Supplemental Materials

ACCORD Trial Description

Briefly, ACCORD was a multicenter, randomized, controlled trial of patients with T2DM and HbA1c ≥ 7.5% who were randomized to intensive glycemic control targeting a HbA1c level < 6.0% or standard therapy with a HbA1c goal of 7.0 to 7.9%. Participants of the trial were 40 to 79 years of age with established cardiovascular disease or 55 to 79 years of age with evidence of atherosclerosis, left ventricular hypertrophy, albuminuria, or at least two of the following cardiovascular risk factors: hypertension, dyslipidemia, obesity, or current smoker. All participants provided written informed consent and the institutional review board or ethics committee of each center approved the study protocol. As reported previously, intensive glycemic control did not affect the risk of the primary composite outcome (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) or HF compared with standard glucose control (1). During ACCORDION follow-up, select participants continued with long-term observational follow-up for up to 7 additional years (2). For the present analyses, de-identified data were obtained from the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center. The present study, results, and interpretation do not necessarily reflect the opinions or views of the ACCORD investigators or the NHLBI.

Assessment of clinical covariates in ACCORD trial

Demographics, medical history, and medication use were self-reported. Anthropometrics, including height and weight, were measured. Body mass index (BMI) was calculated by dividing the weight in kilograms by the height in meters^2. Systolic and diastolic blood pressure (BP) were

measured during a standardized physical examination. Lipids and glucose were measured from fasting blood samples. HbA1c was measured at a National Glycohemoglobin Standardization Program (NGSP) certified central laboratory. Patients randomized to intensive glucose control underwent monthly visits for the first 4 months followed by visits every 2 months including at least one phone call between visits to achieve target glucose levels. Patients randomized to standard glucose control visited clinical centers every 4 months for glycemia management

References

1. Action to Control Cardiovascular Risk in Diabetes Study G, Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH, Jr., Probstfield JL, Simons-Morton DG, Friedewald WT: Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-2559

2. Group AS: Nine-Year Effects of 3.7 Years of Intensive Glycemic Control on Cardiovascular Outcomes. Diabetes Care 2016;39:701-708

Supplemental Table 1: Baseline characteristics of participants stratified by baseline HbA1c

	HbA1c <7% [<53 mmol/mol] (n = 470)	**HbA1c 7-8.5% [53-69 mmol/mol]** (n = 5,037)	**HbA1c >8.5% [>69 mmol/mol]** (n = 3,056)	**P value**
HgbA1c, % [mmol/mol]	6.6 (0.3) [49]	7.8 (0.4) [62]	9.4 (0.8) [79]	<0.01
Age, years	62.4 (6.7)	63.2 (6.5)	61.7 (6.3)	<0.01
Female	171 (36.4)	1,919 (38.1)	1,194 (39.1)	0.45
BMI, kg/m^2	31.98 (5.56)	32.27 (5.42)	32.07 (5.30)	0.20
Intensive glycemic control	251 (53.4)	2519 (50.0)	1491(48.8)	0.15
Race				<0.01
Black	78 (16.6)	805 (16.0)	681 (22.3)	
Hispanic	32 (6.8)	299 (5.9)	255 (8.3)	
Other	67 (14.3)	587 (11.7)	370 (12.1)	
White	293 (62.3)	3,346 (66.4)	1,750 (57.3)	
Education				<0.01
Less than high school	65 (13.9)	648 (12.9)	492 (16.1)	
High school (or GED)	119 (25.4)	1,326 (26.3)	783 (25.6)	
Some college	150 (32.0)	1,665 (33.1)	1,012 (33.1)	
College	135 (28.8)	1395 (27.7)	768 (25.1)	
Established cardiovascular disease	140 (29.8)	1,590 (31.6)	1,019 (33.3)	0.14
Alcoholic drinks per week	1.1 (3.2)	1.1 (2.8)	0.9 (2.4)	<0.01
Current smoker	56 (11.9)	657 (13.0)	456 (14.9)	0.03
Systolic BP, mm Hg	135 (17)	136 (17)	137 (17)	0.01
Serum creatinine, mg/dL	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	0.02
Total cholesterol, mg/dL	177 (39)	180 (39)	191 (46)	<0.01
LDL-c, mg/dL	101 (32)	103 (32)	110 (37)	<0.01
HDL-c, mg/dL	42 (13)	42 (11)	42 (12)	0.47
Anithypertensive medication use	401 (85.5)	4,220 (83.9)	2,473 (81.3)	<0.01
Insulin use	74 (17.2)	1,056 (23.1)	808 (29.7)	<0.01

Data presented as mean (standard deviation) for continuous variables or n (%) for categorical variables.

BMI = body mass index; BP = blood pressure; GED = General Education Development; HbA1c = glycated hemoglobin; HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol.

