



30-Year Cardiovascular Disease in Type 1 Diabetes: Risk and Risk Factors Differ by Long-term Patterns of Glycemic Control

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OBJECTIVE

We hypothesized that there is heterogeneity in long-term patterns of glycemic control with respect to cardiovascular disease (CVD) development in type 1 diabetes and that risk factors for CVD differ by glycemic control pattern. Thus, we estimated associations between data-derived latent HbA_{1c} trajectories and 30-year CVD risk in the Pittsburgh Epidemiology of Diabetes Complications (EDC) study of childhood-onset (<17 years old) type 1 diabetes.

RESEARCH DESIGN AND METHODS

Participants ($n = 536$ with two or more HbA_{1c} measurements [median 6] and CVD-free at baseline; mean age 27 and diabetes duration 18 years) were followed from 1986 to 1988 to 2016 to 2018 to ascertain CVD incidence (CVD death, myocardial infarction, stroke, coronary revascularization or blockage $\geq 50\%$, ischemic electrocardiogram, or angina). Latent HbA_{1c} trajectories and their association with time-to-CVD incidence were simultaneously assessed using joint latent class mixed models.

RESULTS

Two HbA_{1c} trajectories with respect to differential CVD risk were identified: low (HbA_{1c} $\sim 8\%$ [64 mmol/mol] and improving over follow-up, 76% of cohort) and high (HbA_{1c} $\sim 10\%$ [86 mmol/mol] and stable, 24%). Overall, 30-year CVD incidence was 47.4% ($n = 253$); major adverse cardiovascular event incidence was 31.0% ($n = 176$). High HbA_{1c} was associated with threefold increased CVD risk versus low HbA_{1c}. Both groups had similar age and diabetes duration. Non-HDL cholesterol and estimated glomerular filtration rate were associated with CVD risk only in low HbA_{1c}; albumin excretion rate was associated with CVD risk only in high HbA_{1c}.

CONCLUSIONS

These risk factor differences suggest that pathways to CVD may differ by glycemic control, potentially resulting in important implications for prognosis in type 1 diabetes.

While the relationship between HbA_{1c} and cardiovascular disease (CVD) has historically been inconsistent in type 1 diabetes (1–7), its importance as a key CVD risk factor has become more apparent in recent years (8–11). We have previously

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shown in the Pittsburgh Epidemiology of Diabetes Complications (EDC) type 1 diabetes cohort that HbA_{1c} was associated with 25-year CVD risk (10). That analysis estimated the average overall association among longitudinal, continuous HbA_{1c}, and CVD risk. We have more recently identified heterogeneous longitudinal HbA_{1c} trajectories in the EDC cohort, demonstrating distinct long-term glycemic control patterns with varying risk factor profiles (12).

Recent comparative analyses suggest that nephropathy is the predominant CVD risk factor in some type 1 diabetes cohorts, while HbA_{1c} predominates in others (11). Determining whether specific patterns of HbA_{1c} are associated with differential CVD risk and risk factors could have important implications for prognosis and treatment. Thus, we hypothesized that there is heterogeneity in long-term patterns of glycemic control with respect to risk of CVD development in type 1 diabetes and that other risk factors for CVD differ by pattern of glycemic control. In particular, as the role of kidney disease separate from hyperglycemia is unclear, we hypothesize its role will vary by HbA_{1c} pattern. To assess these hypotheses, we estimated associations between HbA_{1c} trajectories and 30-year risk of total CVD and major adverse cardiovascular events (MACE) in type 1 diabetes and examined risk factor differences by HbA_{1c} trajectory in the EDC cohort.

RESEARCH DESIGN AND METHODS

Study Population

The EDC Study is a prospective cohort study of childhood-onset (<17 years old) type 1 diabetes. Participants (*n* = 658) were diagnosed with type 1 diabetes, or seen within 1 year of diagnosis, at Children's Hospital of Pittsburgh between 1950 and 1980. The cohort has been described in detail elsewhere (13). Briefly, participants were followed from 1986 to 1988, initially with biennial examinations for 10 years and thereafter with biennial questionnaires and further examinations at 18, 25, and 30 years. The University of Pittsburgh institutional review board approved research protocols. All participants provided written informed consent.

Ascertainment of Cardiovascular Outcomes

Participants were followed from 1986–1988 to 2016–2018 to assess 30-year total CVD incidence, defined as the first instance of CVD death, nonfatal myocardial infarction (MI; including clinical events and subclinical MI on electrocardiogram [i.e., Minnesota code 1.1 or 1.2]), nonfatal stroke, coronary revascularization procedure, blockage $\geq 50\%$, ischemic electrocardiogram at a study visit (Minnesota codes 1.3, 4.1–4.3, 5.1–5.3, and 7.1), or EDC physician-diagnosed angina. The secondary outcome, MACE, was the first instance of CVD death, nonfatal MI, or nonfatal stroke. Fatal CVD events were ascertained using medical records, death certificates, autopsy reports, and/or interview with next of kin and classified according to the Diabetes Epidemiology Research International system (14). Nonfatal MI, stroke, coronary revascularization, and blockage were confirmed with medical records.

HbA_{1c} Assessment

HbA_{1c} was measured at six visits (1986–1988, 1988–1990, 1990–1992, 1992–1994, 1994–1996, and 1996–1998); HbA_{1c} was measured at two visits (2004–2006 and 2011–2013). Thus, each participant could have a maximum of eight measures. From 1986 to 1998, HbA_{1c} was measured using automated high-performance liquid chromatography (Diamat; Bio-Rad Laboratories, Hercules, CA) and converted to Diabetes Control and Complications Trial (DCCT)-aligned HbA_{1c} values using a validated regression equation derived from duplicate assays (DCCT HbA_{1c} = 0.14 + 0.83 [EDC HbA_{1c}]) (8). At the 2004–2006 and 2011–2013 visits, HbA_{1c} was measured using the DCA 2000 analyzer (Bayer Healthcare LLC, Elkhart, IN) and converted to DCCT-aligned HbA_{1c} with the equation: DCCT HbA_{1c} = (EDC HbA_{1c} – 1.13)/0.81 (8).

