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C-reactive protein and venous thromboembolism: a prospective investigation in the ARIC cohort

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Summary

The role of inflammation in the causation of venous thromboembolism (VTE) is uncertain. In 10,505 participants of the Atherosclerosis Risk in Communities (ARIC) Study, we assessed the association of the systemic inflammation marker, elevated C-reactive protein (CRP), with incidence of VTE ($n=221$) over a median of 8.3 years of follow-up. Adjusted for age, race, and sex, the hazard ratios of VTE across quintiles of CRP were 1.0, 1.61, 1.16, 1.56, and 2.31 (p for trend $p<0.0007$). For CRP above the upper 10 percentile (≥ 8.55 mg/L), compared with the lowest 90% of CRP values, the hazard ratio of VTE was 2.07 (95% CI 1.47, 2.94). Further adjustment for baseline hormone replacement therapy, diabetes, and body mass index attenuated the hazard ratios only slightly. For example, the adjusted hazard ratio of VTE was 1.76 (95% CI 1.23, 2.52) for CRP above versus below the 90th percentile. In conclusion, this prospective, population-based study suggests elevated CRP is independently associated with increased risk of VTE.

Keywords

C-reactive protein; prospective study; pulmonary embolus; venous thrombosis

Introduction

There is strong evidence that inflammation, as reflected by increased blood levels of C-reactive protein (CRP), is associated with increased risk of atherothrombosis (1,2). In contrast, whether there is any association between CRP and venous thromboembolism (VTE) is unclear. Three cohort (2-4) studies, with limited numbers of VTE events, reported no association between CRP and VTE. Two case-control studies (5-6) reported a positive univariate association between CRP and VTE, but not after multivariable adjustment (6). Genetic polymorphisms that increase CRP levels have not been associated with risk of VTE (7,8), but such studies are limited by the low proportion of CRP variance explained by the polymorphisms. The Leiden Thrombophilia Study has suggested that other blood markers of inflammation, such as certain cytokines, may be associated with VTE risk (9,10). A review article concluded that more research is needed on inflammation and VTE (11).

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The prospective Longitudinal Investigation of Thromboembolism Etiology (LITE) found no relation of CRP with venous thromboembolism incidence in early follow-up of two cohorts: the middle-aged Atherosclerosis Risk in Communities (ARIC) Study (nested case-control analysis) and the older-aged Cardiovascular Health Study (3). However, measurement of CRP in the fourth ARIC examination offered an opportunity to re-examine the association of CRP with a greater number of VTE cases.

Methods

In 1987-89, the ARIC Study recruited to a baseline examination a cohort of 15,792 men and women aged 45-64 years, predominantly whites or African Americans, from four U.S. communities (12). Participants were re-examined in 1990-92 (93% response), 1993-95 (86%) and 1996-98 (80%). Participants in the ARIC Visit 4 examination serve as the cohort for the present analysis.

CRP was measured in 2008 on plasma frozen at -70°C from Visit 4 by the immunoturbidimetric assay using the Siemens (Dade Behring) BNII analyzer (Dade Behring, Deerfield, Ill), performed according to the manufacturer's protocol. Approximately 4% of samples were split and measured as blinded replicates on different dates to assess repeatability. The reliability coefficient for blinded quality control replicates of CRP was 0.99 (421 blinded replicates). Body mass index was assessed as weight (kg) in a scrub suit divided by height (m) squared. Statins were assessed by reviewing participants' medication containers. After Visit 4, cholesterol-lowering medications were self-reported during annual telephone contact. Factor VIII_c and aPTT were not measured at Visit 4 so the Visit 1 value (3,13) was used. Factor V Leiden and the prothrombin G20210A polymorphism were not measured in the whole ARIC cohort.

