The Hemoglobin Glycation Index Identifies Subpopulations With Harms or Benefits From Intensive Treatment in the ACCORD Trial

James M. Hempe,[1] Shuqian Liu,[2] Leann Myers,[3] Robert J. McCarter,[4] John B. Buse,[5] and Vivian Fonseca[2]

OBJECTIVE

This study tested the hypothesis that intensive treatment in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial disproportionately produced adverse outcomes in patients with diabetes with a high hemoglobin glycation index (HGI = observed HbA_{1c} − predicted HbA_{1c}).

RESEARCH DESIGN AND METHODS

ACCORD was a randomized controlled trial of 10,251 patients with type 2 diabetes assigned to standard or intensive treatment with HbA_{1c} goals of 7.0% to 7.9% (53 to 63 mmol/mol) and less than 6% (42 mmol/mol), respectively. In this ancillary study, a linear regression equation (HbA_{1c} = 0.009 × fasting plasma glucose [FPG] [mg/dL] + 6.8) was derived from 1,000 randomly extracted participants at baseline. Baseline FPG values were used to calculate predicted HbA_{1c} and HGI for the remaining 9,125 participants. Kaplan-Meier and Cox regression were used to assess the effects of intensive treatment on outcomes in patients with a low, moderate, or high HGI.

RESULTS

Intensive treatment was associated with improved primary outcomes (composite of cardiovascular events) in the low (hazard ratio [HR] 0.75 [95% CI 0.59–0.95]) and moderate (HR 0.77 [95% CI 0.61–0.97]) HGI subgroups but not in the high HGI subgroup (HR 1.14 [95% CI 0.93–1.40]). Higher total mortality in intensively treated patients was confined to the high HGI subgroup (HR 1.41 [95% CI 1.10–1.80]). A high HGI was associated with a greater risk for hypoglycemia in the standard and intensive treatment groups.

CONCLUSIONS

HGI calculated at baseline identified subpopulations in ACCORD with harms or benefits from intensive glycemic control. HbA_{1c} is not a one-size-fits-all indicator of blood glucose control, and taking this into account when making management decisions could improve diabetes care.

The purpose of this ancillary study was to determine if the risk for diabetes complications in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) glycemia trial differed among individuals with lower or higher HbA_{1c} levels than predicted by fasting plasma glucose (FPG). ACCORD participants were middle-aged and older people with type 2 diabetes and established cardiovascular disease (CVD) or known cardiovascular risk factors (1). The trial tested whether intensive treatment

targeting HbA_{1c} levels of less than 6% (42 mmol/mol) would reduce the rate of cardiovascular events compared with a strategy targeting HbA_{1c} levels between 7.0% and 7.9% (53 and 63 mmol/mol). This hypothesis was not supported: Intensive treatment failed to improve primary cardiovascular outcomes and was instead associated with 22% greater total mortality compared with standard treatment. The ACCORD trial thus demonstrated that increased mortality was a previously unrecognized harm of intensive glucose-lowering therapy in high-risk patients with type 2 diabetes. Although symptomatic severe hypoglycemia was associated with an increased risk of death in the intensive and standard treatment groups, differences in HbA_{1c} or rates of hypoglycemia between the two groups did not explain the greater mortality observed in the intensive-treatment group (2).

Treating patients with diabetes with drugs that lower blood glucose levels inherently increases the risk for hypoglycemia. Intensively treating patients with diabetes to a low HbA_{1c} target implicitly assumes that all patients will have roughly the same blood glucose level when they reach the target. Miller et al. (3) paradoxically reported that ACCORD participants with higher HbA_{1c} levels had greater risk for hypoglycemia. If HbA_{1c} were an unbiased estimate of blood glucose, this observation would incongruously suggest that participants with higher blood glucose levels had greater risk for hypoglycemia. Numerous studies have shown, however, that some patients with diabetes have HbA_{1c} levels that are persistently lower or higher than predicted compared with other individuals with similar blood glucose levels (4–10).

We reasoned that intensive treatment to a one-size-fits-all HbA_{1c} target of less than 6% (42 mmol/mol) may have inadvertently and disproportionately produced adverse outcomes in a subgroup of ACCORD patients with diabetes with lower blood glucose levels than their HbA_{1c} would predict. To test this hypothesis, we used the hemoglobin glycation index (HGI) to identify ACCORD participants with incongruous HbA_{1c} and FPG at baseline. HGI is the calculated difference between an individual's observed HbA_{1c} and a predicted HbA_{1c} derived by inserting the individual's blood glucose concentration into a population regression equation describing the linear relationship

between HbA_{1c} and blood glucose (HGI = observed HbA_{1c} − predicted HbA_{1c}) (4,9).

Assessment of HGI in the Diabetes Control and Complications Trial (DCCT) showed that patients with type 1 diabetes with a high HGI had a threefold greater risk for retinopathy and a sixfold greater risk for nephropathy (6). Most prior HGI research calculated predicted HbA_{1c} based on mean blood glucose (self-monitored (4,9), timed profiles (6), or continuous glucose monitoring (11)). HGIs calculated using all glucose data downloaded from patient meters were highly correlated with HGIs calculated using only prebreakfast glucose data (4). The feasibility of using FPG to calculate the HGI in patients with type 2 diabetes was previously proposed (12). The glycation gap developed by Cohen et al. (5) is calculated in exactly the same way as HGI except fructosamine replaces directly measured glucose for obtaining a predicted HbA_{1c}. Several studies have shown that patients with type 2 diabetes with a high glycation gap have greater risk for microvascular or macrovascular complications (5,10,13,14). HGI and the glycation gap are strongly positively correlated, which suggests they reflect the same biological phenomenon (15).

