

Combination therapy with warfarin

Key points

- The mechanisms of action of aspirin and warfarin are complementary.
- Combination therapy with aspirin and warfarin may be more effective than monotherapy with either agent alone in certain groups at high risk of ischaemic heart disease, though the evidence is equivocal.
- It is unclear whether combined therapy is associated with an increased risk of adverse effects.

Current guidelines only recommend combination therapy with aspirin and warfarin as prophylaxis against ischaemic stroke in patients with atrial fibrillation aged ≥ 65 years.

The rationale for using combination therapy to prevent thrombotic events is that these agents have complementary mechanisms of action (warfarin inhibits the coagulation cascade and aspirin inhibits platelet aggregation). In recent years, a number of studies have suggested that combination therapy may be more effective than monotherapy with either agent alone in certain groups at risk of ischaemic heart disease.

In the UK Medical Research Council's Thrombosis Prevention Trial, 5,499 men aged 45 to 69 years at high risk of ischaemic heart disease were randomised to treatment with low-intensity warfarin (mean INR 1.47), low-dose aspirin (75 mg/day), a combination of both or placebo (1). Warfarin and aspirin monotherapy each reduced non-fatal and fatal ischaemic heart disease by approximately 20% compared with placebo; in combination, they reduced all ischaemic heart disease by 34%. Warfarin monotherapy significantly reduced fatal events whereas aspirin alone reduced non-fatal events. Conversely, the combination increased the incidence of haemorrhagic and fatal strokes.

In a 12-month study, 135 patients with acute coronary syndrome and prior coronary artery bypass were randomised to treatment with aspirin 80 mg/day, warfarin (INR range 2.0 - 2.5) or a combination of both (2). There were fewer fatal and non-fatal ischaemic events in the warfarin group (14.1%) than in the aspirin (11.5%) or combination group (11.4%) but more deaths in the combination group (1.6%) than with warfarin (0.7%) or aspirin (0%) alone. However, this study was relatively small and the authors recommended no change to current protocols for the management of high-risk patients with a prior bypass.

No additional benefit with combined therapy was reported in a non-blinded 5-year study of secondary prevention of ischaemic heart events following a myocardial infarction (3). 5,059 patients were assigned to aspirin (162 mg/day) or combination therapy with warfarin (INR range 1.5 - 2.5 plus aspirin 81 mg/day) within 14 days of a myocardial infarction. There were no significant differences in deaths due to

ischaemic events (17.3% for aspirin vs. 17.6% for the combination), recurrent myocardial infarction (13.1% vs. 13.3%) and stroke (3.5% vs. 3.1%).

This study is contradicted by ASPECT-2, which compared three regimens for secondary prevention of ischaemic events after myocardial infarction (4). 999 patients were randomised to treatment with a coumarin anticoagulant (INR range 3 -4), aspirin 80 mg/day or aspirin 80 mg/day plus coumarin anticoagulants (INR range 2 - 2.5) within 8 weeks of their myocardial infarction. The primary endpoint was a composite of the first occurrence of myocardial infarction, stroke or death. After a maximum follow-up of 26 months, this end point was reached in 9% of the aspirin group and in 5% of both the coumarin monotherapy and combined treatment groups. The rationale for using a lower intensity of anticoagulation in the combination group was to avoid the increased risk of bleeding associated with anticoagulants. However, bleeding was more frequent in the combination group (15%) than with aspirin (5%) or anticoagulant monotherapy (8%). The design of this study does not correspond with current clinical practice: it is usually recommended that patients are treated with higher doses of aspirin (150 - 300 mg/day) for the first few weeks after an acute ischaemic event.

More recently, combined prophylaxis with aspirin and warfarin had been shown to be superior to aspirin alone following a myocardial infarction (5). In this study, 3,630 patients were randomised to warfarin (INR range 2.8 - 4.2), aspirin 160 mg/day or warfarin (INR range 2 - 2.5) plus aspirin 75 mg/day). The primary composite end point (death, recurrent myocardial infarction or ischaemic stroke) occurred in 20% of patients taking aspirin alone, 16.7% taking warfarin and 15% taking the combination. The incidence of major, non-fatal bleeding was higher in both warfarin groups (0.62%) than in the aspirin group (0.17%).

References

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