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)

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In a recent Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study report, mean HbA_{1c} was the strongest predictor of cardiovascular disease (CVD) after age. In DCCT/EDIC, mean diabetes duration was 6 years (median 4) at baseline and those with high blood pressure or cholesterol were excluded. We now replicate these analyses in the Pittsburgh Epidemiology of Diabetes Complications (EDC) prospective cohort study of childhood-onset (at <17 years of age) type 1 diabetes, with similar age (mean 27 years in both studies) but longer diabetes duration (mean 19 years and median 18 years) and no CVD risk factor exclusion at baseline. CVD incidence (CVD death, myocardial infarction (MI), stroke, revascularization, angina, or ischemic electrocardiogram) was associated with diabetes duration, most recent albumin excretion rate (AER), updated mean triglycerides, baseline hypertension, baseline LDL cholesterol, and most recent HbA_{1c}. Major atherosclerotic cardiovascular events (CVD death, MI, or stroke) were associated with diabetes duration, most recent AER, baseline systolic blood pressure, baseline smoking, and updated mean HbA_{1c}. Compared with findings in DCCT/EDIC, traditional risk factors similarly predicted CVD; however AER predominates in EDC and HbA_{1c} in DCCT/EDIC. Thus, the relative impact of HbA_{1c} and kidney disease in type 1 diabetes varies according to diabetes duration.

Despite improvements in treatments, contemporary estimates show that individuals with type 1 diabetes continue to be at a dramatically increased risk of cardiovascular disease (CVD) compared with the background population, particularly at younger ages (1–3). Intriguingly, this increased risk does not seem to be fully accounted for by the hyperglycemia that characterizes type 1 diabetes (4). Similarly, the levels of traditional CVD risk factors, including LDL cholesterol (LDLc), are not generally elevated in type 1 diabetes (5); thus, no single factor has been implicated in this increased CVD risk. Investigators from the Diabetes Control and Complications Trial and its Epidemiology of Diabetes Interventions and Complications follow-up study (DCCT/EDIC) have recently performed a comprehensive examination of risk factors for 27-year incidence of CVD in type 1 diabetes (6). We now report on similar analyses of risk factors for CVD incidence over 25 years of follow-up in the Pittsburgh Epidemiology of Diabetes Complications (EDC) study cohort. The EDC study differs from DCCT/EDIC in several key aspects. First, the EDC cohort is exclusively comprised by subjects with childhood-onset diabetes, and the distributions of age at type 1 diabetes onset in the two studies only overlap by 3 years (adolescents aged 13–16 years). Additionally, while the age distributions themselves are similar (mean age 27 years at baseline in both studies), the mean type 1 diabetes duration at study baseline was 13 years greater in EDC (19 years compared with only 6 years in DCCT/EDIC) (Supplementary Table 1), which enables the examination of the natural history of individuals through longer durations. The DCCT

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also excluded individuals with high blood pressure or cholesterol and with more than minimal retinopathy or albuminuria at baseline (7), so it is unclear whether the findings apply to populations without risk factor or microvascular complication exclusion. Finally, while the observational EDC study does not have randomized groups, we can characterize risk factor exposures in a real-world setting and thus support the generalizability of the DCCT/EDIC findings in a complementary cohort. Therefore, our objective was to comprehensively assess baseline and time-varying risk factors for 25-year total CVD and major atherosclerotic coronary event (MACE) incidence in the Pittsburgh EDC and compare the findings with those of the DCCT/EDIC.

RESEARCH DESIGN AND METHODS

Study Population

The EDC study is a prospective cohort study of childhood-onset (<17 years old) type 1 diabetes. All participants (n = 658) were diagnosed, or seen within 1 year of diagnosis, at Children's Hospital of Pittsburgh between 1950 and 1980. The cohort has previously been described in detail (8,9). In brief, participants have been followed since 1986–1988, initially with biennial examinations for 10 years and thereafter with biennial questionnaires and further examinations at 18- and 25-years postbaseline. Research protocols were approved by the University of Pittsburgh institutional review board, and all participants provided written informed consent.

Cardiovascular Outcomes

EDC participants were followed for 25 years to assess the incidence of total CVD, 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 ≥50%, ischemic electrocardiogram at EDC study visit (Minnesota codes 1.3, 4.1–4.3, 5.1–5.3, 7.1), or EDC physician-diagnosed angina. The secondary outcome, MACE, was defined as the first instance of CVD death, nonfatal MI, and nonfatal stroke. Fatal events were ascertained using medical records, death certificates, autopsy reports, or interview with next of kin and classified according to the Diabetes Epidemiology Research International (DERI) system (10). Nonfatal MI, stroke, coronary revascularization, and blockage were confirmed with medical records.

