


ORIGINAL RESEARCH

# Long-Term Association of Venous Thromboembolism With Frailty, Physical Functioning, and Quality of Life: The Atherosclerosis Risk in Communities Study

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**BACKGROUND:** Relatively little is known about the long-term consequences of venous thromboembolism (VTE) on physical functioning. We compared long-term frailty status, physical function, and quality of life among survivors of VTE with survivors of coronary heart disease (CHD) and stroke, and with those without these diseases.

**METHODS AND RESULTS:** Cases of VTE, CHD, and stroke were continuously identified since ARIC (Atherosclerosis Risk in Communities Study) recruitment during 1987 to 1989. Functional measures were objectively captured at ARIC clinic visits 5 (2011–2013) and 6 (2016–2017); quality of life was self-reported. The 6161 participants at visit 5 were, on average, 75.7 (range, 66–90) years of age. By visit 5, 3.2% had had a VTE, 6.9% CHD, and 3.4% stroke. Compared with those without any of these conditions, VTE survivors were more likely to be frail (odds ratio [OR], 3.11; 95% CI, 1.80–5.36) and have low (<10) versus good scores on the Short Physical Performance Battery (OR, 3.59; 95% CI, 2.36–5.47). They also had slower gait speed, less endurance, and lower physical quality of life. VTE survivors were similar to coronary heart disease and stroke survivors on categorical frailty and outcomes on Short Physical Performance Battery assessment. When score on the Short Physical Performance Battery instrument was modeled continuously, VTE survivors performed better than stroke survivors but worse than CHD survivors.

**CONCLUSIONS:** VTE survivors had triple the odds of frailty and poorer physical function than those without the vascular diseases considered. Their function was somewhat worse than that of CHD survivors, but better than stroke survivors. These findings suggest that VTE patients may benefit from additional efforts to improve postevent physical functioning.

**Key Words:** frailty ■ physical function ■ quality of life ■ venous thromboembolism

Venous thromboembolism (VTE), consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE), confers a lifetime risk of 1 in 12<sup>1</sup> after 45 years of age and affects ≈1 million Americans annually.<sup>2</sup> The 30-day case fatality for VTE is ≈10%, and the 1-year mortality is about 25%.<sup>3</sup> VTE survivors face a number of challenges, as patients must manage anticoagulation regimens,<sup>4,5</sup> and many have complications.

Among DVT patients, 20% to 50% develop post-thrombotic syndrome, characterized by leg pain, swelling, edema, and skin discoloration/dryness, and ≈4% have venous stasis ulcers.<sup>6–8</sup> After PE, patients may also have difficulty breathing or decreased cardiopulmonary reserve,<sup>9–13</sup> and ≈4% of PE patients are afflicted by chronic thromboembolic pulmonary hypertension.<sup>14,15</sup> Furthermore, VTE recurrence is common.<sup>16–18</sup> Bleeding is also a major potential complication due to

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Supplementary Materials for this article are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.015656>

For Sources of Funding and Disclosures, see page 9.

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## CLINICAL PERSPECTIVE

### What Is New?

- Venous thromboembolism (VTE) is often viewed as an acute condition; this study demonstrated that VTE survivors were more likely to be frail and have poor physical function long after their initial VTE event.
- Physical function in VTE survivors was somewhat worse when compared with coronary heart disease survivors, but better than that observed in stroke survivors.

### What Are the Clinical Implications?

- Patients with VTE may represent a group with a high risk of functional decline who warrant screening, and potentially interventions, to preserve physical function.

## Nonstandard Abbreviations and Acronyms

<b>ARIC</b>	Atherosclerosis Risk in Communities Study
<b>CHD</b>	coronary heart disease
<b>DVT</b>	deep vein thrombosis
<b>PE</b>	pulmonary embolism
<b>SF-36</b>	Medical Outcomes Short Form-36
<b>SPPB</b>	Short Physical Performance Battery
<b>QOL</b>	quality of life
<b>VTE</b>	venous thromboembolism

the use of anticoagulant therapy to treat the initial VTE event and prevent recurrence.<sup>19,20</sup>

Research on the physical functioning of long-term VTE survivors is limited and has focused on self-reported rather than objective measures. In the Nurses' Health Study, women who survived VTE had a decline in physical function, as assessed by the physical function domain of the Medical Outcomes Study 36-item Short Form Health Survey (SF-36), equivalent to a physical decline of 5.4 years of aging. Likewise, Women's Health Initiative participants with prevalent VTE who survived to 80 years of age had lower physical functioning, as assessed by SF-36 score, than did their counterparts without VTE.<sup>21</sup> Small clinical studies, with variable comparison groups, have also reported low quality of life (QOL) for VTE patients.<sup>10,22–24</sup> Norwegian VTE patients were also more likely than the general working-age population to be granted permanent work-related disability.<sup>25</sup> In addition, VTE patients with postthrombotic syndrome have less mobility and diminished health-related QOL compared with VTE

patients without postthrombotic syndrome.<sup>26,27</sup> The relatively few studies that did assess objective measures of physical function among VTE survivors were small, not population-based, and/or without appropriate control groups for comparison.

Using data collected at the ARIC (Atherosclerosis Risk in Communities) study's fifth (2011–2013) clinic examination, we assessed frailty, physical function (using the Short Physical Performance Battery [SPPB] instrument and gait speed), and QOL among VTE survivors. At the sixth (2016–2017) clinic exam, we assessed functional endurance using the 2-minute walk test. We compared survivors of VTE with: (1) survivors of coronary heart disease (CHD); (2) survivors of stroke; and (3) those without VTE, CHD, or stroke. CHD and stroke were selected as comparators because, similar to VTE, both are acute, severe vascular events and are associated with postevent functional deficits. The ARIC Study has previously demonstrated that self-reported functional status post-CHD declined relative to pre-event levels, but improved to close to pre-CHD levels within 3 years, whereas declines in poststroke functional status remained over time.<sup>28</sup> We hypothesized that VTE survivors would be more frail and have lower physical function and QOL than those who were CHD survivors or remained free of these vascular conditions, but that functional measures would be better for VTE survivors than for stroke survivors.

## METHODS

Data from the ARIC study can be accessed, with appropriate approval, through the National Heart, Lung, and Blood Institute's BioLINCC repository (<https://biolincc.nhlbi.nih.gov/home/>) or by contacting the ARIC Coordinating Center (<http://www2.csc.unc.edu/aric/distribution-agreements>).

During the period from 1987 to 1989, the ARIC study recruited a total of 15 792 men and women from 4 US communities (ie, suburbs of Minneapolis, Minnesota; Jackson, Mississippi; Forsyth County, North Carolina; and Washington County, Maryland) into a population-based prospective cohort.<sup>29</sup> Participants were 45 to 64 years of age at the time of the initial clinic visit and included both blacks and whites. We followed these individuals continuously for hospitalizations and deaths, and also conducted numerous follow-up clinical visits. Local institutional review boards approved the protocol, and all participants gave written informed consent.

Relevant to this analysis, 6538 participants attended the fifth clinic visit, which took place between 2011 and 2013. Table S1 shows participants' characteristics, stratified by disease state, according to

visit 5 attendance and vital status. We excluded participants who self-reported their race as other than black or white (n=18); blacks from Maryland and Minnesota (n=25); those self-reporting prevalent VTE at visit 1 but who had no incident VTE event during follow-up (n=92); those who had an incident non-leg DVT only (n=11); those self-reporting prevalent CHD at visit 1 but no incident CHD event (n=71); those self-reporting prevalent stroke at visit 1 but no incident stroke event (n=34); and those who were missing information on key covariates (n=126). The final visit 5 analytic sample included 6161 participants.

The sixth ARIC Study clinic visit (2016–2017) was attended by 4003 participants. After applying the same exclusions as described for visit 5 to the visit 6 sample, the final visit 6 analytic sample included 3756 participants.

### Ascertainment of Previous VTE, CHD, and Stroke

We followed participants for hospitalizations and deaths through telephone calls (annually before 2012; twice yearly since that time) to participants or proxies and active surveillance of local hospital discharge indices. Trained abstractors collected information from all hospitalizations, including *International Classification of Diseases—Ninth Revision, Clinical Modification (ICD-9)* codes for discharge diagnoses and procedures associated with each hospitalization. We identified potential VTE, CHD, and stroke events from hospital records with ICD codes indicating possible events. For all 3 event types, records of potential cases were then abstracted, and independently reviewed by physicians. DVT was defined on the basis of duplex ultrasound or venogram or, in rare cases, by impedance plethysmography, computed tomography, or autopsy.<sup>30</sup> Definite PE required presence in the medical record of evidence of ventilation/perfusion scanning showing multiple segmental or subsegmental mismatched perfusion defects, or a positive pulmonary angiogram or computed tomography.<sup>30</sup> For the present analyses, DVTs occurring outside the legs (in the absence of PE) were not classified as VTE cases. Events were further classified as unprovoked or provoked (occurring within 90 days of major trauma, surgery, hospitalization, or marked immobility, or associated with active cancer or chemotherapy).

