Does the Combination of Warfarin and Aspirin Have a Place in Secondary Stroke Prevention?  
No

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The combined use of warfarin plus aspirin for secondary stroke prevention occurs primarily in patients with atrial fibrillation (AF) who have concomitant coronary artery disease (CAD). This drug combination is also used in patients with mechanical heart valves or occasionally in stroke/TIA patients who are deemed to be at high-risk for recurrent events. It is estimated that approximately 20% of patients on warfarin also receive aspirin and aside from patients with mechanical heart valves the use of this combination is tenuous.1,2

The most common clinical scenario for using warfarin plus aspirin is for primary or secondary stroke prevention in AF patients who also have CAD. The rationale for using this combination typically is the widespread belief that the use of warfarin, although clearly of benefit for stroke risk reduction, should be supplemented with aspirin for reducing the risk of coronary ischemic events. The basis for this assumption is unclear, and the combined use of warfarin plus aspirin substantially increases the risk of major bleeding side effects, including intracerebral hemorrhage (ICH).3

The efficacy of aspirin for reducing ischemic events and mortality in CAD patients is well documented, and aspirin is widely used in patients with acute coronary syndromes and stable CAD.3 Prior studies have evaluated the efficacy of oral anticoagulation in CAD patients. Several studies in myocardial infarction (MI) patients demonstrated that oral anticoagulation demonstrated no difference in subsequent mortality or reinfarction in patients treated with oral anticoagulants versus aspirin over a wide range of doses.4 In some more recent studies such as the ASPECT-2 trial and the WARIS II trial, the warfarin group had a significantly reduced rate of the primary combined end point of death, MI, or stroke.5,6 These studies suggest that warfarin is at least as efficacious and maybe more so as compared to aspirin in MI patients for preventing ischemic events and death. Warfarin is rarely used after MI for secondary prevention unless another indication is present, primarily because aspirin is much easier to prescribe and does not require long-term INR monitoring and dosage adjustment. Additionally, warfarin use is associated with a higher risk of major bleeding side effects.4

If warfarin usage alone is associated with an increased bleeding risk, what are current estimates of the bleeding risk for warfarin plus aspirin? Using a Medicare database, Shireman et al compared the risk of major bleeding events in 10,093 elderly AF patients who were discharged from the hospital on warfarin alone (80.6%) versus warfarin plus antiplatelets (19.4%), mainly aspirin (89.7%).7 The absolute risk of major bleeding at 90 days was 1.3% in the warfarin alone group and 1.9% in the combined therapy group (OR 0.46 CI 0.998 to 2.12). At 180 days the major bleeding rates were 2.0% and 2.8% and at both time points ICH risk was increased 3-fold with combination therapy. A recent exploratory analysis of the Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) trials supports this concern about the increased of major bleeding with the combined use of warfarin plus aspirin.8 In the SPORTIF trials, 11,251 patients with nonvalvular AF were randomized to warfarin or ximelegatran. At the discretion of the investigator, aspirin could be added to either therapy. 481 patients received aspirin plus warfarin, and 531 received aspirin plus ximelegatran. The aspirin plus patients were more likely to be male, Asian, have a history of stroke or TIA, and have diabetes and a history of CAD (69 versus 41%). In this posthoc analysis the combination of aspirin plus warfarin was associated with a significantly increased annual risk for major bleeding side effects, 3.9% versus 2.3% (P=0.01), whereas the combination of ximelegatran plus aspirin had no such effect on bleeding risk, 2.0% versus 1.9%. Primary embolic event rates were similar in all four groups.

Concerning the possibility that the combination of warfarin plus aspirin may afford better protection that warfarin alone for cerebral ischemic events, several studies have not shown such added efficacy.9,10 Although, it must be acknowledged that low-dose warfarin was used in these trials and an INR target (2–3) typically used for stroke prevention with AF was not evaluated. Given the previously described major bleeding risk with standard INR targets plus aspirin, it is very unlikely that such a combination will have a favorable risk/benefit ratio for stroke prevention in AF patients.
In conclusion, the combination of warfarin plus aspirin should not be used, with the exception of patients with mechanical heart valves at high stroke risk. In the typical clinical scenario where such a combination is considered, i.e., a patient with stable CAD or recent MI without a coronary stent and AF, there is no evidence of additional benefit of the combination versus warfarin alone. There is mounting evidence of an increased risk for major bleeding side effects with the combination, albeit not from a prospective randomized clinical trial. Another vexing clinical situation with little or no information on which to base clinical decision making is the patient with AF who has recently undergone coronary artery stenting, requiring dual antiplatelet therapy to prevent stent thrombosis. Such patients are rife for a clinical trial comparing dual antiplatelet therapy alone versus dual antiplatelet therapy plus warfarin to determine whether triple therapy is more effective than dual therapy for preventing coronary and cerebral ischemic events and at what risk for bleeding side effects.

Disclosures

None.

References


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