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Heart Rate Variability and Incident Stroke: The Atherosclerosis Risk in Communities Study

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Abstract

Background and Purpose—Low heart rate variability (HRV), a marker of cardiac autonomic dysfunction, has been associated with increased all-cause and cardiovascular mortality. We examined the association between reduced HRV and incident stroke in a community-based cohort.

Methods—The Atherosclerosis Risk in Communities (ARIC) Study measured HRV using 2-minute electrocardiogram readings in 12,550 middle-aged adults at baseline (1987-89). HRV indices were calculated using the standard deviation of RR intervals (SD_{NN}), the mean of all normal RR intervals ($Mean_{NN}$), the root mean square of successive differences of successive RR intervals (RMSSD), low (LF) and high (HF) frequency power, and the LF/HF ratio. All HRV measures were categorized into quintiles. Incident stroke was adjudicated through 2011. Cox regression was used to estimate hazard ratios (HR) with the lowest HRV quintile as the reference, with and without stratification by prevalent diabetes.

Results—Over a median follow-up of 22 years, 816 (6.5%) participants experienced incident stroke. After covariate adjustment, there was no strong evidence of association between HRV and stroke risk. In stratified analyses, the lowest HRV quintile was associated with higher stroke risk compared to the highest quintile for SD_{NN} (HR = 2.0, 95% CI = 1.1-4.0), RMSSD (HR = 1.7, 95% CI = 0.9-3.2), LF (HR = 1.5, 95% CI = 0.8-3.0), and HF (HR = 1.7, 95% CI = 0.9-3.0) only among people with diabetes.

Conclusions—Lower HRV was associated with higher risk of incident stroke among middle-aged adults with prevalent diabetes, but not among people without diabetes.

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Keywords

Heart rate variability; autonomic function; stroke; diabetes mellitus; Atherosclerosis Risk in Communities Study

INTRODUCTION

Stroke is the most severe form of cerebrovascular disease, with 795,000 cases in the U.S. each year.[1] Stroke is the fourth leading cause of death in the U.S., leaving 50% of survivors disabled.[2] In 2008 the U.S. spent $18.8 billion on healthcare for strokes, and $15.5 billion was lost in productivity.[1,2] Numerous studies have identified risk factors for incident stroke – the most prominent being older age, male sex, African American vs. White race, hypertension, diabetes, obesity, and smoking.[3] More recently, autonomic nervous system (ANS) dysfunction has been associated with increased post-stroke morbidity and mortality.[4] Proposed mechanisms include the influence of the ANS on cerebral circulatory autoregulation, blood pressure, and essential hypertension.[5–7]

Heart rate variability (HRV) is a commonly examined marker for ANS dysfunction.[8] Heart rate is regulated by a balance between the sympathetic and parasympathetic nervous systems, consequently ANS dysfunction leads to measurable differences in heart rate and HRV.[8] Low HRV has been positively associated with cardiovascular disease risk factors, and multiple cardiovascular outcomes including cardiovascular mortality and incident coronary heart disease among others.[9–11] The association between HRV and cardiovascular outcomes has been shown to be stronger in people with diabetes.[10,11]

A previous study has identified an association between low HRV and the risk of all-cause mortality and cardiovascular mortality in older stroke survivors.[12] Another study reported an association between low nighttime HRV and increased risk of incident ischemic stroke,[13] but was limited by small sample size and few stroke events. The clinical value of HRV for identifying people at high risk of stroke is unknown; no studies have evaluated daytime HRV as would be assessed in a routine clinic visit. These unresolved questions have clinical and public health implications as HRV may represent a target for stroke prevention through medication or lifestyle changes that improve or preserve ANS function.[14] Furthermore, identification of high-risk groups could prove valuable for stroke prevention. We analyzed data from the Atherosclerosis Risk in Communities (ARIC) cohort study to estimate the association between HRV and primary incident stroke.

