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

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. HbA1c was the strongest modifiable risk factor for a first CVD event (CVD: HR 1.38 [95% CI 1.21, 1.56] per 1% higher HbA1c; 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 HbA1c, is the strongest modifiable risk factor.
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 HbA1c 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). HbA1c 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 HbA1c, 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 HbA1c 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 HbA1c−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.
Individual CVD outcomes in proportional rate models

| Event Type | Mean HR (95% CI) | P-value |
|------------|------------------|---------|
| CVD death  | 1.14 (1.02, 1.27) | 0.01    |
| Acute MI   | 1.54 (1.34, 1.79) | 0.01    |
| Silent MI  | 1.45 (1.26, 1.68) | 0.01    |
| Stroke     | 1.79 (1.62, 1.99) | 0.01    |
| CHF        | 1.14 (1.03, 1.26) | 0.01    |

Table 1: Number and rate of CVD events separately by event type and the incidence ratios (IRs) for age- and mean HbA1c-subtracted associations between risk factors and individual CVD outcomes in proportional rate models.
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 previous 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 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 HbA1c 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.
Adjusted for age and mean HbA1c, 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 HbA1c, 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), PCTA/CABG (z = 6.01), and angina (z = 3.38) (Fig. 1). Adjusted for age, higher levels of mean HbA1c were associated with increased risk of CVD death (z = 5.19), acute MI (z = 4.98), stroke (z = 3.07), CHF (z = 4.82), PCTA/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 HbA1c, 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 HbA1c. After age (z = 8.33 for CVD and z = 7.32 for MACE), mean HbA1c 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 HbA1c (IR 1.54 per 1% or 11 mmol/mocrease; z = 5.16; 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 3A) and the first MACE (Table 3C). 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 3B) using time since the previous CVD event (i.e., gap time) and for subsequent MACE (Table 3D) using the time since the previous MACE.

In general, the covariate HRs for the time to the first CVD or MACE (Table 3A and C) are similar to those published previously (6). Table 3B 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 3B), age, mean HbA1c, and mean pulse remain significant, but the associations of mean SBP and triglycerides are substantially dampened. Similarly, for subsequent MACE (Table 3D), in addition to age and mean HbA1c, 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...
the results that included those events (Supplementary Table 4 vs. Table 3A 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 3C 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 HbA1c 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 HbA1c, 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 HbA1c were associated with the risk of subsequent (second, third, and so on) CVD events and subsequent MACE. In addition to mean HbA1c, 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 HbA1c, 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 HbA1c are the primary determinants of recurrent CVD events in this T1D population.

While the z scores for mean HbA1c 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 HbA1c was the strongest risk factor for CVD death, CHF, and angina. HbA1c was the second strongest risk factor (after age) for acute MI and PTCA/CABG.

| Risk factor/predictor | A. Risk of first CVD event* | B. Risk of subsequent CVD events |
|-----------------------|----------------------------|-------------------------------|
|                       | HR (95% CI)                | z    | P value                   | IR (95% CI)    | z    | P value                   |
| 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 HbA1c (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                    |

**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)**

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.
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 HbA1c, 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 HbA1c 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 HbA1c 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 HbA1c, 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 HbA1c 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.

**Funding.** The DCCT/EDIC has been supported by cooperative agreement grants (1982–1993 and 2012–2017) and contracts (1982–2012) with the Division of Diabetes, Endocrinology, and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Disease (grants U01-DK-094176 and U01-DK-094157) and through support from the National Eye Institute, the National Institute of Neurological Disorders and Stroke, the General Clinical Research Centers Program (1993–2007), and Clinical and Translational Science Center Program (2006 to present) (Bethesda, MD).

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

**Author Contributions.** I.B., T.O., and J.M.L. designed the study. I.B. wrote the initial draft of the manuscript with assistance from J.M.L. and conducted all analyses. D.S., B.B., M.K., M.L.-V., E.Z.S., W.H.H., D.A.B., and A.W. contributed to the specification of the analyses and critically reviewed and edited the manuscript. I.B. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**References**

1. Orchard TJ, Costacou T, Kretowski A, Nesto RW. Type 1 diabetes and coronary artery disease. Diabetes Care 2006;29:2528–2538
2. Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawson RA, Colhoun HM. High risk of cardiovascular disease in patients with type 1 diabetes in the U.K.: a cohort study using the general practice research database. Diabetes Care 2006;29:798–804
3. Livingstone SJ, Looker HC, Hothersal EJ, et al. Risk of cardiovascular disease and total mortality in adults with type 1 diabetes: Scottish registry linkage study. PLoS Med 2012;9:e1001321
4. de Ferrari 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
5. Nathan DM, Cleary PA, Backlund JY, et al.; Diabetes Control and Complications Trials/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
6. Diabetes Control and Complications Trials/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Risk factors for cardiovascular disease in type 1 diabetes. Diabetes 2016;65:1370–1379
7. Bebu I, Braffett BH, Pop-Busui R, Orchard TJ, Nathan DM, Lachin JM; DCCT/EDIC Research Group. The relationship of blood glucose with cardiovascular disease is mediated over time by traditional risk factors in type 1 diabetes: the DCCT/EDIC study. Diabetologia 2017;60:2084–2091
8. Bebu I, Braffett BH, Orchard TJ, Lorenzi GM, Lachin JM; DCCT/EDIC Research Group. Mediation of the effect of glycemia on the risk of CVD outcomes in type 1 diabetes: the DCCT/EDIC Study. Diabetes Care 2014;39:1284–1289
9. The DCCT Research Group. The Diabetes Control and Complications Trial (DCCT). Design and methodologic considerations for the feasibility phase. Diabetes 1986;35:530–545
10. The DCCT/EDIC Research Group. Epidemiology of Diabetes Interventions and Complications (EDIC). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. Diabetes Care 1999;22:99–111
11. Writing Group for the DCCT/EDIC Research Group. Copropression of cardiovascular risk factors in type 1 diabetes during 30 years of follow-up in the DCCT/EDIC study. Diabetes Care 2016;39:1621–1630
12. Therneau TM, Grambsch PM. Modeling Survival Data: Extending the Cox Model. New-York, Springer-Verlag, 2000
13. Davidson MH. Reducing residual risk for patients on statin therapy: the potential role of combination therapy. Am J Cardiol 2005;96:3K–13K; discussion 34K–35K
14. 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
15. van der Heijden AA, Van’t Riet E, Bot SD, et al. Risk of a recurrent cardiovascular event in individuals with type 2 diabetes or intermediate hyperglycemia: the Hoorn Study. Diabetes Care 2013;36:3498–3502
16. Giorda CB, Avogaro A, Maggini M, et al.; Diabetes and Informatics Study Group. Recurrence of the overall type I error.
of cardiovascular events in patients with type 2 diabetes: epidemiology and risk factors. Diabetes Care 2008;31:2154–2159
17. Laing SP, Swerdlow AJ, Slater SD, et al. The British Diabetic Association Cohort Study, II: cause-specific mortality in patients with insulin-treated diabetes mellitus. Diabet Med 1999;16:466–471
18. Poirier P, Bertrand OF, Leipsic J, Mancini GB, Raggi P, Roussin A; Diabetes Canada Clinical Practice Guidelines Expert Committee. Screening for the presence of cardiovascular disease. Can J Diabetes 2018;42(Suppl. 1):S170–S177
19. Pop-Busui R, Low PA, Waberski BH, et al.; DCCT/EDIC Research Group. Effects of prior intensive insulin therapy on cardiac autonomic nervous system function in type 1 diabetes mellitus: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC). Circulation 2009;119:2886–2893
20. 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