Oral Anticoagulation, Aspirin, or Both in Coronary Disease?

Van Es RF, Jonker JJC, Verheugt FW, et al. Aspirin and coumadin after coronary syndromes (the ASPECT-2 study): a randomised controlled trial. Lancet 2002;360:109–13.

Study Overview

Objective. To compare treatment with aspirin, oral anticoagulation (OA), and their combination for secondary prevention of events in acute coronary syndrome.

Design. 3-arm, open-label, randomized trial.

Setting and participants. Men or non-pregnant women admitted to the hospital in the past 8 weeks with an acute myocardial infarction (MI) or unstable angina from 53 Dutch sites were eligible. Patients were excluded if they had another indication for one of the treatments (eg, atrial fibrillation, a mechanical heart valve or a ventricular aneurysm in the case of OA, or angioplasty or coronary stenting in the case of aspirin). Patients also were excluded if any of the study drugs were contraindicated, revascularization was planned, there was an increased risk of bleeding, there was a history of prior stroke, or certain hematologic disorders were present. Most subjects were enrolled within 2 weeks of hospitalization. The mean age was 61 years, and 78% of patients were under 70 years of age.

Intervention. Patients received either 80 mg aspirin per day, OA with a target international normalized ratio (INR) of 3.0 to 4.0, or aspirin and OA with a target INR of 2.0 to 2.5.

Main outcome measure. The primary endpoint was the composite of death, myocardial infarction, or stroke. Other outcomes examined were death from any cause, major bleeding (fatal bleeding, intracranial hemorrhage, or bleeding requiring hospitalization), and several other cardiovascular events. Endpoints were determined using patient questionnaires that were judged by blinded physicians. The median follow-up was 12 months.

Main results. 999 patients were enrolled. The primary endpoint was reached in 9.2% of patients in the aspirin-only group, 5.2% in the OA group (hazard ratio [HR], 0.55 [95% confidence interval {CI}, 0.30–1.00]), and 4.8% of the aspirin plus OA group (HR, 0.50 [95% CI, 0.27–0.92]). Major bleeding occurred in 0.9% of patients taking aspirin, 0.9% on OA alone (HR, 1.03 [95% CI, 0.21–5.08]), and 2.1% on OA and aspirin (HR, 2.35 [95% CI, 0.61–9.10]). Hemorrhagic stroke occurred in only 1 patient, who was in the combined treatment group. Death occurred in 4.5% of the aspirin group, 1.2% of the OA group (HR, 0.28 [95% CI, 0.09–0.82]), and 2.7% of the combined OA and aspirin group (HR, 0.60 [95% CI, 0.26–1.36]).

Conclusion. High-intensity OA alone and medium-intensity OA plus aspirin were more effective than aspirin alone for preventing major cardiovascular events in patients recently admitted with an acute coronary syndrome. Combination therapy was associated with an increase in major bleeding.

Commentary

Despite many recent advances, recurrent cardiovascular events following an initial acute coronary syndrome continue to be common and are a major cause of morbidity and mortality. Trials examining the role of OA in ischemic heart disease have been performed since the 1960s and have had varying results. While antiplatelet agents such as aspirin are moderately effective in reducing subsequent cardiac events and are generally well tolerated at the doses required, whether or not OA should be added or used instead of antiplatelet agents has been less clear. A recent meta-analysis demonstrated that high-intensity OA in patients with coronary disease led to a statistically significant 3.3% absolute decrease in total mortality and a 5.6% decrease in fatal or nonfatal MI compared with controls [1]. However, in studies of moderate- and high-intensity OA versus aspirin, there was no significant difference in mortality or the combination of death, MI, and stroke between the OA and aspirin groups [1]. Likewise, the addition of low-dose OA to aspirin was not associated with benefit, and there was a nonsignificant increase in major bleeding [1]. When analyzed together, 3 small studies that compared high- or moderate-dose OA plus aspirin with aspirin alone suggested that there was a reduction in the combined endpoint of death, MI, and stroke (5.4% versus 10.8%) and approximately double the chance of major bleeding (3.3% versus 1.7%) [1]. The findings in the combination therapy arm but not the high-intensity OA arm of the Van Es et al study are in agreement with the earlier meta-analysis.

The results of ASPECT-2 support the use of moderate OA plus aspirin for secondary prevention following an acute

coronary event. However, the issue remains complicated. While this study did use random group assignment, patients and their physicians were not blinded to treatment. It is possible that the ascertainment of events was influenced by the knowledge of drug assignment. Second, while this study was fairly large (325–336 patients per group), it was not big enough to provide precise estimates of the differences in benefits or bleeding risks between groups. Lastly, it is not clear how well these findings will apply to a general population with coronary disease. This study population was fairly young, and the risk of hemorrhage from anticoagulation is much higher in the elderly than it is for middle-aged adults [2]. Prior studies combining aspirin with moderate or high level OA showed higher rates of major bleeding than reported here [1]. In addition, the monitoring and dose adjustment required for safer anticoagulation may not be easily achieved in all clinical settings.

Applications for Clinical Practice

The combination of moderate intensity oral anticoagulation (INR, 2.0–2.5) and low-dose aspirin promises to be an effective preventive strategy following acute coronary events, but it comes at an increased risk of major hemorrhage. The relative magnitude of these risks and benefits is not entirely defined.

–Review by Stephen D. Persell, MD

References

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