Risk Factors for Longitudinal Resting Heart Rate and Its Associations With Cardiovascular Outcomes in the DCCT/EDIC Study

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OBJECTIVE

Individuals with diabetes have higher resting heart rate compared with those without, which may be predictive of long-term cardiovascular disease (CVD) risk. Using data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, we evaluated whether the beneficial effect of intensive versus conventional diabetes therapy on heart rate persisted, the factors mediating the differences in heart rate between treatment groups, and the effects of heart rate on future CVD risk.

RESEARCH DESIGN AND METHODS

Longitudinal changes in heart rate, from annual electrocardiograms over 22 years of EDIC follow-up, were evaluated in 1,402 participants with type 1 diabetes. Linear mixed models were used to assess the effect of DCCT treatment group on mean heart rate over time, and Cox proportional hazards models were used to estimate the effect of heart rate on CVD risk during DCCT/EDIC.

RESULTS

At DCCT closeout, 52% of participants were male and mean ± SD age was 33 ± 7 years, diabetes duration 12 ± 5 years, and HbA_{1c} 7.4 ± 1.2% (intensive) and 9.1 ± 1.6% (conventional). Through EDIC, participants in the intensive group had significantly lower heart rate in comparison with the conventional group. While significant group differences in heart rate were fully attenuated by DCCT/EDIC mean HbA_{1c}, higher heart rate predicted CVD and major adverse cardiovascular events independent of other risk factors.

CONCLUSIONS

After 22 years of follow-up, former intensive versus conventional therapy remained significantly associated with lower heart rate, consistent with the long-term beneficial effects of intensive therapy on CVD. DCCT treatment group effects on heart rate were explained by differences in DCCT/EDIC mean HbA_{1c}.

Individuals with diabetes have higher resting heart rate compared with those without diabetes; however, the mechanisms are not clear (1–3). Additionally, higher heart rate is associated with an increased risk of cardiovascular disease (CVD) and cardiovascular mortality (4–10). Previous reports from the Diabetes Control and Complications Trial (DCCT) demonstrated that intensive compared with conventional diabetes therapy

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was associated with a significantly lower resting heart rate, with differences in means of 1.4 bpm for adults and 3 bpm for adolescents ($P = 0.0014$ and 0.013, respectively) (11). During the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study, resting heart rate remained significantly lower in the former intensively treated group ($P < 0.01$) through EDIC year 10, with a 1–2 bpm difference in comparison with the former conventional group. Adjustment for various covariates, including use of antihypertensive medication, such as β-blockers, and physical activity, did not attenuate these effects. More recent work by the DCCT/EDIC study examining risk factors for CVD in type 1 diabetes demonstrated that higher mean pulse rate, measured during annual physical examinations, was an independent, significant predictor of both any CVD and major adverse cardiovascular events (MACE) (12).

Herein, we evaluate how long the beneficial effect of former intensive therapy persists on resting heart rate over an additional 12 years of EDIC follow-up and what factors account for or mediate the differences observed between the two former DCCT treatment groups during EDIC ($n = 1,402$). Furthermore, we evaluate the effect of resting heart rate, as derived from annual electrocardiograms (ECGs), as a predictor of CVD risk during the combined DCCT and EDIC study ($n = 1,441$).

RESEARCH DESIGN AND METHODS

The DCCT/EDIC study has previously been described (13–15). Briefly, 1,441 participants with type 1 diabetes aged 13–39 years were enrolled between 1983 and 1989 in the DCCT, a randomized clinical trial designed to evaluate the relationship between glycemic control and the development and progression of microvascular complications. Approximately one-half of the cohort ($n = 711$) was randomized to receive intensive diabetes therapy with a goal of maintaining blood glucose and HbA_{1c} levels within a near-normal nondiabetes range while minimizing the frequency of significant hypoglycemia as much as possible. The remaining participants ($n = 730$) were assigned to conventional therapy with a goal of clinical well-being and freedom from symptoms related to hyper- and hypoglycemia without preconceived targets of blood glucose and HbA_{1c}. Two parallel cohorts were recruited. The primary prevention cohort ($n = 726$) had 1–5 years' diabetes duration, no diabetic retinopathy (absence of microaneurysms or worse), and a urine albumin excretion rate (AER) <40 mg/24 h at DCCT baseline. The secondary intervention cohort ($n = 715$) had 1–15 years of diabetes duration, mild-to-moderate nonproliferative diabetic retinopathy, and an AER ≤200 mg/24 h at DCCT baseline.

