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ORIGINAL ARTICLE

Utility of using electrocardiogram measures of heart rate variability as a measure of cardiovascular autonomic neuropathy in type 1 diabetes patients

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ABSTRACT

Aims/Introduction: Cardiovascular autonomic neuropathy (CAN) is a predictor of cardiovascular disease and mortality. Cardiovascular reflex tests (CARTs) are the gold standard for the diagnosis of CAN, but might not be feasible in large research cohorts or in clinical care. We investigated whether measures of heart rate variability obtained from standard electrocardiogram (ECG) recordings provide a reliable measure of CAN.

Materials and Methods: Standardized CARTs (R-R response to paced breathing, Valsalva, postural changes) and digitized 12-lead resting ECGs were obtained concomitantly in Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications participants (n = 311). Standard deviation of normally conducted R-R intervals (SDNN) and the root mean square of successive differences between normal-to-normal R-R intervals (rMSSD) were measured from ECG. Sensitivity, specificity, probability of correct classification and Kappa statistics evaluated the agreement between ECG-derived CAN and CARTs-defined CAN.

Results: Participants with CARTs-defined CAN had significantly lower SDNN and rMSSD compared with those without CAN ($P < 0.001$). The optimal cut-off points of ECG-derived CAN were <17.13 and <24.94 ms for SDNN and rMSSD, respectively. SDNN plays a dominant role in defining CAN, with an area under the curve of 0.73, indicating fair test performance. The Kappa statistic for SDNN was 0.41 (95% confidence interval 0.30–0.51) for the optimal cut-off point, showing fair agreement with CARTs-defined CAN. Combining SDNN and rMSSD optimal cut-off points does not provide additional predictive power for CAN.

Conclusions: These analyses are the first to show the agreement between indices of heart rate variability derived from ECGs and the gold standard CARTs, thus supporting potential use as a measure of CAN in clinical research and clinical care.

INTRODUCTION

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study showed that intensive glycemic control lowered the risk of cardiovascular autonomic neuropathy (CAN) in type 1 diabetes patients by 45% over the 6.5 years average follow-up period of DCCT, and that this reduced risk persisted through an additional 13 years in the EDIC observational follow-up study[1]. Although often overlooked in practice, CAN has serious consequences, as it is an independent predictor of myocardial dysfunction[2], cardiovascular disease (CVD)[3,4] and mortality[5,6] in diabetes.

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The gold standard for diagnosis of CAN involves several standardized cardiovascular reflex tests (CARTs), including R-R response to deep breathing, the Valsalva maneuver and postural changes in blood pressure[7]. Alternative tests, such as indices of heart rate variability (HRV) obtained from long-term Holter-type electrocardiogram (ECGs), have also been proposed to evaluate CAN[8]. However, these tests are cumbersome to carry out, and might not be easily implemented in clinical practice.

More recently, HRV-derived indices from standard 10-s 12-lead ECG recordings have emerged as more feasible alternative measures of CAN in population studies, and have been shown to independently predict CVD morbidity and mortality in several large cohorts of people with diabetes[5,6]. However, rigorous validation studies evaluating the sensitivity and specificity of these ECG-based HRV indices compared with the gold standard CARTs assessment have not yet been reported.

Herein, we assessed whether optimal diagnostic thresholds for indices of HRV derived from standard 10-s 12-lead ECG recordings could provide a reliable measure of CAN in type 1 diabetes. The DCCT/EDIC study provides a unique opportunity to leverage concomitantly acquired standardized cardiovascular reflex tests and ECG recordings to address this question in a large cohort of individuals with type 1 diabetes.

