Heart-type fatty acid-binding protein in the early diagnosis of acute myocardial infarction: a systematic review and meta-analysis

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Published in:
Heart

DOI:
10.1136/hrt.2010.208272

Citation for published version (APA):
Heart-type fatty acid-binding protein in the early diagnosis of acute myocardial infarction: a systematic review and meta-analysis

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ABSTRACT

Objective To determine the accuracy of heart-type fatty acid-binding protein (H-FABP) as a new and early cardiac biomarker in the early diagnosis of acute myocardial infarction (AMI). The introduction of early and safe biomarkers could lead to (a) a large reduction in unnecessary hospital referrals of patients suspected of, but not having AMI and (b) an earlier start of treatment in patients with AMI.

Design Diagnostic meta-analysis.

Setting Hospital and pre-hospital.

Patients Consecutive patients suspected of having AMI.

Main outcome measures A summary estimate for sensitivity and specificity was calculated using the bivariate random-effects approach, and covariate analysis was used to examine sources of heterogeneity between studies.

Results A systematic search yielded 16 studies (3709 patients, prevalence of AMI 13–74%, male gender 49–94%, median age 64–76 years). The summary estimate was 84% (95% CI 76% to 90%) for sensitivity and 84% (95% CI 76% to 89%) for specificity. Covariate analyses revealed that the use of troponin in the reference standard for AMI (as opposed to creatine kinase or creatine kinase-myocardial band) had a significant impact on sensitivity.

Conclusion H-FABP does not fulfil the requirements needed for a safe and early diagnosis of AMI when used as a stand-alone test. Sound diagnostic studies examining the additional role of H-FABP combined with clinical findings and other diagnostic tests are needed to further clarify a potential future role for this cardiac biomarker.

INTRODUCTION

Timely diagnosis of acute myocardial infarction (AMI) is crucial, as this allows earlier initiation of appropriate treatment and improves patient outcome. According to guidelines,1 the diagnosis of AMI is based on a combination of history taking, ECG findings and the presence in serum of at least one biomarker for myocardial damage, preferably cardiac troponin I or T. A major limitation of troponin is its low sensitivity in detecting myocardial infarction in the hours immediately after the event: depending on the infarction size, troponin is increased in serum 6–8 h after the onset of symptoms. This means that myocardial infarction may go undetected during these first hours, as history taking, physical examination, ECG and current biomarker tests are often inconclusive.1,2

In primary care, patients with a clear suspicion of AMI will be referred to hospital for further testing. There is a need, however, to more reliably rule out AMI in the many patients with a (much) lower suspicion of AMI in primary care. Currently, many of these patients are (unnecessarily) referred to hospital. This leads to a large burden for both patients and the healthcare system. Also, in secondary care, there is the need for a more rapid diagnosis of AMI. Currently, when the initial ECG and troponin test are negative, many patients are subjected to hours of hospital monitoring and repeated blood testing.1 An earlier biomarker that can safely exclude or diagnose AMI in troponin-negative patients would greatly accelerate the diagnosis, thereby improving efficiency and quality of healthcare.

A potentially useful early biomarker is heart-type fatty acid-binding protein (H-FABP).3 This small unbound cytoplasmic protein is present in high concentrations in the myocardial cell and released into the circulation within minutes of myocardial ischaemia. Quite recently, several point-of-care tests for H-FABP have been introduced, enabling testing in a ‘near-patient situation’. Given these properties of early release and the availability of point-of-care testing, H-FABP may be a valuable diagnostic tool for AMI in both primary and secondary care.

The diagnostic performance of H-FABP has been investigated in several studies, yielding varying results. The aim of this systematic review was to determine the accuracy of H-FABP as a cardiac biomarker in the early diagnosis of AMI.

METHODS

Literature search

We performed a systematic electronic search of the PubMed and Embase databases for original articles published until 1 September 2009. Search terms used were ‘acute coronary syndrome’ and synonyms such as ‘ischaemic heart disease’ combined with ‘heart-type fatty acid-binding protein’. Box 1 shows the exact search terms used. For all relevant publications, the records retrieved with the ‘related articles’ link in PubMed were screened; reference lists were checked for other relevant studies.