Supplemental Table 2: Baseline and follow-up characteristics of participants stratified by % change in HbA1c

	≥10% decrease (n = 1,078)	**<10% decrease to <10% increase** (n = 4,449)	**≥10% increase** (n = 1,395)	**P value**
% change in HbA1c, %	-16.3 (5.6)	-0.28 (5.3)	21.0 (13.1)	<0.01
Age, years	62.6 (6.3)	62.9 (6.4)	62.0 (6.4)	<0.01
Female	408 (37.8)	1,655 (37.2)	545 (39.1)	0.45
BMI, kg/m^2	32.4 (5.4)	32.0 (5.3)	32.8 (5.4)	<0.01
Intensive glycemic control	484 (44.9)	2,507 (56.3)	554 (39.7)	<0.01
Race				0.08
Black	212 (19.7)	731 (16.4)	231 (16.6)	
Hispanic	65 (6.0)	249 (5.6)	99 (7.1)	
Other	131 (12.2)	543 (12.2)	167 (12.0)	
White	670 (62.2)	2,926 (65.8)	898 (64.4)	
Education				0.19
Less than high school	167 (15.5)	579 (13.0)	186 (13.3)	
High school (or GED)	257 (23.8)	1,198 (26.9)	355 (25.5)	
Some college	368 (34.1)	1,455 (32.7)	478 (34.3)	
College	286 (26.5)	1,214 (27.3)	375 (26.9)	
Established cardiovascular disease	378 (35.1)	1,406 (31.6)	438 (31.4)	0.08
Alcoholic drinks per week	1.0 (2.8)	1.1 (2.8)	0.8 (2.5)	0.03
Current smoker	131 (12.2)	588 (13.2)	201 (14.4)	0.25
Systolic BP, mm Hg	137 (17)	136 (17)	136 (17)	0.06
Serum creatinine, mg/dL	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	0.68
HgbA1c, % [mmol/mol]	8.5 (1.1) [69]	8.2 (1.0) [66]	8.4 (1.1) [68]	<0.01
Total cholesterol, mg/dL	182 (42)	182 (41)	185 (42)	0.08
LDL-c, mg/dL	104 (34)	103 (33)	106 (33)	0.17
HDL-c, mg/dL	42 (12)	42 (11)	41 (11)	0.09
Anithypertensive medication use	917 (85.4)	3,650 (82.2)	1,177 (84.6)	0.01
Insulin use	302 (31.0)	972 (24.1)	304 (24.3)	<0.01
% change in systolic BP, %	-6.1 (13.0)	-5.1 (13.9)	-4.4 (13.6)	0.01

% change in serum creatinine, %	15.2 (29.4)	13.0 (23.0)	14.0 (23.0)	0.02
% change in BMI, %	2.5 (7.9)	2.1 (7.3)	2.3 (7.2)	0.40
HbA1c ASV, %	0.59 (0.35)	0.42 (0.27)	0.63 (0.39)	<0.01

Data presented as mean (standard deviation) for continuous variables or n (%) for categorical variables. % change in cardiometabolic parameters was calculated from baseline to 3 years of follow-up. HbA1c ASV was calculated from 8 months to 3 years of follow-up.

ASV = average successive variability; BMI = body mass index; BP = blood pressure; GED = General Education Development; HbA1c = glycated hemoglobin; HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol.

Supplemental Table 3. Multivariable-adjusted associations of baseline HbA1c and % change in HbA1c with risk of incident HF

	Model 1		**Model 2**	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Baseline HbA1c (Per 1 unit higher)	1.20 (1.08-1.33)	0.001	1.24 (1.13-1.36)	<0.001
Δ HbA1c (% change in A1c from baseline to 3-year follow-up)				
<10% decrease to <10% increase	*NA*		*Referent group*	
≥10% decrease			1.32 (1.08-1.75)	0.007
≥10% increase			1.55 (1.19-2.04)	0.002

HR refers to the association of continuous measures of baseline HbA1c / categories of % change in HbA1c with risk of incident HF. % change in cardiometabolic parameters was calculated from baseline to 3 years of follow-up.

Model 1 included demographic characteristics (age, sex, race, level of education), intensive glycemic control treatment group, history of cardiovascular disease (MI, stroke, or coronary revascularization), risk factors (systolic BP, alcohol use, cigarette use, BMI, total cholesterol, serum creatinine, LDL-c, HDL-c), medication use (angiotensin receptor blocker, ACE-inhibitor, beta-blocker, loop diuretic, thiazide diuretic, calcium channel blocker, insulin use, sulfonylurea, biguanide, meglitinide, and alpha-glucosidase inhibitor), baseline HbA1c

Model 2 included covariates from Model 1 plus % change in HbA1c, % change in systolic BP, % change in BMI, % change in creatinine, and incident MI as a time-dependent variable.

ACE = angiotensin converting enzyme; BMI = body mass index; BP = blood pressure; HbA1c = glycated hemoglobin; HDL-c = high-density lipoprotein cholesterol; HF = heart failure; HR = hazard ratio; LDL-c = low-density lipoprotein cholesterol; MI = myocardial infarction.