Participants were followed from Visit 4 (1996-98, $n = 11,573$) through 2005 to identify hospitalized VTE events. These were validated by physician review using a standardized protocol (14). A total of 263 VTE events were identified, of which only 7 had been included in our previous analysis of baseline CRP and VTE through June 1997 (3). Excluding these 7 events had no impact on this analysis, so we chose to include them.

Our hypothesis was that CRP would be associated positively with VTE incidence. From the 11,573 participants at Visit 4, we excluded 320 who were missing CRP; 331 with CRP values >20 mg/L, due to possible acute phase response; 342 who had a prior history of VTE; or 204 who were taking warfarin. This left 10,505 at risk: 8,219 whites, 2,255 African Americans, and 31 others, who were grouped with African Americans for this analysis. Follow-up time ended when the participant had a VTE, died, was lost to follow-up, or else until December 31, 2005. Cox proportional hazards regression was used to model the association between CRP and VTE incidence, and to derive hazard ratios and 95% confidence intervals. Hazard ratios were calculated for each of the four highest quintile groups compared with the first, but also for high CRP categories (90th or 95th percentile) versus all others, to study the possible impact of high CRP on VTE. Covariates included previous VTE risk factors measured in the whole ARIC cohort, measured at Visit 4 unless otherwise specified: age (continuous), race (African American, white), sex/hormone replacement therapy (men, women taking HRT, women not taking HRT), diabetes (yes, no), body mass index (continuous), Visit 1 factor VIII_c, and Visit 1 aPTT. Other factors related to CRP (e.g., smoking, lipid levels, physical activity) were not VTE risk factors in ARIC, and thus not included.

Results

In this sample of 10,505 participants with no history of VTE and no current warfarin use, the median CRP value was 2.3 mg/L and the interquartile range was 4.0 mg/L. CRP was higher in women than men and in African Americans than whites (Table 1). CRP was positively associated with BMI, HRT use, diabetes, and Visit 1 values of factor VIII_c and aPTT.

Over a median of 8.3 years of follow-up, 221 incident VTE events occurred (75 idiopathic, 153 not cancer related), yielding a crude total VTE incidence of 2.6 per 1000 person-years. The median CRP value was 3.2 mg/L in those who developed VTE and 2.3 mg/L in those who did not.

CRP was positively associated with total VTE incidence, with the increased VTE risk most apparent for very high CRP levels. Adjusted for age, race, and sex (Model 1), the VTE hazard ratio was 2.31 (95% CI = 1.48, 3.60) for the highest versus lowest quintile (Table 2), or 1.29 (95% CI = 1.14, 1.46) per 4 mg/L increment of CRP (not shown). For the highest 10 percent or highest 5 percent of CRP values, compared with the remainder, the hazard ratio of VTE was significantly elevated 2.0-fold. Additional adjustment for BMI, HRT, and diabetes (Model 2) attenuated the CRP and VTE association moderately, and further adjustment for Visit 1 factor VIII_c and aPTT (Model 3) had little impact. Yet, the hazard ratios for total VTE comparing the highest versus lower percentiles remained statistically significant in Model 3 (Table 2), as did the hazard ratio per 4 mg/L CRP increment (1.20; 95% CI = 1.05, 1.38).

The positive CRP association was somewhat stronger for secondary VTE than idiopathic VTE in the quintile analysis. However, the opposite was true for high versus low CRP, because of a nonlinear association (Table 2). The fully-adjusted hazard ratios of idiopathic VTE or non-cancer VTE were approximately 2.0 ($p < 0.05$) for the highest 10th or 5th percentiles of CRP.

As shown in Table 3, the association of high CRP (above 90th percentile) with total VTE did not vary significantly (interaction $p > 0.20$) by Visit 4 age, race, sex, HRT use, BMI, or statin use. Only 7 percent of participants at Visit 4 in 1996-98 were taking statins. When we updated cholesterol medication use from Visit 4 through 2005, the adjusted hazard ratio (95% CI) of VTE in relation to high CRP was 2.10 (1.42-3.11) for no statin use versus 0.81 (0.31, 2.09) for any statin use (p interaction = 0.05).