Risk Factors

Risk factors were assessed at baseline and repeated at 2 , 4 , 6 , 8 , 10 , and 18 years of follow-up. From baseline through 10 years of follow-up, HbA_1 values were converted to DCCT-aligned HbA_{1c} values using a regression equation derived from duplicate assays (DCCT HbA_{1c} = 0.14 + 0.83 [EDC HbA_1]) (11). At the 18-year examination, HbA_{1c} was measured using the DCA 2000 analyzer (Bayer HealthCare LLC, Elkhart, IN) and converted to DCCT-aligned HbA_{1c} by the following equation: DCCT HbA_{1c} = (EDC HbA_{1c} − 1.13)/0.81. From baseline through the 10-year examination, serum total cholesterol and triglycerides were determined enzymatically (12,13) and HDL cholesterol was determined using a modified precipitation technique (14) based on the Lipid Research Clinics method (15). At the 18-year examination, serum lipids were measured using the Cholestech LDX (Cholestech, Hayward, CA). Blood pressure was measured according to the Hypertension Detection and Follow-Up protocol (16) with a random-zero sphygmomanometer, replaced by an aneroid sphygmomanometer at the 18-year exam. Hypertension was defined as blood pressure ≥140/90 mmHg or use of blood pressure–lowering medication. Pulse pressure was calculated as the difference between systolic and diastolic pressures. Pulse rate (bpm) was determined by palpitating the radial pulse for 30 s and multiplying by 2. Serum creatinine was measured using an Ektachem 400 Analyzer (Eastman Kodak Co.). Serum and urinary albumin was measured by immunonephelometry (17). 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. Overt nephropathy was defined as AER >200 μg/min in at least two of the three timed urine samples. Estimated glomerular filtration rate (eGFR) was calculated with the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation (18). 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. Insulin dose was calculated as total insulin units per day divided by body weight (kg). Information on past and current smoking status, alcohol consumption, medications, and first-degree family history of hypertension, MI, diabetes before age 30 years, and diabetes after age 30 years was obtained by self-administered questionnaire. Physical activity was assessed using the Paffenbarger Questionnaire (19), and average total weekly energy expenditure was calculated (kcal/week). Hypoglycemia requiring assistance was defined as reporting at least one hypoglycemic episode in the past 2 years resulting in unconsciousness or hospitalization or a hypoglycemic episode in the past 12 months that was not recognized by the participant (i.e., someone else had to tell or help the participant). Estimated glucose disposal rate (eGDR), a validated measure of insulin sensitivity (20), was calculated as follows: eGDR (mg/kg/min) = 24.395 − (12.971 × waist-to-hip ratio) − (3.388 × hypertension) − (0.601 × HbA_{1c}).

Statistical Analyses

Participants with prevalent CVD (n = 54) or MACE (n = 16) at baseline were excluded from the corresponding analyses. Risk factors were grouped into the following blocks, corresponding with the DCCT/EDIC report (6):

1) Demographic:
   a. Physical (sex, age, weight, BMI)
   b. Behavioral (smoking, alcohol intake, physical activity)
   c. Family history (hypertension, MI, diabetes diagnosed before age 30 years, diabetes diagnosed after age 30 years)

2) Traditional:
   a. Blood pressure (systolic and diastolic blood pressure, pulse pressure, pulse rate)
   b. Medications (ACE inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, lipid lowering)
   c. Lipids (total cholesterol, triglycerides, LDLc, HDL cholesterol)

3) Diabetes-related factors:
   a. History (diabetes duration, insulin dose, eGDR)
   b. Nephropathy (eGFR, AER, overt nephropathy)
   c. Hypoglycemia (hypoglycemia requiring assistance)
   d. Glycemic exposure (HbA_{1c})

Three variable forms were assessed: *1*) fixed baseline level, *2*) time-varying most recent level (i.e., current), and *3*) time-varying updated mean level. Cox models were used to estimate the relative risk associated with a 1-unit increment in the risk factors at three levels of adjustment: *1*) unadjusted/univariable models for each form of each factor individually; *2*) within-block multivariable models, fit using backward selection, minimally adjusted for age and mean HbA_{1c}; and *3*) fully adjusted multivariable models, incorporating variables from all blocks. These fully adjusted models were fit by offering the variables in stages, by block, with the best fitting model including the variables from block one using backward selection fit first and then offering all variables from block two and again performing backward selection. A threshold of $P < 0.05$ was applied to retain each variable in the model. Then, the variables from block three were added to this new model, and backward selection was again performed. This process was repeated until variables from all blocks were incorporated and a final model was selected. At each step, any of the variables retained in prior steps could be dropped from the model if the P value rose >0.05. Alternative models were fit offering eGDR in place of its components (HbA_{1c}, hypertension, and waist-to-hip ratio), and these models were compared with the primary models using the Akaike information criterion (AIC) (17). The same analyses were repeated with time to first MACE as the outcome. Cox analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

In sensitivity analyses, two additional variable selection approaches were used: *1)* starting with all variables having a univariable association with the outcome of $P < 0.10$ and fitting a final model using backward selection and a significance threshold of $P < 0.05$ and *2*) starting with all variables regardless of univariable association and fitting a Cox model with backward selection using a significance threshold of $P < 0.05$.

