Clinical Chemistry 61:2
000–000 (2015)

Editorials

Is Venous Thromboembolism a Chronic Inflammatory Disease?

Gregory Piazza[1] and Paul M Ridker[1,2*]

Venous thromboembolism (VTE)[3] traditionally has been considered a time-limited acute disease. Patients with deep vein thrombosis (DVT) or pulmonary embolism (PE) following major surgery, trauma, or periods of immobility are frequently treated with anticoagulation for a limited duration of 3 to 6 months. However, a subset of patients who suffer idiopathic (unprovoked) VTE have a high risk of recurrence, exceeding 50% over 10 years, if not treated with extended-duration anticoagulation *(1, 2)*. Even patients who suffer VTE in the setting of identifiable provoking factors have an enduring risk of recurrence that exceeds 20% over 10 years *(2)*. An analysis of the Danish National Registry of Patients demonstrated that patients with VTE have increased mortality over 30 years of follow-up and that recurrent PE remained an important cause of death throughout this time period *(3)*. Extended-duration low-intensity anticoagulation with warfarin for patients with idiopathic VTE dramatically reduces the risk of recurrent events compared with time-limited anticoagulation *(4)*. These data support the hypothesis that VTE is a chronic disease with pathophysiology rooted in enduring as well as transient risk factors.

Chronic inflammation plays a key role in the pathophysiology of atherothrombosis *(5)*. Furthermore, modulation of inflammation with antiplatelet therapy *(6)* and statins reduces the risk of atherothrombotic events *(7)*. Until recently, VTE was believed to be pathophysiologically distinct from atherothrombotic disorders such as acute coronary syndromes and stroke. However, recent data have challenged this "silo thinking" and suggest that VTE should be considered as part of a pan-cardiovascular syndrome that includes coronary artery disease, cerebrovascular disease, and peripheral artery disease *(8)*.

In addition to sharing cardiovascular risk factors such as obesity, hypertension, dyslipidemia, diabetes, and smoking, VTE and atherothrombosis result from common pathophysiological mechanisms including hypercoagulability, endothelial injury, and inflammation (Fig. 1) *(8)*. The increased frequency of DVT and PE in patients with chronic inflammatory disorders such as rheumatoid arthritis highlights the role of inflammation in VTE *(9)*. Further, increases of the inflammatory biomarker C-reactive protein (CRP) have been linked to an increased risk of VTE. In an analysis of 10 505 participants in the ARIC (Atherosclerosis Risk In Communities) study followed for incident DVT or PE over 8.3 years, increased CRP concentration above the 90th percentile was associated with a 76% increase in the risk of VTE vs lower percentiles *(10)*. Furthermore, polymorphisms in genes encoding factor VII, interleukin-1β (IL-1β), and IL-10 modulate the risk of idiopathic VTE *(11)*. The presence of neutrophils and neutrophil extracellular traps in human venous thrombus further highlight the importance of inflammation to the development of VTE *(12)*.

In this issue of *Clinical Chemistry*, Meyer-Olesen and colleagues provide elegant prospective epidemiologic data linking another inflammatory biomarker, rheumatoid factor, to the development of DVT *(13)*. In brief, the investigators analyzed data from the Copenhagen City Heart Study and the Copenhagen General Population Study to evaluate whether increased concentrations of rheumatoid factor, an antibody directed against the Fc portion of IgG, increased the risk of VTE in individuals without overt autoimmune disease. This is a creative strategy for an epidemiologic exploration of inflammation and thrombosis, because high titers against rheumatoid factor may be detected in autoimmune disorders such as rheumatoid arthritis or in certain chronic infections, yet the importance of low titers is uncertain in otherwise asymptomatic individuals.

