Cardiovascular Autonomic Neuropathy and Cardiovascular Outcomes in the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study

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Diabetes Care 2017;40:94–100 | DOI: 10.2337/dc16-1397

OBJECTIVE

To examine whether cardiovascular autonomic neuropathy (CAN) is an independent risk factor of cardiovascular disease (CVD) events during DCCT/EDIC.

RESEARCH DESIGN AND METHODS

Standardized cardiovascular autonomic reflex tests (R-R response to paced breathing, Valsalva maneuver, postural changes in blood pressure) were performed at DCCT baseline, every 2 years throughout DCCT, and at two time points in EDIC. CVD events were ascertained throughout the study and adjudicated by a review committee. Cox proportional hazards models were used to estimate the effect of CAN at DCCT closeout on subsequent CVD risk.

RESULTS

There were 299 adjudicated CVD events in 165 participants following the DCCT closeout assessment: 132 of 1,262 subjects (10%) without CAN at DCCT closeout who experienced 244 CVD events versus 33 of 131 subjects (25%) with CAN at DCCT closeout who experienced 55 events (hazard ratio 2.79, 95% CI 1.91–4.09 for time to first CVD event). The cumulative incidence of the first occurrence of any CVD event during EDIC was significantly higher in participants with CAN at DCCT closeout compared with those without CAN. The association remained marginally significant after adjustment for multiple risk factors, including the EDIC updated mean HbA_{1c}. When analyzed as a continuous variable, R-R variation was significantly lower at DCCT closeout in participants who experienced a CVD event compared with those who did not ($P = 0.0012$).

CONCLUSIONS

In the DCCT/EDIC cohort, individuals diagnosed with CAN at DCCT closeout experienced a higher long-term risk of CVD events during follow-up in EDIC. This association was not independent of historic glycemic exposure and its metabolic memory effect, the principal determinant of both long-term CVD risk and CAN in type 1 diabetes.

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Received 29 June 2016 and accepted 4 October 2016.

Clinical trial reg. nos. NCT00360815 and NCT00360893, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-1397/-/DC1.

**A complete list of participants in the DCCT/EDIC Research Group is presented in the Supplementary Material published online for the article in N Engl J Med 2015;372:1722–33.*

Cardiovascular mortality remains the main cause of excess mortality among individuals with type 1 diabetes (T1D) (1,2). The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study demonstrated that intensive treatment of hyperglycemia applied early in the course of the disease substantially reduces the risk of cardiovascular disease (CVD) (3). Despite the reduction in CVD risk resulting from intensive diabetes management, the cardiovascular event rate during DCCT/EDIC remains higher than that observed in the general population, suggesting that other factors may also play a role (1).

Autonomic innervation is the primary extrinsic control mechanism regulating heart rate and cardiac performance (4–6). Cardiovascular autonomic neuropathy (CAN), a common complication of diabetes resulting from autonomic neural dysfunction induced by chronic hyperglycemia and its downstream consequences (4–6), has been shown to be an independent predictor of CVD mortality in T1D and type 2 diabetes (T2D) (7–9). In addition, presence of CAN has been shown to have an adverse effect on cardiac remodeling in the DCCT/EDIC cohort (10).

In this study, we examined whether the presence of CAN at the end of the DCCT predicts subsequent CVD events during the EDIC study. Specifically, we determined whether CAN was an independent predictor of CVD during EDIC.

RESEARCH DESIGN AND METHODS

Subjects

The DCCT/EDIC study has been described in detail (11,12). Briefly, 1,441 subjects with T1D for 1–15 years with no (primary prevention cohort) or minimal (secondary intervention cohort) diabetic retinopathy were enrolled in the DCCT between 1983 and 1989. Subjects were randomly assigned to receive intensive or conventional therapy and were followed for 3–9 years (mean 6.5 years). At the end of the DCCT, intensive therapy was recommended for all participants and subjects returned to their own health care providers for diabetes care. In 1994, 96% of the surviving DCCT cohort enrolled in the EDIC observational study, and after an additional 20 years of follow-up, 1,251 participants continue to be followed (94% of survivors).