Patients with diabetes with low and high HGI have HbA_{1c} levels that are lower or higher than predicted, respectively, compared with other patients with similar blood glucose levels. We hypothesized that intensive treatment produced disproportionately lower blood glucose levels and increased hypoglycemia in the subgroup of ACCORD participants with a high HGI. This could explain the otherwise paradoxical results reported by Miller et al. (3). Also, higher baseline HbA_{1c} and higher average on-treatment HbA_{1c} were both strong predictors of mortality associated with intensive treatment in ACCORD (16,17). Because HGI was associated with increased complications risk in patients with type 1 diabetes in the DCCT, we also hypothesized that patients with type 2 diabetes with high HGI in ACCORD might also have a greater risk for primary cardiovascular outcomes, total mortality, and microvascular disease.

RESEARCH DESIGN AND METHODS
This research was approved by the institutional review boards at the Louisiana State University Health Sciences Center and Children's Hospital, New Orleans, LA.

ACCORD Study Design
ACCORD was a multicenter, randomized clinical trial that used a double 2 × 2 factorial design to incorporate intervention trials for glycemia, hyperlipidemia, and hypertension. The lipid intervention trial tested in 5,518 participants the hypothesis that a hypolipidemic agent would improve outcomes in subjects with good glycemic control. The blood pressure intervention trial tested in the remaining 4,733 participants the hypothesis that a therapeutic strategy that targets a systolic blood pressure of <120 mmHg will reduce the rate of CVD events compared with a strategy that targets a systolic blood pressure of <140 mmHg. All participants enrolled in the ACCORD trial had type 2 diabetes and had experienced a prior cardiovascular event or had other evidence of high risk for CVD. Median follow-up time was 5.0 years (mean 5.0; range 0.01–8.4). The rationale, study design, inclusion criteria, and other details of the ACCORD trial are described elsewhere (1,18–20).

The glycemia intervention trial included all 10,251 ACCORD participants, who were randomly assigned at baseline to a standard treatment group or an intensive treatment group. Any antihyperglycemic agent or combination of agents approved by regulatory authorities could be used as considered appropriate to achieve protocol-mandated target HbA_{1c} levels of 7.0% to 7.9% (53 to 63 mmol/mol) in the standard treatment group, or less than 6.0% (42 mmol/mol) in the intensive treatment group. During the trial, excess mortality was demonstrated at 3.5 years of average follow-up, at which time all participants in the intensive treatment group were converted to the standard treatment regimen (20). Data for this ancillary study were obtained from the ACCORD coordinating center on all enrolled participants. Only data from participants with FPG and HbA_{1c} recorded at baseline (n = 10,125) were used in these analyses.

Primary and Secondary Outcomes
The prespecified primary outcome for ACCORD was a composite of the first occurrence of nonfatal myocardial infarction (MI), nonfatal stroke, or death from cardiovascular causes (18). Causes of cardiovascular death included fatal MI, congestive heart failure, documented arrhythmia, death after invasive cardiovascular

interventions, death after noncardiovascular surgery, fatal stroke, unexpected death due to ischemic CVD occurring less than 24 h after the onset of symptoms, and death due to other vascular diseases such as pulmonary emboli or abdominal aortic aneurysm rupture. Death from any cause was one of several prespecified secondary outcomes (1). Primary and secondary outcomes were assessed from baseline through the last set of scheduled study visits (March–June 2009) (20).

Definition of Severe Hypoglycemia
Symptomatic, severe hypoglycemia requiring any assistance was defined as an episode of hypoglycemia with a documented blood glucose concentration of less than 50 mg/dL (2.8 mmol/L) in which the participant reported receiving medical care or assistance from another individual or recovery with carbohydrate treatment. Symptomatic, severe hypoglycemia requiring medical assistance was defined as an episode of hypoglycemia in which the participant received care at a hospital or emergency department or from medical personnel. Hypoglycemia assessment included hypoglycemia events from baseline up to the transition period when intensive glycemic intervention was terminated (February 2008).

Deriving HGI from the HbA$_{1c}$ Versus FPG Regression Equation
Baseline FPG and HbA$_{1c}$ data from a random subsample of 1,000 ACCORD participants were used to estimate the linear relationship between FPG and HbA$_{1c}$ in the study population. A predicted HbA$_{1c}$ was calculated for the remaining 9,125 participants by inserting the baseline FPG into the subsample linear regression equation (HbA$_{1c}$ = 0.009 FPG [mg/dL] + 6.8). Baseline HGI was calculated by subtracting the predicted HbA$_{1c}$ from the observed HbA$_{1c}$. The 9,125 participants were then assigned to low, moderate, or high HGI subgroups based on baseline HGI and HGI cut points that divided the population into three equally sized subgroups (low HGI $\leq$ −0.520 [n = 3,041], 33.3%; moderate HGI −0.520 to 0.202 [n = 3,042], 33.3%; high HGI >0.202 [n = 3,042], 33.3%). The use of a tertile classification system is by convention for consistency with previous HGI studies. We compared HGI classifications using simple linear regression with HGI classifications based on cubic spline regression and observed

more than 90% identity. We chose the linear regression model because this approach is simpler and has precedent.