After an average of 6.5 years (range 3–9) of follow-up, the DCCT demonstrated the beneficial effects of intensive therapy, and all participants were encouraged to adopt intensive therapy and returned to their own health care providers for ongoing diabetes care. In 1994, 96% of the surviving DCCT cohort enrolled in the EDIC observational study, designed to evaluate the longer-term effects of glycemic control on the risk of both micro- and macrovascular complications. Of survivors, 94% percent ($n = 1,251$) continue to be followed after an additional 22 years of EDIC follow-up (total mean follow-up of ~29 years).

DCCT/EDIC Evaluations

Quarterly DCCT and annual EDIC visits included a detailed medical history that included collection of demographic and behavioral risk factors and medical outcomes with standardized data forms and a physical examination that included measurements of height, weight, and sitting blood pressure and pulse rate (15). Blood samples were collected at each study visit and assayed centrally for HbA_{1c} with high-performance ion-exchange liquid chromatography (16). Fasting lipids (triglycerides and total and HDL cholesterol) were measured annually during DCCT and on alternate years during EDIC and evaluated centrally. LDL was calculated with the Friedewald equation (17).

Renal assessments (AER or albumin-creatinine ratio) were measured annually during the DCCT and on alternate years during EDIC. AER was measured from 4-hour urine samples from DCCT baseline to EDIC year 18 and subsequently from spot urine samples, with AER estimated using the ratio of urine albumin and creatinine concentrations (18). The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation from annually measured serum creatinine. Persistent microalbuminuria was defined as a sustained AER ≥30 mg/24 h at two consecutive visits. Kidney disease was defined as an impaired estimated glomerular filtration rate <60 mL/min/1.73 m^2. Standardized seven-field fundus photographs were obtained every 6 months during DCCT and in one-quarter of the cohort annually during EDIC and graded centrally. Based on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, proliferative diabetic retinopathy was defined by neovascularization observed on fundus photograph grading or self-reported and/or confirmed scatter photocoagulation. Cardiovascular autonomic neuropathy (CAN) was assessed with standardized cardiovascular reflex tests (R-R response to paced breathing [R-R variation], the Valsalva maneuver, and postural changes in blood pressure) administered up to five times during DCCT (baseline and years 2, 4, 6, and 8) and twice during EDIC (years 13/14 and 16/17) as previously described (19). Testing was performed with Hokanson ANS2000 devices (Hokanson, Bellevue, WA), and results were analyzed centrally. CAN was defined as either R-R variation <15, or R-R variation between 15 and 19.9 plus either a Valsalva ratio ≤1.5 or a supine-to-standing drop of 10 mmHg in diastolic blood pressure (19,20).

Electrocardiography

Twelve-lead ECGs were obtained at DCCT baseline, every 2 years during the DCCT, at closeout of the DCCT, and annually during EDIC with a standardized procedure with the participant at rest in the supine position. ECG abnormalities were classified with the standards of the Minnesota ECG classification (21). ECGs were processed centrally at the University of Minnesota ECG Reading Center, Minneapolis, MN, during DCCT and EDIC years 1–11 and at the Epidemiological Cardiology Research Center (EPICARE) at Wake Forest School of Medicine during EDIC years 12–22. For the purpose of this analysis, resting heart rate was measured only from ECGs showing normal sinus rhythm with exclusion of those with atrial fibrillation/flutter, supraventricular/ventricular rhythm, advanced atrioventricular block, electronic pacemaker, wandering atrial pacemaker, Wolff-Parkinson-White pattern, or any non-sinus rhythm ECG. A comparison between sitting pulse rate measured during the physical examination, which was used for prior DCCT/EDIC reports, and resting heart rate by ECG from the same visit

demonstrated high agreement between the two methods (Supplementary Fig. 1).

