Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials

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CRD summary
This review concluded that, compared with conservative therapy, the use of early invasive therapy to treat non-ST-segment elevation acute coronary syndromes improves long-term survival and reduces the risk of late myocardial infarction and rehospitalisation for unstable angina. Overall, the conclusions follow from the data presented, but the lack of a validity assessment makes it difficult to assess their reliability.

Authors' objectives
To determine whether early invasive therapy for the management of non-ST-segment elevation acute coronary syndromes (NSTE-ACS) improves survival and reduces adverse cardiovascular events.

Searching
MEDLINE and Google Scholar were searched from 1990 to 2006; the search terms were reported. In addition, experts were contacted for additional studies and the Science Citation Index was used to cross-reference any relevant studies. Only English language studies were eligible for inclusion in the review.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were included in the review.

Specific interventions included in the review
Studies that compared early invasive therapy for the management of non-ST-segment elevation with a more conservative approach were eligible for inclusion. In addition, eligible studies had to ensure that glycoprotein IIb/IIIa inhibitors and/or thienopyridines and coronary stents were available for use during percutaneous coronary intervention (PCI). All of the included patients received aspirin and either unfractionated or low molecular weight heparin. Glycoprotein inhibitors were available during PCI and medical stabilisation in all but 3 trials; thienopyridines were used in all trials of PCI. All invasively treated patients were treated in catheterisation laboratories and continued medical treatment or underwent PCI or coronary artery bypass grafting, dependent on coronary anatomy. The majority of conservatively treated patients received antiplatelet and antithrombin agents; if symptoms persisted or in the event of haemodynamic or electrical instability or a large ischaemic burden on pre-discharge stress testing, patients were treated in the catheterisation laboratory.

Participants included in the review
Studies of patients with a diagnosis of NSTE-ACS were eligible for inclusion. Patients who had chronic stable angina or with ST-segment elevation myocardial infarction (MI), and who used fibrinolytic agents were excluded from the review. The mean or median age of the included participants ranged from 62 to 70 years; 27 to 39% were women; 12 to 39% had diabetes; 22% to 39% had had a previous MI; and 21 to 41% were current smokers.

Outcomes assessed in the review
The primary outcome assessed in the review was all-cause mortality. The secondary end points included nonfatal MI, recurrent unstable angina that required rehospitalisation and the rate of revascularisation.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.
Data extraction
Three reviewers independently extracted the outcome data and any disagreements were resolved through the intervention of a fourth reviewer. Intention-to-treat data were extracted for each outcome, along with adjunctive medications and the proportion of patients who received glycoprotein IIb/IIIa inhibitors and coronary stents. Risk ratios (RRs) with 95% confidence intervals (CIs) and the number-needed-to-treat were calculated.

Methods of synthesis
How were the studies combined?
The studies were combined and pooled RRs with 95% CIs calculated using a fixed-effect (Mantel-Haenszel) model. Publication bias was assessed using funnel plots.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q statistic. Subgroup analyses were performed on studies with a similar relative difference in the use of revascularisation between treatment arms at follow-up and on studies with a similar median time of angiography.

Results of the review
Seven RCTs (n=8,375) were included in the review.

For mortality and MI, the mean follow-up time was 23.7 months. Compared with conservative therapy, early invasive therapy reduced the risk of all-cause mortality (RR 0.75, 95% CI: 0.63, 0.90, p=0.001) and nonfatal MI (RR 0.83, 95% CI: 0.50, 1.34, p=0.43) at 2 years' follow-up. When analyses for specific time points were performed, no significant reductions were seen for earlier times (1, 6 or 12 months). The rate of rehospitalisation for unstable angina was also reduced in the invasive therapy group at a mean of 13 months' follow-up (RR 0.69, 95% CI: 0.65, 0.74, p<0.0001). With the exception of heterogeneity in the analysis of nonfatal MI, which was due to the inclusion of one particular trial, there was no evidence of publication bias or heterogeneity.

Authors' conclusions
The use of early invasive therapy, compared with conservative therapy, to treat NSTE-ACS improves the long-term survival of patients and reduces the risk of late MI and rehospitalisation for unstable angina.

CRD commentary
This review answered a clear review question. The literature search appears adequate and considered the risk of publication bias, although some studies might have been missed through the exclusion of non-English language studies. The authors took appropriate steps to reduce bias and error during the data extraction process, but it is unclear whether similar steps were taken at the study selection stage. It is also difficult to assess the reliability of the data since the authors do not appear to have carried out a validity assessment. They did, however, consider the differences between the studies and try to determine the effects of heterogeneity through subgroup analyses. Overall, the conclusions appear to follow from the data presented, but the lack of a validity assessment makes it difficult to assess the reliability of the data.

Implications of the review for practice and research
Practice: The authors stated ‘the current body of evidence clearly supports early invasive therapy in the management of NSTE-ACS’.

Research: The authors stated that further research is required to determine more precisely the ‘optimal timing of this approach [invasive therapy], the appropriate concomitant adjuvant therapy required, and whether additional risk stratification is needed before angiography is performed’.

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