EDITORIAL

Aspirin and the Prevention of Venous Thromboembolism

Richard C. Becker, M.D.

Venous thromboembolism, including deep-vein thrombosis and pulmonary embolism, is a common condition, with an annual incidence of 2 to 3 cases per 1000 in the general population.[1] Although the risk of recurrence is only about 1% per year in patients with a transient risk factor (provoked venous thromboembolism), those with spontaneous events (unprovoked venous thromboembolism) remain at high risk, with a 10% annual recurrence rate after the discontinuation of anticoagulant therapy.[2]

In their systematic overview in 2002, the Antiplatelet Trialists' Collaboration[3] suggested that antiplatelet therapy, predominantly with aspirin, could reduce the risk of venous thromboembolism in patients at high risk, with a relative risk reduction of 39% ($P<0.001$). Aspirin was similarly effective in a study reported in 2000 by the Pulmonary Embolism Prevention investigators,[4] with a 36% relative risk reduction ($P=0.003$) for symptomatic venous thromboembolism, including fatal pulmonary embolism, among 13,356 patients undergoing surgery for hip fractures or elective joint arthroplasty.

In this issue of the *Journal*,[5] Becattini and colleagues report a marked — and perhaps greater than one might have anticipated — reduction in recurrent venous thromboembolism among 402 carefully selected patients with unprovoked events who were randomly assigned to either aspirin (100 mg daily) or placebo and were followed for 2 years (recurrence rate per year, 6.6% vs. 11.2%; hazard ratio, 0.58; 95% confidence interval, 0.36 to 0.93). The adverse-event profile accompanying aspirin treatment was acceptable to most patients and physicians. A majority of the recurrences of venous thromboembolism occurred in the absence of known risk factors; death attributed to pulmonary embolism was infrequent, and major or clinically relevant nonmajor bleeding was rare.

Venous thrombi are characterized by layers of fibrin, platelets, red cells, and leukocytes and occur under conditions of stasis, lowered oxygen tension, oxidative stress, proinflammatory gene up-regulation, and impaired endothelial-cell regulatory capacity (Fig. 1). Although the relative proportion of platelets is low, they play a pivotal role by releasing polyphosphates, microparticles, and proinflammatory mediators and by interacting with neutrophils to generate DNA–histone–granule constituent complexes.[6] These nuclear materials induce platelet adhesion, activation, and aggregation; the expression of factors V and Va and von Willebrand factor; prothrombinase assembly; and thrombin generation. The potential effect of aspirin on one or more of these processes is unknown; however, several groups, including our own, are investigating related questions.

Studies performed by Schulman et al.,[7] Kearon et al.,[8] and Agnelli et al.[9] have shown convincingly that anticoagulant therapy of extended duration, predominantly with warfarin, reduces the risk of recurrent venous thromboembolism by 60 to 90%. Recently published guidelines from the American College of Chest Physicians[10] highlight the importance of considering both risk for recurrence at baseline and major bleeding. Among patients with a first unprovoked event, the projected absolute difference in recurrent venous thromboembolism between patients with 5 years of treatment and patients with no extended anticoagulation is 264 (10 fatal), with differences of 24 (3 fatal) major bleeding episodes per 1000 treated for those at low risk for bleeding, 29 (5 fatal) for those at intermediate risk, and 98 (11 fatal) for those at high risk. After a second unprovoked

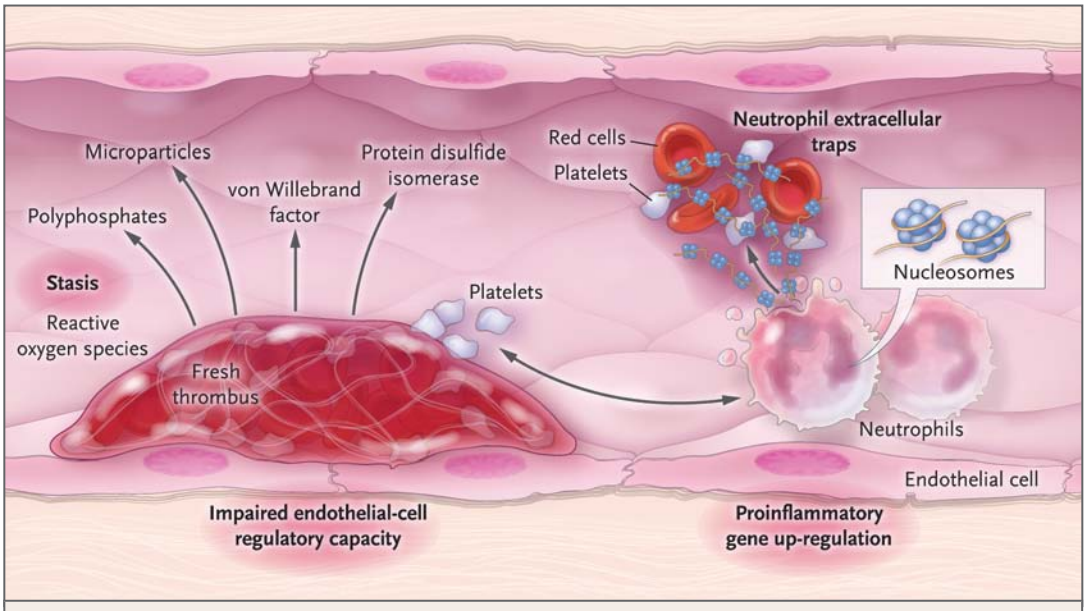

Figure 1. **The Vascular, Rheologic, Biochemical, and Molecular Environment after Deep-Vein Thrombosis.**

event, recurrent venous thromboembolism may be reduced by as many as 396 events (14 fatal) per 1000 patients treated.

On the basis of the available evidence, patients with unprovoked venous thromboembolism who are at low-to-moderate risk for bleeding are expected to derive the greatest overall benefit from extending anticoagulant therapy. The findings of the Aspirin for the Prevention of Recurrent Venous Thromboembolism (the Warfarin and Aspirin [WARFASA]) study are compelling and may signal an important step in the evolution of care; however, confirmatory studies will be required to establish a role in daily clinical practice for the use of aspirin among patients who are at high risk for bleeding due to anticoagulant therapy or for whom ongoing investigations identify and subsequently validate a clinical or biomarker-based profile associated with a low risk of recurring venous thromboembolism. The ongoing Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) study (Australian New Zealand Clinical Trials Registry number, ACTRN012605000004662) has recruited 822 patients with a first unprovoked event, as documented by means of objective testing, who have received warfarin anticoagulant therapy for 3 to 6 months (but not longer than 12 months). Patients have been randomly assigned to either aspirin (100 mg daily) or placebo for a median of 3 years and are being followed for a first occurrence of symptomatic and objectively confirmed deep-vein thrombosis or nonfatal or fatal pulmonary embolism with the use of an intention-to-treat approach. Results of this study are expected during 2012. A prospectively planned combined analysis of the ASPIRE and WARFASA trials (ACTRN12611000684921) may provide more reliable evidence of the effect of aspirin in patients with first unprovoked venous thromboembolism.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Duke Clinical Research Institute, Duke University Medical Center, Durham, NC.

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