DCCT/EDIC Evaluations

Follow-up visits occurred quarterly during the DCCT and annually throughout EDIC and included a detailed medical history and physical examination for measurements of height, weight, and blood pressure. Fasting lipids and albumin excretion rate (AER) were measured annually during DCCT and in alternate years during EDIC and evaluated centrally (11,12). Hemoglobin A_{1c} (HbA_{1c}) levels were measured at baseline and quarterly during DCCT and annually in EDIC using high-performance ion-exchange liquid chromatography. The DCCT/EDIC time-weighted mean HbA_{1c} represents the total glycemic exposure during DCCT/EDIC with weights of 0.25 and 1 assigned to quarterly DCCT and annual EDIC values, respectively. The EDIC updated mean HbA_{1c} represents the running average during EDIC.

CAN Evaluations

Standardized CAN evaluations included cardiovascular autonomic reflex tests that assessed the R-R response to paced breathing (R-R variation), the Valsalva maneuver, and postural changes in blood pressure. Evaluations were performed at DCCT baseline, every 2 years during DCCT, DCCT closeout, and EDIC years 13/14 and 16/17 as previously amply described (13–16) (Supplementary Fig. 1). These tests are objective, standardized, highly reproducible, and endorsed by the Toronto Consensus Panel on Diabetic Neuropathy as the gold standard test for CAN (6). All subjects were asked to fast and avoid caffeine and tobacco products for 8 h prior to testing and to hold all prescription and over-the-counter medicines (except for basal insulin) until testing was completed (14,15). Subjects who experienced hypoglycemia after midnight or in the morning of testing (defined as a blood glucose $\leq$50 mg/dL [2.775 mmol/L]) were excluded. CAN testing was performed with Hokanson ANS2000 devices (Hokanson, Inc., Bellevue, WA), and all results were reviewed by a single investigator masked to DCCT treatment.

The presence of CAN was defined in DCCT and EDIC as either an R-R variation $<$15 or an R-R variation 15–19.9 in combination with a Valsalva ratio $\leq$1.5 or a decrease of $>$10 mmHg in diastolic blood pressure upon and while standing for 10 min (14,15). Secondary CAN outcome measures included changes in age-adjusted continuous measures of R-R variation and Valsalva ratio.

Cardiovascular Outcomes

The primary outcome was defined as the time to the first of any of the following CVD events from the DCCT closeout assessment: nonfatal myocardial infarction or stroke; death judged to be secondary to CVD; subclinical ("silent") myocardial infarction detected on an annual electrocardiogram; angina confirmed by ischemic changes with exercise tolerance testing or by clinically significant obstruction on coronary angiography; congestive heart failure with paroxysmal nocturnal dyspnea, orthopnea, or marked limitation of physical activity caused by heart disease; or revascularization with angioplasty and/or coronary artery bypass. We also evaluated CAN in relationship to the traditional major adverse cardiovascular events (MACE) defined as nonfatal myocardial infarction or stroke or CVD death.

Cardiovascular events were documented during annual study visits. Medical records describing cardiovascular events, including electrocardiograms and cardiac enzymes, were obtained and centrally adjudicated by a Mortality and Morbidity Review Committee masked to DCCT treatment assignment, HbA_{1c}, and glucose levels as previously described (17).

Statistical Analysis

Clinical characteristics were compared between those with and without CAN at DCCT closeout and EDIC year 13/14 using the Wilcoxon rank sum test for quantitative variables and the χ^2 test for categorical variables. The Kaplan-Meier method was used to estimate the cumulative incidence of the first occurrence of any cardiovascular event. The Cox proportional hazards model was used to estimate the effect of CAN at DCCT closeout on subsequent CVD risk during EDIC (18). Adjustments were made for fixed covariates (DCCT treatment group, DCCT primary prevention vs. secondary intervention cohort, DCCT closeout age and duration of diabetes) and time-dependent covariates (systolic and diastolic blood pressure, total cholesterol, triglycerides, microalbuminuria defined as a sustained AER $\geq$30 mg/24 h at two consecutive visits

or end-stage renal disease (ESRD) defined as dialysis or renal transplantation, and EDIC updated mean HbA_{1c}). These risk factors were chosen on the basis of a prior analysis of CVD risk factors in the DCCT/EDIC cohort (19). Additional Cox proportional hazards models were used to estimate the effect of all autonomic neuropathy measures as time-dependent covariates on the risk of any CVD and MACE. Since the number of neuropathy assessments was a function of the year of entry into the DCCT study, the models with time-dependent autonomic measurements were stratified by the year of entry. Two-sided $P \leq 0.05$ was considered statistically significant. All analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC).