Supplemental Table 4. Sensitivity analysis among individuals without hypoglycemic events on follow-up: association of % change in HbA1c from baseline to 3-year follow-up with risk of incident HF

	Model	
	HR (95% CI)	**P value**
<10% decrease to <10% increase	*Referent group*	
≥10% decrease	1.36 (0.86-2.13)	0.18
≥10% increase	1.87 (1.15-3.04)	0.02

HR refers to the association of categories of % change in HbA1c with risk of incident HF. % change in cardiometabolic parameters was calculated from baseline to 3 years of follow-up.

Model included demographic characteristics (age, sex, race, level of education), intensive glycemic control treatment group, history of cardiovascular disease (MI, stroke, or coronary revascularization), risk factors (systolic BP, alcohol use, cigarette use, BMI, total cholesterol, serum creatinine, LDL-c, HDL-c), medication use (angiotensin receptor blocker, ACE-inhibitor, beta-blocker, loop diuretic, thiazide diuretic, calcium channel blocker, insulin use, sulfonylurea, biguanide, meglitinide, and alpha-glucosidase inhibitor), baseline HbA1c, % change in HbA1c, % change in systolic BP, % change in BMI, % change in creatinine, and incident MI as a time-dependent variable.

ACE = angiotensin converting enzyme; BMI = body mass index; BP = blood pressure; HbA1c = glycated hemoglobin; HDL-c = high-density lipoprotein cholesterol; HF = heart failure; HR = hazard ratio; LDL-c = low-density lipoprotein cholesterol; MI = myocardial infarction.

Supplemental Table 5. Multivariable-adjusted association of long-term variability in HbA1c with risk of incident HF stratified by glucose treatment strategy

Variability measure	Model 1		Model 2	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Standard glucose control (n = 4,310)				
Per 1 SD higher ASV	1.30 (1.13-1.51)	<0.001	1.35 (1.13-1.62)	0.001
Per 1 SD higher CV	1.31 (1.12-1.52)	<0.001	1.37 (1.14-1.64)	<0.001
Per 1 SD higher SD	1.33 (1.14-1.54)	<0.001	1.39 (1.16-1.67)	<0.001
Intensive glucose control (n = 4,266)				
Per 1 SD higher ASV	1.24 (1.06-1.46)	0.007	1.21 (1.02-1.49)	0.03
Per 1 SD higher CV	1.26 (1.09-1.45)	0.001	1.24 (1.01-1.53)	0.04
Per 1 SD higher SD	1.26 (1.10-1.46)	0.001	1.23 (0.97-1.56)	0.09

HR refers to the association of 1-SD higher measure of long-term variability in HbA1c with risk of incident HF. Long-term variability in HbA1c was calculated from 8 months to 3 years of follow-up. % change in cardiometabolic parameters was calculated from baseline to 3 years of follow-up.

Model 1 included demographic characteristics (age, sex, race, level of education), intensive glycemic control treatment group, history of cardiovascular disease (MI, stroke, or coronary revascularization), risk factors (systolic BP, alcohol use, cigarette use, BMI, total cholesterol, serum creatinine, LDL-c, HDL-c), medication use (angiotensin receptor blocker, ACE-inhibitor, beta-blocker, loop diuretic, thiazide diuretic, calcium channel blocker, insulin use, sulfonylurea, biguanide, meglitinide, and alpha-glucosidase inhibitor), and baseline HbA1c.

Model 2 included covariates from Model 1 plus % change in HbA1c, % change in systolic BP, % change in BMI, % change in creatinine, and incident MI as a time-dependent variable.

ACE = angiotensin converting enzyme; ASV = average successive variation; BMI = body mass index; BP = blood pressure; CV = coefficient of variation; HbA1c = glycated hemoglobin; HDL-c = high-density lipoprotein cholesterol; HF = heart failure; HR = hazard ratio; LDL-c = low-density lipoprotein cholesterol; MI = myocardial infarction; SD = standard deviation.

Supplemental Table 6. Multivariable-adjusted association of long-term variability in HbA1c with risk of incident HF stratified by BP treatment strategy.

Variability measure	Model 1		Model 2	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Standard BP control (N = 2,013)				
Per 1 SD higher ASV	1.27 (1.04-1.56)	0.02	1.30 (0.93-1.83)	0.13
Per 1 SD higher CV	1.37 (1.09-1.71)	0.007	1.46 (1.05-2.04)	0.02
Per 1 SD higher SD	1.40 (1.12-1.75)	0.003	1.51 (1.09-2.11)	0.01
Intensive BP control (N = 1,991)				
Per 1 SD higher ASV	1.07 (0.80-1.44)	0.65	1.32 (0.94-1.84)	0.10
Per 1 SD higher CV	0.97 (0.73-1.29)	0.85	1.11 (0.80-1.53)	0.53
Per 1 SD higher SD	0.99 (0.74-1.33)	0.97	1.16 (0.83-1.62)	0.40

HR refers to the association of 1-SD higher long-term variability in HbA1c with risk of incident HF. Long-term variability in HbA1c was calculated from 8 months to 3 years of follow-up. % change in cardiometabolic parameters was calculated from baseline to 3 years of follow-up.