RESULTS

Univariate Analyses

Baseline Risk Factors

Participant baseline characteristics by total CVD incidence status and the unadjusted hazard ratios (HRs) associated with a 1-unit increment in each factor are shown in Table 1. Of the 604 participants free of CVD at baseline, 236 (39.1%) had an incident CVD event and 162 (25.2%) had an incident MACE during follow-up. Kaplan-Meier survival curves for total CVD and MACE are shown in Fig. 1. Those who went on to develop CVD were more likely to be older; more likely to be smokers; more likely to have lower physical activity energy expenditure; more likely to have a family history of MI and diabetes; and more likely to have higher systolic and diastolic blood pressures, higher pulse pressure and pulse rate, higher total cholesterol, higher LDLc, higher non-HDL cholesterol, higher triglycerides, lower HDL cholesterol, longer diabetes duration, higher AER, and higher HbA_{1c}. The proportions developing CVD were similar by sex (40% men vs. 38% women, $P = 0.59$). Men who went on to develop CVD were more likely to have higher weight and BMI, while there were no differences in weight or BMI by CVD incidence in women.

Time-Varying Risk Factors

The unadjusted HRs for a 1-unit increment in each time-varying most recent (i.e., current) or updated mean risk factor are presented in Table 2. Most recent older age, higher BMI (men only), smoking, less physical activity, higher systolic and diastolic blood pressures, higher pulse pressure, hypertension, higher pulse rate, higher total and LDLc, lower HDL cholesterol (marginally significant), higher triglycerides, lower eGDR, lower eGFR, higher AER, and higher HbA_{1c} were associated with an increased risk of any CVD. Most recent use of ACE inhibitors, β-blockers, calcium channel blockers, and lipid-lowering medications was also associated with an increased risk of CVD in these unadjusted models. The risk associated with updated mean levels of risk factors was similar, with the exception of higher updated mean insulin dose, which was associated with a lower risk of CVD, while most recent insulin dose had no association with risk.

For MACE, the unadjusted associations with the time-varying risk factors were similar, with a few exceptions. BMI was not associated with risk of MACE. Both most recent and ever hypertension status and triglycerides were somewhat more strongly associated with MACE than with any CVD. Most recent use of lipid-lowering medications and mean insulin dose were not associated with MACE. While the association between most recent AER and MACE (HR 1.5) was similar to the association between AER and

Table 1—Baseline characteristics of EDC participants by 25-tear total CVD incidence status

	Total CVD incidence status				
	No (n = 368)	Yes (n = 236)	HR†	95% CI	P
Demographic					
Physical					
Male sex	49.5 (182)	51.7 (122)	1.139	0.882, 1.471	0.320
Age (years)	24 (20, 29)	32 (26, 36)	1.112	1.092, 1.131	<0.0001
Weight, men (kg)	69 (63, 77)	72 (65, 78)	1.020	1.004, 1.035	0.013
Weight, women (kg)	60 (55, 65)	59 (54, 69)	1.010	0.992, 1.029	0.273
BMI, men (kg/m^2)	23 (21, 25)	24 (22, 26)	1.105	1.041, 1.172	0.001
BMI, women (kg/m^2)	23 (21, 25)	23 (21, 27)	1.047	0.992, 1.104	0.093
Behavioral					
Smoking	17.9 (66)	31.8 (75)	2.018	1.532, 2.657	<0.0001
Alcohol (drinks/week)	0 (0, 2)	0 (0, 2)	1.002	0.980, 1.024	0.893
Activity (kcal expended/week)	1,837 (723, 3,385)	1,232 (560, 2,428)	0.659	0.508, 0.855	0.002
Family history					
Hypertension	36.6 (127)	49.1 (114)	1.071	0.957, 1.198	0.232
MI	10.8 (37)	26.0 (59)	2.079	1.544, 2.799	<0.0001
Diabetes before age 30 years	5.0 (17)	7.9 (18)	1.564	0.965, 2.533	0.069
Diabetes after age 30 years	7.6 (26)	12.3 (28)	1.563	1.051, 2.325	0.027
Traditional					
Blood pressure					
Systolic (mmHg)	108 (101, 115)	114 (108, 124)	1.039	1.031, 1.047	<0.0001
Diastolic (mmHg)	70 (65, 76)	74 (67, 83)	1.047	1.034, 1.059	<0.0001
Pulse pressure (mmHg)	38 (32, 44)	41 (36, 49)	1.035	1.023, 1.048	<0.0001
Pulse rate (bpm)	78 (72, 84)	80 (72, 84)	1.020	1.007, 1.033	0.003
Lipids					
Total cholesterol (mg/dL)	174 (156, 199)	195 (175, 227)	1.011	1.008, 1.014	<0.0001
Triglycerides (mg/dL)	75 (56, 102)	95 (71, 143)	1.003	1.002, 1.004	<0.0001
HDL cholesterol (mg/dL)	53 (47, 62)	51 (43, 60)	0.982	0.971, 0.994	0.003
Non-HDL cholesterol (mg/dL)	118 (100, 143)	143 (122, 173)	1.012	1.009, 1.014	<0.0001
LDLc (mg/dL)	103 (87, 122)	123 (104, 146)	1.014	1.011, 1.018	<0.0001
Diabetes related					
History: duration of diabetes (months)	192 (132, 252)	288 (204, 348)	1.009	1.007, 1.010	<0.0001
Nephropathy: AER (μg/min)‡	11.9 (7.5, 33.1)	44.7 (10.8, 469)	1.371	1.291, 1.456	<0.0001
Glycemia: HbA_{1c}					
%	8.5 (7.7, 9.6)	8.6 (7.7, 9.7)	1.039	0.953, 1.131	0.386
mmol/mol	69 (61, 81)	70 (61, 83)			

Data are median (interquartile range) or % (n) unless otherwise indicated. †Per-unit increment. ‡Natural log transformed before modeling.

