








ORIGINAL ARTICLE

Resting heart rate and incidence of venous thromboembolism

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Abstract

Background/Objectives: Higher resting heart rate is a risk factor for arterial cardiovascular diseases. We assessed whether higher heart rate is a risk factor for venous thromboembolism (VTE).

Methods: In a prospective epidemiologic cohort, the Atherosclerosis Risk in Communities (ARIC) Study, we associated resting heart rate by electrocardiogram with physician-validated incident hospitalized VTE through 2015. We also examined whether lower heart rate variability (HRV), a marker of cardiac autonomic imbalance, might be a risk factor for VTE.

Results: Resting heart rate at Visit 1 (1987-1989), when participants were 45 to 64 years old (mean, 54 years), was not associated with incidence of VTE (n = 882 cases). However, heart rate at Visit 4 (1996-1998; mean age, 63 years) was associated positively with VTE (n = 557 cases). The adjusted hazard ratios (95% confidence intervals) of VTE across Visit 4 heart rate categories of <60, 60 to 69, 70 to 79, and ≥80 bpm were 1 (reference), 1.22 (1.01-1.49), 1.39 (1.09-1.78), and 1.44 (1.01-2.06), respectively, and when evaluated continuously 1.11 (1.02-1.21) per 10 bpm greater heart rate. For the most part, HRV indices were not associated with VTE or associations were explained by inverse correlations of HRV indices with heart rate.

Conclusion: We found a significant positive and independent association of resting heart rate at ARIC Visit 4 with incidence of VTE. The reason why high heart rate is a risk marker for VTE warrants further exploration.

KEYWORDS

heart rate, heart rate variability, prospective study, pulmonary embolism, venous thromboembolism

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Essentials

- Higher resting heart rate may be associated with increased risk of venous thromboembolism (VTE).
- We tested this hypothesis in a prospective population-based cohort followed nearly 2 decades.
- VTE incidence showed a dose-response with heart rate: 1.44-fold higher risk for ≥ 80 versus < 60 .
- Why high heart rate is a risk marker for VTE warrants further exploration.

1 | INTRODUCTION

Considerable epidemiologic evidence has indicated that a higher resting heart rate is a risk factor for arterial cardiovascular diseases, total mortality, higher blood pressure, lower physical fitness, and higher inflammatory markers in the general population.¹⁻⁵ Yet, to our knowledge, only the prospective Multi-Ethnic Study of Atherosclerosis (MESA) has examined whether higher resting heart rate is a risk factor for venous thromboembolism (VTE—deep vein thrombosis [DVT] or pulmonary embolism [PE]).⁶ MESA participants with a resting heart rate ≥ 80 beats per minutes (bpm) had double the risk of hospitalized VTE—as documented via discharge codes—compared to participants with a heart rate < 60 bpm.⁶

Possible mechanisms for a positive association of heart rate with VTE are speculative, but according to Virchow's triad should operate via hypercoagulability, venous injury, or venous stasis. Higher heart rate is correlated positively with multiple plasma inflammatory markers, like interleukin-6, C-reactive protein, and fibrinogen^{5,7}; inflammatory processes could contribute to hypercoagulability by upregulating tissue factor⁸ or by causing venous injury or insufficiency.^{9,10} Higher heart rate also typically reflects excessive sympathetic to parasympathetic activity, which might also contribute to venous injury or hypercoagulability. Conversely, it seems unlikely that a higher heart rate would increase the venous stasis component of Virchow's triad. In contrast, it may be that the MESA association is artifactual, due to residual confounding from low physical fitness, the metabolic syndrome, or other unmeasured variables that might increase VTE risk.

We therefore sought to verify whether higher resting heart rate is a VTE risk factor in another prospective epidemiologic cohort, the Atherosclerosis Risk in Communities (ARIC) Study. Importantly, the ARIC Study, unlike MESA, has validated VTE outcomes. As a secondary analysis, we also examined whether another measure of sympathetic to parasympathetic activity—lower heart rate variability (HRV)—might also be a risk factor for VTE.

2 | METHODS

2.1 | Study sample and design

Previous publications described the overall ARIC study design, methods, and VTE incidence rates in detail.^{11,12} Briefly, 15 792 predominantly black or white men and women aged 45 to 64 years from 4 US communities enrolled and underwent a baseline (Visit 1) examination in 1987 to 1989. The institutional review committees at each study center approved the methods, and ARIC staff obtained

informed participant consent. ARIC maintained contact with the participants via annual or semiannual telephone calls and reexamined 93% of the cohort still alive in 1990-1992 (Visit 2), 86% in 1993-1995 (Visit 3), 81% in 1996-1998 (Visit 4), and 65% in 2011-2013 (Visit 5).

