Novel biochemical markers in suspected acute coronary syndrome: systematic review and critical appraisal

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ABSTRACT

Context Early recognition of acute coronary syndrome (ACS) is essential. Cardiac troponins are not consistently elevated within the first hours after symptom onset.

Objective Review current guidelines recommendations regarding biomarkers in the early assessment of ACS and review the evidence for using established and specific new diagnostic biomarkers.

Data sources MEDLINE and EMBASE.

Study selection Articles on diagnostic accuracy of ACS biomarkers.

Data extraction Relevance of clinical domain, adequacy of measures of clinical utility and outcome assessment.

Results The 73 articles identified on early biochemical markers CK-MB, myoglobin, heart-type fatty acid binding protein (H-FABP), ischemia modified albumin (IMA), pregnancy-associated plasma protein A, glycogen phosphorylase isoenzyme BB and myeloid-related protein (H-FABP) seem to be promising biomarkers in the early assessment of ACS. There is an urgent need for adequately designed diagnostic studies of (novel) ACS markers against contemporary troponin assays.

Conclusions IMA and H-FABP seem to be promising biomarkers in the early assessment of ACS. There is an urgent need for adequately designed diagnostic studies of (novel) ACS markers against contemporary troponin assays.

METHODS

A literature search was conducted using the MEDLINE and EMBASE databases. Guidelines were searched published in English since 2000 of diagnosis and treatment of (non ST-elevation) ACS. When more than one guideline was available since 2000 the most recently published version was used. Lateral references were also searched. In addition, websites of agencies involved in guideline development were searched, including the Scottish Intercollegiate Guidelines Network (SIGN), the British Cardiac Society (BCS) and the Royal Australian College of General Practitioners (RACGP).

To find papers on novel biochemical markers in suspected ACS patients, the following key terms were used: ‘Biological Markers’ (Mesh) AND/OR (((‘Heart’ (Mesh:noxexp) OR ‘Myocardium’ (Mesh)) OR (‘Ischemia’ (Mesh) OR ‘Myocardial Ischemia’ (Mesh))) OR ‘Necrosis’ (Mesh)) AND (English (lang)) AND (((Humans(Mesh)) AND: (delta CK-MB OR CK-MB OR delta creatinine kinase-myocardial band OR creatinine kinase-myocardial band), (myoglobin), (H-FABP OR FABP OR fatty acid binding protein), (ischemia modified albumin OR IMA), (Pregnancy associated plasma protein A OR PAPP-A), (glycogen phosphorylase isoenzyme BB OR GPBB), (myeloid-related protein 8/14 OR MRP)). Because of the well-established role of troponin (recommended in all guidelines) and because this marker is generally not elevated in the first 6 h on ACS symptoms onset, this marker was not included.

1–5 The search was limited to the last 20 publication years (since 1988). Titles and abstracts were screened. Articles that studied the diagnostic accuracy of biomarkers in patients with (suspected) ACS were included. Prognostic studies and studies that focused on a clinical domain other than ACS and MI were excluded. Data extraction of available studies was based on three essential aspects of diagnostic research.

1. Relevance of the clinical domain.

2. Data extraction of available studies was based on three essential aspects of diagnostic research.

3. Data extraction of available studies was based on three essential aspects of diagnostic research.

4. Data extraction of available studies was based on three essential aspects of diagnostic research.

5. Data extraction of available studies was based on three essential aspects of diagnostic research.

6. Data extraction of available studies was based on three essential aspects of diagnostic research.

7. Data extraction of available studies was based on three essential aspects of diagnostic research.

8. Data extraction of available studies was based on three essential aspects of diagnostic research.

9. Data extraction of available studies was based on three essential aspects of diagnostic research.

INTRODUCTION

Early recognition of acute coronary syndrome (ACS) is essential because of the prognostic benefit following timely interventions, and early ruling out of ACS is important in view of the costs (eg, diagnostic procedures, hospital admissions) and the patient burden involved.

Early diagnostic assessment of patients suspected of having ACS (ie, ST-elevation myocardial infarction, non ST-elevation myocardial infarction or unstable angina) remains a challenge, especially when the ECG is inconclusive. Currently, definitive assessment of the presence of myocardial infarction (MI) is based on elevation of biochemical markers of myocardial necrosis, cardiac troponin I or T (cTnI or cTnT) or creatinine kinase-MB isoenzyme (CK-MB) if cTnI is not available, in the context of clinical and ECG findings.1–5 Unfortunately, these biomarkers are not consistently elevated within the first few (<6) hours after onset of symptoms, which makes them less suitable for early evaluation of patients suspected of having ACS.

New diagnostic biomarkers for ischaemia or cardiac necrosis are being developed and tested, some of which are expected to be particularly helpful in the first hours after symptom onset. In addition, recently developed point of care (POC) tests provide the opportunity to shift the diagnostic assessment of patients suspected of having ACS to an earlier timeframe (even to the prehospital setting) than is possible using lab-based immunoassay methods.

The aim of this study is to review current clinical guideline recommendations regarding the use of biomarkers in the early assessment (ie, within 6 h of symptom onset) of suspected ACS and critically review evidence for the use of established and specific new diagnostic biomarkers in this timeframe.
suspected ACS. Studies that focus on patients with confirmed ACS, with or without a comparison with non-ACS patients (ie, not suspected of ACS), were considered irrelevant for this review.