METHODS

Study Population

The ARIC study is a longitudinal prospective cohort study initiated in 1987-89. Originally, 15,792 men and women ages 45-64 years of age were recruited from 4 U.S. communities: suburbs of Minneapolis, Minnesota; Jackson, Mississippi; Washington County, Maryland; and Forsyth County, North Carolina. Four follow-up visits were conducted: visit 2 (1990-92), visit 3 (1993-95), visit 4 (1996-98), and visit 5 (2011-13).[15] At each study, visit participants underwent extensive clinical exams; visits 1 and 4 included electrocardiogram

(ECG) assessment of HRV. Written informed consent was collected from all study participants and all affiliated Institutional Review Boards approved the study protocol.

Heart Rate Variability Assessment

The Task Force of The European Society of Cardiology and others have documented standards and procedures for HRV measurement. In short, heart rate is measured from the intervals between R waves of successive heartbeats (RR interval); HRV reflects the magnitude of RR interval variation over time.[8,16] Protocols for data processing and analysis in ARIC have been previously published (online supplement, eTables I and II, please see http://stroke.ahajournals.org).[10,17] Briefly, ARIC measured HRV twice: (i) 2-minute ECG readings at visit 1, and (ii) 6-minute ECG readings at visit 4. All data were collected on resting participants in a supine position, reflect short-term daytime HRV, and were analyzed using ECG software (time-domain) or a previously developed computer algorithm (frequency-domain).[10,17,18] Our primary analysis used visit 1 HRV measures, with secondary analyses using visit 4 HRV measures and participants who remained stroke-free at that exam. HRV indices are commonly divided into time- and frequency-domain measurements. Time-domain measures are calculated directly from heart rate or the duration between successive RR intervals. Frequency-domain measures are calculated from spectral imaging of the ECG recording. We evaluated three time-domain measures of HRV: (i) the standard deviation of all normal-to-normal (NN) RR intervals (SD_{NN}) which characterizes overall HRV, (ii) the mean of all RR intervals ($Mean_{NN}$), and (iii) the root mean square of successive differences in RR intervals (RMSSD) which is thought to reflect parasympathetic nervous system activity. We also evaluated three frequency-domain measures of HRV: (i) low frequency power (LF; 0.04-0.15 Hz), considered to include both sympathetic and parasympathetic nervous system activity, (ii) high frequency power (HF; 0.15-0.40 Hz), thought to reflect parasympathetic nervous system activity, and (iii) low:high frequency power ratio (LF:HF), which estimates the balance between sympathetic and parasympathetic nervous system activity.[8]

Incident Stroke Ascertainment

Stroke events were identified between visit 1 (1987-89) and December 31, 2011.[19] Annual telephone calls to study participants assessed hospitalizations and deaths possibly attributed to strokes in the previous year. In addition, hospital discharge summaries were reviewed for International Classification of Diseases, 9th Revision (ICD-9) codes 430-436 which are indicative of cerebrovascular events, and state death registries were reviewed for cerebrovascular-related mortality. Study personnel documented whether hospital discharge ICD-9 codes included cerebrovascular disease, if cerebrovascular disease was noted in the discharge summary, or a cerebrovascular finding was referenced in the neuroimaging report study. Study staff then abstracted, from the hospital record, stroke signs and symptoms and findings from cerebrovascular imaging (computed tomography or magnetic resonance). Based on National Survey of Stroke criteria,[20] a computer algorithm and study physician categorized all possible incident stroke events; an additional study reviewer adjudicated discrepancies. For the present analysis, incident stroke included ischemic and hemorrhagic strokes defined by the presence of an acute infarction or hemorrhage respectively on neurological imaging or autopsy.

Covariates

Sociodemographic and lifestyle variables in our primary (visit 1) and secondary (visit 4) analyses included ARIC field site, age in years at the clinic exam, sex, race (African American, White), total years of education (less than completed high school, completed high school or equivalent, and at least some college), cigarette smoking and alcohol consumption (both coded as current, former, never), and physical activity (score of leisure time sports activity). Clinical variables included body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), self-reported current use of antihypertensive medication, blood lipids, and diabetes (fasting glucose ≥ 126 mg/dL, non-fasting glucose ≥ 200 mg/dL, currently taking medication for diabetes, or self-reported physician diagnosis of diabetes).[15] SBP, DBP, and use of antihypertensive medication were excluded as covariates in sensitivity analyses.