RESULTS

The characteristics of the DCCT/EDIC participants by CAN status at DCCT closeout and EDIC year 13/14 are presented in Table 1. The prevalence of CAN was 9% at DCCT closeout and increased to 31% by EDIC year 13/14. The majority of participants with CAN were from the former conventional treatment group and secondary intervention cohort. Participants with CAN were older with a longer duration of diabetes, higher systolic and diastolic blood pressure, increased heart rate, higher total cholesterol and triglyceride levels, and elevated urinary AER. Current and updated mean HbA_{1c} levels were also significantly higher among those with CAN. At EDIC year 13/14, participants with CAN were more likely to be smokers and had a significantly higher mean BMI.

Throughout the DCCT/EDIC study there were a total of 183 (13%) participants who experienced a CVD event, and 165 (12%) of these had an event that occurred after DCCT closeout (Table 2). Because of the low prevalence of CAN at DCCT baseline (66 participants or 5%) and therefore minimal power to detect an association with CAN early on in the study, the presence of CAN at DCCT closeout was evaluated as the primary exposure. Subsequent CVD events during EDIC occurred in more participants with CAN at DCCT closeout compared with those without CAN (25% vs. 10%) (Table 2).

The association between CAN status at DCCT closeout and each type of subsequent CVD event during EDIC is presented in Table 3. There were 299 adjudicated events in 165 participants, 132 among 1,262 subjects (10%) without CAN at DCCT closeout who experienced 244 CVD events versus 33 among 131 subjects (25%) with CAN at DCCT closeout who experienced 55 events (hazard ratio [HR] 2.79, 95% CI 1.91–4.09) (Table 3). The majority of CVD events experienced were nonfatal myocardial infarction, silent myocardial

Table 1—Clinical characteristics among participants in the DCCT/EDIC cohort by CAN status at DCCT closeout and EDIC year 13/14

	DCCT closeout (1993)			EDIC year 13/14 (2006/2007)		
Characteristics	No CAN	CAN		No CAN	CAN	
N	1,262	131		770	340	
Age (years)	33 ± 7	37 ± 7	*	47 ± 7	50 ± 7	*
Female sex	588 (47)	70 (53)		358 (46)	166 (49)	
Intensive group	638 (51)	52 (40)	†	415 (54)	159 (47)	†
Secondary cohort	595 (47)	93 (71)	*	349 (45)	191 (56)	*
Duration of diabetes (years)	12 ± 5	14 ± 5	*	25 ± 5	26 ± 5	*
Current cigarette smoker	291 (23)	28 (22)		85 (11)	65 (19)	*
BMI (kg/m^2)	26 ± 4	26 ± 5		28 ± 5	29 ± 6	†
Blood pressure (mmHg)						
Systolic	116 ± 11	121 ± 14	*	118 ± 13	124 ± 16	*
Diastolic	74 ± 9	77 ± 9	*	73 ± 8	74 ± 10	
Heart rate (bpm)	70 ± 29	76 ± 13	*	67 ± 10	72 ± 12	*
Lipids (mg/dL)						
HDL cholesterol	51 ± 13	52 ± 13		56 ± 16	57 ± 17	
LDL cholesterol	113 ± 29	118 ± 35		103 ± 29	103 ± 35	
Total cholesterol	181 ± 33	190 ± 42	*	175 ± 34	177 ± 41	
Triglycerides	84 ± 47	100 ± 58	*	79 ± 57	89 ± 65	*
Renal function						
Sustained microalbuminuria‡	114 (9)	35 (27)	*	72 (10)	88 (27)	*
Macroalbuminuria§	18 (1)	11 (9)	*	19 (3)	36 (11)	*
HbA_{1c} (%)	8.2 ± 1.6	8.9 ± 1.8	*	7.7 ± 1.1	8.0 ± 1.3	*
HbA_{1c} (mmol/mol)	66 ± 17	74 ± 20	*	61 ± 12	64 ± 14	*
DCCT/EDIC time-weighted mean HbA_{1c} (%)	8.1 ± 1.4	8.8 ± 1.6	*	7.8 ± 0.9	8.3 ± 1.0	*
DCCT/EDIC time-weighted mean HbA_{1c} (mmol/mol)	65 ± 15	73 ± 17	*	62 ± 10	67 ± 11	*
EDIC updated mean HbA_{1c} (%)				7.8 ± 0.9	8.2 ± 1.2	*
EDIC updated mean HbA_{1c} (mmol/mol)				62 ± 10	67 ± 13	*

