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IN FOCUS

Subclinical atherosclerosis and the risk of future venous thrombosis in the Cardiovascular Health Study

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Summary. *Background:* Recent reports have suggested an association of atherosclerosis with risk of venous thrombosis. *Objective:* To confirm whether subclinical atherosclerosis is a risk factor for venous thrombosis (VT) among men and women age 65 and older. *Methods:* Participants of the Cardiovascular Health Study ($n = 4108$) without baseline clinical cardiovascular disease, anticoagulant use or previous VT were followed for a median of 11.7 years after non-invasive assessment of subclinical atherosclerosis using carotid ultrasound (intima-media thickness and presence of plaques), ankle-brachial blood pressure index and electrocardiogram. Each event was classified as idiopathic or secondary. We used Cox proportional hazards regression to estimate the relative risk of overall and idiopathic VT for individuals with and without baseline subclinical atherosclerosis. *Results:* There were 133 first time VT events. No subclinical atherosclerosis measures were associated with increased risk of overall or idiopathic VT. The adjusted relative risks of overall and idiopathic VT for presence of any type of subclinical disease were 0.60 (95% confidence interval 0.39–0.91) and 0.32 (0.18–0.59), respectively. Most of this association was explained by an inverse association of high-risk carotid plaques (prevalent in 54% of those at risk) with VT. *Conclusion:* Non-invasively measured subclinical atherosclerosis was not associated with increased risk of overall or idiopathic VT in this observational study. Carotid plaques and arterial events during follow up were inversely associated, a finding that requires further study.

Keywords: atherosclerosis, deep vein thrombosis, pulmonary embolism, risk factor.

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Venous thrombosis affects 1–3 per 1000 adults each year in developed countries [1–5]. It is the third most common cardiovascular disease in the USA [6]. It is most commonly manifested in the deep veins of the leg or as a pulmonary embolism (PE); both fall under the broader term venous thrombosis (VT).

Although VT shares some risk factors with atherosclerosis, such as older age, male sex, and obesity, little information is available about whether the presence of atherosclerosis, at

either a subclinical or a clinical level, is associated with increased risk of VT.

Classical atherosclerotic risk factors, such as hypertension, hyperlipidemia and smoking are not considered risk factors for VT, so it would seem unlikely that atherosclerotic disease would be related to risk of VT. Less common risk factors such as hyperhomocysteinemia and antiphospholipid antibodies appear to relate to both arterial and venous disease [7–9]. A recent study by Prandoni and colleagues [10] reported a higher frequency of carotid plaques (as an indicator of atherosclerosis) in patients who had previous idiopathic VT compared to hospitalized controls. A similar association was not observed among patients with secondary VT. Further confirmation of this finding is not available.

The aim of this study was to examine the association between non-invasively measured subclinical arterial disease and the risk of future VT in a population-based cohort study, the Cardiovascular Health Study (CHS).

Methods

Participants

The CHS is a population-based longitudinal study initially of 5201 adults enrolled in 1989–1990. An additional 687 African-Americans were recruited 3 years later to increase their representation. The study design has been published [11]. Participants aged 65 years and older were recruited from four areas in the USA: Forsyth County, NC; Washington County, MD; Sacramento County, CA; and Pittsburgh, PA. Potential subjects were excluded if they were institutionalized, undergoing treatment for active cancer, planning to move from the area within 2 years, or unable to give informed consent. Twice yearly follow-up involved alternating telephone calls and clinic visits. The study was approved by the institutional review board at each field center, and all participants gave informed consent.

Exclusion criteria for this analysis were prevalent clinical arterial disease ($n = 1570$), warfarin use at baseline ($n = 98$) or previous VT ($n = 354$). There were 188 participants with two of these criteria and 27 with all three. Prevalent clinical arterial disease was defined as a history of myocardial infarction, stroke, claudication, angina, transient ischemic attack, congestive heart failure, carotid endarterectomy, coronary artery bypass or angioplasty, or leg artery bypass or angioplasty. These prebaseline events were confirmed by medical record review.