Exclusions and Missing Data

Of the 15,792 participants at visit 1, we excluded individuals for the following reasons: 1) racial identification of Asian, American Indian, "Other," or African American race from the predominantly white ARIC field sites ($n = 103$); 2) taking medication known to affect HRV (beta-blockers, antiarrythmics, calcium channel blockers, or digoxin; $n = 2259$); 3) prevalent stroke at the baseline exam ($n = 204$); and 4) prevalent coronary heart disease or heart failure ($n = 676$). Our final sample size was 12,550 observations. An additional 2667 individuals would have been excluded due to missing HRV data at baseline. To preserve sample size and minimize the possibility of selection bias, we used multiple imputation by chained equations (MICE) with 100 repetitions to impute missing data for the 2667 people who would have been excluded in a complete case analysis based on missing HRV data.[21]

Statistical Analysis

Cox proportional hazards regression was used to estimate hazard ratios (HR) for the relationship between each HRV measure and incident stroke. Person-time was calculated as number of years from the visit 1 exam to date of incident stroke or censoring (either death, loss to follow-up, or administrative censoring on December 31, 2011). Due to non-linear trends observed in preliminary descriptive analyses and a restricted cubic spline analysis, we categorized each HRV measure into quintiles (highest category serving as the reference for all comparisons).

In the primary analysis we fit two adjusted models: (i) Model 1 adjusted for baseline age, sex, and race, and (ii) Model 2 additionally adjusted for other baseline lifestyle and clinical covariates (Model 1 + education, smoking, alcohol consumption, physical activity, body mass index, SBP, DBP, blood lipids, prevalent diabetes, antihypertensive medication, and heart rate (except $Mean_{NN}$)). We excluded heart rate from models for the mean RR interval ($Mean_{NN}$) because of collinearity. Due to concerns that hypertension could be a possible mediator between HRV and stroke, we performed a sensitivity analysis excluding SBP, DBP, and antihypertensive use. Results were nearly identical; we included blood pressure variables in our models to address any possibility of confounding effects of blood pressure on the relationship between HRV and risk of incident stroke. Previous studies examining the association between HRV and heart disease reported effect modification by diabetes

status.[10,11] Therefore, we evaluated statistical evidence for interaction in the full model and estimated stratified associations by diabetes prevalence at baseline. All results for our primary analysis incorporate imputed data using MICE.

In secondary analyses we evaluated the association between 6-minute HRV measured at visit 4 and subsequent stroke; we examined statistical evidence for interaction and estimated stratified associations by prevalent diabetes status. The latter analysis was restricted to cohort members who were stroke-free at their visit 4 exam. Because results between the complete case analysis and non-imputed data set in our primary analysis (visit 1) were similar, we did not perform MICE for our sensitivity analysis for visit 4. We tested all models and detected no evidence of violation of the proportional hazard assumption. We used Stata version 14 and *R* for data management and statistical analyses.[22,23]

RESULTS

Of the 12,550 ARIC participants included in our analysis at visit 1, 6.5% ($n = 816$) experienced a stroke during follow-up. Table 1 shows descriptive statistics for baseline variables presented separately by SD_{NN} quintile. In general groups with lower SD_{NN} values tended to have higher proportions of females, lower education, and higher blood pressure, heart rate, and proportions of people with hypertension and taking antihypertensive medication. Groups with lower SD_{NN} tended to have higher proportions of people with prevalent diabetes, with a strikingly higher proportion in the lowest SD_{NN} quintile. Crude cumulative stroke incidence was consistent with higher risk in the lowest HRV quintiles (online supplement, Figure, please see http://stroke.ahajournals.org). Ranges for all HRV measurements by quintile are reported in the online supplement, eTable III, please see http://stroke.ahajournals.org.