2. Adequate assessment of outcome. The outcome in diagnostic research is mostly dichotomous: the presence or absence of a specific disease. Ideally there is a reference (or ‘gold’) standard for the disease without false positive and false negative test results. In this review this should be ACS or acute myocardial infarction (AMI) according to the guidelines available at the time the articles were published.

3. Use of adequate measures of clinical utility, that is (absolute) predictive values in univariate analysis and ORs and area under the receiver operating characteristics curve (ROC curve) (AUC) in multivariate analysis. The first step to estimate clinical utility is to assess predictive values in univariate analysis; positive predictive value (PPV) is the probability of the presence of a disease given a positive test result, negative predictive value (NPV) is the probability of the absence of a disease given a negative test result. Sensitivity (the probability of a positive test result given a disease) and specificity (the probability of a negative test result given the absence of disease) are closely related to PPV and NPV, but are clinically of less importance. PPV, NPV, sensitivity, and specificity can be calculated from a simple 2×2 table. To determine the value of a biomarker in addition to routinely available diagnostic items, for example age, signs and symptoms, first a multivariable (logistic) regression analysis including the routinely available test should be done. The diagnostic value of such a multivariable ‘clinical’ model can be quantified by the AUC or c-statistic indicating the probability that two patients (one with and one without ACS) are classified correctly. Next, the new biomarker is included in this model and its added value can be assessed by performing the likelihood ratio test or by the increase in AUC or c-statistic.

The essence of diagnosis is the probability of disease as function of multiple tests. It is important to investigate the value of a specific test in addition to other known parameters such as age, patient history, physical examination and electrocardiography. This requires multivariable statistical techniques.

RESULTS

Six guidelines were identified in the English language published since 2000 (table 1): guidelines from the European Society of Cardiology (ESC), the American College of Cardiology and American Heart Association (ACC/AHA), and national guidelines from the USA, Australia and New Zealand, Scotland and the United Kingdom.

Seventy-three articles (of which 27 articles on two different biomarkers, table 2) that studied the diagnostic accuracy of biomarkers in patients with (suspected) ACS published since 1988 were identified (appendix).

Current guidelines

Table 1 shows the biomarkers recommended by the current guidelines. Currently all six guidelines advocate cTn (I or T), with an elevation of cTn above the 99th percentile of normal, as preferred markers of MI in the setting of a clinical syndrome suggestive of myocardial ischaemia. Only two guidelines include specific recommendations for the first 6 h after symptom onset: measurement of myoglobin or measurement of 2 h changes in CK-MB in conjunction with 2 h changes in cTn. Four guidelines recommend CK-MB or 2 h change in CK-MB level. The National Academy of Clinical Biochemistry Laboratory Medicine Practice (NACB) guidelines advocate CK-MB measurement as an acceptable alternative only when cTn is not available. The British Cardiac Society (BCS) guidelines do not recommend CK-MB measurements, but mention that patients with normal cTn, normal ECG and normal CK-MB do not need admission to a coronary care unit. All guidelines recommend repeated blood sampling and measurements on admission and 6–12 h after admission and after any further episode of chest discomfort.

NACB guidelines mention that the biomarker ischaemia modified albumin (IMA) has been approved by the US Food and Drug Administration (FDA) for clinical use, but that the diagnostic value in a population of patients suspected of ACS remains an area for further investigation. None of the other guidelines mention potential new diagnostic biochemical markers.

<table>
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<th>Table 1 Current guidelines</th>
<th>Recommended biomarkers</th>
<th>Mentioned biomarkers</th>
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<td><strong>Guidelines</strong></td>
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<tr>
<td>ESC&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Troponin I or T&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Myeloperoxidase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Soluble CD40 ligand</td>
</tr>
<tr>
<td>ACC/AHA&lt;sup&gt;1&lt;/sup&gt;,&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Troponin I or T</td>
<td>IMA myeloperoxidase for risk stratification</td>
</tr>
<tr>
<td></td>
<td>&lt;6 h: 2 h ΔCK-MB in conjunction with 2 h Δtroponin (Class IIb)</td>
<td>Soluble CD40 ligand for risk stratification</td>
</tr>
<tr>
<td></td>
<td>&lt;6 h: myoglobin in conjunction with CK-MB mass or troponin (Class IIb)</td>
<td></td>
</tr>
<tr>
<td>NACB&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Troponin I or T</td>
<td>IMA myeloperoxidase for risk stratification</td>
</tr>
<tr>
<td></td>
<td>CK-MB when troponin I or T is not available</td>
<td>Soluble CD40 ligand for risk stratification</td>
</tr>
<tr>
<td></td>
<td>&lt;6 h: myoglobin</td>
<td></td>
</tr>
<tr>
<td>NHFA/CSANZ&lt;sup&gt;2&lt;/sup&gt;,&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Troponin I or T*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total CK</td>
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<td></td>
<td>CK-MB if troponin I or T is not available</td>
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<tr>
<td>SIGN&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Troponin I or T*</td>
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<tr>
<td></td>
<td>CK-MB</td>
<td></td>
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<tr>
<td>BCS&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Troponin I or T*</td>
<td></td>
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<tr>
<td></td>
<td>CK-MB</td>
<td></td>
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</tbody>
</table>

*No recommendations according to time of presentation (< or > 6 h of presentation).