Model 1 included demographic characteristics (age, sex, race, level of education), intensive glycemic control treatment group, history of cardiovascular disease (MI, stroke, or coronary revascularization), risk factors (systolic BP, alcohol use, cigarette use, BMI, total cholesterol, serum creatinine, LDL-c, HDL-c), medication use (angiotensin receptor blocker, ACE-inhibitor, beta-blocker, loop diuretic, thiazide diuretic, calcium channel blocker, insulin use, sulfonylurea, biguanide, meglitinide, and alpha-glucosidase inhibitor), and baseline HbA1c.

Model 2 included covariates from Model 1 plus % change in HbA1c, % change in systolic BP, % change in BMI, % change in creatinine, and incident MI as a time-dependent variable.

ACE = angiotensin converting enzyme; ASV = average successive variation; BMI = body mass index; BP = blood pressure; CV = coefficient of variation; HbA1c = glycated hemoglobin; HDL-c = high-density lipoprotein cholesterol; HF = heart failure; HR = hazard ratio; LDL-c = low-density lipoprotein cholesterol; MI = myocardial infarction; SD = standard deviation.

Supplemental Table 7. Multivariable-adjusted association of long-term variability in HbA1c with risk of incident HF stratified by history of MI, CABG, or PCI prior to HF event.

Variability measure	Model 1		Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value
History of MI, CABG, or PCI prior to HF event (N = 3,265)				
Per 1 SD higher ASV	1.28 (1.10-1.49)	0.002	1.25 (1.03-1.51)	0.02
Per 1 SD higher CV	1.27 (1.10-1.46)	0.001	1.26 (1.06-1.50)	0.01
Per 1 SD higher SD	1.31 (1.13-1.51)	<0.001	1.31 (1.09-1.59)	0.005
No history of MI, CABG, or PCI prior to HF event (N = 5,311)				
Per 1 SD higher ASV	1.35 (1.14-1.60)	0.001	1.50 (1.19-1.90)	<0.001
Per 1 SD higher CV	1.37 (1.17-1.62)	<0.001	1.43 (1.15-1.78)	0.001
Per 1 SD higher SD	1.37 (1.15-1.62)	<0.002	1.45 (1.14-1.83)	0.002

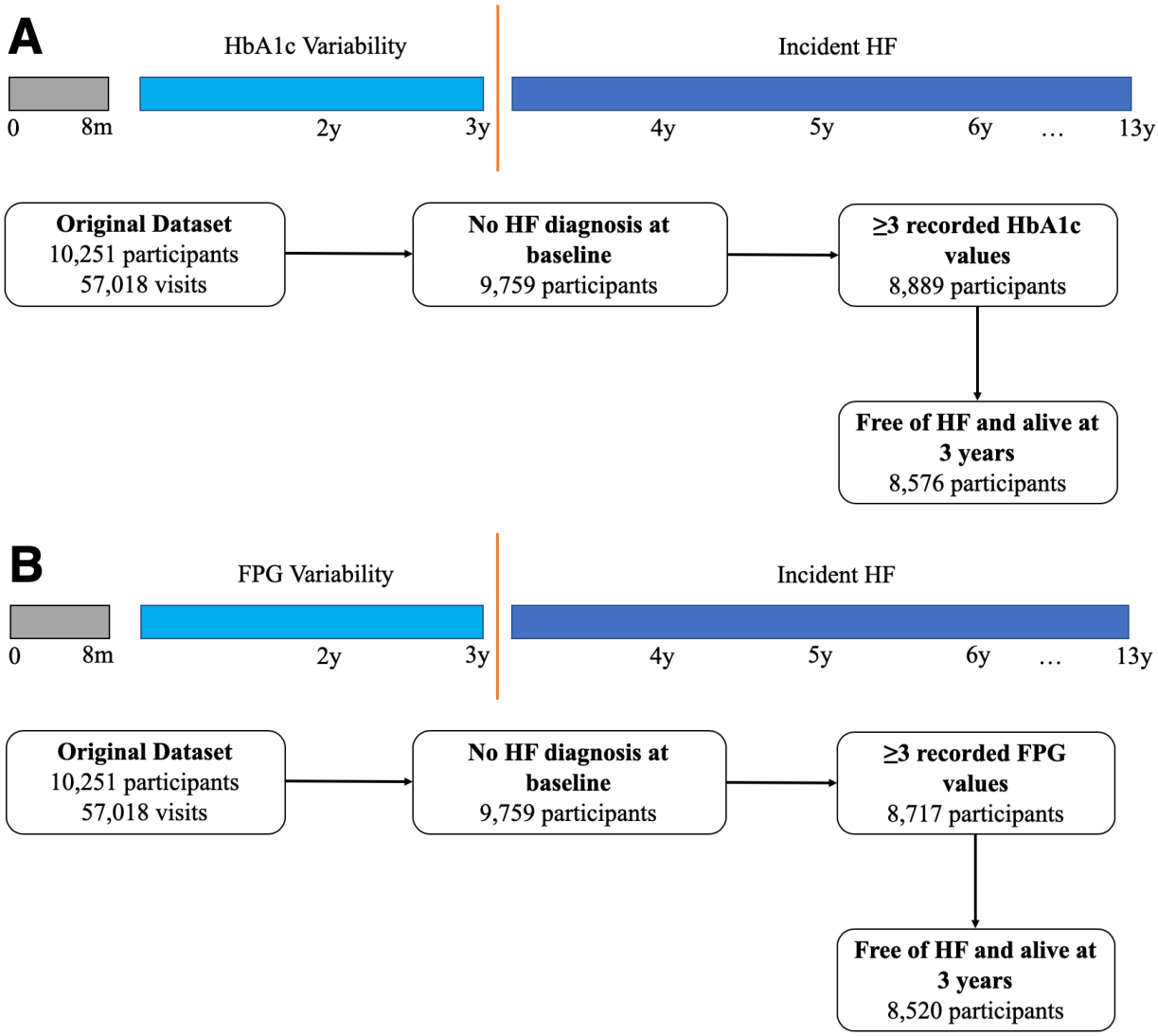
HR refers to the association of 1-SD higher long-term variability in HbA1c with risk of incident HF. Long-term variability in HbA1c was calculated from 8 months to 3 years of follow-up. % change in cardiometabolic parameters was calculated from baseline to 3 years of follow-up.