In sensitivity analyses, returning the 331 subjects with CRP values > 20 mg/dL yielded similar results. For example, for Model 2, the revised VTE hazard ratio for the highest versus lowest quintile of CRP was 1.72 (95% CI = 1.10, 2.71) and the p for trend across quintiles was $p = 0.03$. The revised Model 2 hazard ratio for the highest 10 percent versus lower values of CRP was 1.63 (95% CI = 1.17, 2.29).

Discussion

This prospective population-based study provides evidence that high levels of CRP may be independently associated with increased risk of VTE. For most VTE subtypes, the hazards ratios were approximately 1.6 to 2-fold for values above versus below the 90th percentile of CRP (8.55 mg/L).

Prior cohort and case-control studies (2-6) found little association between CRP and VTE (Table 4). Our current findings even contrast with our previous ARIC results (3). The previous report used a different high-sensitivity CRP assay (15), but the correlation with Dade assay used here is very high (unpublished). The ARIC cohort had aged 9 years since the first analysis, and the previous case group overlapped the current larger sample of 221 VTEs only slightly ($n = 7$). Thus, limited statistical power or a younger age may be reasons for the previous

negative ARIC finding. Based primarily on the larger sample size, we believe the current findings represent a more valid assessment of the association between CRP and VTE in ARIC than our previous report (3). Although the totality of evidence suggests elevated CRP may not increase risk of VTE (Table 4), our results suggest that further research may be warranted. The JUPITER Study recently showed that statins lower the risk of VTE (16). This prompts speculation of whether CRP-lowering by statins may contribute to their preventing VTE. In our data, the CRP association with VTE appeared to be stronger in non-users of cholesterol medication, but we had limited power to address such an interaction.

Although inflammation and elevated CRP may promote a procoagulant state (17,18), and they increase atherothrombosis risk (1,2), it may not necessarily follow that inflammation would also elevate risk of venous thrombosis. Some studies suggest that atherosclerotic disease is a VTE precursor, but others do not (19-22). Some risk factors are similar between atherothrombosis and venous thrombosis (e.g., age and obesity); others are not (e.g., hyperlipidemia with atherothrombosis) (23,24). Fibrinogen, another acute phase reactant elevated by inflammation, is more consistently associated with atherothrombosis (25) than with VTE (3,26). Yet, other inflammatory markers (IL-6, IL-8, TNF-alpha) were positively associated with VTE in the Leiden Thrombophilia Study (9,10). Thus, whether there is a causal link between inflammation and VTE is, at the moment, unsettled.

Drawbacks of our study warrant consideration. Firstly, we did not have measures of Factor V Leiden or the prothrombin G20210A polymorphism, and the Factor VIII_c and aPTT values were taken 9 years before the CRP values. It seems unlikely however that genetic predisposition to VTE would confound the observed association of CRP with VTE. Secondly, we had only a single measure of CRP. To the extent there is within person variability in CRP, we may have underestimated the true association of CRP with VTE over 8.3 years of follow-up.

In conclusion, this cohort study indicates that a high level of CRP, and therefore inflammation, may be a risk factor for VTE.

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Table 1

Characteristics (mean or prevalence) according to CRP quintile, ARIC (*n* = 10,505), 1996-98

