Risk Factors for First and Subsequent CVD Events in Type 1 Diabetes: The DCCT/EDIC Study

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OBJECTIVE

The Diabetes Control and Complications Trial (DCCT) and its observational follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) demonstrated the dominant role of glycemia, second only to age, as a risk factor for a first cardiovascular event in type 1 diabetes (T1D). We now investigate the association between established risk factors and the total cardiovascular disease (CVD) burden, including subsequent (i.e., recurrent) events.

RESEARCH DESIGN AND METHODS

CVD events in the 1,441 DCCT/EDIC participants were analyzed separately by type (CVD death, acute myocardial infarction [MI], stroke, silent MI, angina, percutaneous transluminal coronary angioplasty/coronary artery bypass graft [PTCA/CABG], and congestive heart failure [CHF]) or as composite outcomes (CVD or major adverse cardiovascular events [MACE]). Proportional rate models and conditional models assessed associations between risk factors and CVD outcomes.

RESULTS

Over a median follow-up of 29 years, 239 participants had 421 CVD events, and 120 individuals had 149 MACE. Age was the strongest risk factor for acute MI, silent MI, stroke, and PTCA/CABG, while glycemia was the strongest risk factor for CVD death, CHF, and angina, second strongest for acute MI and PTCA/CABG, third strongest for stroke, and not associated with silent MI. HbA_{1c} was the strongest modifiable risk factor for a first CVD event (CVD: HR 1.38 [95% CI 1.21, 1.56] per 1% higher HbA_{1c}; MACE: HR 1.54 [1.30, 1.82]) and also for subsequent CVD events (CVD: incidence ratio [IR] 1.28 [95% CI 1.09, 1.51]; MACE: IR 1.89 [1.36, 2.61]).

CONCLUSIONS

Intensive glycemic management is recommended to lower the risk of initial CVD events in T1D. After a first event, optimal glycemic control may reduce the risk of recurrent CVD events and should be maintained.

Individuals with type 1 diabetes (T1D) have higher risk of cardiovascular disease (CVD) compared with age-matched individuals without diabetes (1–4). While the exact mechanisms remain unclear, the Diabetes Control and Complications Trial (DCCT) and its observational follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) demonstrated that an early period of ~6.5 years of intensive glycemic control significantly reduced the risk of CVD over a mean follow-up of 17 years (5).

Additional comprehensive risk factor analyses in the DCCT/EDIC study have demonstrated that glycemia, as measured by HbA_{1c}, is the strongest modifiable risk

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factor for CVD (6), although other risk factors (systolic blood pressure, lipids, and pulse rate) made major contributions as well, mediating over half of the HbA_{1c} effect in later years (7,8). To date, these analyses were limited to the risk of a first CVD event, without consideration of subsequent CVD events. Little is known about risk factors for recurrent CVD events in T1D, and addressing this gap in knowledge is important to better understand the drivers of the total CVD burden in this vulnerable population.

In this study, we investigate the association between established risk factors and the risk of CVD events, including subsequent (i.e., recurrent) events, to represent the total CVD burden. Both individual CVD events (CVD death, acute myocardial infarction [MI], silent MI, stroke, congestive heart failure [CHF], percutaneous transluminal coronary angioplasty/coronary artery bypass graft [PTCA/CABG], and angina pectoris) and composite events (CVD and major adverse cardiovascular events [MACE]) were considered. The associations between risk factors and CVD were evaluated first for any event and then separately for the first event plus any subsequent events.

RESEARCH DESIGN AND METHODS

The methods of the DCCT and EDIC studies have been previously described in detail (9,10). Briefly, 1,441 participants with T1D were randomized to receive either intensive therapy (INT; $n = 711$), aimed at lowering glycemic levels to as close to the nondiabetic range as safely possible, or conventional therapy (CON; $n = 730$), aimed at maintaining clinical well-being with no prespecified glucose targets. Participants were enrolled into either the primary prevention cohort (1–5 years' diabetes duration, no retinopathy based on stereoscopic fundus photography, and $<$40 mg of albuminuria per 24 h at baseline; $n = 726$) or the secondary intervention cohort (1–15 years' duration of T1D, minimal to moderate nonproliferative retinopathy, and $<$200 mg of albuminuria per 24 h at baseline; $n = 715$). After an average of 6.5 years of follow-up, the DCCT ended in 1993, and all participants were instructed in intensive therapy methods and referred to their primary health care providers for ongoing care. In 1994, 96% of the surviving DCCT cohort enrolled in the EDIC observational study, with 94% of the survivors still actively participating in annual evaluations after ~25 years from the start of EDIC.