During 368 381 person-years of follow-up in these 2 Copenhagen cohorts, 670 patients developed DVT and 539 developed PE. Compared with a rheumatoid factor concentration of $\leq$100 IU/mL, a concentration $\geq$100 IU/mL was strongly associated with DVT, with multivariable adjusted hazard ratios of 9.0 for 1-year follow-up, 4.3 for 5-year follow-up, and 3.1 for up to 32 years of follow-up. During maximal follow-up, increasing concentrations of rheumatoid factor were associated with higher risk of DVT. Even after adjustment for additional variables such as CRP and thrombophilias, increased

[1] Cardiovascular Division and [2] Center for Cardiovascular Disease Prevention, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.
* Address correspondence to this author at: Center for Cardiovascular Disease Prevention, Division of Preventive Medicine, 900 Commonwealth Ave., Boston, MA 02215. Fax 617-734-1508; e-mail pridker@partners.org.
Received October 14, 2014; accepted October 16, 2014.
Previously published online at DOI: 10.1373/clinchem.2014.234088
[3] Nonstandard abbreviations: VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; CRP, C-reactive protein; IL-6, interleukin-6; CANTOS, Canakinumab Antiinflammatory Thrombosis Outcomes Study; CRT, Cardiovascular Inflammation Reduction Trial.

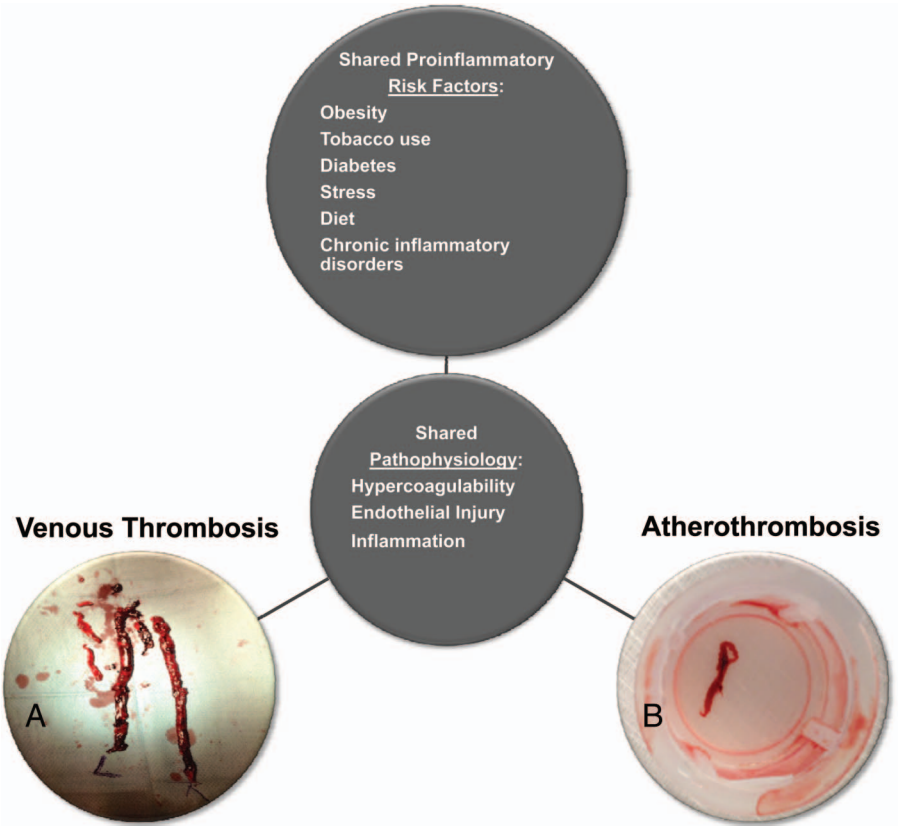

Fig. 1. Venous thromboembolism and atherothrombosis as chronic inflammatory diseases with shared risk factors and pathophysiology.

Large pulmonary embolism removed during open surgical embolectomy (A). Intracoronary artery thrombus aspirated from a patient with acute myocardial infarction (B).

concentrations of rheumatoid factor remained strongly correlated with risk of DVT.