Incident CHD was defined by definite or probable CHD, coronary angioplasty, or coronary artery bypass surgery, according to previously described procedures.<sup>31</sup> Definite/probable hospitalized strokes were classified by a combination of computer algorithm and physician review, using standardized criteria.<sup>32</sup>

### Indicators of QOL and Physical Functioning

At ARIC Study visit 5, trained and certified staff conducted standardized measurements of the following:

1. **QOL:** The QOL was assessed using a modified version of the 12-item Short Form Health Survey version 2. We analyzed the physical and mental components separately, with the scale modeled continuously.
2. **Frailty:** Frailty was operationalized using Cardiovascular Health Study criteria, as implemented previously in the ARIC study.<sup>33</sup> Briefly, this definition incorporates measures of weight loss, exhaustion, slow walking speed (based on gait speed >4 meters), low physical activity, and low grip strength. For analyses, the scale was modeled both continuously and categorically (as frail, pre-frail, or not frail).
3. **SPPB<sup>34,35</sup>:** The SPPB instrument is composed of 3 standardized tests, namely balance (standing, semitandem, or tandem stands held for up to 10 s each), usual gait speed, and time to rise from a seated position 5 times without using the arms. Each task was scored from 0 (worse) to 4 (best) based on population norms and summed to create a composite score ranging from 0 to 12; participants who were unable to perform a task received a score of 0. For analyses, the SPPB score was modeled, both continuously and categorically, as low (0–6), fair (7–9), and good (10–12, reference).
4. **Gait speed (mobility):** Participants were timed walking 4 meters at their usual speed, and the faster of the 2 trials was recorded for analysis. Participants were encouraged not to use walking aids, but aids were allowed per participants' discretion. Although gait speed is a component of the SPPB and frailty, it was included as a separate continuous outcome because it may be substantially impacted by VTE.

Endurance assessment at ARIC visit 6 was as follows:

1. **Two-minute walk:** The 2-minute walk protocol, validated and described in the National Institutes of Health toolkit, was offered to all participants who completed the 4-meter walk test without a walking aid. The 2-minute walk is a measure of functional endurance and may also be a more sensitive measure than gait speed or SPPB, such as among high-functioning adults.

### Covariates

Covariate information was collected by trained and certified staff using standardized protocols at visit 5 (or visit 6 for the endurance analyses), with the exception of established demographic information collected

**Table 1. Visit 5 Characteristics by Prevalent Disease Status (VTE, CHD, Stroke, or No Events) in the ARIC Study, 2011–2013**

	Prevalent VTE*	Prevalent CHD*	Prevalent Stroke*	No Prevalent Events
n	195	425	208	5409
Age, y	76.6 (5.2)	77.2 (5.4)	77.2 (5.7)	75.5 (5.2)
Sex, %				
Female	59.5	39.1	49.0	60.5
Male	40.5	60.9	51.0	39.5
Race, %				
White	68.7	77.6	66.3	77.5
Black	31.3	22.4	33.7	22.5
Body mass index, kg/m <sup>2</sup>	29.7 (7.5)	27.7 (6.3)	27.8 (6.3)	28.3 (6.2)
Smoking status, %				
Current	2.0	8.2	5.8	5.5
Former	43.6	51.8	50.0	45.3
Never	39.5	24.2	25.5	38.3
Unknown	14.9	15.8	18.8	10.9
Diabetes mellitus, %	42.6	42.8	45.2	30.5
Hypertension medication, %	84.6	95.8	88.5	73.0
Prevalent COPD, %	15.4	13.9	8.7	9.1
Prevalent heart failure, %	22.6	49.7	30.3	9.5
Prevalent peripheral artery disease, %	13.3	18.4	17.8	7.5
Systolic blood pressure, mm Hg	129.5 (17.6)	129.9 (19.7)	135.3 (21.6)	130.5 (18.2)
Quality of life <sup>†</sup>				
Mental score	55.0 (8.6)	55.4 (8.2)	55.4 (9.0)	55.3 (7.6)
Physical score	40.9 (11.7)	42.6 (11.4)	40.7 (10.8)	46.7 (10.0)
Frailty, % <sup>‡</sup>				
Frail	12.8	9.4	12.0	5.3
Pre-frail	49.7	46.8	46.6	42.6
Not frail	23.1	29.9	22.6	43.6
SPPB score <sup>†</sup>				
Low (0–6)	7.5 (3.3)	8.6 (2.9)	7.3 (3.4)	9.4 (2.4)
Fair (7–9)	31.8	19.3	33.7	11.3
Good (10–12)	25.6	28.0	25.0	27.6
Good (10–12)	31.3	40.2	26.4	54.0
Gait speed—4-m walk, m/s <sup>†</sup>	0.84 (0.2)	0.88 (0.2)	0.80 (0.2)	0.95 (0.2)
Gait speed—4-m walk (SPPB score 0–4) <sup>†</sup>				
0	3.1 (1.0)	3.4 (0.9)	3.0 (1.1)	3.6 (0.7)
1	3.1	1.2	2.9	0.1
2	3.1	2.8	8.2	1.7
3	15.4	9.7	13.9	6.2
4	25.1	21.4	23.1	19.2
4	41.5	52.2	37.0	65.0

Data are presented as percent for categorical variables and as mean (standard deviation) for continuous variables. ARIC indicates Atherosclerosis Risk in Communities; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; SPPB, Short Physical Performance Battery; and VTE, venous thromboembolism.

\*Prevalent VTE, CHD, and stroke events are not mutually exclusive.

<sup>†</sup>Higher scores indicate better quality of life.

<sup>‡</sup>Sample size modestly smaller due to additional missing data.

at visit 1. Smoking status was assessed by questionnaire. Height and weight were measured using standard methods, and body mass index was calculated as weight per height squared (kg/m<sup>2</sup>). Medications taken in the previous 4 weeks were brought to the clinic visit, and coded. Systolic and diastolic blood pressure levels

were measured in triplicate after a 5-minute rest; the mean of the 2 most recent measurements was used for analysis. Diabetes mellitus was defined by fasting glucose  $\geq 126$  mg/dL, nonfasting glucose  $\geq 200$  mg/dL, a self-report of physician diagnosis, or current medication use for diabetes mellitus. Chronic obstructive



pulmonary disease was determined through a self-reported physician diagnosis of chronic bronchitis or emphysema. Prevalent heart failure was adjudicated according to standard ARIC procedures.<sup>36</sup> Peripheral artery disease was ascertained from an ankle/brachial index <0.9 at ARIC visits 3 or 4, or by identification of hospital discharge diagnoses for peripheral artery disease during follow up.

## Statistical Analysis

Visit 5 data were used cross-sectionally for the primary analysis. Descriptive characteristics are provided according to 4 categories: VTE survivors; CHD survivors; stroke survivors; and none of these (ie, no previous VTE, CHD, or stroke). The VTE, CHD, and stroke categories are not mutually exclusive in Table 1. However, for analyses comparing VTE survivors with CHD or stroke survivors (all subsequent tables), individuals with both conditions were excluded.

SAS version 9.4 (SAS Institute, Cary, NC) was used for all data analyses. For the primary analysis involving visit 5, comparisons were made between VTE survivors and: (1) survivors of CHD; (2) survivors of stroke; and (3) individuals with no previous VTE, CHD, or stroke. The outcomes include both categorical and continuous variables. Linear regression was used for the continuous outcomes. For multilevel categorical outcomes (ie, frailty or SPPB score), we conducted analyses using polytomous (multinomial) regression with a generalized logit function (glogit link in SAS). For all analyses, model 1 adjusted for age at visit 5, sex, race and site (a 5-level variable: MN whites, MD whites, MS blacks, NC whites, and NC blacks), and body mass index. Model 2 additionally adjusted for smoking status and comorbidities (diabetes mellitus, systolic blood pressure, hypertension medications, chronic obstructive pulmonary disease, heart failure, and peripheral artery disease). Sensitivity analyses were conducted: (1) restricting to unprovoked VTE as the exposure, as it is likely less confounded by disease status than provoked VTE; (2) evaluating prevalent PE and DVT separately; and (3) removing disease events in the 2 years before visit 5 to isolate the long-term impact of the conditions on physical function.

Visit 6 analyses of the 2-minute walk test were conducted cross-sectionally, in a similar manner to the visit 5 analyses. Prevalent VTE, CHD, and stroke status, and all covariates except for chronic obstructive pulmonary disease (which was only assessed at visit 5) were obtained at the time of visit 6.

## RESULTS

The 6161 participants in our analytic visit 5 sample were, on average, 75.7±5.2 years of age, 58.8% female, and 23.0% black. Among these, 195 (3.2%) were VTE

survivors, 425 (6.9%) CHD survivors, and 208 (3.4%) stroke survivors. On average (mean±standard deviation), VTE events occurred 7.5±6.0 years before the visit 5 clinic examination, CHD events 9.1±6.1 years before the visit, and stroke events 7.9±5.9 years before the visit (for individuals with recurrence, the date of the most recent event was used). A total of 24 individuals had both VTE and CHD, and 16 had both VTE and stroke. Table 1 presents the visit 5 participants' characteristics—including indices of frailty, physical function, and QOL—according to prevalence of VTE, CHD, stroke, or the comparison group with none of these diseases. As compared with those having no prevalent disease, VTE survivors tended to be black, have higher body mass index, and have more comorbidities. In these unadjusted analyses, VTE survivors also had greater frailty (12.8% vs 5.3%), higher prevalence of low SPPB (31.8% vs 11.3%), and slower gait speed (0.84 m/s vs 0.95 m/s) when compared with those having no prevalent disease.

The crude findings persisted when adjusted for demographics (model 1) and also for behaviors and comorbidities (model 2) (Table 2 Figure 1, and Table S2). Participants with prevalent VTE had slower gait speed and lower scores on the SPPB and QOL physical domain when compared with participants with no prevalent disease. Compared with participants having prevalent CHD, those with prevalent VTE performed more poorly on the SPPB, and in model 2 had slower gait speed. However, compared with participants having prevalent stroke, those with prevalent VTE performed better on the SPPB and had faster gait speed. There was no difference in QOL mental domain across any of the comparisons.