Model 1 included demographic characteristics (age, sex, race, level of education), intensive glycemic control treatment group, history of cardiovascular disease (MI, stroke, or coronary revascularization), risk factors (systolic BP, alcohol use, cigarette use, BMI, total cholesterol, serum creatinine, LDL-c, HDL-c), medication use (angiotensin receptor blocker, ACE-inhibitor, beta-blocker, loop diuretic, thiazide diuretic, calcium channel blocker, insulin use, sulfonylurea, biguanide, meglitinide, and alpha-glucosidase inhibitor), and baseline HbA1c.

Model 2 included covariates from Model 1 plus % change in HbA1c, % change in systolic BP, % change in BMI, % change in creatinine, and incident MI as a time-dependent variable.

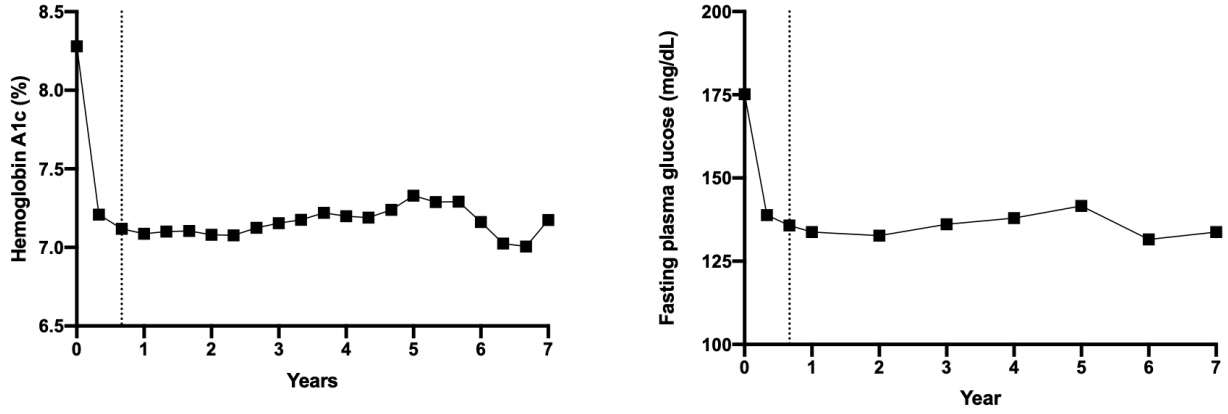
ACE = angiotensin converting enzyme; ASV = average successive variation; BMI = body mass index; BP = blood pressure; CABG = coronary artery bypass graft; CV = coefficient of variation; HbA1c = glycated hemoglobin; HDL-c = high-density lipoprotein cholesterol; HF = heart failure; HR = hazard ratio; LDL-c = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation.

Supplemental Figure 1: Overview of the study population for the analysis of long-term variability in HbA1c (**A**) and FPG (**B**).



