Coumadin alone or aspirin plus coumadin reduced coronary events and death after acute myocardial infarction or unstable angina


Question
In patients who have had acute myocardial infarction (MI) or unstable angina, is high-intensity coumadin or aspirin plus moderate-intensity coumadin more effective than aspirin alone for reducing coronary events and all-cause mortality?

Design
Randomized (allocation concealed*), unblinded,* controlled trial with up to 26-month follow-up.

Setting
53 hospitals in the Netherlands.

Patients
999 patients who had had acute MI (88%) or unstable angina (13%) within the preceding 8 weeks. Exclusion criteria included planned revascularization or recent intracoronary stenting, thrombocytopenia, anaemia, and history of stroke. Follow-up was 99% (mean age 61 y, 77% men).

Intervention
Patients were allocated to phenprocoumon or acenocoumarol with target international normalized ratio (INR) of 3.0 to 4.0 (n = 330); aspirin, 80 mg/d, plus phenprocoumon or acenocoumarol with target INR of 2.0 to 2.5 (n = 333); or aspirin, 80 mg/d (n = 366).

Outcome Measures
The primary outcome was a composite of all-cause mortality, MI, or stroke. The major secondary outcome was bleeding.

Main Results
Analysis was by intention to treat. The incidence of the composite outcome of all-cause mortality, MI, or stroke was lower in the coumadin and combination groups than in the aspirin group (Table). The incidence of minor bleeding was greater in the combination group than in the aspirin group (Table). The groups did not differ for major bleeding (Table).

Commentary
Clinical interest in coumadin therapy after MI declined in the 1990s after several studies showed no benefit over aspirin. Therefore, recent guidelines recommend the use of aspirin and other antiplatelet therapies (e.g., clopidogrel) at discharge for patients with acute coronary syndromes (ACSs).

The ASPECT-2 study by van Es and colleagues and 2 other recent trials (1, 2) suggest that long-term coumadin therapy compared with aspirin improves outcomes in patients after ACS. In ASPECT-2, fewer patients in both the aspirin-plus-coumadin group (hazard ratio 0.50, 95% CI 0.27 to 0.92) and the coumadin-alone group (hazard ratio 0.55, CI 0.30 to 1.00) reached the primary end point (death, MI, or stroke) than those in the aspirin group after 12 months. The benefits from coumadin therapy were further supported by secondary analyses showing lower rates of death, vascular death, MI, unstable angina, stroke, and revascularization in patients receiving coumadin or aspirin-plus-coumadin therapy than in those receiving aspirin alone. However, the aspirin-plus-coumadin group had a 2-fold higher rate of major bleeding and a 3-fold higher rate of minor bleeding than the aspirin-alone group.

Clinical application of the ASPECT-2 findings and widespread use of coumadin therapy after ACS are doubtful in contemporary cardio-vascular practice. In ASPECT-2, bleeding concerns, study design, and eligibility criteria largely excluded patients receiving early revascularization, intracoronary stents, or clopidogrel. Prohibition of such patients limits the determination of the additive benefit or therapeutic role of coumadin in ACS management. In addition, the narrow pharmacologic efficacy of coumadin (i.e., safety margin and requirement for prothrombin time/INR monitoring) reduces physician and patient acceptance. Consequently, ASPECT-2 is unlikely to propel coumadin to the forefront of ACS therapies ahead of aspirin and clopidogrel. The study should, however, stimulate development of new oral anticoagulants and additional comparison trials of antiplatelet–anticoagulant drug regimens.

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References