Risk Factor Assessment

Risk factors were assessed at the same time points as HbA_{1c} described above. From baseline until the 10-year examination, serum total cholesterol and triglycerides were determined enzymatically (15,16), and HDL cholesterol (HDLc) was determined using a modified precipitation technique (17) based

on the Lipid Research Clinics method (18). At 18 and 25 years, serum lipids were measured using the Cholestech LDX (Cholestech Corp., Hayward, CA). Non-HDLc was calculated by subtracting HDLc from total cholesterol. Blood pressure (BP) was measured according to the Hypertension Detection and Follow-Up protocol (19) with a random-zero sphygmomanometer, replaced by an aneroid sphygmomanometer at 18 years. Hypertension was BP $\geq 140/90$ mmHg or use of BP-lowering medication. Serum creatinine was measured using an Ektachem 400 Analyzer (Eastman Kodak Co.). Urinary albumin was measured by immunonephelometry (20). Albumin excretion rate (AER) was calculated for each of three timed urine samples (24-h, overnight, and 4-h collections obtained over a 2-week period); the median of the three AERs was used in analyses. AER measurements were not available at the 25-year time point, so data from the 18-year time point were carried forward for time-varying analyses. Estimated glomerular filtration rate (eGFR) was estimated by the Chronic Kidney Disease Epidemiology Collaboration creatinine equation (21). Height and weight were measured using standard methods to calculate BMI. Waist and hip circumference were measured at least twice; the average of each was used to calculate the waist-to-hip ratio. Estimated glucose disposal rate (eGDR), a validated estimate of insulin sensitivity (22), was calculated using the following equation: eGDR (mg/kg/min) = 24.395 – (12.971 * waist-to-hip ratio) – (3.388 * hypertension) – (0.601 * HbA_{1c}).

Smoking history, insulin regimen, hypoglycemia, lipid (World Health Organization ATC group C10) and BP (ATC group C02) medication and aspirin use, and first-degree family history of MI were obtained by self-administered questionnaire. Insulin dose was calculated as total insulin units per day/body weight (kilograms). Hypoglycemia requiring assistance was defined as any hypoglycemic episode resulting in unconsciousness and/or hospitalization in the past 2 years or a hypoglycemic episode not recognized by the participant (i.e., someone else had to tell or help the participant) in the past 12 months.

Statistical Methods

Analytic approaches in which latent classes of a risk factor are first identified and then subsequently entered as categorical variables in time-to-event analysis violate the assumptions of Cox models (e.g., including future information measured after an event is observed) and do not account for how a longitudinal risk factor trajectory itself may be altered by the occurrence of the event. Thus, we used joint latent class mixed models (JLCMM), which address these limitations (23), to simultaneously model latent clusters of longitudinal HbA_{1c} and time-to-CVD or MACE. Baseline hazards were estimated using a Weibull function with proportional hazards across the latent classes. Maximum likelihood estimates of the model parameters were obtained using a modified Marquardt algorithm. To ensure convergence to the global maximum of the log-likelihood, models with two or more latent classes were run specifying initial values for the iterative estimation process that were randomly drawn from the asymptotic distribution of the maximum likelihood estimates from the one-class model. Separately for total CVD and MACE, we evaluated the fit of one to four HbA_{1c} trajectories. Models with increasing number of trajectories were compared using the Bayesian information criterion (BIC) and posterior classification proportions. We required, a priori, for a model to be selected that all trajectories must comprise $\geq 5\%$ of the cohort. For each outcome, after the optimal number of trajectories was determined, the optimal functional form (linear, quadratic, or cubic) of the trajectories was assessed using the significance level of each polynomial term in the equation. In this step, all trajectories were first modeled as cubic functions (i.e., third-order polynomial, $\beta_0 + \beta_1 t + \beta_2 t^2 + \beta_3 t^3$), and any term with $P > 0.05$ was eliminated. Analyses were restricted to participants with two or more HbA_{1c} measurements. JLCMM were fit using the *lcmm* package (24) in R (R Foundation for Statistical Computing, Vienna, Austria).

We summarized baseline characteristics within each HbA_{1c} trajectory using means (SD), median (interquartile range), or percent (*n*). Data were stratified by HbA_{1c} trajectory, and separate Cox

models were fit using backward selection to estimate associations between risk factors and time-to-CVD within each HbA_{1c} trajectory. Three models were fit: 1) fixed baseline characteristics ($P < 0.10$ to retain); 2) time-varying most recent characteristics ($P < 0.10$ to retain); and 3) models offering both the fixed baseline and time-varying characteristics identified in models 1 and 2 to obtain a final multivariable model ($P < 0.05$ to retain). All analyses were repeated for time-to-MACE. Cox analyses were performed using SAS v. 9.4 (SAS Institute, Inc., Cary, NC).

Comparison of the <45-Year-Old EDC Subcohort to the Background Population, 2010–2014

As we have previously reported (25), data on CVD events in the background Allegheny County, Pennsylvania population are available for the years 2010 to 2014 in individuals <45 years old. Thus, we repeated our prior comparisons of absolute total CVD and MACE to the background rates in the corresponding subset of EDC data stratified by HbA_{1c} trajectory group. Rate ratios and exact 95% CIs were calculated using OpenEpi calculators (26).

