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ORIGINAL RESEARCH

Cardiac Autonomic Dysfunction and Risk of Silent Myocardial Infarction Among Adults With Type 2 Diabetes

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BACKGROUND: There is a paucity of large-scale epidemiological studies on the link between cardiac autonomic neuropathy (CAN) and the risk of silent myocardial infarction (SMI) in type 2 diabetes. We evaluated the association between CAN and the risk of SMI in a large sample of adults with type 2 diabetes.

METHODS AND RESULTS: Participants with type 2 diabetes from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study without atherosclerotic cardiovascular disease at baseline were included. CAN was ascertained using heart rate variability indices calculated from 10-s resting electrocardiograms. The heart rate variability indices included standard deviation of all normal-to-normal R-R intervals and root mean square of successive differences between normal-to-normal R-R intervals. CAN was defined as both the standard deviation of all normal-to-normal R-R intervals and root mean square of successive differences between normal-to-normal R-R intervals less than the fifth percentile of the general population. We used Cox proportional hazards regression to generate hazard ratios (HRs) for incident SMI in relation to CAN measures. Among 4842 participants (mean age, 62.5 years; 46.6% women; 60.2% White), there were 73 incident SMI cases over a median follow-up of 4.9 years (incidence rate 3.1 out of 1000 person-years [95% CI, 2.5–3.9]). After adjusting for confounders, low heart rate variability was associated with a higher risk of SMI (HR, 1.67 [95% CI, 1.02–2.72] and HR, 1.56 [95% CI, 0.94–2.58] for low standard deviation of all normal-to-normal R-R intervals and root mean square of successive differences between normal-to-normal R-R intervals, respectively). Participants with CAN had a 1.9-fold greater risk of SMI (HR, 1.91 [95% CI, 1.14–3.20]).

CONCLUSIONS: In a large cohort of adults with type 2 diabetes, CAN was significantly associated with an increased risk of incident SMI.

Key Words: cardiac autonomic neuropathy ■ heart rate variability ■ silent myocardial infarction ■ type 2 diabetes

Type 2 diabetes is highly prevalent in the United States.[1] Cardiac autonomic neuropathy (CAN) is a frequently overlooked and serious complication of diabetes.[2] CAN encompasses damage to the autonomic nerve fibers that control the heart and blood vessels, leading to abnormalities in vascular dynamics and heart rate control.[2] Extant evidence suggests that CAN may be associated with increased risks of adverse outcomes including clinical atherosclerotic cardiovascular disease, heart failure, and mortality.[3–8] Although the exact pathways linking CAN to higher mortality are unclear, the higher rates of silent myocardial ischemia and infarction among individuals with CAN compared with those without CAN may play a role.[2] Several cross-sectional studies found that compared with individuals without CAN, people with diabetes and CAN have a higher prevalence of silent myocardial ischemia.[2,9] However, these studies were limited by the cross-sectional nature of their design. To date, there is a dearth of prospective studies evaluating the relation of CAN with the incidence of

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CLINICAL PERSPECTIVE

What Is New?

- There is a paucity of large-scale epidemiological studies on the link between cardiac autonomic neuropathy and the risk of silent myocardial infarction in type 2 diabetes.
- In a large cohort of adults with type 2 diabetes, cardiac autonomic neuropathy, ascertained using measures of heart rate variability, was associated with a high risk of incident silent myocardial infarction, independently of traditional atherosclerotic risk factors.

What Are the Clinical Implications?

- Our findings underscore the potential usefulness of cardiac autonomic neuropathy for optimizing the approach to identify asymptomatic coronary heart disease in people with type 2 diabetes.

Nonstandard Abbreviations and Acronyms

CAN	cardiac autonomic neuropathy
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
SMI	silent myocardial infarction

silent myocardial infarction (SMI) among adults with type 2 diabetes. SMI is common, representing up to 25% of the cases of myocardial infarction.[10] Approximately 1 in 4 individuals with diabetes have SMI, and the latter is associated with a higher risk of adverse cardiovascular events.[11–14]

We aimed to investigate the associations of CAN measures with incident SMI in a large sample of adults with type 2 diabetes using data from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study. We hypothesized that CAN would be associated with a higher risk of SMI.

METHODS

The data that support the findings of this study are publicly available through the National Heart, Lung, and Blood Institute biorepository (BioLINCC), and can also be made available from the corresponding author upon reasonable request.

Study Design

This report followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for observational studies.[15] We conducted a prospective cohort analysis of the ACCORD study. The design and methods of the ACCORD study have been reported elsewhere.[16] The ACCORD study was a randomized 2-by-2 factorial clinical trial that enrolled 10 251 adults with type 2 diabetes in the United States and Canada between January 2001 and October 2005. These participants were randomly assigned to either an intensive glucose-lowering arm aiming for of a glycated hemoglobin (HbA_{1C}) <6% or a standard treatment arm with an HbA_{1C} goal of 7.0% to 7.9%, as well as specific blood pressure (BP) and lipid intervention arms. For the current analysis, we excluded participants who at baseline had established atherosclerotic cardiovascular disease (defined as prior myocardial infarction [MI], angina, stroke, history of coronary revascularization, carotid or peripheral revascularization; n=3609), artificial pacemaker (n=23), an atrioventricular conduction defect (n=232), atrial fibrillation/flutter (n=73), premature beats and other arrhythmias (n=456), missing ECG (n=650), or poor-quality ECG (n=236). We further excluded participants with clinically recognized MI during follow-up (n=130). After the relevant exclusions, our final simple included 4842 participants. The process of selecting study participants, including the various reasons for exclusion, is shown in Figure S1. A comparison of the baseline characteristics of ACCORD participants who were included to those excluded from the final sample is shown Table S1. The study was approved by an institutional review committee. Informed consent was obtained from all participants.

Assessment of CAN

We assessed CAN at baseline using heart rate variability (HRV) metrics derived from a digitalized 12-lead ECG. The digital ECG acquisition and procession, including among other signal processing, filtering, sampling frequency, and management of ectopic beats, were performed using standardized procedures.[17]

ECGs were recorded over 10 consecutive seconds at 10 mm/mV calibration and a speed of 25 mm/s (GE MAC 1200 electrocardiograph system; GE, Milwaukee, WI) among fasting participants (who also abstained from smoking and drinking alcohol) lying flat.[7] ECGs were electronically transmitted to the reading center where they were analyzed and reviewed for technical quality before they were automatically processed using GE 12-SL Marquette Version 2001 (GE). ECG reading was performed centrally at the Epidemiological Cardiology Research Center, Wake Forest School of Medicine, Winston-Salem, North Carolina. The ECG recordings were used to derive 2 HRV time-domain indices: the

standard deviation of all normal-to-normal R-R intervals (SDNN) and the root mean square of successive differences between normal-to-normal R-R intervals (rMSSD).

