

## Aspirin for Long-Term Prevention of Recurrent Venous Thromboembolism?

Brighton TA, Eikelboom JW, Mann K, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med* 2012;367:1979–87.

### Study Overview

**Objective.** To determine if low-dose aspirin can prevent recurrence of unprovoked venous thromboembolism (VTE)

**Design.** Randomized double-blind trial of aspirin 100 mg versus placebo, called the Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE). Randomization was stratified by the duration of oral anticoagulant therapy ( $\leq 26$  weeks or  $> 26$  weeks). Patients were instructed to take the medication for at least 2 years and were followed for up to 4 years after randomization.

**Setting and participants.** 822 patients in 56 clinical sites in 5 countries who had their first unprovoked VTE less than 2 years prior to enrollment and completed a course of anticoagulant therapy for at least 6 weeks but no longer than 24 months. Patients were eligible if they were  $\geq 18$  years of age and had their first objectively determined acute pulmonary embolism (PE) or a symptomatic deep vein thrombosis (DVT) in the popliteal vein or a vein more proximal. Patients were excluded if they had another indication or contraindication for aspirin, other

antiplatelet therapy, or a nonsteroidal anti-inflammatory medication; had another indication for continuation of an oral anticoagulant; had other medical problems that would interfere with study participation or life expectancy; or had any of the following risk factors in the 2 months prior to their diagnosis that could provoke a VTE: bed confinement  $> 1$  week, major surgery, cast after trauma, pregnancy, or the use of oral contraceptives or hormone replacement therapy. To assess for recurrence, research staff instructed patients to contact them if they had any symptoms of recurrent VTE or adverse events. Further, patients were examined in person 1 month after randomization and every 6 months thereafter and were contacted by phone or email midway between each visit. Patients with prior DVTs had ultrasounds within 1 month after randomization as a baseline to evaluate for residual thrombus, from which research staff could compare subsequent evaluations if symptoms developed.

**Main outcome measures.** Recurrence of VTE was the primary outcome. A composite of major vascular events (VTE, myocardial infarction, stroke, or cardiovascular

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death) was a secondary outcome. An independent committee unaware of treatment assignment adjudicated the outcomes.

**Main results.** Mean age was 54 and 55 years respectively for the placebo and aspirin groups, and over one-half of subjects were male. 34% and 39% were obese (BMI  $\geq 30$  kg/m<sup>2</sup>), 56% and 57% had a DVT only, 29% and 27% had a PE only, and 14% in each arm had both. For prior anticoagulation therapy, the large majority received warfarin; 16% and 15%, respectively, received another anticoagulant (another vitamin K antagonist, direct thrombin inhibitor, or factor Xa inhibitor); and 1% in each arm received low-molecular-weight heparin. After a median follow-up duration of 37.2 months, 14% (57 of 411) in the aspirin group and 18% (73/411 patients) in the placebo group had a recurrent VTE, with a hazard ratio of 0.74 (4.8% rate of recurrence annually for aspirin vs. 6.5% annually for placebo, 95% confidence interval [CI], 0.52–1.05,  $P = 0.09$ ). After adjustment for age, sex, BMI, smoking history, type of VTE, and duration of initial anticoagulation, the hazard ratio was 0.72 for aspirin (95% CI, 0.51–1.01,  $P = 0.06$ ). 70% of recurrent DVTs, without PEs, occurred in subjects who had only a DVT prior to enrollment; 73% of the recurrent PEs occurred in subjects who had a PE prior to enrollment. Recurrence was highest in the first year of follow-up. 23% of recurrent VTEs occurred more than 7 days after the subject had discontinued the study drug. Subjects randomized to aspirin had a lower rate of recurrence while they were taking the study drug compared with those in the placebo group (event rate of 4.8% per year compared with 7.6% per year with placebo, hazard ratio 0.65, 95% CI 0.44–0.96,  $P = 0.03$ ). The secondary composite outcome was lower in the aspirin group (88 patients in the placebo arm, 62 in the aspirin arm, hazard ratio 0.66, 95% CI 0.48–0.92,  $P = 0.01$ ). Major bleeding occurred in 6 patients in the placebo group and 8 in the aspirin group.

**Conclusion.** After initial anticoagulation treatment, use of low-dose aspirin for a first unprovoked VTE lowers major vascular events and may lower recurrent VTE if patients are adherent.