Data and Resource Availability

Data and associated documentation are available under a data-sharing agreement in accordance with University of Pittsburgh and Institutional Review Board policies and regulations.

RESULTS

Of the 658 EDC participants examined at study baseline, 536 were free of total CVD at baseline and had two or more HbA_{1c} measurements over follow-up and were thus eligible for the total CVD analysis (Supplementary Fig. 1A). For MACE, 567 were eligible (Supplementary Fig. 1B). Over 30 years, 47.4% developed total CVD ($n = 253$ incident cases) and 31.0% developed MACE ($n = 176$). The median number of HbA_{1c} measures per participant for both outcomes was six (interquartile range 4–7).

HbA_{1c} Trajectories for Total CVD Risk Supplementary Table 1 shows BIC for each number of trajectories. Though models with three and four trajectories had a similar BIC to the two-trajectory

model, each of those models had a small group comprising 3% of the cohort. Thus, for total CVD, the model with two HbA_{1c} trajectories was selected as having the best fit. The low HbA_{1c} trajectory group began with a mean HbA_{1c} of 8.4% (68 mmol/mol), improving to 7.7% (61 mmol/mol) over follow-up and comprised 76% of the cohort ($n = 410$); 38% ($n = 156$) developed CVD by 30 years. The high HbA_{1c} trajectory group, 24% of the cohort ($n = 126$), maintained a mean HbA_{1c} $\sim 10\%$ (86 mmol/mol) over follow-up; 77% ($n = 97$) developed CVD by 30 years. Neither trajectory significantly deviated from linearity. Plots of mean HbA_{1c} by trajectory over time and the corresponding CVD-free survival curves from JLCMM are shown in Fig. 1. After adjustment for baseline covariates, high HbA_{1c} was associated with threefold increased risk of CVD (hazard ratio [HR] 3.07 [95% CI 1.72, 5.47]; $P = 0.0001$) compared with low HbA_{1c}.

Risk Factors for CVD by HbA_{1c} Trajectory

Baseline characteristics by HbA_{1c} trajectory group for total CVD are shown in Supplementary Table 2. Age, diabetes duration, BMI, history of hypoglycemia requiring assistance, family history of MI, and lipid and BP medication and aspirin use were similar in both groups. The high HbA_{1c} group comprised a smaller proportion of women, had lower insulin sensitivity (i.e., eGDR), had higher non-HDLc, triglycerides, systolic and diastolic BP, white blood cell count, AER, and eGFR and lower HDLc, and a greater proportion were current smokers.

Baseline characteristics and associations with CVD within each HbA_{1c} trajectory group separately are shown in Table 1. While absolute levels of risk factors were generally worse in the high HbA_{1c} group, their associations with CVD risk were similar to the low HbA_{1c} group. Exceptions were that in the high HbA_{1c} group, the association between CVD and insulin dose was stronger compared with the low HbA_{1c} group, while the association with triglycerides was weaker. Additionally, within the low HbA_{1c} group, higher HbA_{1c} was associated with slightly lower CVD risk, though this association only reached marginal statistical significance ($P =$

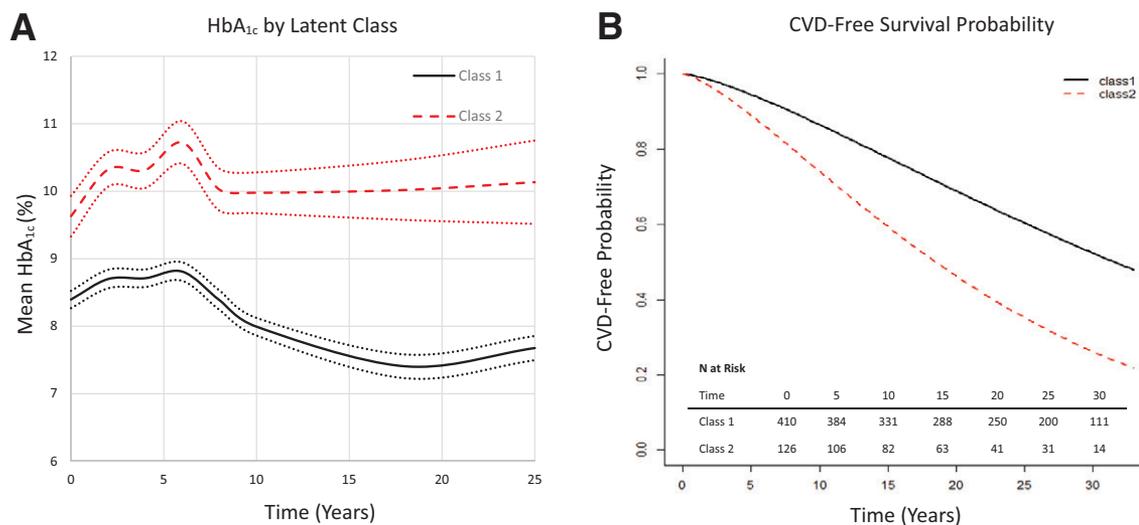


Figure 1—HbA_{1c} trajectories (A) and corresponding 30-year total CVD survival curves (B) from JLCMM.

0.046). Finally, a family history of MI was associated with higher CVD risk in the low HbA_{1c} group only.

In the final multivariable baseline risk factor model for those with low HbA_{1c}, longer diabetes duration, lower HbA_{1c}, and higher non-HDLc, systolic BP, BP medication use, white blood cell count, and AER were associated with increased CVD risk (Supplementary Table 3). For high HbA_{1c}, longer diabetes duration, BP medication use, and higher AER were associated with CVD risk. Two alternative models, 1) offering a hypertension indicator variable instead of individual BP variables and 2) offering eGDR in place of its individual components, were also fit. Results were similar, but the primary models offering the individual components had the best fit (i.e., lowest Akaike information criterion) (Supplementary Table 3).