2.2 | Measurements of heart rate and HRV

At Visit 1 and subsequent visits, ARIC performed a standard supine 12-lead electrocardiogram (ECG) and calculated resting heart rate as the mean RR interval of successive heart beats. Participants took their medications as usual on the morning of each visit. They rested supine on the examination table while ARIC staff placed the electrodes and then for 2 to 3 additional minutes before the ECG was taken. Our initial focus was on Visit 1, but because associations differed markedly from MESA,⁶ we sought replication using ARIC Visit 4. We also picked Visit 4 because Visits 2 and 3 were too close to Visit 1, Visit 4 best matched the years of MESA and also had HRV data, and there have been too few VTEs so far after Visit 5. ARIC also recorded at Visit 1 a 2-minute ECG rhythm strip to assess short-term daytime HRV, as described elsewhere¹³ and following published guidelines.¹⁴ At Visit 4, ARIC obtained a 6-minute rhythm strip and derived identical HRV indices¹⁵: 2 time-domain HRV measures directly from heart rate or the duration between successive RR intervals: (1) the standard deviation of all normal-to-normal RR intervals, which characterizes overall HRV; and (2) the root mean square of successive differences in normal-to-normal RR intervals, which is thought to reflect parasympathetic nervous system activity. The HRV analysts also calculated three frequency-domain measures from spectral imaging of the ECG recording: (1) low-frequency (LF), power (0.04-0.15 Hz), considered to include both sympathetic and parasympathetic activities; (2) high-frequency (HF) power (0.15-0.40 Hz), thought to reflect parasympathetic activity; and (3) low- and high-frequency (LF/HF) power ratio, which estimates the balance between sympathetic and parasympathetic activity. Previous publications have described the validity and reliability of short-duration HRV metrics.^{16,17} For this report, we used Visit 4 HRV data.

2.3 | Other measurements

We measured other potential VTE risk factors at Visit 1 and Visit 4, except where noted below, to allow us to adjust for them as possible confounding variables. Participants reported their race category, smoking status, and history of venous thrombosis or cancer. ARIC staff recorded current medication use via review of medication bottles, including atrioventricular (AV) nodal blocking medications (β -blockers,

calcium channel blockers, digoxin, or amiodarone). Staff also assessed sports physical activity using the Baecke questionnaire¹⁸ at Visits 1 and 3 only. ARIC technicians measured sitting blood pressure 3 times via a random-zero sphygmomanometer after a 5-minute rest. ARIC technicians measured weight and height to derive body mass index (BMI). We defined diabetes as a fasting serum glucose of ≥ 126 mg/dL, nonfasting serum glucose of ≥ 200 mg/dL, a physician diagnosis of diabetes, or use of antidiabetic medication in the past 2 weeks. ARIC estimated glomerular filtration rate (eGFR) from creatinine using the Chronic Kidney Disease Epidemiology Collaboration algorithm,¹⁹ and we defined chronic kidney disease (CKD) as eGFR < 60 mL/min/1.73 m². ARIC measured plasma factor VIII and von Willebrand factor at Visit 1 only, as previously described.²⁰ ARIC also isolated genomic DNA and measured 5 key variants important for VTE (*F5* Leiden rs6025, *F2* rs1799963, *ABO* rs8176719 [O vs. non-O groups], *FGG* rs2066865, and *F11* rs2036914) and created a weighted genetic risk score for VTE, as previously reported.²¹

2.4 | Identification of incident VTE

After the Visit 1 examination, ARIC staff telephoned participants annually or semiannually and asked about all hospitalizations in the previous year. Staff then obtained and recorded in-hospital International Classification of Diseases, 9th edition. Clinical Modification (ICD-9-CM) codes for all discharge diagnoses and copied selected hospital record material for VTE validation through 2015. To validate VTE events, 2 physicians reviewed the records using standardized criteria,¹² requiring positive imaging tests for diagnosis of clinically recognized DVT. "Definite DVT" required a positive venogram, compression ultrasound, or autopsy, but in the 1980s and 1990s, we sometimes accepted a positive Doppler examination or impedance plethysmography as a "probable DVT." In previous analyses, lumping the few probable DVTs with definite DVTs yielded similar associations, so they were pooled here. PE required computed tomography showing PE, a high probability of PE or at least 2 segmental perfusion defects without ventilation defects on ventilation-perfusion scanning, or a positive autopsy. The physicians subclassified VTEs as provoked (associated with cancer, major trauma, surgery, or marked immobility) or unprovoked (none of these causes). For this report, we restricted DVTs to those in the lower extremity or vena cava because upper extremity DVTs were relatively few and almost always the result of indwelling venous catheters.

