Meta-analysis of ischemia-modified albumin to rule out acute coronary syndromes in the emergency department  

CRD summary
The authors concluded that the combination of negative electrocardiogram, negative troponin and negative ischaemia-modified albumin within 3 hours of chest pain has a high probability of excluding acute coronary syndrome in the emergency department. The poor reporting of review methods and differences in results between studies meant it was not possible to confirm the reliability of these results.

Authors’ objectives
To assess the performance of ischaemia-modified albumin (IMA) in ruling out acute coronary syndrome (ACS) in patients attending the emergency department (ED).

Searching
MEDLINE was searched and unpublished data were obtained from known investigators.

Study selection

Inclusion criteria were not specified with respect to the study design.

Specific interventions included in the review
Studies that reported results for IMA obtained within 3 hours of symptoms were eligible for inclusion. Studies had to measure IMA using the automated albumin-cobalt binding assay as instructed by the manufacturer, report the analyser used, define an elevated IMA and document its derivation. Studies that also measured troponin had to measure it in the same sample as IMA. The included studies evaluated the following tests, either alone or in various combinations: IMA, cardiac troponin, myoglobin, rest myocardial perfusion imaging (MPI), electrocardiograph (ECG), creatine kinase-MB. In most studies the cut-off value for IMA was 85 U/mL; other studies used 75 U/mL. The review defined a negative IMA as an IMA of less than or equal to 85 U/mL, or as reported by the local institution receiver operating curve analysis. Some tests and combinations of tests that did not involve IMA were also included.

Reference standard test against which the new test was compared
Studies that reported an ACS diagnosis after completion of a chest pain evaluation protocol (acute diagnosis), discharge or defined post-discharge events (follow-up studies) were eligible for inclusion. In the review, an acute ACS diagnosis was defined as a discharge diagnosis of ST-elevation MI (STEMI), non-STEMI, or expert consensus diagnosis of ischaemia by a retrospective review of clinical data. All of the included studies offered stress testing and MPI in the evaluation of chest pain. In the review, post-discharge events (follow-up) included the composite of cardiac death, nonfatal myocardial infarction, the need for revascularisation, a positive diagnostic test for cardiac ischaemia, or symptoms for which ACS could not be excluded.

Participants included in the review
Studies of patients presenting in the ED with suspected ACS were eligible for inclusion. Studies had to clearly define the entry criteria and had to report the ACS pre-test probability. The review classified populations according to the baseline rate of MI and ACS prevalence as ’higher’ (17%) or ’lower’ (8%) risk.

Outcomes assessed in the review
Studies that reported composite outcomes had to report adverse events and losses to follow-up. The studies also had to define end points. The review assessed the sensitivity and negative predictive value (NPV).

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**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

For each study, the sensitivity and NPV were calculated for each test or combination of tests reported. For studies reporting serial troponin levels, the maximal value within the first 6 hours was used. In follow-up studies, patients without follow-up data were classified as lost to follow-up. In the review, the triple prediction test (TPT) was defined as positive if any one of ECG, troponin or IMA were positive; a negative TPT was defined as three negative tests.

**Methods of synthesis**

How were the studies combined?
The studies were grouped as acute ACS diagnosis studies and follow-up studies. The 'pooled' sensitivity and NPV values were calculated by summing the individual numerators and denominators. Point estimates and 95% confidence intervals (CIs) were calculated for each combination of tests. 'Pooled' analyses were based on data from between 1 and 3 studies.

How were differences between studies investigated?
Differences between the studies were discussed with respect to ACS rates.

**Results of the review**
Eight studies were included. There were 6 acute diagnosis studies (n=1,612) and 5 follow-up studies (n=1,307; 1,197 of whom were analysed); some studies were classified as both acute diagnosis studies and follow-up studies (classified according to the reference standard used).

Acute diagnosis studies.

Ten different combinations of tests were evaluated. Studies varied with respect to ACS rate: 2 studies had ACS rates of approximately 8%, 3 studies had ACS rates of approximately 17%, and 1 study had an ACS rate of 63%. The results of the individual studies were presented in forest plots (acute diagnosis and follow-up studies presented separately).

The sensitivity of the TPT was 94.4% (95% CI: 90, 97; based on 2 studies, n=571) and the NPV was 97.1% (95% CI: 95, 99; based on 3 studies, n=1,062). The addition of rest MPI to the TPT did not significantly improve sensitivity.

Follow-up studies.

Ten different combinations of tests were evaluated. The duration of follow-up ranged from 30 days to 6 months. Studies varied with respect to ACS rate: the rates ranged from 3.9% at 6 months in 1 study to 42.6% at 30 days in 1 study. The sensitivity of the TPT was 89.2% (95% CI: 82, 94; based on 1 study, n=519) and the NPV was 94.5% (95% CI: 95, 99; based on 2 studies, n=1,010). The addition of rest MPI to the TPT did not significantly improve sensitivity.

**Authors' conclusions**
The combination of a negative ECG, negative troponin and negative IMA has a high probability of ruling out ACS in the ED.

**CRD commentary**
The review appeared to address a clear question that was defined in terms of the participants and outcomes. The inclusion criteria stated that studies that evaluated IMA were eligible, but the review also evaluated IMA as part of the TPT and a variety of other tests and combinations of tests that did and did not contain IMA. Thus, the inclusion criteria were not strictly adhered to. Only one database was searched and attempts were made to locate unpublished data, but it is possible that some relevant studies might have been missed. In addition, it was not reported whether any language restriction had been applied. Study validity was not assessed, so the results from these studies and any synthesis might not be reliable. Sensitivity and NPV values were combined by simple averaging (effectively a fixed-effect meta-analysis weighted by sample size). It was not possible to determine if pooling was appropriate since statistical heterogeneity was not assessed and results for the individual studies were not reported. The lack of reporting of review methods, lack of a quality assessment of the individual studies, lack of reporting of differences in results between the studies, and probably inappropriate methods of pooling meant it was not possible to confirm the reliability of these results.

Implications of the review for practice and research

Practice: The authors stated that the results from the review are not generalisable and do not support the routine use of the TPT in clinical practice. Patients with a negative TPT but with a high-risk history or physical findings may still require further evaluation. Patients with an elevated IMA should be evaluated according to the usual protocols for ACS.

Research: The authors stated that an international trial (IMAGINE) is currently evaluating the role of IMA.

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