We defined low HRV using cutoff values derived from healthy US adult populations: low SDNN defined as SDNN <8.2 ms; low rMSSD defined as rMSSD <8.0 ms.[18] We used a composite measure of CAN, which was derived as SDNN and rMSSD both being below the fifth percentile of the general population distribution (SDNN <8.2 ms and rMSSD <8.0 ms).[18,19]

Ascertainment of Silent MI

The participants were prospectively followed from the baseline visit until the occurrence of SMI, death, or study end (in June 2009). Baseline and follow-up resting ECGs were obtained in all ACCORD sites.[16] Incident SMI cases were ascertained from 12-lead ECGs obtained at the biennial follow-up visits. We defined incident SMI as the presence of a major Q-wave abnormality or minor Q/QS waves in the setting of major ST-T abnormalities in the absence of history of clinical cardiovascular disease, which is consistent with prior studies.[13] We excluded individuals with clinically recognizable MI from the analyses. The events were adjudicated by an expert committee in ACCORD.[16,20]

Covariates

The covariates, selected a priori based on their relation with CAN or SMI, included age, sex, race and ethnicity, treatment arm, history of retinopathy, duration of diabetes, cigarette smoking, alcohol consumption, body mass index, BP, use of BP-lowering medications, use of medications that can affect HRV (calcium channel blockers, β-blockers, digitalis, and other antiarrhythmics), total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, HbA_{1C}, and serum creatinine,[16] and estimated glomerular filtration rate was calculated based on the Modification of Diet in Renal Disease formula.[21] Cholesterol fractions were measured at the ACCORD central laboratory using standard biochemical methods.[16] Serum creatinine was measured via enzymatic methods on a Roche Double Modular *P* Analytics automated analyzer.

Statistical Analysis

We compared the baseline characteristics of study participants by CAN status using the *t* test or Kruskal-Wallis test for continuous variables depending on their distribution and the χ^2 test for categorical variables.

We calculated incidence rates and their associated 95% CIs by dividing the number of SMIs by the total at-risk person-years, with the person-years estimated from baseline through the earliest of SMI, date of death, or study termination (June 2009). We used multivariable Cox proportional hazards regression models to generate hazard ratio (HR) and 95% CI for SMI. Model 1 adjusted for age, sex, race and ethnicity, and treatment arm. Model 2 included variables in Model 1 plus duration of diabetes, glycated hemoglobin, cigarette smoking, alcohol intake, body mass index, systolic BP, use of BP-lowering medications, estimated glomerular filtration rate, and total/high-density lipoprotein cholesterol ratio. Model 3 included the Model 2 variables with further adjustment for use of medications affecting HRV (β-blockers, calcium channel blockers, digitalis, and antiarrhythmics). Model 4 included variables in Model 3 plus history of retinopathy at baseline.

In supplementary analyses, we examined the association of CAN status and each HRV index with the incidence of clinically recognized (overt) MI and overall MI (including both clinically recognized and silent MI events).

We calculated the sensitivity, specificity, and positive and negative predictive values of CAN for the detection of SMI.

All analyses were performed using Stata 14.2 (StataCorp, College Station, TX). A 2-sided *P* value of <0.05 was deemed statistically significant.

RESULTS

Baseline Characteristics of the Study Population

A total of 4842 participants were included in our investigation (mean age, 62.5 [SD, 5.7] years; 46.6% women; 60.2% White). The prevalence of CAN at baseline in the analytical sample was 18.6% (903/4842). Table 1 displays the characteristics of included participants according to their CAN status at baseline. The participants with low HRV had higher body mass index, HbA_{1C}, duration of diabetes, lower high-density lipoprotein cholesterol or estimated glomerular filtration rate, and were more likely to be current smokers, insulin users, or to have a history of retinopathy (Table 1).

CAN and Incidence of SMI

Over a median follow-up of 4.9 years, 73 participants experienced an SMI (incidence rate 3.1/1000 person-years [95% CI, 2.5–3.9]). In terms of absolute risk, the crude incidence rate of SMI was >1.5-fold higher among those with CAN as compared with those without CAN (Table 2).

After multivariable adjustment, CAN was associated with an increased risk of SMI (HR, 1.91 [95% CI, 1.14–3.18], Model 2, Table 2). The magnitude and significance of this association remained unchanged after further adjustments for medications affecting HRV (HR, 1.92 [95% CI, 1.15–3.20], Model 3; Table 2) and history of retinopathy at baseline (HR, 1.91 [95% CI, 1.14–3.20], Model 4; Table 2).

Table 1. Baseline Characteristics of Participants by Evidence of CAN

Variable	Total	CAN absent	CAN present	*P* value
N	4842	3939	903	…
Age, y	62.5 (5.7)	62.5 (5.7)	62.5 (5.6)	0.791
Women, %	46.6	48.1	39.8	<0.001
Race and ethnicity, %				0.005
White	60.2	59.0	65.3	
Black	20.4	21.1	17.5	
Hispanic	7.8	8.1	6.6	
Other	11.6	11.9	10.5	
Treatment arm, %				0.039
Intensive glycemia	49.7	49.0	52.8	
Standard glycemia	50.3	51.0	47.2	
Body mass index, kg/m^2	32.4 (5.4)	32.3 (5.4)	32.8 (5.4)	0.003
Current smoking, %	12.9	12.5	14.9	0.045
Alcohol drinking, %	23.5	24.0	21.7	0.149
Systolic BP, mm Hg	136.4 (16.6)	136.5 (16.8)	136.0 (16.0)	0.492
Diastolic BP, mm Hg	76.0 (10.1)	75.9 (10.1)	76.5 (10.4)	0.117
Heart rate, bpm	70.5 (10.4)	68.8 (9.5)	78.0 (10.5)	<0.001
Use of BP-lowering drug, %	79.5	79.4	79.9	0.727
Use of insulin, %	31.3	29.3	40.1	<0.001
Use of sulfonylurea, %	54.4	54.2	55.0	0.649
Hemoglobin A_{1C}, %	8.3 (1.0)	8.2 (1.0)	8.4 (1.1)	<0.001
Duration of diabetes, y	9.0 (5.0–14.0)	8.0 (5.0–14.0)	10.0 (6.0–16.0)	<0.001
Total cholesterol, mg/dL	187.4 (41.7)	187.2 (40.9)	188.4 (45.2)	0.416
HDL cholesterol, mg/dL	43.1 (11.8)	43.2 (11.9)	42.4 (11.5)	0.044
LDL cholesterol, mg/dL	107.8 (34.1)	108.2 (34.1)	106.0 (34.2)	0.084
Total/HDL cholesterol ratio	4.6 (1.7)	4.6 (1.7)	4.8 (2.0)	0.084
eGFR, mL/min per 1.73 m^2	92.5 (26.3)	92.8 (26.7)	91.0 (24.5)	0.060
Retinopathy, %	8.8	7.7	14.0	<0.001