MATERIALS AND METHODS

Participants

The DCCT/EDIC study has been previously described in detail[9,10]. Briefly, 1,441 individuals with type 1 diabetes enrolled in the DCCT (aged 13–39 years) were randomly assigned to receive either intensive (n = 711) or conventional (n = 730) diabetes therapy. At the end of DCCT (average follow-up period of 6.5 years), participants in the conventional therapy group were taught intensive therapy, and all participants returned to their own healthcare providers for ongoing diabetes care[11]. In 1994, 1,375 (96%) of the surviving DCCT cohort enrolled in the EDIC observational study, and 1,202 (89%) of the surviving cohort continued to actively participate in EDIC year 16 or 17 (2009–2010). In 2010, concurrent CARTs and ECG data were available for 1,089 of these participants (Figure S1).

The George Washington University Committee on Human Research approved the present study (approval number/ID: IRB #040637; approval granted on 10 January 2017).

CARTs-defined CAN evaluations

The DCCT/EDIC study utilized the following CARTs as part of the protocol: deep breathing test (with pacing), Valsalva maneuver and the lying-to-standing (postural) test, with assessments of the heart rate variation (R-R response) and blood pressure response during administration. These tests are considered the gold standard tests for CAN, as endorsed by the Toronto Consensus on Diabetic Neuropathy and the American Diabetes Association[7,12]. These assessments were obtained at DCCT baseline, and DCCT years 2, 4, 6 and 8, and at EDIC years 13/14 and 16/17[1,13,14]. Participants were required to fast, and avoid caffeine and tobacco products, as well as prescription medications (except for their usual insulin regimens), for at least 8 h before CARTs testing. Testing was carried out using the Hokanson ANS2000 devices (Hokanson Inc., Bellevue, WA, USA) and results were analyzed centrally.

CAN, the primary outcome, was defined as either an R-R variation <15, or an R-R variation between 15–19.9 in combination with a Valsalva ratio ≤1.5, or a decrease of >10 mmHg in diastolic blood pressure during 10 min of standing, consistent also with our prior CAN analyses in this large cohort[1,14].

ECG

Twelve-lead resting ECGs were obtained at DCCT baseline, biennially during the DCCT, at DCCT closeout and annually during EDIC using a standardized procedure with the participant at rest in the supine position[15]. ECG tracings were processed centrally at the ECG Reading Center, initially at the University of Minnesota ECG Reading Center (Minneapolis, MN, USA; DCCT baseline to EDIC year 12) and thereafter at the Epidemiological Cardiology Research (EPICARE) Center at Wake Forest School of Medicine (Winston-Salem, NC, USA). In EDIC year 16–17, the former analog paper-based ECG recordings were replaced with digital recordings using GE MAC 1200 electrocardiographs (GE, Milwaukee, WI, USA). Digital ECGs were transmitted electronically through analog phone lines to the ECG Reading Center. After visual inspection for technical errors and quality, digital ECGs were automatically processed using the 2001 version of the GE Marquette 12-SL program (GE). Using the automatically measured R-R intervals, two time-domain HRVs were calculated: (i) the standard deviation of normally conducted R-R intervals (SDNN); and (ii) the root mean square of successive differences between normal-to-normal R-R intervals (rMSSD). The EPICARE ECG Reading Center digitized the paper ECG tracings that could not be read automatically using the Marquette 12-SL program (GE), and developed customized software to derive HRV. Following the recommended standards for measurements of HRV[8], only the ECGs from participants in sinus rhythm were used, and ECGs with arrhythmias, conduction defects and >50% ectopic beats were excluded. The automated measurement of HRV excluded the beat before and the beat after ectopic beats from the HRV measurements. Lower SDNN and rMSSD represented worse autonomic function.

DCCT/EDIC evaluations

The DCCT/EDIC Central Biochemistry Laboratory (University of Minnesota, Minneapolis, MN, USA) carried out all laboratory measurements with standardized methods and quality control assessments. Glycated hemoglobin (HbA1c) was measured quarterly during DCCT and annually during EDIC using high-performance liquid chromatography. The time-weighted mean HbA1c was calculated with weights proportional to the time-interval between visits (1/4 during DCCT, and 1 during EDIC).