ACC/AHA, American College of Cardiology/American Heart Association; BCS, British Cardiac Society; CK, creatinine kinase; CK-MB, creatinine kinase-MB isoenzyme; ESC, European Society of Cardiology; IMA, ischaemia modified albumin; NHFA/CSANZ, National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand; SIGN, Scottish Intercollegiate Guidelines Network.
<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Admission time</th>
<th>Study domain</th>
<th>Outcome</th>
<th>Markers</th>
<th>Predictive values AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruzgar, 2006&lt;sup&gt;46&lt;/sup&gt;</td>
<td>40</td>
<td>&lt;24 h</td>
<td>Chest pain patients admitted to the CCU with suspected ACS</td>
<td>ACS (ECG, cTnT, CK-MB)</td>
<td>CK-MB</td>
<td>Not provided</td>
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<tr>
<td>Haastrup 2000&lt;sup&gt;15&lt;/sup&gt;</td>
<td>130</td>
<td>2.8 h</td>
<td>Patients with typical chest pain</td>
<td>AMI (WHO)</td>
<td>CK-MB</td>
<td>PPV 84%</td>
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<tr>
<td>Nagurney 2005&lt;sup&gt;41&lt;/sup&gt;</td>
<td>346</td>
<td>&lt;24 h</td>
<td>Patients at the ED with suspected ACS</td>
<td>AMI (WHO)</td>
<td>CK-MB</td>
<td>PPV 84%</td>
</tr>
<tr>
<td>Fesmire 2004&lt;sup&gt;19&lt;/sup&gt;</td>
<td>975</td>
<td>4 h</td>
<td>Chest pain patients with a baseline cTn ≤1.0 ng/ml and initial non-diagnostic ECG</td>
<td>AMI (history, cTn, ECG)</td>
<td>CK-MB&lt;sub&gt;0&lt;/sub&gt;/ CK-MB&lt;sub&gt;2&lt;/sub&gt;/ CK-MB&lt;sub&gt;D&lt;/sub&gt;</td>
<td>PPV 8/16/44%</td>
</tr>
<tr>
<td>Nagurney 2005&lt;sup&gt;41&lt;/sup&gt;</td>
<td>346</td>
<td>&lt;24 h</td>
<td>Patients at the ED with suspected ACS</td>
<td>AMI (WHO)</td>
<td>CK-MB</td>
<td>AUC 0.89</td>
</tr>
<tr>
<td>Fesmire 2004&lt;sup&gt;19&lt;/sup&gt;</td>
<td>975</td>
<td>4 h</td>
<td>Chest pain patients with a baseline cTn ≤1.0 ng/ml and initial non-diagnostic ECG</td>
<td>AMI (history, cTn, ECG)</td>
<td>CK-MB&lt;sub&gt;0&lt;/sub&gt;/ CK-MB&lt;sub&gt;2&lt;/sub&gt;/ CK-MB&lt;sub&gt;D&lt;/sub&gt;</td>
<td>AUC 0.89</td>
</tr>
<tr>
<td>Eggers 2004&lt;sup&gt;14&lt;/sup&gt;</td>
<td>197</td>
<td>5.5 h (3.4–9.6 h)</td>
<td>Patients with chest pain and a non-diagnostic ECG for AMI</td>
<td>AMI (ESC/ACC 2000)</td>
<td>CK-MB</td>
<td>PPV 8/16/44%</td>
</tr>
<tr>
<td>Collinson 2003&lt;sup&gt;33&lt;/sup&gt;</td>
<td>1105</td>
<td>&lt;24 h</td>
<td>Patients with suspected ACS</td>
<td>AMI (WHO)</td>
<td>CK-MB</td>
<td>PPV 8/16/44%</td>
</tr>
<tr>
<td>Penttila 2002&lt;sup&gt;43&lt;/sup&gt;</td>
<td>440</td>
<td>&lt;12 h</td>
<td>Patients with acute chest pain at the ED</td>
<td>AMI (ESC/ACC 2000)</td>
<td>CK-MB</td>
<td>PPV 8/16/44%</td>
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<td>Huggon 2001&lt;sup&gt;18&lt;/sup&gt;</td>
<td>227</td>
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<td>AMI (symptoms, ECG, CK)</td>
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<td>PPV 8/16/44%</td>
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<td>Jurlander 2000&lt;sup&gt;38&lt;/sup&gt;</td>
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<td>Patients with suspected AMI</td>
<td>AMI (WHO)</td>
<td>CK-MB</td>
<td>PPV 8/16/44%</td>
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<tr>
<td>Jernberg 2000&lt;sup&gt;37&lt;/sup&gt;</td>
<td>738</td>
<td>&lt;3 h</td>
<td>Patients admitted to CCU suggestive of non-STEMI</td>
<td>AMI (ECG, CK-MB)</td>
<td>CK-MB&lt;sub&gt;0&lt;/sub&gt;/ CK-MB&lt;sub&gt;2&lt;/sub&gt;/ CK-MB&lt;sub&gt;D&lt;/sub&gt;</td>
<td>PPV 8/16/44%</td>
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<td>Ng 2001&lt;sup&gt;42&lt;/sup&gt;</td>
<td>1285</td>
<td>29% &lt;6 h</td>
<td>Patients admitted to the ED suggestive of cardiac ischemia</td>
<td>AMI (WHO)</td>
<td>CK-MB</td>
<td>PPV 8/16/44%</td>
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<td>Esses 2001&lt;sup&gt;20&lt;/sup&gt;</td>
<td>519</td>
<td>Not provided</td>
<td>Patients at the ED with symptoms consistent with myocardial ischemia</td>
<td>AMI (WHO)</td>
<td>CK-MB</td>
<td>PPV 8/16/44%</td>
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<tr>
<td>Ellestad 2000&lt;sup&gt;35&lt;/sup&gt;</td>
<td>1338</td>
<td>5.7–6.2 h</td>
<td>Patients presenting to the ED with symptoms suggestive of coronary artery disease</td>
<td>AMI (WHO)</td>
<td>CK-MB&lt;sub&gt;0&lt;/sub&gt;/ CK-MB&lt;sub&gt;2&lt;/sub&gt;/ CK-MB&lt;sub&gt;D&lt;/sub&gt;</td>
<td>PPV 8/16/44%</td>
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<tr>
<td>Zimmerman 1999&lt;sup&gt;39&lt;/sup&gt;</td>
<td>955</td>
<td>5.7 h +/- 4.7</td>
<td>Patients with chest pain presenting to the ED</td>
<td>AMI (WHO)</td>
<td>CK-MB&lt;sub&gt;0&lt;/sub&gt;/ CK-MB&lt;sub&gt;2&lt;/sub&gt;/ CK-MB&lt;sub&gt;D&lt;/sub&gt;</td>
<td>PPV 8/16/44%</td>
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<th>AUC</th>
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</thead>
<tbody>
<tr>
<td>Apple 1999</td>
<td>192</td>
<td>7.0 h (3.8–10.8 h)</td>
<td>Patients experiencing symptoms of AMI</td>
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<td>CK-MB</td>
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<td>Kontos 1997</td>
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<td>CK-MB</td>
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<td>0.819</td>
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<td>Mair 1995</td>
<td>114</td>
<td>3 h (0.33–22 h)</td>
<td>Non-traumatic chest pain patients</td>
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<td>CK-MB</td>
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<td>0.96</td>
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<td>De Winter 1995</td>
<td>309</td>
<td>135 min</td>
<td>Patients presenting with chest pain at the ED</td>
<td>AMI (symptoms, ECG, CK-MB)</td>
<td>CK-MB</td>
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<td>0.87</td>
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<td>Brogan 1994</td>
<td>189</td>
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<td>CK-MB</td>
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<td>0.83</td>
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<td>Castaldo 1994</td>
<td>157</td>
<td>&lt;2 h</td>
<td>Chest pain patients</td>
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<td>CK-MB</td>
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<td>77</td>
<td>&lt;12 h</td>
<td>Patients presenting to the ED with chest</td>
<td>AMI (ESC/ACC 2000)</td>
<td>Myoglobin</td>
<td></td>
<td>0.938</td>
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<tr>
<td>Alansari 2004</td>
<td>296</td>
<td>5 h (3–12 h)</td>
<td>Patients presenting with chest pain</td>
<td>AMI (ESC/ACC 2000)</td>
<td>Myoglobin</td>
<td></td>
<td>0.998</td>
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<tr>
<td>Nakata 2003</td>
<td>133</td>
<td>74&lt;6h, 59&gt;6h</td>
<td>Patients presenting to the ED with acute</td>
<td>ACS (ECG, CK-MB)</td>
<td>Myoglobin</td>
<td></td>
<td>0.860</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>chest pain suggestive of ACS</td>
<td></td>
<td>H-FABP</td>
<td></td>
<td>0.856</td>
</tr>
</tbody>
</table>

