Proportion of participants with incident HF across quintiles of long-term variability in $HbA_{1c}$ (*A*) and FPG (*B*).

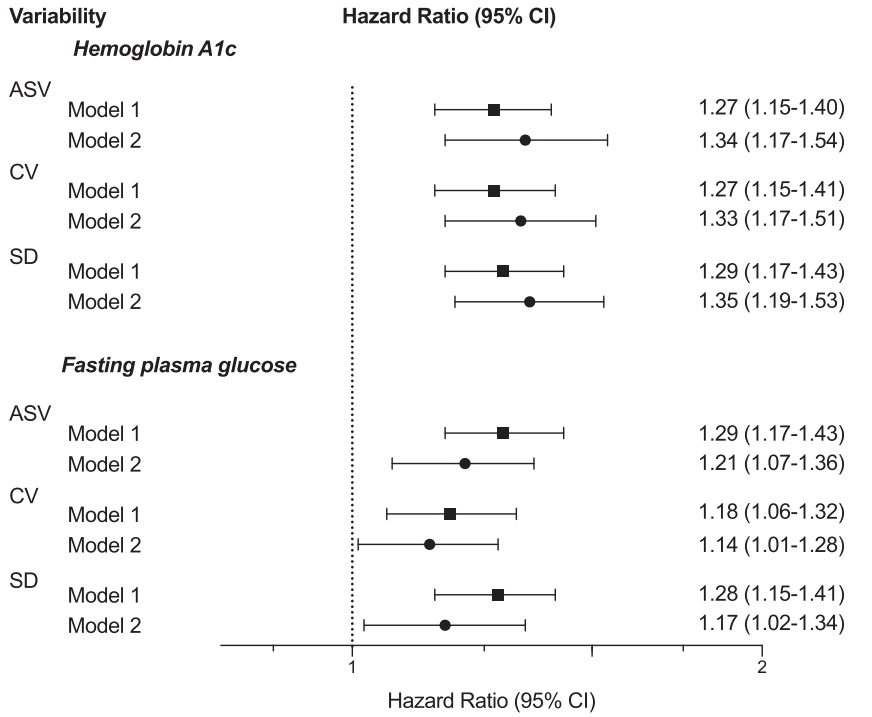


**Figure 3**—Multivariable-adjusted association of long-term variability in $HbA_{1c}$ (top) and FPG (bottom) with risk of incident HF. HR data refer to the association of 1 SD higher measure of long-term variability in $HbA_{1c}$/FPG with risk of incident HF. Model 1 included demographic characteristics (age, sex, race, and level of education), intensive glycemic control treatment group, history of CVD (MI, stroke, or coronary revascularization), risk factors (systolic BP, alcohol use, cigarette use, BMI, total cholesterol, serum creatinine, LDL-c, and HDL-c), medication use (angiotensin receptor blocker, ACE inhibitor, β-blocker, loop diuretic, thiazide diuretic, calcium channel blocker, insulin, sulfonylurea, biguanide, meglitinide, and α-glucosidase inhibitor) and baseline $HbA_{1c}$/FPG level. Model 2 included covariates from model 1 plus $\Delta HbA_{1c}$/ΔFPG, Δsystolic BP, ΔBMI, Δcreatinine, and incident MI as a time-dependent variable.

another measure of glycemic status, was also significantly associated with higher risk of HF. Finally, greater glycemic variability was also significantly associated with higher risk of acute ischemic cardiac events. Taken together, these findings highlight the prognostic significance of substantial fluctuations in glycemia among patients with T2DM in forecasting future risk of adverse cardiovascular events.

Consistent with our observations, prior studies have demonstrated a significant association between hyperglycemia and risk of HF (6–8). However, the relationship between long-term changes in $HbA_{1c}$ and risk of HF is less well established. In a large cohort study from the Kaiser Permanente Health System, Nichols et al. (23) observed that a decline in $HbA_{1c}$ in patients with T2DM was associated with lower likelihood of HF on follow-up. In a time-updated analysis from a cohort of patients with T2DM from the U.K., both higher (>10% [>86 mmol/mol]) and lower (<6% [<42 mmol/mol]) $HbA_{1c}$ levels on longitudinal follow-up were associated with higher risk of HF compared with risk in individuals with $HbA_{1c}$ in the range of 6–7% (42–53 mmol/mol) (24). However, these studies were limited by evaluation of a referral population, use of administrative data codes to identify HF events, and confounding by indication for $HbA_{1c}$ testing. In the present analysis, using data from a large, multicenter, randomized controlled trial that included intensive and standard glycemic control strategies, protocolized and prespecified serial $HbA_{1c}$ testing, and clinically adjudicated incident HF outcomes, there was a nonlinear relationship between long-term changes in $HbA_{1c}$ and risk of HF, with a higher risk associated with substantial changes in $HbA_{1c}$ levels at either extreme.