Cardiovascular Outcomes

Cardiovascular outcomes were ascertained by self-report during all visits (22). If reported, nonstudy medical records and annual graded ECGs were centrally adjudicated by a Mortality and Morbidity Review Committee masked to DCCT treatment group, HbA_{1c}, and glucose levels. The primary CVD outcome (any CVD) was defined as the time to cardiovascular death or time to the first occurrence of nonfatal myocardial infarction (MI), nonfatal stroke, subclinical MI detected on an annual ECG, angina confirmed by ischemic changes with exercise tolerance testing or by clinically significant obstruction on coronary angiography, revascularization (with angioplasty or coronary artery bypass), or congestive heart failure (paroxysmal nocturnal dyspnea, orthopnea, or marked limitation of physical activity caused by heart disease). The secondary CVD outcome was MACE, defined as the time to cardiovascular death, nonfatal MI, or nonfatal stroke (12). Based on an a priori power assessment, the DCCT/EDIC study embargoed CVD risk factor analysis until 100 former DCCT conventional treatment group participants had experienced a CVD event. The embargo criteria were met midway through EDIC year 20, and the CVD data presented herein are based on the data lock that occurred on 31 December 2013.

Statistical Analyses

For this analysis, in addition to the current value, the updated DCCT mean, updated EDIC mean, and time-weighted DCCT/EDIC mean HbA_{1c} values are reported. The updated DCCT mean HbA_{1c} reflects the cumulative glycemic exposure from DCCT baseline up to and including the HbA_{1c} at DCCT closeout, while the EDIC mean HbA_{1c} reflects the average from EDIC year 1 to 22. The time-weighted DCCT/EDIC HbA_{1c} mean was calculated by weighting each value by the time interval since the last measurement.

Linear mixed models were used for assessment of the effect of treatment group on mean resting heart rate by ECG over repeated time points between EDIC years 1 and 22, unadjusted and minimally adjusted for primary prevention versus secondary intervention cohort, sex, race, and DCCT closeout age and duration of diabetes. The EDIC study year was included in the models as a class effect, and each model assumed a compound symmetry structure. The signed *t* statistic was used as a measure of the magnitude and direction of the association between each risk factor and heart rate. The interaction between treatment group and time was evaluated. Additional factors, specifically current smoking, BMI, blood pressure, lipids, renal function, retinopathy status, medication use, and glycemic control, were included separately as time-dependent covariates in the linear mixed models to evaluate the potential mediating effect of each factor on the relationship between treatment group and resting heart rate. Data on 1,402 participants with follow-up data between EDIC years 1 and 22 were used ($n = 698$ intensive group, $n = 704$ conventional group).

Separate linear models were used to test the prolonged benefit of intensive therapy despite similar HbA_{1c} levels between treatment groups in EDIC, referred to as the metabolic memory hypothesis (23), by evaluation of treatment group differences in mean heart rate separately at each EDIC year with adjustment for the DCCT closeout heart rate. This assumes that the two treatment groups have the same heart rate at DCCT closeout, with examination of changes during EDIC. Each model was also adjusted for primary prevention versus secondary intervention cohort, sex, race, DCCT closeout age, and duration of diabetes.

Cox proportional hazards regression models were used to estimate the effect of resting heart rate on the risk of CVD or MACE during both the DCCT and EDIC study periods ($n = 1,441$). The same set of risk factors identified in a previous DCCT/EDIC analysis (12) was included in each model, with the exception of substitution of heart rate (derived from ECGs) for pulse rate. Based on the previous findings, smoking, physical activity, and BMI were not retained as significant predictors in the final multivariable model for any CVD and were therefore not included in these analyses. Risk factors were included in the models as fixed (e.g., baseline age and duration of diabetes) or time-dependent covariates representing the current (most recent) measurement or the updated mean of all follow-up values. Covariates are listed in the order of significance as indicated by the unsigned *z* value, used to differentiate covariate effects with $P < 0.0001$ (two-sided), equivalent to a $|z| \geq 3.89$. All analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC). Two-sided $P \leq 0.05$ was considered statistically significant.

RESULTS

The characteristics of participants at DCCT closeout by DCCT treatment group are presented in Table 1. By design, at the end of the DCCT, participants in the intensive group had significantly lower HbA_{1c} values compared with those in the conventional group (mean ± SD 7.4 ± 1.2% vs. 9.1 ± 1.6%, respectively; $P < 0.0001$). As previously reported, intensively treated participants had a lower prevalence of microalbuminuria, retinopathy, and CAN ($P < 0.05$) (24). However, intensive treatment was associated with a significant increase in BMI (mean difference 1.5 kg/m^2; $P < 0.0001$). At DCCT closeout, heart rate was significantly lower in the intensive versus conventional group (68.9 ± 11.5 vs. 70.8 ± 11.7 bpm, respectively; $P = 0.0029$).