2.5 | Statistical analysis

We used 2 follow-up time frames for analyses: (1) Visit 1 (1987-1989) heart rate through 2015 and (2) Visit 4 (1999-1996) heart rate through 2015 (more similar to the follow-up time for MESA⁶). For the Visit 1 start point, we excluded from the 15 792 ARIC participants 48 who were not black or white, 276 with prevalent VTE, 73 using

anticoagulants, 105 with missing resting heart rate data, and 376 with missing covariate information, leaving 14 914 for analysis. For the Visit 4 start point, we excluded from the 11 656 participants 31 who were not black or white, 339 with prevalent VTE, 192 using anticoagulants, 88 with missing resting heart rate data, and 706 with missing covariate information, leaving 10 300 for analysis. As a supplemental analysis, we also examined heart rate at all 4 visits as a time-dependent variable.

We categorized resting heart rate as ≤ 60 , 60 to 69, 70 to 79, or ≥ 80 bpm, as done in MESA,⁶ and compared participant characteristics (means or frequencies) across these categories to identify possible confounding variables. We plotted Kaplan-Meier and restricted cubic spline curves to illustrate the cumulative incidence of VTE by heart rate categories. Using Cox proportional hazards models, we estimated the hazard ratios of VTE by resting heart rate categories and per 10 bpm of continuous heart rate. We also separately analyzed DVT vs. PE and provoked versus unprovoked VTE; hazard ratios for VTE unrelated to cancer were almost identical to those for unprovoked and thus not shown separately. We tested the proportional hazard assumption for heart rate, using an interaction term between heart rate and time and the examination of Schoenfeld residuals and log(-log) survival curves and found the assumption to be valid. Cox Model 1 adjusted for age, race (black, white), and sex (after verifying no multiplicative interaction between heart rate and age, race, or sex at $P > 0.01$, because of multiple testing). Model 2 additionally adjusted for BMI, diabetes status (yes/no), current cigarette smoking status (yes/no), sports physical activity score, AV nodal blocking medication (yes/no), CKD status (yes/no), systolic blood pressure, antihypertensive medication use (yes/no), von Willebrand factor, and factor VIII. To examine for effect modification by VTE genetic risk, we tested the interaction between continuous heart rate and the weighted VTE genetic risk score. As a supplemental analysis, we also calculated hazard ratios after excluding participants with atrial fibrillation or AV nodal blocking medication.

Finally, Model 3 started with Model 2 and adjusted (separately) for the 5 natural log transformed HRV indices to determine (1) whether Visit 4 HRV might independently be associated with VTE and (2) whether Visit HRV potentially could explain any observed association of Visit 4 resting heart rate with VTE.

3 | RESULTS

3.1 | Descriptive information

Among the included 14 914 ARIC participants (54.8% female, 26.0% black) aged 45 to 64 and free of VTE at Visit 1 in 1987-1989, the mean resting heart rate was 66.7 bpm (SD = 10). Among participants attending at least 1 of the next 4 ARIC visits through 2011-2013, mean heart rate declined slightly—66, 66, 63, and 63 bpm, respectively. The age-, sex-, and race-adjusted Pearson correlation between Visit 1 heart rate and Visit 4 heart rate was $r = 0.53$, whereas the correlation for Visit 1 vs. Visit 5, spanning nearly 2.5 decades, was $r = 0.36$, suggesting only moderate resting heart rate tracking over time.

TABLE 1 Venous thromboembolism risk factor levels (mean or %) by Visit 1 (1987-1989) and Visit 4 (1996-1998) resting heart rate group, ARIC

	Visit 1 resting heart rate (bpm)				Visit 4 resting heart rate (bpm)			
	<60	60-69	70-79	≥80	<60	60-69	70-79	≥80
n	3694	5872	3713	1635	4124	3950	1613	613
Age, y	54	54	54	54	63	63	63	63
Sex, %								
Male	57	45	38	37	52	41	35	39
Female	43	55	62	63	48	59	65	61
Race, %								
White	72	76	76	69	83	81	76	70
Black	28	24	24	31	17	19	24	30
Body mass index, kg/m ²	27	27	28	29	28	29	30	30
Current smoker, %	26	25	27	27	13	15	17	22
Diabetes, %	8	9	13	25	10	15	25	38
Chronic kidney disease, %	1.3	1.0	1.1	2.7	6.1	4.9	6.8	9.0
Sport index ^a	2.6	2.5	2.4	2.2	2.7	2.5	2.4	2.3
Systolic blood pressure, mm Hg	119	120	122	127	126	127	129	132
Antihypertensive medication, %	33	27	29	36	43	38	45	52
Atrioventricular nodal blocking medication, %	20	12	11	11	29	20	21	23
Factor VIII, % ^b	125	129	134	146	124	127	133	134
von Willebrand factor, % ^b	114	115	119	133	111	113	118	121
Weighted genetic risk score (F5, F2, ABO, F11, FGG variants) ^c	1.43	1.45	1.43	1.43	1.44	1.43	1.48	1.36

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; bpm, beats per minute.

^aFrom Visit 3 when presented under Visit 4 resting heart rate group.