Descriptive statistics for most recent risk factors and univariate associations between time-varying most recent risk factors and CVD by HbA_{1c} trajectory group are shown in Supplementary Table 4. In multivariable models offering time-varying risk factors (Supplementary Table 5), longer diabetes duration, BP medication use, higher white blood cell count, and lower eGFR were associated with increased CVD risk in both HbA_{1c} trajectory groups. Additionally, in the low HbA_{1c} group only, higher most recent systolic BP, higher triglycerides, and current smoking were also associated with CVD risk.

Final models were fit, offering the fixed baseline and time-varying most recent risk factors that were retained in the final models above (Table 2). BP-lowering medication use and higher white blood cell count were similarly associated with increased CVD risk in both trajectories, though at different time points. In the low HbA_{1c} group only, lower baseline HbA_{1c}, higher baseline non-HDLc, lower most recent eGFR, and most recent smoking status were additionally associated with CVD risk, while in the high HbA_{1c} group, higher baseline AER was associated with increased CVD risk.

HbA_{1c} Trajectories for MACE Risk

For MACE, the model with two HbA_{1c} trajectories was also selected as the best fitting model (Supplementary Table 1). The low HbA_{1c} trajectory group comprised 86% ($n = 485$) of the cohort; 24.5% developed MACE over 30 years. The high HbA_{1c} trajectory group comprised 14% ($n = 82$) of the cohort; 69.5% developed MACE. Plots of the estimated HbA_{1c} trajectories and the corresponding MACE-free survival curves from JLCMM are shown in Supplementary Fig. 2. After adjustment for baseline covariates, high HbA_{1c} trajectory was associated with a fivefold increased hazard of MACE (HR 5.10 [95% CI 2.94, 8.86]; $P < 0.0001$) compared with low HbA_{1c}.

Risk Factors for MACE by HbA_{1c} Trajectory

Baseline characteristics and associations with MACE by HbA_{1c} trajectory group are shown in Supplementary Table 6. Lower insulin dose was strongly associated with MACE in those with high HbA_{1c} only, while triglycerides, current smoking, and family history of MI were associated with MACE only in the low HbA_{1c} group. In the final baseline multivariable models (Supplementary Table 7), diabetes duration was the only shared risk factor for MACE across both HbA_{1c} groups. In those with low HbA_{1c}, higher non-HDLc, higher systolic BP, BP medication use, and higher white blood cell count were associated with increased MACE risk, while in those with high HbA_{1c}, higher AER, lower eGFR, and ever smoking were associated with MACE. Final multivariable models of time-varying risk factors for MACE are shown in Supplementary Table 8.

In models for MACE (Table 3) offering both the fixed baseline and time-varying most recent risk factors, diabetes duration was again the only shared risk factor across both HbA_{1c} groups. In the low HbA_{1c} group, higher baseline non-HDLc, higher baseline systolic BP, most recent BP medication use, and higher baseline white blood cell count were associated with MACE risk, while in the high HbA_{1c} group, higher baseline AER, lower baseline and most recent eGFR, and most recent smoking were associated with MACE.

Table 1—Baseline characteristics by 30-year total CVD incidence status and HbA_{1c} trajectory