Statistical Analysis
Baseline characteristics and other variables were compared among low, moderate, and high HGI subgroups. Group comparisons used ANOVA or Kruskal-Wallis tests for normally distributed and nonnormally distributed continuous variables, respectively, and χ^2 tests were used for categorical variables. Kaplan-Meier curves and log-rank tests were used to compare the distribution of time to first event. Post hoc analyses were performed to compare risk of primary outcomes, total mortality, and hypoglycemia between the intensive and standard glycemia treatment groups and among HGI subgroups with adjustment for covariates. Hazard ratios and 95% CI were determined by stratified Cox proportional hazards regression models. Tests of statistical significance were based on a two-tailed type 1 error at $P < 0.05$. The interaction term of HGI subgroup with glycemia treatment was added to each model, and a likelihood ratio test was applied. Whenever the interaction test did not meet the criteria for statistical significance, a Bonferroni correction for multiple comparisons was applied when evaluating the effect of treatment by subgroup. Proportional hazards assumptions were assessed by cumulative sums martingale residuals over follow-up times using Kolmogorov-type supremum tests and no violation was found.

Covariates included baseline characteristics, study location among the seven clinical-center networks, and for other ACCORD intervention assignments (the blood pressure trial, assignment to the intensive blood pressure intervention group, or the lipid trial, assignment to receive fibrate in the lipid trial). Sensitivity analyses were performed to determine hazard ratio stability after including intervention assignments in the Cox model as stratifying factors rather than as covariates. Baseline characteristics were age, sex, ethnicity, education level, medical history (smoking history, duration of diabetes, retinopathy detected at baseline, history of CVD, high risk of congestive heart failure, evidence of significant atherosclerosis, albuminuria), and laboratory and clinical measures at baseline (FPG, diastolic blood pressure, estimated

glomerular filtration rate, LDL-cholesterol, HDL-cholesterol, and triglycerides). Outcomes based on Cox regression models were similar to those obtained using logistic regression. We used Cox regression in reporting our results to account for the fact that ACCORD participants were monitored for different lengths of time, leading to a changing denominator over time that is not adequately modeled by the constant average denominator imposed by the logistic model. Statistical analyses were performed using SAS 9.3 or STATA 13 software.

RESULTS
Figure 1C shows the linear relationship between HbA$_{1c}$ and FPG in the ACCORD population at baseline. Figure 1A and B shows that the frequency distribution of HbA$_{1c}$ was markedly different in the low, moderate, and high HGI subgroups. In contrast, FPG distribution was similar among the subgroups. Selected baseline demographic, biochemical, and clinical characteristics are compared among the HGI subgroups in Table 1. Of
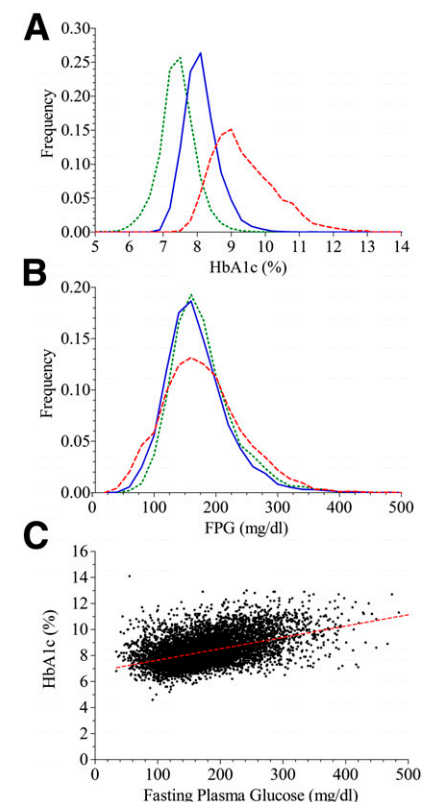

Figure 1—Assessment of HbA$_{1c}$ and FPG at baseline. The low, moderate, and high HGI subgroups have green, blue, or red lines, respectively. A: Distribution of HbA$_{1c}$ by HGI subgroup. B: Distribution of FPG by HGI subgroup. C: The red dotted line is the simple linear population regression line.