Cardiovascular Risk Factors

The results reported in this study are based on data obtained during the entire DCCT/EDIC follow-up for all 1,441 participants. The periodic evaluations (quarterly during DCCT, annually during EDIC) included detailed medical histories, physical examinations (e.g., blood pressure and pulse rate), and the collection of biospecimens (e.g., blood and urine samples). The risk factors considered for this analysis were selected based on our previous analyses of CVD risk factors in this cohort (6,11). HbA_{1c} was measured using high-performance liquid chromatography quarterly during DCCT and annually during EDIC. Fasting lipids (triglycerides and total and HDL cholesterol) were measured centrally, and LDL cholesterol (LDLc) was calculated using the Friedewald equation (9,10). Use of ACE inhibitors (yes/no; only available during EDIC), smoking (yes/no), and family history of MI (yes/no) were self-reported. A risk factor was included in the model as a fixed or baseline covariate (sex and family history of MI), as a time-dependent covariate using the current (most recent) measurement (age, duration of T1D, triglycerides, smoking, and use of ACE inhibitors), or as the updated mean of all follow-up values between DCCT randomization and that particular time point (mean HbA_{1c}, systolic blood pressure [SBP], pulse, and LDLc). The updated means reported account for the different measurement frequencies during DCCT and EDIC with each value weighted by the time interval between measurements.

Cardiovascular Outcomes

Annual medical histories and electrocardiograms were used to ascertain CVD events. All CVD events were adjudicated based on documentation in external medical records by a committee masked to DCCT treatment group and HbA_{1c} levels. The individual CVD events considered were CVD death, nonfatal MI (acute MI), nonfatal stroke, subclinical MI on electrocardiogram (silent MI), angina confirmed by ischemic changes with exercise tolerance testing or by clinically significant obstruction on coronary angiography, revascularization (with angioplasty or coronary artery bypass and PTCA/CABG), and CHF (paroxysmal nocturnal dyspnea, orthopnea, or marked limitation of physical activity caused by heart disease and CHF). Assessment of CHF began in EDIC year 13 (~2007). In addition, two composite CVD events were considered. CVD was defined as the time to the first or subsequent occurrence of any of the individual CVD events defined above, while MACE was a composite CVD event defined as the time to the first or subsequent occurrence of any of CVD death, nonfatal MI, or nonfatal stroke.

The duration of follow-up for each participant was the time from enrollment (initial DCCT randomization) to the last visit prior to 18 May 2017, which represents $>$3 years' greater follow-up than previously reported. All CVD events (including the recurrent events) that occurred prior to that date were included in these analyses.

Statistical Analysis

The number of CVD events (including recurrent events) was reported separately by event type (such as acute MI) or composite outcome (i.e., CVD and MACE), with crude rates calculated as the number of events per 1,000 patient-years at risk. The expected number of CVD events and MACE over time (including recurrent events) per individual are described using mean cumulative event functions (12).

The association between risk factors and the risk of recurrent events can be assessed using Poisson models, multiplicative intensity models, and proportional rate models or conditional models. Poisson models assume a constant background intensity rate over time, which is typically too restrictive. Multiplicative intensity models relax this assumption, generalizing the standard Cox proportional hazards model, with SEs for the effect of covariates obtained from a model-based covariance estimate. Our analyses used proportional rate models and conditional models that extend the multiplicative intensity models by using robust (sandwich) SEs valid under departures from assumptions (12). The conditional models were conducted using gap time (i.e., time since baseline or the previous event in which time is reset to zero every time an individual event occurs).

The z scores from the age- and mean HbA_{1c}–adjusted models were depicted using spider-web plots. Similar proportional rate models then assessed the association between the risk factors and the risk of CVD events and MACE.

Table 1—Number and rate of CVD events separately by event type and the incidence ratios (IRs) for age- and mean HbA_{1c}–adjusted associations between risk factors and individual CVD outcomes in proportional rate models

