Invasive therapy along with glycoprotein IIb/IIIa inhibitors and intracoronary stents improves survival in non-ST-segment elevation acute coronary syndromes: a meta-analysis and review of the literature

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CRD summary
This review found that a routine invasive approach, with adjunctive use of glycoprotein IIb/IIIa inhibitors and stents, improves survival in patients with acute coronary syndromes, compared with standard medical therapy. Although the conclusions appear to follow from the evidence presented, the poor reporting of some of the review methods makes it difficult to verify the findings.

Authors' objectives
The authors' aim was to determine whether a routine invasive approach, with adjunctive use of glycoprotein IIb/IIIa inhibitors (GPIIb/IIIa) and intracoronary stents, improves survival over standard medical therapy in people with acute coronary syndromes (i.e. unstable angina and non-ST-segment elevation myocardial infarction).

Searching
MEDLINE, EMBASE, CRISP, meta Register of Controlled Trials and the Cochrane Library were searched from 1990 to 2003 for randomised clinical trials; the search terms were reported. In addition, relevant journals were handsearched, investigators and experts were contacted, and the Science Citation Index was used to cross-reference articles meeting the inclusion criteria.

Study selection
Study designs of evaluations included in the review
Randomised clinical trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared routine invasive therapy (i.e. percutaneous transluminal coronary angioplasty) with conservative management were eligible for inclusion. Use of enhanced antiplatelets agents, such as GPIIb/IIIa or thienopyridines, and intracoronary stents also formed part of the inclusion criteria. In one of the included studies, ticlopidine and aspirin were used as the enhanced antiplatelet agents. GPIIb/IIIa inhibitors were used in 0 to 94% of the participants. Studies in which fibrinolytic therapy was administered during the index hospitalisation were excluded, as were studies that compared early versus late invasive therapy. All of the included trials also used anti-anginal drugs, standard antiplatelet medications (i.e. aspirin), and antithrombin agents (unfractionated or low molecular weight heparin).

Participants included in the review
Studies with participants who had a diagnosis of unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) were eligible for inclusion. Studies with participants having a diagnosis of ST-segment elevation myocardial infarction or chronic stable angina were excluded. Full baseline characteristics of the participants randomised to each group were given for each trial. The median age of the participants ranged from 61 to 66 years, with males accounting for 58 to 75% of the participants in each randomised group. Pre-existing coronary artery disease was present in 0 to 39% of the participants, with 3 to 100% of the included participants being enrolled because of a diagnosis of NSTEMI. The percentage of participants showing an ischaemic electrocardiogram (defined as ST-segment depression on electrocardiogram at entry) ranged from 0 to 47%. Coronary stent use varied from 18 to 65% at trial level: this ranged from 31 to 69% in the intervention arm, and from 6 to 70% in the control (noninvasive) arm.

Outcomes assessed in the review
Studies that reported mortality data for at least 6 months' follow-up were eligible for inclusion. The authors presented results for death, and death or myocardial infarction (MI). Death at 6 to 12 months was considered to be the primary
outcome, with secondary outcomes being 1-month mortality, 24-month mortality, and a composite end point of death or MI based on gender and troponin status.

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
Two independent reviewers extracted the data, although the authors did not state how any discrepancies were resolved. Data were extracted for death, death or MI, and death or MI based on gender and troponin status (elevated troponin equates to a troponin T level greater than 0.01 ng/mL). Mortality at 1 month was defined as 'early', at 6 to 12 months as 'intermediate', and at 24 months as 'late'. Where both 6- and 12-month data were given, the latter was used. The data extracted were tabulated and the risk ratio (invasive versus conservative management) for each outcome at each time point (1, 6, 12 and 24 months) was calculated.

Methods of synthesis
How were the studies combined?
Pooled analyses using fixed-effect and random-effects (DerSimonian and Laird) models were computed. Fixed-effect, pooled relative risk (RR) estimates and 95% confidence intervals (CIs) were reported. Publication bias was investigated using both Begg's funnel plot and Egger's plot. The RRs from 3 trials completed prior to the GPIIb/IIIa inhibitor and intracoronary stent era were also pooled.

