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Cardiac Autonomic Neuropathy and Risk of Incident Heart Failure Among Adults with Type 2 Diabetes

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Abstract

Aims: Community-based data on the association between cardiac autonomic neuropathy (CAN) and incident heart failure (HF) in type 2 diabetes are limited. We evaluated the association of CAN with incident HF in adults with type 2 diabetes.

Methods and results: This analysis included participants from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study without HF at baseline. CAN was assessed by ECG-based measures of heart rate variability (HRV) and QT interval index (QTI). HRV was measured using standard deviation of all normal-to-normal intervals (SDNN) and root mean square of successive differences between normal-to-normal intervals (rMSSD). CAN was defined using composite measures of the lowest quartile of SDNN and highest quartiles of QTI and heart rate. Multivariable Cox regression models were used to generate adjusted hazard ratios (aHR) for HF in relation to various CAN measures. A total of 7,160 participants (mean age 62.3 [SD:6.4] years, 40.8% women, 61.9% white) were included. Over a median follow-up of 4.9 years (interquartile range:4.0–5.7), 222 participants developed incident HF. After multivariable adjustment for relevant confounders, lower HRV as assessed by SDNN was associated with a higher risk of HF (aHR for the lowest vs highest quartile of SDNN: 1.70 [95%CI 1.14–2.54]). Participants with CAN (defined as lowest quartile of SDNN and highest quartiles of QTI and heart rate) had a 2.7-fold greater risk of HF (aHR 2.65, 95%CI 1.57–4.48).

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CONFLICT OF INTEREST

Dr Fonarow reports consulting for Abbott, Amgen, AstraZeneca, Bayer, Cytokinetics, Janssen, Medtronic, Merck, and Novartis. The remaining authors have nothing to disclose.

Conclusions—In a large cohort of adults with type 2 diabetes, CAN was independently associated with higher risk of incident HF.

Keywords

Cardiac autonomic neuropathy; Type 2 diabetes; Heart failure; Risk

INTRODUCTION

Type 2 diabetes and cardiovascular disease (CVD) are increasingly common in the US.[1,2] Cardiovascular complications represent the single most important cause of morbidity and mortality among individuals with type 2 diabetes.[1,2] While atherosclerotic CVD (ASCVD) constitutes a huge proportion of these complications, heart failure (HF) is also a major diabetes-related complication. Indeed, extant evidence indicates a two- to four-fold higher risk of HF among adults with type 2 diabetes, independently of known risk factors such as dyslipidemia, hypertension, and coronary artery disease (CAD).[3] The diabetes-related changes in the myocardial structure and function and the consequential HF have been referred to as diabetic cardiomyopathy.[4] The exact mechanisms of diabetes-related cardiac-dysfunction are incompletely understood, but cardiac autonomic neuropathy (CAN) may play a role in its pathophysiology, and part of the neurohormonal modulation pathway.[5] Indeed, autonomic nervous system dysfunction is a hallmark of type 2 diabetes.[6] It is highly prevalent among individuals with type 2 diabetes as compared to non-diabetic individuals, with up to 34% diabetic individuals harboring the condition.[7,8] The role of autonomic dysfunction, which is part of the neuromodulation pathway, in the pathogenesis of HF has been described.[5] While there have been studies showing an increased mortality risk among diabetic individuals with CAN compared with those without it,[9] there is a paucity of epidemiological data on the relation of CAN with incident HF among adults with type 2 diabetes.

The associations of CAN with incident HF events, using data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study were investigated. We hypothesized that cardiac autonomic dysfunction would be associated with higher risk of incident HF.

METHODS

Study Design

This is a secondary cohort analysis of the ACCORD data. The details on the design and methods of ACCORD have previously been published.[10] In brief, 10251 adults with type 2 diabetes were enrolled at 77 locations across the US and Canada in a double two-by-two factorial trial. Participants were recruited in two noncontiguous periods (January 2001 through June 2001, and January 2003 to October 2005) and were randomized to receive either an intensive glucose lowering intervention aiming for a glycated hemoglobin (HbA_{1C}) of less than 6% or standard treatment targeting an HbA_{1C} of 7.0–7.9%. To be included in ACCORD, participants had to be aged 40 to 79 years (with a history of cardiovascular disease [CVD]) or 55 to 79 years (with significant albuminuria, atherosclerosis, left ventricular hypertrophy, or a minimum of two CVD risk factors).[10]

For the current analysis, we excluded participants with history of HF at baseline (N=495), artificial pacemaker (N=46), atrioventricular conduction defect (N=401), atrial fibrillation/flutter (N=95), premature beats and other arrhythmias (N=762). We also excluded those with missing ECG data (N=929) or with poor quality of ECG (N=363). After these exclusions, 7,160 participants were included in our main analyses (Supplementary Figure S1).