^bFrom Visit 1.

^cSample size modestly smaller due to additional missing data.

The mean age of participants was 54 at Visit 1 and 63 years at Visit 4. As shown in Table 1, Visit 1 resting heart rate was higher in women than in men and associated positively with BMI, systolic blood pressure, and prevalences of diabetes and CKD; heart rate was inversely associated with sports physical activity and AV nodal blocking medication. Visit 1 heart rate was associated positively with plasma factor VIII and von Willebrand factor concentrations, but heart rate was not associated with the genetic risk score for VTE. Most of these associations were similar at Visit 4, but by Visit 4, blacks and current smokers had higher heart rates than did whites and nonsmokers, and those in the highest heart rate category had a lower genetic risk score for VTE than did other categories. More notably, AV nodal blocking medications and risk factors were more common at Visit 4 than at Visit 1.

3.2 | Association of Visit 1 resting heart rate with incident VTE

Over a median of 26 years of follow-up (maximum 29 years), from Visit 1 through 2015, we identified 882 incident VTE events (446 PE, 436

DVT only). Visit 1 heart rate was not associated with VTE incidence (Table 2). After adjusting for confounding variables (Table 2, Model 2), for each 10 bpm greater heart rate at Visit 1 the hazard ratio (95% CI) of VTE was 0.96 (0.90-1.03). There also was no association of Visit 1 heart rate with PE or with DVT only, or with provoked or unprovoked VTE.

3.3 | Association of Visit 4 resting heart rate with incident VTE

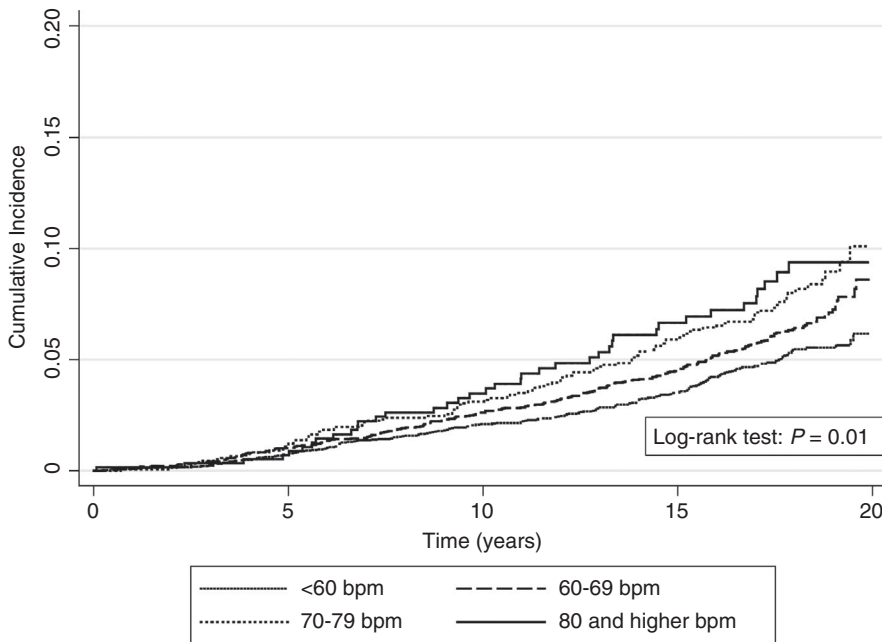
In contrast with the Visit 1 heart rate, the Visit 4 (1996-1998) heart rate was positively and statistically significant associated with incident VTE (Figures 1 and 2). These findings were based on 557 incident VTE events (315 PE, 242 DVT only) over a median of 18 years of follow-up (maximum 20 years). As shown in Table 3, the Model 2 adjusted hazard ratios of VTE across heart rate categories of <60, 60 to 69, 70 to 79, and ≥80 bpm were 1 (reference), 1.22 (1.01-1.49), 1.39 (1.09-1.78), and 1.44 (1.01-2.06), respectively. The Model 2 VTE hazard ratio was 1.11 (1.02-1.21) per 10 bpm greater heart rate. The Model 2 hazard ratio per 10 bpm heart rate increment was similar when we instead

TABLE 2 Hazard ratios (95% CIs) of VTE by groups or 10 bpm increments of Visit 1 resting heart rate, ARIC, 1987-1989 through 2015

	Resting heart rate (bpm)				
	<60	60-69	70-79	≥80	Per 10 greater
n	3694	5872	3713	1635	14 914
Incident VTE, n	236	352	203	91	882
Person-years at risk	82 267	132 396	81 127	32 131	327 922
Crude VTE incidence rate (per 1000 person-years)	2.9	2.7	2.5	2.8	2.7
Model 1 HR (95% CI)	1 (Reference)	0.97 (0.82-1.14)	0.95 (0.78-1.14)	1.08 (0.85-1.38)	1.03 (0.97-1.11)
Model 2 HR (95% CI)	1 (Reference)	0.92 (0.77-1.08)	0.84 (0.69-1.01)	0.85 (0.66-1.10)	0.96 (0.90-1.03)

Note: Model 1 Adjusted for Visit 1 age, race, and sex. Model 2: Adjusted for Visit 1 age, race, sex, body mass index, current cigarette smoking status, diabetes, sports index, systolic blood pressure, antihypertensive medications, atrioventricular nodal blocking medication, chronic kidney disease, von Willebrand factor, and factor VIII.

