Aspirin in secondary prevention of recurrent venous thromboembolism

Kochawan Boonyawat · Mark A. Crowther

Aspirin in venous thromboembolism

Aspirin is well established in its efficacy for secondary prevention of arterial thrombosis [1]. In venous thrombosis, however, several early studies failed to demonstrate a beneficial effect during aspirin use for the prevention of venous thromboembolism (VTE). However these early studies were, in general, small and thus may have lacked power to detect the efficacy of aspirin for the prevention of VTE.

The first convincing evidence to the efficacy of aspirin for VTE prevention was a meta-analysis from the Antiplatelet Trialists’ Collaboration. This study included more than 8000 patients from 53 randomized trials of antiplatelet thromboprophylaxis including patients undergoing general surgery, orthopedic surgery and high risk medical patients [2]. This trial found that antiplatelet therapies (mostly aspirin) were associated with a significant reduction in the incidence of VTE (reduction 39 %; P = 0.00001) without a significant increase in the risk of major or fatal bleeding.

Subsequently, the Pulmonary Embolism Prevention (PEP) trial confirmed the efficacy of antiplatelet agents for primary prevention of VTE [3]. This trial studied 13,356 patients undergoing orthopedic surgery, randomized one group of patients to receive aspirin prophylaxis and another group to placebo. In the aspirin group, there was a reduction in VTE of 36 % (P = 0.003) and no difference in fatal bleeding compared with placebo group. From the promising results of these two trials along with growing evidence supporting the role of platelet activation in VTE [4], aspirin has subsequently been studied for secondary prevention for VTE.

Aspirin for secondary prevention of venous thromboembolism

The first trial to demonstrate the efficacy of aspirin in secondary prevention of VTE was conducted in the 1980’s. This study was the small prospective randomized controlled trial that studied 38 patients for recurrent VTE and compared combination of dipyridamole 100 mg a day and aspirin 1200 mg a day with placebo. Recurrent venous thrombosis occurred with significantly lower frequency in the treatment group (5.3 vs 36.8 %) (P < 0.05) [5].

Recently, two large studies confirmed that aspirin is effective for secondary prevention of VTE. The first was the WARFASA study [6] that studied 403 patients who had been treated with warfarin for 6–18 months for a first episode of symptomatic unprovoked VTE. This study excluded patients with previous symptomatic complication of atherosclerosis requiring treatment with aspirin. After warfarin discontinuation, patients were randomized to aspirin 100 mg or a placebo group. During a median follow-up period of 24.6 months, recurrent VTE occurred in 28/205 (6.6 % per year) patients in the aspirin group and 43/197 (11.2 % per year) in patients in the placebo group (Hazard ratio 0.58; 95 % CI 0.36–0.93; P = 0.02). While taking the study drug, 23 patients in the aspirin group and 39 patients in the placebo group had a recurrence (5.9 vs 11 % per year; hazard ratio 0.55; 95 % CI 0.33–0.92; P = 0.02). Non-fatal major bleeding occurred in one
patient in each group. Non major bleeding occurred in three patients in each group. This study thus found that aspirin was effective for the secondary prevention of VTE with no difference in major bleeding compared to placebo. However, this study failed to demonstrate a significant reduction in the rate of major cardiovascular events, a well-known effect of aspirin, likely due to inadequate power and a short period of follow-up.

The second trial, the ASPIRE study [7], was a multi-center study that enrolled 822 patients with unprovoked symptomatic VTE who had completed anticoagulation treatment, and randomized the patients to an aspirin 100 mg group or a matching placebo group. This trial was pre-designed to combine results with the WARFASA study; thus the studies had similar eligibility criteria. With a median duration of follow-up of 37.2 months, there was no significant difference in recurrent VTE rates between the study groups. Recurrent VTE occurred in 57/411 (14 %) patients in the aspirin group and 73/411 (18 %) patients in the placebo group (a rate of 4.8 % per year vs 6.5 % per year; hazard ratio with aspirin 0.74; 95 % CI 0.52–1.05; P = 0.09). However, secondary outcomes [major vascular events (a composite of VTE, myocardial infarction, stroke, or cardiovascular death)] were significantly reduced in the aspirin group (a rate of 5.2 % per year for aspirin group vs 8 % per year for placebo group; hazard ratio with aspirin 0.66; 95 % CI 0.48–0.92; P = 0.01). The rate of all bleeding episodes was not significantly different between the study groups. The results of this study confirmed the role of aspirin for reduction of major vascular events but not for recurrent VTE.