Data are mean (SD), median (interquartile range), or proportion (%) unless otherwise indicated. CAN was defined as SDNN <8.2 ms and rMSSD <8.0 ms. BP indicates blood pressure; CAN, cardiac autonomic neuropathy; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; rMSSD, root mean square of successive differences between normal-to-normal R-R intervals; and SDNN, standard deviation of all normal-to-normal R-R intervals.

Examination of each of the HRV indices in isolation (Table 3) showed that low HRV was significantly associated with a higher risk of SMI. A 1-SD decrease in SDNN was associated with a 1.29-fold greater risk of SMI (HR, 1.29 [95% CI, 1.02–1.65]). Participants with low SDNN had a 1.67-fold higher risk of SMI compared with those with normal SDNN (HR, 1.67 [95% CI, 1.02–2.72]). Low rMSSD was associated with a higher, but nonstatistically significant, risk of SMI (HR, 1.56 [95% CI, 0.94–2.58]; Table 3). The sensitivity, specificity, and positive and negative predictive values of CAN for the detection of SMI were 30.1%, 81.5%, 2.4%, and 98.7%, respectively.

Supplementary Analyses: Association of CAN and HRV Indices With Clinically Recognized MI and Overall MI

The individuals who experienced SMI did not substantially differ from those who experienced clinically recognized MI (Table S2). After full adjustment, CAN was associated with increased risks of clinically recognized MI (HR, 1.60 [95% CI, 1.08–2.36], Model 4; Table S3) and of overall MI (including both overt and silent MI events; HR, 1.70 [95% CI, 1.24–2.31], Model 4; Table S4). Similar positive associations were observed for relation of each HRV index (SDNN and rMSSD) with clinically recognized MI on one hand (Table S5) and overall MI on the other hand (Table S6).

DISCUSSION

In a large sample of individuals with type 2 diabetes, we evaluated the association of CAN, assessed by ultra-short-term heart rate variability measurement, with incident SMI. We observed a higher absolute risk of SMI among participants with CAN compared with those without CAN, as well as a positive association

Table 2. Rates and Hazard Ratios for Silent Myocardial Infarction by Evidence of Cardiac Autonomic Neuropathy

Variable	CAN absent	CAN present	*P* value
Events/at risk, n	51/3939	22/903	…
Person-years	18 986.5	4289.7	…
Rate/1000 person-years	2.7 (2.0–3.5)	5.1 (3.4–7.8)	…
Hazard ratio (95% CI)			
Model 1	1 (reference)	1.80 (1.09–2.98)	0.021
Model 2	1 (reference)	1.91 (1.14–3.18)	0.013
Model 3	1 (reference)	1.92 (1.15–3.20)	0.013
Model 4	1 (reference)	1.91 (1.14–3.20)	0.013

Data are hazard ratios (95% CIs) unless otherwise specified. Model 1 adjusted for age, sex, race and ethnicity, and treatment arm. Model 2 includes Model 1 plus duration of diabetes, glycated hemoglobin, cigarette smoking, alcohol intake, body mass index, estimated glomerular filtration rate, total/high-density lipoprotein cholesterol ratio, systolic blood pressure, and use of antihypertensive medication. Model 3 includes Model 2 plus use of medications affecting heart rate variability (β-blockers, calcium channel blockers, digitalis, and antiarrhythmics). Model 4 includes Model 3 plus history of retinopathy at baseline. CAN was defined as SDNN <8.2 ms and rMSSD <8.0 ms. CAN indicates cardiac autonomic neuropathy; rMSSD, root mean square of successive differences between normal-to-normal R-R intervals; and SDNN, standard deviation of all normal-to-normal R-R intervals.

between CAN with an increased risk of SMI, after accounting for several important risk factors including the extent of glycemic control (as captured by HbA_{1C}), duration of diabetes, smoking, systolic BP, and the use of blood pressure-lowering medications. Furthermore, the magnitude of the association of CAN with SMI was slightly greater than that observed with clinically recognized MI.

Although several studies have examined the prognostic significance of SMI among individuals with type 2 diabetes,[11–14] there is a scarcity of studies that have assessed the association of CAN and incident SMI among adults with type 2 diabetes using a prospective design.[9] Most of the existing are cross-sectional and indicate a higher prevalence of SMI among patients with diabetes as compared with those without diabetes.[22–25] In the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study, including patients with type 2 diabetes with no symptoms of cardiovascular disease, CAN was associated with a ≈3-fold higher odds of having a silent ischemia as compared with those without CAN.[26] A small prospective study including patients with type 1 and type 2 diabetes showed a higher incidence of SMI among those with CAN as compared with those without CAN.[27] The vast majority of previous studies were cross-sectional in their design, relatively small in size, and did not include a racial and ethnic mix. Our study extends prior findings by providing prospective evidence from a large multiethnic and multiracial sample of patients with type 2 diabetes.