Definitions

Baseline measures of subclinical atherosclerosis were ankle brachial index (ABI), internal and common carotid ultrasound to assess intima-media thickness (IMT) and presence of plaque, and resting 12-lead electrocardiogram (ECG). All participants underwent duplicate resting measurements of the ankle and arm blood pressures to calculate the ABI as the ratio of the ankle to arm systolic blood pressure [12]. High-resolution B-mode ultrasonography of the carotid arteries was used. Trained technicians acquired one longitudinal image of the common carotid artery and three images of the internal carotid artery [13]. Ultrasounds were centrally read as previously described at the Ultrasound Reading Center in Boston, MA, USA [14]. Carotid plaque, defined by the appearance of the largest focal lesion, was classified by surface characteristics, echogenicity, and texture. Surface characteristics were classified as smooth, mildly irregular (height variations of 0.4 mm or less), markedly irregular (height variations of more than 0.4 mm), or ulcerated (a discrete depression of more than 2 mm in width extended into the media). Lesion echogenicity was characterized as hypoechoic, isoechoic, hyperechoic, or calcified. Lesion texture was classified as homogeneous or heterogeneous. Plaques were defined in three groups: absent, intermediate risk, or high risk. Absence of plaque was defined as a smooth intimal surface with no regional discrete plaque. Intermediate risk plaques were hyperdense, calcified or homogeneous plaques, or those with a mildly irregular surface. High-risk plaques had an irregular or ulcerated surface, or were hypodense or heterogeneous plaques occupying more than 50% of the total plaque volume. Major ECG abnormalities were defined as ventricular conduction defect, major Q-wave abnormalities, left ventricular hypertrophy, isolated ST-T wave abnormalities, atrial fibrillation, or first-degree atrio-ventricular block [15]. We defined presence of subclinical atherosclerosis as any one of the following: ABI < 0.9, maximal internal or common carotid IMT in the top quintile (internal 1.93 mm for men, 1.68 mm for women; common 1.23 mm for men, 1.14 mm for women), presence of carotid plaques, or major ECG abnormalities [15].

Race was categorized based on participant self-report as white, black, or other. Diabetes was defined by the American Diabetes Association criteria [16]. Body mass index (BMI) was used to define normal weight (BMI < 25 kg m^{-2}), overweight (BMI 25–30 kg m^{-2}), and obese (BMI > 30 kg m^{-2}) [17]. During the baseline examination fasting glucose and lipid levels were measured [11]. Aspirin and statin use were assessed at baseline by medication inventory.

Follow-up

Ascertainment of VT events during follow-up has been described in detail [18]. All hospitalization data were ascertained based on self-report or the Health Care Financing Administration Database. If there was an indication of a possible thrombosis event based on self-report or discharge diagnosis codes, hospital records were reviewed using standardized criteria by two physicians to determine whether a VT had occurred. Deep vein thrombosis (DVT) events required positive duplex or Doppler ultrasound or venogram, and occasionally were based on impedance plethysmography. PE events required positive ventilation-perfusion lung imaging, computed tomography, or autopsy. Each event was classified as idiopathic or secondary (occurring within 90 days of major trauma, surgery, or marked immobility, or associated with active cancer or chemotherapy) [18]. Incident VT events that occurred between baseline and the end of 2001 were included in these analyses.

Statistical analysis

Incidence rates of VT during follow-up were calculated in participants with and without subclinical atherosclerosis at baseline by dividing the total number of cases by the number of person-years of observation. The Poisson distribution was used to calculate 95% confidence intervals (CI) [19]. Cox proportional hazards regression was used to estimate the relative risk (hazard ratios) of overall and idiopathic VT for individuals with compared to those without subclinical atherosclerosis. These analyses were performed for the various types of subclinical atherosclerosis. We first estimated unadjusted hazard ratios and subsequently adjusted for baseline age, sex, race, FVIII level and obesity status, which were previously reported as risk factors for VT in this cohort [17]. Participants were censored from analyses at the time of death or the end of follow-up. To assess important subgroups we performed analyses stratified by sex, race, baseline obesity status, and baseline age (above or below 75 years).

Table 1 Baseline characteristics of participants with or without subclinical disease

Characteristic	Subclinical atherosclerosis present ($n = 3332$)	Subclinical atherosclerosis absent ($n = 776$)
Mean age, years (range)	72.8 (68–76)	70.7 (67–73)
Sex, female	1952 (58.6)	553 (71.3)
Race		
White	2786 (83.6)	674 (86.9)
Black	520 (15.6)	99 (12.8)
Other	26 (0.8)	3 (0.4)
Diabetes status		
Normal	2334 (70.7)	613 (79.6)
Impaired fasting glucose	460 (13.9)	98 (12.7)
Diabetes	506 (15.3)	59 (7.7)
Body mass index (kg m^{-2})		
< 25	1289 (38.8)	328 (42.5)
25 to < 30	1391 (41.9)	306 (39.6)
≥ 30	643 (19.4)	138 (17.9)
Cancer: ever diagnosed	460 (13.8)	98 (12.6)
Regular aspirin use	936 (28.1)	215 (27.7)
Statin use	58 (1.7)	9 (1.2)

Values are number (%) or mean (interquartile range).

