Direct thrombin inhibitors in acute coronary syndromes: principal results of a meta-analysis based on individual patients' data

The Direct Thrombin Inhibitor Trialists' Collaborative Group

Authors' objectives
To obtain reliable and precise estimates of the effect of direct thrombin inhibitors in the management of acute coronary syndromes and during percutaneous coronary intervention, and to assess treatment benefit in clinically important subgroups, using individual patient data (IPD).

Searching
Potentially eligible trials were identified by formal computer-aided searches of MEDLINE, EMBASE and the Cochrane Controlled Trials Register. In addition, the reference lists of trials and review articles, abstracts, meeting proceedings and trial registries were examined. Other investigators and the manufacturers of direct thrombin inhibitors were also contacted. A collaborative group was formed and a protocol was published (see Other Publications of Related Interest no.1).

Study selection
Study designs of evaluations included in the review
The review was prospectively limited to IPD from randomised trials involving a minimum of 200 patients, with at least 100 patients in the control group.

Specific interventions included in the review
Comparisons of direct thrombin inhibitors (hirudin, bivalirudin, argatroban, efegatran or inogatran) with heparin were included. The various doses and treatment durations were reported in the paper. Trials that used excessive and clinically irrelevant doses of direct thrombin inhibitor or heparin were excluded.

Participants included in the review
The participants had to be patients with acute coronary syndromes who had ST elevation and were eligible for thrombolytic therapy, those with acute coronary syndromes who did not have ST elevation, or those who were undergoing percutaneous coronary intervention.

Outcomes assessed in the review
The trials had to record data on death and myocardial infarction (MI) to be included. The primary efficacy outcome was the composite of death or MI at the completion of active treatment. These outcomes were also examined at 7 and 30 days and by time-to-event analysis after 30 days. The other outcomes of interest were stroke, major bleeding, intracranial bleeding (all within 24 hours of cessation of study drug treatment), recurrent ischaemic events and the need for revascularisation, including percutaneous coronary intervention and coronary artery bypass graft surgery. The definitions of MI, stroke and major bleeding differed among the trials, although the definition of MI incorporated symptoms, an increase in cardiac enzymes and electrocardiographic changes in each one.

How were decisions on the relevance of primary studies made?
The process by which the study were selected and the reasons for exclusion were described in the paper using a flow diagram. The authors do not state how many of the reviewers were involved in the study selection process. The trial investigators were contacted throughout the review process.

Assessment of study quality
For each study, extensive consistency and completeness checks were carried out by the coordinating centre, followed by preliminary analyses to ensure agreement with the main published result. Any discrepancies were resolved through direct contact with the data management personnel of the individual trials. The authors do not state how many of the reviewers were involved in the validity assessment process. Contact with the trial investigators was maintained.
throughout the review process.

**Data extraction**
IPD were requested on the following: baseline entry characteristics; allocated study treatments; dates of randomisation; dates of scheduled and actual end of treatment; dates of last follow-up; dates of outcome events; and outcomes. The data were transferred in electronic format to the coordinating centre. Any discrepancies were resolved through direct contact with the data management personnel of the individual trials.

**Methods of synthesis**
How were the studies combined?
The outcome data from the different trials were combined using a modified Mantel-Haenszel method (see Other Publications of Related Interest nos.2-3), and odds ratios (ORs) with 95% confidence intervals (CIs) were presented. For time-to-event analyses, the data were analysed by Cox's regression analysis, with study treated as a stratum. The results were presented as hazard ratios with 95% CIs. The survival distribution between the groups was compared using a log rank test.

How were differences between studies investigated?
The trials were examined for statistical evidence of heterogeneity using the chi-squared test. Subgroup analyses were undertaken by qualifying event, by agent and by patients actually undergoing percutaneous coronary intervention. For the purpose of analyses by agent, the univalent thrombin inhibitors (argatroban, efegatran and inogatran) were grouped together.

**Results of the review**
Eleven randomised controlled trials (n=35,970) met the inclusion criteria.

Compared with heparin, direct thrombin inhibitors were associated with a lower risk of death or MI at the end of treatment (OR 0.85, 95% CI: 0.77, 0.94) and at 30 days (OR 0.91, 95% CI: 0.84, 0.99). This was due primarily to a reduction in MIs (OR 0.80, 95% CI: 0.71, 0.90) with no apparent effect on deaths (OR 0.97, 95% CI: 0.83, 1.13). The subgroup analyses suggested a benefit of direct thrombin inhibitors on death or MI in trials of both acute coronary syndromes and percutaneous coronary interventions. A reduction in death or MI was seen with hirudin and bivalirudin but not with univalent agents. Compared with heparin, there was an increased risk of major bleeding with hirudin but a reduction with bivalirudin. There was no excess in intracranial haemorrhage with direct thrombin inhibitors.

**Authors' conclusions**
Direct thrombin inhibitors were superior to heparin for the prevention of death or MI in patients with acute coronary syndromes. This information should prompt further clinical development of direct thrombin inhibitors for the management of arterial thrombosis.

**CRD commentary**
The research question and study selection criteria were clearly stated and have been published as a protocol (see Other Publications of Related Interest no.1). A collaborative group was formed and comprehensive searches were undertaken to identify relevant trials. It seems unlikely that trials will have been missed by this approach. IPD were obtained for all potentially relevant trials and the reasons for excluding trials were given. The data were obtained by direct contact with the trial investigators and were checked and verified appropriately with the trial investigators. The analysis undertaken seems appropriate, although as the authors themselves mention, the number of subgroup analyses means that these results should be interpreted with some caution. This was a very thorough and well-conducted review of IPD.

The authors' conclusions seem appropriate and follow from the results of the review.
Implications of the review for practice and research

Practice: The authors state that the consistency of these results with the findings of other trials confirms the superiority of direct thrombin inhibitors over heparin, and supports the rationale for the further development of these agents for the management of patients with acute coronary syndromes.

Research: The authors state that further studies are needed to assess direct thrombin inhibitors in patients undergoing percutaneous coronary intervention. Further studies may be needed to assess the role of direct thrombin inhibitors in patients with non-ST elevation acute coronary syndromes being treated with a combination of aspirin and clopidogrel, and in those with ST-elevation acute MI receiving a combination of fibrinolytic therapy and a glycoprotein IIb/IIIa inhibitor. The optimum duration of treatment with more potent antithrombotic agents, such as direct thrombin inhibitors, in patients presenting with unstable angina or acute MI, has yet to be defined. Further trials are also needed to clarify the effectiveness of univalent thrombin inhibitors.

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