Characteristic	CRP Quintile (mg/L)				
	Q1 0.15-0.88	Q2 0.89-1.67	Q3 1.68-3.14	Q4 3.15-5.93	Q5 5.93-20.0
Age, years (SD)	62.6 (5.8)	62.8 (5.5)	62.9 (5.7)	62.8 (5.6)	62.6 (5.7)
Male, <i>n</i> (%)	1,179 (56)	1,138 (54)	1,009 (48)	748 (36)	606 (29)
African Americans, <i>n</i> (%)	369 (18)	372 (18)	415 (20)	448 (23)	682 (32)
HRT Use *, <i>n</i> (%)	181 (20)	192 (20)	267 (24)	396 (29)	512 (34)
BMI, kg/m ² (SD)	25.8 (4.0)	27.6 (4.3)	28.6 (4.7)	29.9 (5.5)	31.3 (6.4)
Diabetes, <i>n</i> (%)	203 (10)	260 (12)	330 (16)	404 (19)	496 (24)
Factor VIII **, % (SD)	123 (34)	124 (35)	127 (34)	130 (36)	134 (39)
aPTT **, seconds (SD)	29.3 (2.9)	29.1 (2.8)	29.2 (3.2)	29.0 (2.9)	29.1 (3.1)

* Women only

** Visit 1 value (1987-89)

Table 2

Hazard ratios (95% confidence intervals) of venous thromboembolism (VTE) in relation to quintiles of CRP, or high versus low CRP, ARIC, 1996-2005

CRP Quintile (mg/L)										High vs. Low CRP	
Endpoint		Q1 0.15-0.88	Q2 0.89-1.67	Q3 1.68-3.14	Q4 3.15-5.93	Q5 5.93-20.0	P-trend	Upper 10% (≥8.55 mg/L) vs. lower 90%	Upper 5% (≥9.99 mg/L) vs. Lower 95%		
Total VTE	N events	29	47	34	45	66		41	23		
	Model 1	1.00	1.61 (1.01, 2.55)	1.16 (0.71, 1.91)	1.56 (0.98, 2.50)	2.31 (1.48, 3.60)	0.0007	2.07 (1.47, 2.94)	2.20 (1.42, 3.41)		
	Model 2	1.00	1.44 (0.91, 2.30)	1.02 (0.62, 1.68)	1.28 (0.80, 2.08)	1.78 (1.12, 2.84)	0.04	1.76 (1.23, 2.52)	1.85 (1.18, 2.90)		
	Model 3	1.00	1.37 (0.86, 2.19)	1.02 (0.62, 1.67)	1.21 (0.75, 1.97)	1.74 (1.09, 2.79)	0.05	1.73 (1.21, 2.49)	1.79 (1.13, 2.82)		
Idiopathic VTE	N events	12	15	13	13	22		15	9		
	Model 1	1.00	1.24 (0.58, 2.65)	1.07 (0.49, 2.34)	1.09 (0.50, 2.41)	1.89 (0.92, 3.87)	0.13	2.37 (1.33, 4.22)	2.71 (1.33, 5.49)		
	Model 2	1.00	1.18 (0.55, 2.52)	0.98 (0.44, 2.16)	0.96 (0.43, 2.16)	1.59 (0.75, 3.37)	0.34	2.15 (1.18, 3.91)	2.45 (1.19, 5.05)		
	Model 3	1.00	1.08 (0.50, 2.35)	0.98 (0.44, 2.16)	0.86 (0.38, 1.96)	1.61 (0.76, 3.43)	0.32	2.18 (1.20, 3.97)	2.51 (1.22, 5.19)		
Secondary VTE	N events	17	32	21	32	44		26	14		
	Model 1	1.00	1.87 (1.04, 3.37)	1.23 (0.65, 2.33)	1.90 (1.05, 3.44)	2.62 (1.48, 4.64)	0.002	1.94 (1.26, 3.00)	1.97 (1.13, 3.45)		
	Model 2	1.00	1.64 (0.91, 2.97)	1.05 (0.55, 2.00)	1.51 (0.82, 2.76)	1.93 (1.06, 3.50)	0.07	1.59 (1.01, 2.50)	1.60 (0.91, 2.84)		
	Model 3	1.00	1.58 (0.87, 2.87)	1.05 (0.55, 2.00)	1.45 (0.79, 2.67)	1.87 (1.03, 3.41)	0.08	1.54 (0.97, 2.43)	1.50 (0.83, 2.71)		
Non-Cancer VTE	N events	21	34	23	27	48		31	17		
	Model 1	1.00	1.60 (0.93, 2.76)	1.07 (0.59, 1.93)	1.26 (0.71, 2.24)	2.22 (1.32, 3.74)	0.01	2.25 (1.50, 3.37)	2.29 (1.37, 3.83)		
	Model 2	1.00	1.41 (0.82, 2.45)	0.92 (0.51, 1.67)	1.01 (0.56, 1.82)	1.65 (0.95, 2.85)	0.22	1.89 (1.24, 2.87)	1.91 (1.13, 3.22)		
	Model 3	1.00	1.31 (0.75, 2.29)	0.92 (0.51, 1.68)	0.92 (0.51, 1.67)	1.65 (0.95, 2.86)	0.21	1.93 (1.27, 2.94)	1.95 (1.15, 3.29)		