	CVD death		Acute MI		Silent MI		Stroke		CHF		PTCA/CABG		Angina	
n (rate):*	35 (0.87)		86 (2.15)		73 (1.83)		28 (0.70)		22 (0.55)		181 (4.53)		56 (1.40)	
	IR (LL, UL)	*P* value	IR (LL, UL)	*P* value	IR (LL, UL)	*P* value	IR (LL, UL)	*P* value	IR (LL, UL)	*P* value	IR (LL, UL)	*P* value	IR (LL, UL)	*P* value
Group (INT vs. CON)	1.06 (0.53, 2.15)	0.86	0.87 (0.54, 1.42)	0.59	1.24 (0.78, 1.98)	0.37	1.06 (0.39, 2.88)	0.91	2.60 (0.84, 8.06)	0.10	0.69 (0.44, 1.1)	0.12	0.86 (0.46, 1.62)	0.64
Cohort (SCND vs. PRIM)	1.11 (0.58, 2.14)	0.75	1.86 (1.11, 3.1)	**0.02**	1.11 (0.68, 1.81)	0.68	1.12 (0.46, 2.73)	0.80	1.16 (0.44, 3.03)	0.77	1.38 (0.84, 2.27)	0.20	1.87 (0.97, 3.61)	0.06
Age (per 5 years)**	1.34 (1.1, 1.64)	**<0.01**	1.54 (1.34, 1.77)	**<0.01**	1.43 (1.21, 1.69)	**<0.01**	2.55 (1.67, 3.9)	**<0.01**	2.16 (1.43, 3.27)	**<0.01**	1.53 (1.33, 1.76)	**<0.01**	1.47 (1.18, 1.84)	**<0.01**
Sex (male vs. female)	2.28 (1.15, 4.5)	**0.02**	1.09 (0.68, 1.75)	0.71	0.97 (0.6, 1.57)	0.89	1.05 (0.46, 2.43)	0.91	1.75 (0.63, 4.83)	0.28	1.07 (0.66, 1.74)	0.78	0.64 (0.34, 1.22)	0.18
Mean HbA_{1c}** (per 1%)	2.54 (1.79, 3.61)	**<0.01**	1.79 (1.42, 2.25)	**<0.01**	1.14 (0.91, 1.44)	0.26	1.57 (1.18, 2.1)	**<0.01**	3.15 (1.98, 5.02)	**<0.01**	1.81 (1.46, 2.24)	**<0.01**	1.92 (1.47, 2.52)	**<0.01**
Mean SBP (per 10 mmHg)	2.00 (1.42, 2.82)	**<0.01**	1.46 (1.14, 1.87)	**<0.01**	1.35 (1.02, 1.79)	**0.04**	1.35 (0.89, 2.05)	0.16	2.21 (1.24, 3.92)	**0.01**	1.26 (0.99, 1.61)	0.06	1.26 (0.89, 1.78)	0.19
TRIG (log) (per 10 mg/dL)	2.68 (1.53, 4.70)	**<0.01**	1.84 (1.14, 2.97)	**0.01**	1.97 (1.34, 2.88)	**<0.01**	2.64 (1.64, 4.25)	**<0.01**	3.06 (1.39, 6.74)	**0.01**	1.43 (1, 2.03)	0.05	1.93 (1.12, 3.32)	**0.02**
Mean pulse (per 10 bpm)	1.58 (0.9, 2.79)	0.11	1.55 (1.11, 2.16)	**0.01**	1.30 (0.82, 2.04)	0.26	2.69 (1.2, 6.04)	**0.02**	1.94 (1.07, 3.52)	**0.03**	1.36 (0.9, 2.06)	0.14	2.38 (1.61, 3.52)	**<0.01**
Duration (per 5 years)	1.38 (0.93, 2.04)	0.11	1.53 (1.13, 2.08)	**0.01**	1.08 (0.82, 1.43)	0.59	0.94 (0.54, 1.61)	0.81	1.23 (0.66, 2.28)	0.52	1.40 (1.09, 1.79)	**0.01**	1.86 (1.27, 2.73)	**<0.01**
ACE inhibitor use (yes vs. no)	1.19 (0.57, 2.48)	0.64	0.60 (0.36, 0.99)	0.05	0.72 (0.43, 1.23)	0.23	0.29 (0.12, 0.7)	**0.01**	0.42 (0.16, 1.13)	0.09	1.02 (0.69, 1.49)	0.94	0.86 (0.45, 1.65)	0.65
FAM Hx MI (yes vs. no)	0.92 (0.47, 1.79)	0.80	1.68 (1.05, 2.69)	**0.03**	1.33 (0.82, 2.13)	0.24	1.05 (0.45, 2.46)	0.91	0.69 (0.25, 1.92)	0.48	2.17 (1.38, 3.4)	**<0.01**	2.87 (1.4, 5.89)	**<0.01**
Mean LDLc (per 10 mg/dL)	1.07 (0.91, 1.27)	0.39	1.17 (1.05, 1.3)	**<0.01**	1.06 (0.96, 1.19)	0.26	1.19 (1.01, 1.41)	**0.04**	0.93 (0.73, 1.19)	0.56	1.14 (1.03, 1.25)	**<0.01**	1.01 (0.91, 1.13)	0.85
Smoking (yes vs. no)	3.08 (1.53, 6.22)	**<0.01**	1.59 (0.92, 2.74)	0.09	1.49 (0.85, 2.61)	0.16	1.46 (0.61, 3.49)	0.39	1.75 (0.51, 5.97)	0.37	0.99 (0.62, 1.59)	0.97	1.10 (0.55, 2.19)	0.79

Covariates are listed in the descending order of importance in the multivariable risk factor model for the first of CVD events published previously (6). Treatment group, cohort, sex, and smoking were added to this list. *P* values <0.05 appear in boldface type. bpm, beats per minute; CON, conventional group; FAM Hx MI, family history of MI; INT, intensive group; LL, lower limit for 95% CI; PRIM, primary cohort; SCND, secondary cohort; TRIG, triglycerides; UL, upper limit for 95% CI. **n* is number of events (rate per 1,000 person-years). **Models for age were adjusted only for mean HbA_{1c}, and the models for mean HbA_{1c} were only adjusted for age. All of the other models were adjusted for both age and mean HbA_{1c}.