Statistical analysis

Among the 1,089 DCCT/EDIC participants with concurrent CAN and ECG measurements at EDIC year 16/17, a simple random sample of 350 participants (Figure S1) was selected for analysis. In this sample, the HRV indices could not be calculated for a total of 39 participants (11%) due to the presence of arrhythmias (n = 8) or poor ECG recording quality (n = 31). The prevalence of CAN was 39% at EDIC year 16/17. The effective sample size of 311 provides approximately 80% power to detect a difference of approximately 0.15 in Kappa value (e.g., 0.35 to 0.5), and a difference of 0.5 standard deviations in a quantitative variable (e.g., age and HbA1c) between readable (n = 311) and un-readable (n = 39) ECGs.

Two approaches for SDNN and rMSSD measures of ECG-derived CAN were used. Based on the prevalence of 39% for CAN at EDIC year 16/17, we first defined SDNN and rMSSD measures using the 39th percentiles of SDNN and rMSSD, respectively. The second approach classified each participant into whichever class (i.e., CAN present or not) had the greatest posterior probability, with optimal cut-off points determined using the Bayes decision rule, as to maximize the probability of correct classification[16–18]. The probability of correct classification was computed as the {(prevalence × sensitivity) + [(1 − prevalence) × specificity]}, where the prevalence was 39%, estimated from the EDIC year 16/17 gold standard CAN evaluation.

To assess whether SDNN and rMSSD can provide a reliable measure of CAN, we evaluated the sensitivity, specificity, probability of a correct classification and the Kappa statistic of each measurement in predicting CAN using the gold standard CART. Sensitivity is the probability of having a positive predicted CAN outcome (based on SDNN or rMSSD) in the presence of CAN assessed by CARTs. Specificity is the probability of having a negative predicted CAN outcome (based on SDNN or rMSSD) in the absence of CAN, as assessed by CARTs. The Kappa statistic evaluated the agreement between CAN, as assessed by CART, and by SDNN and rMSSD. A receiver operating characteristic curve for SDNN was constructed to represent the relationship between the true positive ratio (sensitivity) and the false positive ratio (1-specificity). The area under the receiver operating characteristic curve (AUC) was used to measure the performance of HRV from ECG (e.g., SDNN) in predicting CAN. An AUC value of 0.5 indicates random predictions, whereas an AUC value of 1 indicates perfect prediction. AUC values between 0.70 and 0.79 indicate fair performance.

Separate logistic regression models, adjusted for sex and attained age, assessed whether the associations between mean HbA1c, attained type 1 diabetes duration, systolic blood pressure and any sustained albumin excretion rate (AER) ≥30 mg/day, with the CARTs-defined CAN, were similar to the associations between these risk factors and the ECG-derived CAN. Two-sided P-values <0.05 were considered nominally significant. All analyses used SAS software (version 9.4; SAS Institute, Cary, NC, USA).

RESULTS

The characteristics of the evaluable EDIC cohort (n = 1,089) that had simultaneous evaluations of CAN by CARTs and ECG at EDIC year 16/17, and the randomly selected sample of 350 participants are presented in Table S1. The random sample of 350 participants and 1089 EDIC evaluable cohort were similar in terms of age (51 ± 7 *vs* 51 ± 7 years), sex (43% *vs* 47% female) and mean HbA1c (7.9 ± 1.0 *vs* 8.0 ± 1.0%). Additionally, the characteristics of the 311 participants with valid HRV indices by ECG were similar to the 350 random sample participants and to the 1,089 evaluable EDIC cohort. However, the 39 participants without readable ECGs were slightly older (53 ± 7 years; P = 0.0434) and had higher mean HbA1c levels (8.2 ± 0.7%; P = 0.0276) compared with 311 participants with readable ECG. Of the 311 participants included in these analyses, 120 (38.6%) had CAN based on the gold standard CARTs assessment, compared with 16 (41%) of the 39 participants excluded; there was no difference in beta-blocker use between these groups (data not shown).