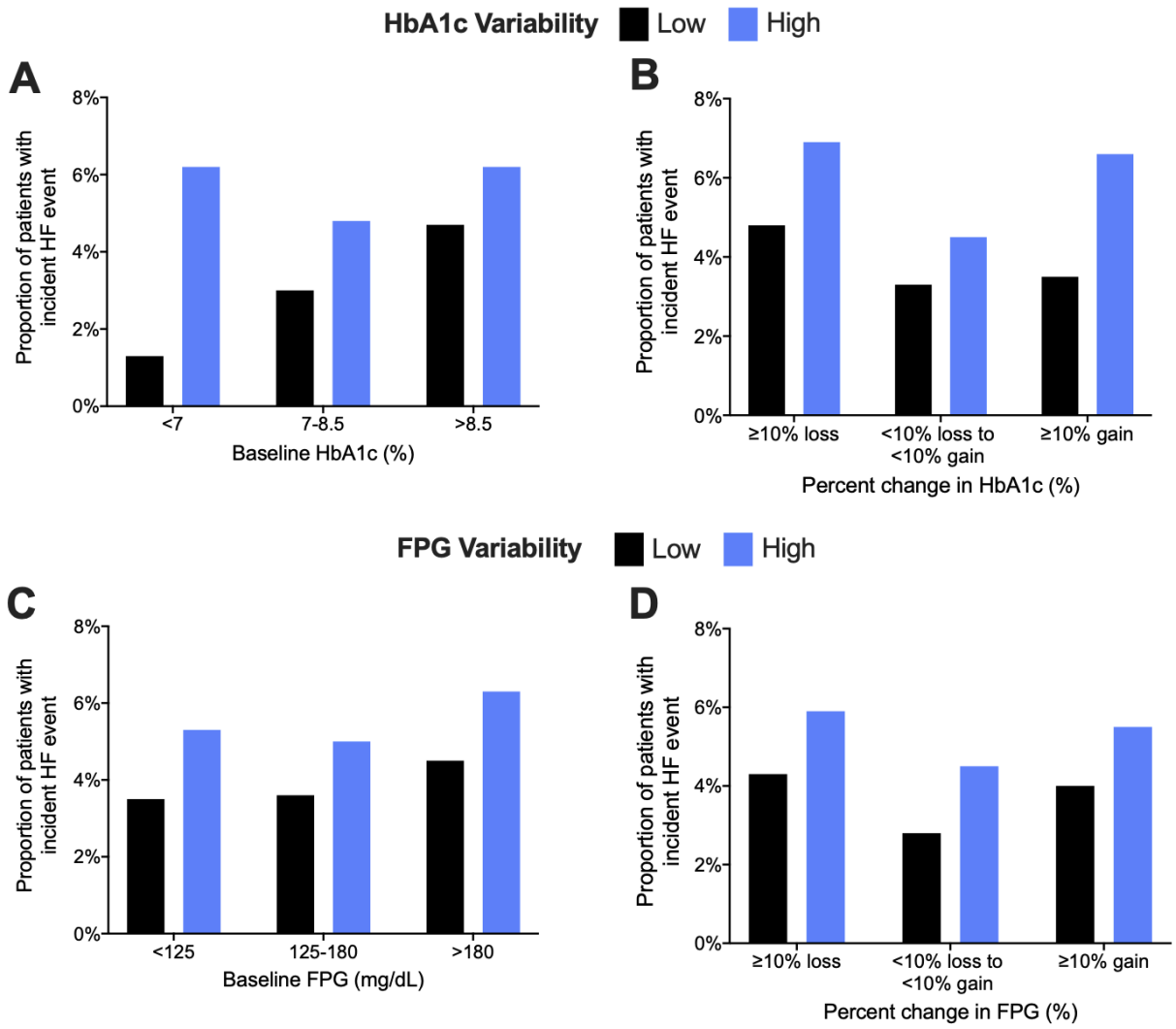
FPG = fasting plasma glucose; HbA1c = glycated hemoglobin; HF = heart failure

Supplemental Figure 2: Mean HbA1c and FPG at each study visit. The vertical line (month 8) is the established baseline for the variability analysis after stabilization in the glycemic markers.



FPG = fasting plasma glucose; HbA1c = glycated hemoglobin

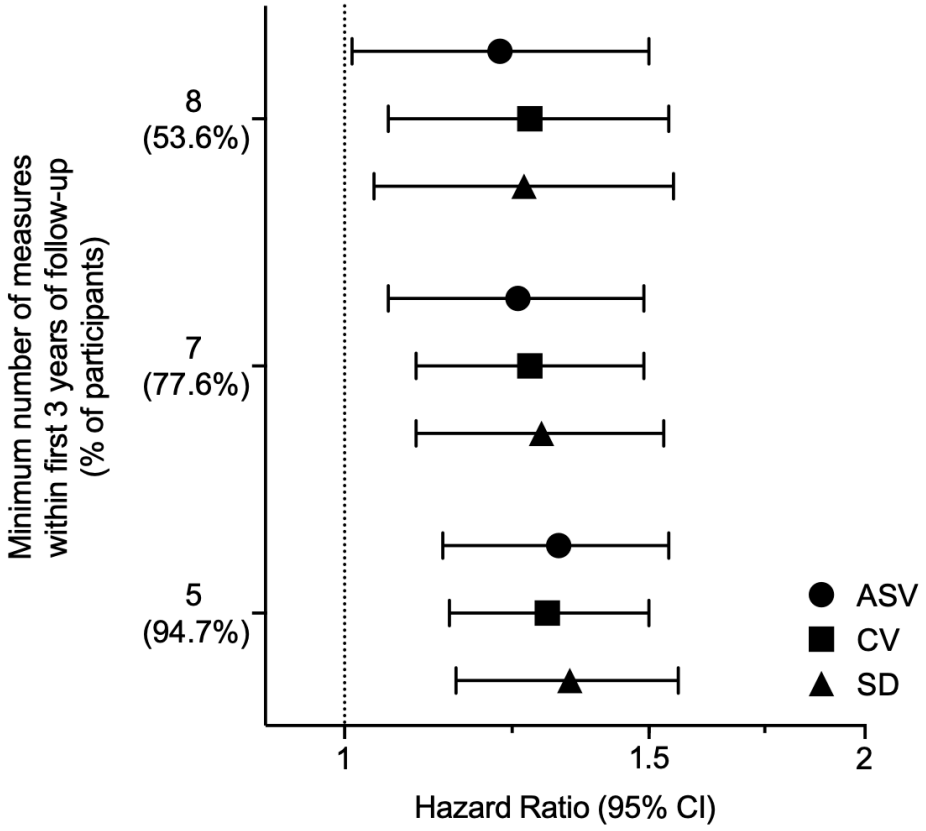
Supplemental Figure 3: Long-term variability in HbA1c / FPG and risk of incident HF across different levels of baseline HbA1c / FPG (**Panel A / C**) and % change in HbA1c / FPG (**Panel B / D**).