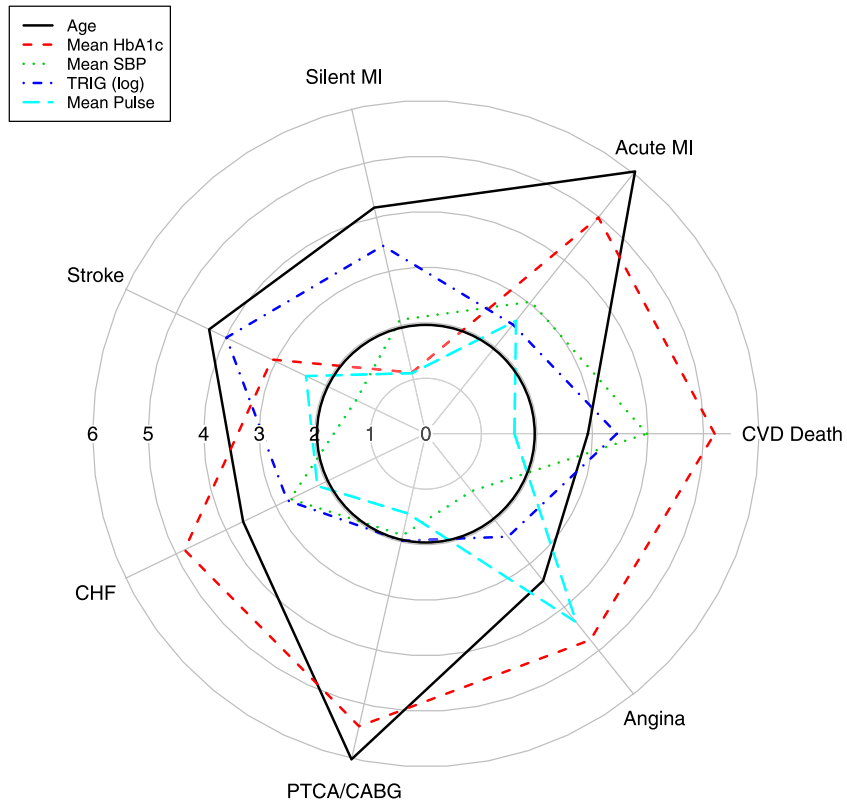

Figure 1—*z* scores for the association between the five most important risk factors (largest *z* values) and individual CVD outcomes in proportional rate models adjusted for age and mean HbA_{1c}. The gray circles describe *z* scores with values between 1 and 6, and risk factors with *z* scores >1.96 in absolute value (outside the black circle) are considered nominally significant. For example, mean HbA_{1c} was the strongest risk factor for CVD death, CHF, and angina ($z = 5.20$, 4.82, and 4.75, respectively), while age was the strongest risk factor for acute MI, silent MI, and PTCA/CABG ($z = 6.04$, 4.18, and 6.02, respectively).

The risk factors for CVD and MACE used in this study included DCCT treatment group, cohort assignment, sex, as well as the final risk factors selected in our previously published models for CVD and MACE, which examined a shorter follow-up period (6), 13 factors in total. Similar to hazard ratios (HRs) in Cox proportional hazards models for time-to-first event outcomes, incidence ratios (IRs) describe relative risks in proportional rate models and conditional models for recurrent events. The HR and IR for a given covariate would be identical in an analysis using only the first observed event (without recurrence) for the same individual.

At the time of non-CVD death, the potential follow-up time(s) for the other CVD events and MACE are right censored (i.e., non-CVD death is a competing risk). Sensitivity analyses assessed whether the results were robust with respect to the effect of non-CVD mortality on the analyses of these cardiovascular events. These analyses considered non-CVD death as a separate stratum in the conditional models (in addition to the two strata, one for the first CVD event and the second for subsequent CVD events) and used frailty terms to account for within-subject correlation between the risk of CVD events and the risk of death (other than CVD death).

CVD events and MACE that occurred on different dates were considered as separate events. Sensitivity analyses investigated the effect of discarding events that occurred within 1 month from a previous event for the same individual.

While the HR/IRs can be made arbitrarily large (or small) by decreasing (or increasing) the measurement units for the covariates, the *z* scores (or equivalently, the *P* values) remain unchanged and better capture the strength of the associations, with higher absolute values of *z* scores corresponding to stronger associations. Positive *z* scores correspond to positive associations (i.e., higher values of the risk factor are associated with higher risk of CVD events), while negative *z* scores correspond to negative associations (i.e., higher values of the risk factor are associated with lower risk of CVD events).