The pathways linking CAN and SMI among individuals with diabetes are not completely understood. Several experimental studies have suggested that global sympathetic innervation is disturbed among individuals with diabetes, possibly contributing to SMI.[9,28] Studies using meta-iodobenzylguanidine have shown a significantly reduced myocardial sympathetic innervation among individuals with diabetes compared with those without diabetes, and evidence of a diffuse abnormality in meta-iodobenzylguanidine uptake among patients with diabetes with silent myocardial ischemia consistent with sympathetic denervation.[29] In autopsy studies, individuals with diabetes exhibited

Table 3. Rates and Hazard Ratios for Silent Myocardial Infarction by Heart Rate Variability Metrics

Variable	SDNN			rMSSD		
	Low SDNN		Per 1-SD lower log (SDNN)	Low rMSSD		Per 1-SD lower log (rMSSD)
	Absent	Present		Absent	Present	
Events/at risk, n	45/3575	28/1267	73/4842	49/3675	24/1167	73/4842
Person-years	17 213.2	6063.1	23 276.2	17 723.8	5552.4	23 276.2
Rate/1000 person-years	2.6 (2.0–3.5)	4.6 (3.2–6.7)	3.1 (2.5–3.9)	2.8 (2.1–3.7)	4.3 (2.9–6.4)	3.1 (2.5–3.9)
Hazard ratio (95% CI)						
Model 1	1 (reference)	1.68 (1.05–2.70)*	1.30 (1.03–1.64)*	1 (reference)	1.47 (0.90–2.40)	1.16 (0.91–1.47)
Model 2	1 (reference)	1.68 (1.03–2.73)*	1.30 (1.02–1.65)*	1 (reference)	1.55 (0.94–2.56)	1.16 (0.90–1.48)
Model 3	1 (reference)	1.67 (1.03–2.72)*	1.30 (1.02–1.65)*	1 (reference)	1.56 (0.95–2.58)	1.16 (0.91–1.49)
Model 4	1 (reference)	1.67 (1.02–2.72)*	1.29 (1.02–1.65)*	1 (reference)	1.56 (0.94–2.58)	1.16 (0.91–1.49)

Data are hazard ratios (95% CIs) unless otherwise specified. Model 1 adjusted for age, sex, race and ethnicity, and treatment arm. Model 2 includes Model 1 plus duration of diabetes, glycated hemoglobin, cigarette smoking, alcohol intake, body mass index, estimated glomerular filtration rate, total/high-density lipoprotein cholesterol ratio, systolic blood pressure, and use of antihypertensive medication. Model 3 includes Model 2 plus use of medications affecting heart rate variability (β-blockers, calcium channel blockers, digitalis, and antiarrhythmics). Model 4 includes Model 3 plus history of retinopathy at baseline. Cardiac autonomic neuropathy was defined as SDNN <8.2 ms and rMSSD <8.0 ms. rMSSD indicates root mean square of successive differences between normal-to-normal R-R intervals; and SDNN, standard deviation of all normal-to-normal R-R intervals.

*$P<0.05$.

a fragmentation of afferent sympathetic fibers in myocardium, a reduced number of fibers, and beaded thickening of nerves, which are all consistent with an autonomic sensory neuropathy and could explain silent ischemia in diabetes.[30] In brief, the cause of silent ischemia in the setting of diabetes seems to involve anatomic disruption of cardiac sensory nerve fibers.

Our findings have potential clinical implications. Individuals with SMI have a higher risk of developing new coronary or other cardiovascular events than those without SMI,[11–14] pointing to the need for a more aggressive detection of SMI and consequently its management. Our results suggest that the presence of CAN among individuals with type 2 diabetes could be used as a criterion for a more in-depth screening for SMI using an appropriate myocardial imaging approach.[31] There is a need for more practical criteria or tools to guide screening for asymptomatic coronary heart disease among individuals with type 2 diabetes.[32] There is also a need to assess the extent of the yield of any SMI detection based on the presence of CAN.

Our findings should be interpreted in the context of a few limitations. First, CAN was assessed using time-domain indices derived using 10-s ECG recordings only. We did not perform cardiovascular autonomic reflex tests,[2] the gold standard to diagnose CAN. It is therefore possible that we missed some cases of CAN; thus, we may have underestimated the effect of CAN on incident SMI among individuals with type 2 diabetes. However, it is generally accepted that cardiovascular autonomic reflex tests may not be feasible in large-scale epidemiological studies, and major professional societies agree with the use of HRV time-domain indices to define CAN in large clinical studies of adults with diabetes.[33] We also did not have a repeat evaluation of CAN over time. Although anatomical and pathophysiological disruption of cardiac sympathetic fibers may explain the reduced HRV, a low HRV may also reflect the complexity of neural modulation and thus physiological adaptations to various factors such as environmental changes and sleep.[34,35] Second, we did not use ECG data recorded over a longer period of time. Nevertheless, HRV indices measured using ultra-short-term ECG recordings have been shown to have a strong correlation with longer ECG recordings.[36,37] Third, SMI was diagnosed using ECGs only; we did not have data on myocardial perfusion imaging or cardiovascular magnetic resonance imaging with late gadolinium enhancement, the gold standard for the identification of unrecognized MI.[38] ECGs have been shown to have a good specificity for the diagnosis of SMI.[39,40] Given the limited sensitivity of ECGs for the identification of prior MI especially given that the Q wave can disappear with time,[41] it is possible that our study missed some cases of SMI, leading to a further attenuation of the effect estimates toward the null. Fourth, the power to detect the full extent of the association of the cardiac autonomic dysfunction exposures and SMI may have been limited by the relatively small number of events. Finally, this study was observational; hence, there is a possibility of residual confounding.

The strengths of this study include the use of a large, diverse, and well-characterized cohort of adults with type 2 diabetes, the rigorous assessment of HRV measures, the standardized adjudication of SMI cases, and the robust adjustment of potential confounders.

CONCLUSIONS

In a large cohort of adults with type 2 diabetes, cardiac autonomic dysfunction was significantly associated with a higher risk of incident SMI, after adjusting for traditional atherosclerotic risk factors. Our findings underscore the potential usefulness of CAN for optimization of the approach to identify asymptomatic coronary heart disease in people with type 2 diabetes.

ARTICLE INFORMATION

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Disclosures

Dr Fonarow reports consulting for Abbott, Amgen, AstraZeneca, Bayer, Cytokinetics, Eli Lilly, Janssen, Medtronic, Merck, Novartis, and Pfizer. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S6
Figure S1

