Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis


CRD summary
This review concluded that invasive treatment strategies appear to have comparable benefit in reducing composite end points in both men and high-risk women with non ST-segment elevation acute coronary syndromes. However, evidence supports the use of a conservative strategy in low-risk women. Concerns about the reliability of the data suggest that the conclusions should be interpreted with caution.

Authors' objectives
To compare the effects of early invasive versus conservative strategies for the management of unstable angina and non ST-segment elevation myocardial infarction (STEMI) in men and women.

Searching
MEDLINE and the Cochrane CENTRAL Register were searched from 1970 to April 2008; the search terms were reported and no other search restrictions were applied. Topic experts were contacted and abstracts from major cardiology meeting were checked for additional studies. Only peer-reviewed studies were eligible for inclusion.

Study selection
Randomised controlled trials (RCTs) comparing invasive and conservative treatment strategies in individuals with a diagnosis of non ST-segment elevation acute coronary syndromes (STE ACS) were eligible for inclusion. Eligible outcomes included mortality, nonfatal myocardial infarction (MI) and rehospitalisation with ACS, or any composite of these outcomes. Invasive treatments were defined as referral for coronary angiography followed by revascularisation if appropriate. Conservative treatments were defined as pharmacological management with referral for angiography only in cases of recurrent symptoms of unprovoked ischaemia or objective evidence of inducible ischaemia or noninvasive testing. Trials were excluded from the review if they enrolled primarily patients with stable angina or acute STEMI; if fibrinolytic therapy was administered to all patients; if patients received coronary angiography before enrolment; or if reliable gender-specific outcome data were not available.

In the included studies, the weighted mean age was 64.1 years for women and 61.3 years for men. Male participants were significantly more likely to be active smokers, to have a history of MI, and to have elevated cardiac biomarkers at the time of randomisation. Female participants were significantly more likely to have co-morbidities at baseline including diabetes mellitus, hyperlipidaemia and hypertension. Similar incidences of ST segment depression were reported in both men and women. In half of the trials glycoprotein IIb/IIIa inhibitors could be used. Women who underwent coronary angiography in the invasive treatment group were more likely to have no significant coronary artery disease (CAD); men were found to more likely have three vessel or left main disease.

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
Outcome event rates were collected for the following time points: randomisation to hospital discharge, hospital discharge to 12 months' follow-up, and randomisation to 12 months' follow-up. Study authors were approached for gender-specific data. Data were also extracted and substratified by the presence or absence of cardiac biomarker elevation (creatine kinase MB or troponin) and ST-segment deviation on electrocardiogram. Patients without such data were excluded from the analysis. The authors also recorded outcomes for those patients in each treatment or control group who eventually underwent percutaneous coronary intervention or coronary artery bypass graft (CABG) surgery. For those patients in the invasive study group, the extent of CAD at the time of coronary angiography was also
recorded; diseased vessels were defined as a major epicardial vessel or CABG with at least 50% stenosis. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each outcome.

The authors did not state how many reviewers performed the data extraction, but all the collected data were verified by the individual study authors.

**Methods of synthesis**

The studies were combined and pooled ORs, with 95% CIs, were calculated using a DerSimonian and Laird random-effects model; heterogeneity was assessed using the $\chi^2$ statistic. The authors stated that the meta-analysis had 80% power to detect a 33% difference in the relative odds of mortality, MI or rehospitalisation with ACS in the treatment groups between men and women. Heterogeneity between genders and between high-risk subgroups was assessed by calculating interaction terms between treatment strategy and subgroup for each individual trial. A p-value was calculated for the combined interaction effect using a random-effects model, and a value of less than 0.05 was considered significant. The authors stated that they did not make any corrections for multiple hypothesis testing.

**Results of the review**

Eight RCTs with 10,412 participants (3,152 women and 7,260 men) were included in the review. Sample sizes ranged from 131 to 2,220.

The authors reported that none of the trials was adequately powered to identify differences in outcomes between specific subgroups defined according to risk level or gender.

Overall, the only statistically significant difference between invasive and conservative strategies was for rehospitalisation with ACS (OR 0.68, 95% CI: 0.55, 0.84), which favoured the invasive strategy.

A statistically significant difference in favour of an invasive strategy was reported for the composite outcome of death, MI or ACS in men (OR 0.73, 95% CI: 0.55, 0.98); the OR for women was not statistically significant and no significant heterogeneity between genders was identified (p-value for interaction, 0.26). A statistically significant reduction in the composite outcome was reported for biomarker-positive women in favour of the invasive strategy (OR 0.67, 95% CI: 0.50, 0.88), but the difference in death or MI was not statistically significant. There were no statistically significant differences between invasive and conservative strategies in biomarker-negative women for either the composite outcome or the outcome of death or MI. However, the latter showed a non significant increase in favour of conservative management (OR 1.35, 95% CI: 0.78, 2.35; p-value for interaction, 0.08). A significantly better composite outcome was reported in favour of invasive management for biomarker-positive men (OR 0.56, 95% CI: 0.46, 0.67). Corresponding differences in biomarker-negative men were not statistically significant. Significant statistical heterogeneity was detected for the composite end point ($\chi^2=39.7; p<0.001$) and for death or MI ($\chi^2=34.5; p<0.001$) in men, and for death or MI in women ($\chi^2=17.0; p=0.02$). Sensitivity analyses suggested that three trials were responsible for the largest contribution in heterogeneity, and that this was not explained by the publication year or concomitant therapies alone. Other analyses and subgroup analyses were reported in the review.

**Authors' conclusions**

Invasive treatment strategies appear to have comparable benefit in men and high-risk women with non STE ACS in reducing the composite end point of death, MI or rehospitalisation with ACS. However, in low-risk women, the evidence supports new recommendations for the use of a conservative strategy.

**CRD commentary**

This review answered a clear research question and a number of appropriate literature sources were searched. However, the authors only included data from peer-reviewed studies which may mean that some relevant data, albeit of questionable validity, was not included in the analysis. The risk of reviewer error and bias is difficult to assess as the reviewers did not report their methods clearly, although data extracted from the studies were validated by the original study authors. The reviewers also fail to carry out an assessment of study validity, which makes it difficult to assess the reliability of their findings. Sources of heterogeneity were, however, identified and investigated in supplementary analyses. The authors also acknowledged and discussed the potential effects of a number of limitations of their review.
In particular, they highlighted significant statistical heterogeneity in a number of analyses and stated that their subgroup analyses were based on data from trials not sufficiently powered to detect differences in outcome. In conclusion, given concerns about the differences between trials, the reliability of subgroup data and the lack of information about trial quality, it is difficult to assess the reliability of the review findings and so a cautious interpretation is advised.

Implications of the review for practice and research

Practice: The authors stated that this review provides evidence to support the updated guidelines of the American College of Cardiology/American Heart Association, which recommend using a conservative strategy in low risk women with non STE ACS.

Research: The authors stated that further research, which includes novel methods for identifying women who may be at high risk of developing adverse outcomes after non STE ACS and whose risk may be modifiable by use of an invasive strategy, is required. They also reported that their findings about the modification of high-risk findings according to gender need confirmation in prospective trials.

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Bibliographic details

Other publications of related interest
Granger CB. Review: an early invasive strategy has similar benefits in men and women with NSTEMI or unstable angina. Evid Based Med 2009;14:19

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.