Participants with prevalent VTE had higher odds of frailty compared with participants without prevalent disease after accounting for demographics (odds ratio for model 1 [ $OR_{\text{model 1}}$ ], 3.81; 95% CI, 2.25–6.45) and when additionally adjusting for behaviors and comorbidities ( $OR_{\text{model 2}}$ , 3.11; 95% CI, 1.80–5.36) (Table 3 and Figure 2). Odds of frailty were not statistically different when comparing participants with prevalent VTE versus those with prevalent CHD ( $OR_{\text{model 1}}$ , 1.28; 95% CI, 0.63–2.61) or prevalent stroke ( $OR_{\text{model 1}}$ , 0.68; 95% CI, 0.30–1.54). The OR for low SPPB among participants with prevalent VTE versus no prevalent disease was 4.18 (95% CI, 2.77–6.30) in model 1 and 3.59 (95% CI, 2.36–5.47) in model 2. ORs of low SPPB comparing prevalent VTE with prevalent CHD or stroke, after model 1 adjustments, were 1.52 (95% CI, 0.90–2.59) and 0.55 (95% CI, 0.30–1.01), respectively.

Results are similar in analyses restricted to unprovoked VTE (Tables S3 and S4). Likewise, results are generally similar when we looked separately at prevalent PE (Tables S5 and S6) and DVT (Tables S7 and S8), and when we removed events that occurred within 2 years of the visit 5 date (Tables S9 and S10).

**Table 2. Linear Regression of Prevalent VTE With Physical Function and Quality of Life Outcomes in the ARIC Study, 2011–2013 and 2016–2017**

		Prevalent VTE vs No Prevalent Events			Prevalent VTE vs Prevalent CHD*			Prevalent VTE vs Prevalent Stroke*		
		n	Coefficient (95% CI)	P Value	n	Coefficient (95% CI)	P Value	n	Coefficient (95% CI)	P Value
Quality of life—mental score										
Model 1	Prevalent VTE	190	−0.12 (−1.21 to 0.97)	0.83	166	−0.24 (−1.84 to 1.37)	0.77	175	−0.23 (−2.11 to 1.64)	0.81
	Comparison	5295	(Reference)		384	(Reference)		180	(Reference)	
Model 2	Prevalent VTE	190	0.21 (−0.88 to 1.30)	0.70	166	0.38 (−1.38 to 2.15)	0.67	175	0.19 (−1.77 to 2.14)	0.85
	Comparison	5295	(Reference)		384	(Reference)		180	(Reference)	
Quality of life—physical score										
Model 1	Prevalent VTE	190	−4.57 (−5.95 to −3.19)	<0.0001	166	−0.27 (−2.40 to 1.87)	0.81	175	1.11 (−1.21 to 3.42)	0.35
	Comparison	5295	(Reference)		384	(Reference)		180	(Reference)	
Model 2	Prevalent VTE	190	−3.25 (−4.57 to −1.93)	<0.0001	166	−1.75 (−3.91 to 0.40)	0.11	175	0.57 (−1.74 to 2.87)	0.63
	Comparison	5295	(Reference)		384	(Reference)		180	(Reference)	
Gait speed—4-m walk, m/s										
Model 1	Prevalent VTE	166	−0.07 (−0.10 to −0.04)	<0.0001	147	−0.0001 (−0.04 to 0.04)	0.99	154	0.06 (0.02 to 0.11)	0.01
	Comparison	4981	(Reference)		347	(Reference)		159	(Reference)	
Model 2	Prevalent VTE	166	−0.06 (−0.09 to −0.03)	<0.0001	147	−0.02 (−0.06 to 0.03)	0.41	154	0.06 (0.01 to 0.11)	0.01
	Comparison	4981	(Reference)		347	(Reference)		159	(Reference)	
Endurance, feet <sup>†</sup>										
Model 1	Prevalent VTE	86	−19.21 (−35.98 to −2.44)	0.02	78	16.12 (−7.55 to 39.78)	0.18	82	36.59 (11.03 to 62.14)	0.01
	Comparison	2528	(Reference)		172	(Reference)		85	(Reference)	
Model 2	Prevalent VTE	86	−15.00 (−31.39 to 1.38)	0.07	78	15.46 (−10.02 to 40.94)	0.23	82	29.41 (2.51 to 56.32)	0.03
	Comparison	2528	(Reference)		172	(Reference)		85	(Reference)	

Model 1: Linear regression adjusted for age, race/center, sex, and body mass index. Model 2: model 1 plus additional adjustment for chronic obstructive pulmonary disease, diabetes mellitus, hypertensive medication, smoking status, systolic blood pressure, prevalent heart failure, and prevalent peripheral artery disease. Linear regression coefficient represents the difference between prevalent venous thromboembolism and the comparison group of each physical function and quality-of-life outcome. ARIC indicates Atherosclerosis Risk in Communities; CHD, coronary heart disease; and VTE, venous thromboembolism.

\*Prevalent VTE, CHD, and stroke events are mutually exclusive.

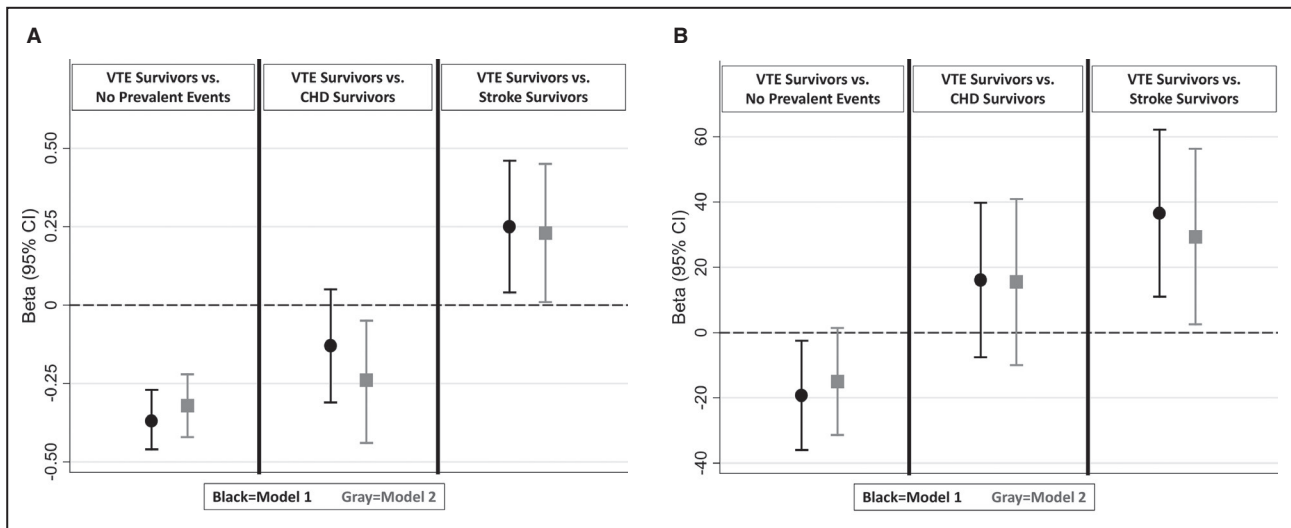
<sup>†</sup>Data from visit 6. The linear regression models include the same covariates from visit 6, except for chronic obstructive pulmonary disease, which is from visit 5.

Among the 3756 participants in our visit 6 analytic sample (average age, 79.5±4.7 years; 59.0% female; and 23.5% black [Table S11]), 148 (3.9%) were VTE survivors, 271 (7.2%) CHD survivors, and 160 (4.3%) stroke survivors. As shown in the lower portion of Table 2, VTE survivors had poorer endurance than those with no prevalent disease, similar endurance to CHD survivors, but better endurance than stroke survivors.

## DISCUSSION

In this community-based sample of older adults, VTE survivors were 3 times more likely to be frail and have poorer physical functioning than those without a history

of VTE, CHD, or stroke. There is some evidence that VTE survivors had more long-term physical problems than CHD survivors, but fewer than stroke survivors. Specifically, VTE survivors performed more poorly than CHD survivors on the SPPB and had slower gait speed. These findings enhance understanding of the long-term functioning of VTE patients. VTE is typically viewed as an acute condition, but the pervasiveness of physical limitations observed in our data highlight the need for continued monitoring, and suggest that interventions to improve physical functioning after a VTE event may be useful. Furthermore, directly comparing adults with a diagnosis of VTE to CHD and stroke survivors provides clinical context on the importance of these long-term limitations. Overall, the prevalence of



**Figure 1. Linear regression of prevalent VTE events with gait speed and endurance in the Atherosclerosis Risk in Communities Study, 2011–2013 and 2016–2017.**

**A,** Gait speed—4-m walk (in meters per second). **B,** Endurance (in feet). CHD indicates coronary heart disease; and VTE, venous thromboembolism.

frailty was 12.8% among VTE survivors, 9.4% among CHD survivors, 12.0% among stroke survivors, and 5.3% in those with no prevalent events.

Our study has provided new information about long-term function after a VTE diagnosis, as few studies have approached this issue using objective measures. The Evaluation of Long-Term Outcomes After Pulmonary Embolism cohort study reported that, among 100 PE patients who were assessed at the time of diagnosis, and 1, 3, 6, and 12 months post-PE, average QOL, dyspnea, and walking distance improved during the year after PE.<sup>37</sup> A study from Australia also reported that 120 long-term survivors of PE (time since index PE  $\geq$ 4 years, and, on average, 7.7 years) demonstrated poor exercise capacity, heart rate recovery, and mild pulmonary hypertension.<sup>38</sup> Both of the aforementioned studies are limited in that they did not include a non-PE comparison group.

Our finding that VTE was associated with poorer self-reported physical QOL is consistent with previous literature. A Nurses' Health Study analysis reported a greater decline in physical functioning—as assessed by the physical domain of the SF-36—among women with VTE as compared with those without a greater decline.<sup>39</sup> The decline was steep soon after VTE; in later time periods, physical function remained lower, but the rate of decline returned to the expected rate of decline associated with aging.<sup>39</sup> Likewise, physical function, as assessed by the SF-36 physical function score, was also lower among Women's Health Initiative participants with prevalent VTE who survived to 80 years of age than it was among their counterparts without VTE.<sup>21</sup> There is some evidence that the lower physical

function was more pronounced among PE survivors than those without PE, and when the SF-36 items were evaluated individually, the most common limitations were with vigorous activities, climbing several flights of stairs, walking more than 1 mile, and kneeling/bending. In the present analysis, frailty and physical function tended to be similar between DVT and PE survivors, relative to those with no prevalent disease.