REFERENCES

1. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988-2012. *JAMA*. 2015;314:1021–1029. doi: 10.1001/jama.2015.10029
2. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation*. 2007;115:387–397. doi: 10.1161/CIRCULATIONAHA.106.634949
3. Yun J-S, Park Y-M, Cha S-A, Ahn Y-B, Ko S-H. Progression of cardiovascular autonomic neuropathy and cardiovascular disease in type 2 diabetes. *Cardiovasc Diabetol*. 2018;17:109. doi: 10.1186/s12933-018-0752-6
4. Liao D, Carnethon M, Evans GW, Cascio WE, Heiss G. Lower heart rate variability is associated with the development of coronary heart disease in individuals with diabetes: the atherosclerosis risk in communities (ARIC) study. *Diabetes*. 2002;51:3524–3531. doi: 10.2337/diabetes.51.12.3524
5. Fyfe-Johnson AL, Muller CJ, Alonso A, Folsom AR, Gottesman RF, Rosamond WD, Whitsel EA, Agarwal SK, MacLehose RF. Heart rate variability and incident stroke: the Atherosclerosis Risk in Communities study. *Stroke*. 2016;47:1452–1458. doi: 10.1161/STROKEAHA.116.012662
6. Kaze AD, Yuyun MF, Erqou S, Fonarow GC, Echouffo-Tcheugui JB. Cardiac autonomic neuropathy and risk of incident heart failure among adults with type 2 diabetes. *Eur J Heart Fail*. 2022;24:634–641. doi: 10.1002/ejhf.2432
7. Pop-Busui R, Evans GW, Gerstein HC, Fonseca V, Fleg JL, Hoogwerf BJ, Genuth S, Grimm RH, Corson MA, Prineas R. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care*. 2010;33:1578–1584. doi: 10.2337/dc10-0125
8. Maser RE, Mitchell BD, Vinik AI, Freeman R. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. *Diabetes Care*. 2003;26:1895–1901. doi: 10.2337/diacare.26.6.1895
9. Airaksinen KEJ. Silent coronary artery disease in diabetes–a feature of autonomic neuropathy or accelerated atherosclerosis? *Diabetologia*. 2001;44:259–266. doi: 10.1007/s001250051609
10. Cohn PF, Fox KM, Daly C. Silent myocardial ischemia. *Circulation*. 2003;108:1263–1277. doi: 10.1161/01.CIR.0000088001.59265.EE
11. Davis TME, Fortun P, Mulder J, Davis WA, Bruce DG. Silent myocardial infarction and its prognosis in a community-based cohort of type 2 diabetic patients: the Fremantle Diabetes Study. *Diabetologia*. 2004;47:395–399. doi: 10.1007/s00125-004-1344-4
12. Davis TME, Coleman RL, Holman RR. Prognostic significance of silent myocardial infarction in newly diagnosed type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 79. *Circulation*. 2013;127:980–987. doi: 10.1161/CIRCULATIONAHA.112.000908
13. Singleton MJ, German CA, Bertoni AG, Ambrosius WT, Bhave PD, Soliman EZ, Yeboah J. Association of silent myocardial infarction with major cardiovascular events in diabetes: the ACCORD trial. *Diabetes Care*. 2020;43:e45–e46. doi: 10.2337/dc19-2201
14. Rutter MK, Wahid ST, McComb JM, Marshall SM. Significance of silent ischemia and microalbuminuria in predicting coronary events in asymptomatic patients with type 2 diabetes. *J Am Coll Cardiol*. 2002;40:56–61. doi: 10.1016/S0735-1097(02)01910-1
15. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med*. 2007;147:573–577. doi: 10.7326/0003-4819-147-8-200710160-00010
16. Buse JB, Bigger JT, Byington RP, Cooper LS, Cushman WC, Friedewald WT, Genuth S, Gerstein HC, Ginsberg HN, Goff DCJ, et al. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. *Am J Cardiol*. 2007;99:21i–33i.
17. Kligfield P, Gettes LS, Bailey JJ, Childers R, Deal BJ, Hancock EW, van Herpen G, Kors JA, Macfarlane P, Mirvis DM, et al. Recommendations for the standardization and interpretation of the electrocardiogram: part I: the electrocardiogram and its technology: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. *Circulation*. 2007;115:1306–1324. doi: 10.1161/CIRCULATIONAHA.106.180200
18. O'Neal WT, Chen LY, Nazarian S, Soliman EZ. Reference ranges for short-term heart rate variability measures in individuals free of cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *J Electrocardiol*. 2016;49:686–690. doi: 10.1016/j.jelectrocard.2016.06.008
19. Tang Y, Shah H, Bueno Junior CR, Sun X, Mitri J, Sambataro M, Sambado L, Gerstein HC, Fonseca V, Doria A, et al. Intensive risk factor management and cardiovascular autonomic neuropathy in type 2 diabetes: the ACCORD trial. *Diabetes Care*. 2021;44:164–173. doi: 10.2337/dc20-1842
20. Cushman WC, Evans GW, Byington RP, Goff DCJ, Grimm RHJ, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575–1585. doi: 10.1056/NEJMoa1001286
21. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med*. 2003;139:137–147. doi: 10.7326/0003-4819-139-2-200307150-00013
22. Murray DP, O'Brien T, Mulrooney R, O'Sullivan DJ. Autonomic dysfunction and silent myocardial ischaemia on exercise testing in diabetes mellitus. *Diabet Med*. 1990;7:580–584. doi: 10.1111/j.1464-5491.1990.tb01452.x
23. O'Sullivan JJ, Conroy RM, MacDonald K, McKenna TJ, Maurer BJ. Silent ischaemia in diabetic men with autonomic neuropathy. *Br Heart J*. 1991;66:313–315. doi: 10.1136/hrt.66.4.313
24. Marchant B, Umachandran V, Stevenson R, Kopelman PG, Timmis AD. Silent myocardial ischemia: role of subclinical neuropathy in patients with and without diabetes. *J Am Coll Cardiol*. 1993;22:1433–1437. doi: 10.1016/0735-1097(93)90554-E
25. Hume L, Oakley GD, Boulton AJM, Hardisty C, Ward JD. Asymptomatic myocardial ischemia in diabetes and its relationship to diabetic neuropathy: an exercise electrocardiography study in middle-aged diabetic men. *Diabetes Care*. 1986;9:384–388. doi: 10.2337/diacare.9.4.384
26. Wackers FJT, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Wittlin SD, Heller GV, Filipchuk N, et al. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care*. 2004;27:1954–1961. doi: 10.2337/diacare.27.8.1954
27. Niakan E, Harati Y, Rolak LA, Comstock JP, Rokey R. Silent myocardial infarction and diabetic cardiovascular autonomic neuropathy. *Arch Intern Med*. 1986;146:2229–2230. doi: 10.1001/archinte.1986.00360230169023
28. Gutterman DD. Silent myocardial ischemia. *Circ J*. 2009;73:785–797. doi: 10.1253/circj.CJ-08-1209
29. Langer A, Freeman MR, Josse RG, Armstrong PW. Metaiodobenzylguanidine imaging in diabetes mellitus: assessment of cardiac sympathetic denervation and its relation to autonomic dysfunction and silent myocardial ischemia. *J Am Coll Cardiol*. 1995;25:610–618. doi: 10.1016/0735-1097(94)00459-4
30. Faerman I, Faccio E, Milei J, Nuñez R, Jadzinsky M, Fox D, Rapaport M. Autonomic neuropathy and painless myocardial infarction in diabetic patients. Histologic evidence of their relationship. *Diabetes*. 1977;26:1147–1158. doi: 10.2337/diab.26.12.1147
31. Rajagopalan N, Miller TD, Hodge DO, Frye RL, Gibbons RJ. Identifying high-risk asymptomatic diabetic patients who are candidates for screening stress single-photon emission computed tomography imaging. *J Am Coll Cardiol*. 2005;45:43–49. doi: 10.1016/j.jacc.2004.06.078
32. Swoboda PP, McDiarmid AK, Erhayiem B, Haaf P, Kidambi A, Fent GJ, Dobson LE, Musa TA, Garg P, Law GR, et al. A novel and practical screening tool for the detection of silent myocardial infarction in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2016;101:3316–3323. doi: 10.1210/jc.2016-1318
33. Pop-Busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, Sosenko JM, Ziegler D. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care*. 2017;40:136–154. doi: 10.2337/dc16-2042
34. Bauer A, Camm AJ, Cerutti S, Guzik P, Huikuri H, Lombardi F, Malik M, Peng C-K, Porta A, Sassi R, et al. Reference values of heart rate variability. *Heart Rhythm*. 2017;14:302–303. doi: 10.1016/j.hrthm.2016.12.015
35. Goldberger AL, Peng C-K, Lipsitz LA. What is physiologic complexity and how does it change with aging and disease? *Neurobiol Aging*. 2002;23:23–26. doi: 10.1016/S0197-4580(01)00266-4
36. Esco MR, Flatt AA. Ultra-short-term heart rate variability indexes at rest and post-exercise in athletes: evaluating the agreement with accepted recommendations. *J Sports Sci Med*. 2014;13:535–541.