CVD (HR 1.4), a history of ever having overt nephropathy was more strongly associated with MACE (HR 4.9 vs. 3.6 for any CVD).

Multivariable Analyses

Within-Block Multivariable Models

HRs from the within-block multivariable models, after adjustment for age and mean HbA_{1c}, are presented in Table 3. Within the demographic variable block, higher baseline BMI and baseline smoking were associated with increased risk of any CVD, while higher physical activity was associated with lower risk, after adjustment. Only baseline BMI and smoking remained associated with MACE after adjustment.

Within the traditional variable block, most recent systolic blood pressure, baseline hypertension, most recent ACE inhibitor use, mean triglycerides, and baseline LDLc were associated with increased risk of any CVD, while most recent lipid-lowering medication use was protective, after adjustment. For MACE, mean systolic blood pressure, most recent hypertension, and mean triglycerides were associated with increased risk.

In a model offering diabetes-related factors, longer diabetes duration, lower most recent eGFR, higher most recent AER, and higher most recent HbA_{1c} were associated with increased risk of any CVD. In consideration of eGDR instead of HbA_{1c}, most recent eGDR was associated with a lower risk of any CVD. Otherwise, this alternative model was nearly identical to the primary model with HbA_{1c} but had a better fit as assessed by AIC (AIC = 2,384.4 vs. 2,392.9 for the model with HbA_{1c}). The difference between the two AICs was Δ = 8.5, which does not provide support for the model with HbA_{1c} being a better approximation of the data than the model with eGDR (21). The primary model for MACE was similar to that for any CVD, except that mean HbA_{1c} was retained instead of most recent HbA_{1c} and both it and AER were slightly more strongly associated with MACE than with any CVD. In the model considering eGDR, which had a worse fit than the primary

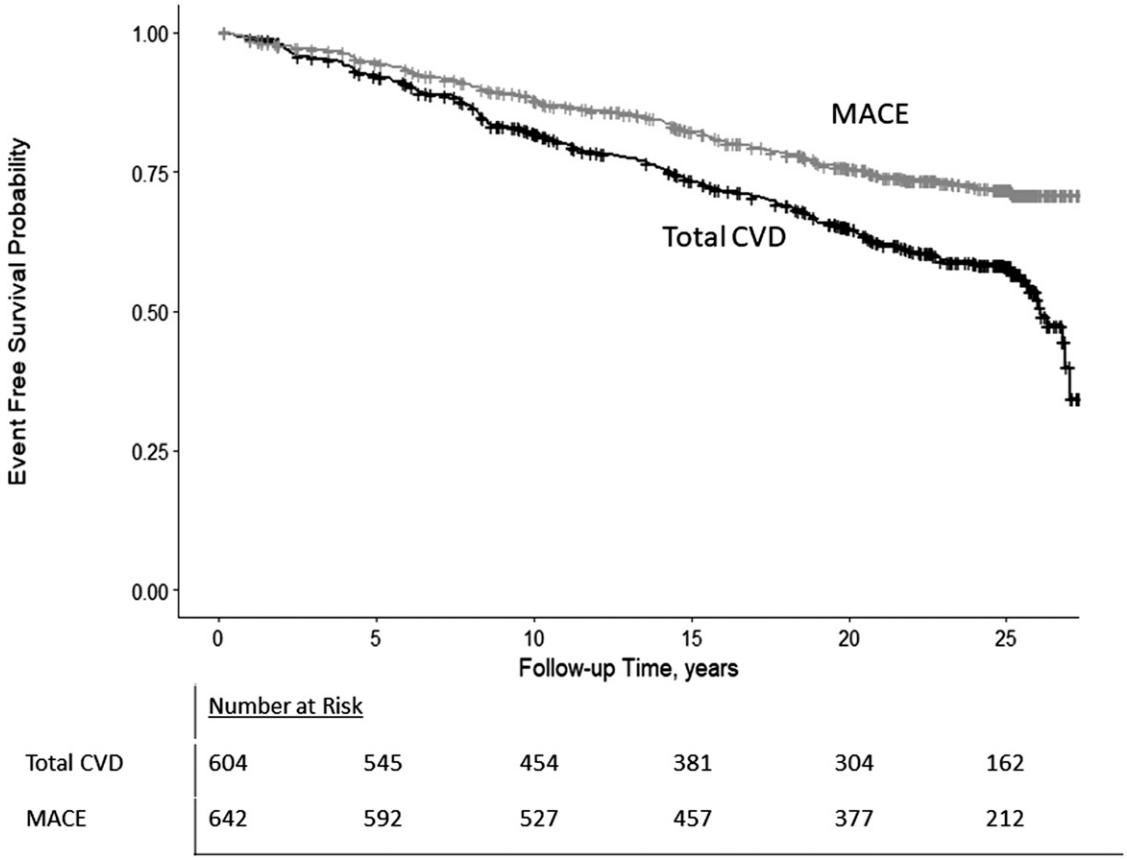

Figure 1—Kaplan-Meier survival curves for total CVD and MACE.

model, higher most recent eGDR was protective against MACE, but eGFR was not retained as it had been for any CVD.