The ACCORD study was conducted in accordance with the Helsinki declaration principles. The research protocol was approved by the institutional review board or ethics committee at all the participating centers and all participants provided gave an informed consent.[10]

Assessment of Cardiac Autonomic Neuropathy

The measures of CAN were obtained at baseline using 12-lead digitalized electrocardiograms (ECG) recorded over 10 consecutive seconds with the patient resting supine after an overnight fast (GE MAC 1200 electrocardiograph system) as described previously.[11] The ECG recordings were electronically transmitted to the reading center and were analyzed and reviewed for their technical quality. The following time-domain indices of heart rate variability (HRV) were derived: standard deviation of all normal-to-normal R-Rs intervals (SDNN) and root mean square of successive differences between normal-to-normal R-R intervals (rMSSD).[11] QT intervals were recorded from simultaneous lead ECGs, and the QT interval index (QTI) was computed as observed/predicted QT duration with the predicted value derived based on Bazett's correction ($QTc = QT/R\text{-}R^{1/2}$).[11] Resting heart rate (HR) was computed from simultaneous recordings. SDNN reflects the combined sympathetic and parasympathetic regulation of HRV in the time domain.[12] QTI is controlled in part by sympathetic inputs.[13] Lower HRV is an early marker of CAN in the course of diabetes mellitus.[14]

In this study, CAN was defined using three composite measures of HRV and QTI: 1) first measure (CAN1) was defined as both SDNN and rMSSD being below the fifth percentile of the general population (SDNN < 8.2 ms and rMSSD < 8.0 ms);[15,16] 2) the second measure (CAN2) was defined as the lowest quartile of SDNN in our sample (< 7.815 ms) and the highest quartile of QTI (> 104.32%); 3) the third measure (CAN3) as the lowest quartile of SDNN and highest quartiles of QTI and resting HR (>77 bpm).[11,15,16] We opted to use these composite definitions based on recent evidence showing the higher predictive values of these measures than either abnormality alone for adverse outcomes in individuals with diabetes mellitus.[11,13,15,17] Furthermore, QTI has been shown to measure autonomic dysfunction.[18]

Ascertainment of Incident Heart Failure events

The ascertainment of HF events was conducted during clinic visits every 4-month based on participant responses to questions regarding emergency room visits, hospital admissions, and out-of-hospital procedures occurring since the previous visit. In case participants did not attend clinic visits, clinic staff contacted the participant and performed events ascertainment via telephone. HF events were defined as first hospitalization for HF or death from "congestive heart failure", whichever occurred first. HF was diagnosed based on clinical and radiologic evidence. The HF events were adjudicated by an expert adjudication committee.[10]

Participants were followed from baseline through the occurrence of HF events, death or the end of the study (June 2009).

Covariates

The covariates included data on age, sex, race, treatment arm, current cigarette smoking, alcohol consumption, body mass index, blood pressure (BP), duration of diabetes, and past medical history including medication use (including classes of antihypertensives, glucose-lowering medications, and antiarrhythmic medications [beta blockers, non-dihydropyridine calcium channel blockers, digitalis and other antiarrhythmics]) and history of retinopathy; all of which were collected at baseline.[10] Prevalent atherosclerotic CVD (ASCVD) was defined as prior myocardial infarction, angina, stroke, history of coronary revascularization, carotid or peripheral revascularization). Left ventricular hypertrophy was defined by Cornell Voltage criteria on the baseline EKG. Total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, HbA_{1C} and serum creatinine were measured on blood samples collected at baseline as previously described.[10] Estimated glomerular filtration rate was calculated based on the Modification of Diet in Renal Disease equation. Incident coronary artery disease (CAD: defined as cases of myocardial infarction and angina) was recorded during follow-up and modelled as a time-varying covariate.[10]

Statistical analyses

For each composite CAN measure, we compared the baseline characteristics of participants by presence/absence of CAN using the *t*-test or Kruskal-Wallis test for continuous variables; and the χ^2 test for categorical variables.

Using Poisson models, we calculated incidence rates (IRs) as the ratio of the cumulative number of HF events to the total person-years. The person-years were estimated from the baseline visit to the earliest of HF event, date of death, or trial termination.

We assessed the time-to-event distributions for HF by CAN using the Kaplan-Meier curve and compared these using the log-rank test. We used multivariable Cox proportional hazards regression models to compute adjusted hazard ratios (aHRs) and associated 95% confidence intervals (CI) relating each CAN measure to incident HF. Similar analyses were performed relating the HF events to HRV measures (SDNN and rMSSD, assessed as continuous measures and quartiles). For the analyses including HRV measures as continuous variables, SDNN and rMSSD were logarithmically transformed and effect estimates calculated per each standard deviation decrease of each of these HRV indices. We constructed several sequential regression models. Model 1 included age, sex, race, and treatment arm; model 2 adjusted for variables in model 1 plus cigarette smoking, alcohol intake, body mass index, systolic BP, use of antihypertensive medication, estimated glomerular filtration rate, total/HDL cholesterol ratio, duration of diabetes, HbA_{1C}, use of insulin/sulfonylurea, use of thiazolidinediones, use of medications that affect HRV (beta blockers, non-dihydropyridine calcium channel blockers, digitalis and other antiarrhythmics), and left ventricular hypertrophy. Model 3 included further adjustment for history of ASCVD at baseline; model 4 included model 3 with additional adjustment for incident CAD as a time-varying variable; model 5 further accounted for history of retinopathy at baseline.