Results

The mean age of the 4108 participants at baseline was 72.4 years. About 61% were women, 84% were white and over 81% had subclinical atherosclerosis. The most common type of subclinical disease was presence of high-risk carotid plaques, present in 54% of these elderly participants. Table 1 shows the baseline characteristics based on subclinical disease status. As expected, atherosclerotic risk factors such as older age and diabetes were more common among those with subclinical disease. Statin use at baseline was rare.

There were 133 first-time venous thrombosis events; 52 (39%) were idiopathic. Incident VT was more likely with older age ($P = 0.07$) and with obesity, but not in the presence of specific atherosclerotic risk factors such as hypertension, increased cholesterol, diabetes and smoking (data not shown).

As shown in Table 2, the incidence rate of overall VT was lower in participants with compared to without any form of subclinical atherosclerosis (3.10 and 3.98 per 1000 person-years). Some forms of subclinical atherosclerosis were associated with higher incidence of overall VT (ankle-brachial index < 0.9 and elevated common carotid IMT), while other forms were associated with lower incidence (presence of carotid plaques and major ECG abnormalities). For idiopathic VT similar patterns were generally observed. To further address carotid IMT, we divided the distribution of IMT into quartiles for analysis (bottom of Table 2). While the incidence of overall VT rose across quartiles of common carotid IMT, there was no such pattern for idiopathic VT, and VT incidence declined across internal carotid IMT quartiles, particularly for idiopathic VT.

In Table 3, Cox proportional-hazard models before and after adjustment for age, sex, race, FVIII, and obesity status, suggested that some forms of subclinical atherosclerosis were associated with a lower risk of VT. For example, the adjusted hazard ratio of overall VT for high-risk carotid plaques was 0.65 (0.42–1.00), and for major ECG abnormalities was 0.50 (0.27–0.92). For idiopathic VT the inverse associations were sometimes stronger; the adjusted hazard ratio of idiopathic VT for elevated internal carotid IMT was 0.27 (95% CI 0.08–0.87). Intermediate or high-risk carotid plaques were associated with more than a 50% lower risk of idiopathic VT; adjusted hazard ratios were 0.42 (95% CI 0.19–0.96) and 0.34 (0.18–0.65), respectively. In secondary analyses assessing carotid IMT in quartiles, the fourth quartile of internal carotid IMT was associated with a significantly lower risk of overall and idiopathic VT. Among those with any type of subclinical atherosclerosis, there was a 40% lower risk of overall VT and a 70% lower risk of idiopathic VT. This was largely a reflection of the high prevalence of carotid plaques and their inverse association with VT.

In an effort to explain the inverse association of atherosclerosis with VT, we assessed whether participants with subclinical atherosclerosis were less likely to be exposed to VT risk situations by analyzing the incidence of hospitalization overall or for pneumonia according to quintiles of carotid IMT. Hospitalizations during follow-up were more common among those with subclinical disease (data not shown). In addition, we assessed the occurrence of arterial events during follow-up prior to a diagnosis of VT (or the end of follow-up for those without VT), and the risk of VT comparing those with or without an interim arterial event. The rate of arterial events in those with or without VT was 21% and 27%, respectively ($P = 0.16$). Further the relative risk of VT in those with arterial events was 0.73 (95% CI 0.48–1.10) before adjustment and 0.62 (0.39–0.98) after adjustment for other risk factors.

Stratification of the Cox models for sex, race, obesity status, aspirin or statin use and age above or below 75 years did not reveal any differences in associations based on these factors (data not shown).

Table 2 Incidence rates per 1000 person-years of venous thromboembolism according to subclinical disease status at baseline, 1989–2001