Data are means ± SD or *n* (%), unless otherwise noted. *n* is based on the number of subjects still at risk for a CVD event at each point in time. *$P < 0.01$ by the Wilcoxon rank sum test or the χ^2 test comparing No CAN vs. CAN. †$P < 0.05$ by the Wilcoxon rank sum test or the χ^2 test comparing No CAN vs. CAN. ‡Sustained AER ≥30 mg/24 h at two consecutive visits or ESRD defined as dialysis or renal transplantation. §AER ≥300 mg/24 h or ESRD.

Table 2—Association between CAN measures at DCCT baseline, DCCT closeout, and EDIC year 13/14 and any subsequent CVD events

		R-R variation <15		Valsalva ratio ≤1.5		CAN	
	N	No	Yes	No	Yes	No	Yes
DCCT baseline	1,435	1,362	55	1,316	83	1,369	66
Patients with event	183 (13)	167 (12)	15 (27)	167 (13)	13 (16)	165 (12)	18 (27)
DCCT closeout	1,393	1,220	121	1,153	113	1,262	131
Patients with event	165 (12)	130 (11)	30 (25)	125 (11)	21 (19)	132 (10)	33 (25)
EDIC year 13/14	1,121	836	283	712	255	770	340
Patients with event	66 (6)	43 (5)	23 (8)	29 (4)	21 (8)	35 (5)	29 (9)

Data are *N* or *n* (%).

infarction, and revascularization (72% in those without CAN vs. 64% in those with CAN) (Table 3).

A MACE event during EDIC occurred in 12% of participants with CAN compared with 5% of participants without CAN (HR 2.93, 95% CI 1.68–5.09). Death from CVD was noted in 3% of participants with CAN and in 1% of those without CAN.

The cumulative incidence of the first occurrence of any CVD event (Fig. 1*A*) and of MACE (Fig. 1*B*) during EDIC were significantly higher in participants with CAN at DCCT closeout compared with those without CAN ($P < 0.0001$ for both). In a multivariate model adjusted for age, treatment group, primary prevention versus secondary intervention cohort, diabetes duration, systolic and diastolic blood pressure, total cholesterol, triglycerides, and microalbuminuria, the HR for the first occurrence of any CVD event was attenuated but remained significant (HR 1.53, 95% CI 1.01–2.32, $P = 0.0468$). After further adjustment for the EDIC updated mean HbA_{1c}, the magnitude of the HR and significance was similar (HR 1.53, $P = 0.0474$) (Table 3). For the MACE outcome, adjustment for covariates and also HbA_{1c} reduced the HR to 1.78 (95% CI 0.98–3.24, $P = 0.0603$) and 1.56 (95% CI 0.84–2.88, $P = 0.1566$), respectively, which were not statistically significant.

When analyzed as time-dependent covariates, only R-R variation remained marginally associated with a higher risk of any CVD or MACE after minimal adjustment for DCCT baseline age (Supplementary Table 1). However, the R-R variation was significantly lower at DCCT closeout in participants who experienced a CVD event compared with those who did not (34.4 ± 20.4 vs. 40.6 ± 20.3; $P < 0.0001$).

CONCLUSIONS

This study examined the associations between CAN and CVD events in patients with T1D and found that the presence of CAN at DCCT closeout was associated with a higher risk of CVD events during EDIC. These associations remained marginally significant even after adjusting for known CVD risk factors and for glucose control over time as documented by the updated mean HbA_{1c} throughout EDIC.

Age is one of the strongest risk factors for CAN (5,6,20) and for CVD events (19) as demonstrated by the DCCT/EDIC Research Group and others. Our group has recently reported that, in addition to age, several CVD risk factors traditionally associated with risk in patients with T2D including higher mean systolic blood pressure, triglycerides, cholesterol, and diabetes duration were significantly associated with the risk of any CVD or MACE in the DCCT/EDIC cohort as previously discussed (19). After adjusting for age and all of these factors, the independent association of the presence of CAN with the occurrence of any CVD events, the primary CVD outcome remained marginally significant and no longer significant with MACE likely because of the even smaller number of MACE events.