Several factors may underlie the observed higher risk of HF among individuals with substantial increase or decrease in $HbA_{1c}$. First, we observed that the higher risk of HF among individuals with substantial decrease in $HbA_{1c}$ was largely driven by hypoglycemic events and not observed in individuals without downstream hypoglycemic events. Second, while there was no statistically significant interaction between changes in $HbA_{1c}$ levels and $HbA_{1c}$ variability for the risk of HF, we observed greater incidence of HF among individuals with substantial increase or decrease in $HbA_{1c}$ (vs. those without significant change in $HbA_{1c}$) in the high variability strata. In contrast, among individuals with lesser $HbA_{1c}$ variability, the difference in incidence of HF across $HbA_{1c}$ change categories was not as contrasting. This suggests that greater variability in $HbA_{1c}$ at the extremes of $HbA_{1c}$ change distribution may also have contributed to higher risk of HF. Finally, substantial changes in $HbA_{1c}$ may also be associated with increased oxidative stress, endothelial dysfunction, and proinflammatory state, which may contribute the observed higher risk of HF (25,26).

Besides substantial changes in $HbA_{1c}$, greater long-term variabilities in measures of $HbA_{1c}$ and FPG on follow-up were each significantly associated with risk of HF. Prior studies have demonstrated associations between long-term variability in glycemic control and risk of adverse clinical outcomes including all-cause mortality and risk of microvascular complications such as nephropathy and retinopathy (15,27). However, the data on associations between long-term variability in glycemic control and risk of adverse cardiovascular outcomes are mixed. Some studies have demonstrated that greater long-term variability in $HbA_{1c}$ or FPG is associated with higher risk of adverse cardiovascular outcomes including CV death and nonfatal atherosclerotic events (15,27,28). Furthermore, two studies using large administrative databases in Europe and Republic of Korea have demonstrated a significant association of variability in $HbA_{1c}$ or FPG with risk of incident HF (24,29). However, these studies were limited due to nonprotocolized measurement of glycemic levels and use of administrative codes for HF outcome ascertainment. In the study by Kwon et al. (29), patients with a history of diabetes were excluded from the analysis. Other studies have failed to observe a consistent, independent association between glycemic variability and risk of adverse cardiovascular outcomes (19). Secondary analysis of trials comparing usual versus intensive glycemic control in patients with T2DM have demonstrated

a significant association between glycemic variability and risk of adverse CV events only in the intensive control arm—not in the usual care arm (30,31). The current study findings add to the existing literature by demonstrating a robust, significant association between multiple measures of long-term glycemic variability and risk of HF that was consistent across both standard and intensive glycemic control treatment groups. Two separate markers of glycemia were measured according to a standardized procedure. HF events were adjudicated by a committee as part of a prespecified secondary outcome.

The mechanisms underlying the observed associations between long-term variability in $HbA_{1c}$ and risk of HF are not well established. One potential mechanism could be the increased incidence of hypoglycemic events among individuals with higher variability in $HbA_{1c}$. Prior studies have demonstrated a strong association between hypoglycemic events and risk of adverse cardiovascular outcomes (13,32). We observed greater likelihood of hypoglycemic events among individuals with greater long-term variability in $HbA_{1c}$. Furthermore, the rates of HF were also higher in individuals with downstream hypoglycemic events. However, the risk of HF associated with greater variability in $HbA_{1c}$ was consistent among individuals without a hypoglycemic event on follow-up and across both intensive and standard glucose control arms. Taken together, these observations suggest that the risk of HF associated with higher glycemic variability may be independent of the intensity of glycemic control and associated hypoglycemic events. Among other potential mechanisms, glycemic variability is associated with higher risk of atherosclerotic CV disease outcomes, adverse cardiac remodeling patterns, and systolic dysfunction, all of which are key factors in development of HF (30,33,34). Furthermore, greater glycemic variability is associated with upregulation of stress hormones, activation of inflammation cascade, and downstream oxidative stress and endothelial dysfunction, which may lead to the observed higher risk of HF (25,26). Finally, it is possible that higher glycemic variability may reflect inconsistent compliance with medications, use of steroids, underlying infections, drastic weight changes, or other unmeasured confounders. Fluctuations in cardiometabolic parameters, including glucose, BMI, and lipid levels, are each associated with adverse CV events and may suggest an underlying systemic process (35–37).

