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ABSTRACT

Background: To determine the diagnostic accuracy of a rapid heart-type fatty acid-binding protein (H-FABP) test in patients suspected of acute coronary syndrome (ACS) in primary care.
Methods: General practitioners included 298 patients suspected of ACS. In all patients, whether referred to hospital or not, ECG and cardiac biomarker testing was performed. ACS was determined in accordance with international guidelines. Multivariate analysis was used to determine the value of H-FABP in addition to clinical findings.
Results: Mean patient age was 66 years (SD 14), 52% was female and 66 patients (22%) were diagnosed with ACS. The H-FABP bedside test was performed within 24 h (median 3.1, IQR 1.5 to 7.1) after symptom onset. The positive predictive value (PPV) of H-FABP was 65% (95% confidence interval (CI) 50–78). The negative predictive value (NPV) was 85% (95% CI 80–88). Sensitivity was 39% (29–51%) and specificity 94% (90–96%). Within 6 h after symptom onset, the PPV was 72% (55–84) and the NPV was 83% (77–88), sensitivity 43% (31–57%) and specificity 94% (89–97%). Adding the H-FABP test to a diagnostic model for ACS led to an increase in the area under the receiver operating curve from 0.66 (95% CI 0.58–0.73) to 0.75 (95% CI 0.68–0.82).
Conclusion: The H-FABP rapid test provides modest additional diagnostic certainty in primary care. It cannot be used to safely exclude rule out ACS. The test can only be used safely in patients otherwise NOT referred to hospital by the GP, as an extra precaution not to miss ACS ('rule in').

1. Introduction

Early interventions aimed at restoring coronary blood flow in patients with acute coronary syndrome (ACS) reduces myocardial damage and improves patient outcome. Yet, a timely diagnosis can be a diagnostic challenge for the clinician. In the majority of European countries, including the Netherlands, many patients suspected of ACS – comprising acute myocardial infarction (AMI) and unstable angina – will contact a general practitioner (GP) first. Typically, the GP will assess patients suspected of ACS by history taking and physical examination. Using these limited diagnostic tools, it is notoriously difficult to accurately exclude or confirm ACS, notably in patients with atypical symptoms [1]. Additional diagnostic information such as electrocardiography (ECG) is often not available in primary care, while ECGs taken early after the onset of complaints will not always reveal the typical ST-segment elevation or Q-wave changes indicative of myocardial infarction [2]. Alternatively, plasma biomarkers of myocardial damage have shown to be very accurate in detecting myocardial necrosis. Of these biomarkers, troponin, which is typically elevated 6–9 h after the onset of ischemia [3,2,4], has become an indispensable diagnostic tool in the diagnosis of ACS. Most patients with symptoms suggestive of ACS, however, present themselves to the GP as early as 1 and 3 h after symptom onset [5–7]. Several uncertain hours therefore remain, in which current troponin assays (including high-sensitive tests) cannot provide the diagnostic certainty needed to accurately exclude or confirm ACS. This makes heart-type fatty acid-binding protein (H-FABP) an interesting new biomarker, as it is released into the circulation very rapidly after the onset of cardiac ischemia and elevated levels have been detected already from 1 h onwards [8–10]. Especially in a primary care setting, a bedside test for H-FABP, providing results within 15 min [11], could be a helpful diagnostic tool, but the accuracy of such a test has not been assessed in primary care. Therefore, our aim in this study was to determine the diagnostic accuracy, additional value in combination with clinical findings and feasibility of a rapid H-FABP bedside test in patients suspected of ACS in primary care.

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2. Methods

The design and methods of this study have been described extensively elsewhere [12]. In short, all patients suspected of an acute coronary syndrome by the GP (e.g. patients presenting with chest pain, or other more 'vague' symptoms such as abdominal discomfort or shortness of breath, prompting a GP to suspect ACS) were consecutively included in three out-of-hours GP services in the Utrecht region (one urban and two semi-urban). Additionally, 25 GPs from 9 group practices recruited patients during daytime hours. We excluded patients with complaints lasting more than 24 h and patients requiring instant hospital referral, as judged by the GP. Diagnostic assessment during the initial GP consultation consisted of standardized history taking and physical examination with performance of a blinded H-FABP bedside test. Only after making the referral decision, the GP de-blinded the H-FABP test and recorded the test result on a standardized case record form. The decision about hospital referral was thus made in accordance with current daily practice, using only history taking and physical examination and, when available, ECG. However, for safety reasons an exception was made for patients with a *positive* H-FABP test result in whom the GP initially decided *not* to refer. In these cases, the GP was instructed to change his initial management decision in favour of hospital referral.