Fully Adjusted Final Multivariable Models

The final multivariable models, accounting for variables in all blocks, are presented in Table 4. For total CVD, baseline diabetes duration, most recent AER, mean triglycerides, baseline hypertension, baseline LDLc, and most recent HbA_{1c} were associated with risk of an event. In the alternative model, higher current eGDR was protective. Otherwise, the same risk factors were retained in the model considering eGDR as in the primary model, with very similar model fit. In the primary model for MACE, baseline diabetes duration, most recent AER, baseline systolic blood pressure, baseline smoking, and mean HbA_{1c} were associated with increased risk. In the model considering eGDR for MACE, in addition to diabetes duration, most recent eGDR, most recent AER, and mean triglyceride level were retained, while smoking was not. For MACE, the primary model with HbA_{1c} had better fit (AIC 1,725.0) than the alternative model with eGDR (AIC 1,741.6).

For both total CVD and MACE, the two approaches used in sensitivity analyses both resulted in the same final models, shown in Table 4.

DISCUSSION

As expected, traditional CVD risk factors, including blood pressure/hypertension and lipids, are strongly associated with total CVD and MACE incidence. Mean HbA_{1c} was also a contributor to total CVD and MACE risk, though it was relatively weaker than other independent risk factors, except for LDLc for total CVD. In alternative models, eGDR, a derived measure of insulin sensitivity (20), was more strongly related to total CVD than even LDLc or eGFR. However, the model with eGDR had a poorer fit for MACE than the primary model offering HbA_{1c}, suggesting that insulin sensitivity may be a better predictor of softer CVD end points in type 1 diabetes.

Our results show both similarities and important differences compared with those recently reported by DCCT/EDIC (6). In EDC, 39% developed total CVD and 27% developed MACE, over 25 years of follow-up, compared with 13 and 6%, respectively, in DCCT/EDIC over 27 years. Much of this difference is likely driven by the differing diabetes durations of the two studies, with EDC having mean duration of 19 years (median 18 years) vs. 6 years (median 4 years) in DCCT/EDIC. In the final multivariable models for total CVD, diabetes duration, triglycerides, and LDLc predicted CVD similarly in both studies. However, a key difference was that mean HbA_{1c} was a much stronger predictor of CVD in DCCT/EDIC than in EDC. Meanwhile,

Table 2—Univariate associations between time-dependent risk factors and incidence of CVD

		Any CVD (236 events)			MACE (162 events)		
	Type*	HR†	95% CI	*P*	HR†	95% CI	*P*
Demographic							
Physical							
Age (years)	C	1.103	1.084, 1.122	<0.0001	1.097	1.075, 1.119	<0.0001
Weight, men (kg)	C	1.007	0.992, 1.022	0.384	0.986	0.968, 1.004	0.115
Weight, women (kg)	C	1.000	0.984, 1.016	0.99	0.987	0.967, 1.008	0.211
Mean BMI (kg/m^2)	M	1.055	1.014, 1.098	0.0080	1.022	0.974, 1.073	0.370
BMI, men (kg/m^2)	C	1.051	0.997, 1.107	0.063	0.957	0.900, 1.019	0.168
BMI, women (kg/m^2)	C	1.011	0.968, 1.056	0.616	0.994	0.945, 1.045	0.807
Behavioral							
Smoking (yes vs. no)	C	1.500	1.106, 2.034	0.009	1.537	1.065, 2.216	0.022
Alcohol (occasional/regular vs. none)	C	0.883	0.676, 1.153	0.359	0.733	0.534, 1.008	0.056
Activity (≥1,512 kcal/week)	C	0.570	0.431, 0.754	<0.0001	0.535	0.379, 0.756	0.0004
Traditional							
Blood pressure							
Systolic (mmHg)	C	1.039	1.032, 1.046	<0.0001	1.032	1.025, 1.038	<0.0001
Mean systolic (mmHg)	M	1.051	1.043, 1.060	<0.0001	1.044	1.036, 1.051	<0.0001
Diastolic (mmHg)	C	1.037	1.025, 1.049	<0.0001	1.035	1.023, 1.048	<0.0001
Mean diastolic (mmHg)	M	1.055	1.041, 1.070	<0.0001	1.062	1.046, 1.078	<0.0001
Pulse pressure (mmHg)	C	1.036	1.028, 1.044	<0.0001	1.030	1.021, 1.040	<0.0001
Hypertension (yes vs. no)	C	3.369	2.601, 4.363	<0.0001	3.720	2.723, 5.081	<0.0001
Any hypertension	E	3.165	2.442, 4.103	<0.0001	3.962	2.873, 5.465	<0.0001
Pulse rate (bpm)	C	1.018	1.007, 1.029	0.002	1.021	1.008, 1.034	0.0014
Mean pulse rate (bpm)	M	1.027	1.013, 1.041	0.0002	1.036	1.019, 1.052	<0.0001
Medications							
ACE inhibitor (yes vs. no)	C	2.015	1.503, 2.700	<0.0001	2.162	1.522, 3.069	<0.0001
ARB (yes vs. no)	C	1.331	0.709, 2.500	0.374	1.382	0.630, 3.030	0.420
β-Blocker (yes vs. no)	C	3.209	2.046, 5.034	<0.0001	3.251	2.062, 5.172	<0.0001
Calcium channel blocker (yes vs. no)	C	2.410	1.571, 3.698	<0.0001	3.580	2.413, 5.314	<0.0001
Lipid lowering (yes vs. no)	C	1.542	1.035, 2.296	0.033	1.322	0.801, 2.181	0.276
Lipids							
Total cholesterol (mg/dL)	C	1.010	1.008, 1.013	<0.0001	1.011	1.008, 1.014	<0.0001
Mean total cholesterol (mg/dL)	M	1.013	1.010, 1.016	<0.0001	1.015	1.011, 1.018	<0.0001
ln(triglycerides) (mg/dL)	C	2.124	1.707, 2.643	<0.0001	2.584	2.015, 3.313	<0.0001
ln(mean triglycerides) (mg/dL)	M	2.507	1.988, 3.159	<0.0001	3.057	2.351, 3.975	<0.0001
HDL cholesterol (mg/dL)	C	0.989	0.978, 1.001	0.064	0.980	0.966, 0.994	0.005
Mean HDL cholesterol (mg/dL)	M	0.987	0.975, 0.999	0.030	0.984	0.970, 0.998	0.029
LDLc (mg/dL)	C	1.011	1.008, 1.014	<0.0001	1.011	1.007, 1.014	<0.0001
Mean LDLc (mg/dL)	M	1.015	1.012, 1.019	<0.0001	1.015	1.011, 1.019	<0.0001
Hyperlipidemia (yes vs. no)	C	2.030	1.562, 2.639	<0.0001	2.275	1.653, 3.132	<0.0001

