Review: High- and moderate-dose oral anticoagulants reduce events in CAD but increase major bleeding and are no more effective than aspirin

Anand SS, Yusuf S. **Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis.** JAMA. 1999 Dec 1;282:2058-67.

QUESTIONS

Do oral anticoagulants (OAs) reduce death, recurrent myocardial infarction (MI), and stroke and increase bleeding in patients with established coronary artery disease (CAD)? Do the effects vary with intensity of OA and aspirin use?

DATA SOURCES

Studies published between 1960 and July 1999 were identified by searching MEDLINE, EMBASE/Excerpta Medica, and Current Contents using combinations of terms related to OAs and vascular disease; reviewing bibliographies of relevant papers; and contacting experts and pharmaceutical companies.

STUDY SELECTION

Randomized trials were selected if they included patients who had established CAD, used OAs, and continued treatment for ≥ 3 months.

DATA EXTRACTION

Data were extracted on baseline patient characteristics, intensity of OA therapy, time of initiation of therapy, duration of therapy, and number of patients discontinuing therapy.

MAIN RESULTS

30 reports of 31 trials were included in the analysis. Data were analyzed by strata that were based on intensity of anticoagulation:

high-intensity OAs (international normalized ratio [INR] > 2.8, 20 trials); moderate-intensity OAs (INR 2 to 3, 8 trials); and low-intensity OAs (INR < 2, 3 trials). More patients who received high-intensity OAs (16 trials) had reduced total mortality; fatal and nonfatal MI, stroke; and the combined end point of death, MI; or stroke than did control patients who did not receive aspirin. Patients receiving OAs had increased major bleeding (Table). Moderate-intensity OAs reduced fatal and nonfatal MI, and stroke but increased major bleeding more than did control therapy (4 trials) (Table). High- or moderate-intensity OAs showed no more reduction in end points than did aspirin but increased major bleeding (7 trials) (Table). Low-intensity OAs plus aspirin had no more effect on any of the above-mentioned outcomes than did aspirin alone (3 trials).

CONCLUSIONS

In patients with coronary artery disease, high-intensity oral anticoagulants (OAs) reduce total mortality, myocardial infarction, and stroke but increase major bleeding; moderate-intensity OAs reduce myocardial infarction and stroke but increase major bleeding. High- or moderate-intensity OAs increase bleeding but do not reduce end points more than aspirin. Low-intensity OAs plus aspirin do not differ in effect from aspirin alone.

Source of funding: No external funding.

For correspondence: Dr. S.S. Anand, Hamilton General Hospital, McMaster Clinic, 237 Barton Street East, Hamilton, Ontario L8L 2X2, Canada. FAX 905-527-9642. ∎

Oral anticoagulants (OAs) vs control therapy in patients with established coronary artery disease*

Outcomes	OA intensity and comparison	OAs	Control	Odds reduction (95% CI)	NNT (CI)
Death, MI, or stroke	High vs control	20.3%	30.1%	43% (37 to 49)	10 (9 to 12)
	Moderate vs control	31.3%	33.7%	16% (−34 to 20)	Not significant
	High or moderate vs aspirin	11.3%	12.6%	4% (−34 to 20)	Not significant

				Odds increase (CI)	NNH (CI)
Major bleeding	High vs control	4.6%	0.7%	600% (440 to 820)	30 (21 to 44)
	Moderate vs control	3.5%	0%	770% (330 to 1760)	151 (42 to 437)†
	High or moderate vs aspirin	3.7%	1.0%	1.4% (0.6 to 2.6)	74 (40 to 170)

*Abbreviations defined in Glossary; NNTs and NNHs calculated from data in article. Follow-up data not available.
†Approximate value calculated assuming a control event rate of 0.1%.

COMMENTARY

CAD is the leading cause of morbidity and mortality in the United States. Patients with CAD are living longer and are a growing cohort that remains at risk for recurrent ischemic events and death (1). The meta-analysis by Anand and Yusuf provides an important look at the use of OAs in CAD, but the evidence is not sufficient to recommend the routine use of OAs after MI given the justifiable and widespread use of aspirin. Only one third of the trials included in the analysis (*n* = 9) were published in the past decade; most were small trials done 20 to 40 years ago. Generalizations from these studies are problematic for 2 reasons. First, the clinical management of CAD and the management of OA therapy has changed (i.e., the widespread use of aspirin, the use of the INR for monitoring anticoagulant effect, the frequency of monitoring, the use of anticoagulant services, the use of portable prothrombin time monitors, and newer thrombolytics). Second, patients with CAD have changed. Differences in the comorbid conditions of these patients and the treatment of these conditions (e.g., treatment of *Helicobacter pylori* in peptic ulcer disease) have simultaneously occurred. Thus, direct extrapolation to the present day is not practical.

Two important questions remain unanswered: Which patients with CAD would benefit most from OAs in the presence of aspirin? What INR level is most beneficial? Currently, it is reasonable to conclude that long-term use of OAs after MI can be recommended for secondary prevention of MI in patients unable to tolerate daily aspirin, patients with persistent atrial fibrillation, and patients with left ventricular thrombus (2). Preliminary results from the Combination Hemotherapy and Mortality Prevention (CHAMP) trial support this conclusion (3). Warfarin alone or in combination with aspirin at INR values < 2.0 does not appear to be clinically effective in secondary prevention of MI.

Rebecca J. Beyth, MD, MS
Baylor College of Medicine
Houston, Texas, USA

References
1. **Hunink MG, Goldman L, Tosteson AN, et al.** JAMA. 1997;277:535-42.
2. **Cairns JA, Theroux P, Lewis HD Jr., et al.** Chest. 1998;114:611S-33S.
3. **Fiore LD, Ezekowitz MD.** http://www.maveric.org/projects/study12.html.