Selection of publications

We screened title and abstract of all studies for relevancy. Full-text publications were retrieved for relevant articles written in English, Dutch, German or French. Studies were selected on the basis of (1)
the population included (ie, adults suspected of having an AMI),
(2) outcome (unstable angina and/or AMI), (3) index test
(quantitative or qualitative measurement of H-FABP), (4) refer-
test (clear description of the reference test used; ie, ‘gold
standard’), and (5) completeness of data (availability of absolute
numbers of true-positive, false-positive, true-negative and false-
negative H-FABP results to allow reconstruction of the diagnostic
2 by 2 table).

Consequently, we excluded studies on test development and
test calibration, notably those that reported on H-FABP test
results in confirmed AMI patients and compared these with test
results in healthy controls (‘diagnostic case–control study’),
because such patients are not representative of the relevant
clinical domain—that is, patients suspected of having AMI.

Methods appraisal and data extraction
Information on study characteristics (design and quality),
number and type of participants, characteristics and execution
of the test and diagnostic test results was collected using
a standardised data extraction form.

Each study was assessed by two authors (MBS and GvdH) for
quality, based on the criteria as proposed by the QUADAS
checklist (Quality Assessment of Diagnostic Accuracy Studies).4
The following criteria were used: (1) use of a valid reference
standard in accordance with international AMI guidelines; (2)
performance of the same reference standard in all patients;
(3) independent interpretation of the index and reference tests;
(4) cut-off value for positive index test pre-specified and not
derived from study data; (5) completeness of data, notably
reporting of withdrawals from the study; (6) reporting of
indistinct test results of the H-FABP index test. Information
provided in the published report of the study for all criteria was
scored as clear or unclear. When sufficiently clear information
was provided, criteria were scored as satisfied (no/yes).

Data analysis
From each included study we aimed to extract the number of
patients with a true-positive, false-positive, false-negative and
true-negative test result either directly or through recalculation
based on reported measures of accuracy in combination with the
prevalence and sample size of a study. Sensitivity and specificity
together with 95% CIs were calculated for each study based on
the 2 by 2 table. Graphically, we plotted the individual study’s
points of sensitivity and specificity in the same receiver oper-
ating characteristics (ROC) curve, together with a ROC point
summarising all studies. In a ROC curve, sensitivity on the
y-axis is plotted against 1—specificity on the x-axis.

The bivariate random-effects approach was used to analyse
our data. The bivariate approach uses a random-effects approach
for both (logit transformed) sensitivity and specificity within
a single model, thereby incorporating any (negative) correlation
that might exist between these measures. The random-effects
approach estimates and incorporates the amount of between-
study variability in both sensitivity and specificity. The within-
study variability (ie, precision) was accounted for by using the
binomial distribution. This means that more weight is given in
the estimation of sensitivity to studies having more patients
with AMI, whereas the weighting for specificity is linked to the
number of patients without AMI. We extended the basic
bivariate model with covariates to assess the impact of study
evel covariates on sensitivity or specificity or both. The bivariate
model produces summary estimates for sensitivity and speci-
ficity based on a random-effects approach.5 The interpretation of
summary estimates is most straightforward when the amount
of between-study variation is small to moderate. We examined
whether differences in study population, in index test properties,
or in design could explain the observed heterogeneity in results
by adding these factors as covariates to the bivariate model.
These factors included: the use of a point-of-care test; the use of
a reference standard incorporating troponin; the prevalence of
the outcome; the cut-off value of the H-FABP test used. We used
Stata Statistical Software Release 10 and SAS Statistical Soft-
ware (V9.2) for all meta-analytical analyses and SPSS V15.0 for
all other analyses.

RESULTS
Of the 1395 articles that we identified by our electronic litera-
ture search, 16 unique studies were eventually included in our
systematic review (figure 1).

The main reasons for exclusion were duplicates between the
PubMed and Embase database, use of an inappropriate patient
domain (eg, established AMI patients versus healthy controls),
use of an inappropriate outcome (eg, heart failure), multiple
reporting of the same data, and reporting of insufficient data
to allow reconstruction of the 2 by 2 table.

