Optimal timing of coronary invasive strategy in non-ST-segment elevation acute coronary syndromes: a systematic review and meta-analysis


CRD summary
This review concluded that there was insufficient evidence in favour of or against an early invasive approach in patients with NSTE-ACS. A more definitive RCT was warranted in order to guide clinical practice. The authors’ conclusions and recommendations for a future RCT accurately reflect the inconclusive evidence base and are likely to be reliable.

Authors’ objectives
To assess the evidence for early compared to late invasive treatment for non-ST-segment elevation acute coronary syndromes (NSTE-ACS). This paper updated a previous review (see Other Publications of Related Interest).

Searching
PubMed and Google Scholar, two clinical trials registries and conference proceedings from five relevant scientific associations were searched. The PubMed search strategy was reported. The search for randomised controlled trials (RCTs) updated the previous review search and sought trials published between September 2010 and May 2012. The search for observational studies covered 1994 to May 2012.

Study selection
RCTs and observational studies that assessed allocation to early or delayed coronary revascularisation in patients with NSTE-ACS were eligible for inclusion. Coronary revascularisation could be either percutaneous coronary intervention or coronary artery bypass grafting. In RCTs intervention less than 20 hours after hospitalisation was considered early; in observational studies the cut-off was 24 hours. Delayed intervention groups had to be treated with standard medical therapy before subsequent surgery. Studies that compared invasive with conservative strategies or with selective intervention for refractory angina only were excluded. The primary outcome was overall mortality; secondary outcomes (defined in the review) were recurrent myocardial infarction, major bleeding complications, refractory ischaemia and repeated revascularisation.

In the included RCTs timing of the invasive treatment ranged from 0.5 to 14 hours in the early intervention groups and from 20.5 to 86 hours in the delayed intervention groups. Follow-up was at six months in five trials and at one month in two trials. One RCT used glycoprotein IIb/IIIa inhibitors in the delayed strategy arm only and one observational study primarily in the early strategy arm; all other studies used them equally across arms. Average age ranged from 62 to 70 years. Most patients were male. From 13% to 46% of the patients with three vessel disease (reported for RCTs only). Between 13% and 95% of patients had ST-segment depression. Between 13% and 38% of patients had diabetes.

The authors did not state how many reviewers assessed the papers for inclusion.

Assessment of study quality
Two reviewers assessed the quality of the included studies using the Cochrane Collaboration risk of bias tool for RCTs and the Newcastle-Ottawa scale for cohort studies for observational studies.

Data extraction
Data to enable calculation of odds ratios (OR) with 95% confidence intervals (CI) were extracted on an intention-to-treat basis. The longest available follow-up was used for outcome assessment.

Two reviewers independently extracted data using prespecified forms.

Methods of synthesis
Pooled odds ratios with 95% confidence intervals were calculated using the DerSimonian and Laird random-effects model with a 0.5 continuity correction for zero events. Statistical heterogeneity was assessed using the X² and I² statistics. Sensitivity analyses were used to assess the impact of removing individual studies from the analysis and of
including events from immediate and early treatment groups from a three arm trial. Observational studies were included in a separate analysis.

**Results of the review**

Eleven studies were included in the review: seven RCTs (two new trials) with 5,370 patients and four observational studies (all new studies) with 77,499 patients. The RCTs were generally at low risk of bias but two had unclear randomisation and allocation concealment and in one it was unclear whether the outcome assessment was blinded. The observational studies were large and generally well-conducted: two scored a maximum 9 on the Newcastle-Ottawa scale, one scored 8 and one scored 7.

**Overall mortality:** There was no statistically significant difference between the groups in the proportion of patients who died; 3.9% of those in the early treatment groups died compared to 4.7% in the delayed groups (OR 0.83, 95% CI 0.64 to 1.09; seven RCTs; $I^2=0\%$). This result was replicated in the analysis of observational studies but significant heterogeneity was present ($I^2=78\%$).

**Secondary outcomes:** There was a statistically significant lower chance of refractory ischaemia in the early intervention groups compared to delayed intervention (3.8% versus 7.3%; OR 0.55, 95% CI 0.35 to 0.86; six RCTs; $I^2=60\%$). There was evidence of moderate heterogeneity but the direction of effect was consistent.

There were no statistically significant differences between the groups for the outcomes of recurrent myocardial infarction, major bleeding or repeat revascularisation in the RCTs and the observational studies.

Sensitivity analyses did not alter the estimates of effect for any outcome.

**Authors’ conclusions**

There was insufficient evidence in favour of or against an early invasive approach in patients with NSTE-ACS.

**CRD commentary**

This updated review had a clear question and specific reproducible inclusion criteria that were broader than the previous review as observational studies were included. The search was reasonable and not subject to restrictions. Two reviewers were involved in quality appraisal and data extraction, which reduced the chances of bias or error; this was not reported for study selection. The assessment of study validity used appropriate tools and was fully reported. Study quality was generally high.

The synthesis used appropriate methods. Use of separate analyses for observational studies was reasonable. Heterogeneity was assessed and some attempts made to explore this; the presence of substantial heterogeneity was recognised in the synthesis and conclusions where appropriate. The analysis did not distinguish between percutaneous coronary intervention and coronary artery bypass grafting and therefore did not investigate any difference in the impact of delay between these populations. The available studies may not have allowed for the review to consider these separately but this diversity in the study populations should be borne in mind.

The authors’ conclusions accurately reflect the inconclusive evidence base and are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated a need for a more definitive RCT to compare early versus delayed surgical intervention (revascularisation) in patients with NSTE-ACS. They made detailed recommendations for the conduct of such a trial, including the power required to detect the 30-day mortality estimated in their analysis. They also stated that high risk groups should be a focus of such a trials, patients should be followed up for one year and adjunctive medical therapy should be planned. Secondary endpoints should include subsequent myocardial infarction and major bleeding.

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