Venous thromboembolism (VTE) 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 physiopathological 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 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 population 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 lowdose 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.

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