Effect of DCCT Treatment on Heart Rate

Between DCCT closeout and EDIC year 1, the mean heart rate decreased by 1.4 bpm (1.8 in the intensive group and 0.9 in the conventional group). Figure 1 presents the unadjusted means and SEs for heart rate by DCCT treatment group over the course of the EDIC study follow-up. During EDIC, heart rate increased in both treatment groups during the first 7 years and began to decline steadily thereafter. Participants in the intensive treatment group had a significantly lower mean ± SE heart rate than participants in the conventional treatment group (difference −1.76 ± 0.48 bpm, $P = 0.0003$) (Fig. 1 and Table 2). There was a significant interaction between treatment group and duration of follow-up in EDIC ($P = 0.0001$). The mean difference in heart rate between groups (intensive vs. conventional) was −2.14 ± 0.50 bpm ($P < 0.0001$) for the first 10 years in EDIC and −1.15 ± 0.52 bpm ($P = 0.0276$) for EDIC years 11–22.

To address metabolic memory in EDIC since the end of the DCCT, we regressed heart rate on treatment group adjusting

Table 1—Demographic and clinical characteristics of DCCT/EDIC participants at DCCT closeout by DCCT treatment group

	Intensive (N = 698)	Conventional (N = 704)	P*
Cohort (% primary prevention)	341 (49)	364 (52)	0.28
Sex (% female)	343 (49)	326 (46)	0.28
Race (% White)	673 (96)	678 (96)	0.91
Age (years)	33.7 ± 7.0	33.1 ± 7.0	0.10
Duration of diabetes (years)	12.3 ± 4.9	11.9 ± 4.8	0.10
Current cigarette smoker	160 (23)	158 (23)	0.81
Physical activity			
Light	259 (37)	226 (32)	0.19
Mild	353 (51)	391 (56)	
Moderate	37 (5)	33 (5)	
Strenuous	44 (6)	49 (7)	
BMI (kg/m^2)	26.6 ± 4.3	25.1 ± 3.1	<0.0001
Blood pressure (mmHg)			
Systolic	116.6 ± 11.5	116.5 ± 11.9	0.74
Diastolic	74.9 ± 8.7	74.3 ± 8.9	0.27
Lipids (mg/dL)			
Total cholesterol	180.5 ± 30.8	184.1 ± 37.5	0.13
Triglycerides	84.4 ± 52.7	87.9 ± 51.1	0.05
HDL cholesterol	51.0 ± 12.9	51.8 ± 13.0	0.24
LDL cholesterol	112.6 ± 27.3	114.8 ± 31.9	0.24
Microvascular complications			
Sustained AER ≥30 mg/24 h	53 (8)	99 (14)	<0.0001
Proliferative diabetic retinopathy	12 (2)	40 (6)	<0.0001
CAN	52 (8)	78 (11)	0.02
Glycemic control: HbA$_{1c}$ (%)			
DCCT current HbA$_{1c}$	7.4 ± 1.2	9.1 ± 1.6	<0.0001
DCCT mean HbA$_{1c}$†	7.2 ± 0.9	9.1 ± 1.3	<0.0001
Glycemic control (mmol/mol)			
DCCT current HbA$_{1c}$	57.5 ± 12.7	76.3 ± 17.1	<0.0001
DCCT mean HbA$_{1c}$†	55.6 ± 10.1	75.8 ± 13.9	<0.0001
Heart rate (bpm)‡	68.9 ± 11.5	70.8 ± 11.7	0.0029

Data are means ± SD or N (%). *Treatment group comparisons were made with use of the Wilcoxon rank sum test for quantitative measurements or the χ^2 test for categorical variables. †The DCCT mean HbA$_{1c}$ reflects the cumulative glycemic exposure from DCCT baseline up to and including the HbA$_{1c}$ at DCCT closeout. ‡Heart rate derived from DCCT closeout ECG.

for the DCCT closeout heart rate. Mean heart rate was significantly lower in the former intensive treatment group compared with the conventional group up through EDIC year 5 ($P < 0.05$) but not thereafter. In addition, the magnitude of the effect of former intensive treatment on heart rate declined over time (Supplementary Table 1).