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; bpm, beats per minute; CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism.

**FIGURE 1** Kaplan-Meier curves of venous thromboembolism (VTE) by Visit 4 resting heart rate group, ARIC, 1996-1998 through 2015. bpm, beats per minute

included the 4 heart rate measures from ARIC Visits 1 through 4 as a time-dependent variable (1.12 [1.05-1.19]) (Table S1); when we instead excluded participants with atrial fibrillation ($n = 168$) or AV nodal blocking medication ($n = 2332$) at Visit 4 (1.15 [1.05-1.27]) (Table S2); or when we instead censored follow-up time when incident myocardial infarction, heart failure, or atrial fibrillation happened before VTE (1.11 [1.00-1.24]) (Table S3).

Table 3 also shows that the Model 2 hazard ratio per 10 bpm greater Visit 4 heart rate was somewhat but not statistically significantly, and stronger for PE (1.13 [1.01-1.27]) than DVT (1.08 [0.96-1.23]) and for provoked (1.15 [1.04-1.28]) than unprovoked VTE (1.05 [0.91-1.21]). The Model 2 hazard ratio for PE was 1.82 (1.16-2.84) for heart rate category ≥ 80 bpm compared with the <60 bpm category.

None of these associations were appreciably modified by age, sex, or race, nor was there an interaction between continuous

heart rate and the VTE genetic risk score ($P > 0.01$ for all interaction tests).

3.4 | Association of Visit 4 HRV with incident VTE

As previously reported²², the 5 HRV indices we examined were moderately to highly correlated among themselves. All HRV indices except LF/HF were correlated negatively with heart rate (Pearson's r ranged from -0.10 to -0.53). As shown in Table 4, most HRV indices were not significantly independently associated with VTE through 2015. Furthermore, for the most part, the positive and significant association of Visit 4 heart rate with VTE persisted after adjustment for Visit 4 HRV indices (Table 5), suggesting that lower HRV did not mediate the association between higher heart rate and increased incidence of VTE.

FIGURE 2 Restricted cubic spline plot of venous thromboembolism (VTE) by Visit 4 resting heart rate, ARIC, 1996-1998 through 2015. Cox proportional hazards model using restricted cubic splines with knots at the 5th (48 BPM), 27.5th (56 BPM), 50th (62 BPM), 72.5th (68 bpm) and 95th (81 bpm) percentiles. Hazard ratio (solid line) and 95% confidence intervals (shaded area) are adjusted for age, race, and sex. The reference is the median value of the baseline resting heart rate (hazard ratio = 1), and the histogram represents the frequency distribution of the baseline resting heart rate in the study sample. bpm, beats per minute

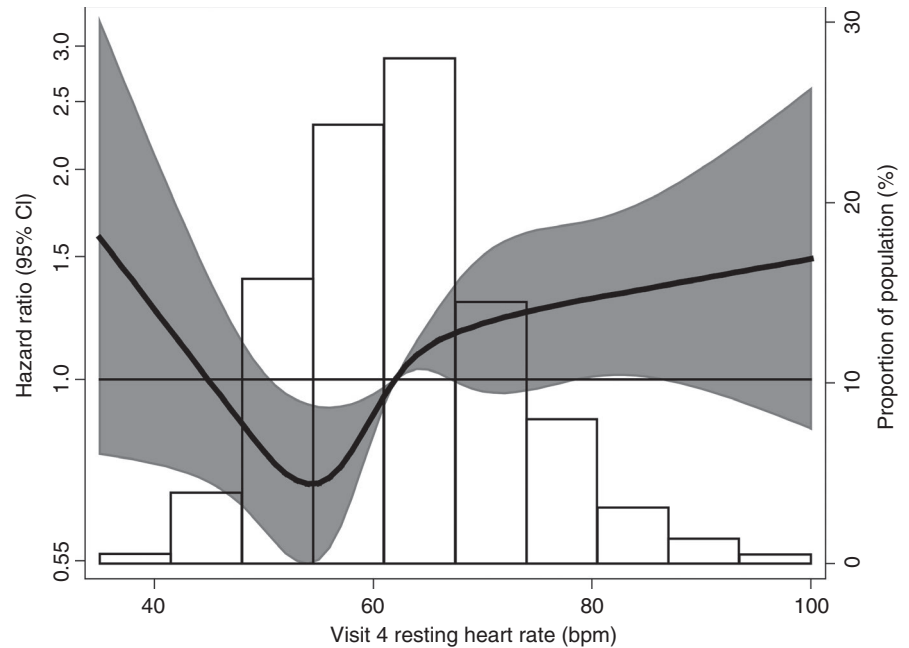


TABLE 3 Hazard ratios (95% CIs) of venous thromboembolism (VTE) by groups or 10 bpm increments of Visit 4 resting heart rate, ARIC, 1996-98 through 2015