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Table 2—Continued

		Any CVD (236 events)			MACE (162 events)		
	Type*	HR†	95% CI	*P*	HR†	95% CI	*P*
Diabetes related							
History							
Insulin dose (units/kg/day)	C	0.799	0.458, 1.395	0.430	1.200	0.626, 2.301	0.583
Mean insulin dose (units/kg/day)	M	0.457	0.235, 0.890	0.021	0.627	0.287, 1.368	0.241
eGDR (mg/kg/min)	C	0.750	0.710, 0.792	<0.0001	0.736	0.688, 0.789	<0.0001
Nephropathy							
eGFR (mL/min/1.73 m^2)	C	0.980	0.976, 0.984	<0.0001	0.978	0.974, 0.983	<0.0001
AER (μg/min)	C	1.391	1.316, 1.470	<0.0001	1.462	1.365, 1.566	<0.0001
Overt nephropathy (yes vs. no)	E	3.573	2.767, 4.613	<0.0001	4.913	3.579, 6.745	<0.0001
Hypoglycemia							
Requiring assistance (yes vs. no)	C	1.085	0.839, 1.403	0.534	0.828	0.605, 1.133	0.237
Glycemia							
HbA_{1c} (%)	C	1.145	1.061, 1.236	0.001	1.115	1.041, 1.195	0.002
Mean HbA_{1c} (%)	M	1.170	1.060, 1.292	0.002	1.284	1.144, 1.440	<0.0001

ARB, angiotensin receptor blocker. *Type of time-dependent covariate: C, current/most recent; E, ever during follow-up prior to event or censoring; M, updated mean. †Per-unit increment.

AER was the strongest risk factor for total CVD in EDC, while no renal markers were independent risk factors for CVD in DCCT/EDIC. Additionally, ACE inhibitor use was protective and family history of MI was associated with increased total CVD risk in DCCT/EDIC, but neither were independently associated with CVD in EDC.

Diabetes duration, systolic blood pressure, and smoking predicted MACE with similar effect sizes in both EDC and DCCT/EDIC. However, ACE inhibitors were protective and pulse rate predicted MACE in DCCT/EDIC, but neither was associated with MACE in EDC. Again, HbA_{1c} was associated with MACE in EDC but not as strongly as in DCCT/EDIC. AER was the strongest predictor of MACE after type 1 diabetes duration in EDC, while no renal markers were independently predictive of MACE in DCCT/EDIC—results that likely reflect the delay in developing renal disease in DCCT/EDIC due to intensive insulin therapy.