In Cox regression analysis for the full cohort (Table 2), people in the lowest HRV quintiles showed higher risk of stroke compared to the reference group in demographic-adjusted models, but these associations were attenuated after full covariate adjustment. Only the interaction between prevalent diabetes and SD_{NN} was statistically significant (Table 3). Stratified analyses restricted to people with diabetes consistently showed higher stroke risk associated with the lowest HRV quintiles for SD_{NN} (HR = 2.0, 95% CI = 1.1-4.0), RMSSD (HR = 1.7, 95% CI = 0.9-3.2), LF (HR = 1.5, 95% CI = 0.8-3.0), and HF (HR = 1.7, 95% CI = 0.9-3.0). Importantly, there was substantial variability among the quintiles for many of these outcomes (Table 3). No associations were evident for $Mean_{NN}$ or the LF/HF ratio among people with diabetes, and no relationship between HRV and incident stroke was evident for any measure among people without diabetes. Despite the fact that not all of these results were statistically significant, the lowest values of HRV were consistently associated with increased risk of incident stroke across most HRV measures among diabetics. Excluding heart rate or blood pressure variables (SBP, DPB, and antihypertensive use) resulted in negligible changes to point estimates and confidence intervals. We observed similar results for the sensitivity analysis using HRV measured at visit 4 (online supplement, eTable IV, please see http://stroke.ahajournals.org); of the 8041 ARIC participants included in this analysis, 4.6% (n=372) experienced a stroke during follow-up.

DISCUSSION

In this prospective population-based analysis of ARIC participants, we found some evidence of increased risk of stroke among diabetic participants in the lowest quintile of HRV relative to those in the highest quintile. We observed little evidence of an association between low HRV and incident stroke among non-diabetic participants. These results were consistent across most, but not all, of the time- and frequency-domain HRV measures.

One previous study reported a positive association between low nighttime HRV (15-minute recording) and incident ischemic stroke.[13] Though informative, this study was limited by a small sample size, few stroke events, and examination of time-domain HRV measures only. We have expanded on this work by utilizing a large prospective bi-racial cohort, time- and frequency-domain HRV indices, and by evaluating potential effect modification by diabetes status.

Individuals with type 2 diabetes are known to have an elevated risk of cardiovascular disease; previous studies have found positive associations between elevated fasting insulin or type 2 diabetes and ANS dysfunction.[24] Our results are consistent with previous findings in ARIC in which diabetes was found to be an effect modifier: participants with diabetes in the lowest quartile of HRV had an elevated risk of incident coronary heart disease compared to those in the highest quartile; no association was observed among people without diabetes.[11]

The primary mechanisms providing insight into a possible association of HRV and incident stroke include circulatory autoregulation[5,25] and blood pressure.[7,19] First, the dynamics between blood pressure and blood flow in the cerebral vessels, circulatory autoregulation, are essential for brain health. The sympathetic nervous system plays a critical role in circulatory autoregulation; slow pressure and blood flow changes are physiologically controlled, whereas fast changes are not closely regulated.[5,25] It is unknown how HRV impacts changes in cerebral vascular pressure; it is possible low HRV triggers fast pressure changes in cerebral vasculature, goes unregulated, and impacts vascular health and subsequent stroke risk. Second, hypertension presents another possible mechanism linking HRV and stroke. The onset and progression of hypertension are a result of elevated sympathetic tone.[7,8] Furthermore, arterial stiffness and left ventricular hypertrophy (LVH) are a result of increased ANS activity; both increase vascular resistance, a known contributor to hypertension.[26] We were initially concerned that blood pressure variables were possible mediators in the association between HRV and incident stroke. Simultaneously, hypertension is an established risk factor for incident stroke[27] and is known to be associated with autonomic dysfunction.[28] We performed a sensitivity analysis examining results with blood pressure variables excluded from the models. The results from the sensitivity and main analyses were quite similar. To be conservative, we retained blood pressure variables in our models to address any potential confounding effects of blood pressure on the relationship between HRV and risk of incident stroke. Finally, despite the fact that we did not find an association between low HRV and incident stroke in our primary analysis, these mechanisms may become physiologically relevant when other disease processes, such as diabetes, are present. Previous studies report that low HRV precedes coronary heart disease[10] and mortality post-myocardial infarction.[9] These same studies have hypothesized that low HRV

may be an early indicator of declining health. If low HRV reflects poor general health, it is possible that autonomic dysfunction has more impact in populations already at risk (i.e. type 2 diabetes).