Long-term variability in HbA1c / FPG was calculated from 8 months to 3 years of follow-up. Low variability defined as below median ASV. High variability defined as above median ASV. % change in HbA1c / FPG was calculated from baseline to 3 years of follow-up.

ASV = average successive variability; FPG = fasting plasma glucose; HbA1c = glycated hemoglobin; HF = heart failure

Supplemental Figure 4. Association of long-term variability in HbA1c with risk of incident HF across varying minimum quantities of repeated measures of HbA1c over the same period.

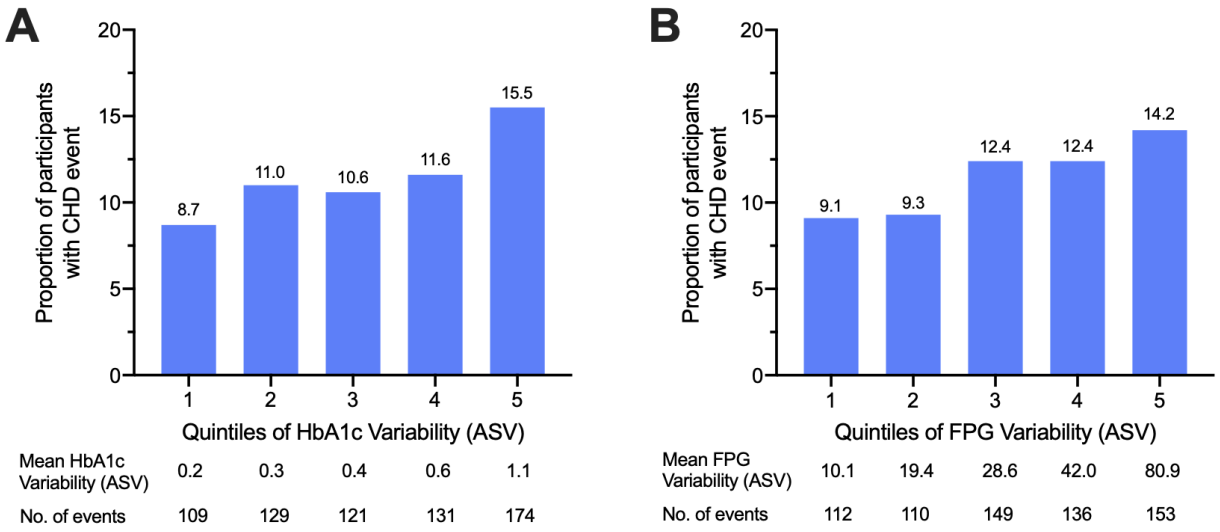


HR refers to the association of 1-SD higher measure of long-term variability in HbA1c with risk of incident HF. The % of participants indicates the proportion of participants with the specified minimum number of repeated measures of HbA1c measures from 8 months to 3 years of follow-up. Long-term variability in HbA1c was calculated from 8 months to 3 years of follow-up. % change in cardiometabolic parameters was calculated from baseline to 3 years of follow-up.

Model included demographic characteristics (age, sex, race, level of education), intensive glycemic control treatment group, history of cardiovascular disease (MI, stroke, or coronary revascularization), risk factors (systolic BP, alcohol use, cigarette use, BMI, total cholesterol, serum creatinine, LDL-c, HDL-c), medication use (angiotensin receptor blocker, ACE-inhibitor, beta-blocker, loop diuretic, thiazide diuretic, calcium channel blocker, insulin use, sulfonylurea, biguanide, meglitinide, and alpha-glucosidase inhibitor), baseline HbA1c, % change in HbA1c, % change in systolic BP, % change in BMI, % change in creatinine, and incident MI as a time-dependent variable.

