Editorial

Does aspirin have a role in preventing unprovoked recurrent thromboembolism?

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Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a frequently recurring and serious complication after cessation of anticoagulant therapy. Several studies indicate that 10 years after cessation of anticoagulant therapy the risk of recurrent VTE is 39.9% and nearly 50% for unprovoked VTE.[1]

Administration of vitamin K antagonists has been shown to be effective in reducing the risk of recurrent VTE but does not increase survival rate. Cessation of anticoagulants before the recommended time is frequently due to the increasing risk of hemorrhage upon long-term use. To attain the recommended international normalized ratio (INR), laboratory investigation and adjustment of dosage are required.[2]

Aspirin retards platelet aggregation by inhibiting cyclooxigenase-1. Low-dose aspirin is inexpensive and readily available, and does not require laboratory monitoring to evaluate its effectiveness. This drug has been shown to be effective for prevention of arterial vascular events and for primary prevention of VTE in high-risk patients.[3,4]

The recently published results of the Warfarin and Aspirin (WARFASA) study[5] show that aspirin presumably plays a role in reducing the recurrence risk of unprovoked VTE following a first-ever unprovoked VTE after cessation of oral anticoagulant therapy, without increasing the risk of major hemorrhage. This multicenter investigator-initiated double blind placebo-controlled trial was carried out on patients with first ever unprovoked VTE who had completed oral anticoagulant therapy for 6 to 18 months. The patients were randomly assigned to either aspirin 100 mg/day (N= 205) or placebo (N= 197) with the option to extend the duration of the study (median study duration 24.6 months). The results of this study showed that the percentage of VTE recurrences in the group receiving aspirin was lower than that in the placebo group (6.6% vs 11.2% per year; hazard ratio = 0.58; 95% confidence interval [CI]= 0.36 – 0.92). Adverse events were similar in both groups. The investigators acknowledge that this study was underpowered to be able to demonstrate an effect of aspirin on the incidence of ischemic heart disease or cardiovascular disease. Therefore the results of this study cannot be applied to patients who require aspirin for prevention of arterial events.

A systematic review comprising 17 studies showed that the mean incidence of arterial cardiovascular events per patient-year was higher in patients with unprovoked VTE (0.46%; 95% CI=0.34 – 0.59), in comparison with provoked VTE (0.35%; 95% CI=0.24 – 0.49).[6]

A meta-analysis conducted on 6 studies showed that the risk of arterial cardiovascular events was higher in patients with unprovoked VTE than in controls (incidence rate ratio [IRR]= 1.87;

95% CI=1.32-2.65] or in patients with provoked VTE (IRR=1.86; 95% CI=1.19 – 2.89). These studies showed that patients with unprovoked VTE were at higher risk for arterial cardiovascular events in comparison with controls or patients with provoked VTE after long-term follow-up.[6] The Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE)[7] trial aimed to look for recurrences after first-ever unprovoked VTE. This study also included patients with major vascular events and had a median study duration of 37.2 months. The patients received either aspirin 100 mg/day (n=411) or placebo (n=411). The results of this study demonstrated a lower VTE recurrence in the aspirin group as compared with the placebo group. However, the decrease was statistically not signuificant (4.8% vs 6.5% per year; hazard ratio of aspirin = 0.74; 95% CI=0.52 – 1.05; P=0.09). In comparison with placebo, aspirin significantly reduced the rate of the two prespecified secondary composite outcomes. Venous thromboembolism, myocardial infarction, stroke, or cardiovascular mortality decreased up to 34% (aspirin 5.2% vs placebo 8.0% per year; hazard ratio of aspirin = 0.66; 95% CI=0.48 – 0.92; P=0.01) and VTE, myocardial infarction, stroke, major bleeding, or all-cause mortality decreased up to 33% (hazard ratio = 0.67; 95% CI=0.49 – 0.91; P=0.01). No statistically significant difference was found between the two groups with regard to bleeding and other serious adverse effects. In this study aspirin did not significantly reduce VTE recurrence in comparison with placebo, but significantly reduced major vascular events. This study supports the benefit of aspirin therapy in preventing first-ever unprovoked VTE when administered to patients after initial anticoagulant therapy.

The WARFASA and ASPIRE trials provide evidence of the benefit of aspirin in the prevention of unprovoked VTE, with the added of advantage of preventing major vascular events. Apart from these studies, the Guidelines on Antithrombotic Therapy and Prevention of Thrombosis issued by the American College of Chest Physicians (2012) recommend that patients with first-ever unprovoked VTE should be given oral anticoagulants for at least 3 months, targetting an international normalized ratio (INR) of 2.0 - 3.0. The decision for continuation or cessation of anticoagulants after this period should be made for each patient individually and balanced againts his or her hemorrhagic risk.[2]

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