Potential Mediators of Treatment Group Differences in Heart Rate

Table 2 presents the association of DCCT treatment group and other risk factors with heart rate during EDIC. Treatment group differences in heart rate remained significant ($P = 0.0002$) after minimal adjustment for primary prevention versus secondary intervention cohort, sex, race, and DCCT closeout age and duration of diabetes. For evaluation of the potential mediating effect of glycemia and other risk factors on the relationship between treatment group and heart rate, separate adjustments were made for each covariate listed in Table 2. Longitudinal changes in heart rate were positively associated with higher BMI, systolic and diastolic blood pressure, total cholesterol, triglycerides, and HbA$_{1c}$ and smoking. Participants with microalbuminuria had significantly higher mean ± SE heart rates during EDIC compared with those with normoalbuminuria (2.55 ± 0.25 bpm, $P < 0.0001$), and concurrent β-blocker usage significantly decreased mean heart rate by 5.55 ± 0.25 bpm ($P < 0.0001$).

The significant treatment group differences in mean ± SE heart rate ($\beta = -1.77 \pm 0.47$, $P = 0.0002$ minimally adjusted) were largely unaffected by separate inclusion of the EDIC current or EDIC mean HbA$_{1c}$ in the models but were fully attenuated after separate adjustment for the DCCT/EDIC mean HbA$_{1c}$ (0.65 ± 0.45 bpm, $P = 0.1435$).

Association of Heart Rate with Cardiovascular Risk

During the combined DCCT/EDIC study, there were 184 participants who experienced a CVD event: 82 from the former intensive treatment group versus 102 from the conventional treatment group. Specifically for MACE, there were 88 participants who experienced an event: 39 intensive versus 49 conventional. Table 3 presents the association of heart rate with the risk of any CVD or MACE during both DCCT and EDIC after adjustment for other known CVD risk factors. The hazard ratio (HR) for heart rate per 10 bpm, with adjustment only for DCCT baseline age, was 1.11 (95% CI 1.07, 1.15) for any CVD and 1.14 (95% CI 1.07, 1.21) for MACE. After adjustment for other known risk factors identified in previous DCCT/EDIC analyses (Table 3), the HRs decreased slightly (HR 1.09 [95% CI 1.03, 1.15] for any CVD and HR 1.13 [95% CI 1.05, 1.21] for MACE) but remained statistically significant ($P < 0.01$).

CONCLUSIONS

The results of this study demonstrate that the beneficial effect of former diabetes intensive therapy on heart rate persisted for >22 years of follow-up in EDIC. On average, participants in the former intensive treatment group had a lower mean ± SE heart rate of 1.76 ± 0.48 bpm compared with those in the conventional treatment group, with larger differences observed during EDIC years 1–10 than during EDIC years 11–22. The ~2 bpm difference in heart rate over 22 years of follow-up in DCCT/EDIC indicates that an average intensive treatment group participant had ~23 million fewer heart beats than an average conventional participant.

Our analyses demonstrate a pattern of an initial increase in heart rate followed by a decline in both treatment groups over time. Curiously, the Pittsburgh Epidemiology of Diabetes Complications (EDC) prospective cohort study of childhood-onset type 1 diabetes also demonstrated a decline in pulse rate after 8 years of follow-up, similar to Fig. 1; however, diabetes duration at EDC year 8 was ~26 years

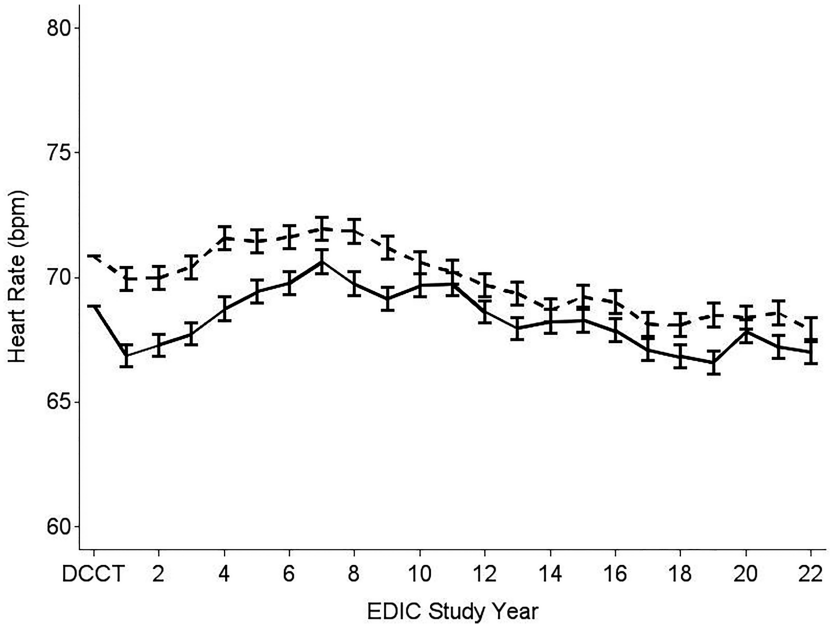

Figure 1—Unadjusted mean ± SE heart rate during EDIC by DCCT treatment group (conventional, dashed; intensive, solid). The DCCT value is the measurement taken at DCCT closeout.