Evidence that early intervention may improve physical functioning and QOL among VTE survivors is scant but suggestive. A small trial of 19 VTE patients, randomized to either a 3-month exercise and weight loss intervention or a control group with neither, showed that those in the intervention group were more active, had greater weight loss, and had higher objectively measured fitness ( $VO_{2peak}$ ).<sup>40</sup> Observational studies of inpatient rehabilitation after PE suggest that in-hospital rehabilitation is safe,<sup>41,42</sup> but whether this translates to long-term improvements in physical function and QOL remains uncertain. Comprehensive cardiac rehabilitation, incorporating numerous secondary prevention strategies (eg, nutritional, lifestyle, psychosocial, and smoking counseling; risk factor management; and education about medications and compliance) is a mainstay management strategy after myocardial infarction.<sup>43,44</sup> Among cardiac rehabilitation patients presenting with low SPPB scores, cardiac rehabilitation was found to be associated with significant improvements in physical function.<sup>45</sup> Comprehensive guidelines also exist for stroke rehabilitation and recovery.<sup>46</sup> It is unclear whether VTE patients would benefit from standardized rehabilitation. The extent of long-term physical function deficits observed among VTE

**Table 3. Polytomous Logistic Regression of Prevalent VTE With Physical Function and Quality-of-Life Outcomes in the ARIC Study, 2011–2013**

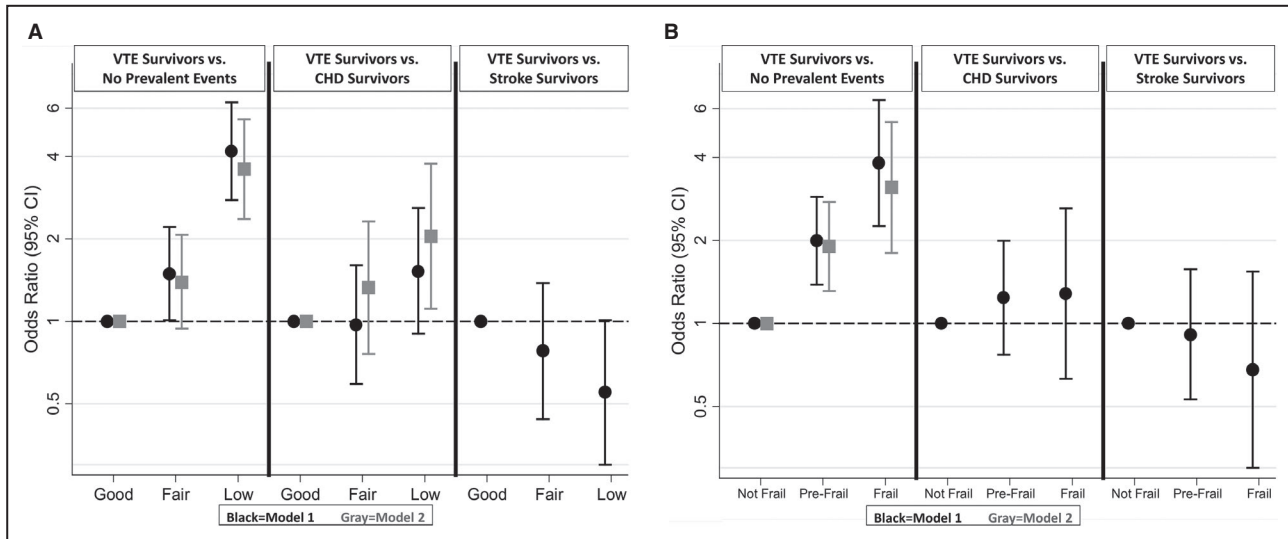
	Prevalent VTE vs No Prevalent Events				Prevalent VTE vs Prevalent CHD*				Prevalent VTE vs Prevalent Stroke*			
	N	VTE, n	OR (95% CI)	P Value	n	VTE, n	OR (95% CI)	P Value	n	VTE, n	OR (95% CI)	P Value
Frailty												
Model 1	Frail	25	3.81 (2.25–6.45)	<0.0001	59	22	1.28 (0.63–2.61)	0.50	40	20	0.68 (0.30–1.54)	0.35
	Pre-frail	97	1.99 (1.38–2.87)	0.0003	274	86	1.24 (0.77–1.99)	0.38	180	90	0.91 (0.53–1.57)	0.74
	Not frail	45	1 (Reference)		162	40	1 (Reference)		90	44	1 (Reference)	
Model 2	Frail	25	3.11 (1.80–5.36)	<0.0001	59	22	...		40	20	...	
	Pre-frail	97	1.90 (1.31–2.75)	0.001	274	86	...		180	90	...	
	Not frail	45	1 (Reference)		162	40	1 (Reference)		90	44	1 (Reference)	
SPPB groups												
Model 1	Low (0–6)	62	4.18 (2.77–6.30)	<0.0001	132	56	1.52 (0.90–2.59)	0.12	110	51	0.55 (0.30–1.01)	0.05
	Fair (7–9)	50	1.49 (1.01–2.21)	0.05	157	44	0.97 (0.59–1.60)	0.90	100	49	0.78 (0.44–1.38)	0.39
	Good (10–12)	61	1 (Reference)		218	54	1 (Reference)		110	58	1 (Reference)	
Model 2	Low (0–6)	62	3.59 (2.36–5.47)	<0.0001	132	56	2.04 (1.11–3.77)	0.02	110	51	...	
	Fair (7–9)	50	1.39 (0.94–2.07)	0.10	157	44	1.33 (0.76–2.32)	0.33	100	49	...	
	Good (10–12)	61	1 (Reference)		218	54	1 (Reference)		110	58	1 (Reference)	

Model 1: Polytomous logistic regression adjusted for age, race/center, sex, and body mass index. Model 2: Model 1 plus additional adjustment for chronic obstructive pulmonary disease, diabetes mellitus, hypertension medication, smoking status, systolic blood pressure, prevalent heart failure at visit 5, and prevalent peripheral artery disease at visit 5. The odds ratios compare those with prevalent VTE versus the comparison group within each physical function and quality-of-life outcome group. ARIC indicates Atherosclerosis Risk in Communities; OR, odds ratio; SPPB, Short Physical Performance Battery; and VTE, venous thromboembolism.

\*Prevalent VTE, coronary heart disease, and stroke events are mutually exclusive.

<sup>†</sup>Model failed to converge due to the small sample size and some covariates lacking individuals within their categories.





**Figure 2.** Polytomous logistic regression of prevalent VTE with Short Physical Performance Battery score and frailty in the Atherosclerosis Risk in Communities Study, 2011–2013.

**A**, SPPB score. **B**, Frailty. CHD indicates coronary heart disease; and VTE, venous thromboembolism.

survivors in the present analysis indicates potential targets for intervention studies that can maximize QOL and healthy aging among VTE patients.

The strengths of this study are its: (1) community-based sample, including men and women and blacks and whites; (2) adjudication of incident VTE, CHD, and stroke events; and (3) perhaps most importantly, objective and standardized measurements of physical function. The fact that the length of time varied between the clinical events and the visit 5 assessments may also be considered a strength of the study, as it makes our findings more generalizable to the patients a clinician may see in a general practice setting. Yet, in recent decades there is evidence that smaller, PEs<sup>47</sup> and possibly DVTs are being detected. Thus, ARIC VTE survivors may have more functional limitations than contemporary VTE survivors.

Selection bias is a possible drawback of this study, because frail participants were probably less likely to have attended the clinic visit than those with better function. Likewise, survivors of VTE, CHD, or stroke whose initial events were severe may be less likely to participate in clinic visits. As with all observational studies, it is possible that uncontrolled confounding may underlie our findings. For this specific analysis, factors that provoke VTE are strong candidates for confounding. However, results are similar in the sensitivity analyses restricted to individuals with unprovoked VTE. Finally, given the cross-sectional design and lack of functional assessments before visit 5, we cannot rule out reverse causality—that is, that lower functional status throughout adulthood led to increased risk of VTE, rather than vice versa.

Maintenance of physical function—the ability to perform basic and instrumental activities of daily living<sup>48</sup>—is an essential component of healthy aging, QOL, and preserving independence. Patients with VTE may represent a group with high risk of functional decline who warrant screening and, potentially, interventions to preserve physical function.

## ARTICLE INFORMATION

Received January 7, 2020; accepted April 23, 2020.

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### Acknowledgments

The authors thank the staff and participants in the Atherosclerosis Risk in Communities Study for their valuable contributions.

### Sources of Funding

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by the National Heart, Lung, and Blood Institute (award nos. HHSN268201700001, HHSN268201700002, HHSN268201700003, HHSN268201700005, HHSN268201700004). VTE work is supported by NHLBI R01 HL59367. Neurocognitive data and physical function data were collected through grants from the National Institutes for Health (NHLBI, NINDS, NIA, and NIDCD) (award nos. U01 2U01HL096812, 2U01HL096814, 2U01HL096899, 2U01HL096902, 2U01HL096917).

### Disclosures

None.