We tested for statistical interaction by age, sex, treatment arm, race/ethnicity, left ventricular hypertrophy, use of thiazolidinediones, use of insulin/sulfonylurea, and degree of glycemic control. In sensitivity analyses, we restricted the analyses to the sample of participants not taking medications that can affect HRV, which include beta blockers, non-dihydropyridine calcium channel blockers, digitalis and other antiarrhythmic medications. We additionally evaluated the association of baseline HR with incident HF. Finally, as impaired baroreceptor-heart rate reflex sensitivity (BRS) has been shown to predict HF outcomes even in the presence of beta blockade, we conducted subgroup analyses limited to participants on beta blockers, given that despite the blunting effects of these medications, there are indications from the literature that effects of HRV can still be detected while on these drugs.[19]

The statistical analyses were performed using STATA 14.2 (Stata, Inc, College Station, TX). A *P*-value of < 0.05 for a two-sided null hypothesis was considered statistically significant.

RESULTS

Baseline Characteristics of Study Participants

A comparison of the characteristics of participants included in the final sample to those excluded (reasons for exclusion detailed in Figure S1) is displayed in Table S1. A total of 7,160 participants (mean age 62.3 [SD: 6.4] years, 40.8% women, 61.9% white) were included in our analysis. The prevalence of CAN varied according to the definition used: 19.5% for CAN1; 6.5% for CAN2; and 3.0% for CAN3.

Participants with CAN generally had higher BMI, HbA_{1C}, and longer duration of diabetes; they were also more likely to be on insulin, and less likely to be on beta blockers (Table 1). The proportions of participants on beta blockers were 23.5%, 30.3%, and 18.9% among those with cardiac autonomic dysfunction as defined by CAN1, CAN2, and CAN3, respectively.

Compared to those with higher HRV measure (highest quartile), participants in the lowest quartile of HRV measure were more likely to be men, white, current smokers, or insulin users. They also had higher resting heart rate, HbA_{1C}, longer diabetes duration and lower eGFR (Supplementary Tables S2 & S3).

Incident Heart Failure by Cardiac Autonomic Neuropathy Status

Over a median follow-up of 4.9 years (interquartile range: 4.0–5.7), 222 participants developed incident HF. In unadjusted comparisons, participants with CAN had a higher cumulative risk of incident of HF compared to those without CAN (Figure 1, *P*-value-log rank < 0.001).

In multivariable adjusted analyses, lower HRV was associated with a greater risk of incident HF. Indeed, each SD decrease in SDNN was associated with a 23% higher risk of HF (aHR 1.24 [95% CI 1.09–1.42], Model 3, Table 2). Further adjustment for interval CAD during follow-up did not affect the magnitude or significance of the association (aHR 1.23, 95% CI 1.08–1.41, Model 4, Table 2). Compared to those in the highest quartile (Q4), participants

in the lowest quartile (Q1) of SDNN had a 70% greater risk of HF (aHR 1.70, 95% CI 1.14–2.54). The aHR for HF comparing Q1 vs Q4 of rMSSD was 1.44 (95% CI 0.99–2.10).

The aHRs of the HF association with CAN1, CAN2, and CAN3 were 1.59 (95% CI 1.19–2.13), 1.68 (95% CI 1.12–2.50), and 2.66 (95% CI 1.58–4.48), respectively (Model 3, Table 3). The magnitude and significance of these associations essentially remained unchanged after additional adjustment for incident CAD (aHR 1.53 [95% CI 1.14–2.05], 1.63 [95% CI 1.09–2.44], and 2.65 [95% CI 1.57–4.48] for CAN1, CAN2, and CAN3, respectively - Model 4, Table 3). Further adjustment for history of retinopathy at baseline did not affect the magnitude or significance of the associations (Model 5, Table 3).

Additional analyses

We also observed a significant association between HR (considered as an individual's measure of variability) and incident HF, with participants in the lowest HR quartile having the lowest relative risk of HF as compared to those in the highest quartile (aHR 0.40 [95% CI 0.27–0.59], Tables S4& S5).

We did not observe any effect modification by age, sex, treatment arm (intensity of glycemic management), race, left ventricular hypertrophy, use of thiazolidinediones, use of insulin/sulfonylurea and degree of glycemic control (baseline HbA_{1C}). sex, race, glycemia treatment arm, left ventricular hypertrophy, use of insulin/sulfonylurea, use of thiazolidinediones, and degree of glycemic control (All P interaction>0.05).