Strengths of this study include the use of a prospective design with long-term follow-up, a large sample size, and multiple imputation methods to minimize the possibility of selection bias. In addition, the present study used a community-based bi-racial cohort, measurement of multiple time and frequency domain HRV indices, and comprehensive collection of cardiovascular risk factors for confounding adjustment. HRV and incident stroke were both objectively measured for all analyses. Secondary analyses using 6-minute ECG recordings at visit 4 (online supplement, eTable IV, please see http://stroke.ahajournals.org) yielded nearly identical results to the primary analysis (Table 3). There are a number of limitations of this study. First, HRV was measured using a 2-minute and 6-minute ECG at visits 1 and 4 respectively. Collection of long-term (>18 hours) Holter ECG recordings is generally preferred to short-term (˜5 minutes) ECG recordings because length of ECG recording impacts measurement variability.[16] Our results, however, did not change using 2-minute (visit 1) and 6-minute (visit 4) ECG data giving confidence to minimal measurement error. Furthermore, previous studies have demonstrated that 2-minute, 15-minute, and 24-hour HRV indices are correlated (most ≥ 0.75).[9] A more robust measurement of HRV (24-hour Holter ECG) could have yielded a more accurate measure of HRV. Second, it should be noted that our data reflect daytime HRV, and may not represent the overall variations of sympathetic and parasympathetic activity that occur in a 24-hour period. Third, although losses to follow-up are relatively small in ARIC the possibility of selection bias exists; the association we report may not be generalizable. Fourth, there is considerable imprecision in many of our hazard ratios and studies with more events may help estimate the associations more accurately. Finally, despite our attempts to statistically adjust for known confounders, residual confounding may be present.

Implications

Identification of new indicators that contribute to incident stroke provides the opportunity to identify individuals at high risk and develop protocols for early intervention. Although newer guidelines for HRV assessment in diabetics have been proposed,[29] current guidelines recommend measuring HRV in two situations: (i) to measure risk of mortality in individuals post-myocardial infarction, and (ii) to examine possible autonomic neuropathy in individuals with diabetes.[8] Since these guidelines were published nearly two decades ago, lower HRV has consistently been found to predict cardiovascular disease morbidity and mortality.[9–11] Expanding the clinical scope and relevance of HRV may be warranted.

SUMMARY/CONCLUSIONS

In conclusion, in this large community-based bi-racial cohort lower HRV was associated with a modest risk of incident stroke in persons with diabetes, independent of traditional cardiovascular risk factors. Further studies are warranted, and additional exploration of the etiology of cardiac autonomic dysfunction and stroke in individuals with diabetes may be beneficial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline (visit 1) characteristics for study sample by SD_{NN} quintile, ARIC, 1987-89 (n=12,550).

