Use of new-generation oral anticoagulant agents in patients receiving antiplatelet therapy after an acute coronary syndrome: systematic review and meta-analysis of randomised controlled trials

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CRD summary
This review concluded that use of orally activated Xa antagonist or direct thrombin inhibitors after acute coronary syndrome significantly increased major bleeding which might offset ischaemic benefits in patients receiving antiplatelet therapy. Despite potential for missed studies and the unknown quality of the included studies, the results across the studies are consistent and support the authors conclusions.

Authors' objectives
To evaluate the efficacy and safety of new generation oral anticoagulant agents compared with placebo in patients receiving antiplatelet therapy after acute coronary syndrome (ACS).

Searching
PubMed, ClinicalTrials.gov and Scopus were searched without language restriction for studies published between 2000 and December 2011; search terms were reported. Reference lists of studies, reviews, editorials and letters and relevant conference proceedings were searched.

Study selection
Randomised placebo-controlled trials (RCTs) that evaluated the clinical efficacy and safety of an anticoagulant protocol that included orally activated Xa antagonist (anti-Xa) and direct thrombin inhibitors in patients who received antiplatelet therapy after ACS were eligible for inclusion. Studies of vitamin K antagonists, parenteral anticoagulant agents and the clinical effects of more potent antiplatelet protocols (details given) were excluded.

Included patients had unstable angina pectoris, ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction. The treatment regimen varied across studies. Time between an ACS event and entry into the trial ranged from six to 14 days. The included trials were either dose-finding or superiority trials. Exclusion criteria varied, but patients with severe cardiac, renal or liver insufficiency and patients with excessive risk for bleeding were excluded; patients with prior stroke were excluded in most studies. The mean age of participants ranged from 57 to 67 years. The proportion of participants who had prior percutaneous coronary intervention ranged from 8.3% to 75%. Nearly all the included patients were receiving aspirin and most were receiving a thienopyridine.

Two independent reviewers selected studies for the review; disagreements were resolved by consensus.

Assessment of study quality
Trial quality was not assessed.

Data extraction
Data were extracted by two independent reviewers to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for overall mortality, definite or probable stent thrombosis and the composite end point of death, myocardial infarction, ischaemic stroke and severe recurrent ischaemia. Net clinical benefit was the sum of ischaemic and major bleeding events.

Methods of synthesis
Pooled odds ratios and 95% CI were calculated using a inverse variance random-effects model; a fixed-effect model was used as a sensitivity analysis. Subgroup analyses were performed to investigate the impact of the type of intervention (anti-Xa; direct thrombin inhibitors), phase of the trials (two or three) and whether the trial was completed or discontinued early. Heterogeneity was assessed using the I² statistic. Publication bias was investigated using funnel plots and the Egger test.
Results of the review
Seven RCTs met the inclusion criteria (31,286 participants, range 1,279 to 15,526). Follow-up ranged from 26 to 124 weeks. The rate of trial drug discontinuation ranged from 15% to 44%.

New generation oral anticoagulant agents were associated with a three-fold increase in major bleeding events (OR 3.03, 95% CI, 2.20 to 4.16; I²=0%) and a more than two-fold increase in any bleeding event (OR 2.26, 95% CI, 2.01 to 2.56; I²=8%). There were statistically significant reductions in the risk of stent thrombosis (OR 0.73, 95% CI, 0.54 to 0.98; I²=17%) and the composite of ischaemic events (OR 0.86, 95% CI, 0.79 to 0.94; I²=0%) but not overall mortality. There was no statistically significant net clinical benefit of new generation oral anticoagulant agents over placebo (OR 0.98, 95% CI, 0.90 to 1.06).

Results from subgroup and sensitivity analyses were reported. There was no evidence of publication bias.

Authors’ conclusions
Use of anti-Xa or direct thrombin inhibitors was associated with a dramatic increase in major bleeding events which might offset all ischaemic benefits in patients receiving antiplatelet therapy after ACS.

CRD commentary
The authors addressed a clear review question supported by reproducible inclusion criteria. Several relevant sources were searched without language restrictions. Attempts were made to identify unpublished studies. Some sources (such as EMBASE) that could have identified unique studies were not searched. Publication bias was investigated but with so few studies the results of such investigations would not be reliable. Study selection and data extraction were conducted by two independent reviewers, which reduced risks of error and bias. Trial quality was not assessed and insufficient details regarding methodology were provided for the reader to make an assessment. The included studies seemed to be clinically heterogeneous, although the outcome estimates seemed fairly consistent across studies; therefore, the use of a random effects meta-analysis seemed appropriate. Potential sources of heterogeneity were investigated.

Although there are some concerns regarding the potential for missed studies and the unknown methodological quality of the included studies, the results across the seven included studies are consistent and support the authors conclusions.

Implications of the review for practice and research
Practice: The authors stated that the results suggested that unrestricted use of new generation oral anticoagulant agents as an adjunct to dual antiplatelet therapy after ACS cannot be recommended. They also stated that unrestricted use of triple antithrombotic therapy in patients after ACS may not be the right way forward.

Research: The authors did not state any implications for research.

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