Optimal antithrombotic management of anticoagulated patients with a history of myocardial infarction

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CRD summary

This review assessed the efficacy and safety of oral anticoagulation, with or without aspirin, for secondary prevention of myocardial infarction. The authors concluded that oral anticoagulation was at least as effective as aspirin, but there was insufficient evidence for combined treatment versus oral anticoagulation alone. Limitations in the reporting and analysis of the results make it difficult to adequately assess the robustness of these conclusions.

Authors' objectives

To assess the efficacy and safety of oral anticoagulation, with and without aspirin, for the secondary prevention of myocardial infarction (MI).

Searching

MEDLINE (1966 to October 2003), Current Contents (Clinical Medicine) (1998 to October 2003) and the Cochrane Library (Issue 4, 2002) were searched for studies published in full, in English, using the reported search terms. The reference lists in retrieved articles were screened.

Study selection

Study designs of evaluations included in the review

Randomised controlled trials (RCTs) with at least 1 year of follow-up were eligible for inclusion, regardless of study quality. The included studies followed up patients for between 1 and 4 years.

Specific interventions included in the review

Studies that compared 75 to 325 mg aspirin alone with oral anticoagulation, and/or combination aspirin plus oral anticoagulation, were eligible for inclusion. The included studies compared 80 to 162 mg aspirin with 74 to 81 mg aspirin plus warfarin (all but 1 study) or phenprocoumon or acenocoumarol (1 study).

Participants included in the review

Studies of patients with a previous diagnosis of MI were eligible for inclusion. Studies were excluded if they recruited patients following procedures such as coronary artery bypass graft or percutaneous coronary angioplasty with no diagnosis of MI. The included studies were of patients hospitalised with acute MI, and patients with acute MI or unstable angina in the past 14 days to 8 weeks. One of the included studies was in patients who had previously undergone a coronary artery bypass graft.

Outcomes assessed in the review

Studies were eligible if they objectively assessed recurrent MI, all-cause mortality and safety outcomes (including major and/or minor bleeding defined using objective criteria). The review reported definitions of outcomes used in the individual studies (where these were given).

How were decisions on the relevance of primary studies made?

At least two reviewers independently selected studies; the reviewers were not blinded to journal title, authors or institutions. Any disagreements were resolved by discussion.

Assessment of study quality

Validity was assessed and scored using the Jadad scale, which considers the reporting and handling of randomisation, blinding and the handling of withdrawals. The maximum possible score was 5 points.

Three reviewers independently scored validity.

Data extraction

Under the heading of data extraction, the reviewers stated that 'systematic methods were used to minimise bias' but no further details were given. For each study, event rates were extracted for each outcome of interest for each treatment group. One author was contacted for additional data.

Methods of synthesis

How were the studies combined?

The studies were combined in a narrative.

How were differences between studies investigated?

The studies were grouped by the interventions compared. Further differences between the studies were apparent from the tables and were discussed in the text.

Results of the review

Five RCTs (n=18,626) were included.

One study scored 4 points for study quality, three scored 3 points and one scored 2 points. Two studies were double-blind; the others were open-label trials.

No RCTs were found that statistically compared oral anticoagulation versus oral anticoagulation plus aspirin for long-term secondary prophylaxis. No studies were identified that assessed oral anticoagulants at the currently recommended International Normalised Ratio (INR) range of 2.0 to 3.5.

Oral anticoagulation versus aspirin (3 RCTs).

Efficacy: one study found that oral anticoagulation significantly reduced the risk of MI compared with aspirin (7.4% versus 9.7%, P<0.001); the other two studies found no significant difference between treatments. One study (a different study from the single positive study above) found that oral anticoagulation significantly reduced all-cause mortality compared with aspirin (1.2% versus 4.5%, P<0.05); the other two studies found no significant difference between treatments.

Safety: two studies found no significant difference in major bleeding between treatments; the other study did not report the statistical significance of the difference. One study found that oral anticoagulation significantly increased minor bleeding compared with aspirin (8.9% versus 1.5%, P=0.02); one study did not report the statistical significance of the difference and the other found no significant difference between treatments.

Oral anticoagulation plus aspirin versus aspirin alone (5 RCTs).

Efficacy: one study found that oral anticoagulation plus aspirin significantly reduced MI compared with aspirin alone (5.7% versus 9.7%, P=0.03); the other four studies found no significant difference between treatments. None of the studies found any significant difference in all-cause mortality between treatments.

Safety: one study found that oral anticoagulation plus aspirin significantly increased major bleeding compared with aspirin alone (3.5% versus 2.0, P<0.001); one study did not report the statistical significance of the difference and the others found no significant difference between treatments. Three studies found that oral anticoagulation significantly increased minor bleeding compared with aspirin alone (15.1% versus 4.8%, P<0.05; 9.8% versus 1.5%, P<0.05; and 13.8% versus 3.0%, P<0.001 respectively); one study found that combination treatment increased minor bleeding but the statistical significance was not reported; the other study did not report minor bleeding.

Oral anticoagulation versus oral anticoagulation plus aspirin (3 studies).

None of the studies statistically compared efficacy or safety outcomes between treatments.

Efficacy: the review reported that event rates for mortality and MI were similar between treatments, but no data were presented.

Safety: the studies reported mixed results for major bleeding: two found increased major bleeding with oral anticoagulation alone and the other found increased major bleeding with combination treatment. All three studies found that oral anticoagulation plus aspirin increased minor bleeding compared with oral anticoagulation alone, but the statistical significance was not reported.

Authors' conclusions

The authors' conclusion appears to be that oral anticoagulation is at least as effective as aspirin for the secondary prevention of MI, but there is a lack of evidence for the efficacy of oral anticoagulation plus aspirin versus oral anticoagulation alone. Bleeding appeared to be increased when using the combination of oral anticoagulation plus aspirin compared with oral anticoagulation alone.

CRD commentary

The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. The authors searched several relevant databases. However, restricting the search to studies published in full in English, without any attempt to locate unpublished studies, raises the possibility of publication and language bias. Methods were used to minimise errors and bias in the study selection, validity assessment and data extraction processes, although the methods used to extract the data were not described in full. Validity was assessed using established criteria, validity scores were reported, and some other methodological limitations of the primary studies were discussed in the text.

An examination of between-study differences was limited by the lack of reported 95% confidence intervals for the results of all studies. Some studies did not report the statistical significance of the results, and it was unclear why the reviewers did not seek this information from the authors or compare treatments statistically themselves. The studies were grouped and combined in a narrative, but the authors did not state why a meta-analysis was not considered; this might have increased the power of the analysis. Limitations in the reporting and analysis of the results make it difficult to adequately assess the robustness of the authors' conclusions.

Implications of the review for practice and research

Practice: The authors stated that the best regimen for patients who require anticoagulation treatment and have a history of MI involves stopping aspirin and starting oral anticoagulation at an appropriate target INR range.

Research: The authors stated that there is a need for further studies to definitively determine the risks and benefits of oral anticoagulation compared with oral anticoagulation plus aspirin. They also stated that there is a need for further research into the safety, efficacy and cost-effectiveness of newer agents that could be used for MI prophylaxis, such as newer antiplatelet agents (e.g clopidogrel) and antithrombotics (ximelagatran and other direct thrombin inhibitors).

Bibliographic details

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