Table 1—Baseline characteristics of ACCORD participants by HGI subgroup

Variable[a]	Low HGI n = 3,041	Moderate HGI n = 3,042	High HGI n = 3,042	P value[b]
HbA$_{1c}$ (%)	7.4 ± 0.5	8.1 ± 0.5	9.4 ± 0.9	<0.001
Median HbA$_{1c}$ (%)	7.4	8.1	9.2	
HbA$_{1c}$ (mmol/mol)	57.4 ± 18.0	65.0 ± 18.0	79.2 ± 13.7	
FPG (mg/dL)	178.5 ± 52.3	169.0 ± 51	178.3 ± 64.2	<0.001
FPG (mmol/L)	9.9 ± 2.9	9.4 ± 2.8	9.9 ± 3.6	
HGI (%)	−0.961 ± 0.4	−0.183 ± 0.2	0.996 ± 0.7	<0.001
Age (years)	62.6 ± 6.8	62.7 ± 6.9	61.5 ± 6.8	<0.001
Median [IQR] duration of diabetes (years)	8 [10]	10 [10]	10 [11]	<0.001
Female sex	1,072 (35.3)	1,196 (39.3)	1,235 (40.6)	<0.001
Race or ethnic group (group %)				<0.001
White	2,148 (37.6)	1,957 (34.3)	1,606 (28.1)	
Black	375 (21.7)	551 (31.9)	799 (46.3)	
Hispanic	162 (24.9)	211 (32.5)	277 (42.6)	
Other	356 (34.3)	323 (31.1)	360 (34.6)	
Education				<0.001
Less than high school	377 (12.4)	438 (14.4)	523 (17.2)	
High school graduate	773 (25.4)	800 (26.3)	825 (27.1)	
Some college	1,017 (33.5)	1,035 (34.1)	950 (31.3)	
College degree or higher	872 (28.7)	767 (25.2)	742 (24.4)	
Cigarette smoking status				<0.01
Current	399 (13.1)	437 (14.4)	452 (14.9)	
Former	1,415 (46.6)	1,348 (44.3)	1,271 (41.9)	
Never	1,223 (40.3)	1,255 (41.3)	1,314 (43.3)	
Alcohol use	798 (26.3)	755 (24.8)	640 (21.1)	<0.001
Insulin use	835 (27.5)	1,036 (34.1)	1,321 (43.4)	<0.001
Metformin use	1,887 (62.1)	1,877 (61.7)	1,681 (55.3)	<0.001
Sulfonylurea use	1,576 (51.8)	1,584 (52.1)	1,433 (47.1)	<0.001
Thiazolidinedione use	595 (19.6)	645 (21.2)	538 (17.7)	0.025
History of hypertension	2,856 (93.9)	2,864 (94.2)	2,837 (93.3)	0.33
Previous CVD	1,014 (33.3)	1,114 (36.6)	1,085 (35.7)	0.02
High risk of heart failure	75 (2.5)	70 (2.3)	69 (2.3)	0.86
History of albuminuria	944 (31.0)	990 (32.5)	1,133 (37.3)	<0.001
History of left ventricular hypertrophy	125 (4.1)	107 (3.5)	151 (5)	0.02
History of arterial stenosis	141 (4.6)	158 (5.2)	157 (5.2)	0.53
Retinopathy at baseline	697 (22.9)	819 (26.9)	883 (29.0)	<0.001
Neuropathy at baseline	1,889 (62.2)	1,951 (64.3)	1,920 (63.1)	0.25
Serum creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.12
Estimated GFR (mL/min/1.73 m^2)	89.7 ± 27.8	90.8 ± 24.8	92.8 ± 29	<0.001
Cholesterol (mg/dL)				
Total	180.3 ± 39.5	182.3 ± 41.6	187 ± 44	<0.001
LDL	101.1 ± 32	104.4 ± 33.7	108.6 ± 35.3	<0.001
HDL				
Men	38.6 ± 9.8	38.2 ± 8.9	39.0 ± 10.0	<0.001
Women	46.7 ± 12.0	46.7 ± 12.7	47.9 ± 13.1	<0.001
Median [IQR] triglycerides (mg/dL)	160 [126]	155 [120]	149 [122]	<0.001
Blood pressure (mmHg)				
Diastolic	74.8 ± 10.7	74.3 ± 10.6	75.4 ± 10.7	<0.001
Systolic	136 ± 16.6	136.2 ± 17.1	136.8 ± 17.6	0.21
BMI (kg/m^2)	32.2 ± 5.4	32.3 ± 5.4	32.2 ± 5.6	0.56
Waist circumference (cm)	107 ± 13.8	107.1 ± 13.9	106.4 ± 14.1	0.15

GFR, glomerular filtration rate; IQR, interquartile range. [a]Unless otherwise noted, values are means ± SD for continuous variables or number (%) for categorical variables. [b]Overall differences between HGI groups using ANOVA, Kruskal-Wallis tests, or χ^2 tests.

particular note, there were disproportionately more black and Hispanic participants and fewer white participants in the high HGI subgroup. Furthermore, high HGI participants were younger, had longer duration of diabetes, were more likely to already have retinopathy and a history of albuminuria at baseline, and were more likely to have

used insulin before the start of the study.

After 1 year of standard (Fig. 2A) or intensive (Fig. 2B) treatment, mean HbA$_{1c}$ remained significantly different ($P < 0.001$) between HGI subgroups and was highest in the high HGI subgroup. In contrast, the mean FPG was significantly lower ($P < 0.001$) in the moderate and high HGI subgroups after 1 year of standard treatment (Fig. 2A) and was not different ($P > 0.05$) between HGI subgroups after 1 year of intensive treatment (Fig. 2B). The number of participants above or below the HbA$_{1c}$ intensification thresholds varied after 1 year in the standard treatment arm: 43.0% of high HGI participants remained above the 8% (64 mmol/mol) intensification threshold compared with only 30.6% of moderate and 21.9% of low HGI participants. After 1 year in the intensive treatment arm, 88.7% of high HGI participants remained above the 6% (42 mmol/mol) intensification threshold compared with 83.9% of moderate and 72.7% of low HGI participants. Barring mitigating circumstances, such as a recent hypoglycemic event, having disproportionately more participants above the intensification threshold should have resulted in greater treatment intensification at the 1-year visit.

Kaplan-Meier (Fig. 3) and Cox regression analyses (Table 2) show that the effect of intensive treatment differed markedly among the HGI subgroups. For example, if we ignore HGI, the event rate for primary outcomes was not significantly different ($P = 0.09$) between the intensive (9.8%) and standard (10.7%) treatment groups (Table 2 and Fig. 3A). A statistically significant interaction was detected between treatment and HGI ($P = 0.0091$). Subsequent HGI subgroup analysis showed that intensive treatment reduced primary outcomes by 25% ($P = 0.02$) in the low HGI subgroup and by 23% ($P = 0.02$) in the moderate HGI subgroup (Table 2 and Fig. 3B). In contrast, primary outcomes in the high HGI subgroup were not significantly different between the standard and intensive glycemia treatment groups ($P = 0.20$).