Continued
### Systematic review

The ESC and NACB guidelines do mention a number of novel biomarkers (markers of oxidative stress such as myeloperoxidase, and markers of thrombosis and inflammation such as soluble CD40 ligand and matrix metalloproteinases) but only as a prognostic tool.2 3

#### Empirical evidence on biomarkers

Of the collected articles (n=73), 33 (45%) were on CK-MB (total number of patients 20 078), 30 (41%) on myoglobin (total number of patients 12 704), 21 (29%) on heart-type fatty acid binding protein (H-FABP) (total number of patients 3655), nine (12%) on IMA (total number of patients 5893), three (4%) on PAPP-A (total number of patients 288), three (4%) on GPBB (total number of patients 502) and one (1%) on myeloid-related protein 8/14 protein (MRP) (116 patients).

Sixty-four (87%) of the studies were performed in the appropriate clinical domain, that is patients with suspected ACS. The outcome definition was appropriate in 70 (96%) articles. Most clinical studies used WHO or joint ESC/ACC criteria to define AMI or ACS. The definitions used in the studies evaluated are provided in the appendix and — in case the 2000 myocardial infarction definition was used — information on the use of troponin (either a threshold set at the 99th percentile of a reference group or the lowest concentration measurable with a coefficient of variation<10%). Forty-nine (67%) articles reported predictive values or a 2×2 table from which predictive values could be calculated. Multivariable analysis was performed in 12 (16%) of the articles.

#### Individual biomarkers

**Creatinine kinase — MB isoenzyme**

CK-MB used to be the standard marker for diagnosing AMI; however, cTn has proven more accurate in confirming or excluding AMI. CK-MB is more abundant in myocardial muscle cells than in skeletal muscle cells. CK-MB can be measured by mass or activity; mass is more accurate because it is not complicated by artefacts as is the case with CK-MB activity.14 Because CK-MB (mass) rises within 5–4 h of cardiac ischaemia/necrosis, CK-MB or 2 h ΔCK-MB may have some potential in the early assessment of patients suspected of having ACS. CK-MB levels returns to normal within 2–3 days after AMI.3 CK-MB is measured by immunoassay or point of care (POC) test. All but one of the 33 studies on CK-MB were performed in the appropriate study domain.15–46 48 All studies had the appropriate outcome, that is AMI (WHO n=29, Joint ESC/ACC consensus 2000 n=2, other definition n=1) or ACS (n=1). Predictive values were provided in 18 (55%) studies, and three (10%) studies performed multivariable analysis (table 3). There follows a brief discussion of the largest and most valid studies.