Characteristic	Incidence rate of all VTE			Incidence rate of idiopathic VTE		
	Cases (*n*)/at risk (*n*)	Incidence rate	95% CI	Cases (*n*)/at risk (*n*)	Incidence rate	95% CI
ABI						
≥ 0.9	115/3640	3.12	2.60, 3.75	46/3640	1.25	0.94, 1.67
< 0.9	12/383	4.03	2.29, 7.09	4/383	1.34	0.50, 3.58
ICA IMT (Sex specific*)						
< 80th percentile	110/3292	3.30	2.74, 3.98	48/3292	1.44	1.08, 1.91
≥ 80th percentile	23/816	3.18	2.12, 4.79	4/816	0.55	0.21, 1.47
CCA IMT (Sex specific*)						
< 80th percentile	107/3317	3.18	2.63, 3.85	45/3317	1.34	1.00, 1.79
≥ 80th percentile	26/791	3.74	2.55, 5.49	7/791	1.01	0.48, 2.11
Major ECG abnormalities						
No	109/3103	3.46	2.87, 4.17	44/3103	1.40	1.04, 1.88
Yes	20/884	2.53	1.63, 3.93	8/884	1.01	0.51, 2.03
Carotid plaque risk groups						
Absent	40/1000	3.79	2.78, 5.17	23/1000	2.18	1.45, 3.28
Intermediate	25/864	2.92	1.97, 4.32	8/864	0.93	0.47, 1.87
High	67/2220	3.15	2.48, 4.00	21/2220	0.99	0.64, 1.51
Any subclinical atherosclerosis						
No	33/776	3.98	2.83, 5.60	20/776	2.41	1.56, 3.74
Yes	100/3332	3.10	2.55, 3.77	32/3332	0.99	0.70, 1.40
Secondary analyses for IMT						
ICA IMT quartiles						
First	39/1023	3.63	2.65, 4.96	21/1023	1.95	1.27, 2.99
Second	28/1022	2.67	1.85, 3.87	13/1022	1.24	0.72, 2.14
Third	38/1021	3.80	2.76, 5.22	12/1021	1.20	0.68, 2.11
Fourth	27/1020	2.94	2.02, 4.29	6/1020	0.65	0.29, 1.45
CCA IMT quartiles						
First	31/1054	2.80	1.97, 3.98	16/1054	1.44	0.88, 2.36
Second	34/1000	3.33	2.38, 4.66	11/1000	1.08	0.60, 1.94
Third	34/1047	3.30	2.36, 4.62	16/1047	1.55	0.95, 2.54
Fourth	33/986	3.74	2.66, 5.26	9/986	1.02	0.53, 1.96

ABI, ankle-brachial index; CCA, common carotid artery; ICA, internal carotid artery; IMT, intima-media thickness; ECG, electrocardiogram.
*80th percentile values: ICA IMT men 1.93 mm; ICA IMT women 1.68 mm; CCA IMT men 1.23 mm; CCA IMT women 1.14 mm.

Discussion

In this cohort study of older men and women without clinical arterial vascular disease, baseline measurements of subclinical atherosclerosis, including carotid artery disease, were not associated with increased risk of VT. Unexpectedly, presence of some forms of subclinical atherosclerosis, in particular carotid plaques, was associated with a lower risk of future VT. An inverse association of arterial disease events during with follow-up with subsequent VT supports this finding.

Prandoni and colleagues [10] reported a higher prevalence of carotid plaques among participants with previous idiopathic VT compared with hospitalized controls. Their study included slightly younger subjects (by ~5 years) and defined carotid plaques differently. Regardless, our findings suggest that bias or confounding may have played a role in the positive findings of that study. Use of hospitalized controls and measurement of risk factors after hospitalization for VT, not prior to VT as in a prospective study, may help explain differences in findings. It is possible that the plaques observed in the Prandoni study had more thrombogenic characteristics, thus were more common in VT patients, however in our study high-risk plaques, which would be more likely thrombogenic, were inversely associated with VT risk. In our study, with a median of 12 years of follow-up after measurement of subclinical atherosclerosis, we observed an inverse association of carotid plaques with future VT, with a stronger inverse relationship for idiopathic compared to overall VT.

One might argue that the inverse association we observed between some forms of subclinical atherosclerosis and future VT was due to interventions received after baseline by participants with subclinical disease (e.g. aspirin, statins, anticoagulants). However, participants were not informed of subclinical disease status unless there was severe carotid stenosis, so this seems an unlikely explanation. It is also possible that the definition of carotid plaques used here explains the unexpected finding; however associations were similarly inverse in analyses of internal carotid IMT, a well-validated measure that predicts future clinical atherosclerotic events. Given the lack of a hypothesis explaining these associations, it is possible that they represent a chance finding and further study is required.

Previous reports showed varying results concerning the associations of VT with atherosclerotic risk factors such as cigarette smoking, dyslipidemia, and hypertension, although most evidence points to the absence of an association [20–24]. The large prospective LITE (Longitudinal Investigation of Thromboembolism Etiology) cohort, which includes the CHS cohort, reported no association of any of these cardiovascular

Table 3 Hazard ratios (HR) of venous thromboembolism (VTE) according to subclinical disease status at baseline, 1989–2001