Ignoring HGI again, total mortality (Table 2 and Fig. 3C) was significantly greater ($P = 0.02$) in the intensive treatment group (7.7%) compared with the standard treatment group (6.3%). There was no interaction between treatment
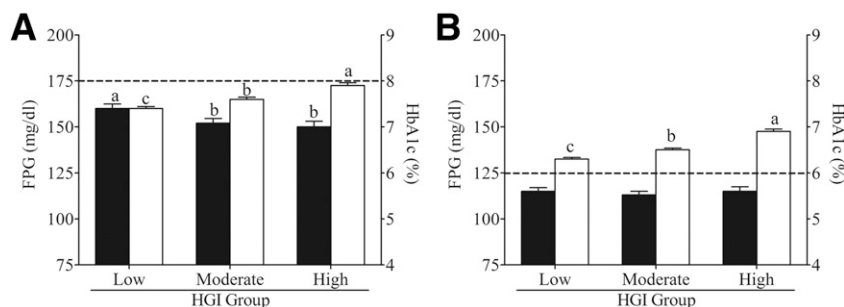

Figure 2—HbA$_{1c}$ and FPG disparity among HGI subgroups. Mean ($\pm$ 95% CI) HbA$_{1c}$ ($\square$) and FPG levels ($\blacksquare$) for low, moderate, and high HGI subgroups after 1 year of standard (A) or intensive (B) glycemia treatment. For each panel, HbA$_{1c}$ or FPG values with different superscripts (a, b, c) are significantly different ($P < 0.05$). The dotted lines denote protocol-mandated HbA$_{1c}$ treatment-intensification thresholds.

and HGI ($P = 0.22$). HGI subgroup analysis showed that although intensive treatment significantly increased total mortality by 41% ($P = 0.02$) in the high HGI subgroup, it had no effect on mortality in the moderate or low HGI subgroups compared with standard treatment (Table 2 and Fig. 3D).
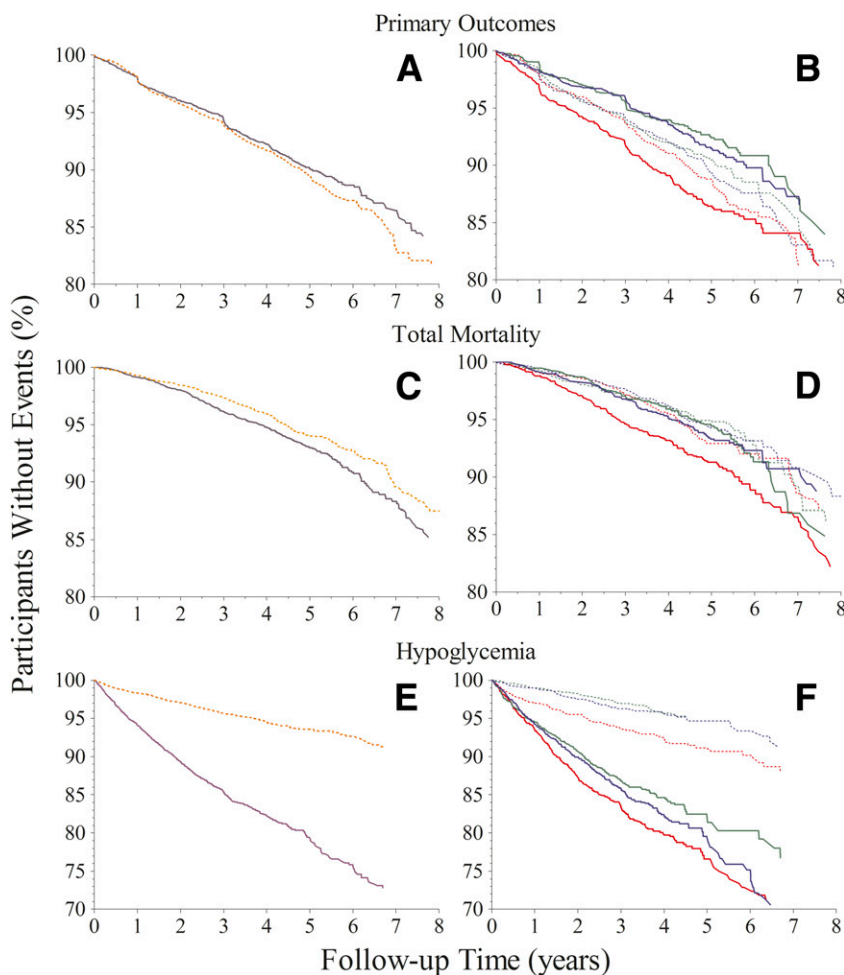

Figure 3—Kaplan-Meier curves for primary outcomes, total mortality, and hypoglycemia requiring any assistance. Proportions of participants free of the specified outcome over time are compared between standard and intensive treatment groups (panels A, C, D) and among the HGI subgroups (panels B, D, F). Standard treatment is depicted by orange dashed lines and intensive treatment by solid purple lines. Low, moderate, and high HGI subgroups have green, blue, or red lines, respectively.

Table 2—Risk and adjusted hazard ratios of composite primary outcomes, total mortality, and hypoglycemia by glycemia treatment group and HGI subgroup