	Resting heart rate (bpm)				
	<60	60-69	70-79	≥80	Per 10 greater
n	4124	3950	1613	613	10 300
Incident VTE, n	188	224	106	39	557
Person-years at risk	65 573	61 935	23 949	8304	159 761
Crude VTE incidence rate (per 1000 person-years)	2.9	3.6	4.4	4.7	3.5
Model 1 HR (95% CI)	1 (reference)	1.30 (1.07-1.58)	1.59 (1.25-2.02)	1.68 (1.18-2.37)	1.18 (1.09-1.28)
Model 2 HR (95% CI)	1 (reference)	1.22 (1.01-1.49)	1.39 (1.09-1.78)	1.44 (1.01-2.06)	1.11 (1.02-1.21)
Incident pulmonary embolism, n	102	134	53	26	315
Model 1 HR (95% CI)	1 (reference)	1.41 (1.09-1.82)	1.45 (1.03-2.02)	2.08 (1.35-3.21)	1.20 (1.08-1.33)
Model 2 HR (95% CI)	1 (reference)	1.31 (1.01-1.70)	1.26 (0.90-1.78)	1.82 (1.16-2.84)	1.13 (1.01-1.27)
Incident deep vein thrombosis only, n	86	90	53	13	242
Model 1 HR (95% CI)	1 (reference)	1.16 (0.86-1.56)	1.76 (1.24-2.49)	1.21 (0.67-2.17)	1.15 (1.02-1.30)
Model 2 HR (95% CI)	1 (reference)	1.12 (0.83-1.51)	1.53 (1.08-2.19)	1.01 (0.55-1.84)	1.08 (0.96-1.23)
Incident provoked VTE, n	108	140	71	24	343
Model 1 HR (95% CI)	1 (reference)	1.40 (1.09-1.81)	1.84 (1.36-2.48)	1.77 (1.13-2.76)	1.22 (1.10-1.35)
Model 2 HR (95% CI)	1 (reference)	1.34 (1.04-1.72)	1.62 (1.19-2.21)	1.51 (0.96-2.39)	1.15 (1.04-1.28)
Incident unprovoked VTE, n	80	84	35	15	214
Model 1 HR (95% CI)	1 (reference)	1.15 (0.85-1.57)	1.25 (0.84-1.87)	1.55 (0.89-2.71)	1.12 (0.98-1.28)
Model 2 HR	1 (reference)	1.07 (0.78-1.46)	1.08 (0.72-1.62)	1.35 (0.76-2.39)	1.05 (0.91-1.21)

Note: Model 1: Adjusted for Visit 4 age, race, and sex. Model 2: Adjusted for Visit 4 age, race, sex, body mass index, current cigarette smoking status, diabetes, systolic blood pressure, antihypertensive medications, atrioventricular nodal blocking medication, chronic kidney disease, sports index (Visit 3), von Willebrand factor (Visit 1), and factor VIII (Visit 1).

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; bpm, beats per minute; CI, confidence interval; HR, hazard ratio; VTE, venous thromboembolism.

TABLE 4 Hazard ratios (95% CIs) of VTE by quartiles or per 1 standard deviation (SD) decrease of Visit 4 heart rate variability indices, ARIC, 1996-1998 through 2015