One explanation for these intriguing findings is that rheumatoid factor is an indirect serum marker for chronic low-grade inflammation that may contribute to both hypercoagulability and endothelial injury. Prior work has shown that increased concentrations of the inflammatory mediators tumor necrosis factor-α, IL-6, and IL-8 were potent risk predictors for VTE, even after adjustment for covariates, including CRP *(14)*. Similarly, the current study demonstrates a robust association of rheumatoid factor with VTE even in patients without increased CRP. An alternative explanation is that rheumatoid factor itself contributes to endothelial dysfunction and injury directly, even in the absence of detectable systemic inflammation. In a study of rheumatoid arthritis patients, the presence of rheumatoid factor and anti-CCP (anti–cyclic citrullinated peptide antibodies) was independently associated with impaired endothelial function as measured by reactive hyperemic index *(15)*. In another study in rheumatoid arthritis patients, IL-6 and rheumatoid factor titers were independently predictive of endothelial dysfunction, as determined by serum biomarkers of VCAM-1 (vascular cell adhesion molecule-1), ICAM-1 (intercellular adhesion molecule-1), and ELAM-1 (endothelial leukocyte adhesion molecule) *(16)*.

A major strength of the current study is its large sample size (>54 000 participants) and high quality of follow-up and retention. Particularly impressive, the 2 Copenhagen cohorts did not lose any patients to follow-up over the 368 381 person-years observed. In addition, the authors performed extensive sensitivity analyses to support the study findings. Nevertheless, the homogeneous composition of the study population may limit the ability to generalize the findings to other populations of varying ethnicity and race. Further, by selecting the lowest cutpoint value that revealed a significant association between rheumatoid factor and DVT (≥15 IU/mL), the authors included nearly 17% of the study pop-

ulation in the "rheumatoid factor–positive" group. Such a prevalence of rheumatoid factor seropositivity is much higher than has been previously reported in the Danish general population (4.3% in the Copenhagen City Heart Study, using a more traditional cutpoint for seropositivity of 25 IU/mL) *(17)*. The observation that increased rheumatoid factor concentration was predictive of incident DVT but not PE will require external validation.

The current study adds to the body of evidence supporting inflammation as a critical component in the pathophysiology of venous thrombosis. Additional evidence for the hypothesis that VTE is a chronic inflammatory disease may come from large completed and ongoing randomized controlled trials aimed to reducing thrombotic events by modulating inflammation. In an analysis of the randomized controlled JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study, rosuvastatin 20 mg orally daily reduced the rate of new-onset symptomatic VTE by 43% in an initially healthy population with evidence of chronic systemic inflammation as defined by an increased CRP concentration *(18)*.

Prospective evaluation of VTE is also ongoing in 2 trials directly testing the inflammation hypothesis of atherothrombosis. The Canakinumab Antiinflammatory Thrombosis Outcomes Study (CANTOS) (NCT01327846) is an ongoing randomized placebo-controlled trial of a human monoclonal antibody to IL-1β in 10 000 stable patients following myocardial infarction who have persistently increased high-sensitivity CRP *(19)*. Designed to test the hypothesis that IL-1β inhibition will reduce the primary outcome of myocardial infarction, stroke, and cardiovascular death, CANTOS will also specifically evaluate the impact of inflammatory modulation on VTE. Similarly, the Cardiovascular Inflammation Reduction Trial (CIRT) (NCT01594333), another ongoing randomized placebo-controlled trial, is investigating the use of low-dose methotrexate in 7000 patients with either stable myocardial infarction or multivessel coronary artery disease and either type 2 diabetes mellitus or the metabolic syndrome to test the hypothesis that a commonly used antiinflammatory regimen can prevent atherothrombotic complications of myocardial infarction, stroke, and cardiovascular death *(20)*. CIRT will also assess the impact of antiinflammatory therapy on incident VTE.

The current study provides incremental evidence supporting the hypothesis that chronic systemic inflammation may precede incident VTE. Should either of these large ongoing randomized controlled trials of antiinflammatory therapy demonstrate a reduction in the rate of DVT and PE, VTE may no longer be considered a time-limited disease treated with a few short months of anticoagulation but rather a chronic disorder requiring long-term antiinflammatory therapy.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:*

Employment or Leadership: None declared.
Consultant or Advisory Role: None declared.
Stock Ownership: None declared.
Honoraria: None declared.
Research Funding: EKOS/BTG, Daiichi-Sankyo, and Thrombosis Research Institute.
Expert Testimony: None declared.
Patents: None declared.