Given the exploratory nature of our analyses, no adjustment was made for multiple testing. *P* values ≤0.05 are cited as nominally significant.

RESULTS

The baseline characteristics of the DCCT/EDIC cohort have been previously described in detail (9,10). Briefly, the mean age was 27 years, 53% of participants were men, average HbA_{1c} was 8.9% (74 mol/mol), and mean diabetes duration was 5.8 years.

Over a median of 29 years at risk, there were 35 CVD deaths, 74 participants had 86 acute MI events, 69 had 73 silent MIs, 24 had 28 strokes, 17 had 22 episodes of CHF, 119 had 181 PTCA/CABGs performed, and 44 individuals had 56 angina events (Table 1). In addition, 239 participants had 421 CVD events (rate of 10.6 events per 1,000 individuals at risk for 1 year), and 120 individuals had 149 MACE (rate of 3.7 events per 1,000 individuals at risk for 1 year).

There were 155 participants with only one CVD event, 49 participants with two CVD events, and 35 participants with three or more CVD events. Likewise, there were 100 participants with only one MACE, 12 with two MACE, and 8 with three or more MACE.

Supplementary Figure 1 shows the mean cumulative functions (number of events) for CVD and MACE. For example, by 25 years after enrollment into the DCCT, participants experienced an average of ~0.18 CVD events or, equivalently, one CVD event for approximately every 5.5 (= 1/0.18) years. Likewise, by 25 years after enrollment into the DCCT, participants experienced ~0.07 MACE or, equivalently, one MACE approximately every 14.3 years.

Association Between Risk Factors and Individual CVD Events

Table 1 describes the associations between risk factors and the risk of each type of CVD event in proportional rate models minimally adjusted for age and mean HbA_{1c}, in which each cell represents an individual model. The *z* scores of the more important covariates in these models are depicted in Fig. 1, in which higher values correspond to stronger associations.

Table 2—Multivariable proportional rate models for all (including recurrent) CVD events and MACE

	Type*	IR (95% CI)	*z* score	*P* value
CVD				
Age (per 5 years)	C	1.51 (1.35, 1.68)	7.325	**<0.001**
Mean HbA_{1c} (per 1% or 11 mmol/mol)	M	1.53 (1.30, 1.80)	5.165	**<0.001**
Mean SBP (per 10 mmHg)	M	1.28 (1.07, 1.53)	2.736	**0.006**
Triglycerides (log) (per 10 mg/dL)	C	1.47 (1.13, 1.92)	2.883	**0.004**
Mean pulse (per 10 bpm)	M	1.41 (1.08, 1.85)	2.530	**0.011**
Duration of T1D (per 5 years)	C	1.25 (1.04, 1.50)	2.388	**0.017**
ACE inhibitor (yes vs. no)	C	0.67 (0.51, 0.88)	−2.821	**0.005**
Family history of MI (yes vs. no)	B	1.48 (1.08, 2.04)	2.449	**0.014**
Mean LDLc (per 10 mg/dL)	M	1.03 (0.96, 1.11)	1.018	0.309
MACE				
Age (per 5 years)	C	1.57 (1.37, 1.79)	6.729	**<0.001**
Mean HbA_{1c} (per 1% or 11 mmol/mol)	M	1.61 (1.32, 1.95)	4.850	**<0.001**
Mean pulse (per 10 bpm)	M	1.46 (1.08, 1.98)	2.479	**0.013**
Triglycerides (log) (per 10 mg/dL)	C	1.69 (1.13, 2.53)	2.571	**0.010**
Mean SBP (per 10 mmHg)	M	1.42 (1.18, 1.71)	3.701	**<0.001**
Smoking (yes vs. no)	C	1.84 (1.23, 2.77)	2.956	**0.003**
Duration of T1D (per 10 years)	C	1.27 (1.00, 1.63)	1.988	**0.047**
ACE inhibitor (yes vs. no)	C	0.53 (0.37, 0.77)	−3.301	**<0.001**
Mean LDLc (per 10 mg/dL)	M	1.06 (0.97, 1.16)	1.433	0.152

P values <0.05 appear in boldface type. bpm, beats per minute. *B, baseline value; C, current (or most recent) value; M, updated mean value (categories C and M correspond to time-dependent covariates assessed or measured at or most recently prior to the particular time point).

Adjusted for age and mean HbA_{1c}, there were no differences in the numbers of events between the INT and CON treatment groups, and there was a nominally significantly higher risk of acute MI (IR 1.86; $P = 0.02$) in the secondary compared with the primary cohort.