Two of the 16 selected studies satisfied all criteria of the
methods appraisal, while nine studies satisfied three or fewer
of these criteria (table 1). In three studies, the cut-off point for
a positive H-FABP test was derived from the study data. Six of
the 16 selected studies used the World Health Organization
(WHO) criteria (without troponin) as reference standard.
Patient characteristics

Overall, the selected 16 studies included 3709 patients suspected of having AMI. The study size ranged from 30 to 791 patients (median 149, IQR 102–352). The proportion of males ranged from 49% to 84% (median 71%; IQR 64–76%). The mean age of patients in the included studies ranged from 54 to 69 years (median 63 years; IQR 61–67). In two studies using a mobile intensive care unit, patients were included outside the hospital, whereas in the remaining studies, patients were included in a hospital setting (table 2). The median duration of symptoms at the time of testing was 3.8 h (IQR 2.8–5.0). The median prevalence of AMI in the 16 included studies was 36% (range 13–74%).

For nine studies a separate diagnostic 2 by 2 table could be reconstructed including a subgroup of patients tested for H-FABP within 6 h of onset of symptoms only.

H-FABP assay

A laboratory ELISA for H-FABP was used in six studies, giving a quantitative result for H-FABP. In three studies, the value that offered maximum predictive accuracy was taken as the cut-off level for a positive H-FABP test, while three studies used healthy controls or previously published decision limits. The cut-off values used by these different studies ranged from 5.0 to 16.8 ng/ml. Two studies used the Evidence Cardiac Panel, which is a biochip cardiac panel measuring not only H-FABP but also other cardiac biomarkers (including troponin and creatine kinase-myocardial band (CK-MB)). This Evidence Cardiac Panel is performed in a laboratory setting by applying a serum blood sample (obtained through venepuncture) to a biochip, adding a chemiluminescent reagent and measuring the strength of the light signal—using a special camera—which is then converted into a marker concentration.

In the remaining eight studies, two different point-of-care tests were used: Cardiodetect and Rapicheck. The Cardiodetect test is a rapid chromatographic immunoassay that is performed by applying three drops of whole blood (capillary blood from the patient’s finger or venepuncture) to a test strip. After 15 min, the qualitative test result can be read.

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Table 1 Methods appraisal of studies included

<table>
<thead>
<tr>
<th>First author</th>
<th>Performance of same reference standard in all patients</th>
<th>Index test interpreted independently of reference test</th>
<th>Withdrawals reported</th>
<th>Cut-off value index test determined without bias (yes/no)</th>
<th>Valid reference standard (ESC/ACC criteria)</th>
<th>Unclear test results reported</th>
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<td>yes</td>
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</tr>
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<td>yes</td>
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<td>yes</td>
<td>yes</td>
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<td>yes</td>
<td>yes</td>
<td>no</td>
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<td>yes*</td>
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<td>no</td>
<td>yes</td>
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<td>yes</td>
<td>no</td>
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<td>yes*</td>
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<td>no</td>
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<td>yes</td>
<td>no</td>
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<td>no</td>
<td>no</td>
<td>no</td>
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<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
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<tr>
<td>Ishii</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>—</td>
</tr>
</tbody>
</table>

*— not applicable (did not use immunochromatographic test).

ESC, European Society of Cardiology; ACC, American College of Cardiology.
as the appearance of one or two red strips in the test card window. One red strip (control; test performed correctly) is a negative test result, and two red strips (control and H-FABP; test performed correctly and H-FABP present in sample) represents a positive test result. The Cardiodetect test used by Lefevre et al.\textsuperscript{17} has a detection limit for H-FABP of 6.2 ng/ml, while the Cardiodetect test used in the remaining studies uses a cut-off value for a positive test of 7 ng/ml.\textsuperscript{6, 12, 16, 18} The Rapicheck test is a similar point-of-care chromatographic immunoassay test, also providing one or two red lines that can be judged by the physician after 15 min. The cut-off value for a positive Rapicheck test is 6.2 ng/ml.