| | HGI subgroup | Intensive treatment (I) | | | Standard treatment (S) | | | Adjusted hazard ratio (I/S) | | | Interaction between treatment and HGI |
		At risk	Events	%	At risk	Events	%	Estimate	95% CI	P value	P value
Primary outcomes[a]	Overall	4,570	446	9.8	4,555	487	10.7	0.89	0.97–1.02	0.09	
	Low	1,532	119	7.8	1,509	147	9.7	0.75	0.59–0.95	0.02	0.0091
	Moderate	1,515	128	8.4	1,527	161	10.5	0.77	0.61–0.97	0.02	
	High	1,523	199	13.1	1,519	179	11.8	1.14	0.93–1.40	0.20	
Total mortality[b]	Overall	4,570	350	7.7	4,555	287	6.3	1.21	1.04–1.42	0.02	
	Low	1,532	97	6.3	1,509	86	5.7	1.08	0.81–1.44	1.00[d]	0.2240
	Moderate	1,515	102	6.7	1,527	92	6.0	1.06	0.80–1.41	1.00[d]	
	High	1,523	151	9.9	1,519	109	7.2	1.41	1.10–1.81	0.02[d]	
Hypoglycemia[c]	Overall	4,570	763	16.7	4,555	238	5.2	3.64	3.14–4.21	<0.001	
	Low	1,532	222	14.5	1,509	56	3.7	4.27	3.21–5.78	<0.001	0.0350
	Moderate	1,515	254	16.8	1,527	68	4.5	4.32	3.32–5.68	<0.001	
	High	1,523	287	18.8	1,519	114	7.5	2.91	2.35–3.63	<0.001	

[a]First occurrence of nonfatal MI, nonfatal stroke, or death from cardiovascular events. Covariates include age, sex, race, education, diabetes duration, history of smoking, previous CVD, high risk of heart failure, history of arterial stenosis, history of albuminuria, retinopathy at baseline, estimated glomerular filtration rate, HDL-cholesterol, LDL-cholesterol, and intervention trial (hypertension treatment, intensive vs. standard; hypertension trial vs. lipid trial; hyperlipidemia treatment, fibrate vs. no fibrate). [b]Death from any cause. Covariates include age, sex, race, education, history of smoking, statin uses, insulin uses, previous CVD, history of albuminuria, history of arterial stenosis, retinopathy at baseline, and intervention trial (hypertension treatment, intensive vs. standard; hypertension trial vs. lipid trial; hyperlipidemia treatment, fibrate vs. no fibrate). [c]Symptomatic, severe hypoglycemia requiring any assistance. Covariates include age, sex, race, education, diabetes duration, living alone or not, insulin uses, previous CVD, retinopathy at baseline, neuropathy at baseline, and estimated glomerular filtration rate. [d]Bonferroni correction for multiple comparisons.

Ignoring HGI once more, hypoglycemia requiring any assistance was more than threefold greater ($P < 0.001$) in the intensive treatment group compared with the standard treatment group (Table 2 and Fig. 3E). HGI subgroup analysis showed that the incidence of hypoglycemia was progressively higher in the low, moderate, and high HGI subgroups in the intensive (14.5, 16.8, and 18.8%, respectively) and standard (3.7, 4.5, and 7.5%, respectively) glycemia treatment groups (Table 2 and Fig. 3F). Results were similar for hypoglycemia requiring medical assistance. Sensitivity analyses that included other intervention assignments as stratifying factors in the Cox models, rather than as covariates, showed that the estimated HRs for primary outcomes, total mortality, and hypoglycemia remained stable.

CONCLUSIONS

Interindividual variation in HbA_{1c} caused by factors other than blood glucose concentration appears to be partly hereditary (21,22) and has been reported in patients with type 1 diabetes (4–9,23,24), with type 2 diabetes (12–14,25–27), and without diabetes (28–32). Pediatric patients with type 1 diabetes with higher HGI had higher levels of skin advanced glycation end products (33). HbA_{1c} levels

that are persistently lower or higher than expected among individuals with similar blood glucose levels have been detected in studies where blood glucose was estimated based on FPG (12), self-monitored mean blood glucose (4,8,9,34), 7-point mean blood glucose profile sets (6,35), continuous glucose monitoring (7,11), or fructosamine (5,26,27). Unlike other methods for estimating blood glucose, continuous glucose monitoring and fructosamine are relatively free of sampling bias yet produce similar results when assessing interindividual variation in HbA_{1c}.

The present studies indicate that subjects in ACCORD with high HGIs had more retinopathy and nephropathy at baseline, as previously reported in the DCCT (6). The differences in drug use observed between HGI subgroups at baseline could be related to the fact that insulin is more likely to be prescribed for individuals with persistently higher HbA_{1c} (high HGI). Alternatively, different drugs have been shown to influence the quantitative relationship between HbA_{1c} and blood glucose concentration (36), which could in turn influence the HGI. Higher HGI among black ACCORD participants supports our previous observation of racial variation in HGI in children with type 1 diabetes (8). Evidence of clinically significant interindividual variation

in the quantitative relationship between blood glucose concentration and HbA_{1c} markedly complicates the use of HbA_{1c} for the diagnosis and management of diabetes, especially in mixed-race populations (37–42).

Heterogeneity of Treatment Outcomes Among HGI Subgroups in ACCORD

Our present analyses examine the ACCORD glycemia trial through a new lens, namely, the HGI calculated using FPG and HbA_{1c} measured at baseline. As previously reported by the ACCORD investigators, we observed no difference in primary outcomes between the standard and intensive treatment groups despite our use of a slightly different data set (we omitted patients without HbA_{1c} or FPG at baseline) and different statistical methods. HGI subgroup analysis indicated, however, that intensive treatment actually improved primary outcomes in low and moderate HGI participants, a beneficial effect that was offset and masked by the apparently detrimental effects of intensive treatment in the high HGI subgroup. Although total mortality was significantly higher in the intensive treatment group, HGI subgroup analysis showed that the higher mortality associated with intensive treatment was restricted to the

high HGI subgroup. Collectively, these observations show that HGI identifies two subpopulations in ACCORD, one that experiences benefits and one that experiences harms from the same intensive glucose-lowering strategy.