The study protocol was approved by the Medical Ethics Committee of the University Medical Center Utrecht. All patients provided written consent. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

The H-FABP bedside test (Cardiodetect® Rennesens GmbH, Berlin) used in this study is a rapid chromatographic immunotest designed for qualitative determination of H-FABP in whole blood samples with a threshold of 7 ng/ml. It consists of a sample pad (blood separator), a conjugate pad, a nitrocellulose membrane and an absorbent pad incorporated in a test card that has the size of a credit card. Immobilized on the membrane is a test line made of a specific capture monoclonal antibody for H-FABP and a second line, acting as control, consisting of anti-mouse IgG. The test is performed by drawing four drops of capillary whole blood from the patient's finger and applying them onto the test-strip. Within 15 min the H-FABP test result (two red lines for elevated plasma H-FABP and one red line for non-elevated plasma H-FABP) can be read. For study purposes the test result was concealed by a blinding-strip. The test was de-blinded by the GP after he/she had made the referral decision. The GP documented the results on a standardized case report form, together with findings from history taking and physical examination. Other items on the form included age, gender and prior history of AMI or revascularisation (bypass surgery or percutaneous coronary intervention).

In all patients, irrespective of whether they were referred to hospital or not, a venous blood sample was collected between 12 and 36 h after onset of complaints, for measurement of cardiac biomarkers (troponin, creatinin kinase (CK) and creatinin kinase-myocardial band (CK-MB)). Also, we obtained a twelve-lead ECG in every patient. In referred patients these measurements were performed as part of routine care. Patients who were not referred to hospital were visited at home by qualified GP laboratory service personnel for performance of these tests.

An expert panel consisting of two cardiologists and one GP established the final diagnosis in each patient. The panel used all available patient information, including information from medical history taking and physical examination, ECG analysis, biomarker levels, specialist letters and follow-up results up to one month after the event (obtained by contacting the GPs of the patients). The expert panel was blinded to the H-FABP rapid test results.

ACS was defined in accordance with guidelines from the European Society of Cardiology and the American College of Cardiology [2,4]. The diagnosis of AMI was established when patients had suggestive symptoms, e.g. chest pain, and a maximal concentration of troponin T or I exceeding the decision limit, i.e., 99th percentile of the values for a reference control group, within the first 36 h after the onset of complaints, or CK-MB values greater than two times the upper reference limit on at least one occasion during the same time frame, or both. The presence of ST- and T-wave changes on the ECG, notably ST elevations and Q-waves, could further confirm AMI. Unstable angina was defined as symptoms of chest pain and ST- and/or T-wave changes on the ECG suggestive of ischemia, but without elevation of troponin and CK-MB above the decision limits. When the diagnosis ACS or unstable angina could not be made, the panel identified the most likely alternative diagnosis on the basis of the available information.

2.1. Data analysis

To evaluate the diagnostic value of the H-FABP test we constructed 2 by 2 tables with the number of true positive (TP), false positive (FP), true negative (TN) and false negative (FN) H-FABP test results and calculated positive and negative predictive values (PPV and NPV) with 95% confidence intervals. We used ACS as the primary outcome.