	Low HbA _{1c}			High HbA _{1c}			
	CVD incidence (n = 156)	No CVD (n = 254)	HR (95% CI)	CVD incidence (n = 97)	No CVD (n = 29)	HR (95% CI)	P value
Age, years	31.4 (6.7)	24.6 (6.9)	1.115 (1.091, 1.140)	28.0 (7.5)	21.8 (7.9)	1.123 (1.090, 1.158)	<0.0001
T1D duration, years	23.0 (6.9)	16.5 (6.3)	1.115 (1.091, 1.140)	19.8 (8.0)	13.4 (6.8)	1.125 (1.092, 1.158)	<0.0001
Female sex, %	54.5 (85)	51.0 (132)	1.010 (0.737, 1.385)	40.2 (39)	34.5 (10)	1.062 (0.705, 1.599)	0.7742
HbA _{1c} , %	8.2 (1.2)	8.5 (1.4)	0.878 (0.773, 0.998)	9.5 (1.5)	10.0 (2.1)	1.012 (0.898, 1.141)	0.8395
HbA _{1c} , mmol/mol	66.0 (12.9)	69.7 (15.0)	0.988 (0.977, 1.000)	80.6 (16.9)	85.7 (22.8)	1.001 (0.990, 1.012)	0.8395
BMI, kg/m ²	24.1 (3.2)	23.2 (3.2)	1.084 (1.033, 1.139)	23.9 (3.3)	23.0 (3.8)	1.062 (1.000, 1.127)	0.0481
Insulin dose, units/kg	0.74 (0.24)	0.81 (0.23)	0.360 (0.167, 0.773)	0.82 (0.26)	0.90 (0.30)	0.132 (0.049, 0.359)	<0.0001
≥3 insulin injections/day or pump, %	11.2 (17/152)	7.0 (17/242)	1.404 (0.847, 2.327)	5.2 (5)	0 (0)	1.127 (0.456, 2.783)	0.7958
Hypoglycemia requiring assistance, %	46.7 (71)	37.8 (91)	1.295 (0.941, 1.781)	46.8 (44)	25.0 (7)	1.350 (0.892, 2.045)	0.1560
eGDR, mg/kg/min	7.9 (1.9)	8.5 (1.5)	0.787 (0.719, 0.861)	6.8 (1.9)	7.1 (1.8)	0.829 (0.742, 0.925)	0.0008
Non-HDLc, mg/dL	144.4 (42.6)	120.3 (32.1)	1.013 (1.009, 1.016)	153.1 (39.1)	135.2 (48.3)	1.009 (1.005, 1.014)	<0.0001
HDLc, mg/dL	53.8 (11.8)	55.8 (12.6)	0.986 (0.973, 1.000)	51.8 (11.7)	53.1 (12.8)	0.985 (0.968, 1.003)	0.0939
Triglycerides, mg/dL	88 (64, 127)	71 (54, 95)	2.128 (1.613, 2.807)*	101 (72, 160)	84.5 (68, 135)	1.465 (1.029, 2.086)*	0.0339
Lipid-lowering medications, %	1.3 (2)	0 (0)	19.783 (4.766, 82.124)	1.0 (1)	0 (0)	0.799 (0.111, 5.757)	0.8236
Systolic BP, mmHg	116.0 (15.5)	108.4 (11.8)	1.036 (1.026, 1.046)	117.1 (15.8)	109.3 (9.7)	1.038 (1.023, 1.052)	<0.0001
Diastolic BP, mmHg	74.4 (12.3)	70.0 (9.2)	1.043 (1.027, 1.059)	74.3 (11.1)	71.8 (8.7)	1.042 (1.022, 1.063)	<0.0001
BP-lowering medications, %	13.8% (21)	3.7% (9)	3.678 (2.311, 5.854)	12.5% (12)	3.6% (1)	7.566 (3.804, 15.049)	<0.0001
White blood cell count, × 10 ⁹ /L	6.8 (1.9)	6.1 (1.6)	1.253 (1.157, 1.358)	7.2 (2.2)	6.6 (1.9)	1.118 (1.024, 1.219)	0.0123
AER, µg/min	30.9 (8.5, 306.8)	10.1 (6.1, 25.7)	1.316 (1.222, 1.418)*	24.3 (9.2, 337)	20.2 (9.0, 60)	1.363 (1.215, 1.533)*	<0.0001
eGFR, mL/min/1.73 m ²	95.4 (30.0)	108.2 (26.7)	0.985 (0.980, 0.990)	108.3 (29.2)	117.8 (34.6)	0.989 (0.983, 0.995)	0.0005
Ever smoker, %	46.2 (72)	26.4 (67)	2.103 (1.534, 2.882)	45.4 (44)	34.5 (10)	1.992 (1.318, 3.010)	0.0011
Current smoker, %	25.0 (39)	14.6 (37)	1.782 (1.239, 2.562)	35.1 (34)	25.6 (8)	1.637 (1.070, 2.505)	0.0230
Family history of MI, %	26.4 (39/148)	11.3 (27/238)	2.193 (1.517, 3.171)	16.0 (15)	18 (5)	1.565 (0.893, 2.743)	0.1179

Values in boldface indicate significance <0.05. *Natural log transformed prior to modeling. Data are mean (SD), median (p25, p75), % (n), or % (n in category/total n with available data).

Table 2—Final multivariable models for total CVD by HbA_{1c} trajectory, offering both fixed baseline and time-varying risk factors

Variables	Type	Low HbA _{1c}		High HbA _{1c}	
		HR (95% CI)	P value	HR (95% CI)	P value
T1D duration	B	1.100 (1.074, 1.127)	<0.0001	1.126 (1.090, 1.164)	<0.0001
HbA _{1c}	B	0.848 (0.736, 0.977)	0.0227	Not offered	—
Non-HDLc	B	1.009 (1.005, 1.014)	<0.0001	Not offered	—
BP-lowering medication use	B	Not retained	—	3.030 (1.468, 6.254)	0.0027
	MR	1.528 (1.070, 2.183)	0.0198	1.931 (1.254, 2.974)	0.0028
White blood cell count	B	1.110 (1.014, 1.215)	0.0239	Not offered	—
	MR	Not retained	—	1.143 (1.026, 1.274)	0.0150
ln(AER)	B	Not offered	—	1.151 (1.013, 1.309)	0.0314
eGFR	MR	0.989 (0.983, 0.995)	0.0005	Not retained	—
Current smoking	MR	1.639 (1.045, 2.569)	0.0313	Not offered	—

Models were offered the variables that were significant in the final fixed baseline and final time-varying models. B indicates fixed baseline variable, and MR is time-varying, most recent variable. Low HbA_{1c} model offered: baseline diabetes duration, HbA_{1c}, non-HDLc, systolic BP, BP-lowering medication use, white blood cell count, and AER; and time-varying systolic BP, BP medication use, white blood cell count, eGFR, current smoking, and triglycerides. High HbA_{1c} model offered: baseline diabetes duration, BP medication use, and AER; and time-varying BP medication use, white blood cell count, and eGFR.

EDC <45-Year-Old Subcohort Comparison With the Background Population

Rate ratios and 95% CIs compared with the background Allegheny County population for each HbA_{1c} trajectory are shown in Supplementary Fig. 3. For total CVD, low HbA_{1c} had sixfold increased risk (95% CI 3.5, 12.0), while high HbA_{1c} had 19-fold increased risk (95% CI 7.9, 45.5) over background. For MACE, risk was not significantly increased in low HbA_{1c} (rate ratio 1.7 [95% CI 0.4, 7.0]),

while high HbA_{1c} had 25.5-fold increased risk (95% CI 14.9, 35.9).