After excluding participants who were taking medication that affect HRV including beta blockers, non-dihydropyridine calcium-channel blockers, digitalis or other antiarrhythmic medications, CAN remained significantly associated with a higher risk of HF (aHRs 1.73 [95% CI 1.13–2.64], 1.90 [95% CI 1.09–3.33], 3.01 [95% CI 1.58–5.72] for CAN1, CAN2, and CAN3, respectively, Model 4, Table S6). In the subgroup of participants on beta blockers (N=1900), CAN remained associated with incident HF (Tables S7 & S8).

DISCUSSION

In this study, we evaluated the association of CAN with incident HF in a large sample of individuals with type 2 diabetes. We observed that CAN was associated with a higher risk of HF, after adjusting for known risk factors including the degree of blood glucose control, diabetes duration, incident coronary artery disease, and the use of antiarrhythmic medications. Our findings were consistent across definitions of CAN and various sensitivity analyses. This study is one of the first to show a significant association between cardiac autonomic dysfunction and incident HF

Our study is one of the few epidemiological investigations to assess the relation of cardiac autonomic dysfunction to incident HF, specifically among individuals with type 2 diabetes. Our findings complement the body of knowledge on the adverse cardiovascular effects of CAN in people with type 2 diabetes. Prior investigations studying the effects of CAN on CVD have mainly focused on individuals with type 1 diabetes.[17,20,21] The studies including individuals with type 2 diabetes have focused on ASCVD events and mortality,

and not always included HF as an outcome. These findings corroborate prior reports which also noted increased risks of cardiovascular mortality, all-cause mortality, and ASCVD outcomes in relation to cardiac autonomic dysfunction in adults with diabetes mellitus.[9,11] Additionally, our results are in agreement with prior reports of a positive association between cardiac autonomic alterations and subclinical myocardial injury measured by high-sensitivity troponin T levels, as well as subclinical cardiac dysfunction evaluated using echocardiography or magnetic resonance imaging both in patients with type 2 diabetes,[22,23] and type 1 diabetes.[24] Our results are also in tune with prior ACCORD study analyses that have shown a significant association between orthostatic hypotension (thought to be a hallmark of diabetes autonomic neuropathy) and a high risk of HF incidence.[25]

Experimental studies have provided insight on the potential mechanistic pathways that may explain the positive association observed in this study between CAN and incident HF among individuals with type 2 diabetes.[26] First, cardiac autonomic dysfunction may increase the risk of silent myocardial ischemia due to a defective angina warning system in people with type 2 diabetes.[27] Notably, the positive association between CAN and HF in our study persisted even after accounting for MI including silent MI, suggesting that silent MI alone does not explain the increased risk of HF in those of CAN. Second, CAN in diabetes is associated with chronic increases in plasma norepinephrine with associated decreased vagal response, resulting in resting tachycardia and increased oxygen demand by the myocardium. Furthermore, CAN leads to the activation of the renin-angiotensin system which promote adverse cardiac remodeling.[28] Additionally, CAN in type 2 diabetes leads to sympathetic denervation, depletion of myocardial catecholamines, and impairment in cardiac sympathetic nerve fibers. These processes may increase the rates of both systolic and diastolic heart failure,[29] as well as myocardial electrical instability.[30] CAN in diabetes usually occur as part of diffuse microvascular changes resulting from advanced glycation end-products that may deposit in arteriolar walls and the endothelium. The resulting endothelial damages and impaired nitric oxide bioavailability may lead to a decreased coronary blood flow reserve and myocardial hypertrophy with ensuing diastolic HF.[29]

The positive association between CAN indices and HF persisted in the subset of participants on beta blockers, but these analyses were probably limited by the lack of power (small sample size and number of HF events), as evidenced by the wide confidence intervals of effect estimates. This finding corroborates prior data suggesting that modification of the autonomic nervous system by beta blockade may not affect the predictive value of baroreceptor-heart rate reflex sensitivity BRS for HF outcomes.[19]

This study has implications for patients with type 2 diabetes. Our findings provide additional evidence for the putative role of CAN in the genesis of diabetes-related cardiomyopathy and indicate that CAN may be useful in HF risk stratification among individuals with type 2 diabetes. Our study suggests that modifying the autonomic system can help address HF among patients with type 2 diabetes, with potential intervention including interventions such as baro-reflex activation.[31] Prevention of CAN occurrence and progression in this population may help reduce the burden of HF on the healthcare system. Additionally, a tool as simple as the standard 12-lead EKG may help identify individuals with type 2 diabetes at high risk

of HF. Further research is needed to investigate the potential pathways linking CAN to HF as well as the incremental predictive value of CAN for HF discrimination in type 2 diabetes.