	SD_{NN} Quintile				
Category	**1**	**2**	**3**	**4**	**5**
Range, *ms*	**0.5-23.4**	**23.5-30.4**	**30.5-38.0**	**38.1-49.5**	**49.6-394**
N total	**2519**	**2512**	**2510**	**2504**	**2505**
Age, *mean years (SD)*	55 (6)	54 (6)	54 (6)	53 (6)	53 (6)
Female, %	61	59	56	54	49
Black race, %	28	24	25	26	29
Education (total years), %					
Less than completed high school	25	22	22	20	21
Completed high school or equivalent	41	41	42	43	39
At least some college	34	37	36	37	40
Cigarette smoking, %					
Current	27	26	25	26	28
Former	30	31	31	33	32
Never	44	44	44	41	41
Alcohol consumption, %					
Current	54	59	56	60	59
Former	19	15	18	17	18
Never	27	26	26	23	23
Sport PA, *mean score (SD)*	2.4 (0.8)	2.4 (0.8)	2.4 (0.8)	2.5 (0.9)	2.5 (0.9)
Body mass index, *mean kg/m^2 (SD)*	28 (6)	27 (6)	27 (6)	27 (5)	27 (5)
Systolic BP, *mean mmHg (SD)*	124 (21)	121 (19)	120 (18)	119 (19)	118 (19)
DiastolicBP, *mean mmHg (SD)*	75 (12)	74 (11)	73 (12)	73 (12)	72 (12)
Heart rate, *mean beats per minute (SD)*	74 (12)	68 (10)	67 (9)	65 (9)	62 (9)
HDL, *mean mg/dL (SD)*	53 (19)	54 (18)	53 (18)	53 (18)	52 (18)
LDL, *mean mg/dL (SD)*	139 (43)	137 (42)	136 (42)	137 (41)	135 (41)
Antihypertensive medication, %	25	16	15	14	14
Prevalent hypertension, %	35	26	24	22	21
Prevalent diabetes, %	17.1	9.8	7.9	7.2	6.5

Abbreviations: Standard deviation of all normal-to-normal RR intervals SD_{NN}; standard deviation, SD; physical activity, PA; kilograms/meter squared, kg/m^2; blood pressure, BP; millimeters of mercury, mmHg; high-density lipoprotein cholesterol, HDL; low-density lipoprotein cholesterol, LDL; milligrams/deciliter, mg/dL.

Table 2

Time-domain (top) and frequency-domain (bottom) heart rate variability at visit 1 and stroke risk. Total n = 12,550; split into approximately 2510 observations per quintile for each HRV measure; total strokes n = 816.

Time-Domain						
	Model 1			Model 2		
	SD_{NN}	$Mean_{NN}$	RMSSD	SD_{NN}	$Mean_{NN}$	RMSSD
Contrast	***HR (95% CI)***	***HR (95% CI)***	***HR (95% CI)***	***HR (95% CI)***	***HR (95% CI)***	***HR (95% CI)***
Quintile 1	1.4 (1.1, 1.7)	1.7 (1.3, 2.1)	1.4 (1.2, 1.8)	1.0 (0.8, 1.3)	1.2 (0.9, 1.5)	1.1 (0.8, 1.4)
Quintile 2	1.0 (0.8, 1.3)	1.3 (1.0, 1.6)	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)	1.0 (0.8, 1.3)	0.8 (0.7, 1.1)
Quintile 3	1.1 (0.9, 1.4)	1.2 (0.9, 1.5)	1.1 (0.9, 1.4)	1.1 (0.8, 1.3)	1.1 (0.8, 1.4)	1.1 (0.8, 1.4)
Quintile 4	1.0 (0.7, 1.2)	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)	0.9 (0.7, 1.2)	1.0 (0.8, 1.3)	1.1 (0.9, 1.4)
Quintile 5	Ref	Ref	Ref	Ref	Ref	Ref

Frequency-Domain						
	Model 1			Model 2		
	LF	HF	LF:HF	LF	HF	LF:HF
Contrast	***HR (95% CI)***	***HR (95% CI)***	***HR (95% CI)***	***HR (95% CI)***	***HR (95% CI)***	***HR (95% CI)***
Quintile 1	1.3 (1.0, 1.7)	1.2 (0.9, 1.5)	1.1 (0.9, 1.4)	1.1 (0.8, 1.4)	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)
Quintile 2	1.2 (1.0, 1.6)	0.9 (0.7, 1.1)	1.0 (0.8, 1.2)	1.2 (0.9, 1.5)	0.9 (0.7, 1.1)	0.9 (0.7, 1.2)
Quintile 3	1.0 (0.8, 1.4)	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)	1.0 (0.8, 1.2)
Quintile 4	1.1 (0.9, 1.5)	0.9 (0.7, 1.2)	0.9 (0.7, 1.1)	1.1 (0.8, 1.4)	0.9 (0.7, 1.2)	0.8 (0.7, 1.1)
Quintile 5	Ref	Ref	Ref	Ref	Ref	Ref

Abbreviations: Hazard ratio, HR; confidence interval, CI; reference quintile, Ref.

