VTE: Aspirin for prolonged prophylaxis after anticoagulation ceases

People who have experienced venous thromboembolism (VTE) are at risk of it recurring. NICE guidance recommends treatment with an anticoagulant drug for 3 months, or longer in some circumstances. A pre-specified meta-analysis of 2 RCTs suggests that using low dose aspirin for prolonged VTE prophylaxis when anticoagulation is completed can further reduce the risk of recurrence of VTE and of major vascular events, compared with placebo. The appropriateness of aspirin for an individual person will depend on an assessment of their particular risks of VTE, vascular events and bleeding.

Overview and current advice

People who experience an episode of venous thromboembolism (VTE) are at risk of it recurring. Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing (NICE clinical guideline 144) advises that they should be offered treatment with an anticoagulant drug for a period after the VTE, usually 3 months.

The risk of recurrence of VTE after anticoagulant therapy ceases is high after an unprovoked VTE. NICE clinical guideline 144 advises that anticoagulant treatment beyond 3 months should be offered to people with an unprovoked pulmonary embolism (PE) and should be considered in people with unprovoked deep vein thrombosis (DVT). The decision on whether to extend anticoagulant treatment, and its duration, should take into account the person's risk of VTE recurrence and of bleeding.

See the NHS Evidence topic page on venous thromboembolism for a general overview of the condition. The NICE Pathway: venous thromboembolism brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence

A multicentre, double blind, randomised controlled trial (RCT), the ASPIRE study, evaluated the use of aspirin for long-term prophylaxis in 822 adults with unprovoked VTE who had received anticoagulation...
therapy with warfarin for 6 weeks–24 months (6–12 months treatment was recommended). Participants were randomised in equal numbers to receive aspirin 100 mg once daily or placebo for up to 4 years (median 37.2 months). The method used for treatment allocation means that this would have been concealed. The authors of the ASPIRE study also conducted and reported a pre-planned meta-analysis of their study and the WARFASA study.

The primary outcome of the ASPIRE study was VTE recurrence, defined as a composite of fatal or nonfatal PE, or symptomatic, objectively confirmed DVT. In the intention to treat (ITT) analysis, this risk was not reduced to a statistically significant extent by aspirin compared with placebo (hazard ratio [HR] 0.74, 95% confidence interval [CI] 95%CI 0.52 to 1.05, p=0.09). Aspirin did statistically significantly reduce the risk of the prespecified secondary outcome of major vascular events (VTE, myocardial infarction [MI], stroke or death from cardiovascular causes; HR 0.66, 95%CI 0.48 to 0.92, p=0.01).

Aspirin did not lead to a statistically significant increase in the risk of clinically relevant bleeding, defined as major bleeding or bleeding which required discontinuation of the study drug for more than 14 days (HR 1.73, 95%CI 0.72 to 4.11, p=0.22). (Major bleeding was defined as bleeding that: caused a decrease in haemoglobin of 2 g/dl or more; or required transfusion of 2 or more units of blood; or occurred in a critical site; or was disabling, required surgery or contributed to death).

The pre-specified meta-analysis looked at the effect of aspirin on ‘net clinical benefit’ – that is, a composite of VTE, MI, stroke, major bleeds, or death from any cause. It found a statistically significant benefit from aspirin compared with placebo (HR 0.67, 95%CI 0.49 to 0.91, p=0.01).

ASPIRE recruited far fewer people than originally intended and was not powered to detect a difference in the primary outcome. Results relating to secondary outcomes therefore need to be treated circumspectly. However, the study protocols of ASPIRE and a similar study, WARFASA, had been prospectively harmonised to allow the results to be combined in a post hoc analysis.

WARFASA compared aspirin 100 mg daily with placebo in a very similar population to ASPIRE over a median of 23.9 months. It was discussed in the Eyes on Evidence commentary aspirin for secondary prevention of VTE after warfarin prophylaxis is discontinued. Although WARFASA recruited only about half as many people as ASPIRE, it found a statistically significant reduction in the risk of VTE recurrence with aspirin compared with placebo (HR 0.58, 95% CI 0.36 to 0.93, p=0.02). The reason the result reached statistical significance in WARFASA but not in ASPIRE might be because the event rate was much higher in WARFASA (the rate of VTE in the placebo group was 11.2% per year in WARFASA compared with 6.5% per year in ASPIRE).

Combining the results of ASPIRE and WARFASA found a statistically significant reduction in the risk of VTE (HR 0.68, 95% CI 0.51 to 0.90, p=0.007) and major vascular events (HR 0.66, 95% CI 0.51 to 0.86, p=0.002) with aspirin compared with placebo, and no statistically significant increase in the risk of clinically relevant bleeding (HR 1.47, 95% CI 0.70 to 3.08, p=0.31). The 95% confidence interval for the risk of clinically relevant bleeding was wide. This imprecision reflects the low absolute rate of bleeding (14 clinically relevant bleeding events in the ASPIRE aspirin group of 411 people and 4 events in the WARFASA aspirin group of 205 people).

When translating the results of these RCTs to the care of an individual person, health professionals will need to remember that the absolute benefits and risks from aspirin will depend on the person’s baseline risk of VTE, vascular events and bleeding.

Commentary

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Unlike WARFASA, ASPIRE was ultimately underpowered to measure the primary end point because of a lower than expected rate of recurrent VTE in the placebo arm and under recruitment to the trial overall. However, the planned meta-analysis of the WARFASA and ASPIRE trials shows a 32% reduction in recurrent VTE and 34% reduction in major vascular events with aspirin 100 mg daily with minimal excess bleeding risk. So is it time to change practice in patients completing oral anticoagulation?

Typically, patients who complete a course of oral anticoagulation following unprovoked VTE will stop the drug abruptly. An antiplatelet agent would currently only be restarted or continued in patients with pre-established arteriovascular disease. Aspirin for prolonged VTE prophylaxis is now an option, but with caveats. As noted in the editorial accompanying this study, aspirin is cheap, requires no monitoring, can be used in patients with renal disease and is easy to manage for surgical procedures. However for patients with unprovoked VTE the default recommendation is increasingly to continue long term oral anticoagulation unless there is a reason to stop in view of a recurrence rate of up to 40% over 5 to 10 years. Patients who are not suitable for long term oral anticoagulation therapy may not be suitable for antiplatelet therapy either if bleeding is the concern. The median age of patients in the ASPIRE study was 55 but limited evidence suggests that aspirin may be associated with higher rates of serious bleeding in people aged over 75 years than in younger people and these rates may even be similar to those seen with warfarin and newer oral anticoagulants. Another question is whether the dose of 75 mg used in the UK likely to be equally effective as the 100 mg dose used in the studies? If cyclooxygenase inhibition in the platelet and vascular endothelium is the sole mechanism of aspirin effect, there is no clear evidence to suggest that 75 mg would be significantly inferior to 100 mg, but a further study using the 75 mg should ideally be performed.

References

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