The limitations to our study should be acknowledged. First, CAN measures were derived from short ECG recordings with HRV assessed using time-domain indices only, and we did not use ECG data recorded over a longer period of time or perform dynamic cardiovascular autonomic reflex tests,[8] the gold standard for CAN diagnosis. Therefore, it is possible that we missed some cases of CAN and thus underestimated the true contribution of CAN on HF risk among individuals with type 2 diabetes. However, we used several definitions of CAN with the persistence of association across these; additionally, cardiovascular autonomic reflex tests may not be practical in large clinical studies and guidelines from major societies recommend the use of resting HR, QTI and HRV time-domain measures in large epidemiological studies of people with diabetes mellitus, and these measures have been shown to have a prognostic value (in term of mortality and ASCVD outcomes).[11] Furthermore, HRV indices measured using ultra-short term ECG recordings have been shown to have a strong correlation with longer ECG recordings.[32,33] Second, we did not have data on incident arrhythmias and could not assess the pathways from cardiac autonomic dysfunction to HF. Third, echocardiographic data were not collected in the ACCORD study. Thus, we did not have information on left ventricular ejection fraction (EF); and could not evaluate the association of CAN with HF subtypes (HF with reduced EF vs HF with preserved EF); likewise, although participants with HF at baseline were excluded, we did not have data on asymptomatic left ventricular dysfunction which might be associated with CAN; hence, we could not evaluate the interplay between CAN, asymptomatic left ventricular dysfunction, and incident HF. Fourth, while our study sample included a significant proportion of participants (33%) on drugs (beta blockers, non-dihydropyridine calcium-channel blockers, digitalis and other antiarrhythmic medications) that may affect HRV, the significant and positive association between CAN and HF risk persisted after excluding participants taking those medications. Finally, we did not have data on risk factors such as physical activity that may influence the autonomic nervous system, hence there is a possibility of residual or unmeasured confounding.

Notwithstanding these limitations, the strengths of this study are numerous. These include the large, diverse sample of adults with type 2 diabetes (which is one of the leading causes of primary autonomic dysfunction), the use several definitions of CAN, the standardized ascertainment of incident HF events, and the rigorous adjustment for relevant confounders such as the degree of blood glucose control, the duration of diabetes, the use of medications that affect HRV, and incident coronary artery disease (including silent MI). We also tested the robustness of our findings by conducting several sensitivity analyses.

In conclusion, in a large cohort of individuals with type 2 diabetes, CAN was associated with increased risk of incident HF, independently of known risk factors. These findings support the relevance of CAN in the estimation of HF risk among people with type 2 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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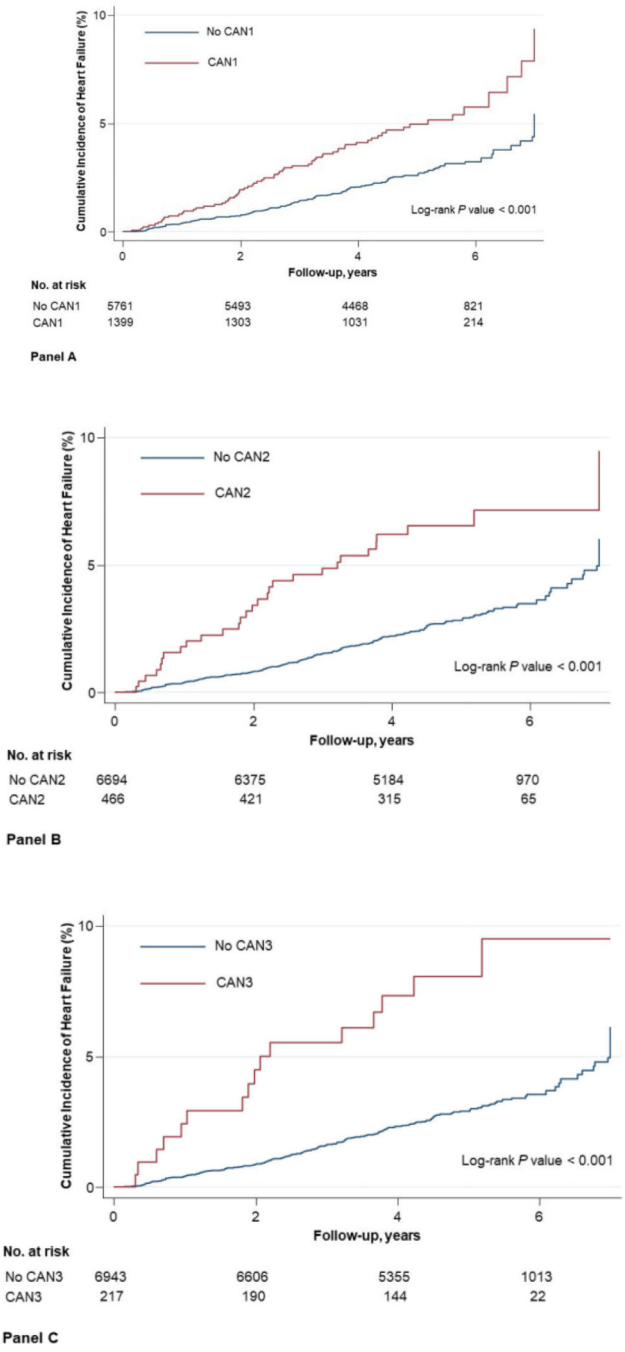