	Hazard ratios of all VTE				Hazard ratios of idiopathic VTE			
	Unadjusted HR		Adjusted HR†		Unadjusted HR		Adjusted HR†	
Characteristic	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
ABI								
≥ 0.9	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
< 0.9	1.33	0.73, 2.41	0.91	0.44, 1.91	1.13	0.40, 3.13	0.52	0.12, 2.17
ICA IMT (Sex specific*)								
< 80th percentile	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
≥ 80th percentile	0.98	0.62, 1.54	0.73	0.43, 1.24	0.39	0.14, 1.09	0.27	0.08, 0.87
CCA IMT (Sex specific*)								
< 80th percentile	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
≥ 80th percentile	1.19	0.78, 1.84	0.93	0.56, 1.54	0.77	0.35, 1.71	0.66	0.28, 1.59
Major ECG abnormalities								
No	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Yes	0.74	0.46, 1.19	0.50	0.27, 0.92	0.74	0.35, 1.57	0.59	0.25, 1.40
Carotid plaque risk groups								
Absent	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Intermediate	0.78	0.47, 1.28	0.73	0.43, 1.24	0.43	0.19, 0.97	0.42	0.19, 0.96
High	0.84	0.57, 1.24	0.65	0.42, 1.00	0.46	0.25, 0.83	0.34	0.18, 0.65
Any subclinical atherosclerosis								
No	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Yes	0.79	0.53, 1.17	0.60	0.39, 0.91	0.42	0.24, 0.73	0.32	0.18, 0.59
Secondary analyses of carotid IMT								
ICA IMT quartiles								
First	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Second	0.74	0.46, 1.20	0.65	0.38, 1.10	0.64	0.32, 1.28	0.56	0.27, 1.17
Third	1.06	0.68, 1.65	0.93	0.58, 1.51	0.62	0.31, 1.26	0.52	0.24, 1.09
Fourth	0.82	0.50, 1.35	0.54	0.31, 0.95	0.34	0.14, 0.85	0.18	0.06, 0.55
CCA IMT quartiles								
First	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Second	1.19	0.73, 1.94	0.90	0.53, 1.54	0.75	0.35, 1.61	0.60	0.26, 1.37
Third	1.19	0.73, 1.93	0.94	0.55, 1.59	1.09	0.54, 2.17	0.85	0.40, 1.80
Fourth	1.36	0.83, 2.22	0.95	0.55, 1.66	0.72	0.32, 1.64	0.57	0.23, 1.39

ABI, ankle-brachial index; CCA, common carotid artery; ICA, internal carotid artery; IMT, intima-media thickness; ECG, electrocardiogram.
*80th percentile values: ICA IMT men 1.93 mm; ICA IMT women 1.68 mm; CCA IMT men 1.23 mm; CCA IMT women 1.14 mm. †Adjusted for age, sex, race, factor VIII, and obesity status.

risk factors with VT incidence [17]. There was an association of diabetes with VT incidence, but with longer follow-up here, including only the older CHS participants, that association was no longer present.

Taken together with a finding of no association of carotid IMT with risk of future VT in the ARIC (Atherosclerosis Risks in Communities) study (25), our study provides prospective data against a hypothesis that atherosclerosis is a risk factor for VT. A few studies have evaluated VT as a predictor of subsequent arterial events. For example, a 38-month observational study evaluating the clinical course of patients with a first episode of idiopathic or secondary PE reported a higher incidence of arterial events in patients with idiopathic than secondary PE [26]. Another study reported a higher prevalence of coronary artery calcification in patients with previous idiopathic VT than in a control group [27]. In both of these studies patients with VT were more likely than those free of VT to have classical arterial disease risk factors, and since these are not generally considered VT risk factors, results may be confounded.

Limitations of this study should be considered. There was a relatively small number of VT events, however, given the high prevalence of subclinical atherosclerosis in this older group, 133 VT events provided acceptable power for reliable analysis. We did not adjust for treatments or high-risk periods for VT (e.g. surgery) during follow-up, but most of these exposures would not likely differ by subclinical atherosclerosis status, which was not generally known by participants. It is possible that exclusion of patients with prevalent clinical disease and inclusion of relatively healthy elderly subjects might have biased findings toward the null hypothesis. However, we believe these design features strengthened our ability to study associations of subclinical atherosclerosis and future VT without confounding. The strengths of this study were the wide array of subclinical disease measures and the prospective design, which reduces many types of bias.

In summary, these data, which included assessment of multiple arterial vascular beds using extensive non-invasive testing, do not support a hypothesis that atherosclerosis is a risk factor for VT in elderly men and women without clinical arterial disease. The findings would support the opposite conclusion; that some types of atherosclerosis are associated with a lower risk of VT. As this was not anticipated, further study is indicated.

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Disclosure of Conflicts of Interest

The authors state that they have no conflict of interest.

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