CONCLUSIONS

We have identified two long-term HbA_{1c} trajectories associated with differential risk of CVD in the Pittsburgh EDC childhood-onset type 1 diabetes cohort, as well as important CVD risk factor differences by HbA_{1c} trajectory group. In those with low HbA_{1c}, non-HDLc, eGFR, and smoking were strongly

associated with total CVD risk, while in those with high HbA_{1c}, BP medication use, likely acting as a marker of hypertension severity, and AER predominated. For MACE, no independent risk factors overlapped across the HbA_{1c} groups, with non-HDLc, systolic BP, and white blood cell count associated with MACE in low HbA_{1c} and kidney disease markers, AER and eGFR, and smoking associated with MACE in high HbA_{1c}. Recent findings from DCCT/EDIC have suggested that traditional CVD risk

Table 3—Final multivariable models for MACE by HbA_{1c} trajectory, offering both fixed baseline and time-varying risk factors

Variables	Type	Low HbA _{1c}		High HbA _{1c}	
		HR (95% CI)	P value	HR (95% CI)	P value
T1D duration	B	1.083 (1.054, 1.113)	<0.0001	1.124 (1.076, 1.175)	<0.0001
Non-HDLc	B	1.005 (1.001, 1.010)	0.0179	Not offered	—
Systolic BP	B	1.020 (1.007, 1.033)	0.0024	Not offered	—
BP-lowering medication use	MR	1.709 (1.135, 2.575)	0.0103	Not offered	—
White blood cell count	B	1.247 (1.137, 1.367)	<0.0001	Not offered	—
ln(AER)	B	Not offered	—	1.439 (1.227, 1.689)	<0.0001
eGFR	B	Not offered	—	0.988 (0.979, 0.997)	0.0118
	MR	Not retained	—	0.990 (0.982, 0.998)	0.0112
Current smoking	MR	Not offered	—	4.054 (1.911, 8.600)	0.0003

Models were offered the variables that were significant in the final fixed baseline and final time-varying models. B indicates fixed baseline variable, and MR is time-varying, most recent variable. Low HbA_{1c} model offered: baseline diabetes duration, non-HDLc, systolic BP, BP medication use, and white blood cell count; and time-varying diastolic BP, BP medication use, white blood cell count, and eGFR. High HbA_{1c} model offered: baseline diabetes duration, AER, eGFR, and ever smoking; and time-varying BMI, eGFR, and current smoking.

factors moderate the effect of HbA_{1c} on CVD risk (27). Our current observations in EDC suggest that the inverse may also be true: long-term HbA_{1c} trajectory may modify the effect of other risk factors on CVD risk. Most notably, our results support prior evidence of distinct nonalbuminuric and albuminuric kidney disease phenotypes in type 1 diabetes (28,29) and suggest that they may be related to glycemic control.

We have previously estimated the association among longitudinal, continuous HbA_{1c}, and CVD overall, in which each one-unit HbA_{1c} increase was associated with HR of 1.26 (10). The difference in HbA_{1c} between the two trajectories identified in this study is approximately two units on average over follow-up with HR of 3.1; thus, the increased risk associated with a high trajectory is similar to, but perhaps slightly higher than, expected based on continuous HbA_{1c}. It is important to note that while we have characterized two latent HbA_{1c} trajectories associated with differential CVD risk, we have not identified a specific HbA_{1c} cut point at which increased risk begins. This risk threshold issue warrants a thorough, focused assessment and should be the objective of future research.

We performed a limited comparison with the background population in the EDC subcohort <45 years old between 2010 and 2014, on which we have previously reported (25). As expected, high HbA_{1c} was associated with greatly increased risk of total CVD and MACE. More interestingly, the low HbA_{1c} group had a sixfold increased risk of total CVD, but did not have significantly increased risk of MACE. Indeed, 80% of the incident CVD events observed in low HbA_{1c} were coronary revascularization without prior MI, while the high HbA_{1c} group had only MACE (Supplementary Fig. 3). These findings suggest that CVD is more likely to be identified prior to MACE in those with better glycemic control and underscore the complexities associated with including revascularizations in composite CVD definitions, as we have previously highlighted (30).

We observed a notable difference in the associations between kidney damage (i.e., AER) and function (i.e., eGFR) and CVD risk by HbA_{1c} trajectory. Kidney disease is a robust risk factor for CVD in type 1 diabetes (2,11,31,32), and we

have previously shown AER to be the second strongest risk factor for CVD in the EDC cohort, after diabetes duration (11). Now looking at long-term HbA_{1c} exposure, those with low HbA_{1c}, despite still having suboptimal glycemic control on average, had median AER in the normal/nonalbuminuric range throughout follow-up. Furthermore, AER was not independently associated with total CVD in this low HbA_{1c} group, while it worsened over time and was a strong risk factor for total CVD in the high HbA_{1c} group. In contrast, eGFR declined similarly regardless of HbA_{1c}. For MACE, neither AER nor eGFR was independently associated with risk in low HbA_{1c}, while both were strongly associated with MACE in the high HbA_{1c} group. These findings support prior evidence of distinct albuminuric and nonalbuminuric kidney disease phenotypes in type 1 diabetes (28,29) and suggest that both phenotypes may be associated with total CVD risk, but may have different associations with the more severe CVD manifestations captured by MACE depending on the level of glycemic exposure. More research is warranted to examine that hypothesis directly.

From a clinical perspective, our findings suggest that in patients with poor glycemic control, traditional risk factors, such as cholesterol and smoking, may be overshadowed by HbA_{1c}, thus playing a smaller role in discriminating long-term CVD risk. In patients with chronically elevated HbA_{1c}, there is likely greater direct vascular damage via hyperglycemia itself. The strong association between AER and CVD risk observed in those with high HbA_{1c} may be reflecting the predominance of this vascular damage in the presence of high glycemic exposure. However, in the context of lower glycemic exposure, the importance of traditional CVD risk factors is more apparent. Thus, one clinical message is that while it is important to treat dyslipidemia and high BP in type 1 diabetes regardless of glycemic control (33), it may become increasingly beneficial to focus on these factors in those with relatively low HbA_{1c}.