Figure 1 shows the density plots of SDNN and rMSSD, and their scatter plots separately by CAN status (present/absent). At EDIC year 16/17, the cut-off points based on ECG using the 39% prevalence of CAN were <17.67 and <22.86 ms for SDNN and rMSSD, respectively, and the optimal cut-off points were <17.13 and < 24.94 ms for SDNN and rMSSD, respectively.

Table 1 shows the association between CARTs and the two HRV measurements, SDNN and rMSSD. Participants with CAN had significantly lower SDNN (18.5 ± 11.0 *vs* 27.3 ± 13.8 ms, $p < 0.0001$) and rMSSD (25.0 ± 13.3 *vs* 32.3 ± 15.8 ms, $P < 0.0001$) relative to participants without CAN.

Table 2 presents the sensitivity, specificity and probability of correct classification of HRV indices in predicting CAN, as well as the Kappa statistics for agreement between HRV indices and CAN. Five thresholds are presented, two for the 39% cut-offs and two for the optimal cut-offs for SDNN and rMSSD separately, and then using the optimal cut-offs for SDNN and rMSSD combined.

Using the 39% prevalence cut-off thresholds, the SDNN and rMSSD had 63.3 and 51.7% sensitivity, 77 and 69.6% specificity, and 71.7 and 62.7% probability of correct classification, respectively. Likewise, using the optimal individual cut-off thresholds, the SDNN and rMSSD had 61.7 and 65.8% sensitivity, 78.5 and 63.4% specificity, and 72 and 64.3% probability of correct classification, respectively. Using the optimal combined cut-off thresholds, the sensitivity, specificity and the probability of correct classification were 61.7, 78.5 and 72%, respectively.

For the ECG-derived CAN measure based on SDNN, the Kappa statistic was 0.40 (95% confidence interval [CI] 0.30–0.51) for the 39% prevalence cut-off threshold, and 0.41 (95% CI 0.30–0.51) for the optimal cut-off threshold. Likewise, for

