Randomised controlled trial

Aspirin given for up to 2 years after initial anticoagulant treatment reduces the risk of venous thromboembolism recurrence without increasing risk of major bleeding

Henry G Watson

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Department of Haematology, Aberdeen Royal Infirmary, Foresterhill Health Campus, Aberdeen, UK

Correspondence to:
Dr Henry G Watson
Department of Haematology, Aberdeen Royal Infirmary, Foresterhill Health Campus, Aberdeen AB25 2ZN, UK;
henrywatson@nhs.net

Implications for practice and research

- The use of aspirin to prevent recurrent venous thromboembolism (VTE) after a first idiopathic event should not currently become a standard practice.
- Further studies are required before the use of aspirin following anticoagulation with warfarin for a first episode of venous thromboembolism becomes adopted as routine clinical practice.
- A direct comparison between low-dose aspirin and standard intensity warfarin is required.

Context

Venous thromboembolism, which encompasses deep vein thrombosis and pulmonary embolism, is a relatively common disorder with an incidence in western countries of around 1/1000 per annum.[1] Events are categorised as either provoked, that is occurring in the context of a known temporary risk factor such as surgery, or unprovoked, that is occurring without an associated known risk factor. There is a general consensus that provoked events have a low risk of recurrence and should be treated for a finite period of anticoagulation. However, unprovoked events have a higher rate of recurrence (8–10% per annum) following discontinuation of anticoagulation.[2]

This high rate of recurrence has prompted debate around the optimal duration of anticoagulant therapy for this group of patients. The dilemma is that prolonged anticoagulation reduces the risk of recurrent thrombosis while increasing the risk of bleeding events including potentially fatal intracranial bleeding. Efforts to resolve this dilemma have two main approaches. The first is to identify patient features and markers that predict risk of recurrence. The second is to continue thromboprophylaxis using less intense anticoagulation in anticipation that this might confer a benefit in terms of reducing thrombosis recurrence without significantly increasing the risk of bleeding. Previous investigation into such an approach using low-intensity anticoagulation with warfarin (aiming for an international normalised ratio of 1.5–2) showed that although there appeared to be a benefit for low intensity warfarin it was inferior to conventional intensity warfarin with no reduction in major bleeding.[3 4]

Methods

This randomised controlled study compared aspirin 100 mg once daily with placebo in a group of patients with a first episode of unprovoked venous thromboembolism, who had completed an adequate period of anticoagulation with warfarin.[5] The rationale for using aspirin is based on the analysis of large studies of patients taking aspirin for other defined indications which reported a 20% reduction in VTE (as an additional benefit). The primary efficacy endpoint was objectively confirmed venous thromboembolism; the primary safety outcome was major bleeding.

Findings

Patients (n=402) were randomised to aspirin or placebo. The median duration of treatment was 23 months. Venous thromboembolism recurred in 28 of 205 patients taking aspirin compared with 43 of 197 patients taking placebo (6.6% vs 11.2% per annum HR 0.58 95% CI 0.36 to 0.93). One patient in each group had a major haemorrhage. The authors concluded that low-dose aspirin reduces the risk of recurrence when given to patients with a first episode of unprovoked venous thromboembolism, apparently without an increased risk of major bleeding.

Commentary

The study was adequately powered, the clinical endpoints are appropriate and the definition of major bleeding is one which is generally accepted. Criticism of the study might be that it recruited very slowly suggesting some selection bias of patients, it excluded patients who had experienced bleeding while on warfarin (who may also be at a higher risk of bleeding on aspirin) and it excluded patients with 'clinically significant thrombophilia' although this was not further defined.

So should aspirin be used to reduce recurrence in this group of patients? The answer is possibly. Before this is adopted as routine clinical practice it would require a further high-quality clinical study to confirm these findings. It would also be optimal to see a comparison made between continued anticoagulation with

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warfarin at normal intensity and low-dose aspirin. Therefore, there are several possible options that may be considered for patients deemed to be at high risk of recurrent VTE following an initial period of anticoagulation. Reproduction of data such as these would confirm that low-dose aspirin is one of them.

Competing interests None.

References

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