Figure 1. Cumulative Incidence of heart failure by cardiac autonomic dysfunction (CAN) status among individuals with type 2 diabetes

CAN1 defined as both standard deviation of all normal-to-normal R-Rs intervals (SDNN) SDNN and root mean square of successive differences between normal-to-normal R-R intervals (rMSSD) being below the fifth percentile of the general population distribution (SDNN < 8.2 ms and rMSSD < 8.0 ms)

CAN2 defined as the lowest quartile of SDNN (< 7.815 ms) and the highest quartile of QTI (> 104.32%)

CAN3 as the lowest quartile of SDNN and highest quartiles of QT index (QTI) and resting heart rate (>77 bpm)

P value for log –rank test

Table 1.

Characteristics of Participants by Evidence of Cardiac Autonomic Neuropathy at Baseline

Variable	Total	CAN1			CAN2			CAN3		
		No	Yes	*P*	No	Yes	P	No	Yes	P
N	7160	5761	1399	…	6694	466	…	6943	217	…
Age, years	62.3 (6.4)	62.2 (6.4)	62.5 (6.4)	0.237	62.2 (6.4)	62.9 (6.4)	0.028	62.3 (6.4)	62.1 (6.1)	0.678
Women, %	40.8	42.4	34.5	<0.001	40.1	51.9	<0.001	40.4	55.8	<0.001
Race/ethnicity, %				<0.001			0.051			0.402
White	61.9	60.6	67.6		61.5	67.8		61.8	67.3	
Black	18.6	19.4	15.2		18.9	14.8		18.7	16.1	
Hispanic	7.8	8.1	6.9		7.9	7.1		7.9	7.4	
Other	11.6	11.9	10.4		11.7	10.3		11.7	9.2	
Treatment arm, %				0.336			0.758			0.833
Intensive glycemic management	49.5	49.2	50.7		49.5	50.2		49.5	50.2	
Standard glycemia management	50.5	50.8	49.3		50.5	49.8		50.5	49.8	
Body mass index, kg/m^2	32.2 (5.4)	32.1 (5.3)	32.5 (5.4)	0.017	32.2 (5.4)	32.9 (5.3)	0.005	32.2 (5.4)	33.0 (5.2)	0.025
Current smoking, %	13.9	13.3	16.2	0.005	13.8	15.2	0.382	13.7	19.8	0.010
Alcohol drinking, %	23.7	24.3	21.6	0.035	23.9	21.5	0.231	23.8	21.2	0.371
Systolic BP, mm Hg	136.2 (16.7)	136.3 (16.8)	135.7 (16.3)	0.234	136.1 (16.7)	137.6 (17.0)	0.056	136.1 (16.7)	137.3 (16.4)	0.317
Diastolic BP, mm Hg	75.3 (10.4)	75.3 (10.3)	75.3 (10.5)	0.910	75.3 (10.3)	76.1 (10.5)	0.104	75.2 (10.3)	78.7 (10.7)	<0.001
Heart rate, bpm	69.8 (10.5)	68.1 (9.7)	76.8 (10.6)	<0.001	69.3 (10.2)	76.3 (11.4)	<0.001	69.3 (10.2)	86.2 (6.1)	<0.001
Use of BP-lowering drug, %	82.6	82.6	82.7	0.909	82.5	84.6	0.250	82.6	81.6	0.684
Use of beta blocker, %	26.6	27.3	23.5	0.003	26.3	30.3	0.063	26.8	18.9	0.009
Use of ACEI/ARB, %	68.9	68.6	70.1	0.311	68.9	68.9	0.984	69.0	66.8	0.496
Use of Non-DHP CCB, %	7.9	7.8	7.9	0.968	7.9	7.5	0.779	7.9	5.5	0.197
Use of HRV-modifying drug, *%	32.9	33.6	30.0	0.010	32.7	35.6	0.199	33.2	24.0	0.004
Use of insulin, %	33.7	31.5	42.5	<0.001	32.9	45.3	<0.001	33.4	42.9	0.004
Use of sulfonylurea, %	54.0	53.9	54.1	0.895	54.4	48.1	0.008	54.1	49.3	0.163
Use of thiazolidinediones, %	22.5	22.2	23.8	0.208	22.6	22.1	0.815	22.6	20.3	0.417
Hemoglobin A_{1C}, %	8.3 (1.1)	8.3 (1.0)	8.4 (1.1)	<0.001	8.3 (1.0)	8.5 (1.2)	<0.001	8.3 (1.1)	8.4 (1.2)	0.035
Duration of diabetes, years	9.0 (5.0–15.0)	9.0 (5.0–14.0)	10.0 (6.0–16.0)	<0.001	9.0 (5.0–15.0)	10.0 (6.0–17.0)	<0.001	9.0 (5.0–15.0)	9.0 (5.0–15.0)	0.743