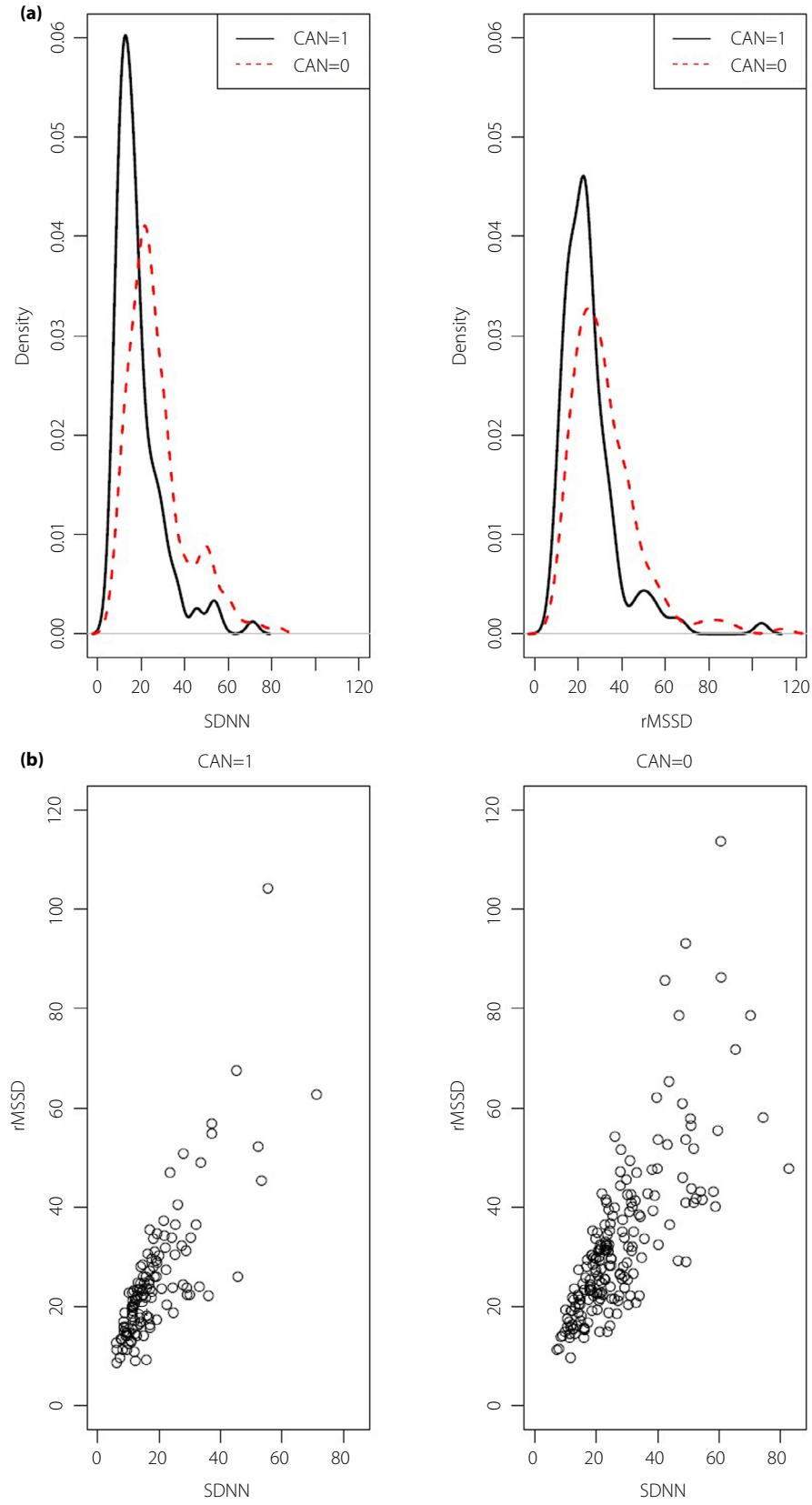

Figure 1 | (a) Density and (b) scatter plots for standard deviation of normally conducted R-R intervals (SDNN) and root mean square of successive differences between normal-to-normal R-R intervals (rMSSD) among cardiovascular autonomic neuropathy (CAN) present (CAN = 1) or absent (CAN = 0).

Table 1 | Distribution of electrocardiogram-derived heart rate variability overall and by cardiovascular autonomic neuropathy presence among a random sample from the Epidemiology of Diabetes Interventions and Complications cohort

CAN Present	SDNN			rMSSD		
	n	Mean ± SD	*P*-value	*n*	Mean ± SD	*P*-value
Total	311	23.9 ± 13.5		311	29.5 ± 15.3	
Yes	120	18.5 ± 11.0	<0.0001	120	25.0 ± 13.3	<0.0001
No	191	27.3 ± 13.8		191	32.3 ± 15.8	

CAN, cardiovascular autonomic neuropathy; rMSSD, root mean square of the successive differences between all normal-to-normal R-R intervals (ms); SD, standard deviation; SDNN, standard deviation of all normal-to-normal R-R intervals (ms).

the ECG-derived CAN measure based on rMSSD, the Kappa statistic was 0.21 (95% CI 0.10–0.32) for the 39% prevalence cut-off threshold, and 0.28 (95% CI 0.17–0.38) for the optimal cut-off threshold.

To further assess whether the ECG-defined CAN indices can be used as a reliable measure of CAN (present or absent), we compared the individual associations between SDNN and risk factors (time-weighted mean HbA1c, attained type 1 diabetes duration, systolic blood pressure and any sustained AER ≥30 mg/dL) to the individual associations between CAN and these risk factors. Adjusted for age and sex, the magnitude and strength of the association between the SDNN-derived CAN (SDNN-CAN) and associated risk factors were similar to using CARTs-defined CAN (Table 3).

Figure 2 shows the receiver operating characteristic curve for the performance of SDNN in predicting CAN. The AUC using the SDNN optimal cut-off was 0.73, indicating a fair test performance for detecting CAN.