The risk for hypoglycemia was greatest in the high HGI subgroup in the standard and intensive treatment groups. More high HGI participants remained above the protocol-mandated HbA$_{1c}$ treatment thresholds after 1 year of standard or intensive treatment. Despite higher mean HbA$_{1c}$, high HGI participants in both glycemia treatment groups had mean FPG values after 1 year that were as low as or lower than those observed in low HGI participants. Collectively, these observations are consistent with our hypothesis that intensive treatment may have inadvertently caused high HGI participants to receive more intensive treatment and could explain the otherwise paradoxical results reported by Miller et al. (3).

Clinical Implications
The twin goals of diabetes management are to keep blood glucose levels low enough to limit the development of long-term diabetes complications but high enough to avoid hypoglycemia. After the ACCORD trial reported that intensive treatment increased mortality and hypoglycemia, the American Diabetes Association (ADA) recommended that HbA$_{1c}$ treatment goals for individual patients should be personalized according to characteristics such as age and frequency of hypoglycemia, while also reiterating that lowering HbA$_{1c}$ generally helps prevent or delay long-term complications (43). Our observations of markedly different outcomes in the different HGI subgroups in response to intensive treatment strongly supports the ADA recommendation for more personalized diabetes management and suggests that HGI could be used to help individualize treatment goals.

Exactly how the results of this study might be used to reinterpret other clinical trials or how the results might be applied in future trial designs or in clinical practice remains to be determined. One reason is that ACCORD participants were older than the general public and selected for elevated risk for CVD. This could explain why the baseline regression equation in ACCORD is markedly different from the linear regression

equations reported by studies such as the A1C-Derived Average Glucose (ADAG) study (44). As such, the results may not be generalizable to other clinical trials or to the general population with diabetes and we cannot recommend the use of the ACCORD regression equation in other populations. Furthermore, only one other study has used FPG to assess the HGI in patients with type 2 diabetes, and these results were only reported in a meeting abstract (12). All other prior HGI and glycation gap studies in patients with diabetes used some estimate of mean blood glucose or fructosamine. Additional studies of HGI in other clinical trials could help determine how best to use the HGI in clinical practice.

Conclusion
Intensive treatment to a low HbA$_{1c}$ target of less than 6% (42 mmol/mol) cannot be recommended for all patients with type 2 diabetes because primary cardiovascular outcomes, total mortality, and hypoglycemia were all adversely affected in high HGI participants in ACCORD. Further studies should determine if the observed beneficial effects of intensive treatment on primary outcomes in low and moderate HGI participants outweigh any detrimental effects that might be caused by the increase in hypoglycemia associated with intensive treatment. Our results confirm that HbA$_{1c}$ is not a one-size-fits-all indicator of blood glucose concentration and suggest that failure to take this into account can result in suboptimal diabetes care.

References
1. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
2. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 2010;340:b4909
3. Miller ME, Bonds DE, Gerstein HC, et al.; ACCORD Investigators. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. BMJ 2010;340:b5444
4. Hempe JM, Gomez R, McCarter RJ Jr, Chalew SA. High and low hemoglobin glycation phenotypes in type 1 diabetes: a challenge for interpretation of glycemic control. J Diabetes Complications 2002;16:313–320
5. Cohen RM, Holmes YR, Chenier TC, Joiner CH. Discordance between HbA1c and fructosamine: evidence for a glycosylation gap and its relation to diabetic nephropathy. Diabetes Care 2003; 26:163–167
6. McCarter RJ, Hempe JM, Gomez R, Chalew SA. Biological variation in HbA1c predicts risk of retinopathy and nephropathy in type 1 diabetes. Diabetes Care 2004;27:1259–1264
7. Diabetes Research in Children Network (DirecNet) Study Group; Wilson DM, Kollman C. Relationship of A1C to glucose concentrations in children with type 1 diabetes: assessments by high-frequency glucose determinations by sensors. Diabetes Care 2008;31:381–385
8. Kamps JL, Hempe JM, Chalew SA. Racial disparity in A1C independent of mean blood glucose in children with type 1 diabetes. Diabetes Care 2010;33:1025–1027
9. Soros AA, Chalew SA, McCarter RJ, Shepard R, Hempe JM. Hemoglobin glycation index: a robust measure of hemoglobin A1c bias in pediatric type 1 diabetes patients. Pediatr Diabetes 2010;11:455–461
10. Rodríguez-Segade S, Rodríguez J, Cabezas-Agricola JM, Casanueva FF, Camiña F. Progression

of nephropathy in type 2 diabetes: the glycation gap is a significant predictor after adjustment for glycohemoglobin (Hb A1c). Clin Chem 2011;57: 264–271

11. Wilson DM, Xing D, Cheng J, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Persistence of individual variations in glycated hemoglobin: analysis of data from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Randomized Trial. Diabetes Care 2011; 34:1315–1317

12. Kim JI, Stevens RJ, Holman RR. The haemoglobin glycation index is an independent risk factor for microvascular complications in UKPDS patients with newly diagnosed type 2 diabetes (Abstract). Diabetes 2005;54:A244–A245

13. Cosson E, Banu I, Cussac-Pillegand C, et al. Glycation gap is associated with macroproteinuria but not with other complications in patients with type 2 diabetes. Diabetes Care 2013;36: 2070–2076

14. Nayak AU, Nevill AM, Bassett P, Singh BM. Association of glycation gap with mortality and vascular complications in diabetes. Diabetes Care 2013;36:3247–3253

15. Chalew SA, McCarter RJ, Thomas J, Thomson JL, Hempe JM. A comparison of the glycosylation gap and hemoglobin glycation index in patients with diabetes. J Diabetes Complications 2005;19:218–222