**Definition of myocardial infarction**

Until 2000, the widely accepted definition of myocardial infarction was based on the WHO criteria for diagnosis of ischaemic heart disease.\textsuperscript{22} These criteria consist of a clinical history of chest pain (typical or atypical) with unequivocal ECG changes and/or unequivocal serum enzyme changes (pattern of rise and fall consistent with time of symptom onset; typically CK and CK-MB were used). Six studies included in this review\textsuperscript{6, 9, 11, 12, 20, 21} published between 1997 and 2004 used these WHO criteria or criteria based thereon. The remaining 10 studies used the criteria published in 2000 in a consensus document by the European Society of Cardiology and American College of Cardiology\textsuperscript{5, 23} or the criteria proposed in the 2007 expert consensus document\textsuperscript{1} as the universal definition of AMI. These diagnostic criteria also encompass a typical clinical history and ECG changes and serum enzyme changes of a cardiac biomarker, but in this case preferably cardiac troponin, which should be measured on the first assessment and 6–9 h later.

**Diagnostic value of H-FABP**

The overall pooled sensitivity of all studies was 0.84 (95% CI 76% to 90%) and overall pooled specificity was 0.84 (95% CI 76% to 89%). However, between-study variation was substantial and attributable to heterogeneity, rather than chance, as indicated by an I-square of 91% for sensitivity results and 96% for specificity results. Also, there was evidence for publication bias, as we found funnel plot asymmetry, indicating significant small-study bias (p=0.09); smaller studies finding high estimates of sensitivity and specificity are more likely to be published than large studies with more modest results. The estimates of sensitivity and specificity of all included studies are shown in a summary ROC curve, together with the summary ROC point (pooled sensitivity against 1−(pooled specificity)). The area under the summary ROC curve (AUC) is 0.91. We also plotted the 95% confidence region (precision of estimation of pooled sensitivity and specificity) and the 95% prediction region (likely range of values for a new study) (figure 2A, B).

**Covariate analysis**

Adding the covariate whether troponin was part of the reference standard to the bivariate model had a significant impact on sensitivity, indicating that it is an important source of heterogeneity between studies. We found that studies using a reference standard including troponin yielded a lower sensitivity of H-FABP (0.76, 95% CI 67% to 84%) than studies that did not use troponin as part of their reference standard (0.91, 95% CI 84% to 95%). Also, the prevalence of the outcome had a significant impact on specificity: studies with a lower prevalence (20%) had a higher specificity than studies with a higher prevalence (40%) (specificity 0.90 (95% CI 82% to 95%) versus 0.84 (95% CI 77% to 89%), respectively).

**Table 2 Study characteristics and population of studies included**

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Number of included patients</th>
<th>H-FABP test</th>
<th>Point-of-care test</th>
<th>Prevalence of AMI overall (%)</th>
<th>Duration of symptoms at time of testing (median, minutes)</th>
<th>H-FABP cut-off (ng/ml)</th>
<th>Reference standard</th>
<th>Biomarker used in standard/ measurement method diagnostic cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alhashemi</td>
<td>2006</td>
<td>64</td>
<td>Cardiodetect</td>
<td>Yes</td>
<td>64</td>
<td>390</td>
<td>7</td>
<td>ESC/ACC</td>
<td>TnI/not mentioned 0.05 µg/l</td>
</tr>
<tr>
<td>Chen</td>
<td>2004</td>
<td>93</td>
<td>ELISA</td>
<td>No</td>
<td>34</td>
<td>Not known</td>
<td>16.8</td>
<td>WHO</td>
<td>CK-MB/corpulence chemiluminescence (Beckman Coulter) 4.0 µg/l</td>
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<tr>
<td>Di Serio</td>
<td>2005</td>
<td>30</td>
<td>Evidence cardiac panel</td>
<td>No</td>
<td>20</td>
<td>204</td>
<td>6.4</td>
<td>ESC/ACC</td>
<td>TnI/Stratus CS (Dade Behring) (0.07 µg/l)/ 0.07 µg/l</td>
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<td>Eccollan</td>
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<td>108</td>
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<td>Yes</td>
<td>51</td>
<td>139</td>
<td>7</td>
<td>≈ ESC/ACC</td>
<td>TK/MB/MB/Cobas bio (Hoffmann-La Roche) 210 UI + 20 UI</td>
</tr>
<tr>
<td>Haastrup</td>
<td>2000</td>
<td>130</td>
<td>ELISA</td>
<td>No</td>
<td>16</td>
<td>168</td>
<td>8</td>
<td>WHO</td>
<td>CK-MB/MB/Cobas bio (Hoffmann-La Roche) 210 UI + 20 UI</td>
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<tr>
<td>Ilva</td>
<td>2008</td>
<td>293</td>
<td>ELISA</td>
<td>No</td>
<td>46</td>
<td>282</td>
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<td>ESC/ACC</td>
<td>TnI/Architect STAT (Abbott) (0.032 µg/l)/0.032 µg/l</td>
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<tr>
<td>Ishii</td>
<td>1997</td>
<td>165</td>
<td>ELISA</td>
<td>No</td>
<td>60</td>
<td>229</td>
<td>12</td>
<td>≈ WHO</td>
<td>CK-MB/MB (NAC -activated assay) (Boehringer Mannheim) 24 UI</td>
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<tr>
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<td>100</td>
<td>Cardiodetect</td>
<td>Yes</td>
<td>36</td>
<td>354</td>
<td>6.2</td>
<td>ESC/ACC</td>
<td>TnI (measured on 5 sites)/Rxl/X Pand (Dade Behring) (0.07 µg/l)/3 sites, Centaur (Siemens) (0.10 µg/l)/2 sites/ 0.07 µg/l, 0.10 µg/l</td>
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<td>ELISA</td>
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<td>48</td>
<td>300</td>
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<tr>
<td>Mion</td>
<td>2007</td>
<td>132</td>
<td>Evidence cardiac panel</td>
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<td>74</td>
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<td>Rapicheck</td>
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<td>129</td>
<td>Rapicheck</td>
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<td>24</td>
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<td>74</td>
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<td>ESC/ACC</td>
<td>TnI, details not provided</td>
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</table>