In a study of 2028 patients presenting at the emergency department after a median of 4 h since chest pain onset, CK-MB had a PPV 42% to predict ACS. The NPV value was 85%.17 Another study, in 1338 similar patients admitted within a median of 5.7 h, found a PPV of 82% and a NPV of 89% for AMI (WHO).35 In a study of 1051 patients presenting within 24 h, the combined use of cTn and CK-MB resulted in a PPV of 100% and a NPV of 95% for AMI (WHO).30

Four studies by Fesmire et al21–24 were found that investigated the role of 2 h ΔCK-MB in the early assessment of AMI (WHO). In a study in 710 chest pain patients admitted on average 108 min after symptom onset, 2 h ΔCK-MB (>1.6 ng/ml) had a PPV of 79% and a NPV of 98% for AMI.21 In a study in 706 patients the same group showed that 2 h ΔCK-MB (≥1.5 ng/ml) had diagnostic value beyond initial ECG, baseline CK-MB and

#### Table 2

<table>
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<th>Reference</th>
<th>N</th>
<th>Admission time</th>
<th>Study domain</th>
<th>Outcome</th>
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<th>Outcome</th>
<th>Markers</th>
<th>Predictive values</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>371</td>
<td>1B(100–149)</td>
<td>&lt;36 h</td>
<td>Patients with suspected AMI and non-diagnostic ECG findings</td>
<td>AMI (WHO)</td>
<td>Patients admitted to CCU with suspected AMI</td>
<td>AMI (WHO)</td>
<td>Patients with confirmed AMI and patients with chest pain without AMI and healthy volunteers</td>
<td>AMI (WHO)</td>
<td>Myoglobin</td>
<td>PPV 94%</td>
<td>AUC 0.859</td>
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<tr>
<td>185</td>
<td>165</td>
<td>&lt;12 h</td>
<td>Patients with confirmed AMI and patients with chest pain without AMI and healthy volunteers</td>
<td>AMI (WHO)</td>
<td>Patients admitted to CCU with suspected AMI</td>
<td>AMI (WHO)</td>
<td>Patients with confirmed AMI and patients with chest pain without AMI and healthy volunteers</td>
<td>AMI (WHO)</td>
<td>Myoglobin</td>
<td>PPV 91%</td>
<td>AUC 0.757</td>
</tr>
<tr>
<td>185</td>
<td>165</td>
<td>&lt;6 h</td>
<td>Patients with confirmed AMI and patients with chest pain without AMI and healthy volunteers</td>
<td>AMI (WHO)</td>
<td>Patients admitted to CCU with suspected AMI</td>
<td>AMI (WHO)</td>
<td>Patients with confirmed AMI and patients with chest pain without AMI and healthy volunteers</td>
<td>AMI (WHO)</td>
<td>Myoglobin</td>
<td>PPV 86%</td>
<td>AUC 0.839</td>
</tr>
<tr>
<td>136</td>
<td>106</td>
<td>&gt;36 h</td>
<td>Patients admitted to CCU with suspected AMI and non-diagnostic ECG findings</td>
<td>AMI (WHO)</td>
<td>Patients admitted to CCU with suspected AMI</td>
<td>AMI (WHO)</td>
<td>Patients with confirmed AMI and patients with chest pain without AMI and healthy volunteers</td>
<td>AMI (WHO)</td>
<td>Myoglobin</td>
<td>PPV 6%</td>
<td>AUC 0.174</td>
</tr>
</tbody>
</table>

**Note:** ACC, American College of Cardiology; ACS, acute coronary syndrome; AMI, acute myocardial infarction; AUC, area under curve; CAG, coronary angiography; CCU, coronary care unit; CK-MB, creatinine kinase-MB isoenzyme; ED, emergency department; ESC, European Society of Cardiology; H-FABP, heart-type fatty acid binding protein; LBBB, left bundle branch block; MI, myocardial infarction; MR, myocardial infarction; NPV, negative predictive value; PPV, positive predictive value; STEMI, ST elevation myocardial infarction; WHO, World Health Organization.
serial ECGs; the AUC increased to 0.95, the AUC without CK-MB, however, was not given. In another study in 578 similar patients, the AUC of 2 h ΔCK-MB (>1.5 ng/ml) was 0.83.22 In a more recent study in 975 patients presenting on average within 4 h of symptom onset, an AUC of 0.97 for AMI (chest pain, serial increase in troponin and ECG) was reported.44

The above mentioned studies show that CK-MB and 2 h ΔCK-MB have potential in diagnosing AMI in the first hours after symptom onset. Whether CK-MB has value in the early diagnostic assessment of ACS in addition to clinical symptoms, ECG or other markers has rarely been studied.

Myoglobin

Myoglobin is a low-molecular weight haem protein, which assists in the transportation of oxygen in cardiac and skeletal muscle cells. It is released into the circulation within 1–3 h after cardiac ischaemia, peaks at 6 h and returns to normal values within 18–24 h.45 Myoglobin can be detected by using immunoassay methods or POC tests.