ACE = angiotensin converting enzyme; ASV = average successive variation; BMI = body mass index; BP = blood pressure; CV = coefficient of variation; HbA1c = glycated hemoglobin; HDL-c = high-density lipoprotein cholesterol; HF = heart failure; HR = hazard ratio; LDL-c = low-density lipoprotein cholesterol; MI = myocardial infarction; SD = standard deviation.

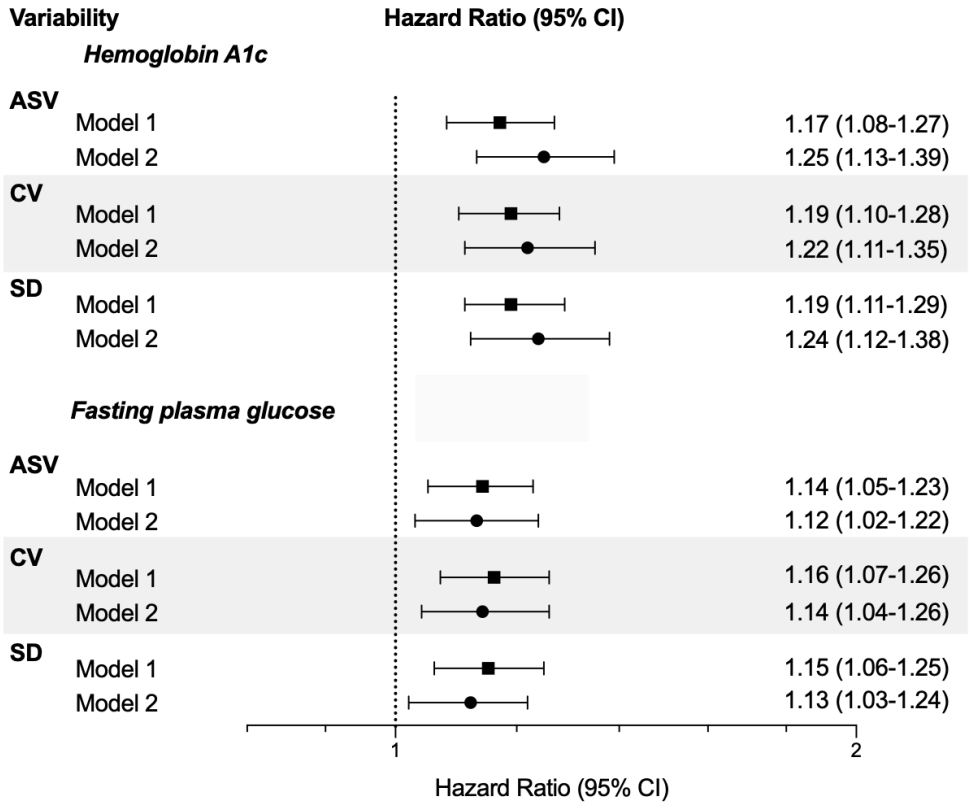
Supplemental Figure 5. Proportion of participants with incident acute coronary ischemic events across quintiles of long-term variability in HbA1c (**Panel A**) and FPG (**Panel B**).



Long-term variability in HbA1c / FPG was calculated from 8 months to 3 years of follow-up. CHD event = composite of cardiovascular death, nonfatal MI, or unstable angina.

ASV = average successive variability; CHD = coronary heart disease; HbA1c = glycated hemoglobin; MI = myocardial infarction

Supplemental Figure 6. Multivariable-adjusted association of long-term variability in HbA1c (top) and FPG (bottom) with risk of incident CHD events.



HR refers to the association of 1-SD higher measure of long-term variability in HbA1c / FPG with risk of incident CHD event. Long-term variability in HbA1c / FPG was calculated from 8 months to 3 years of follow-up. % change in cardiometabolic parameters was calculated from baseline to 3 years of follow-up. CHD event is a composite of cardiovascular death, nonfatal-MI, or unstable angina.

Model 1 included demographic characteristics (age, sex, race, level of education), intensive glycemic control treatment group, history of cardiovascular disease (MI, stroke, or coronary revascularization), risk factors (systolic BP, alcohol use, cigarette use, BMI, total cholesterol, serum creatinine, LDL-c, HDL-c), medication use (angiotensin receptor blocker, ACE-inhibitor, beta-blocker, loop diuretic, thiazide diuretic, calcium channel blocker, insulin use, sulfonylurea, biguanide, meglitinide, and alpha-glucosidase inhibitor), and baseline HbA1c.

Model 2 included covariates from Model 1 plus % change in HbA1c, % change in systolic BP, % change in BMI, % change in creatinine, and incident MI as a time-dependent variable.

ACE = angiotensin converting enzyme; ASV = average successive variation; BMI = body mass index; BP = blood pressure; CV = coefficient of variation; HbA1c = glycated hemoglobin; HDL-c = high-density lipoprotein cholesterol; HF = heart failure; HR = hazard ratio; LDL-c = low-density lipoprotein cholesterol; MI = myocardial infarction; SD = standard deviation.