

ADVANCES IN HEMATOLOGY

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The Reemergence of Aspirin for the Prevention of Venous Thromboembolism

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H&O Historically, what was the role of aspirin in the prevention of venous thromboembolism (VTE)?

JE I think it is fair to say that prior to 1994 there was considerable uncertainty about aspirin's role in the prevention of VTE. From a mechanistic perspective, many hematologists thought that aspirin would not be effective for prevention of venous thrombosis because aspirin inhibits platelets, which are believed to play a more important role in arterial thrombosis than venous thrombosis. Venous thrombi are fibrin-rich and platelet-poor, and thus it was believed that anticoagulants were required for VTE prevention.

In 1994, the Antiplatelet Trialists' Collaboration (APTC) published a meta-analysis which demonstrated that antiplatelet therapy (primarily aspirin) reduced the risk of deep vein thrombosis and pulmonary embolism by about one-third across a wide range of surgical and medical patients. Physicians interpreted these results in 1 of 2 ways. Orthopedic and other surgeons embraced the results, and some adopted aspirin as standard therapy for prevention of VTE in patients undergoing major orthopedic surgery. Other physicians dismissed the results, citing the methodologic limitations and the small size of the trials included in the meta-analysis. Lingering controversy concerning the efficacy of aspirin for prevention of VTE prompted the design and conduct of the PEP (Pulmonary Embolism Prevention) trial, the largest ever

randomized thromboprophylaxis trial. The PEP trial was performed in Europe, South Africa, Australia, and New Zealand and tested the hypothesis that aspirin is effective for the prevention of VTE in patients undergoing major orthopedic surgery. Although the study took about a decade to complete, the results conclusively confirmed the benefits of aspirin for prevention of VTE, with results that were completely consistent with those of the 1994 APTC meta-analysis.

H&O How has aspirin been used for arterial clots?

JE In contrast to venous disease, aspirin has had a clearly established role for the prevention of first-ever and recurrent arterial thrombosis in patients with a history of arterial events and those with multiple risk factors who have not yet experienced an event. Consequently, aspirin has become the cornerstone of management of patients with acute arterial thrombotic events, including coronary, cerebral, and peripheral artery disease, both during the acute phase and the long-term.

H&O Why has the use of aspirin in the prevention of VTE been controversial?

JE Orthopedic surgeons are keen to use aspirin because it is effective, the treatment is simple and inexpensive, and it is relatively safe. The low risk of bleeding with

aspirin is probably the single most important reason it is used because surgeons often attribute less than optimal wound healing and joint function to bleeding caused by anticoagulant prophylaxis. Many nonsurgeons (internists, hematologists, thrombosis physicians) believe that even if aspirin works, it is so much less effective than anticoagulants that it should not be used. Physicians are also inclined to dismiss concerns by the surgeons regarding bleeding. There are no data to support either the claim by surgeons that anticoagulants are associated with worse functional outcomes or the claim by physicians that this is not so. The conclusion by physicians that aspirin is less effective than anticoagulants for prevention of VTE is based on the results of a limited number of small, randomized controlled trials that demonstrated a lower rate of asymptomatic deep vein thrombosis with anticoagulants compared to aspirin. The trial results are, however, inconclusive concerning the effects of anticoagulants compared to aspirin for prevention of symptomatic VTE.

H&O What do current data suggest about the role of aspirin in VTE prevention?

JE The PEP study data were published in 2000, and there have been no new data since this time. Critics of the study have raised concerns that patients were given other forms of prophylaxis, such as stockings and anticoagulants, in addition to randomized treatment with aspirin or placebo. The PEP results indicate, however, that aspirin was effective for VTE prevention irrespective of whether patients received stockings or anticoagulants. The American College of Chest Physicians (ACCP) guidelines for the prevention of VTE adopted the position that aspirin is likely to be less effective than other types of antithrombotic prophylaxis and thus recommended against the use of aspirin for this indication.

What has changed in 2012? The most recent iteration of the ACCP guidelines takes a different view of the aspirin data than that of the 2008 guidelines and provides a clear message that aspirin is effective for the prevention of VTE.

H&O How does aspirin compare to anticoagulants?

JE The only comparisons we have are from small studies that have provided inconclusive results concerning the efficacy and safety of aspirin compared with anticoagulants for the prevention of venous thromboembolic events that matter for patients (ie, symptomatic events).

We need new trials to obtain reliable estimates of the efficacy, safety, and net clinical benefit of aspirin compared with anticoagulants for prevention of symptomatic VTE and major bleeding. Ideally, the trials will also measure the effect of aspirin compared with anticoagulants on quality of life and be properly powered for death because these are the only outcomes that ultimately matter for the patient. However, we are not very good at measuring quality of life, and mortality trials will need many thousands of patients, which may not be feasible.

Further support for the effectiveness of aspirin in inhibiting venous thrombi comes from the recently presented WARFASA (Warfarin and ASA: Aspirin after Six Months of Oral Anticoagulants for the Prevention of Recurrent VTE and CV Events in Patients with Idiopathic VTE) trial results, which demonstrated that “aspirin compared with placebo reduced the risk of recurrent VTE by 40% in patients who had completed initial treatment with a parenteral anticoagulant followed by a vitamin K antagonist.”

H&O Which patients are most likely to benefit from aspirin for the prevention of VTE?

JE The only comprehensive assessment of prevention of VTE with aspirin has been in patients with hip fracture. For these patients, there is a very clear benefit of aspirin compared with placebo. At McMaster, hip fracture patients routinely receive aspirin after the initial in-hospital treatment with an anticoagulant. The aspirin regimen is 162 mg/day, started at the completion of in-hospital anticoagulant therapy and continued until day 30–35 after surgery. Aspirin might also benefit other high-risk patients, but this remains unproven.

Suggested Readings

Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet*. 2000;355:1295-1302.

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