Using the multiple imputation function of SPSS version 17.0 (SPSS, Inc., Chicago Il, USA) missing data, including unclear test results, were imputed. To determine whether the H-FABP test provided added diagnostic value beyond the clinical parameters obtained during history taking and physical examination, we performed multivariate regression analysis with receiver operating characteristic (ROC) curves. We tested two diagnostic models: in the first one we only used an established clinical score based on history taking (13); in the second one we combined the clinical score and the H-FABP test result. The clinical score was previously used in a diagnostic model for ACS by Grijseels et al. [13] and included radiation of chest pain, nausea/sweating, the presence of prior cardiovascular disease and gender. The ability to discriminate between patients with and without ACS was studied with the area under the ROC curve (AUC). We (internally) validated our models with bootstrapping techniques to correct for over-optimism. The agreement between the observed proportions of ACS and the risks predicted by the model, or *calibration*, was studied with a calibration plot.

3. Results

From March 2006 until September 2008, 336 consecutive patients suspected by the GP of acute coronary syndrome were enrolled in the study. We excluded 38 patients (11%). Of these, 12 refused informed consent, 23 had symptoms suggestive of ACS for more than 24 h at the time of testing, and three patients had an undetermined final diagnosis. These last three patients were not referred to a hospital and, due to logistical problems, were not tested for cardiac biomarkers and ECG at home. We could thus analyse the results of 298 patients (Fig. 1, flow diagram).

The mean age of participants was 66 years (SD 14) and 52% was female. Most patients (n = 209; 70%) presented themselves to the GP within 6 h after onset of their complaints. The median duration from the start of complaints until the performance of the H-FABP bedside test was 3.1 (interquartile range (IQR) 1.5; 7.1) hours. Seventy-nine percent of patients had one or more cardiovascular risk factor, while 36% of all patients had a history of cardiac disease (Table 1).

According to the panel 66 (22%) patients suffered an ACS. Of these 66 patients, 14 (21%) were classified as unstable angina, 18 (27%) as ST-segment elevation myocardial infarction (STEMI) and 34 (52%) as non ST-segment elevation myocardial infarction (NSTEMI). The 232 (78%) patients classified as non-ACS suffered from a variety of cardiac and non-cardiac diseases. In 30 patients (13%) stable angina pectoris was considered the alternative diagnosis. The most common non-cardiac causes for the complaints were of gastro-intestinal origin (gastric reflux in 16 patients, gall stones in 8 patients), and myalgia (20 patients). In 106 (35%) patients the panel was unable to establish an alternative explanation for the chest pain symptoms (Table 2).

Overall, 40 patients had a positive H-FABP test, and of these 26 suffered an ACS (PPV 65%, 95% CI 50–78%). Of the 258 patients with a negative test, 218 did not suffer ACS (NPV 84%, 95% CI 80–88%). In a subgroup analysis for women the overall PPV was 65% and the NPV was 88% while for patients over 65 years the PPV was 68% and the NPV was 82% (Table 3, also giving results for sensitivity and specificity).

We separately analysed the results of the 209 (70%) patients who presented to the GP within 6 h after the onset of symptoms. In this 0–6 time interval 32 patients had a positive H-FABP test and of these, 23 suffered an ACS (PPV 72%, 95% CI 55–84%). Of the 177 patients with a negative test 147 did not suffer an ACS (NPV 83%, 95% CI 77–88%) (Table 3, also giving results for sensitivity and specificity). A subgroup analysis for women and patients over 65 years yielded similar results (data not shown).

Two clinical multivariable model using only parameters from history taking had an area under the curve of 0.66 (95%CI: 0.58; 0.73). Adding the result of the H-FABP test led to an AUC of 0.75 (0.68; 0.82) (Fig. 2).

We divided patients into three different risk categories for ACS according to the diagnostic model: low risk (<15% chance of ACS, n = 75), intermediate risk (10–25%, n = 146) and high risk (>25%, n = 76). In the low risk categories 43% of patients with a positive test suffered from ACS and 91% of patients with a negative test did not suffer from ACS. In the intermediate risk group PPV and NPV were 60 and 87% respectively, while in the high risk group the PPV was 85% and the NPV 73%.