Model 1: adjusted for age, sex, and race.

Model 2: Model 1 + education, smoking, alcohol consumption, physical activity, body mass index, systolic and diastolic blood pressure, blood lipids, prevalent diabetes, antihypertensive use, and heart rate (except for $Mean_{NN}$).

Hazard ratios can be interpreted as the comparison between quintiles 1, 2, 3, and 4 with quintile 5 (reference).

Table 3

Time-domain (top) and frequency-domain (bottom) heart rate variability at visit 1 and stroke risk for people without (n = 11,237) and with (n = 1196) prevalent diabetes; total strokes n = 816.

Time Domain						
	SD_{NN}		$Mean_{NN}$		RMSSD	
	No diabetes	Diabetes	No diabetes	Diabetes	No diabetes	Diabetes
	HR (95% CI)	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*
Quintile 1	0.9 (0.6, 1.2)	2.0 (1.1, 4.0)	1.1 (0.9, 1.5)	1.1 (0.6, 1.8)	1.0 (0.7, 1.3)	1.7 (0.9, 3.2)
Quintile 2	0.9 (0.7, 1.2)	1.2 (0.6, 2.4)	1.0 (0.8, 1.4)	0.9 (0.5, 1.5)	0.7 (0.5, 1.0)	1.5 (0.8, 2.7)
Quintile 3	1.0 (0.7, 1.3)	1.7 (0.9, 3.4)	1.1 (0.9, 1.4)	0.9 (0.5, 1.6)	1.1 (0.8, 1.4)	1.0 (0.5, 2.0)
Quintile 4	0.9 (0.7, 1.2)	1.1 (0.5, 2.4)	1.1 (0.8, 1.4)	0.7 (0.3, 1.3)	1.0 (0.8, 1.3)	1.6 (0.9, 3.0)
Quintile 5	Ref	Ref	Ref	Ref	Ref	Ref
$p_{interaction}$	0.01		0.56		0.14	

Frequency Domain						
	Low frequency		High frequency		Low frequency/High frequency	
	No diabetes	Diabetes	No diabetes	Diabetes	No diabetes	Diabetes
	HR (95% CI)	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*
Quintile 1	0.9 (0.7, 1.3)	1.5 (0.8, 3.0)	0.9 (0.6, 1.2)	1.7 (0.9, 3.0)	1.0 (0.8, 1.3)	1.0 (0.6, 1.6)
Quintile 2	1.1 (0.8, 1.4)	1.5 (0.8, 2.9)	0.8 (0.6, 1.1)	1.2 (0.6, 2.2)	0.9 (0.7, 1.2)	0.8 (0.5, 1.3)
Quintile 3	1.0 (0.7, 1.3)	1.2 (0.6, 2.4)	1.0 (0.7, 1.3)	1.2 (0.7, 2.3)	1.0 (0.8, 1.4)	0.8 (0.4, 1.4)
Quintile 4	1.1 (0.8, 1.5)	1.0 (0.5, 2.2)	0.9 (0.7, 1.2)	0.9 (0.5, 1.8)	0.9 (0.7, 1.1)	0.8 (0.4, 1.3)
Quintile 5	Ref	Ref	Ref	Ref	Ref	Ref
$p_{interaction}$	0.10		0.06		0.81	

Abbreviations: Hazard ratio, HR; confidence interval, CI; reference quintile, Ref.

All results from Model 2: adjusted for age, sex, race, education, smoking, alcohol consumption, physical activity, body mass index, systolic and diastolic blood pressure, blood lipids, prevalent diabetes, antihypertensive use, and heart rate (except for $Mean_{NN}$).

Hazard ratios can be interpreted as the comparison between quintiles 1, 2, 3, and 4 with quintile 5 (reference).