Variable	Total	CAN1			CAN2			CAN3		
		No	Yes	*P*	No	Yes	P	No	Yes	P
Prevalent ASCVD	31.6	31.1	33.2	0.130	31.1	38.2	0.001	31.6	31.3	0.945
Total cholesterol, mg/dL	184.5 (41.6)	184.3 (40.9)	185.3 (44.2)	0.395	184.3 (41.6)	187.3 (41.2)	0.133	184.2 (41.5)	193.8 (44.2)	<0.001
HDL-cholesterol, mg/dL	42.0 (11.5)	42.2 (11.6)	41.3 (11.1)	0.009	42.0 (11.5)	42.7 (11.7)	0.185	42.0 (11.5)	42.7 (11.0)	0.423
LDL-cholesterol, mg/dL	105.5 (33.8)	105.8 (33.8)	104.2 (33.8)	0.100	105.5 (33.8)	105.8 (34.5)	0.840	105.3 (33.7)	110.5 (36.7)	0.028
Total/HDL-cholesterol Ratio	4.7 (1.7)	4.0 (1.7)	4.0 (1.4)	0.010	4.7 (1.7)	4.7 (1.7)	0.932	4.7 (1.7)	4.8 (1.7)	0.220
eGFR, mL/min/1.73m^2	92.1 (26.1)	92.5 (26.2)	90.5 (25.9)	0.009	92.2 (26.1)	91.2 (26.7)	0.447	92.0 (26.1)	94.4 (26.1)	0.195
Retinopathy, %	9.7	8.5	14.7	<0.001	9.6	11.4	0.149	9.6	12.4	0.284

Data are mean (standard deviation), median (interquartile range), or proportion (%) unless otherwise indicated.

* HRV-modifying drug includes beta blocker, non-DHP CCBs, digitalis and other antiarrhythmics.

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CAN, cardiac autonomic neuropathy; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HRV, heart rate variability; LDL, low-density lipoprotein; Non-DHP CCBs, non-dihydropyridine calcium channel blockers; QTI, QT index; rMSSD, root mean square of successive differences between normal-to-normal R-R intervals; SDNN, standard deviation of all normal-to-normal R-R intervals. CAN1 was defined as SDNN < 8.2 ms and rMSSD < 8.0 ms; CAN2 as SDNN < 7.815 ms and QTI > 104.32%; CAN3 as SDNN < 7.815 ms, QTI > 104.32% and resting heart rate > 77 bpm.

Table 2.

Rates and Hazard Ratios for Incident Heart Failure by Heart Rate Variability Metrics

HRV Metric	Quartiles of HRV Metrics				P_{trend}	Per 1-SD decrease of ln (metric)
SDNN, ms	**< 7.84**	**7.84–12.40**	**12.41–20.08**	**> 20.08**	…	…
No events /No at risk	79/1790	62/1791	44/1789	37/1790	…	222/7160
Person-years	8433.8	8557.3	8541.8	8588.0	…	34120.9
Rate /1000 person-years	9.4 (7.5–11.7)	7.2 (5.6–9.3)	5.2 (3.8–6.9)	4.3 (3.1–5.9)	…	6.5 (5.7–7.4)
Model 1	2.03 (1.37–3.00) ‡	1.63 (1.08–2.45) *	1.21 (0.78–1.88)	1 (Reference)	<0.001	1.32 (1.15–1.51) ‡
Model 2	1.77 (1.19–2.63) ‡	1.46 (0.97–2.21)	1.16 (0.75–1.82)	1 (Reference)	0.002	1.24 (1.08–1.42) ‡
Model 3	1.75 (1.18–2.61) ‡	1.44 (0.95–2.18)	1.18 (0.76–1.84)	1 (Reference)	0.003	1.24 (1.09–1.42) ‡
Model 4	1.70 (1.14–2.54) ‡	1.43 (0.95–2.17)	1.19 (0.76–1.85)	1 (Reference)	0.005	1.23 (1.08–1.41) ‡
Model 5	1.71 (1.14–2.54) ‡	1.43 (0.95–2.17)	1.19 (0.76–1.85)	1 (Reference)	0.005	1.23 (1.08–1.41) †
rMSSD, ms	**< 8.02**	**8.02–12.70**	**12.70–20.73**	**> 20.73**	…	…
No events /No at risk	78/1800	48/1780	50/1791	46/1789	…	222/7160
Person-years	8454.4	8573.1	8623.9	8469.4	…	34120.9
Rate /1000 person-years	9.2 (7.4–11.5)	5.6 (4.2–7.4)	5.8 (4.4–7.6)	5.4 (4.1–7.3)	…	6.5 (5.7–7.4)
Model 1	1.59 (1.10–2.29) *	1.01 (0.67–1.51)	1.05 (0.71–1.57)	1 (Reference)	0.014	1.19 (1.04–1.36) *
Model 2	1.50 (1.02–2.18) *	1.01 (0.67–1.52)	1.08 (0.72–1.62)	1 (Reference)	0.041	1.15 (1.01–1.32) *
Model 3	1.49 (1.02–2.18) *	1.02 (0.67–1.55)	1.09 (0.72–1.64)	1 (Reference)	0.040	1.16 (1.01–1.32) *
Model 4	1.44 (0.99–2.10)	1.01 (0.67–1.53)	1.10 (0.73–1.65)	1 (Reference)	0.068	1.14 (0.99 −1.30)
Model 5	1.44 (0.99–2.10)	1.01 (0.67–1.53)	1.10 (0.73–1.65)	1 (Reference)	0.068	1.14 (0.99–1.30)