We then investigated the associations between time-weighted mean HbA1c, attained duration of type 1 diabetes, systolic blood pressure and any sustained AER ≥30 mg/dL with SDNN-CAN separately among those with CAN present, and then among those with CAN absent (Table 4). None of the associations were significant among those with CAN absent, whereas higher time-weighted mean HbA1c values and the presence of any sustained AER ≥30 mg/dL were associated with higher odds of a positive SDNN-CAN outcome among participants with CAN present (i.e., with higher sensitivity). These findings suggest that the SDNN is a better measure of CAN among individuals with higher glycemic levels and presence of any sustained AER≥30 mg/dL. Further analyses confirmed that the Kappa value was significantly higher among participants with time-weighted mean HbA1c values >8% compared with ≤8% (Kappa = 0.50 vs 0.2332, $P = 0.0162$), but not significant for any sustained AER ≥30 mg/dL versus not (Kappa = 0.46 vs 0.33, $P = 0.3095$) when glycemia was not included (data not shown).

DISCUSSION

In the present study, we report the first rigorous assessment of the sensitivity, specificity and probability of correct classification of CAN using indices of HRV derived from short ECG recordings in predicting CAN compared with the more laborious method using the gold standard cardiovascular reflex testing. The DCCT/EDIC participants with CAN had significantly lower SDNN and rMSSD compared with those without CAN, and the probabilities of correct classification using either the 39% prevalence or the optimal cut-off thresholds were higher for SDNN than rMSSD. Of the two HRV measures, SDNN played the dominant role in defining CAN, with an AUC of 0.73, showing fair test performance. Combining optimal cut-off points for both SDNN and rMSSD did not provide additional predictive power for CAN.

Using data from the DCCT/EDIC cohort, we derived optimal cut-offs for SDNN and rMSSD using the standardized definition of CAN based on CARTs. It is notable these cut-offs differ from the reported sex- and race-specific reference ranges for SDNN and rMSSD obtained from the same standard 12-lead ECG recordings in the Multi-Ethnic Study of Atherosclerosis (MESA). In approximately 1,700 MESA participants aged ≥45 years, SDDN cut-offs of 6.1 and 8.2 ms, and rMSSD cut-offs of 6 and 8 were defined as abnormal and borderline, respectively[19], which are substantially lower than the cut-offs identified herein. However, it is important to note that the MESA SDNN and rMDDS cut-offs were defined in a sample of participants free of any CVD or CVD risk factors, including diabetes, and then validated in the entire MESA cohort. The abnormal and borderline values were computed based on the sex- and race-specific second and fifth percentiles, respectively, in lieu of the gold standard CARTs for CAN which was not available[19]. Among 311 DCCT/EDIC participants, the second and fifth percentiles were 7.8 and 9.1 ms for SDNN, and 11.3 and 13.4 ms for rMDDS, respectively. These were slightly higher than the cut-off points defined as abnormal and borderline in the MESA study. However, in contrast to the participants in the DCCT/EDIC study who all had type 1 diabetes and were predominantly (93%) white, the MESA participants were 38% white, 27% black, 23% Hispanic and just 14% with type 2 diabetes. In a cohort of participants in the MESA study who were generally healthy and free of CVD risk factors, including diabetes, the normative cut-offs are expected to be much lower than those derived in the DCCT/EDIC cohort of

Table 2 | Sensitivity, specificity, probability of correct classification, and kappa statistic for electrocardiogram-derived indices

CAN	ECG-derived Indices				Both
	SDNN		rMSSD		
	CAN prevalence (39% cut-off)	Optimal cut-off	CAN prevalence (39% cut-off)	Optimal cut-off	Optimal cut-off
Sensitivity (%)	63.3	61.7	51.7	65.8	61.7
Specificity (%)	77.0	78.5	69.6	63.4	78.5
Probability of correct classification (%)	71.7	72.0	62.7	64.3	72.0
	Kappa (95% CI)	Kappa (95% CI)	Kappa (95% CI)	Kappa (95% CI)	
Kappa statistic	0.40 (0.30, 0.51)	0.41 (0.30, 0.51)	0.21 (0.10, 0.32)	0.28 (0.17, 0.38)	