The DCCT/EDIC group also reported several years ago a beneficial effect of glucose control in preventing CVD events in the DCCT/EDIC cohort, in a "metabolic memory" effect (3), although the limited number of CVD events at that time precluded a thorough investigation of risk factors. However, the strong relationship between glycemia and CVD events in this cohort was further confirmed recently when the appropriate number of events was reached demonstrating that besides age, mean HbA_{1c} over time was the strongest risk factor for clinical CVD in this cohort (19). In addition, we have previously reported that glucose control was the strongest predictor of CAN development in the DCCT participants with T1D (15,21). During EDIC, although the prevalence of CAN increased in both former treatment groups, there was a significant reduction in the risk for incident CAN in the former intensive group (14). Virtually all of the treatment group difference in the incidence of CAN was explained by the treatment group differences in mean HbA_{1c} confirming the presence of a metabolic memory effect for CAN in this cohort (14). Similar findings regarding the role of glucose control as a principal determinant of CAN was reported in other cohorts of patients with T1D (6,22). In addition, our group has recently reported a longitudinal coprogression of glycemic CVD risk factors in this cohort (23). Thus, it is not surprising that after adjusting for glucose control as a time-dependent covariate and given the complex interactions between these factors, the relationship between CAN and CVD was attenuated.

Resting heart rate is also a well-known CVD risk factor (24,25), and an indirect measure of CAN (6) and the effects of heart rate on CVD risk has been shown in a prior analysis of the DCCT/EDIC cohort (19).

One of the most serious consequences of CAN is its relationship with mortality risk, which has been reported by several independent groups. A meta-analysis of 15 studies that included 2,900 subjects with both T1D and T2D reported a pooled relative risk of mortality of 3.45 (95% CI 2.66–4.47) in patients with CAN (26), which is progressively higher with an increasing number of abnormal CAN function tests (26). In a large cohort of more than 8,000 participants with T2D enrolled

Table 3—Association between CAN status at DCCT closeout and subsequent CVD events

	No CAN, *n* = 1,262		CAN, *n* = 131		Unadjusted	Minimally adjusted	Fully adjusted	Fully adjusted + HbA_{1c}
	Patients, *n* (%)*	Events, *n*	Patients, *n* (%)*	Events, *n*	HR (95% CI),† *P* value			
Any CVD event	132 (10)	244	33 (25)	55				
Nonfatal acute myocardial infarction	36 (3)	41	9 (7)	9				
Nonfatal cerebrovascular event	16 (1)	18	4 (3)	4				
Death from CVD	13 (1)	13	4 (3)	4	2.79 (1.91–4.09), <0.0001	2.08 (1.41–3.07), 0.0002	1.53 (1.01–2.32), 0.0468	1.53 (1.01–2.32), 0.0474
Silent myocardial infarction	37 (3)	39	6 (5)	6				
Confirmed angina	26 (2)	32	7 (5)	9				
Revascularization	63 (5)	96	18 (14)	20				
Congestive heart failure	7 (1)	8	2 (2)	3				
Nonfatal myocardial infarction or stroke or death from CVD (MACE)	59 (5)	72	16 (12)	17	2.93 (1.68–5.09), 0.0001	2.08 (1.18–3.66), 0.0110	1.78 (0.98–3.24), 0.0603	1.56 (0.84–2.88), 0.1566
Nonfatal acute myocardial infarction	36 (3)	41	9 (7)	9				
Nonfatal cerebrovascular event	16 (1)	18	4 (3)	4				
Death from CVD	13 (1)	13	4 (3)	4				

*Number of patients with each type of event regardless of whether or not it is the initial event for that subject. †Cox proportional hazards regression models for the time to the first CVD event following DCCT closeout, unadjusted; minimally adjusted for DCCT closeout age; fully adjusted to also include DCCT treatment group, primary prevention vs. secondary intervention cohort, DCCT closeout duration of diabetes, systolic and diastolic blood pressure, total cholesterol, triglycerides, and microalbuminuria; fully adjusted to also include EDIC updated mean HbA_{1c}. The following covariates were entered into each model as time-dependent covariates: systolic and diastolic blood pressure, total cholesterol, triglycerides, microalbuminuria, and EDIC updated mean HbA_{1c}.