Adjusted for mean HbA_{1c}, older age was associated with an increased risk of CVD death ($z = 2.91$), acute MI ($z = 6.04$), silent MI ($z = 4.17$), stroke ($z = 4.33$), CHF ($z = 3.65$), PTCA/CABG ($z = 6.01$), and angina ($z = 3.38$) (Fig. 1). Adjusted for age, higher levels of mean HbA_{1c} were associated with increased risk of CVD death ($z = 5.19$), acute MI ($z = 4.98$), stroke ($z = 3.07$), CHF ($z = 4.82$), PTCA/CABG ($z = 5.40$), and angina ($z = 4.75$), but not with silent MI ($z = 1.12$) (Fig. 1).

When adjusted for age and mean HbA_{1c}, men had a higher risk of cardiovascular (CV) death than women, while the risk for the other event types did not differ by sex. Mean SBP was significantly associated with events other than stroke and angina, and triglyceride was associated with all events. Mean pulse was associated with acute MI, stroke, CHF, and angina, while diabetes duration was associated with acute MI, PCTA/CABG, and angina. Use of ACE was associated with a lower risk of stroke but not with other events. Family history of MI was associated with acute MI, PCTA/CABG, and angina. Mean LDLc was associated with acute MI, stroke, and PCTA/CABG. Smoking was associated with CV death but not with other events.

Association Between Risk Factors and the Risk of CVD and MACE

Proportional Rate Models

Supplementary Tables 1 and 2 describe the associations between risk factors and the risk of CVD and MACE, respectively, first unadjusted, then minimally adjusted for age, and then for age and mean HbA_{1c}. After age ($z = 8.33$ for CVD and $z = 7.32$ for MACE), mean HbA_{1c} was the strongest risk factor for CVD ($z = 7.52$) and for MACE ($z = 7.10$).

Multivariable models for CVD and MACE are reported in Table 2. Older age (IR 1.51 per 5 years older age; $z = 7.32$; $P < 0.001$) and higher mean HbA_{1c} (IR 1.54 per 1% or 11 mmol/mol increase; $z = 5.16$; $P < 0.001$) were the two strongest risk factors for the risk of CVD, followed by current triglycerides ($z = 2.88$; $P = 0.004$), mean SBP ($z = 2.73$; $P = 0.006$), mean pulse ($z = 2.53$; $P = 0.011$), family history of MI ($z = 2.44$; $P = 0.014$), duration of T1D ($z = 2.38$; $P = 0.017$), and any prior use of ACE inhibitors ($z = -2.82$; $P = 0.005$), which was protective.

Likewise, older age (IR 1.57 per 5 years older age; $z = 6.72$; $P < 0.001$) and higher levels of mean HbA_{1c} (IR 1.61 per 1% or 11 mmol/mol increase; $z = 4.85$; $P < 0.001$) were the two strongest risk factors for the risk of MACE, followed by mean SBP ($z = 3.70$; $P < 0.001$), smoking ($z = 2.95$; $P = 0.003$), current triglycerides ($z = 2.57$; $P = 0.010$), mean pulse ($z = 2.47$; $P = 0.013$), duration of T1D ($z = 1.98$; $P = 0.047$), and any prior use of ACE inhibitors ($z = -3.30$; $P < 0.001$), which was protective (Table 2). Mean LDLc was not significantly associated with the risk of either CVD ($P = 0.309$) or MACE ($P = 0.152$).

Multivariable Conditional Models

Table 3 reports the multivariable conditional models for the first CVD event (Table 3*A*) and the first MACE (Table 3*C*). These models are updates to the prior published models (6) that include additional CV events observed since then (31 December 2013). Table 3 also presents models for subsequent CVD events (Table 3*B*) using time since the previous CVD event (i.e., gap time) and for subsequent MACE (Table 3*D*) using the time since the previous MACE.

In general, the covariate HRs for the time to the first CVD or MACE (Table 3*A* and *C*) are similar to those published previously (6). Table 3*B* and *D* present the covariate associations with the incidence (risk) of subsequent (second, etc.) or recurrent CVD events and MACE, respectively. Fewer covariates have a significant association owing in part to the smaller number of subsequent events. For subsequent CVD (Table 3*B*), age, mean HbA_{1c}, and mean pulse remain significant, but the associations of mean SBP and triglycerides are substantially dampened. Similarly, for subsequent MACE (Table 3*D*), in addition to age and mean HbA_{1c}, mean SBP and ACE inhibitor use (protectively) have significant associations with incidence of recurrent events.

Supplementary Table 3 describes the multivariable frailty models for CVD and MACE, respectively. The results in the models censoring on non-CVD death and the results in the models accounting for non-CVD death as a separate stratum were qualitatively similar both for the first event and for subsequent events.