CAN, cardiovascular autonomic neuropathy; CI, confidence interval; ECG, electrocardiogram; rMSSD, root mean square of the successive differences between all normal-to-normal R-R intervals (ms); SDNN, standard deviation of all normal-to-normal R-R intervals (ms).

participants with type 1 diabetes of >20 years. The cut-offs were determined in this DCCT/EDIC study were based on gold standard CARTs-defined CAN, which was not available in the MESA study. As the CAN prevalence in the present cohort was 39% (much higher than the 2 and 5% assumed in the MESA study), it is not unexpected that the cut-off values identified in this type 1 diabetes cohort are much higher than those defined in the MESA study.

An important benefit of having reliable and easily obtained measures to assess CAN in large cohort studies or clinical trials, is their use for participant phenotyping for chronic complications including CAN, and for risk stratification. For instance, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed that SDNN values in the lowest quartile (<7.185 ms) combined with prolonged QT intervals were independently associated with an increased risk for CVD and all-cause mortality in participants with type 2 diabetes[5], whereas in the MESA cohort, abnormal HRV values were strongly associated with CVD events and all-cause mortality[19]. These same indices were recently used to assess the prevalence of CAN in a large contemporary cohort of patients with type 2 diabetes of short duration participating in the Glycemia Reductions Approaches in Diabetes (GRADE) study, and the prevalence rate for CAN was comparable with data from other cohorts with early type 2 diabetes, such as the ADDITION study, where CAN was assessed with traditional CARTs[20,21].

The strengths of the present analyses include the detailed and comprehensive phenotypic assessments of the DCCT/EDIC cohort over a period of >30 years, which included concomitant cardiovascular reflex tests for CAN and digitized ECGs, which were not available in other large cohort studies with diabetes.

The sensitivity and specificity of the SDNN cut-offs validated herein might not be ideal, which could limit their applicability. However, they do show fair predictive performance comparable with other instruments that have been used successfully to phenotype diabetic peripheral neuropathy in large and diverse cohorts of patients with type 1 and type 2 diabetes[21–25]. As with any other study, the present findings apply to populations similar to the cohort used herein (i.e., middle aged, mostly white individuals with type 1 diabetes), and generalizing these results to other populations (e.g., adolescents or individuals with type 2 diabetes) necessitates further study.

These DCCT/EDIC analyses are the first to show the level of agreement between indices of HRV derived from standard ECGs and the gold standard CARTs. The present findings provide some support for use of HRV derived from standard ECGS as a measure of CAN in clinical research, particularly in studies involving large cohorts or those where assessment using CARTs is not feasible or available. In addition, the relatively straightforward approach in obtaining the ECGs derived HRV can be more easily translated into clinical care practices, and especially useful in evaluating those patients with type 1 diabetes with suboptimal glycemic control and higher risk factor profiles for other complications.

Table 3 | Associations of selected risk factors with cardiovascular autonomic neuropathy and standard deviation of all normal-to-normal R-R intervals[†] in separate logistic regression models[‡]

Risk factor	CAN (yes vs no)			SDNN (yes vs no)		
	Odds ratio (95% CI)	Wald χ^2	*P*-value	Odds ratio (95% CI)	Wald χ^2	*P*-value
Weighted mean HbA1c (%)	1.80 (1.41–2.30)	21.8	<0.0001	1.91 (1.48–2.46)	25.2	<0.0001
Attained duration (years)	1.04 (0.99–1.09)	2.0	0.1606	1.02 (0.97–1.07)	0.6	0.4332
Systolic blood pressure (mmHg)	1.03 (1.01–1.04)	9.6	0.0020	1.02 (1.00–1.04)	5.4	0.0196
Any sustained AER ≥30 (mg/dL, yes vs no)	3.85 (2.17–6.83)	21.3	<0.0001	3.51 (2.00–6.15)	19.1	<0.0001

AER, albumin excretion rate; CAN, cardiovascular autonomic neuropathy; CI, confidence interval; HbA1c, glycated hemoglobin. [†]Using the optimal cut-off for standard deviation of all normal-to-normal R-R intervals(SDNN). [‡]Adjusted for age and sex.