A pre-planned analysis incorporating the results of the WARFASA and ASPIRE trials using patient-level data was conducted [8]. A total of 1224 patients were analyzed. Patients in the WARFASA study were older, more likely to be male and be a smoker, but less likely to be obese. Median follow-up period was 30.4 months. During the follow-up period, recurrent VTE occurred in 81/616 (13.1 %) patients in the aspirin group and 112/608 (18.4 %) patients in the placebo group (a rate of 5.1 % per year vs 7.5 % per year). There was a 32 % relative reduction in VTE (Hazard ratio 0.68; 95 CI 0.51–0.90; P = 0.008). After adjustment for baseline characteristics, the hazard ratio was similar (0.65; 95 % CI 0.49–0.86; P = 0.003). The calculated number need to treat in each year was 42 patients to prevent one VTE event. For secondary outcomes, aspirin reduced the risk of major vascular events by 34 %. There were no significant difference in the rate of bleeding.

The results of this meta-analysis demonstrate that aspirin is an attractive option for patients with unprovoked VTE with no previous history of coronary heart disease who wish a non-oral anticoagulant option for extended VTE treatment. Whether aspirin has efficacy for venous prophylaxis in patients with coronary heart disease is unknown.

A retrospective cohort study [9], reviewed 1919 clinical charts of patients with a first episode of provoked or unprovoked VTE and examined a follow-up period averaging 4 years after discontinuing anticoagulants. Of the 1919 patients 256 (13.3 %) had a history of symptomatic atherosclerosis. All of these patients received aspirin at doses ranging between 80 and 160 mg once daily after discontinuing warfarin. The remaining 1663 patients without a history of symptomatic atherosclerosis were left without any antithrombotic treatment. Patients with atherosclerosis were older, more likely to be male and had a higher prevalence of unprovoked VTE. During follow-up, recurrent VTE was diagnosed in 44/256 (17.2 %) patients with a history of symptomatic atherosclerosis who were given aspirin and in 330/1663 (19.8 %) in those who were not given aspirin and who did not have a history of atherosclerosis (Hazard ratio after adjustment for age, sex and duration of anticoagulant 0.92; 95 % CI 0.66–1.27). The analysis in the subset of patients with unprovoked VTE showed a similar result (Hazard ratio 0.82; 95 % CI 0.56–1.21). Bleeding events were not presented. Although this study failed to identify a beneficial decrease in recurrent VTE, the treatment groups in the observational study were inherently unequal. The risk of recurrent VTE in an untreated population with atherosclerosis remains unknown.

**From clinical trials to clinical practice**

In patients with unprovoked VTE the rate of recurrent VTE after discontinuing anticoagulant therapy is high [10–13]. Recurrent VTE can be fatal [14]. It increases the risk of post thrombotic syndrome which effects the quality of life of patients [15, 16]. How additional factors (such as residual clot on ultrasound and the d-dimer level) impacts the risk of recurrence, and how such factors are best used in deciding how patients should be treated requires additional study [17–20].

Extended anticoagulant treatment with warfarin or one of the target specific oral anticoagulants (TSOACs) has been shown to effectively reduce the rate of recurrent VTE by up to 90 % compared with placebo [21–23]. However, extended warfarin treatment is associated with inconvenience for patients because of the need for frequent blood monitoring, and warfarin is associated with intracranial bleeding. TSOACs are expensive and of limited availability in some jurisdictions. They also cause bleeding, although at a rate lower than the seen with warfarin [24]. Although aspirin seem to be less effective than these agents
for secondary prevention of VTE (reducing the rate of recurrence by about 32%) it is simple to use, widely available, few clinical significant drug interactions, not reliant upon renal elimination, does not require blood monitoring and did not increase major bleeding compared with placebo.

In summary, initiating aspirin for secondary VTE prophylaxis after anticoagulant discontinuation is an attractive option for selected patients who had a first unprovoked VTE, particularly those with no previous history of atherosclerosis and who wish to discontinue oral anticoagulants. In patients with additional risk factors for recurrent VTE, or vascular disease, extended treatment with warfarin or TSOACs should be considered. The role of adding aspirin to such patients, particularly those with vascular disease, requires additional study.

References