### Supplementary Materials

Tables S1–S11

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# **SUPPLEMENTAL MATERIAL**

**Table S1. Visit 5 attendance and vital status by prevalent disease status (venous thromboembolism [VTE], coronary heart disease [CHD], stroke, or no events), Atherosclerosis Risk in Communities (ARIC) Study, 2011 to 2013.**

	Prevalent VTE*			Prevalent CHD*			Prevalent Stroke*			No Prevalent Events		
	Analytic Sample	Alive but did not attend Visit 5†	Dead by Visit 5†	Analytic Sample	Alive but did not attend Visit 5†	Dead by Visit 5†	Analytic Sample	Alive but did not attend Visit 5†	Dead by Visit 5†	Analytic Sample	Alive but did not attend Visit 5†	Dead by Visit 5†
n	195	164	413	425	363	1,431	208	270	746	5,409	3,530	3,178
Age at visit 1, years	52.8 (5.1)	56.0 (5.7)	56.5 (5.7)	53.4 (5.3)	54.8 (5.5)	57.1 (5.3)	53.4 (5.6)	54.9 (5.6)	57.3 (5.2)	51.8 (5.1)	53.7 (5.6)	56.7 (5.5)
Age at visit 5, years‡	76.6 (5.2)	79.9 (5.8)	73.0 (7.7)	77.2 (5.4)	78.6 (5.5)	71.5 (7.9)	77.2 (5.7)	78.7 (5.6)	72.4 (7.7)	75.5 (5.2)	77.4 (5.7)	71.1 (8.3)
Sex, %												
Female	59.5	62.8	51.8	39.1	44.1	38.2	49.0	55.2	49.9	60.5	64.2	47.4
Male	40.5	37.2	48.2	60.9	55.9	61.8	51.0	44.8	50.1	39.5	35.8	52.6
Race, %												
Asian	0	0.6	0	0	0.5	0	0	0.4	0.1	0	0.7	0.1
African American	31.3	35.4	38.0	22.4	23.7	32.3	33.7	38.5	42.9	22.5	25.7	30.2
Indian	0	0	0	0	0.3	0.1	0	0	0	0	0.2	0.2
White	68.7	64.0	62.0	77.6	75.5	67.6	66.3	61.1	57.0	77.5	73.4	69.5
BMI, kg/m <sup>2</sup>	29.5 (5.4)	30.0 (6.0)	29.5 (6.0)	27.8 (4.7)	28.1 (5.1)	29.2 (5.7)	27.6 (4.6)	28.9 (5.3)	28.8 (5.7)	27.0 (4.8)	27.7 (5.5)	27.8 (5.8)
Smoking status, %												
Current	10.8	16.5	33.2	27.5	30.0	37.5	23.6	32.6	36.2	17.2	22.8	38.3
Former	38.5	33.5	32.7	37.2	33.1	34.2	35.1	24.8	27.8	32.7	30.7	31.6
Never	50.8	50.0	34.1	35.3	36.9	28.2	41.3	42.6	35.9	50.0	46.4	30.0
Unknown	0	0	0	0	0	0.1	0	0	0.1	0.1	0.1	0.1
Diabetes, %	9.2	11.0	16.2	12.7	15.4	32.0	12.0	15.6	31.0	4.9	8.0	16.4
Hypertension, %	37.4	43.9	47.7	32.2	45.2	58.9	40.4	50.0	63.0	22.7	31.5	41.3

BMI, smoking status, diabetes and hypertension are from visit 1 only.

BMI: Body mass index

\* Prevalent VTE, CHD, and stroke events are not mutually exclusive.

† Censoring date for those who did not attend visit 5: May 4, 2012 (median date of visit 5).

‡ Age at visit 5 indicates the age at death for those dead by visit 5 and age at the median visit 5 date for those who are alive but did not attend visit 5.



**Table S2. Linear regression of prevalent venous thromboembolism (VTE) with overall and gait speed scores on the Short Physical Performance Battery, Atherosclerosis Risk in Communities (ARIC) Study, 2011 to 2013 and 2016 to 2017.**

		Prevalent VTE versus No Prevalent Events			Prevalent VTE versus Prevalent CHD*			Prevalent VTE versus Prevalent Stroke*		
		n	Coefficient (95% CI)	p-value	n	Coefficient (95% CI)	p-value	n	Coefficient (95% CI)	p-value
<b>Short physical performance battery (SPPB) score</b>										
Model 1	Prevalent VTE	173	-1.47 (-1.80, -1.14)	<0.0001	154	-0.60 (-1.16, -0.04)	0.04	158	0.56 (-0.11, 1.23)	0.10
	Comparison	5,018	(Reference)		353	(Reference)		162	(Reference)	
Model 2	Prevalent VTE	173	-1.29 (-1.62, -0.97)	<0.0001	154	-0.97 (-1.57, -0.38)	0.002	158	0.53 (-0.17, 1.23)	0.14
	Comparison	5,018	(Reference)		353	(Reference)		162	(Reference)	
<b>Gait speed - 4m walk (SPPB score 0-4)</b>										
Model 1	Prevalent VTE	172	-0.37 (-0.46, -0.27)	<0.0001	153	-0.13 (-0.31, 0.05)	0.16	157	0.25 (0.04, 0.46)	0.02
	Comparison	4,988	(Reference)		352	(Reference)		162	(Reference)	
Model 2	Prevalent VTE	172	-0.32 (-0.42, -0.22)	<0.0001	153	-0.24 (-0.44, -0.05)	0.01	157	0.23 (0.01, 0.45)	0.04
	Comparison	4,988	(Reference)		352	(Reference)		162	(Reference)	

**Model 1:** Linear regression adjusted for age, race-center, sex, and body mass index.

**Model 2:** Model 1 + additional adjustment for chronic obstructive pulmonary disease, diabetes, hypertensive medication, smoking status, systolic blood pressure, prevalent heart failure, and prevalent peripheral artery disease.

The linear regression coefficient represents the difference between prevalent VTE and the comparison group of each physical function and quality of life outcome.

CI: confidence interval

\* Prevalent VTE, CHD, and stroke events are mutually exclusive.

**Table S3. Linear regression of prevalent unprovoked venous thromboembolism (VTE) with physical function and quality of life outcomes, Atherosclerosis Risk in Communities (ARIC) Study, 2011 to 2013 and 2016 to 2017.**

		Prevalent Unprovoked VTE versus No Prevalent Events			Prevalent Unprovoked VTE versus Prevalent CHD*			Prevalent Unprovoked VTE versus Prevalent Stroke*		
		n	Coefficient (95% CI)	p-value	n	Coefficient (95% CI)	p-value	n	Coefficient (95% CI)	p-value
<b>Quality of life - mental score</b>										
Model 1	Unprovoked VTE	98	0.03 (-1.47, 1.53)	0.97	86	-0.24 (-2.24, 1.75)	0.81	92	-0.09 (-2.35, 2.17)	0.94
	Comparison	5,295	(Reference)		384	(Reference)		180	(Reference)	
Model 2	Unprovoked VTE	98	0.32 (-1.18, 1.81)	0.68	86	0.17 (-1.98, 2.33)	0.88	92	0.05 (-2.34, 2.44)	0.97
	Comparison	5,295	(Reference)		384	(Reference)		180	(Reference)	
<b>Quality of life - physical score</b>										
Model 1	Unprovoked VTE	98	-4.61 (-6.51, -2.72)	<0.0001	86	-0.93 (-3.63, 1.78)	0.50	92	0.96 (-1.76, 3.68)	0.49
	Comparison	5,295	(Reference)		384	(Reference)		180	(Reference)	
Model 2	Unprovoked VTE	98	-3.59 (-5.39, -1.78)	<0.0001	86	-2.93 (-5.60, -0.26)	0.03	92	-0.24 (-2.98, 2.50)	0.86
	Comparison	5,295	(Reference)		384	(Reference)		180	(Reference)	
<b>Short physical performance battery (SPPB) score</b>										
Model 1	Unprovoked VTE	90	-1.36 (-1.81, -0.91)	<0.0001	81	-0.41 (-1.09, 0.27)	0.24	84	0.44 (-0.39, 1.26)	0.30
	Comparison	5,018	(Reference)		353	(Reference)		162	(Reference)	
Model 2	Unprovoked VTE	90	-1.22 (-1.67, -0.78)	<0.0001	81	-0.88 (-1.60, -0.15)	0.02	84	0.38 (-0.49, 1.24)	0.39
	Comparison	5,018	(Reference)		353	(Reference)		162	(Reference)	
<b>Gait speed - 4m walk, m/s</b>										
Model 1	Unprovoked VTE	89	-0.07 (-0.11, -0.03)	0.001	80	0.0001 (-0.05, 0.05)	0.99	83	0.06 (-0.001, 0.12)	0.05
	Comparison	4,981	(Reference)		347	(Reference)		159	(Reference)	
Model 2	Unprovoked VTE	89	-0.06 (-0.10, -0.02)	0.003	80	-0.02 (-0.07, 0.03)	0.45	83	0.05 (-0.01, 0.11)	0.09
	Comparison	4,981	(Reference)		347	(Reference)		159	(Reference)	
<b>Gait speed - 4m walk (SPPB score 0-4)</b>										
Model 1	Unprovoked VTE	89	-0.22 (-0.35, -0.08)	0.002	80	0.01 (-0.21, 0.22)	0.94	83	0.30 (0.04, 0.56)	0.02
	Comparison	4,988	(Reference)		352	(Reference)		162	(Reference)	
Model 2	Unprovoked VTE	89	-0.18 (-0.32, -0.05)	0.01	80	-0.12 (-0.34, 0.11)	0.32	83	0.26 (-0.01, 0.54)	0.06
	Comparison	4,988	(Reference)		352	(Reference)		162	(Reference)	

<b>Endurance, feet†</b>										
Model 1	Unprovoked VTE	48	-32.31 (-54.67, -9.95)	0.005	44	5.00 (-25.08, 35.08)	0.74	47	29.81 (-2.56, 62.18)	0.07
	Comparison	2,528			172			85		
Model 2	Unprovoked VTE	48	-31.06 (-52.83, -9.29)	0.01	44	-2.90 (-34.94, 29.15)	0.86	47	11.65 (-22.80, 46.10)	0.50
	Comparison	2,528	(Reference)		172	(Reference)		85	(Reference)	

**Model 1:** Linear regression adjusted for age, race-center, sex, and body mass index.

**Model 2:** Model 1 + additional adjustment for chronic obstructive pulmonary disease, diabetes, hypertensive medication, smoking status, systolic blood pressure, prevalent heart failure at visit 5, and prevalent peripheral artery disease at visit 5.