37. Nussinovitch U, Cohen O, Kaminer K, Ilani J, Nussinovitch N. Evaluating reliability of ultra-short ECG indices of heart rate variability in diabetes mellitus patients. *J Diabetes Complicat*. 2012;26:450–453. doi: 10.1016/j.jdiacomp.2012.05.001
38. Karamitsos TD, Francis JM, Myerson S, Selvanayagam JB, Neubauer S. The role of cardiovascular magnetic resonance imaging in heart failure. *J Am Coll Cardiol*. 2009;54:1407–1424. doi: 10.1016/j.jacc.2009.04.094
39. Nadour W, Doyle M, Williams RB, Rayarao G, Grant SB, Thompson DV, Yamrozik JA, Biederman RWW. Does the presence of Q waves on the EKG accurately predict prior myocardial infarction when compared to cardiac magnetic resonance using late gadolinium enhancement? A cross-population study of noninfarct vs infarct patients. *Heart Rhythm*. 2014;11:2018–2026. doi: 10.1016/j.hrthm.2014.07.025
40. Andrade JM, Gowdak LHW, Giorgi MCP, de Paula FJ, Kalil-Filho R, de Lima JJG, Rochitte CE. Cardiac MRI for detection of unrecognized myocardial infarction in patients with end-stage renal disease: comparison with ECG and scintigraphy. *AJR Am J Roentgenol*. 2009;193:W25–W32. doi: 10.2214/AJR.08.1389
41. Marcus EB, Yano K, Maclean CJ. Regression of Q waves following acute myocardial infarction. *Am J Epidemiol*. 1989;129:105–111. doi: 10.1093/oxfordjournals.aje.a115099

SUPPLEMENTAL MATERIAL

Table S1. Comparison of Baseline Characteristics of ACCORD Participants Included to Those Excluded from the Main Analyses.

	Included	Excluded	P value
N	4,842	5,409	…
Age, years	62.5 (5.7)	63.0 (7.4)	<0.001
Women, %	46.6	31.4	<0.001
Race/ethnicity, %			<0.001
White	60.2	64.3	
Black	20.4	17.8	
Hispanic	7.8	6.6	
Other	11.6	11.2	
Treatment arm, %			0.575
Intensive glycemia	49.7	50.3	
Standard glycemia	50.3	49.7	
Body mass index, kg/m^2	32.4 (5.4)	32.1 (5.4)	0.013
Current smoking, %	12.9	14.8	0.005
Alcohol drinking, %	23.5	24.3	0.424
Systolic BP, mm Hg	136.4 (16.6)	136.3 (17.5)	0.846
Diastolic BP, mm Hg	76.0 (10.1)	73.8 (11.0)	<0.001
Heart rate, bpm	70.5 (10.4)	68.6 (12.1)	<0.001
Use of BP-lowering drug, %	79.5	87.2	<0.001
Use of insulin, %	31.3	38.2	<0.001
Use of sulfonylurea, %	54.4	52.5	0.067
Hemoglobin A_{1C}, %	8.3 (1.0)	8.3 (1.1)	0.034
Duration of diabetes, years	9.0 (5.0-14.0)	10.0 (5.0-16.0)	<0.001
Total cholesterol, mg/dL	187.4 (41.7)	179.6 (41.6)	<0.001
HDL-cholesterol, mg/dL	43.1 (11.8)	40.8 (11.4)	<0.001
LDL-cholesterol, mg/dL	107.8 (34.1)	102.3 (33.5)	<0.001
Total/HDL-cholesterol Ratio	4.6 (1.7)	4.7 (1.7)	0.157
eGFR, $mL/min/1.73m^2$	92.5 (26.3)	89.8 (27.9)	<0.001
Retinopathy, %	8.8	11.6	<0.001

Data are mean (standard deviation), median (interquartile range), or proportion (%) unless otherwise indicated.
BP indicates blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table S2. Baseline characteristics of participants with overt myocardial infraction vs. those with silent myocardial infraction.