Data are hazard ratios (95% CI) unless otherwise specified. Model 1 adjusted for age, sex, race, treatment arm; model 2 includes model 1 plus duration of diabetes, cigarette smoking, alcohol intake, body mass index, systolic blood pressure, estimated glomerular filtration rate, total/high-density cholesterol ratio, glycated hemoglobin, use of insulin/sulfonylurea, use of antihypertensive medication, use of thiazolidinediones, use of medications affecting HRV, and left ventricular hypertrophy; model 3 includes model 2 plus history of prevalent ASCVD; model 4 includes model 3 plus incident CAD as a time varying covariate; model 5, includes model 4 plus retinopathy at baseline.

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; HRV, heart rate variability; rMSSD, root mean square of successive differences between normal-to-normal R-R intervals; SDNN, standard deviation of all normal-to-normal R-R intervals.

* $P<0.05$,

† $P<0.01$,

‡ $P<0.001$.

Table 3.

Rates and Hazard Ratios for Incident Heart Failure by Evidence of Cardiac Autonomic Neuropathy

CAN Definition	CAN1			CAN2			CAN3		
	Absent	Present	*P*	Absent	Present	*P*	Absent	Present	*P*
No Events/No at risk	154/5761	68/1399	…	193/6694	29/466	…	206/6943	16/217	…
Person-years	27558.6	6562.3	…	32018.7	2102.2	…	33178.3	942.5	…
Rate/1000 person-years	5.6 (4.8–6.5)	10.4 (8.2–13.1)	…	6.0 (5.2–6.9)	13.8 (9.6–19.9)	…	6.2 (5.4–7.1)	17.0 (10.4–27.7)	…
Hazard ratio (95% CI)									
Model 1	1 (Reference)	1.75 (1.31–2.33)	<0.001	1 (Reference)	2.19 (1.48–3.25)	<0.001	1 (Reference)	2.88 (1.73–4.80)	<0.001
Model 2	1 (Reference)	1.61 (1.20–2.15)	0.001	1 (Reference)	1.81 (1.22–2.70)	0.003	1 (Reference)	2.76 (1.64–4.63)	<0.001
Model 3	1 (Reference)	1.59 (1.19–2.13)	0.002	1 (Reference)	1.68 (1.12–2.50)	0.011	1 (Reference)	2.66 (1.58–4.48)	<0.001
Model 4	1 (Reference)	1.53 (1.14–2.05)	0.004	1 (Reference)	1.63 (1.09–2.44)	0.016	1 (Reference)	2.65 (1.57–4.48)	<0.001
Model 5	1 (Reference)	1.53 (1.14–2.05)	0.004	1 (Reference)	1.63 (1.09–2.44)	0.016	1 (Reference)	2.66 (1.57–4.48)	<0.001

Data are hazard ratios (95% CI) unless otherwise specified. Model 1 adjusted for age, sex, race, treatment arm; model 2 includes model 1 plus duration of diabetes, cigarette smoking, alcohol intake, body mass index, systolic blood pressure, estimated glomerular filtration rate, total/high-density cholesterol ratio, glycated hemoglobin, use of insulin/sulfonylurea, use of antihypertensive medication, use of thiazolidinediones, use of medications affecting HRV, and left ventricular hypertrophy; model 3 includes model 2 plus history of prevalent ASCVD; model 4 includes model 3 plus incident CAD as a time varying covariate; model 5, includes model 4 plus retinopathy at baseline.

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CAN, cardiac autonomic neuropathy; QTI, QT index; Ref, reference; rMSSD, root mean square of successive differences between normal-to-normal R-R intervals; SDNN, standard deviation of all normal-to-normal R-R intervals. CAN1 was defined as SDNN < 8.2 ms and rMSSD < 8.0 ms; CAN2 as SDNN < 7.815 ms and QTI > 104.32%; CAN3 as SDNN < 7.815 ms, QTI > 104.32% and resting heart rate > 77 bpm.