Traditional risk factors were similarly associated with total CVD and MACE in both EDC and DCCT/EDIC, supporting the generalizability of DCCT/EDIC despite the stricter eligibility requirements. However, there are notable exceptions of weaker HbA_{1c} associations and stronger renal disease/albuminuria associations in EDC compared with DCCT/EDIC. In EDC, 76% of those developing total CVD and 89% of those developing MACE had at least microalbuminuria before their incident event, and 50 and 60% had macroalbuminuria, respectively. Part of the increased role of renal disease in EDC may reflect the fact that, particularly in the primary cohort of DCCT/EDIC, advanced albuminuria was excluded (7). Interestingly, another analysis from DCCT/EDIC focused on the renal disease–CVD link and reported that advanced albuminuria was predictive of CVD in a less fully adjusted model (22). Our current findings suggest that, at longer type 1 diabetes durations, much of the HbA_{1c} effect on CVD risk captured in DCCT/EDIC may be mediated through other factors. Indeed, in an important recent report from DCCT/EDIC, the authors show that the association of HbA_{1c} with 10-year CVD risk seems to be increasingly mediated by other risk factors with increasing age and diabetes duration (23). Other EDC analyses have also provided evidence that renal disease is a particularly important predictor of CVD at longer type 1 diabetes durations (24). Current AER was a stronger predictor of CVD risk compared with baseline or mean AER in the current analyses, supporting the hypothesis that worsening AER with increasing type 1 diabetes duration is driving the association between AER and CVD incidence. It is important to note, however, that increased albuminuria may reflect not only renal/glomerular damage but also generalized vascular damage. Previous analyses from the EDC study and others have demonstrated that increased albuminuria accounts for all excess mortality in type 1 diabetes compared with the general population (25,26). Finally, differences in HbA_{1c} measurement between the two studies may at least partially account for the difference in the strength of associations. HbA_{1c} was measured more frequently in

Table 3—HRs for CVD and MACE incidence from multivariable models, with each variable block modeled separately

	Any CVD				MACE			
	Type*	HR†	95% CI	*P*	Type*	HR†	95% CI	*P*
Demographic								
BMI (kg/m^2)	B	1.06	1.01, 1.10	0.01	B	1.07	1.02, 1.13	0.01
Smoking (yes vs. no)	B	1.75	1.30, 2.37	0.0003	B	1.92	1.34, 2.73	0.0003
Activity (≥1,512 kcal/week)	C	0.73	0.54, 0.97	0.03	nr	—	—	—
Traditional								
Systolic (mmHg)	C	1.01	1.005, 1.015	0.002	M	1.02	1.002, 1.03	0.02
Hypertension (yes vs. no)	B	2.04	1.43, 2.91	<0.0001	C	1.85	1.20, 2.86	0.005
Lipid-lowering med (yes vs. no)	C	0.62	0.40, 0.97	0.03	nr	—	—	—
ACE inhibitors (yes vs. no)	C	1.40	1.03, 1.92	0.03	nr	—	—	—
Mean ln(Trigs) (mg/dL)	M	2.13	1.54, 2.94	<0.0001	M	2.74	1.84, 4.07	<0.0001
LDLc (mg/dL)	B	1.006	1.00, 1.01	0.003	nr	—	—	—
Diabetes related								
Primary model: HbA_{1c} used								
Diabetes duration (years)	B	1.07	1.03, 1.11	0.0003	B	1.09	1.07, 1.12	<0.0001
eGFR (mL/min/1.73 m^2)	C	0.99	0.987, 0.997	0.002	C	0.993	0.988, 0.999	0.01
ln(AER) (μg/min)	C	1.28	1.19, 1.38	<0.0001	C	1.33	1.23, 1.436	<0.0001
HbA_{1c} (%)	C	1.16	1.07, 1.26	0.0007	M	1.30	1.15, 1.47	<0.0001
AIC			2,392.9				1,680.8	
Alternative model: eGDR used								
Diabetes duration (months)	B	1.10	1.08, 1.12	<0.0001	B	1.09	1.06, 1.11	<0.0001
eGDR (mg/kg/min)	C	0.86	0.80, 0.91	<0.0001	C	0.88	0.81, 0.96	0.002
eGFR (mL/min/1.73 m^2)	C	0.994	0.989, 0.999	0.01	nr	—	—	—
ln(AER) (μg/min)	C	1.24	1.15, 1.34	<0.0001	C	1.33	1.23, 1.45	<0.0001
AIC			2,384.4				1,700.2	

med, medication. *Type of time-dependent covariate: B, baseline (not time varying); C, current/most recent; E, ever during follow-up prior to event or censoring; M, updated mean; nr, not retained after backward selection; Trigs, triglycerides. †Per-unit increment.

Table 4—Final multivariable models for total CVD and MACE, offering variables from all blocks

	Any CVD					MACE				
	Type*	HR†	95% CI	χ^2	*P*	Type*	HR†	95% CI	χ^2	*P*
Primary model: HbA_{1c} and hypertension used but not eGDR										
Diabetes duration (years)	B	1.102	1.080, 1.124	92.80	<0.0001	B	1.092	1.067, 1.118	55.49	<0.0001
ln(AER) (μg/min)	C	1.252	1.168, 1.341	40.34	<0.0001	C	1.250	1.156, 1.352	31.20	<0.0001
Systolic BP (mmHg)	nr					B	1.022	1.012, 1.032	18.90	<0.0001
ln(triglycerides)	M	1.916	1.385, 2.650	15.42	<0.0001	nr				
Smoking (yes vs. no)	nr					B	1.520	1.074, 2.152	5.58	0.018
Hypertension (yes vs. no)	B	1.961	1.396, 2.753	15.10	0.0001	nr				
LDLc (mg/dL)	B	1.005	1.001, 1.009	5.33	0.021	nr				
HbA_{1c} (%)	C	1.096	1.007, 1.194	4.47	0.035	M	1.184	1.041, 1.348	6.58	0.010
AIC‡			2,270.2					1,725.0		
Alternative model: eGDR used but not its individual components										
Diabetes duration (years)	B	1.099	1.078, 1.121	90.26	<0.0001	B	1.096	1.073, 1.121	67.42	<0.0001
ln(AER) (μg/min)	C	1.196	1.107, 1.293	20.54	<0.0001	C	1.298	1.199, 1.406	41.05	<0.0001
ln(triglycerides) (mg/dL)	M	1.803	1.292, 2.514	12.04	0.0005	M	2.009	1.479, 2.730	19.93	<0.0001
eGDR (mg/kg/min)	C	0.902	0.842, 0.965	8.96	0.003	C	0.921	0.849, 0.999	3.890	0.049
LDLc (mg/dL)	B	1.005	1.001, 1.009	6.39	0.012	nr				
eGFR (mL/min/1.73 m^2)	C	0.995	0.990, 1.000	4.41	0.036	nr				
AIC			2,269.6					1,741.6		