ACC, American College of Cardiology; AMI, acute myocardial infarction; CK-MB, creatine kinase-myocardial band; ESC, European Society of Cardiology; NAC, N-acetyl cysteine; TnI, troponin I; TnT, troponin T; WHO, World Health Organization.
To explain heterogeneity in results, we also added other factors to the bivariate model (ie, the use of a point-of-care test and the cut-off value used for the H-FABP test), but these factors had no significant impact on either sensitivity or specificity (table 3).

**DISCUSSION**

To our knowledge, this is the first systematic review and meta-analysis to determine the diagnostic performance of the early cardiac biomarker, H-FABP, in the diagnosis of AMI. Potentially, the introduction of safe and early biomarkers could lead to a considerable reduction in unnecessary hospital referrals of patients without AMI and an earlier start of treatment in patients with AMI. Using the bivariate random-effects approach, we found a summary AUC of 0.91 for H-FABP with a summary estimate of 84% for sensitivity and 84% for specificity. This indicates that the use of H-FABP would lead to a false-negative test result in 16% of patients with AMI and to a false-positive test result in 16% of patients without AMI. For a potentially fatal condition such as AMI, this percentage of missed patients is unacceptably high, making H-FABP unsuitable for use as a stand-alone test in a primary care setting. In a hospital setting, patients with a false-positive test will be unnecessarily subjected to coronary interventions or aggressive thrombolytic therapy, with associated risks.

As a comparison, the AUC for CK-MB and troponin (if provided) in the different studies in this meta-analysis ranged from 0.87–0.93 and 0.88–1.0, respectively, with sensitivity for CK-MB and troponin ranging from 55–99% and 95–100%, respectively, and specificity ranging from 82% to 100% to 65% to 100%, respectively, when measured in the correct time interval for these markers (ie, more than 6 h after the onset of symptoms). Also, recently four highly sensitive troponin assays have become available showing an even higher diagnostic accuracy than that of the currently used standard troponin assay (AUC 0.95, even within 6 h of onset of symptoms), facilitating the earlier and more accurate diagnosis of AMI.24 25

A drawback of this systematic review, which is inherent to the methodology used by the included studies, is that none of the studies addresses the role that H-FABP may play when it is combined with ECG analysis, history taking and physical examination. Instead, the test characteristics of H-FABP are measured as if it was used as a stand-alone diagnostic test for ruling in or ruling out AMI. A more clinically directed approach would be to investigate the added value of H-FABP in combination with findings from medical history taking, physical examination and, if available, ECG analysis.