The linear regression coefficient represents the difference between prevalent unprovoked VTE and the comparison group of each physical function and quality of life outcome.

CI: confidence interval

\* Prevalent unprovoked VTE, CHD, and stroke events are mutually exclusive.

† From visit #6. The linear regression models include the same covariates from visit #6 except for chronic obstructive pulmonary disease, which is from visit #5.

**Table S4. Polytomous logistic regression of prevalent unprovoked venous thromboembolism (VTE) with physical function and quality of life outcomes, Atherosclerosis Risk in Communities (ARIC) Study, 2011 to 2013.**

		Prevalent Unprovoked VTE versus No Prevalent Events				Prevalent Unprovoked VTE versus Prevalent CHD*				Prevalent Unprovoked VTE versus Prevalent Stroke*			
		n	VTE n	OR (95% CI)	p-value	n	VTE n	OR (95% CI)	p-value	n	VTE n	OR (95% CI)	p-value
Frailty													
Model 1	Frail	297	12	3.70 (1.77-7.71)	0.001	49	12	1.38 (0.57-3.29)	0.47	30	10	**	
	Pre-frail	2,354	51	2.05 (1.24-3.38)	0.005	231	43	1.20 (0.67-2.16)	0.54	137	47	**	
	Not frail	2,382	24	1 (Reference)		145	23	1 (Reference)		70	24	1 (Reference)	
Model 2	Frail	297	12	3.11 (1.46-6.64)	0.003	49	12	**		30	10	**	
	Pre-frail	2,354	51	2.02 (1.22-3.36)	0.007	231	43	**		137	47	**	
	Not frail	2,382	24	1 (Reference)		145	23	1 (Reference)		70	24	1 (Reference)	
Short physical performance battery (SPPB) score groups													
Model 1	Low (0-6)	641	32	3.83 (2.20-6.67)	<0.0001	104	28	1.28 (0.66-2.47)	0.47	87	28	0.60 (0.30-1.22)	0.16
	Fair (7-9)	1,514	23	1.23 (0.71-2.14)	0.45	134	21	0.77 (0.41-1.45)	0.42	74	23	0.67 (0.34-1.34)	0.26
	Good (10-12)	2,953	35	1 (Reference)		196	32	1 (Reference)		85	33	1 (Reference)	
Model 2	Low (0-6)	641	32	3.39 (1.91-6.02)	<0.0001	104	28	**		87	28	**	
	Fair (7-9)	1,514	23	1.19 (0.69-2.07)	0.54	134	21	**		74	23	**	
	Good (10-12)	2,953	35	1 (Reference)		196	32	1 (Reference)		85	33	1 (Reference)	

**Model 1:** Multinomial logistic regression adjusted for age, race-center, sex, and body mass index.

**Model 2:** Model 1 + additional adjustment for chronic obstructive pulmonary disease, diabetes, hypertensive medication, smoking status, systolic blood pressure, prevalent heart failure at visit 5 and prevalent peripheral artery disease at visit 5.

The odds ratios are comparing those with prevalent unprovoked VTE to the comparison group within each physical function and quality of life outcome group.

OR: odds ratio; CI: confidence interval

\* Prevalent unprovoked VTE, CHD, and stroke events are mutually exclusive.

\*\* Model failed to converge due to the small sample size and some covariates lacking individuals within their categories.

**Table S5. Linear regression of prevalent pulmonary embolism (PE) with physical function and quality of life outcomes, Atherosclerosis Risk in Communities (ARIC) Study, 2011 to 2013 and 2016 to 2017.**

		Prevalent PE versus No Prevalent Events			Prevalent PE versus Prevalent CHD*			Prevalent PE versus Prevalent Stroke*		
		n	Coefficient (95% CI)	p-value	n	Coefficient (95% CI)	p-value	n	Coefficient (95% CI)	p-value
<b>Quality of life - mental score</b>										
Model 1	Prevalent PE	106	0.96 (-0.48, 2.41)	0.19	93	0.80 (-1.16, 2.76)	0.42	95	0.55 (-1.70, 2.80)	0.63
	Comparison	5,295	(Reference)		384	(Reference)		180	(Reference)	
Model 2	Prevalent PE	106	1.38 (-0.06, 2.82)	0.06	93	1.11 (-1.01, 3.23)	0.30	95	0.65 (-1.69, 3.00)	0.58
	Comparison	5,295	(Reference)		384	(Reference)		180	(Reference)	
<b>Quality of life - physical score</b>										
Model 1	Prevalent PE	106	-4.98 (-6.80, -3.16)	<0.0001	93	-1.08 (-3.73, 1.57)	0.42	95	1.20 (-1.50, 3.90)	0.38
	Comparison	5,295	(Reference)		384	(Reference)		180	(Reference)	
Model 2	Prevalent PE	106	-3.59 (-5.33, -1.85)	<0.0001	93	-2.95 (-5.57, -0.33)	0.03	95	0.53 (-2.14, 3.21)	0.70
	Comparison	5,295	(Reference)		384	(Reference)		180	(Reference)	
<b>Short physical performance battery (SPPB) score</b>										
Model 1	Prevalent PE	97	-1.67 (-2.11, -1.24)	<0.0001	88	-0.70 (-1.38, -0.03)	0.04	87	0.37 (-0.45, 1.19)	0.37
	Comparison	5,018	(Reference)		353	(Reference)		162	(Reference)	
Model 2	Prevalent PE	97	-1.48 (-1.90, -1.05)	<0.0001	88	-1.14 (-1.85, -0.42)	0.002	87	0.33 (-0.52, 1.19)	0.44
	Comparison	5,018	(Reference)		353	(Reference)		162	(Reference)	
<b>Gait speed - 4m walk, m/s</b>										
Model 1	Prevalent PE	92	-0.07 (-0.11, -0.03)	0.001	83	-0.001 (-0.05, 0.05)	0.97	84	0.07 (0.01, 0.13)	0.02
	Comparison	4,981	(Reference)		347	(Reference)		159	(Reference)	
Model 2	Prevalent PE	92	-0.05 (-0.09, -0.02)	0.01	83	-0.02 (-0.07, 0.04)	0.50	84	0.07 (0.01, 0.13)	0.02
	Comparison	4,981	(Reference)		347	(Reference)		159	(Reference)	
<b>Gait speed - 4m walk (SPPB score 0-4)</b>										
Model 1	Prevalent PE	96	-0.42 (-0.55, -0.29)	<0.0001	87	-0.18 (-0.41, 0.04)	0.10	86	0.20 (-0.06, 0.47)	0.13
	Comparison	4,988	(Reference)		352	(Reference)		162	(Reference)	
Model 2	Prevalent PE	96	-0.37 (-0.50, -0.24)	<0.0001	87	-0.30 (-0.54, -0.07)	0.01	86	0.18 (-0.10, 0.46)	0.20
	Comparison	4,988	(Reference)		352	(Reference)		162	(Reference)	



<b>Endurance, feet†</b>										
Model 1	Prevalent PE	56	-18.53 (-39.26, 2.20)	0.08	50	17.92 (-10.73, 46.57)	0.22	52	35.39 (4.30, 66.47)	0.03
	Comparison	2,528	(Reference)		172	(Reference)		85	(Reference)	
Model 2	Prevalent PE	56	-13.63 (-33.84, 6.58)	0.19	50	13.88 (-16.03, 43.80)	0.36	52	24.58 (-7.06, 56.23)	0.13
	Comparison	2,528	(Reference)		172	(Reference)		85	(Reference)	

**Model 1:** Linear regression adjusted for age, race-center, sex, and body mass index.

**Model 2:** Model 1 + additional adjustment for chronic obstructive pulmonary disease, diabetes, hypertensive medication, smoking status, systolic blood pressure, prevalent heart failure at visit 5, and prevalent peripheral artery disease at visit 5.

The linear regression coefficient represents the difference between prevalent PE and the comparison group of each physical function and quality of life outcome.

CI: confidence interval

\* Prevalent PE, CHD, and stroke events are mutually exclusive.

† From visit #6. The linear regression models include the same covariates from visit #6 except for chronic obstructive pulmonary disease, which is from visit #5.

**Table S6. Polytomous logistic regression of prevalent pulmonary embolism (PE) with physical function and quality of life outcomes, Atherosclerosis Risk in Communities (ARIC) Study, 2011 to 2013.**

		Prevalent PE versus No Prevalent Events				Prevalent PE versus Prevalent CHD*				Prevalent PE versus Prevalent Stroke*			
		n	PE n	OR (95% CI)	p-value	n	PE n	OR (95% CI)	p-value	n	PE n	OR (95% CI)	p-value
Frailty													
Model 1	Frail	299	14	3.99 (1.97-8.09)	0.0001	49	12	1.50 (0.62-3.66)	0.37	31	11	**	
	Pre-frail	2,360	57	2.26 (1.37-3.72)	0.002	241	53	1.51 (0.83-2.74)	0.18	142	52	**	
	Not frail	2,381	23	1 (Reference)		142	20	1 (Reference)		68	22	1 (Reference)	
Model 2	Frail	299	14	3.01 (1.45-6.27)	0.003	49	12	**		31	11	**	
	Pre-frail	2,360	57	2.15 (1.29-3.56)	0.003	241	53	**		142	52	**	
	Not frail	2,381	23	1 (Reference)		142	20	1 (Reference)		68	22	1 (Reference)	
Short physical performance battery (SPPB) groups													
Model 1	Low (0-6)	647	38	4.60 (2.65-7.97)	<0.0001	110	34	1.52 (0.78-2.93)	0.22	90	31	0.60 (0.29-1.24)	0.17
	Fair (7-9)	1,518	27	1.50 (0.87-2.56)	0.14	138	25	0.91 (0.48-1.71)	0.77	77	26	0.73 (0.36-1.47)	0.37
	Good (10-12)	2,950	32	1 (Reference)		193	29	1 (Reference)		82	30	1 (Reference)	
Model 2	Low (0-6)	647	38	3.90 (2.22-6.86)	<0.0001	110	34	**		90	31	**	
	Fair (7-9)	1,518	27	1.41 (0.82-2.42)	0.21	138	25	**		77	26	**	
	Good (10-12)	2,950	32	1 (Reference)		193	29	1 (Reference)		82	30	1 (Reference)	

**Model 1:** Polytomous logistic regression adjusted for age, race-center, sex, and body mass index.

**Model 2:** Model 1 + additional adjustment for chronic obstructive pulmonary disease, diabetes, hypertensive medication, smoking status, systolic blood pressure, prevalent heart failure at visit 5 and prevalent peripheral artery disease at visit 5.