Our study findings have important implications for prevention of HF among patients with T2DM. While epidemiologic studies suggest that hyperglycemia is associated with higher risk of HF, clinical trials examining intensive glycemic control targeting lower $HbA_{1c}$ goals among patients with T2DM did not reduce the risk of HF (6–11). It is plausible that the lack of therapeutic benefit of intensive glycemic control on cardiovascular outcomes may be related to greater fluctuations in glycemic control. This is supported by observations from the current study demonstrating increased risk of HF among individuals with substantial changes in $HbA_{1c}$ at either extreme as well as greater long-term glycemic variability. The study findings highlight the importance of long-term variability in $HbA_{1c}$ to identify individuals with T2DM and adequate glycemic control who are at high risk for developing HF. Future studies are needed to determine whether glycemic variability may meaningfully inform glucose control strategies in patients with T2DM to prevent HF. These findings are particularly relevant since the newer antihyperglycemic therapies such as sodium–glucose cotransporter 2 (SGLT2) inhibitors, which are associated with reduction in the risk of incident HF, have been shown to lower glycemic variability (38). However, the extent to which changes in glycemic variability may mediate the favorable effects of these therapies remains unknown. As many patients with high degree of glycemic variability are treated with insulin, these data suggest that selection of insulins with less day-to-day glycemic variability may lessen future HF risk; however, this hypothesis requires prospective testing (39).

There are several strengths to our analysis that add to the robustness of our study findings. These include the large size of the study cohort with 8,576 participants, protocolized assessments of $HbA_{1c}$ at regular intervals, large number of clinically adjudicated cardiovascular events on follow-up, and consistency of the observed associations between greater variability in glycemia and risk of HF across different measures of variability as well as glycemic control ($HbA_{1c}$ and FPG). The current study also has some noteworthy limitations. First, owing to the observational nature of the study, we cannot establish a causal association between glycemic variability and risk of HF and our findings need to be confirmed in future studies. Furthermore, we cannot exclude the possibility of residual or unmeasured confounding given the observational study design of the present analysis. Second, the study population was derived from ACCORD, which included patients with T2DM who had prevalent cardiovascular disease or risk factors. Thus, the findings may not be generalizable to patients with T2DM who are at lower risk for cardiovascular disease outside a clinical trial setting. Third, ACCORD recruited participants until 2005 and there was limited use of contemporary T2DM therapies such as SGLT2 inhibitors and glucagon-like peptide 1 receptor agonists. However, this may have avoided the confounding effects of drug therapy on HF risk, given the reductions in risk of incident HF observed with SGLT2 inhibitors (and, more modestly, with glucagon-like peptide 1 receptor agonists) in T2DM (40,41). Finally, left ventricular ejection fraction and HF subtype data were not available for the present analysis so we cannot evaluate the associations between baseline as well as long-term change and variability in glycemia with risk of incident HF with reduced ejection fraction and HF with preserved ejection fraction.

In conclusion, substantial changes and long-term variability in $HbA_{1c}$ were each independently associated with risk of incident HF among patients with T2DM. Future studies are needed to determine whether long-term glycemic variability may be used to guide glycemic control strategies with use of therapies that have less glucose fluctuations to modify the risk of HF among high-risk patients with T2DM.

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**Author Contributions.** M.W.S., K.V.P., and A.P. developed the study concept and design, interpreted the data, and critically revised and drafted the manuscript. M.V., M.C.C., J.B., G.C.F., J.L.G., and D.K.M. contributed to the discussion and critically revised and reviewed the manuscript. M.W.S. and A.P. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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