Some other methodological and technical issues must also be addressed. First, the interpretation of the summary estimates of the AUC and sensitivity and specificity that we provide is not straightforward, since we found marked heterogeneity between the included studies. This heterogeneity was illustrated in the summary ROC curve, which had a very wide prediction ellipse, indicating that future studies on H-FABP could yield widely differing results, ranging from a test result with a very high sensitivity and specificity to test results that are neither very sensitive nor specific. Covariate analysis revealed that the use of a reference test with troponin was an important explanation for the differences in sensitivity found between the studies: studies that did not use troponin in their reference standard for AMI found a higher sensitivity of H-FABP. This finding is explained by the fact that troponin is considerably more sensitive than CK or CK-MB in detecting even small areas of myocardial infarction. Thus, the use of troponin categorizes more patients as having suffered myocardial infarction, which would have been...
diagnosed with angina pectoris or unstable angina using the less sensitive markers CK and CK-MB. Compared with older biomarkers, H-FABP performs better, showing higher sensitivity, whereas in comparison with troponin, its sensitivity for detecting myocardial infarction will be lower. In this light, the new, highly sensitive cardiac troponin assays that have recently become available may again alter the diagnosis of AMI by providing a more accurate diagnosis, thereby also altering the diagnostic accuracy of newer markers tested against this high-sensitivity troponin.

Second, covariate analysis revealed that the prevalence of the outcome significantly influences the specificity of H-FABP. Studies with a lower prevalence of the outcome found a higher specificity, apparently because of selection of less severely ill patients and hence more true-negative test results. We also added two other factors (use of a point-of-care test and the cut-off value of the H-FABP test) to the covariate analysis, but these did not explain the heterogeneity. Owing to the limited number of studies in this meta-analysis, we restricted the covariate analysis to these four factors, which we pre-specified because they were the most likely cause of variation between the studies.

Obviously, the strength of a meta-analysis depends on the methodological strength of the studies included. In our quality assessment, we found that both withdrawals from the study and, in the case of qualitative tests, unclear test results were poorly reported. Also, there were several studies in which the cut-off point for the index test was derived from the same study data. Poor-quality studies tend to overestimate the diagnostic performance of a test, and data-driven determination of the cut-off point leads to an overestimated sensitivity and specificity. Furthermore, we found evidence for small sample size effects and publication bias, as the test for asymmetry of the funnel plot showed a significant result. Also, the asymmetry could be caused by an inadequate search strategy. Although we performed a very sensitive search in multiple databases and for multiple languages, we did not search for unpublished data, because diagnostic studies, unlike trials, are usually not recorded in research registries. The potential effect of publication bias is therefore unknown, but it is probable that the reported estimates for sensitivity and specificity are overestimations.

In point-of-care testing, different test interpretations may lead to threshold effects in diagnostic test properties. The point-of-care tests used in the studies included in this meta-analysis are judged positive or negative by the physician performing the test according to the appearance of one (control) or two (control and H-FABP) red lines. A vague line by some physicians will be judged as absence of a line, while others will judge this to be a positive test. The (implicit) use of different thresholds for a positive test leads to a trade-off between sensitivity and specificity: lowering the threshold in general leads to an increase in sensitivity, but a decrease in specificity. This is a problem that could be solved by using an automated point-of-care test reader to measure the intensity of the result line made by the chromatographic immunoassay test. A major strength of this systematic review is that we included only studies addressing the relevant patient domain—that is, patients suspected of having AMI. We did not include several diagnostic studies on the performance of H-FABP in diagnosing AMI because they were set up as diagnostic case—control studies (performance of the test in a group of patients already known to have the target disease and a group of healthy controls without the target disease). These studies will yield overestimated values of diagnostic accuracy.

Conclusion
The early biomarker H-FABP does not fulfill the diagnostic requirements needed for a safe and early diagnosis of AMI when it is applied as a stand-alone diagnostic test. Both sensitivity and specificity are too low, and implementation of the test will potentially lead to many missed AMI diagnoses and overtreatment of patients without AMI. Furthermore, many available diagnostic studies do not adequately report the results. Sound diagnostic studies examining the additional role of H-FABP (combined with ECG analysis and medical history taking) are still lacking.

Competing interests
None.

Provenance and peer review
Not commissioned; externally peer reviewed.

REFERENCES