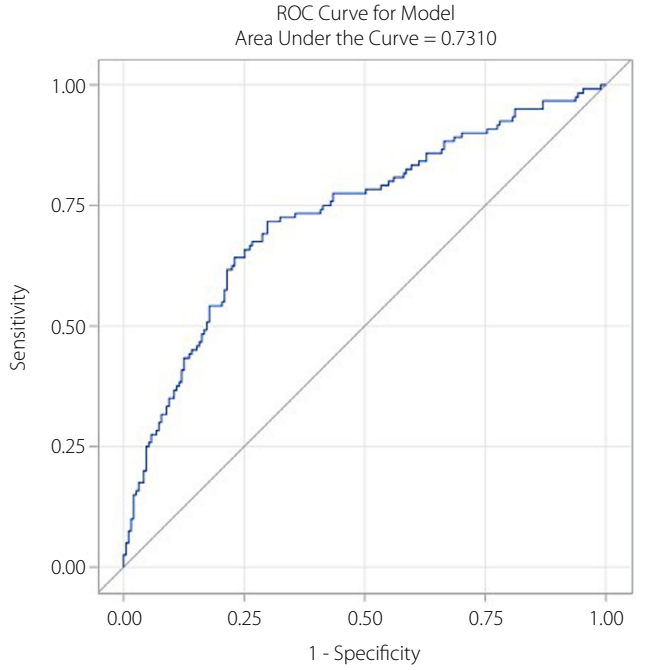

Figure 2 | Receiver operating characteristic (ROC) curve for standard deviation of normally conducted R-R intervals (SDNN).

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A complete list of participants in the DCCT/EDIC Research Group is presented in the Supporting Information.

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Table 4 | Associations between risk factors and standard deviation of all normal-to-normal R-R intervals[†] by cardiovascular autonomic neuropathy status (absent/present) in separate logistic regression models[‡]

	SDNN (CAN absent)			SDNN (CAN present)		
	OR (95% CI)	Wald χ^2	*P*-value	OR (95% CI)	Wald χ^2	*P*-value
Weighted mean HbA1c (%)	1.27 (0.84–1.90)	1.3	0.2549	2.01 (1.37–2.93)	13.0	0.0003
Attained duration (year)	1.00 (0.93–1.07)	0.0	0.9747	1.01 (0.94–1.10)	0.1	0.7270
Systolic blood pressure (mmHg)	1.00 (0.98–1.03)	0.1	0.7391	1.02 (0.99–1.04)	1.3	0.2510
Any sustained AER ≥ 0 (yes vs no)	1.86 (0.76– 4.52)	1.9	0.1730	3.16 (1.30–7.69)	6.4	0.0113

AER, albumin excretion rate; CAN, cardiovascular autonomic neuropathy; CI, confidence interval; HbA1c, glycated hemoglobin. [†]Using the optimal cut-off for standard deviation of all normal-to-normal R-R intervals(SDNN). [‡]Adjusted for age and sex.

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Data collected for the DCCT/EDIC study through 30 June 2017 are available to the public through the NIDDK Repository (https://repository.niddk.nih.gov/studies/edic/). Data collected in the current cycle (July 2017 to June 2022) will be available within 2 years after the end of the funding cycle.

DISCLOSURE

BHB, GL and JML report receiving grants from National Institute of Diabetes, Digestive and Kidney Diseases, during the conduct of the study. RPB, JYB, IB, NHW and EZS declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Cardiovascular autonomic neuropathy (CAN)† electrocardiogram (ECG)-heart rate variability (HRV)‡ sample.
Table S1 | Distributions of age and time-weighted mean glycated hemoglobin overall and by sex.
Appendix S1 | Complete listing of participants in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group.