The observed inverse association between baseline continuous HbA_{1c} and total CVD risk within the low HbA_{1c} trajectory group is intriguing and should be interpreted with caution. First, it is important to consider that the major

contribution of HbA_{1c} to CVD risk has already been accounted for by the trajectories themselves. Second, as mean diabetes duration was 18 years at baseline, earlier glycemic control could not be taken into account. A slightly greater proportion of participants with low HbA_{1c} who developed CVD used three or more insulin injections per day or an insulin pump, raising the possibility that their treatment regimen was intensified prior to study baseline as a result of worsening risk factors, leading to a lower mean HbA_{1c}.

Family history of MI was univariately associated with an increased risk of total CVD and MACE only in those with low HbA_{1c}, suggesting a greater contribution of heritability to CVD risk when glycemic exposure is relatively low. This is consistent with our prior observation that the increased CVD risk conferred by the 2 allele of the *HP* gene is stronger in individuals with lower glycemic exposure (34), suggesting that as glycemic control improves, the genetic susceptibility conferred by *HP* becomes more evident. Both our current and prior observations support the need to consider HbA_{1c} and other clinical risk factors as potential effect modifiers when assessing heritability of complications in type 1 diabetes.

Our study has many strengths. The EDC cohort is a well-characterized, exclusively type 1 diabetes cohort with long-term follow-up, shown to be epidemiologically representative of childhood-onset type 1 diabetes (35,36). The EDC did not exclude participants based on clinical factors at baseline, increasing generalizability. The cohort has been followed for 30 years to ascertain complication incidence and risk factors. CVD events were verified using death certificates and medical records by physician reviewers who were masked to risk factor status. A specific strength of the current analyses is that the JLCMM approach facilitates simultaneous assessment of latent longitudinal risk factor classes and time-to-event data to estimate their relationship without violating Cox regression assumptions.

An inherent limitation of long-term cohort studies is that treatment regimens during the early study period may not represent current therapeutic experiences of more recently diagnosed people with type 1 diabetes. However,

recent data suggest that in the United States, average glycemic control in contemporary youth/young adults with type 1 diabetes remains suboptimal and similar ($HbA_{1c} \sim 8\%$) to that observed in EDC at baseline (37). Additionally, we included time-varying diabetes management factors, lipid and BP medication, and aspirin use variables in our models, accounting for therapeutic changes over time. Another limitation is the potential for “survivor bias,” as prevalent cases of CVD at baseline were excluded. There is also potential for competing risks, particularly death from non-CVD causes. During follow-up, 38 participants died of non-CVD causes prior to developing any CVD (i.e., 13% of noncases). We treated these competing events as censored observations, as Cox regression in the presence of such right censoring due to a competing risk still provides a valid assessment of covariate effects on the CVD cause-specific hazard (38). A further limitation is that the EDC cohort is 98% non-Hispanic White, reflecting the demographics of Allegheny County, Pennsylvania (83% White, 14% Black, and 3% other racial/ethnic groups) and lower incidence of type 1 diabetes among Black patients during the diagnosis period of the cohort. Thus, it is unknown whether these results apply to populations with greater racial/ethnic diversity.

In conclusion, we identified important CVD risk factor differences by HbA_{1c} trajectory group. In particular, eGFR was a stronger risk factor for CVD in those with a low HbA_{1c} trajectory, while AER was a stronger risk factor in those with a high HbA_{1c} trajectory, supporting prior evidence of distinct nonalbuminuric and albuminuric kidney disease phenotypes. More research is needed to determine whether CVD risk is mediated through different pathways depending on degree of long-term glycemic exposure.