	Heart rate variability indices				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Per 1 SD decrease
Root mean square of successive differences of successive RR intervals, ms ^a					
Range	1.5-14.9	15.0-22.0	22.1-32.7	32.8-546.3	
n at risk	2334	2303	2317	2306	9260
Incident VTE, n	140	111	135	106	492
Model 1 HR (95% CI)	1.41 (1.09-1.82)	1.08 (0.83-1.41)	1.31 (1.02-1.70)	1 (Reference)	1.09 (1.00-1.19)
Model 2 HR (95% CI)	1.41 (1.09-1.83)	1.11 (0.85-1.45)	1.32 (1.02-1.70)	1 (Reference)	1.09 (1.00-1.19)
Standard deviation of all normal RR intervals, ms ^a					
Range	1.4-23.9	24.0-32.6	32.7-44.2	44.3-322.5	
n at risk	2320	2331	2304	2305	9260
Incident VTE, n	136	133	116	107	492
Model 1 HR (95% CI)	1.28 (0.99-1.65)	1.23 (0.96-1.59)	1.10 (0.85-1.44)	1 (Reference)	1.10 (1.00-1.20)
Model 2 HR (95% CI)	1.20 (0.93-1.55)	1.21 (0.94-1.57)	1.13 (0.87-1.47)	1 (Reference)	1.07 (0.98-1.17)
Low-frequency (LF) power, ms ^{2a}					
Range	0.1-68.1	68.2-146.9	147.0-311.9	312.0-18,600.0	
n at risk	2318	2321	2307	2314	9260
Incident VTE, n	141	145	108	98	492
Model 1 HR (95% CI)	1.40 (1.08-1.82)	1.44 (1.11-1.86)	1.09 (0.83-1.44)	1 (Reference)	1.09 (1.00-1.20)
Model 2 HR (95% CI)	1.29 (0.99-1.68)	1.44 (1.11-1.87)	1.13 (0.86-1.49)	1 (Reference)	1.06 (0.97-1.16)
High-frequency (HF) power, ms ^{2a}					
Range	0.1-38.2	38.3-82.1	82.2-177.9	178.9-29,700.0	
n at risk	2318	2312	2328	2302	9260
Incident VTE, n	123	120	133	116	492
Model 1 HR (95% CI)	1.12 (0.86-1.45)	1.04 (0.80-1.34)	1.16 (0.90-1.49)	1 (Reference)	1.03 (0.94-1.12)
Model 2 HR (95% CI)	1.14 (0.88-1.48)	1.08 (0.83-1.40)	1.20 (0.93-1.53)	1 (Reference)	1.04 (0.95-1.13)
LF/HF power ratio ^a					
Range	0.03-0.95	≥0.95-1.81	≥1.81-3.30	≥3.30-45.74	
n at risk	2315	2315	2315	2315	9260
Incident VTE, n	133	139	116	104	492
Model 1 HR (95% CI)	1.17 (0.89-1.53)	1.28 (0.99-1.66)	1.09 (0.83-1.42)	1 (Reference)	1.09 (1.00-1.20)
Model 2 HR (95% CI)	1.02 (0.77-1.34)	1.19 (0.92-1.55)	1.05 (0.81-1.38)	1 (Reference)	1.04 (0.94-1.14)

Note: Model 1: Adjusted for age, race, and sex. Model 2: Adjusted for age, race, sex, body mass index, current cigarette smoking status, diabetes, sports index, systolic blood pressure, antihypertensive medications, atrioventricular nodal blocking medication, chronic kidney disease, von Willebrand factor, and factor VIII.

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; CI, confidence interval; HR, hazard ratio; VTE: venous thromboembolism.

^aVariable is log-transformed for calculating HR per 1 SD decrease.

4 | DISCUSSION

This population-based cohort study found no independent association of ARIC Visit 1 resting heart rate or variability in heart rate with incident VTE, but it did find a positive and moderately strong graded association of Visit 4 resting heart rate with incident VTE (adjusted hazard ratio of 1.44 for the highest vs. lowest category of heart rate).

Our contrasting findings by ARIC visit may be due to differences in both cohort age (45-64 years at Visit 1 vs. 54-73 years at Visit 4) and

median follow-up time for VTE (26 vs. 18 years). Heart rate declines on average with age. Between-person differences in resting heart rate may be more random in middle age, but more influenced in older age by the presence or absence of medical conditions contributing to VTE (partly illustrated in Table 1). The fact that heart rate at Visit 1 was only moderately correlated with heart rates at Visits 4 and 5 further suggests that resting heart rate does not track particularly well. Any single heart rate measurement might also not reflect heart rate throughout the day or week. A study of 75 chronic heart failure patients showed that resting heart rate correlated 0.76 with mean 1-day heart rate and 0.73 with

TABLE 5 Hazard ratios (95% CIs) of VTE by groups or 10 bpm increments of Visit 4 resting heart rate, adjusting for Visit 4 HRV indices, ARIC, 1996-1998 through 2015

	Resting heart rate (bpm)				Per 10 greater
	<60	60-69	70-79	≥80	
n	3704	3613	1435	508	9260
Incident VTE, n	163	206	90	33	492
HR (95% CI)	1 (Reference)	1.28 (1.04-1.57)	1.36 (1.04-1.77)	1.50 (1.02-2.21)	1.14 (1.04-1.25)
HR (95% CI) + Log root mean square of successive differences of successive RR intervals	1 (Reference)	1.25 (1.01-1.55)	1.31 (0.98-1.75)	1.42 (0.93-2.17)	1.12 (1.00-1.25)
HR (95% CI) + Log standard deviation of all normal RR intervals	1 (Reference)	1.27 (1.02-1.57)	1.34 (1.01-1.78)	1.47 (0.97-2.23)	1.13 (1.02-1.26)
HR (95% CI) + Log LF power	1 (Reference)	1.26 (1.02-1.56)	1.34 (1.02-1.75)	1.46 (0.98-2.17)	1.13 (1.02-1.24)
HR (95% CI) + Log HF power	1 (Reference)	1.28 (1.03-1.58)	1.36 (1.04-1.79)	1.51 (1.01-2.24)	1.14 (1.03-1.25)
HR (95% CI) + Log LF/HF power ratio	1 (Reference)	1.28 (1.04-1.58)	1.37 (1.05-1.78)	1.50 (1.02-2.21)	1.14 (1.04-1.25)