How were differences between studies investigated?
Heterogeneity was assessed using the Q statistic. Sensitivity analyses investigating differences between genders, and between high and low risk patients, were also conducted.

Results of the review
Five randomised clinical trials (6,766 participants) were included in the pooled analysis.

One-month mortality: the pooled analysis showed no change in mortality (RR 0.98, 95% CI: 0.57, 1.67).

Intermediate mortality (6 to 12 months; data from 5 studies): routine invasive therapy reduced mortality by 20% (RR 0.80, 95% CI: 0.63, 1.03). Although this did not quite reach statistical significance, there was evidence of statistical heterogeneity (P=0.038).

Sensitivity analyses: the analysis using data from high-risk participants showed a greater effect of the intervention (RR 0.70, 95% CI: 0.52, 0.96) at the intermediate time-point and reduced heterogeneity (from P=0.038 when using all participants to P=0.10).

Twenty-four-month mortality (2 studies): routine invasive therapy reduced mortality at 6 or 12 months by 23% (RR 0.77, 95% CI: 0.60, 0.99).

The trend for mortality across the three time points was non significant (Ptrend=0.50).

When using a composite end point of mortality and MI, the RR was significant at all time points: the RR was 0.61 (95% CI: 0.45, 0.84) at 1 month, 0.75 (95% CI: 0.63, 0.89) at 6 months, and 0.78 (95% CI: 0.65, 0.92) at 12 months. The trend across these three time-points was non significant (Ptrend=0.22). No data were available for this outcome at 24 months.

Sensitivity analyses for the composite end point: for the intermediate outcome (6 and 12 months), invasive therapy
reduced the RR for the composite end point to 0.74 (95% CI: 0.59, 0.94) in troponin-positive patients (n=2,322), compared with 0.82 (95% CI: 0.59, 1.14) in troponin-negative patients (n=1,815). For the same time and end point in males (n=4,299), invasive therapy reduced the RR of an event by 32% (RR 0.68, 95% CI: 0.57, 0.81). The RR of an event in women (n=2,188) was 1.07 (95% CI: 0.82, 1.41).

There was no evidence of publication bias (P=0.15 using both Egger's and Begg's plots).

Authors' conclusions
The conclusion reached by the authors was that invasive therapy with adjunctive use of GPIIb/IIIa inhibitors and intracoronary stents improves survival in UA and NSTEMI patients.

CRD commentary
The review question was clearly stated in terms of the intervention, outcomes and study designs eligible for inclusion. However, a certain amount of detail that would help the reader to assess the validity of the study is missing. For example, there was no information on whether or how the validity and methodological quality of the included studies was assessed. The major electronic databases were searched and the search terms were given. There was a further attempt to capture studies not indexed in the databases, but unpublished data might have been under-represented. There was no statement about language restrictions but, since all of the included studies were published in English, the possibility of language bias cannot be ruled out.

Despite some evidence of statistical heterogeneity assessed by the Q statistic, the authors claimed that the random-effects and fixed-effect models showed similar results and consequently reported only the results from the fixed-effect analysis. In the presence of significant heterogeneity, a random-effects model is preferable. There was insufficient information to determine how many of the 5 trials had been combined to give a pooled estimate at 1 month.

The authors acknowledged that the results of their analysis have to be considered within the context of the heterogeneity, and acknowledged the limitations of their study in terms of the limited number of included trials. They did, however, consider that the study had sufficient power to detect a real effect. In addition, not all of the participants were accounted for in the sensitivity analyses. If selective inclusion criteria were used, the validity of the stratified results might be compromised. Furthermore, even when statistically significant, the effect sizes were small. The authors' conclusions should therefore be treated with some caution.

Implications of the review for practice and research
Practice: The authors stated that the study strengthens the American College of Cardiology/American Heart Association guidelines for the management of high-risk UA and NSTEMI patients, and provides greater insight into the care of lower risk patients.

Research: The authors stated that improved risk stratification of troponin-negative patients will be an important direction for research, as will risk-stratification techniques to investigate potential benefits of the invasive therapy in women.

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