in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the presence of CAN based on measures of heart rate variability derived from electrocardiogram recordings independently predicted all-cause and CVD mortality after adjusting for multiple traditional CVD risk factors and medication (9). Specifically for T1D, the EURODIAB Prospective Complications Study of T1DM patients reported that CAN was the strongest predictor for mortality during a 7-year follow-up, exceeding the effect of traditional cardiovascular risk factors (27). While the number of reported deaths in our cohort are too few for detailed risk factor analysis, the data presented herein are consistent with a trend toward increased mortality in the participants with CAN.

In this cohort, myocardial infarction, silent myocardial infarction, and revascularization, often performed for silent ischemia, were the most prevalent types of CVD events. Classically, silent myocardial infarction is considered a characteristic finding of CAN. In a meta-analysis of 12 published studies, Vinik et al. (28). reported an association between CAN and the presence of silent myocardial ischemia, measured by exercise stress testing, with point estimates for the prevalence rate ratios from 0.85–15.53. In the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study (29) of 1,123 patients with T2D, CAN was a strong predictor of silent ischemia and subsequent cardiovascular events. The association between CAN and silent ischemia has important implications, as reduced appreciation for ischemic pain impairs timely recognition of myocardial ischemia or infarction, thereby delaying appropriate therapy. However, in the DCCT/EDIC study, the overall number of events including silent myocardial infarction was low.

In addition, our findings demonstrate that the R-R variation was significantly lower at DCCT closeout in those who experienced a CVD event during EDIC compared with those who did not, further justifying the use of a simple, readily available measure as a prognostic tool in clinical practice.

Limitations of this analysis include the overall relatively low rates of CAN during the DCCT, the low rates of CVD events in EDIC, and thus reduced power to detect a meaningful independent predictive value of CAN for future CVD events. The relatively young age of this cohort, without preexisting hypertension, hyperlipidemia, or CVD at baseline, further limits the applicability of these results to the entire population of patients with T1D (17). The strengths of this analysis include the highly reproducible and sensitive CAN protocol repeated over time in DCCT/EDIC, the robust CAN definitions used, and a cohort of patients with T1D that have been followed for 30 years with careful characterization of multiple cardiovascular complications and risk factors.

In summary, the earlier diagnosis of CAN at DCCT closeout is associated with an increased incidence of subsequent CVD events, although it is not an independent predictor with respect to HbA_{1c} on CVD risk. Since HbA_{1c} is one of the major determinants of CAN in T1D, the diagnosis of CAN identifies individuals with T1D at high risk for major CVD events over time.

Funding. The DCCT/EDIC has been supported by cooperative agreement grants (1982–1993, 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 Diseases (current grant numbers U01-DK-094176 and U01-DK-094157) and by the National Eye Institute, the National Institute of Neurological Disorders and Stroke, the General Clinical Research Centers Program (1993–2007), and the Clinical and Translational Science Awards Program (2006 to present), Bethesda, MD.

The following industry contributors have had no role in the DCCT/EDIC study but have provided free or discounted supplies or equipment to support participant adherence to the study: Abbott Diabetes Care (Alameda, CA), Animas (Westchester, PA), Bayer Diabetes Care (North America Headquarters, Tarrytown, NY), Becton Dickinson (Franklin Lakes, NJ), Eli Lilly (Indianapolis, IN), Extend Nutrition (St. Louis, MO), Insulet Corporation (Bedford, MA), LifeScan (Milpitas, CA), Medtronic Diabetes (Minneapolis, MN), Nipro Home Diagnostics (Ft. Lauderdale, FL), Nova Diabetes Care (Billerica, MA), Omron (Shelton, CT), Perrigo Diabetes Care (Allegan, MI), Roche Diabetes Care (Indianapolis, IN), and Sanofi (Bridgewater, NJ).