Note: Based on Model 2: Adjusted for age, race, sex, body mass index, current cigarette smoking status, diabetes, sports index, systolic blood pressure, antihypertensive medications, atrioventricular nodal blocking medication, chronic kidney disease, von Willebrand factor, factor VIII, plus 1 HRV index at a time.

Abbreviations: ARIC, Atherosclerosis Risk in Communities; bpm, beats per minute; CI, confidence interval; HF, high frequency; HR, hazard ratio; HRV, heart rate variability; LF, low frequency; VTE, venous thromboembolism.

mean 7-day heart rate.²³ Another consideration is that the majority of incident VTEs happened in the last decade of ARIC follow-up. Thus, our early follow-up of middle-aged participants after Visit 1 may be irrelevant to the vast majority of VTEs happening 2 decades later in the elderly. In addition, hospital diagnostic methods for the earlier VTEs captured by ARIC were sometimes less accurate than later ones—that is, Doppler ultrasound rather than duplex imaging for DVT, and ventilation-perfusion scans rather than computed tomography for PE.

A positive association of heart rate in Visit 4 with VTE is consistent in direction but weaker in magnitude with seemingly the only prior report on this topic, that from MESA.⁶ MESA reported a 2-fold higher incidence rate of VTE in the highest vs. lowest category of heart rate,⁶ which contrasts with the 1.44-fold gradient for ARIC. The mean age of the MESA cohort at baseline (62 years) was similar to the mean age of the ARIC cohort at Visit 4 (63 years). Yet ARIC methods for VTE ascertainment differed from MESA in an important way—ARIC physicians reviewed hospital records to identify VTE, whereas MESA used unvalidated hospital discharge ICD codes. An early ARIC publication reported a considerable disagreement rate between ICD codes and physician classification of VTE.¹² Other cohort studies of VTE likely have heart rate information and could help clarify whether there is any association between resting heart rate and VTE and whether it is age dependent.

As outlined in the Introduction, an association between high heart rate and increased VTE risk might reflect a causal relation—operating via high heart rate causing generalized inflammation, leading to VTE through hypercoagulability or venous injury. Against a causal role, a Mendelian randomization study showed that a polygenetic risk score for heart rate was not associated with VTE risk in the general population.²⁴ We speculate that the positive association of heart rate with VTE is less likely to be a direct cause-and-effect than an indirect relation. For example, high heart rate may merely reflect underlying medical

conditions, low physical fitness, the metabolic syndrome, or other risk factors (Table 1), which could predispose to or trigger VTE. However, the post-Visit 4 association did persist after adjusting for a number of risk factors for VTE in this cohort, such as age, race, obesity, diabetes, and physical inactivity. Atherosclerotic cardiovascular diseases should not have confounded the heart rate–VTE association, as they have not been associated with increased risk of VTE in ARIC.

We also tested the hypothesis that HRV might be associated inversely with VTE incidence, first because HRV indices, like heart rate, reflect sympathetic to parasympathetic balance of the cardiac pacemaker tissues, and second because resting heart rate is moderately and inversely correlated HRV. HRV proved mostly unassociated with incident VTE. When we adjusted for HRV indices, the association between heart rate and VTE persisted, suggesting HRV was not a mediator of the association.

A study limitation not already mentioned is that ARIC identified hospitalized VTE patients only, as did MESA. Thus, our VTE case definition should be highly specific but somewhat insensitive. The omission of outpatient VTEs could have led to biased hazard ratios, but the bias would be most severe if proportion of missed VTEs differed by heart rate; this seems unlikely.

In conclusion, we found a significant positive and independent association of resting heart rate at ARIC Visit 4 with incidence of VTE. We found no strong association of HRV with VTE. The reason why high heart rate is a risk marker for VTE warrants further exploration.

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RELATIONSHIP DISCLOSURE

The authors declare nothing to report.

AUTHOR CONTRIBUTIONS

ARF: obtained funding, collected data, and drafted manuscript. PLL: made critical comments on manuscript. ZCP: made critical comments on manuscript. OEF: made critical comments on manuscript. JRM: analyzed data, made critical comments on manuscript. MC: helped design the study, collected data, and made critical comments on manuscript. EDM: conceived the hypothesis and made critical comments on manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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