Long-term benefits of an early invasive management in acute coronary syndromes depend on intracoronary stenting and aggressive antiplatelet treatment: a metaregression


CRD summary
This well-conducted review concluded that the benefits of an early invasive approach in patients with acute coronary syndromes are associated with aggressive antiplatelet treatment and stenting, thus supporting the use of an early invasive approach providing these interventions are involved. This conclusion should be reliable.

Authors' objectives
To evaluate the impact of stenting and aggressive antiplatelet treatment on the effect of early invasive management in patients with acute coronary syndromes (ACS).

Searching
PubMed (from 1966 to March 2004) and BioMed Central, Cardiosource, the Cochrane CENTRAL Register, ClinicalTrials.gov, Current Contents, LILACS and meta Register of Controlled Trials (up to December 2003) without any language restrictions. Only published studies were included in the review.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that used an intention-to-treat analysis were eligible for inclusion. Studies with incomplete (less than 90%) follow-up were excluded.

Specific interventions included in the review
Studies comparing early invasive management with delayed invasive or ischaemia-guided conservative management were eligible for inclusion.

Participants included in the review
Studies of patients with non-ST-elevation ACS were eligible for inclusion. Studies of patients having coronary artery bypass surgery as the sole revascularisation method, or where patients in cardiogenic shock were selected, were excluded. The mean age of the participants ranged from 59 to 70 years, and the percentage of males from 61 to 97%. Between 15 and 43% of the participants had had a previous myocardial infarction (MI).

Outcomes assessed in the review
The primary outcomes were long-term mortality and a long-term composite rate of death or nonfatal MI, measured at the longest follow-up. The outcomes reported in the included studies were death, MI, recurrent ischaemic events, in-hospital stabilisation, rehospitalisation, refractory angina, abnormal exercise tolerance test, duration of hospital stay and size of MI.

How were decisions on the relevance of primary studies made?
One reviewer screened titles and abstracts. Two reviewers independently assessed full manuscripts for inclusion. Any disagreements were resolved by consensus.

Assessment of study quality
The authors cited a prior publication for the quality criteria used. This publication reported using a scoring system, modified from Jadad and Biondi-Zoccai et al., with one point allocated for each of the following: statement of objectives; explicit inclusion and exclusion criteria; description of the interventions; objective means of follow-up; description of adverse events; power analysis; description of statistical methods; multicentre design; discussion of
withdrawals; and details on medical therapy. Two reviewers independently assessed study quality. Any disagreements were resolved by consensus.

Data extraction
Two reviewers independently extracted the data. Any disagreements were resolved by consensus. The proportion of participants experiencing each outcome was extracted from each study.

Methods of synthesis
How were the studies combined?
Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the binary outcomes using a random-effects meta-analysis. Publication bias was assessed using funnel plots.

How were differences between studies investigated?
Heterogeneity was assessed using the Q and I-squared statistics. A meta-regression, using the natural log (OR) as the dependent variable, was used to test for an interaction between covariables and effect size estimates of the management regimens. A weighted least-squares model was used to adjust for study size. The primary meta-regression investigated interactions with aggressive antiplatelet treatment or stenting. The other covariables explored were age, gender, diabetes mellitus, previous MI, admission diagnosis, time to catheterisation, revascularisation/catheterisation ratio, percutaneous coronary intervention/total revascularisation ratio, stress testing, crossover rate to invasive arm, delayed invasive versus conservative management, and control event rate. The Spearman test was used to assess colinearity between significant univariate predictors of log (OR).

Results of the review
Ten RCTs (n=9,990) were included in the review. In the included studies, the longest follow-up period ranged from 1 to 24 months.

Early invasive management showed a statistically significant reduction in the occurrence of death or MI when compared with delayed invasive or conservative management (OR 0.79, 95% CI: 0.65, 0.95, P=0.01), but not long-term mortality rates (OR 0.85, 95% CI: 0.63, 1.15, P=0.29). Aggressive antiplatelet treatment and stent implantation were predictors of the benefits of early invasive management (P=0.005 and P=0.011, respectively), and were associated with improved long-term survival (P=0.009 and P=0.014, respectively). The other significant covariate was the revascularisation/catheterisation ratio (P=0.038), suggesting that the more aggressive the invasive strategy, the greater the clinical benefits. Glycoprotein IIb/IIa inhibitors were significantly associated with treatment effects (P=0.041), but thienopyridines were not (P=0.091). Further sensitivity analyses were conducted that supported these results.

Heterogeneity was statistically significant for the primary outcome (P=0.05, I-squared 47%). However, this was eliminated with stratification according to stenting or aggressive platelet treatment. There was no evidence of publication bias.

Authors’ conclusions
The benefits of an early invasive approach in patients with ACS are significantly associated with aggressive antiplatelet treatment and stenting, thus supporting the use of an early invasive approach providing these interventions are involved.

CRD commentary
The review question was clear in terms of the participants, interventions, outcomes and study design. Several relevant sources were searched for primary studies. The review was restricted to published studies, thus increasing the potential for publication bias, although the authors investigated this and found no evidence of it in their primary outcome. Each stage of the review was conducted in duplicate, thereby reducing the potential for error and bias. The authors stated that quality was assessed, but the tool used was not reported, the results were not discussed, and insufficient study details were provided to assess quality. Appropriate analyses were used, and heterogeneity and associations between variables
were extensively explored. On the whole, this was a well-conducted review and the conclusions should be reliable.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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