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

Author Contributions. R.P.-B. proposed the analyses, participated in the data analysis and interpretation, drafted the manuscript, and

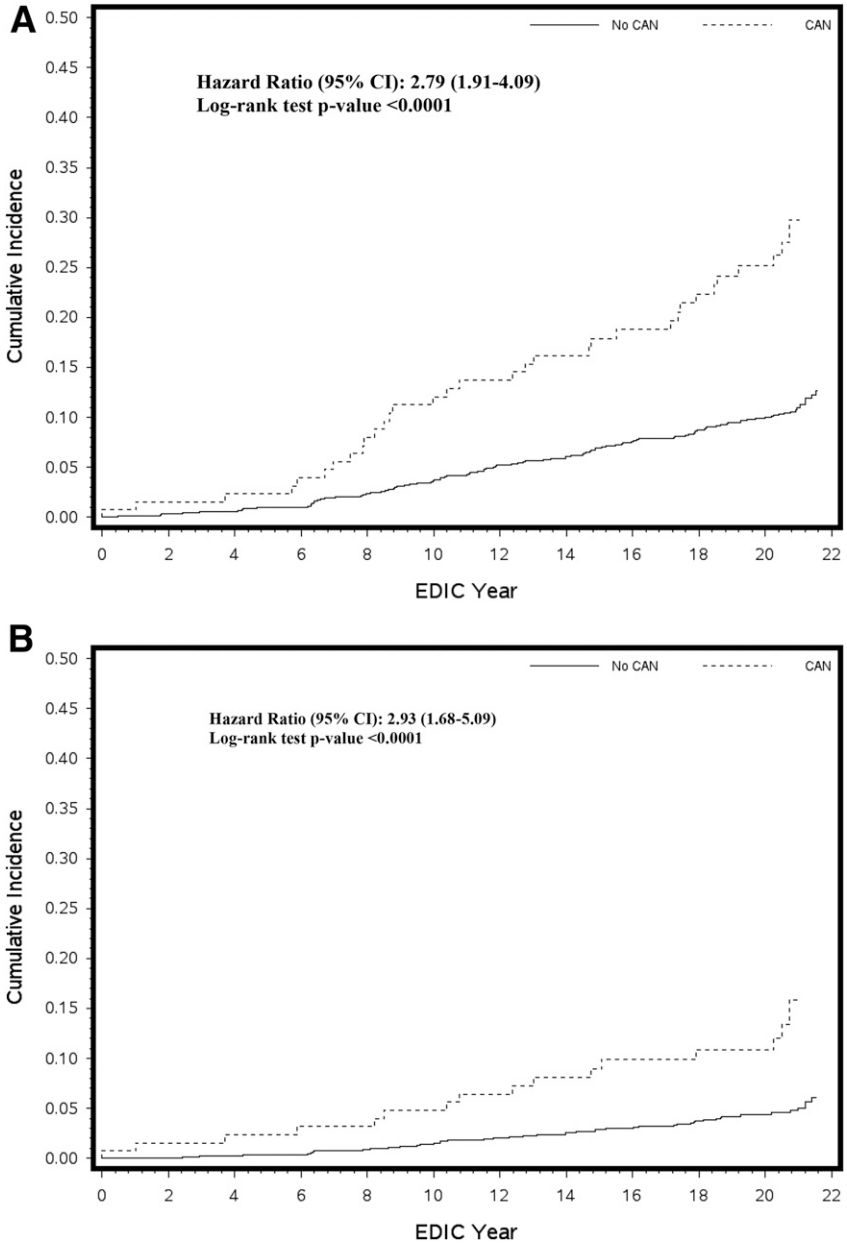

Figure 1—*A*: Cumulative incidence of the first occurrence of any CVD by CAN status at DCCT closeout. *B*: Cumulative incidence of the first occurrence of a nonfatal myocardial infarction, stroke, or death from CVD by CAN status at DCCT closeout.

revised the manuscript for critical content. B.H.B. conducted the statistical analyses and wrote sections of the manuscript. B.Z., C.M., N.H.W., W.H.H., and S.G. reviewed and edited the manuscript. R.G.-K. participated in the data analysis and interpretation, wrote sections of the manuscript, and reviewed and edited the manuscript. B.H.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented at the 52nd European Association for the Study of Diabetes Annual Meeting, Munich, Germany, 12–16 September 2016 and at the 26th Annual Meeting of the Diabetic Neuropathy Study Group of the European Association for the Study of Diabetes, Bucharest, Romania, 9–12 September 2016.

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