An overview of the 50 relevant articles on myoglobin is outlined in table 3.15 18 20 24 28 32–44 48–59 All studies but one were performed in the correct study domain and all studies had the relevant outcome AMI (WHO n=23, Joint ESC/ACC consensus 2000 n=5) or ACS (n=2). Most (73%) articles provided predictive values. Two studies included multivariable analysis.

In a recent study in 537 patients admitted to the emergency department with symptoms suggestive of ACS (admission time unknown), the PPV of myoglobin was 5%, and NPV was 97%.50 A large study consisting of 1338 patients presenting within a median of 5.7 h showed myoglobin had a PPV of 55% and a NPV of 91% for AMI (WHO).53 Another study reported an almost similar NPV of 98% and lower PPV of 16% in 1285 comparable patients.42 Most other studies observed PPVs and NPVs similar to those mentioned above. In one study several predictors of MI were compared, and it was concluded that myoglobin was the strongest individual predictor of MI (WHO).51

These results show that myoglobin might be of value in early ruling out of AMI and ACS in suspected patients because of the relatively high NPV; its PPV, however, is low. However, it is not yet known whether myoglobin has diagnostic value in addition to symptoms, signs and other diagnostic tests (eg, ECG), because of the lack of multivariable analysis.

Heart-type fatty acid-binding protein

The main function of H-FABP, a small (15 kDa) protein, is transportation of intracellular long-chain fatty acids, the most important energy source of the heart. It may also function as a protector of myocytes against the detergent-like effects of high concentrations of long-chain fatty acids during ischaemia. In cases of cell damage by ischaemia, H-FABP diffuses more rapidly through the endothelial clefts into vascular space than larger molecules such as cTn, which makes H-FABP a potentially valuable early marker of myocardial ischaemia and/or necrosis. It is released within 2 h after the onset of ischaemia, peaks at 6 h and returns to normal values within 24–36 h.50 H-FABP can be detected by ELISA, and recently POC tests have been developed.51 H-FABP is not 100% heart-specific as it is also found in skeletal muscle, but its concentration in the heart is two to ten times higher.60–64

An overview of the 21 clinical studies on H-FABP is outlined in table 3.45 46 54–59 64–72 Most (81%) studies were conducted in the appropriate study domain and all studies had the relevant outcome AMI (WHO n=13, Joint ESC/ACC consensus n=7) or ACS (n=2). Seventeen (81%) studies reported predictive values or predicted values could be calculated. None performed multivariable analysis.

Because of the similarities between H-FABP and myoglobin, several researchers compared their potential roles in the early diagnosis of ACS (table 2). In a study in 165 patients with suspected AMI (WHO) within 6 h of chest pain onset, H-FABP had an AUC of 0.898, which was significantly higher than myoglobin.55 Comparable results were found in a study in 135 similar patients, H-FABP had a PPV of 82% (NPV of 54%) and an AUC of 0.907 for AMI (WHO), both higher than for cTnT, CK-MB and myoglobin.56 Another study, however, observed an AUC of 0.636 for AMI (Joint ESC/ACC consensus 2000); lower than the AUC of myoglobin (0.738) in 296 patients with a median symptom onset of 5 h prior.62

A recent study in 419 patients presenting within 3 h of symptom onset showed H-FABP measured by means of a CardioDetect POC test had a PPV of 72% and a NPV of 80% for AMI (Joint ESC/ACC consensus 2000).77 A study in similar patients using the same POC test, reported that H-FABP had a higher PPV (94%) and NPV (88%) in predicting ACS.69 Overall, the PPV of H-FABP in the clinical studies varied between 44% and 100%; the NPV of H-FABP varied between 50% and 100%.

### Table 3 Overview of studies by biomarker

<table>
<thead>
<tr>
<th>Marker</th>
<th>Studies</th>
<th>Total patients</th>
<th>Correct domain*</th>
<th>Correct outcome †</th>
<th>Studies that provided PPV/NPV</th>
<th>Studies that provided multivariable analysis</th>
<th>Well-designed studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK-MB 15–48 48</td>
<td>33</td>
<td>20078 (40–2028)</td>
<td>32 (97%)</td>
<td>33 (100%)</td>
<td>18 (55%) (7.7–100)/(50–99)</td>
<td>3 (10%)</td>
<td>25 (76%)</td>
</tr>
<tr>
<td>Myoglobin 15 18 20 24 28 32–44 48–59</td>
<td>30</td>
<td>12704 (77–1338)</td>
<td>29 (97%)</td>
<td>30 (100%)</td>
<td>22 (73%) (5.3–100)/(51.4–100)</td>
<td>2 (6%)</td>
<td>27 (90%)</td>
</tr>
<tr>
<td>H-FABP 45 48 54–59 65–75</td>
<td>21</td>
<td>3655 (40–460)</td>
<td>17 (81%)</td>
<td>21 (100%)</td>
<td>17 (81%) (44.4–100)/(50–100)</td>
<td>Not provided</td>
<td>15 (71%)</td>
</tr>
<tr>
<td>IMA 100–106</td>
<td>9</td>
<td>3893 (97–539)</td>
<td>9 (100%)</td>
<td>9 (100%)</td>
<td>8 (89%) (16.8–74.0)/(59.0–97.0)</td>
<td>4 (44%)</td>
<td>8 (89%)</td>
</tr>
<tr>
<td>PAPP-A 97 98</td>
<td>3</td>
<td>288 (59–160)</td>
<td>1 (33%)</td>
<td>1 (33%)</td>
<td>Not provided</td>
<td>3 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>GBP 100–102</td>
<td>3</td>
<td>502 (48–278)</td>
<td>2 (67%)</td>
<td>2 (67%)</td>
<td>1 (33%) (94.0)/(78.0)</td>
<td>Not provided</td>
<td>0</td>
</tr>
<tr>
<td>MRP 8/14 100</td>
<td>1</td>
<td>116</td>
<td>0</td>
<td>1 (100%)</td>
<td>Not provided</td>
<td>1 (100%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are given as number (range) and proportion (%).