Variable	Silent myocardial infarction	Overt myocardial infarction	*P* value
N	73	130	…
Age, years	63.5 (5.8)	64.2 (6.2)	0.413
Women, %	34.3	30.8	0.610
Race/ethnicity, %			0.239
White	63.0	74.6	
Black	17.8	14.6	
Hispanic	11.0	4.6	
Other	8.2	6.2	
Treatment arm, %			0.011
Intensive glycemia	52.0	33.8	
Standard glycemia	47.9	66.2	
Body mass index, kg/m^2	30.1 (5.3)	32.5 (5.3)	0.003
Current smoking, %	13.7	19.2	0.317
Alcohol drinking, %	21.9	27.7	0.366
Systolic BP, mm Hg	136.0 (14.8)	136.8 (17.1)	0.762
Diastolic BP, mm Hg	75.0 (9.5)	75.0 (10.9)	0.982
Heart rate, bpm	70.5 (10.5)	71.9 (11.3)	0.411
Use of BP-lowering drug, %	21.9	20.0	0.746
Use of insulin, %	28.8	44.6	0.026
Use of sulfonylurea, %	58.9	47.7	0.125
Hemoglobin A_{1C}, %	8.2 (1.1)	8.5 (1.1)	0.156
Duration of diabetes, years	10.0 (5.5-16.0)	10.0 (6.0-16.0)	0.912
Total cholesterol, mg/dL	192.6 (42.0)	193.6 (38.6)	0.863
HDL-cholesterol, mg/dL	42.8 (11.9)	39.4 (10.0)	0.035
LDL-cholesterol, mg/dL	113.1 (31.9)	112.8 (34.2)	0.953
Total/HDL-cholesterol Ratio	4.8 (1.5)	5.2 (1.6)	0.063
eGFR, $mL/min/1.73m^2$	87.0 (17.8)	90.2 (32.8)	0.437
Retinopathy, %	10.9	11.5	0.901

Data are mean (standard deviation), median (interquartile range), or proportion (%) unless otherwise indicated. BP indicates blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction.

Table S3. Rates and Hazard Ratios for Overt Myocardial Infarction by Evidence of Cardiac Autonomic Neuropathy.

	CAN Absent	**CAN Present***	***P value***
No Events/No at risk	91/4,030	39/942	…
Person-years	19202.6	4391.5	…
Rate/1000 person-years	4.7 (3.9-5.8)	8.9 (6.5-12.2)	…
Hazard ratio (95% CI)			
Model 1	1 (Reference)	1.74 (1.19-2.53)	0.004
Model 2	1 (Reference)	1.59 (1.08-2.34)	0.019
Model 3	1 (Reference)	1.62 (1.10-2.39)	0.014
Model 4	1 (Reference)	1.60 (1.08-2.36)	0.018

Model 1 adjusted for age, sex, race, and treatment arm; model 2 includes model 1 plus duration of diabetes, glycated hemoglobin, cigarette smoking, alcohol intake, body mass index, estimated glomerular filtration rate, total/high-density cholesterol ratio, systolic blood pressure, and use of antihypertensive medication; model 3 includes model 2 plus use of medications affecting heart rate variability (beta blockers, calcium channel blockers, digitalis, and antiarrhythmics), model 4 includes model 3 plus history of retinopathy at baseline.

CAN indicates cardiac autonomic neuropathy; CI, confidence interval

*CAN was defined as defined as standard deviation of all normal-to-normal R-R intervals (SDNN) < 8.2 ms and root mean square of successive differences between normal-to-normal R-R intervals (rMSSD) < 8.0 ms.

Table S4. Rates and Hazard Ratios for All Myocardial Infarction Cases by Evidence of Cardiac Autonomic Neuropathy.

	CAN Absent	CAN Present*	*P value*
No Events/No at risk	142/4,030	61/942	…
Person-years	19202.6	4391.5	…
Rate/1000 person-years	7.4 (6.3-8.7)	13.9 (10.8-17.9)	…
Hazard ratio (95% CI)			
Model 1	1 (Reference)	1.75 (1.30-2.37)	<0.001
Model 2	1 (Reference)	1.69 (1.24-2.30)	0.001
Model 3	1 (Reference)	1.71 (1.26-2.33)	0.001
Model 4	1 (Reference)	1.70 (1.24-2.31)	0.001

Data are hazard ratios (95% CI) unless otherwise specified.

Model 1 adjusted for age, sex, race, and treatment arm; model 2 includes model 1 plus duration of diabetes, glycated hemoglobin, cigarette smoking, alcohol intake, body mass index, estimated glomerular filtration rate, total/high-density cholesterol ratio, systolic blood pressure, and use of antihypertensive medication; model 3 includes model 2 plus use of medications affecting heart rate variability (beta blockers, calcium channel blockers, digitalis, and antiarrhythmics), model 4 includes model 3 plus history of retinopathy at baseline.

CAN indicates cardiac autonomic neuropathy; CI, confidence interval

*****CAN was defined as defined as standard deviation of all normal-to-normal R-R intervals (SDNN) < 8.2 ms and root mean square of successive differences between normal-to-normal R-R intervals (rMSSD) < 8.0 ms.

Table S5. Rates and Hazard Ratios for Overt Myocardial Infarction by Heart Rate Variability Metrics.

	SDNN*				rMSSD †		
	Low SDNN		Per 1-SD lower log (SDNN)		Low rMSSD		Per 1-SD lower log (rMSSD)
	Absent	Present			Absent	Present	
No Events/No at risk	81/ 3,656	49/1,316	130/ 4,972		83/ 3,758	47/ 1,214	130/ 4,972
Person-years	17407.0	6187.1	23594.2		17925.7	5668.5	23594.2
Rate/1000 person-years	4.7 (3.7-5.8)	7.9 (6.0-10.5	5.5 (4.6-6.5)		4.6 (3.7-5.7	8.3 (6.2-11.0	5.5 (4.6-6.5)
Hazard ratio (95% CI)							
Model 1	1 (Reference)	1.58 (1.11-2.26) ‡	1.21 (1.02-1.44) ‡		1 (Reference)	1.62 (1.13-2.32) ‡	1.18 (0.99-1.41)
Model 2	1 (Reference)	1.46 (1.02-2.11) ‡	1.18 (0.99-1.41)		1 (Reference)	1.49 (1.03-2.16) ‡	1.15 (0.96-1.37)
Model 3	1 (Reference)	1.46 (1.02-2.11) ‡	1.18 (0.99-1.41)		1 (Reference)	1.54 (1.07-2.23) ‡	1.16 (0.97-1.39)
Model 4	1 (Reference)	1.45 (1.01-2.09) ‡	1.18 (0.99-1.41)		1 (Reference)	1.52 (1.05-2.21) ‡	1.15 (0.96-1.38)

Data are hazard ratios (95% CI) unless otherwise specified. Model 1 adjusted for age, sex, race, and treatment arm; model 2 includes model 1 plus duration of diabetes, glycated hemoglobin, cigarette smoking, alcohol intake, body mass index, estimated glomerular filtration rate, total/high-density cholesterol ratio, systolic blood pressure, and use of antihypertensive medication; model 3 includes model 2 plus use of medications affecting heart rate variability (beta blockers, calcium channel blockers, digitalis, and antiarrhythmics), model 4 includes model 3 plus history of retinopathy at baseline. CI indicates confidence interval;