The odds ratios are comparing those with prevalent PE to the comparison group within each physical function and quality of life outcome group.

OR: odds ratio; CI: confidence interval

\* Prevalent PE, CHD, and stroke events are mutually exclusive.

\*\* Model failed to converge due to the small sample size and some covariates lacking individuals within their categories.

**Table S7. Linear regression of prevalent deep-vein thrombosis (DVT) with physical function and quality of life outcomes, Atherosclerosis Risk in Communities (ARIC) Study, 2011 to 2013 and 2016 to 2017.**

		Prevalent DVT versus No Prevalent Events			Prevalent DVT versus Prevalent CHD*			Prevalent DVT versus Prevalent Stroke*		
		n	Coefficient (95% CI)	p-value	n	Coefficient (95% CI)	p-value	n	Coefficient (95% CI)	p-value
<b>Quality of life - mental score</b>										
Model 1	Prevalent DVT	84	-1.50 (-3.12, 0.12)	0.07	73	-1.58 (-3.75, 0.59)	0.15	80	-1.03 (-3.46, 1.41)	0.41
	Comparison	5,295	(Reference)		384	(Reference)		180	(Reference)	
Model 2	Prevalent DVT	84	-1.23 (-2.84, 0.39)	0.14	73	-0.93 (-3.24, 1.38)	0.43	80	-0.56 (-3.13, 2.00)	0.67
	Comparison	5,295	(Reference)		384	(Reference)		180	(Reference)	
<b>Quality of life - physical score</b>										
Model 1	Prevalent DVT	84	-4.01 (-6.05, -1.96)	0.0001	73	0.68 (-2.21, 3.57)	0.64	80	1.28 (-1.67, 4.23)	0.39
	Comparison	5,295	(Reference)		384	(Reference)		180	(Reference)	
Model 2	Prevalent DVT	84	-2.80 (-4.76, -0.85)	0.005	73	-0.52 (-3.37, 2.34)	0.72	80	0.67 (-2.31, 3.64)	0.66
	Comparison	5,295	(Reference)		384	(Reference)		180	(Reference)	
<b>Short physical performance battery (SPPB) score</b>										
Model 1	Prevalent DVT	76	-1.22 (-1.71, -0.73)	<0.0001	66	-0.42 (-1.17, 0.33)	0.27	71	0.77 (-0.11, 1.65)	0.09
	Comparison	5,018	(Reference)		353	(Reference)		162	(Reference)	
Model 2	Prevalent DVT	76	-1.06 (-1.54, -0.58)	<0.0001	66	-0.80 (-1.58, -0.01)	0.05	71	0.69 (-0.24, 1.62)	0.15
	Comparison	5,018	(Reference)		353	(Reference)		162	(Reference)	
<b>Gait speed - 4m walk, m/s</b>										
Model 1	Prevalent DVT	74	-0.08 (-0.12, -0.04)	0.0003	64	-0.001 (-0.06, 0.05)	0.98	70	0.05 (-0.01, 0.12)	0.08
	Comparison	4,981	(Reference)		347	(Reference)		159	(Reference)	
Model 2	Prevalent DVT	74	-0.07 (-0.11, -0.03)	0.001	64	-0.02 (-0.08, 0.03)	0.43	70	0.05 (-0.02, 0.11)	0.15
	Comparison	4,981	(Reference)		347	(Reference)		159	(Reference)	
<b>Gait speed - 4m walk (SPPB score 0-4)</b>										
Model 1	Prevalent DVT	76	-0.30 (-0.44, -0.15)	<0.0001	66	-0.05 (-0.29, 0.19)	0.68	71	0.30 (0.02, 0.58)	0.04
	Comparison	4,988	(Reference)		352	(Reference)		162	(Reference)	
Model 2	Prevalent DVT	76	-0.26 (-0.41, -0.12)	0.0004	66	-0.16 (-0.41, 0.09)	0.21	71	0.28 (-0.02, 0.57)	0.07
	Comparison	4,988	(Reference)		352	(Reference)		162	(Reference)	

<b>Endurance, feet†</b>										
Model 1	Prevalent DVT	30	-20.44 (-48.52, 7.64)	0.15	28	13.51 (-21.46, 48.49)	0.45	30	39.98 (4.26, 75.69)	0.03
	Comparison	2,528	(Reference)		172	(Reference)		85	(Reference)	
Model 2	Prevalent DVT	30	-17.31 (-44.64, 10.02)	0.21	28	13.24 (-24.20, 50.68)	0.49	30	20.93 (-17.80, 59.65)	0.29
	Comparison	2,528	(Reference)		172	(Reference)		85	(Reference)	

**Model 1:** Linear regression adjusted for age, race-center, sex, and body mass index.

**Model 2:** Model 1 + additional adjustment for chronic obstructive pulmonary disease, diabetes, hypertensive medication, smoking status, systolic blood pressure, prevalent heart failure at visit 5, and prevalent peripheral artery disease at visit 5.

The linear regression coefficient represents the difference between prevalent DVT and the comparison group of each physical function and quality of life outcome.

CI: confidence interval

\* Prevalent DVT, CHD, and stroke events are mutually exclusive.

† From visit #6. The linear regression models include the same covariates from visit #6 except for chronic obstructive pulmonary disease, which is from visit #5.

**Table S8. Polytomous logistic regression of prevalent deep-vein thrombosis (DVT) with physical function and quality of life outcomes, Atherosclerosis Risk in Communities (ARIC) Study, 2011 to 2013.**

		Prevalent DVT versus No Prevalent Events				Prevalent DVT versus Prevalent CHD*				Prevalent DVT versus Prevalent Stroke*			
		n	DVT n	OR (95% CI)	p-value	n	DVT n	OR (95% CI)	p-value	n	DVT n	OR (95% CI)	p-value
Frailty													
Model 1	Frail	296	11	3.67 (1.71-7.88)	0.001	47	10	1.19 (0.47-3.04)	0.72	29	9	0.60 (0.21-1.70)	0.34
	Pre-frail	2,343	40	1.70 (1.00-2.91)	0.05	221	33	1.02 (0.54-1.93)	0.95	128	38	0.81 (0.41-1.59)	0.53
	Not frail	2,380	22	1 (Reference)		142	20	1 (Reference)		68	22	1 (Reference)	
Model 2	Frail	296	11	3.30 (1.51-7.21)	0.003	47	10	**		29	9	**	
	Pre-frail	2,343	40	1.63 (0.95-2.79)	0.08	221	33	**		128	38	**	
	Not frail	2,380	22	1 (Reference)		142	20	1 (Reference)		68	22	1 (Reference)	
Short physical performance battery (SPPB) groups													
Model 1	Low (0-6)	633	24	3.72 (2.03-6.82)	<0.0001	98	22	1.52 (0.75-3.09)	0.25	79	20	0.50 (0.23-1.08)	0.08
	Fair (7-9)	1,514	23	1.50 (0.85-2.64)	0.17	132	19	0.95 (0.48-1.86)	0.87	74	23	0.80 (0.40-1.63)	0.54
	Good (10-12)	2,947	29	1 (Reference)		189	25	1 (Reference)		80	28	1 (Reference)	
Model 2	Low (0-6)	633	24	3.23 (1.74-6.01)	0.0002	98	22	2.00 (0.90-4.44)	0.09	79	20	**	
	Fair (7-9)	1,514	23	1.37 (0.77-2.43)	0.28	132	19	1.43 (0.68-2.99)	0.35	74	23	**	
	Good (10-12)	2,947	29	1 (Reference)		189	25	1 (Reference)		80	28	1 (Reference)	

**Model 1:** Polytomous logistic regression adjusted for age, race-center, sex, and body mass index.

**Model 2:** Model 1 + additional adjustment for chronic obstructive pulmonary disease, diabetes, hypertensive medication, smoking status, systolic blood pressure, prevalent heart failure at visit 5 and prevalent peripheral artery disease at visit 5.

The odds ratios are comparing those with prevalent DVT to the comparison group within each physical function and quality of life outcome group.

OR: odds ratio; CI: confidence interval

\* Prevalent DVT, CHD, and stroke events are mutually exclusive.

\*\* Model failed to converge due to the small sample size and some covariates lacking individuals within their categories.