References

1. Goldhaber SZ, Piazza G. Optimal duration of anticoagulation after venous thromboembolism. Circulation 2011;123:664–7.
2. Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica 2007;92:199–205.
3. Sogaard KK, Schmidt M, Pedersen L, Horvath-Puho E, Sorensen HT. 30-year mortality after venous thromboembolism: a population-based cohort study. Circulation 2014; 130:829–36.
4. Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med 2003;348:1425–34.
5. Croce K, Libby P. Intertwining of thrombosis and inflammation in atherosclerosis. Curr Op Hematol 2007;14:55–61.
6. Steinhubl SR, Badimon JJ, Bhatt DL, Herbert JM, Luscher TF. Clinical evidence for anti-inflammatory effects of antiplatelet therapy in patients with atherothrombotic disease. Vasc Med 2007;12:113–22.
7. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.
8. Piazza G, Goldhaber SZ. Venous thromboembolism and atherothrombosis. Circulation 2010;121:2146–50.
9. Holmqvist ME, Neovius M, Eriksson J, Mantel A, Wallberg-Jonsson S, Jacobsson LT, et al. Risk of venous thromboembolism in patients with rheumatoid arthritis and association with disease duration and hospitalization. JAMA 2012;308:1350–6.
10. Folsom AR, Lutsey PL, Astor BC, Cushman M. C-reactive protein and venous thromboembolism. A prospective investigation in the ARIC cohort. Thromb Haemost 2009; 102:615–9.
11. Zee RY, Glynn RJ, Cheng S, Steiner L, Rose L, Ridker PM. An evaluation of candidate genes of inflammation and thrombosis in relation to the risk of venous thromboembolism: the Women's Genome Health Study. Circ Cardiovasc Genet 2009;2:57–62.
12. Savchenko AS, Martinod K, Seidman MA, Wong SL, Borissoff JI, Piazza G, et al. Neutrophil extracellular traps form predominantly during the organizing stage of human venous thromboembolism development. J Thromb Haemost 2014;12:860–70.
13. Meyer-Olesen CL, Nielsen SF, Nordestgaard BG. Increased rheumatoid factor and deep vein thrombosis: two cohort studies of 54628 individuals from the general population. Clin Chem 2014;61:XX–XX.
14. Reitsma PH, Rosendaal FR. Activation of innate immunity in patients with venous thrombosis: the Leiden Thrombophilia Study. J Thrombosis Haemost 2004;2: 619–22.
15. Hjeltnes G, Hollan I, Forre O, Wiik A, Mikkelsen K, Agewall S. Anti-CCP and RF IgM: predictors of impaired endothelial function in rheumatoid arthritis patients. Scand J Rheumatol 2011;40:422–7.
16. Dessein PH, Joffe BI, Singh S. Biomarkers of endothelial dysfunction, cardiovascular

risk factors and atherosclerosis in rheumatoid arthritis. Arthritis Res Ther 2005;7: R634–43.
17. Nielsen SF, Bojesen SE, Schnohr P, Nordestgaard BG. Elevated rheumatoid factor and long term risk of rheumatoid arthritis: a prospective cohort study. BMJ 2012;345: e5244.
18. Glynn RJ, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. N Engl J Med 2009;360:1851–61.
19. Ridker PM, Thuren T, Zalewski A, Libby P. Interleukin-1beta inhibition and the prevention of recurrent cardiovascular events: rationale and design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). Am Heart J 2011;162: 597–605.
20. Everett BM, Pradhan AD, Solomon DH, Paynter N, Macfadyen J, Zaharris E, et al. Rationale and design of the Cardiovascular Inflammation Reduction Trial: a test of the inflammatory hypothesis of atherothrombosis. Am Heart J. 2013;166: 199–207.e15.