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CME CREDIT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should patients on long-term warfarin take aspirin for heart disease?

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The decision whether to add aspirin to warfarin therapy should be individualized

A: The literature on this topic is limited, but it suggests that the decision to prescribe aspirin to patients already taking warfarin (Coumadin) should be individualized. On one hand, the cardiovascular benefit of starting or continuing aspirin in patients already on warfarin outweighs the increased risk of bleeding in patients presenting with an acute coronary syndrome or those with mechanical heart valves or coronary stents. However, for patients with stable coronary artery disease or at risk of coronary disease, the benefit of adding aspirin is not substantial, and continuing warfarin alone may be the preferred strategy.

In patients with coronary artery disease, aspirin has been shown to reduce the rate of death due to all causes by about 18% and the rate of vascular events by about 25% to 30%.[1,2] Warfarin is at least as effective as aspirin in reducing the rate of future cardiovascular events (especially if the target international normalized ratio [INR] is greater than 2.5), albeit with a higher bleeding risk.[3–6]

The decision to prescribe or continue aspirin in patients with coronary artery disease who also need long-term anticoagulation with warfarin for an unrelated medical problem, such as pulmonary emboli, requires careful assessment of the individual patient's bleeding risk and cardiovascular benefit.

ESTIMATING THE BLEEDING RISK FOR PATIENTS ON WARFARIN

In patients taking warfarin, the risk of major bleeding (defined in most studies as hospitalization because of bleeding and requiring transfusion of at least two units of packed red cells, or an intracranial, intraperitoneal, or fatal bleeding episode) is reported to be about 2.0% to 3.8% per person-year.[7–11] The risk of major bleeding with aspirin alone is estimated to be 0.13% per person-year,[12] but when aspirin is combined with warfarin, the risk increases significantly.[13] In a meta-analysis of randomized controlled trials,[14] the risk of major bleeding was calculated to be about 1.5 times higher with combination therapy with aspirin and warfarin than with warfarin alone.

The individual's bleeding risk depends on specific risk factors and the intensity of anticoagulation.[15] The outpatient Bleeding Risk Index (BRI) can be used to estimate the bleeding risk for patients on warfarin.[16] The BRI includes four risk factors for major bleeding, each scored as 1 point:

- Age 65 or older
- History of gastrointestinal bleeding
- History of stroke
- One or more comorbid conditions—recent myocardial infarction, anemia (hematocrit < 30%), renal impairment (serum creatinine level > 1.5 mg/dL), or diabetes mellitus.

The risk is low if the score is 0, moderate if the score is 1 or 2, and high if the score is 3 or more. In a validation study of the BRI, the rate of major bleeding was found to be 0.8%, 2.5%, and 10.6% per person-year on warfarin in the low, intermediate, and high-risk groups, respectively.[17] In addition, compared with

patients with a target INR of 2.5, those with a target INR higher than 3.0 have a higher frequency of bleeding episodes.[10,15]

CONDITIONS IN WHICH ADDING ASPIRIN TO WARFARIN IS FAVORABLE

Acute coronary syndromes

Drugs that inhibit platelet function are the mainstay of medical treatment for acute coronary syndromes. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend that aspirin be started in patients who have an acute myocardial infarction even if they have been receiving warfarin long-term and their INR is in the therapeutic range, especially if a percutaneous coronary intervention is anticipated.[4]

After percutaneous coronary intervention

In patients who have undergone percutaneous coronary intervention with stent implantation, dual antiplatelet therapy with aspirin and a thienopyridine—ie, clopidogrel (Plavix) or ticlopidine (Ticlid)—is superior to aspirin or warfarin alone in reducing the risk of stent thrombosis and major adverse cardiovascular events such as myocardial infarction or urgent revascularization.[18,19] If patients have an indication for long-term anticoagulation, triple therapy with aspirin, warfarin, and clopidogrel or ticlopidine may be considered in order to reduce the likelihood of stent thrombosis.[4,20,21] In such patients the INR should be maintained between 2.0 and 3.0 to reduce the risk of bleeding.

The duration of triple therapy is guided by the type of stent used. For bare metal stents, aspirin, clopidogrel or ticlopidine, and warfarin should be given for at least 1 month, after which clopidogrel or ticlopidine may be discontinued. If drug-eluting stents are used, the duration of clopidogrel or ticlopidine therapy should be extended to 1 year or more.[4,22]

Mechanical heart valves

In patients with mechanical heart valves, the combination of aspirin and warfarin has been shown to decrease the frequency of thromboembolism.[23] Guidelines recommend adding aspirin (75 to 100 mg per day) to warfarin in all patients with mechanical valves, especially in patients who have had an embolus while on warfarin therapy or who have a history of cerebrovascular or peripheral vascular disease, a hypercoagulable state, or coronary artery disease.[24]

CONDITIONS IN WHICH WARFARIN ALONE MAY BE SUFFICIENT

At risk of coronary artery disease

Aspirin therapy is generally recommended as primary prevention for patients whose estimated risk of coronary events is 1.5% per year or higher.[25] However, warfarin has also been shown to be effective in the primary prevention of coronary artery disease in men,[26] and for patients already taking warfarin, the possible benefit of adding aspirin for primary prevention is outweighed by the increased risk of major bleeding.[14] The Medical Research Council directly compared low-intensity warfarin therapy (mean INR 1.47), aspirin, and placebo in a two-by-two factorial study of primary prevention of ischemic heart disease in men.[26] Warfarin was more effective than aspirin, and men who received warfarin plus aspirin or warfarin plus placebo had a rate of ischemic heart disease that was 21% lower than those who received aspirin plus placebo or double placebo, and their rate of all-cause mortality was 17% lower. Combining aspirin and warfarin for patients at risk of coronary disease led to a higher rate of major bleeding but no difference in cardiovascular events or all-cause mortality (odds ratio 0.98; 95% confidence interval 0.77–1.25).[14]

In patients with acute coronary syndrome, a coronary stent, or a mechanical valve, combination therapy is usually recommended

Stable coronary artery disease without mechanical heart valves or stents

Large randomized trials have found warfarin to be effective in secondary prevention of coronary artery disease.[4–6] For most patients with stable coronary artery disease (ie, who have had no ischemic events or coronary interventions in the last 6 months) who need anticoagulation because of atrial fibrillation or venous thromboembolism, warfarin alone (target INR 2.0–3.0) should provide satisfactory antithrombotic prophylaxis against both cerebral and myocardial ischemic events.[27] The addition of an antiplatelet agent is not required unless a patient has a coronary stent, a mechanical valve, or an excessive thrombotic risk.[4,24,27]

TAKE-HOME POINTS

For patients receiving warfarin therapy, whether to add or continue aspirin to their treatment is a common clinical question. The risk of bleeding is greater with combination therapy than with warfarin alone. The cardiovascular benefit varies depending on the clinical situation:

- In patients who have had an acute coronary syndrome or who have a coronary stent or mechanical valve, combination therapy is usually recommended because the benefits outweigh the risks.
- In patients with stable coronary artery disease or those without coronary artery disease who are at risk of coronary events, the risks outweigh the benefits. Combination therapy is usually not indicated in these patients.

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