compared with ~20 years in EDIC. Additionally, in a previous analysis of the DCCT/EDIC cohort, we observed a similar trend with diastolic blood pressure, whereby it increased during the DCCT and the first 6–8 years of EDIC and began to fall thereafter (25). This was accompanied by an increasing prevalence of antihypertensive medication use during EDIC (6% at year 1 vs. 60% by year 18), some of which could have also had a direct impact on heart rate. While we have no clear explanation for these findings, some potential reasons for observing this pattern in heart rate could be related to differences in some of the factors known to affect heart rate that can change over time including age, use of various medications, changes in weight, and intensity and duration of physical activity. It is also possible that early intensive therapy had different impacts on the various pathogenic pathways and biological mechanisms associated with autonomic neuronal function and on the temporal relationship of the parasympathetic-sympathetic balance that regulates heart rate.

We previously reported that there were significant DCCT treatment group effects on heart rate, which persisted through EDIC year 10, consistent with other long-term benefits of intensive

Table 2—Association of DCCT treatment group and other CVD risk factors with heart rate during EDIC

	Effect of covariate on heart rate			Intensive vs. conventional adjusted for covariate		
	β ± SE	*t* statistic	*P*	β ± SE	*t* statistic	*P*
Treatment effect on heart rate						
Unadjusted				−1.76 ± 0.48	−3.66	0.0003
Minimally adjusted				−1.77 ± 0.47	−3.77	0.0002
Time-dependent covariates						
Current cigarette smoker (yes vs. no)	0.70 ± 0.23	3.09	0.0021	−1.78 ± 0.47	−3.79	0.0002
BMI (per kg/m^2)	0.23 ± 0.02	9.90	<0.0001	−1.94 ± 1.47	−4.17	<0.0001
Blood pressure (per 10 mmHg)						
Systolic	0.58 ± 0.04	13.98	<0.0001	−1.74 ± 0.46	−3.76	0.0002
Diastolic	0.57 ± 0.06	9.12	<0.0001	−1.79 ± 0.47	−3.84	0.0001
Lipids (per 10 mg/dL)						
Total cholesterol	0.29 ± 0.02	14.64	<0.0001	−1.66 ± 0.47	−3.55	0.0004
Triglycerides	0.15 ± 0.01	12.21	<0.0001	−1.63 ± 0.47	−3.51	0.0005
Microvascular complications (yes vs. no)						
Sustained AER ≥30 mg/24 h	2.55 ± 0.25	10.12	<0.0001	−1.50 ± 0.47	−3.19	0.0014
Estimated GFR <60 mL/min/1.73 m^2	−1.55 ± 0.36	−4.25	<0.0001	−1.81 ± 0.47	−3.83	0.0001
Any proliferative diabetic retinopathy	2.45 ± 0.37	6.61	<0.0001	−1.22 ± 0.48	−2.53	0.0114
Medication use (yes vs. no)						
ACE inhibitor/ARB use	−0.18 ± 0.14	−1.26	0.2079	−1.78 ± 0.47	−3.77	0.0002
β-Blocker use	−5.55 ± 0.25	−21.95	<0.0001	−1.88 ± 0.48	−3.93	<0.0001
Calcium channel blocker use	−0.53 ± 0.26	−2.03	0.0430	−1.77 ± 0.47	−3.76	0.0002
Glycemic control (per 10% increase)						
EDIC current HbA_{1c}	0.44 ± 0.04	9.82	<0.0001	−1.76 ± 0.46	−3.82	0.0001
EDIC mean HbA_{1c}*	1.69 ± 0.09	19.00	<0.0001	−1.45 ± 0.44	−3.30	0.0010
DCCT/EDIC mean HbA_{1c}*	2.24 ± 0.10	22.13	<0.0001	0.65 ± 0.45	1.46	0.1435