*Type of time-dependent covariate: B, baseline (not time varying); BP, blood pressure; C, current/most recent; E, ever during follow-up prior to event or censoring; M, updated mean; nr, not retained after backward selection. †Per-unit increment.

DCCT/EDIC, with quarterly assessments during DCCT and annual assessments during EDIC. In the EDC study, HbA_{1c} was measured every 2 years during the first 10 years of follow-up and once more at 18 years. This difference in frequency of measurement means that the precision of HbA_{1c} over time is higher in DCCT/EDIC, lending greater power to detect an association. Additionally, in EDC, HbA_{1c} measurements were aligned to DCCT values using a validated regression equation (described in the RESEARCH DESIGN AND METHODS), which also introduces additional variability into the EDC measurements, reducing power to detect associations compared with DCCT/EDIC.

In EDC, eGDR, a calculated measure of insulin sensitivity, was a stronger independent predictor of total CVD than MACE, suggesting that insulin resistance may be more strongly associated with softer CVD end points. Interestingly, for total CVD, the model fit was very similar between the two versions of the final models (i.e., primary models offering the individual components and the alternative models offering eGDR). In the past, baseline eGDR has been found to be a stronger risk factor for coronary artery disease than baseline HbA_{1c} in the EDC study (27). Now, as we examine all CVD and have incorporated time-varying risk factors in the current analyses and longitudinal HbA_{1c} trajectories in other recent analyses (28), HbA_{1c} emerges as an independent, though modest, predictor of CVD incidence.

A worsening glycemic trajectory over time may also be more important in predicting who is at highest risk for CVD events than a single HbA_{1c} measurement (11,28). This finding contrasts with the associations with hypertension and LDLc, where baseline variables were selected as independent risk factors of total CVD, suggesting a more stable association with risk over time. This finding is also consistent with other reports in the general population that have found a stronger association between earlier LDLc exposure and the risk of subsequent coronary artery disease compared with more recent LDLc (29–31).

Our study has many strengths. The EDC is a well-characterized, prospective cohort study with 25 years of follow-up to ascertain CVD incidence and risk factors and the cohort has been shown to be epidemiologically representative of those with childhood-onset type 1 diabetes (8,32). CVD events were verified using death certificates and medical records by reviewers who were masked to risk factor status. Risk factors were assessed prospectively using standardized methods. As an observational study, EDC did not exclude participants based on clinical factors at baseline, increasing generalizability. A further strength of this report is that it replicates a recent analysis from the DCCT/EDIC (6). The similarities of our results to those in that DCCT/EDIC report, as well as another more recent DCCT/EDIC report (23), support the reliability of our models.

The first limitation of these analyses is that the follow-up covers a long period, which may not represent the current therapeutic model. Nonetheless, in a recent contemporary follow-up from EDC, we continue to demonstrate high CVD risks (3). Second, there is the potential for "survivor bias," particularly in the older participants, because prevalent cases of CVD at baseline were excluded. A related issue is the potential problem of competing risks, particularly death from non-CVD causes. During the 25-year follow-up, 44 EDC participants died of non-CVD causes prior to developing any CVD (i.e., 12% of noncases). In our analysis, these competing events are treated as censored observations. Cox regression in the presence of such right censoring due to a competing risk provides a valid assessment of covariate effects on the CVD cause-specific hazard (33). A further limitation is that the cohort is 98% Caucasian, owing to the demographics of Allegheny County, Pennsylvania (<15% African American), and lower incidence of type 1 diabetes among African Americans during the period when the cohort was diagnosed. Thus, it is unknown whether these results apply to more diverse populations with type 1 diabetes.

In conclusion, vascular damage, as measured by most recent AER, was the strongest predictor of both total CVD and MACE, after type 1 diabetes duration, in this observational cohort with long-standing type 1 diabetes. Mean HbA_{1c} was also a significant, but weaker, contributor to both total CVD and MACE risk. These results confirm recent findings from DCCT/EDIC (23) that much of the HbA_{1c} effect on CVD risk is mediated through other factors at longer type 1 diabetes durations, suggesting that, in addition to consideration of good glycemic control, CVD risk should be addressed with a broader risk factor–based approach.

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