CLINICAL RESEARCH STUDY

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Long-term Effect of Chronic Oral Anticoagulation with Warfarin after Acute Myocardial Infarction

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ABSTRACT

BACKGROUND: Antiplatelet therapy is the principal component of the antithrombotic regimen after acute myocardial infarction. It remains unclear whether additional chronic oral anticoagulation (OAC) improves outcomes. We set out to evaluate the risk and benefit of long-term OAC after myocardial infarction.

METHODS: We pooled 10 randomized clinical trials comparing warfarin-containing regimens (OAC) with or without aspirin with non-OAC regimens with or without aspirin (No OAC) for patients with recent infarction. The primary endpoint was all-cause mortality. Other endpoints included recurrent infarction, stroke, and major bleeding. We calculated the odds ratio (OR) (fixed effect, OR <1 indicates benefit for OAC) for death and other ischemic and hemorrhagic complications at the longest interval of follow-up available.

RESULTS: Among 24,542 patients, 14,062 were assigned to OAC and 10,480 to no OAC. The patients were followed for 3-63 months, for 89,562 patient-years. Death occurred in 2424 patients (9.9%), 1279 OAC patients, and 1145 in the no OAC group, OR 0.97 (95% confidence interval [CI], 0.88-1.05), $P = .43$. Similarly, there was no effect on recurrent infarction. Stroke occurred in 578 patients (2.4%), 271 in the OAC group and 307 in the no OAC group, OR 0.75 (95% CI, 0.63-0.89), $P = .001$. There was substantially more major bleeding (OR 1.83 [95% CI, 1.50-2.23], $P < .001$) in the OAC group. Separate analyses, performed for patients (n = 11,920) randomized to aspirin versus aspirin and OAC yielded very similar results.

CONCLUSION: As compared with placebo or aspirin, OAC with or without aspirin does not reduce mortality or reinfarction, reduces stroke, but is associated with significantly more major bleeding.

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KEYWORDS: Anticoagulation; Bleeding; Death; Long-term effect; Myocardial infarction

Coronary artery disease remains the most common cause of death among adults in the United States. Anti-platelet therapy is the principal component of the antithrombotic regimen after acute myocardial infarction.[1]

There have been numerous studies over the last 4 decades attempting to address the utility of long-term oral anticoagulation (OAC) after myocardial infarction. Early studies suggested benefit in younger men only, while later ones found all patients to survive longer or to have lower rates of recurrent ischemic events, but not death.[2,3] In the last 20 years, several randomized controlled trials have been conducted to clarify the role of long-term OAC after myocardial infarction, with varying results.[4-15] They utilized different intensities of anticoagulation, starting at varying intervals from index event, and in a wide array of patients with respect to concomitant aspirin or reperfusion therapy.

As uncertainty about the benefit of OAC persists, we performed a meta-analysis of randomized clinical trials

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comparing OAC-based regimens (without or without aspirin) versus no OAC after myocardial infarction (with or without) ST-elevation, to determine whether there was any improvement in survival or other cardiovascular events in those taking OAC. We refined the analysis to evaluate the effect of OAC or placebo in addition to aspirin, which is the standard of care for patients with previous infarction.

CLINICAL SIGNIFICANCE

- Oral anticoagulation does not reduce death or reinfarction in survivors of acute myocardial infarction across a wide range of patients and intensity of therapy.
- Oral anticoagulation reduces the incidence of stroke by ~30%, independent of aspirin therapy, suggesting different mechanisms of cardiac and cerebral protection from ischemic events.
- Oral anticoagulation increases the rate of nonfatal major and minor bleeding.

METHODS

We performed a comprehensive search of OVID SR and PubMed without any language restrictions. The keywords used included warfarin, myocardial infarction, and randomized controlled trials, in accordance with the Meta-analysis Of Observational Studies in Epidemiology guidelines.[16] We retrieved 66 citations, which were reviewed at the title/abstract level. The inclusion criteria were: use of chronic OAC with warfarin post infarction, randomized controlled trial, at least 30-day follow-up, and death listed as outcome. The exclusion criteria were: retrospective study or registry and use of OAC for conditions other than myocardial infarction (Figure 1). Fourteen studies were analyzed in detail. The study by Cohen at al[7] was excluded because it did not provide details about the 2 randomized arms and listed only the results comparing non-Q-wave infarction versus unstable angina. The study by Huynh et al[11] was excluded because it studied a selected group of patients with unstable angina or non-ST-segment elevation myocardial infarction, with prior coronary bypass surgery, and who were poor candidates for a revascularization procedure. The third excluded study was a subgroup analysis of the original Coumadin Aspirin Reinfarction Study (CARS).[17] The Organization to Assess Strategies for Ischemic Syndromes[5] study reported use of aspirin in 85%-87% of patients, however, the study did not report the results separately for those receiving aspirin or not. This study was excluded because it did not report specifically number of deaths, but rather the combination of death, infarction, or stroke.

The primary endpoint for each trial (except 1 trial that used all-cause mortality as endpoint[8]) was a composite of ischemic events, including death, infarction, stroke, or recurrent ischemia in various combinations. While our focus was on all-cause mortality, we examined individually each ischemic event (death, infarction, or stroke) because of the possibility of heterogeneity in response among the components of the composite endpoint. We also analyzed separately major bleeding and minor bleeding, according to the definition in each trial. Statistical analysis was performed using the weighted fixed and random effects methods for meta-analysis. After confirming that there were no substantial differences between the 2 methods, we reported only the pooled fixed-effect results. Heterogeneity was assessed using a standard

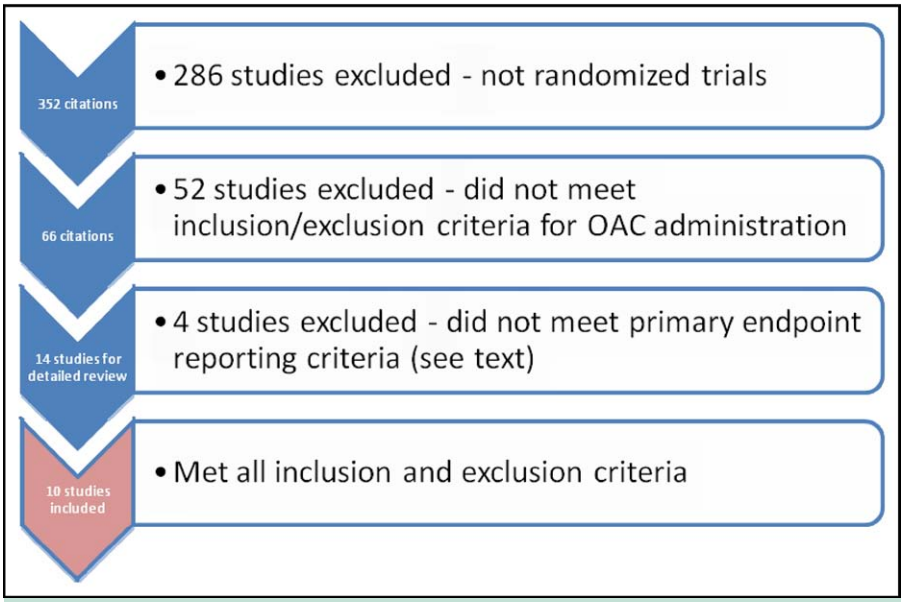

Figure 1 Study inclusion and exclusion process. OAC = oral anticoagulation.