Model 1: Adjusted for age, sex, and race

Model 2: Adjusted for age, sex/HRT use, race, diabetes status, and BMI

Model 3: Adjusted for Model 2 + Factor VIII and aPTT

Table 3

Adjusted hazard ratios of total VTE for participants with CRP above the 90th percentile, compared with those below the 90th percentile, stratified by other risk factors, ARIC, 1996-2005

Risk Factor	Hazard Ratio* of VTE (95% CI) for high CRP
Age (y) [†]	
≤62	1.91 (1.10, 3.31)
>62	1.67 (1.04, 2.70)
Race	
White	1.51 (0.93, 2.47)
African American	2.24 (1.30, 3.85)
Sex/HRT [†]	
Men	1.35 (0.67, 2.73)
Women, No current HRT	1.72 (1.02, 2.90)
Women, Current HRT	2.65 (1.24, 5.68)
BMI (kg/m ²) [†]	
<30	1.76 (0.96, 3.25)
≥30	1.87 (1.20, 2.91)
Statin use [†]	
No	1.82 (1.26, 2.63)
Yes	0.85 (0.18, 4.00)
Cholesterol medication used Visit 4 to 2005	
No	2.10 (1.42, 3.11)
Yes	0.81 (0.31, 2.09)

* Each hazard ratio was from a separate model per row, comparing VTE incidence in those with CRP values ≥8.55 mg/L to those with CRP <8.55 mg/L, and adjusted for age, race, sex, HRT, BMI, and diabetes status.

[†] At Visit 4 (1996-98)

Table 4

Summary of existing studies on C-reactive protein (CRP) and venous thromboembolism (VTE)

Author	Design	Sample	Association
Ridker (2)	Nested case-control*	Male physicians; 101 VTEs, 543 controls	0.14 mg/L higher geometric mean CRP (p = 0.22) in cases; age and smoking-matched
Tsai (3)	Nested case-control*	ARIC: middle-aged adults; 89 VTEs, 307 controls	No association, adjusted for age, sex, and race
	Cohort	CHS: older adults; 65 VTEs	HR = 1.65 (p > 0.05) for CRP > 3.37 vs. <0.95, adjusted for age, sex, and race
Mahmoodi (4)	Cohort	Adults oversampled for albuminuria; 129 VTEs	HR = 1.13 (95% CI = 0.76-1.67) for CRP ≥ 3.0 mg/L, adjusted for age and sex
Kamphuisen (5)	Case-control	474 VTEs, 474 healthy controls	OR = 2.2 for CRP > 9.75 mg/L; age and sex-matched
Vormittag (6)	Case-control	214 VTEs, 104 friend controls	OR = 1.7 (95% CI = 0.7-4.5) per 1 mg/L CRP increment, multiply-adjusted
This study	Cohort	ARIC: older adults; 221 VTEs	HR = 1.73 (95% CI = 1.21, 2.49) for CRP ≥ 8.55 mg/L, multiply-adjusted

HR = hazard ratio, OR = odds ratio

* Within a cohort