There were 32 CVD events that occurred within 1 month of a previous event for the same participant. A sensitivity analysis that did not include those 32 CVD events yielded similar results to

Table 3—Multivariable conditional models for the first event and for subsequent (recurrent) events using the total time gap time (i.e., time since the previous event) for CVD (*A* and *B*) and for MACE (*C* and *D*)

	A. Risk of first CVD event*			*B*. Risk of subsequent CVD events		
	HR (95% CI)	*z*	*P* value	IR (95% CI)	*z*	*P* value
Risk factor/predictor						
Age (per 5 years)	1.46 (1.32, 1.61)	7.506	**<0.001**	1.18 (1.07, 1.31)	3.291	**<0.001**
Mean HbA_{1c} (per 1% or 11 mmol/mol)	1.38 (1.21, 1.56)	4.915	**<0.001**	1.28 (1.09, 1.51)	3.047	**0.002**
Mean SBP (per 10 mmHg)	1.32 (1.13, 1.53)	3.627	**<0.001**	1.06 (0.84, 1.34)	0.504	0.614
Triglycerides (log) (per 10 mg/dL)	1.66 (1.30, 2.11)	4.099	**<0.001**	1.01 (0.72, 1.41)	0.039	0.966
Mean pulse rate (per 10 bpm)	1.25 (1.01, 1.54)	2.086	**0.037**	1.39 (1.02, 1.88)	2.093	**0.036**
Duration of T1D (per 5 years)	1.20 (1.03, 1.39)	2.321	**0.020**	1.08 (0.90, 1.31)	0.843	0.399
ACE inhibitor (yes vs. no)	0.78 (0.59, 1.04)	−1.704	0.088	0.83 (0.53, 1.27)	−0.879	0.379
Family history of MI (yes vs. no)	1.35 (1.03, 1.75)	2.227	**0.026**	1.29 (0.88, 1.89)	1.326	0.185
Mean LDLc (per 10 mg/dL)	1.07 (1.01, 1.14)	2.180	**0.029**	0.95 (0.87, 1.04)	−1.178	0.239
	C. Risk of first MACE*			*D*. Risk of subsequent MACE		
	HR (95% CI)	*z*	*P* value	IR (95% CI)	*z*	*P* value
Risk factor/predictor						
Age (per 5 years)	1.53 (1.33, 1.75)	6.053	**<0.001**	1.69 (1.20, 2.37)	3.010	**0.003**
Mean HbA_{1c} (per 1% or 11 mmol/mol)	1.54 (1.30, 1.82)	4.938	**<0.001**	1.89 (1.36, 2.61)	3.832	**<0.001**
Mean pulse rate (per 10 bpm)	1.33 (0.99, 1.78)	1.925	0.054	1.26 (0.58, 2.73)	0.585	0.559
Triglycerides (log) (per 10 mg/dL)	1.65 (1.18, 2.32)	2.916	**0.004**	1.77 (0.65, 4.79)	1.119	0.263
Mean SBP (per 10 mmHg)	1.35 (1.11, 1.66)	2.878	**0.004**	1.83 (1.14, 2.95)	2.513	**0.012**
Smoking (yes vs. no)	1.95 (1.30, 2.92)	3.236	**0.001**	0.64 (0.29, 1.43)	−1.094	0.274
Duration of T1D (per 10 years)	1.32 (1.06, 1.65)	2.468	**0.014**	0.77 (0.47, 1.28)	−0.997	0.319
ACE inhibitor (yes vs. no)	0.67 (0.44, 1.01)	−1.917	0.055	0.19 (0.06, 0.58)	−2.910	**0.004**
Mean LDLc (per 10 mg/dL)	1.04 (0.95, 1.14)	0.937	0.349	1.18 (0.96, 1.46)	1.564	0.118

P values <0.05 appear in boldface type. bpm, beats per minute. *The analyses for the risk of first CVD event and MACE expand those published previously (6) with longer follow-up (May 2017 vs. December 2013) and larger number of events (239 vs. 184 for CVD and 120 vs. 88 for MACE). Given the relatively low number of participants with three or more CVD events, the conditional models used a class variable with two levels: first CVD event or MACE vs. all subsequent CVD events or MACE.

the results that included those events (Supplementary Table 4 vs. Table 3*A* and *B*). Likewise, there were five MACE that occurred within 1 month of a previous event for the same participant, and discarding those five MACE yielded similar results to the analyses that included those events (Supplementary Table 4 vs. Table 3*C* and *D*).

CONCLUSIONS

Cardiovascular events are common yet unanticipated and difficult to prevent in patients with T1D. However, once alerted to the presence of serious atherosclerosis, the challenge is how to prevent a recurrence, which carries significant morbidity and mortality, even among individuals without diabetes (13). Much remains unknown regarding the pathogenesis of recurrent CVD events in T1D. These analyses provide insight into the potential risk factors contributing to subsequent cardiovascular events.

The DCCT/EDIC study previously demonstrated that poor glycemic control was the strongest modifiable risk factor for a first CVD event, even after adjustment for traditional CVD risk factors (6). In this study, we extended those analyses by extending the period of follow-up from 31 December 2013 to 18 May 2017 and by further considering the association between glycemia and the risk of all CVD events, including subsequent events that occurred after the first CVD event.