Data are β estimates ± SE, *t* statistics, and *P* values from separate linear mixed models unadjusted; minimally adjusted for primary prevention vs. secondary intervention cohort, sex, race, and DCCT closeout age and duration of diabetes; and fully adjusted separately for each risk factor as a time-dependent covariate spanning EDIC years 1–22. The signed *t* statistic corresponds to the magnitude and directionality of the association. HbA_{1c} values were log transformed for analyses. For each measurement of HbA_{1c}, the change in heart rate is presented per 10% increase in HbA_{1c} and calculated as $\log(1.1^{\beta})$. ARB, angiotensin receptor blocker; GFR, glomerular filtration rate. *The EDIC mean HbA_{1c} reflects the cumulative glycemic exposure from EDIC year 1 to 22. The time-weighted HbA_{1c} arithmetic mean was calculated by weighting of each value by the time interval since the last measurement.

Table 3—Final multivariable Cox models for any CVD and MACE as a function of fixed and time-dependent covariates during DCCT/EDIC

	HR (95% CI)	*z* test value	*P*
Any CVD*			
Mean pulse rate (per 10 bpm)	1.39 (1.11, 1.74)	2.83	0.0050
Mean heart rate (per 10 bpm)	1.09 (1.03, 1.15)	2.90	0.0038
MACE†			
Mean pulse rate (per 10 bpm)	1.60 (1.16, 2.20)	2.85	0.0050
Mean heart rate (per 10 bpm)	1.13 (1.05, 1.21)	3.17	0.0015

HRs and *P* values are from four separate multivariable Cox proportional hazards regression models with fixed baseline and time-dependent (current and updated mean) covariates measured during DCCT and EDIC. Models using the mean pulse rate were published in 2016 (12). The current analysis used heart rate measured during the ECGs and replicated the models with the same list of covariates as was used for the previous DCCT/EDIC study. *Any CVD models are adjusted for DCCT baseline age, mean HbA_{1c}, mean systolic blood pressure, current triglycerides, baseline duration of diabetes, current use of ACE inhibitors, baseline family history of MI, and mean LDL cholesterol. †MACE models are adjusted for DCCT baseline age, mean HbA_{1c}, current smoking, current triglycerides, mean systolic blood pressure, current LDL cholesterol, baseline duration of diabetes, and current use of ACE inhibitors.

therapy (11). In models adjusted for heart rate at DCCT closeout, we demonstrated that the former intensive treatment group had significantly lower heart rate compared with the former conventional group up to EDIC year 5, suggesting a waning of the metabolic memory phenomenon that has similarly been demonstrated for other complications such as retinopathy, nephropathy, and neuropathy (26–29). The DCCT/EDIC study has shown a similar prolonged effect of prior intensive therapy on the prevalence and incidence of CAN (19,26), whereby the former DCCT intensively treated participants had a significantly lower prevalence of CAN and a 31% reduced risk of incident CAN in EDIC year 13/14 compared with the DCCT conventionally treated participants. The beneficial effect of former intensive therapy on the risk of incident CAN was mostly explained by the differences in DCCT/EDIC mean HbA_{1c}.

The biological mechanisms underlying the association of mean HbA_{1c} and heart rate are largely unknown; however, mechanisms that impact neuronal function and the balance of parasympathetic tone and sympathetic activity may play a role (30,31). Furthermore, prior investigations in the DCCT/EDIC study shed light on possible mechanisms of metabolic memory. First, noninvasive skin measures of advanced glycation end products (skin intrinsic fluorescence) have previously been shown to be associated with both CAN and R-R variation in participants assigned to the DCCT conventional treatment group, even after adjustment for total glycemic exposure (32). Secondly, in a subset of DCCT/EDIC participants, genome-wide analysis of DNA methylation from blood has identified numerous CpG sites that are highly significantly associated with mean DCCT HbA_{1c}. Some of these methylation sites are also associated with renal and retinal long-term complications of type 1 diabetes (33). However, the mechanisms remain unclear. But whether changes in methylation patterns associate with changes in heart rate over time is not known. Further longitudinal investigations of biological mechanisms may help clarify the exact mechanisms.

In the current study, higher heart rate across 22 years of follow-up was associated with smoking and microalbuminuria and with higher BMI, blood pressure, lipids, and HbA_{1c}—all documented CVD risk factors. Examination of the coprogression of CVD risk factors during 30 years of follow-up in the combined DCCT/EDIC study showed a robust association of current HbA_{1c} level with pulse rate, as measured by physical examination (25). Moreover, both BMI and smoking were positively associated with pulse rate, while physical activity was associated with lower pulse rate.