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References

- Forrest KY, Becker DJ, Kuller LH, Wolfson SK, Orchard TJ. Are predictors of coronary heart disease and lower-extremity arterial disease in type 1 diabetes the same? A prospective study. *Atherosclerosis* 2000;148:159–169
- Orchard TJ, Olson JC, Erbey JR, et al. Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 diabetes: 10-year follow-up data from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care* 2003;26:1374–1379
- Soedamah-Muthu SS, Chaturvedi N, Toeller M, et al.; EURODIAB Prospective Complications Study Group. Risk factors for coronary heart disease in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study. *Diabetes Care* 2004;27:530–537
- Klein BEK, Klein R, McBride PE, et al. Cardiovascular disease, mortality, and retinal microvascular characteristics in type 1 diabetes: Wisconsin epidemiologic study of diabetic retinopathy. *Arch Intern Med* 2004;164:1917–1924
- Secrest AM, Prince CT, Costacou T, Miller RG, Orchard TJ. Predictors of and survival after incident stroke in type 1 diabetes. *Diab Vasc Dis Res* 2013;10:3–10
- Deckert T, Yokoyama H, Mathiesen E, et al. Cohort study of predictive value of urinary albumin excretion for atherosclerotic vascular disease in patients with insulin dependent diabetes. *BMJ* 1996;312:871–874
- Wadén J, Forsblom C, Thorn LM, Gordin D, Saraheimo M; Finnish Diabetic Nephropathy Study Group. A1C variability predicts incident cardiovascular events, microalbuminuria, and overt diabetic nephropathy in patients with type 1 diabetes. *Diabetes* 2009;58:2649–2655
- Prince CT, Becker DJ, Costacou T, Miller RG, Orchard TJ. Changes in glycaemic control and risk of coronary artery disease in type 1 diabetes mellitus: findings from the Pittsburgh Epidemiology of Diabetes Complications Study (EDC). *Diabetologia* 2007;50:2280–2288
- Nathan DM, Bebu I, Braffett BH, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Risk factors for cardiovascular disease in type 1 diabetes. *Diabetes* 2016;65:1370–1379
- Miller RG, Anderson SJ, Costacou T, Sekikawa A, Orchard TJ. Hemoglobin A1c level and cardiovascular disease incidence in persons with type 1 diabetes: an application of joint modeling of longitudinal and time-to-event data in the Pittsburgh Epidemiology of Diabetes Complications Study. *Am J Epidemiol* 2018;187:1520–1529
- Miller RG, Costacou T, Orchard TJ. Risk factor modeling for cardiovascular disease in type 1 diabetes in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study: a comparison with the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC). *Diabetes* 2019;68:409–419
- Miller RG, Orchard TJ, Onengut-Gumuscu S, Chen W-M, Rich SS, Costacou T. Heterogeneous long-term trajectories of glycaemic control in type 1 diabetes. *Diabet Med* 2021;38:e14545
- Orchard TJ, Dorman JS, Maser RE, et al. Prevalence of complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes* 1990;39:1116–1124
- Diabetes Epidemiology Research International Mortality Study Group. International evaluation of cause-specific mortality and IDDM. *Diabetes Care* 1991;14:55–60
- Bucolo G, David H. Quantitative determination of serum triglycerides by the use of enzymes. *Clin Chem* 1973;19:476–482
- Allain CC, Poon LS, Chan CSG, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. *Clin Chem* 1974;20:470–475
- Warnick GR, Albers JJ. Heparin–Mn²⁺ quantitation of high-density-lipoprotein cholesterol: an ultrafiltration procedure for lipemic samples. *Clin Chem* 1978;24:900–904
- Lipid Research Clinics Program. *Manual of Laboratory Operations, Vol 1: Lipid and Lipoprotein Analysis*. Washington, DC, National Institutes of Health, Department of Health, U.S. Govt. Printing Office, 1974
- The hypertension detection and follow-up program. Hypertension detection and follow-up program cooperative group. *Prev Med (Baltim)* 1976;5:207–215
- Ellis D, Coonrod BA, Dorman JS, Kelsey SF, Becker DJ, Avner ED, et al. Choice of urine sample predictive of microalbuminuria in patients with insulin-dependent diabetes mellitus. *Am J Kidney Dis* 1989;13:321–328
- Levey AS, Stevens LA, Schmid CH, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–612
- Williams KV, Erbey JR, Becker D, Arslanian S, Orchard TJ. Can clinical factors estimate insulin resistance in type 1 diabetes? *Diabetes* 2000;49:626–632
- Proust-Lima C, Joly P, Dartigues J, Jacqmin-Gadda H. Joint modelling of multivariate longitudinal outcomes and a time-to-event: a latent class approach. *Comput Stat Data Anal* 2009;53:1142–1154
- Proust-Lima C, Philipps V, Liqueur B. Estimation of extended mixed models using latent classes and latent processes: the R package lamm. *J Stat Softw* 2017;78:1–56
- Miller RG, Mahajan HD, Costacou T, Sekikawa A, Anderson SJ, Orchard TJ. A contemporary estimate of total mortality and cardiovascular disease risk in young adults with type 1 diabetes:

- the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care* 2016;39:2296–2303
26. Dean AG, Sullivan K, Soe M. OpenEpi: Open Source Epidemiologic Statistics for Public Health. 2015. Accessed 7 July 2021. Available from https://openepi.com/Menu/OE_Menu.htm
27. Bebu I, Braffett BH, Orchard TJ, et al. Moderation of the effect of glycemia on the risk of cardiovascular disease in type 1 diabetes: the DCCT/EDIC study. *Diabetes Res Clin Pract* 2021; 171:108591
28. Krolewski AS. Progressive renal decline: the new paradigm of diabetic nephropathy in type 1 diabetes. *Diabetes Care* 2015;38:954–962
29. Penno G, Russo E, Garofolo M, et al. Evidence for two distinct phenotypes of chronic kidney disease in individuals with type 1 diabetes mellitus. *Diabetologia* 2017;60:1102–1113
30. Miller RG, Orchard TJ, Costacou T. Risk factors differ by first manifestation of cardiovascular disease in type 1 diabetes. *Diabetes Res Clin Pract* 2020;163:108141
31. Nathan DM, Cleary PA, Backlund J-YC, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643–2653
32. de Boer IH, Gao X, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Albuminuria changes and cardiovascular and renal outcomes in type 1 diabetes: The DCCT/EDIC study. *Clin J Am Soc Nephrol* 2016;11:1969–1977
33. De Ferranti SD, De Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: A scientific statement from the American Heart Association and American Diabetes Association. *Diabetes Care* 2014;37: 2843–2863.
34. Costacou T, Evans RW, Orchard TJ. Glycaemic control modifies the haptoglobin 2 allele-conferred susceptibility to coronary artery disease in type 1 diabetes. *Diabet Med* 2016; 33:1524–1527
35. Wagener DK, Sacks JM, LaPorte RE, Macgregor JM. The Pittsburgh study of insulin-dependent diabetes mellitus. Risk for diabetes among relatives of IDDM. *Diabetes* 1982;31: 136–144
36. Miller RG, Secrest AM, Sharma RK, Songer TJ, Orchard TJ. Improvements in the life expectancy of type 1 diabetes: the Pittsburgh Epidemiology of Diabetes Complications study cohort. *Diabetes* 2012;61:2987–2992
37. Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D Exchange in 2016–2018. *Diabetes Technol Ther* 2019;21: 66–72
38. Prentice RL, Kalbfleisch JD, Peterson AV Jr, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. *Biometrics* 1978;34:541–554