Age followed by mean HbA_{1c} were the two strongest risk factors for all (i.e., considering an average effect over the first and subsequent events) CVD events and MACE in proportional rate models.

With respect to the time to the first CVD event, the current analyses confirm that glycemia, as captured by HbA_{1c}, is, after age, the strongest risk factor for both CVD and MACE even after adjustment for established CVD risk factors. Moreover, higher levels of mean HbA_{1c} were associated with the risk of subsequent (second, third, and so on) CVD events and subsequent MACE. In addition to mean HbA_{1c}, the risk of subsequent CVD events was associated only with age and mean pulse rate when using the time since the previous CVD event. Likewise, in addition to mean HbA_{1c}, the risk of subsequent MACE was associated only with age, mean SBP, and use of ACE inhibitors (protective) using the time since the previous MACE. Therefore, of the risk factors associated with the risk of a first CVD event or MACE, age and mean HbA_{1c} are the primary determinants of recurrent CVD events in this T1D population.

While the *z* scores for mean HbA_{1c} in these CVD models were slightly higher than those in the corresponding MACE models, the IRs were always higher in the MACE models than in the CVD models, suggesting stronger association between glycemia and more severe CVD events (such as CVD death and nonfatal MI). This apparent discrepancy between the *z* scores and the IRs is likely explained by the larger number of CVD events observed ($n = 421$ CVD events vs. $n = 149$ MACE).

We also investigated the association between risk factors and the risk of individual CVD events, including all subsequent events within the same individual. While age was the strongest risk factor for acute MI, silent MI, stroke, and PTCA/CABG, mean HbA_{1c} was the strongest risk factor for CVD death, CHF, and angina. HbA_{1c} was the second strongest risk factor (after age) for acute MI and PTCA/CABG

and third strongest risk factor (after age and triglycerides) for stroke, but was not associated with silent MI (Fig. 1).

We have previously shown in DCCT/EDIC that women did not have a significantly lower risk of a first CVD event compared with men after adjustment for risk factors (6), consistent with results from the Pittsburgh Epidemiology of Diabetes Complications Study (14). The current analyses, based on additional follow-up and more CVD events, confirm these findings. Moreover, similar results were obtained with respect to the risk of subsequent or recurrent events for both CVD and MACE. This is in contrast to type 2 diabetes, in which results from the Hoorn Study (15) and the Diabetes and Informatics Study (16) showed higher incidence of recurrent CVD events in men compared with women. However, our analyses suggest men are at higher risk of CVD death compared with women after adjustment for age and mean HbA_{1c}, confirming results from the British Diabetic Association Cohort Study (17,18).

Higher mean pulse rate was associated with higher risk of subsequent CVD events. In T1D, higher pulse rate may be associated with parasympathetic denervation, a marker of cardiac autonomic neuropathy and an independent risk factor for sudden cardiac death (19).

Given the exploratory nature of our analyses, no adjustment for multiplicity was conducted, which could yield an inflation of the overall type I error.

Importantly, the DCCT excluded high-risk individuals with hypertension and hypercholesterolemia and thus may not fully represent the whole spectrum of individuals with T1D. However, we have previously shown that the cumulative incidence of CVD in the DCCT conventional group is similar to that of the Pittsburgh Epidemiology of Diabetes Complications (EDC) cohort (17). Furthermore, in a detailed replication of the DCCT/EDIC CVD risk factor modeling (20), similar results concerning traditional risk factors were seen in the EDC study. However, kidney disease was a major contributor in EDC, while HbA_{1c} was less strong, differences thought to reflect the much longer duration of T1D among the EDC participants at baseline, despite similar age compared to the DCCT participants. Indeed, in DCCT/EDIC, the majority of the HbA_{1c} effect was mediated by traditional risk factors after 20 years of follow-up, when duration was similar to that of the EDC participants at baseline (7).

In conclusion, traditional nonmodifiable (such as age, duration of diabetes, and family history of MI) and modifiable (such as HbA_{1c}, blood pressure, lipids, ACE inhibitor use, and smoking) risk factors play important roles in the incidence of all CVD events (including recurrent events) in T1D, thereby extending our prior reports concerning first events alone. Importantly, the current analyses demonstrate that HbA_{1c} is a strong predictor of recurrent events alone, as is blood pressure and use of ACE inhibitors (for MACE). Therefore, intensive management of glycemia, use of antihypertensive medication (ACE inhibitors), lipid control, and smoking prevention/cessation are recommended to lower the risk of initial CVD events in T1D. After a first event has occurred, lower glycemic levels are associated with lower risk of recurrent events. Availability of continuous glucose monitoring and more precise insulin delivery devices that proactively respond to hypoglycemia has made improved glucose control in individuals with T1D more achievable. With overall improvements in glycemic control, CVD, the primary cause of death in T1D, can be reduced.

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