*ACS or AMI according to guidelines.

† ACS or AMI according to guidelines.

ACR, acute coronary syndrome; AMI, acute myocardial infarction; CK-MB, creatinine kinase-MB isoenzyme; GBP, glycogen phosphorylase isoenzyme BB; H-FABP, heart-type fatty acid binding protein; IMA, ischaemia modified albumin; MRP 8/14, myeloid-related protein 8/14; NPV, negative predictive value; PAPP-A, pregnancy-associated plasma protein A; PPV, positive predictive value.
The highest predictive values of H-FABP were shown in patients presenting within 6 h of symptom onset. The results indicate that H-FABP seems to have some potential as an early diagnostic marker of AMI or ACS, but its value in addition to clinical features and other markers has not been studied.

### Ischaemia modified albumin

IMA is a US FDA-approved biomarker that can detect myocardial ischaemia within minutes and continues to increase for 6–12 h, after which its level returns to normal. Myocardial ischaemia results in reduction of the ability of albumin to bind cobalt, which is the basis of the albumin cobalt-binding test for IMA.95 96

The nine studies found on IMA (table 3) were performed in the correct study domain and included the appropriate outcome AMI (Joint ESC/ACC consensus 2000 n=3) or ACS (n=6).80–88

In all but one of the studies predictive values were presented or could be calculated. Four studies (44%) included multivariable analyses.

In a recent study in 413 suspected ACS patients at the emergency department (admission time not given), IMA had the highest NPV (92%) (PPV 40%) as compared to the combined use of myoglobin, CK-MB and cTnT (86%). Addition of IMA to myoglobin, CK-MB and cTnT resulted in a higher NPV of 95%.84

A meta-analysis consisting of eight studies in 1812 similar patients showed that a triple test of ECG, cTn and IMA in the first 5 h after chest pain onset resulted in a NPV of 97%. However, the added value of IMA was not given.96

A study of 208 patients suspected of having ACS presenting within 3 h of symptom onset reported that IMA had a PPV of 72% and NPV of 59%. IMA and ECG had a higher AUC (0.68) than cTnT (0.64). Addition of IMA to ECG and cTnT (AUC 0.74) resulted in a PPV of 74%, NPV of 84% and AUC of 0.83 (an AUC increase of 0.09).83

A study in 151 similar patients showed a PPV of 74%, NPV of 76% and an AUC of 0.78. In multivariable analysis IMA was an independent predictor of ACS with an OR of 14.6. The combined use of IMA and cTnT increased the OR to 21.9. The change in AUC was not calculated.87

The results indicate that IMA could be a potential marker for early ruling out of ACS in chest pain patients because of its relatively high NPV, especially combined with cTn and ECG. However, its PPV is low. Importantly, IMA seems to add relevant diagnostic information to more readily available diagnostic parameters. However, problems with the stability of IMA and its lack of cardioselectivity have been reported.89 Its clinical use needs to be established by future studies, particularly given the withdrawal of commercial sale of the test.

### Pregnancy-associated plasma protein A

PAPP-A is a metalloproteinase enzyme that activates insulin-like growth factor I, a mediator of atherosclerosis.90–93 Its plasma release pattern was studied by Qin et al who found various release patterns in patients with ACS with increases above the reference range between 2 and 50 h.94 Recently, a POC test has been developed in addition to available ELISA.95 96

One of the three articles on PAPP-A (table 3) was performed in the appropriate study domain and had the appropriate outcome (ACS).90 97 98 None of the studies reported predictive values. All three studies performed multivariable analysis.

The first study published suggested PAPP-A as a candidate marker for unstable angina and AMI by demonstrating that PAPP-A was expressed in ruptured and eroded plaques but not in stable plaques measured in eight patients who developed sudden cardiac death.90 The AUC for PAPP-A was 0.94 among patients with AMI and 0.88 among patients with unstable angina. There was no association between levels of PAPP-A and cTn or CK-MB, which suggests PAPP-A to be a marker of ischaemia rather than myocardial necrosis.

A study in 59 patients presenting with chest discomfort to the emergency department demonstrated an adjusted OR of 2.1.90

Another study, however, did not find differences in circulating PAPP-A levels in patients with ST-elevation MI and subjects without MI.97

These (contradictory) results indicate that the diagnostic value of PAPP-A in patients suspected of having ACS has not been evaluated properly.

### Glycogen phosphorylase isoenzyme BB

GPBB is an enzyme in glycogenolysis, which is detectable in cytoplasmic form after onset of tissue ischaemia. It is released into the circulation 2–4 h after the onset of cardiac ischaemia and returns to the reference interval within 1–2 days after AMI onset. Plasma GPBB levels are determined by ELISA techniques.99

Three studies were found on the possible diagnostic value of GPBB in patients with ACS (table 3).100–102 Two of these studies were (partially) conducted in the appropriate study domain and had the correct outcome (AMI according to WHO, and ACS). Predictive values were given in one study. None of the studies showed multivariable results.