16. Calles-Escandón J, Lovato LC, Simons-Morton DG, et al. Effect of intensive compared with standard glycemia treatment strategies on mortality by baseline subgroup characteristics: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care 2010;33: 721–727

17. Riddle MC, Ambrosius WT, Brillon DJ, et al.; Action to Control Cardiovascular Risk in Diabetes Investigators. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. Diabetes Care 2010; 33:983–990

18. Buse JB, Bigger JT, Byington RP, et al.; ACCORD Study Group. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. Am J Cardiol 2007;99:21i–33i

19. Gerstein HC, Riddle MC, Kendall DM, et al.; ACCORD Study Group. Glycemia treatment strategies in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol 2007;99:34i–43i

20. Gerstein HC, Miller ME, Genuth S, et al.; ACCORD Study Group. Long-term effects of

intensive glucose lowering on cardiovascular outcomes. N Engl J Med 2011;364:818–828

21. Cohen RM, Snieder H, Lindsell CJ, et al. Evidence for independent heritability of the glycation gap (glycosylation gap) fraction of HbA1c in nondiabetic twins. Diabetes Care 2006;29: 1739–1743

22. Snieder H, Sawtell PA, Ross L, Walker J, Spector TD, Leslie RD. HbA(1c) levels are genetically determined even in type 1 diabetes: evidence from healthy and diabetic twins. Diabetes 2001;50:2858–2863

23. Madsen H, Kjaergaard JJ, Ditzel J. Relationship between glycosylation of haemoglobin and the duration of diabetes: a study during the third trimester of pregnancy. Diabetologia 1982;22:37–40

24. Hudson PR, Child DF, Jones H, Williams CP. Differences in rates of glycation (glycation index) may significantly affect individual HbA1c results in type 1 diabetes. Ann Clin Biochem 1999;36:451–459

25. Fukudome M, Nakazaki M, Fukushige E, et al. Interindividual divergence in the relationship between the values of plasma glucose and hemoglobin A1c in type 2 diabetes. Intern Med 2009;48:273–279

26. Rodríguez-Segade S, Rodríguez J, García Lopez JM, Casanueva FF, Camiña F. Estimation of the glycation gap in diabetic patients with stable glycemic control. Diabetes Care 2012; 35:2447–2450

27. Zafon C, Ciudin A, Valladares S, Mesa J, Simó R. Variables involved in the discordance between HbA1c and fructosamine: the glycation gap revisited. PLoS One 2013;8:e66696

28. Yudkin JS, Forrest RD, Jackson CA, Ryle AJ, Davie S, Gould BJ. Unexplained variability of glycated haemoglobin in non-diabetic subjects not related to glycaemia. Diabetologia 1990;33: 208–215

29. Gould BJ, Davie SJ, Yudkin JS. Investigation of the mechanism underlying the variability of glycated haemoglobin in non-diabetic subjects not related to glycaemia. Clin Chim Acta 1997; 260:49–64

30. Kilpatrick ES, Maylor PW, Keevil BG. Biological variation of glycated hemoglobin. Implications for diabetes screening and monitoring. Diabetes Care 1998;21:261–264

31. Rohlfing C, Wiedmeyer HM, Little R, et al. Biological variation of glycohemoglobin. Clin Chem 2002;48:1116–1118

32. Khaw KT, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of european prospective

investigation of cancer and nutrition (EPIC-Norfolk). BMJ 2001;322:15–18

33. Felipe DL, Hempe JM, Liu S, et al. Skin intrinsic fluorescence is associated with hemoglobin A1c and hemoglobin glycation index but not mean blood glucose in children with type 1 diabetes. Diabetes Care 2011;34:1816–1820

34. Hempe JM, Soros AA, Chalew SA. Estimated average glucose and self-monitored mean blood glucose are discordant estimates of glycemic control. Diabetes Care 2010;33:1449–1451

35. McCarter RJ, Hempe JM, Chalew SA. Mean blood glucose and biological variation have greater influence on HbA1c levels than glucose instability: an analysis of data from the Diabetes Control and Complications Trial. Diabetes Care 2006;29:352–355

36. Ramachandran A, Riddle MC, Kabali C, Gerstein HC; ORIGIN Investigators. Relationship between A1C and fasting plasma glucose in dysglycemia or type 2 diabetes: an analysis of baseline data from the ORIGIN trial. Diabetes Care 2012;35:749–753

37. Cohen RM. A1C: does one size fit all? Diabetes Care 2007;30:2756–2758

38. Dagogo-Jack S. Pitfalls in the use of HbA1c as a diagnostic test: the ethnic conundrum. Nat Rev Endocrinol 2010;6:589–593

39. Davidson MB, Schriger DL. Effect of age and race/ethnicity on HbA1c levels in people without known diabetes mellitus: implications for the diagnosis of diabetes. Diabetes Res Clin Pract 2010;87:415–421

40. Herman WH, Cohen RM. Racial and ethnic differences in the relationship between HbA1c and blood glucose: implications for the diagnosis of diabetes. J Clin Endocrinol Metab 2012;97: 1067–1072

41. Chalew SA, McCarter RJ, Hempe JM. Biological variation and hemoglobin A1c: relevance to diabetes management and complications. Pediatr Diabetes 2013;14:391–398

42. Wolffenbuttel BHR, Herman WH, Gross JL, Dharmalingam M, Jiang HH, Hardin DS. Ethnic differences in glycemic markers in patients with type 2 diabetes. Diabetes Care 2013;36:2931–2936

43. American Diabetes Association. Standards of medical care in diabetes—2010. Diabetes Care 2010;33(Suppl. 1):S11–S61

44. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ; A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008;31:1473–1478