The treatment group differences in heart rate were largely explained by the differences in DCCT/EDIC mean HbA_{1c} but were unaffected by separate adjustments for the current or EDIC mean HbA_{1c}. As reported previously, HbA_{1c} levels in the two treatment groups came together at the beginning of the EDIC follow-up period and remained similar throughout follow-up. Furthermore, our previous work has demonstrated that, not surprisingly, participants with CAN had significantly higher mean pulse rates, as measured by physical examination, compared with those without CAN (34). However, since we are limited by the low frequency of ascertainment of CAN during EDIC, we cannot accurately assess whether CAN mediates the differences observed between the two former DCCT treatment groups, particularly during the first 10 years of the EDIC study, when the separation was greatest.

Previous studies in people with type 2 diabetes have demonstrated the prognostic importance of resting heart rate on the prediction of all-cause mortality, cardiovascular death, and major cardiovascular outcomes (35). In addition, higher pulse rate has been shown to be associated with poor glycemic control in people with type 1 diabetes (25) and with higher risk of CVD in patients with type 1 diabetes and in the general population (4,5). In a previous analysis of the DCCT/EDIC study, the mediation of the effect of HbA_{1c} on CVD risk was examined, and pulse rate, as measured by physical examination, was identified as one of the potential mediators (36). Those findings demonstrated that >10% of the effect of HbA_{1c} on CVD risk was explained by pulse rate with consideration both individually and jointly in the model.

Acknowledging the lack of standardization for measurement of pulse rate measured during the physical exam, in the current analysis we used heart rate measured during the ECGs and replicated the models with the same list of covariates as was used for the previous DCCT/EDIC study where pulse rate was reported. ECG-measured heart rate was significantly associated with both CVD and MACE and reported as an HR per 10-bpm change (~1 SD) in mean heart rate. Across these two studies, higher heart rate and higher pulse rate both increased CVD risk and shared a common directionality in effect but with variation in the magnitude of the HR. However, although the HR for pulse rate (HR 1.39) was higher in magnitude than the HR for ECG-measured heart rate (HR 1.09), the *z* test values ($z = 2.83$ and 2.90, respectively) were similar, indicating comparable relative importance in the models. The larger effect size may reflect that pulse rate was obtained while the subject

was sitting and heart rate was obtained from ECG while the subject was supine, reflecting different effects of posture, possibly mediated by the autonomic nervous system. Additionally, our results showed that mean pulse rate during EDIC was slightly higher than heart rate derived from ECGs. The reason for this difference may again be related to body position.

After further adjustment for each of the CAN measurements (R-R variation, Valsalva ratio, CAN), the HRs for heart rate presented in Table 3 remained the same (data not shown), suggesting that the association of heart rate with CVD may be independent of CAN. However, it is important to note that the models further adjusted for CAN are only limited to the two time points in which CAN was assessed.

Recently, the association of potential CVD risk factors was examined in the Pittsburgh EDC study (37). Pulse rate was determined by palpating of the radial pulse for 30 s and then multiplying by 2 after a 5-min rest as part of the Hypertension Detection and Follow-up Program (38). In EDC, mean pulse rate was associated with both CVD (HR 1.018 [95% CI 1.007, 1.029]) and MACE (HR 1.021 [95% CI 1.008, 1.034]) in the univariable model but not in the final multivariable model. The mean age of the EDC cohort was similar to that of the EDIC participants; however, the diabetes duration was longer in EDC. Moreover, there was no exclusion for the presence of CVD risk factors at EDC baseline. Whether the differences between the studies relate to the persistence of heart rate as an independent CVD predictor, even after adjustment for CAN measures in DCCT/EDIC but not in EDC, is unclear.

In conclusion, this study has demonstrated that prior DCCT intensive treatment was associated with lower heart rate after 22 years of follow-up in EDIC in comparison with conventional treatment. This treatment group difference in heart rate was largely explained by the differences in DCCT/EDIC mean HbA_{1c}. These findings further emphasize the importance of striving for optimal glycemic control to reduce the risk of CVD associated with type 1 diabetes. As similarly demonstrated in other cohorts, we confirm that heart rate, a common clinical measure, might be used for CVD risk stratification to guide a more personalized approach in managing patients with type 1 diabetes.

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