In a study consisting of 107 chest pain patients, GPBB was more sensitive than CK, CK-MB, myoglobin and cTnT for the diagnosis of AMI and unstable angina within 4 h after chest pain onset with a PPV of 94%, a NPV of 78% and an AUC of 0.91.102 A more recent study found an AUC of 0.984–0.998 for the detection of ACS depending on time since symptom onset.101 These findings suggest that GPBB might be a marker for myocardial ischaemia and myocardial necrosis, although the available research is limited and does not assess the added value of the marker.

### Myeloid-related protein 8/14

Myeloid-related protein 8/14 complex (MRP 8/14) is a marker of phagocyte activation, which is involved in plaque destabilisation. It is mainly expressed in monocytes and neutrophils. MRP-8/14, which is probably raised in AMI patients within 3–4 h, is detected by ELISA.103

One diagnostic study was found measuring MRP 8/14 in the context of ACS (table 3).104 The study was not performed in the appropriate study domain, which makes it hard to extrapolate results to patients with suspected ACS. The outcome was appropriate (ACS). Predictive values were not given, the study included multivariable analysis. The study suggested that MRP 8/14 might be a good marker for the detection of unstable plaques as a significantly elevated expression of MRP 8/14 was found at the site of coronary occlusion and elevated systemic levels in patients with ACS as compared to patients with stable angina or without ACS with an AUC of 0.97. MRP 8/14 was increased prior to necrosis markers such as cTnT, myoglobin and CK-MB.103

More research is needed to evaluate the (added) diagnostic value of MRP 8/14 in patients suspected of having ACS.

### DISCUSSION

Seventy-three clinical studies were identified on the diagnostic accuracy of biomarkers for ACS that can be used within 6 h of
symptom onset, although some studies included patients with unknown symptom onset or symptom onset >6 h. Table 3 summarises the available evidence by biomarker. The studies were mostly performed in the appropriate study domain (87%), that is patients with suspected ACS or MI, and had the appropriate outcome (96%), that is ACS or MI according to the guidelines available at the time the articles were published. However, because of a change in AAMI and ACS definition over the years, the results of older studies are not completely comparable to the results of the most recent studies. The clinical utility, in terms of predictive values, ORs and AUC was often not quantified correctly. The range in PPV and NPV was considerable, varying from 5% to 100% (PPV) and 50% to 100% (NPV). Multivariable analysis, that is analysis of the added value of a specific marker to clinical symptoms and ECG, was often lacking (84%).

Three (PAPP-A, GPBB, MRP 8/14) of the seven biomarkers have not been studied properly as most of the relatively small studies were not performed in the proper domain, outcome was mostly incorrect and none of the studies used adequate measures of clinical utility.

The markers CK-MB, 2 h ΔCK-MB (which takes at least 2 h) and myoglobin, mentioned by the guidelines, seem to have value in the early assessment of ACS, although there is hardly any clinical evidence they have value in addition to other patient characteristics.

IMA and H-FABP seem to be the most promising new markers in the early assessment of patients suspected of having ACS. IMA, relatively well studied in multivariate analysis, is a potential marker for early ruling out of ACS in chest pain patients because of its relatively high NPV, especially combined with cTn and ECG. Its clinical use, however, needs to be established by future studies (ie, multivariate analysis to quantify the value of IMA in addition to signs, symptoms and other diagnostic test). H-FABP seems to have some potential as an early diagnostic marker for ruling out of ACS as well, although its value in addition to clinical features and other markers has not been studied.

Six recent guidelines in English were identified on diagnosis in patients suspected of having ACS. All guidelines advocate cTn (I or T) as the preferred marker of ACS in the setting of a clinical syndrome consistent with myocardial ischaemia. Two guidelines recommend myoglobin in the first 6 h of symptom onset, and four guidelines recommend CK-MB or 2 h ΔCK-MB measurement. However, the evidence that these two markers have added value in addition to clinical symptoms, ECG and cTn is limited.

The introduction of high-sensitivity troponin assays may further improve diagnosis of ACS. A recent study, in patients with suspected AMI presenting at the emergency department, showed that a sensitive cTnI assay had a higher NPV than a standard cTnT assay and comparable PPV for detecting AMI within 6 h of symptom onset. The PPV was 79.3% and 80.7%, respectively; the NPVs were 95.3% and 88.0%, respectively. In another study in comparable patients presenting within 12 h of symptom onset, the NPV of four sensitive cTn assays (98–100%) was higher than the NPV of a standard cTnT assay (97%). The PPV of all four sensitive cTn assays, however, was lower.

It is likely that multimarker strategies, for example a combined test for (high-sensitivity) cTn and H-FABP or IMA, have the largest diagnostic yield in the early diagnostic assessment of suspected ACS patients, but future studies should confirm this hypothesis.

Current guidelines differ in their opinions about the usefulness of POC-tests; according to the ACC/AHA guidelines, POC tests have not succeeded in becoming widely accepted or applied. The ESC guidelines, however, advocate that POC tests for cTn should be used when a central laboratory cannot consistently provide test results within 60 m.

In conclusion, current guidelines advocate the use of cardiac troponin or CK-MB when cTn is not available, and myoglobin in the first 6 h in addition to cTn, in the early evaluation of patients with symptoms suggestive of ACS. IMA and H-FABP seem to be promising diagnostic biomarkers in the early diagnostic assessment of patients suspected of having ACS. There is an urgent need for adequately designed studies of (novel) ACS markers and their combinations against contemporary troponin assays.

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Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES


Systematic review


