

Anticoagulation for Secondary Prevention of Heart Disease

Huynh T, Theroux P, Bogaty P, et al. Aspirin, warfarin, or the combination for secondary prevention of coronary events in patients with acute coronary syndromes and prior coronary artery bypass graft surgery. *Circulation* 2001;103:3069–74.

Study Overview

Objective. To evaluate the benefit of using warfarin, either alone or in combination with aspirin, for secondary prevention of coronary events in patients with prior coronary artery bypass graft (CABG) surgery.

Design. Double-blind randomized trial. Analysis was by intention to treat.

Setting and participants. 135 patients with unstable angina or non-ST-segment elevation myocardial infarction (MI) and prior CABG who were poor candidates for a revascularization procedure were recruited from 4 referral cardiology centers in Canada. Patients were excluded who had undergone coronary angioplasty or repeated CABG during the index hospitalization, had contraindications to or were required to take aspirin or warfarin, had a treatable cause for angina, any major concomitant illness, class 3 or 4 congestive heart failure, blood pressure higher than 180/95 mm Hg, recent major trauma, alcohol or drug abuse, child-bearing potential, or coronary angioplasty in the previous 6 months.

Intervention. Participants were randomized to receive either aspirin plus placebo-warfarin ($n = 46$), warfarin plus placebo-aspirin ($n = 45$), or aspirin plus warfarin ($n = 44$). Aspirin dose was 80 mg/day. Warfarin was titrated to an INR of 2.0 to 2.5. Follow-up visits were scheduled at 1, 3, 6, and 12 months.

Main outcomes measures. The primary endpoint was death or MI or unstable angina requiring a new hospitalization 1 year after randomization.

Main results. Female participants comprised 18% of the aspirin-alone group, 14% of the warfarin-alone group, and 29% of the combination-therapy group. Mean age in the 3 study groups was 68 years, 67 years, and 66 years, respectively. The primary endpoint occurred in 14.6% of patients receiving warfarin alone, 11.5% of patients receiving aspirin alone, and 11.3% of patients receiving combina-

tion therapy ($P = 0.76$). Subgroup analyses by risk features provided no indications that warfarin alone or in combination with aspirin could be of benefit over aspirin alone. Bleeding was more frequent among patients who received warfarin.

Conclusion. Moderate-intensity oral anticoagulation alone or combined with low-dose aspirin does not appear to be superior to low-dose aspirin in the prevention of recurrent ischemic events in patients with non-ST-elevation acute coronary syndromes and previous CABG.

Commentary

The idea that combination therapy (aspirin plus warfarin) may decrease risk for recurrent MI could be well supported by pathophysiologic concepts and even by basic research. However, clinical data to prove this hypothesis have been difficult to compile. A systematic review of 6 randomized controlled trials [1] found that low-intensity anticoagulation therapy (target INR < 1.5) in addition to aspirin did not reduce death or MI when compared with aspirin alone. Data evaluating moderate-intensity therapy (target INR, 2 to 3) versus aspirin have been less reliable but generally have failed to show any significant benefit in the secondary prevention of coronary artery disease. Conversely, risk for minor and major bleeding is always increased with anticoagulant use. Huynh et al designed their study to evaluate moderate-intensity anticoagulation versus aspirin alone. The authors included very high-risk patients to increase the chances of achieving a significant event rate; however, the same criteria aimed at including these patients also limited recruitment efforts. The resulting small sample size and low event rate yielded an underpowered study with inconclusive findings. Larger clinical trials or future meta-analyses will be needed to clarify the true value of combining aspirin and warfarin for prevention of MI.

Applications for Clinical Practice

The importance of aspirin in the secondary prevention of

heart disease cannot be overemphasized. However, routine use of anticoagulation therapy plus aspirin—even for very high-risk patients—is still not supported by clinical evidence.

References

1. Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis [published erratum appears in JAMA 2000;284:45]. JAMA 1999;282:2058-67

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