* SDNN, standard deviation of all normal-to-normal R-R intervals, † rMSSD, root mean square of successive differences between normal-to-normal R-R intervals; SD, standard deviation; ‡ $P<0.05$

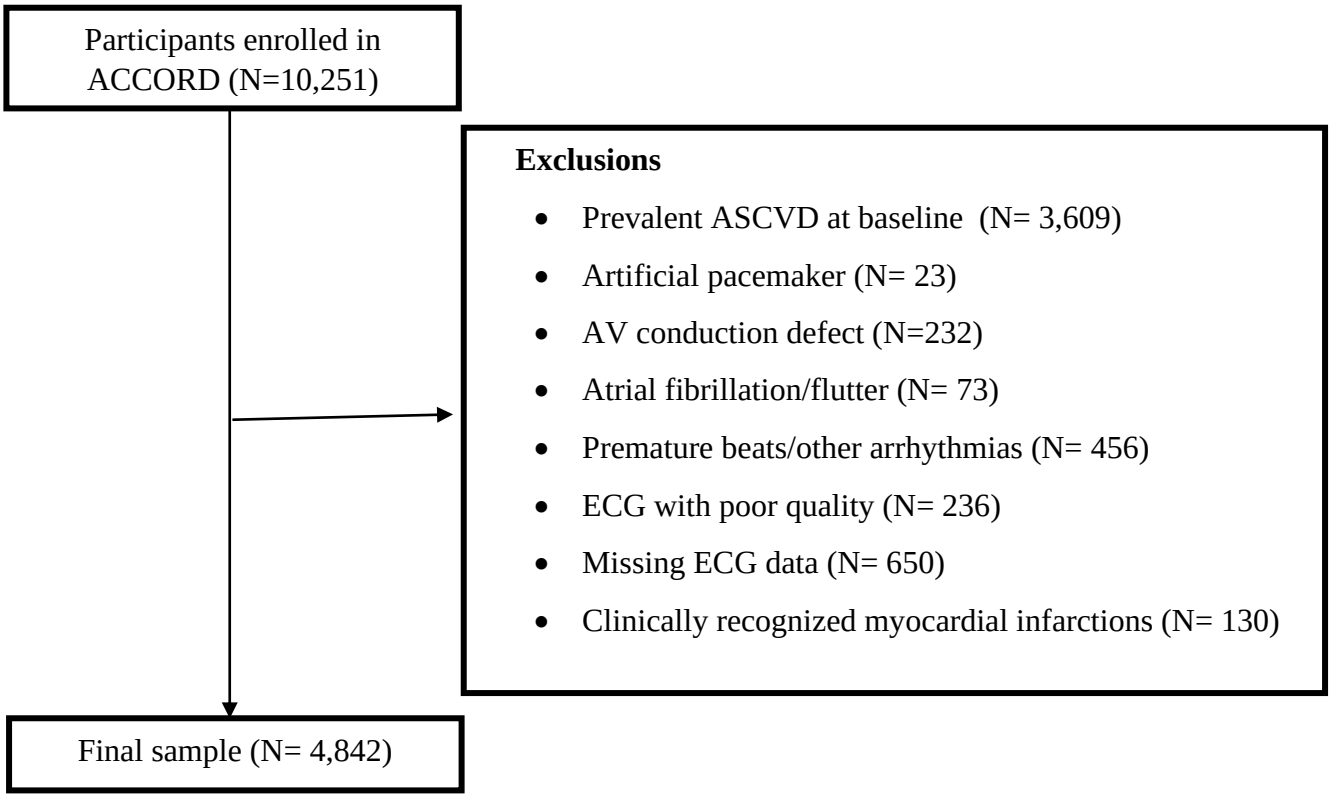
Table S6. Rates and Hazard Ratios for All Myocardial Infarction Cases by Heart Rate Variability Metrics.

	SDNN *				rMSSD †		
	Low SDNN		Per 1-SD lower log (SDNN)		Low rMSSD		Per 1-SD lower log (rMSSD)
	Absent	Present			Absent	Present	
No Events/No at risk	126/ 3,656	77/ 1,316	203/ 4,972		132/ 3,758	71/ 1,214	203/ 4,972
Person-years	17407.0	6187.1	23594.2		17925.7	5668.5	23594.2
Rate/1000 person-years	7.2 (6.1-8.6)	12.4 (10.0 -15.6)	8.6 (7.5-9.9)		7.4 (6.2-8.7)	12.5 (9.9-15.8)	8.6 (7.5-9.9)
Hazard ratio (95% CI)							
Model 1	1 (Reference)	1.62 (1.22-2.15) ‡	1.24 (1.08-1.42) ‡		1 (Reference)	1.56 (1.17-2.09) ‡	1.17 (1.02-1.35) ‡
Model 2	1 (Reference)	1.53 (1.14-2.05) ‡	1.22 (1.06-1.41) ‡		1 (Reference)	1.51 (1.12-2.03) ‡	1.15 (0.99-1.33)
Model 3	1 (Reference)	1.53 (1.14-2.05) ‡	1.22 (1.06-1.41) ‡		1 (Reference)	1.54 (1.15-2.08) ‡	1.16 (1.00-1.34) ‡
Model 4	1 (Reference)	1.52 (1.13-2.03) ‡	1.22 (1.06-1.40) ‡		1 (Reference)	1.53 (1.13-2.06) ‡	1.16 (1.00-1.34)

Data are hazard ratios (95% CI) unless otherwise specified. Model 1 adjusted for age, sex, race, and treatment arm; model 2 includes model 1 plus duration of diabetes, glycated hemoglobin, cigarette smoking, alcohol intake, body mass index, estimated glomerular filtration rate, total/high-density cholesterol ratio, systolic blood pressure, and use of antihypertensive medication; model 3 includes model 2 plus use of medications affecting heart rate variability (beta blockers, calcium channel blockers, digitalis, and antiarrhythmics), model 4 includes model 3 plus history of retinopathy at baseline. CI indicates confidence interval

* SDNN, standard deviation of all normal-to-normal R-R intervals, † rMSSD, root mean square of successive differences between normal-to-normal R-R intervals; SD, standard deviation; ‡ $P<0.05$.

Figure S1. Exclusion criteria for examining the association of cardiac autonomic dysfunction and silent myocardial infarction among participants enrolled in ACCORD.



ACCORD indicates Action to Control Cardiovascular Risk in Diabetes; ASCVD, atherosclerotic cardiovascular disease; AV, atrioventricular; ECG, electrocardiogram