### Commentary

The risk of recurrence after a first unprovoked DVT or PE can be as high as 20 events per 100 person-years in

the initial months after the completion of initial anticoagulation therapy, followed by a long-term recurrence of approximately 5 events per 100 person years [1–3]. Guidelines now typically recommend that patients continue indefinitely on anticoagulation after an unprovoked VTE [4]. Lifelong anticoagulation is a difficult proposition for some patients, and finding an easier prevention strategy would be desirable. Some prior studies have examined the role of using laboratory testing, such as a D-dimer, to stratify people after initial anticoagulation into high- or low-risk groups for recurrent VTE. One recent meta-analysis of over 1000 patients found that patients with a positive D-dimer had a higher rate of recurrent VTE (8.8 per 100 patient-years compared to 3.7 per 100 patient-years with negative D-dimer, hazard ratio 2.59, 95% CI 1.90–3.52) [5]. However, additional treatments that might be more tolerable for patients to use long term would be helpful.

This study by Brighton et al does not by itself provide a conclusive answer to the question of whether alternate therapies exist. The primary outcome in this study, recurrent VTE, was not statistically different between the aspirin and placebo treatment groups. Subjects randomized to receive aspirin did have lower recurrent VTEs than the placebo group when they were taking the study drug, and those taking aspirin also had a lower rate of the composite major vascular event secondary endpoint (which included VTE, myocardial infarction, stroke, and cardiovascular death). Authors attribute the lack of finding a difference in the primary endpoint to the study's lack of power, the primary limitation of this study. This study was initially intended to enroll 3000 patients, but low enrollment led to a reduced study goal of 1500 subjects. Eventually, further declines in enrollment and limited study resources led the study leadership to stop enrollment at 822. Further, the planned follow-up for this reduced sample was somewhat restricted by the publication of another similar study, the Warfarin and Aspirin trial (WARFASA), in March 2012 [6].

To address this obvious limitation in power, the ASPIRE study leadership designed the study to be joined with WARFASA in a pre-planned meta-analysis after the completion of each study. By combining the study with WARFASA, they sought to protect against the possibility that ASPIRE would be underpowered for find a difference in the primary outcome. WARFASA was a study of 402 patients with first unprovoked VTE treated with

aspirin 100 mg daily vs placebo for a median study duration of 24.6 months. In that study, subjects taking aspirin had a lower rate of recurrence, with 28 of 205 aspirin-treated patients having a VTE compared with 43 of 197 placebo-treated patients (event rate of 6.6% vs. 11.2% annually, hazard ratio 0.58, 95% CI 0.36–0.93). This event rate was higher than in ASPIRE, with an event rate in the aspirin-treated group equal to that of the placebo group in WARFASA. WARFASA did not find a significant reduction in the composite of all major vascular events. When the WARFASA and ASPIRE results were combined, VTE occurred in 85 of 616 aspirin-treated patients compared with 116 of 608 placebo-treated patients (hazard ratio 0.68, 95% CI 0.51–0.90,  $P = 0.007$ ). The major vascular event rate also was significantly lower in the aspirin-treated group. In each of these studies, including the combined results from the meta-analysis, bleeding rates were not different for patients taking aspirin or placebo.

The remedy for ASPIRE's primary limitation is a reasonable one. The planned meta-analysis of ASPIRE and WARFASA was predetermined, and the structure of the studies was, by design, quite similar, allowing for an easy combination. The balance of evidence based on these studies strongly suggests that aspirin has some role in the prevention of recurrent VTE. While it is clear that lifelong anticoagulation is the best strategy to prevent recurrent VTE [7], aspirin is an alternative for those patients who either cannot use anticoagulation or will not [2]. And, with ASPIRE and WARFASA, clinicians now have substantial evidence to help decision-making regarding long-term therapy after an unprovoked DVT. Physicians can recommend lifelong anticoagulation as the most effective choice for preventing recurrence and aspirin as a second choice. Testing with D-dimer may provide some information that helps patients make this choice, especially if they are disinclined to use an oral anticoagulant long term. Further useful evidence would be a study that combines strategies, such as determining whether risk-stratification with a D-dimer post-initial treatment, with aspirin used for those at low risk and anticoagulation for those at high risk, is an effective approach for

reducing bleeding rates associated with anticoagulation while preserving low rates of recurrence. Such a study would be difficult because of the need for a large sample size in the low-risk group, especially because of aspirin's only modest effect size in lowering recurrent VTE rates. But this type of approach, even if not endorsed by a trial, could be a useful construct to present to patients considering their long-term choices.

### Applications for Clinical Practice

While results from ASPIRE were not particularly robust, the combination of evidence from ASPIRE and WARFASA demonstrates that treatment with low-dose aspirin after an unprovoked VTE modestly lowers the rates of recurrent VTE. Clinicians can use this information in discussions with patients about the risks and benefits of lifelong anticoagulation or aspirin therapy, and they may choose to use other adjunctive information such as a D-dimer to help with this decision.

—Jason P. Block, MD, MPH

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