**Table S9. Linear regression of prevalent venous thromboembolism (VTE) with physical function and quality of life outcomes, restricted to events that took place more than 2 years before the clinic visit date, Atherosclerosis Risk in Communities (ARIC) Study, 2011 to 2013 and 2016 to 2017.**

		Prevalent VTE versus No Prevalent Events			Prevalent VTE versus Prevalent CHD*			Prevalent VTE versus Prevalent Stroke*		
		n	Coefficient (95% CI)	p-value	n	Coefficient (95% CI)	p-value	n	Coefficient (95% CI)	p-value
<b>Quality of life - mental score</b>										
Model 1	Prevalent VTE	148	-0.09 (-1.32, 1.14)	0.88	127	-0.07 (-1.89, 1.75)	0.94	137	0.04 (-2.05, 2.14)	0.97
	Comparison	5,295	(Reference)		335	(Reference)		157	(Reference)	
Model 2	Prevalent VTE	148	0.24 (-0.98, 1.47)	0.70	127	0.36 (-1.66, 2.38)	0.73	137	0.64 (-1.56, 2.84)	0.57
	Comparison	5,295	(Reference)		335	(Reference)		157	(Reference)	
<b>Quality of life - physical score</b>										
Model 1	Prevalent VTE	148	-4.18 (-5.74, -2.63)	<0.0001	127	0.06 (-2.39, 2.51)	0.96	137	1.55 (-1.04, 4.14)	0.24
	Comparison	5,295	(Reference)		335	(Reference)		157	(Reference)	
Model 2	Prevalent VTE	148	-2.93 (-4.41, -1.45)	0.0001	127	-1.59 (-4.09, 0.90)	0.21	137	1.10 (-1.53, 3.74)	0.41
	Comparison	5,295	(Reference)		335	(Reference)		157	(Reference)	
<b>Short physical performance battery (SPPB) score</b>										
Model 1	Prevalent VTE	136	-1.44 (-1.81, -1.07)	<0.0001	120	-0.54 (-1.17, 0.10)	0.10	125	0.79 (0.02, 1.55)	0.04
	Comparison	5,018	(Reference)		306	(Reference)		142	(Reference)	
Model 2	Prevalent VTE	136	-1.28 (-1.65, -0.92)	<0.0001	120	-0.98 (-1.67, -0.30)	0.01	125	0.75 (-0.07, 1.56)	0.07
	Comparison	5,018	(Reference)		306	(Reference)		142	(Reference)	
<b>Gait speed - 4m walk, m/s</b>										
Model 1	Prevalent VTE	130	-0.07 (-0.11, -0.04)	<0.0001	114	0.01 (-0.04, 0.05)	0.75	121	0.07 (0.02, 0.13)	0.01
	Comparison	4,981	(Reference)		301	(Reference)		139	(Reference)	
Model 2	Prevalent VTE	130	-0.06 (-0.09, -0.03)	0.0003	114	-0.02 (-0.07, 0.04)	0.56	121	0.08 (0.02, 0.13)	0.01
	Comparison	4,981	(Reference)		301	(Reference)		139	(Reference)	
<b>Gait speed - 4m walk (SPPB score 0-4)</b>										
Model 1	Prevalent VTE	135	-0.38 (-0.49, -0.27)	<0.0001	119	-0.12 (-0.32, 0.09)	0.26	124	0.28 (0.03, 0.52)	0.03
	Comparison	4,988	(Reference)		305	(Reference)		142	(Reference)	
Model 2	Prevalent VTE	135	-0.34 (-0.45, -0.23)	<0.0001	119	-0.25 (-0.47, -0.03)	0.03	124	0.25 (-0.01, 0.51)	0.06
	Comparison	4,988	(Reference)		305	(Reference)		142	(Reference)	

<b>Endurance, feet†</b>											
Model 1	Prevalent VTE	79	-16.28 (-33.75, 1.19)	0.07	71	17.04 (-8.18, 42.25)	0.18	75	37.23 (10.16, 64.30)	0.01	
	Comparison	2,528	(Reference)		149	(Reference)		73	(Reference)		
Model 2	Prevalent VTE	79	-11.36 (-28.42, 5.71)	0.19	71	15.37 (-12.02, 42.77)	0.27	75	34.73 (6.24, 63.21)	0.02	
	Comparison	2,528	(Reference)		149	(Reference)		73	(Reference)		

**Model 1:** Linear regression adjusted for age, race-center, sex, and body mass index.

**Model 2:** Model 1 + additional adjustment for chronic obstructive pulmonary disease, diabetes, hypertensive medication, smoking status, systolic blood pressure, prevalent heart failure, and prevalent peripheral artery disease.

The linear regression coefficient represents the difference between prevalent VTE and the comparison group of each physical function and quality of life outcome.

CI: confidence interval

\* Prevalent VTE, CHD, and stroke events are mutually exclusive.

† From visit #6. The linear regression models include the same covariates from visit #6 except for chronic obstructive pulmonary disease, which is from visit #5.

**Table S10. Multinomial logistic regression of prevalent venous thromboembolism (VTE) with physical function and quality of life outcomes, restricted to events that took place more than 2 years before the clinic visit date, Atherosclerosis Risk in Communities (ARIC) Study, 2011 to 2013.**

		Prevalent VTE versus No Prevalent Events				Prevalent VTE versus Prevalent CHD*				Prevalent VTE versus Prevalent Stroke*			
		n	VTE n	OR (95% CI)	p-value	n	VTE n	OR (95% CI)	p-value	n	VTE n	OR (95% CI)	p-value
Frailty													
Model 1	Frail	302	17	3.33 (1.79-6.17)	0.0001	49	15	1.02 (0.45-2.34)	0.96	30	14	**	
	Pre-frail	2,381	78	2.06 (1.37-3.12)	0.001	228	68	1.25 (0.73-2.14)	0.41	154	73	**	
	Not frail	2,393	35	1 (Reference)		137	31	1 (Reference)		74	34	1 (Reference)	
Model 2	Frail	302	17	2.89 (1.54-5.43)	0.001	49	15	**		30	14	**	
	Pre-frail	2,381	78	1.98 (1.30-3.00)	0.001	228	68	**		154	73	**	
	Not frail	2,393	35	1 (Reference)		137	31	1 (Reference)		74	34	1 (Reference)	
Short physical performance battery (SPPB) score													
Model 1	Low (0-6)	657	48	4.06 (2.56-6.44)	<0.0001	108	42	1.47 (0.81-2.68)	0.21	96	40	0.48 (0.25-0.92)	0.03
	Fair (7-9)	1,530	39	1.48 (0.95-2.29)	0.08	134	34	0.94 (0.54-1.64)	0.82	81	38	0.75 (0.39-1.43)	0.38
	Good (10-12)	2,967	49	1 (Reference)		184	44	1 (Reference)		90	47	1 (Reference)	
Model 2	Low (0-6)	657	48	3.50 (2.19-5.61)	<0.0001	108	42	2.17 (1.07-4.40)	0.03	96	40	**	
	Fair (7-9)	1,530	39	1.37 (0.88-2.14)	0.17	134	34	1.33 (0.71-2.49)	0.37	81	38	**	
	Good (10-12)	2,967	49	1 (Reference)		184	44	1 (Reference)		90	47	1 (Reference)	

**Model 1:** Multinomial logistic regression adjusted for age, race-center, sex, and body mass index.

**Model 2:** Model 1 + additional adjustment for chronic obstructive pulmonary disease, diabetes, hypertensive medication, smoking status, systolic blood pressure, prevalent heart failure at visit 5 and prevalent peripheral artery disease at visit 5.

The odds ratios are comparing those with prevalent VTE to the comparison group within each physical function and quality of life outcome group.

OR: odds ratio; CI: confidence interval

\* Prevalent VTE, CHD, and stroke events are mutually exclusive.

\*\* Model failed to converge due to the small sample size and some covariates lacking individuals within their categories.

**Table S11. Visit 6 characteristics by prevalent disease status (venous thromboembolism [VTE], coronary heart disease [CHD], stroke, or no events), Atherosclerosis Risk in Communities (ARIC) Study, 2016 to 2017.**

	Prevalent VTE*	Prevalent CHD*	Prevalent Stroke*	No Prevalent Events
n	148	271	160	3,230
Age, years	80.6 (5.0)	81.1 (5.0)	80.6 (4.8)	79.3 (4.7)
Sex, %				
Female	62.8	39.5	46.9	60.8
Male	37.2	60.5	53.1	39.2
Race, %				
White	71.6	79.7	68.1	76.8
African American	28.4	20.3	31.9	23.2
Body mass index, kg/m <sup>2</sup>	29.4 (6.5)	28.2 (5.0)	28.6 (5.3)	28.3 (5.4)
Smoking status, %				
Current	2.7	10.0	8.8	6.9
Former	39.9	50.6	53.1	45.4
Never	41.9	25.5	23.1	37.1
Unknown	15.5	14.0	15.0	10.6
Diabetes, %	36.5	39.9	46.9	31.0
Hypertension medication, %	83.8	94.1	91.3	75.3
Prevalent chronic obstructive pulmonary disease, %‡	12.8	14.4	7.5	7.8
Prevalent heart failure, %	21.6	46.9	36.9	9.4
Prevalent peripheral artery disease, %	12.2	14.0	15.6	7.4
Systolic blood pressure, mmHg	134.3 (20.1)	135.1 (20.2)	138.0 (19.6)	135.0 (18.9)
Short physical performance battery (SPPB) groups †	7.2 (3.3)	8.0 (3.1)	7.3 (3.1)	8.8 (2.7)
Low (0-6)	31.8	24.0	31.3	16.6
Fair (7-9)	29.7	27.7	26.9	29.1
Good (10-12)	23.7	34.3	22.5	44.6
Gait speed - 4m walk, m/s†	0.86 (0.2)	0.88 (0.2)	0.83 (0.2)	0.94 (0.2)
Gait speed - 4m walk (SPPB score 0-4)†	3.2 (1.1)	3.3 (1.0)	3.2 (1.1)	3.6 (0.8)
0	3.4	2.6	1.9	1.0
1	4.1	1.9	4.4	1.6
2	8.1	10.0	14.4	6.0
3	21.6	22.5	15.6	16.9
4	45.3	46.9	41.9	62.8

Endurance, feet†	425.5 (90.1)	424.5 (101.3)	406.0 (94.7)	455.3 (92.4)
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Data are presented as percent for categorical variables and as mean (standard deviation) for continuous variable.

\* Prevalent VTE, CHD, and stroke events are not mutually exclusive.

† Sample size modestly smaller due to additional missing data.

‡ From visit #5.