3.1. Clinical feasibility of the bedside test

More than 50 GPs or supportive staff members of the out-of-hour practices performed one or more tests. In 235 patients (79%) the test result could be read within 15 min. In 63 patients (21%) there either was an obvious test failure, or the GP was unsure about the

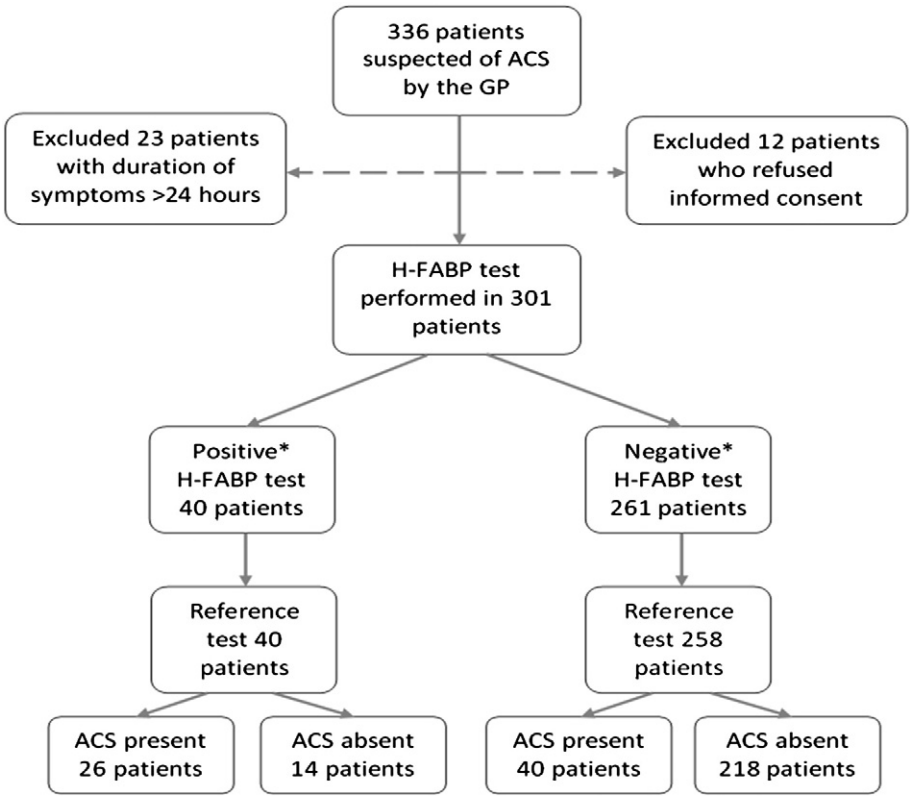

Fig. 1. Patient flow diagram.

appearance of a red line at the H-FABP site and decided the test result was 'unclear'. A second test was performed in 38 (60%) of these patients, giving a test result for 29 (76%) patients. A definite test failure or unclear test result remained in 34 (11%) cases.

4. Discussion

Our study is the first to assess the diagnostic accuracy of an H-FABP bedside test for acute coronary syndrome in a primary care setting. Of the patients suspected by the GP, 22% was diagnosed with ACS. The PPV of the H-FABP rapid test in our study was 65% and we found a NPV of 85%. ROC curve analyses showed that when the H-FABP rapid test was added to a clinical diagnostic score comprising radiation of chest pain, nausea/sweating, prior cardiovascular disease and gender, the area under the curve increased from 0.66 to 0.75, which indicates that the rapid test improves diagnostic accuracy in addition to clinical findings at presentation. In a subgroup of patients presenting within 6 h after the onset of complaints, results were similar.

Several studies investigating the diagnostic test properties of the same bedside test that we used in our study (Cardiodetect©) have yielded varying results. None of these studies were performed in a primary care setting. In these studies the PPV ranged from 63 to 100% and the NPV from 47 to 97% [14–19]. These results of previous studies clearly show that there is uncertainty about the diagnostic properties of the H-FABP rapid test. A direct comparison with our study is difficult, since our study is the first to assess the diagnostic properties of the

Table 1
Characteristics of 298 patients suspected of acute coronary syndrome, presenting to the general practitioner.

Characteristics	Number (%)
Age (mean, years)	66 (SD 14)
Male sex	143 (48)
History of AMI, bypass, PCI, angina pectoris	108 (36)
Presence of cardiovascular risk factors[a]	236 (79)
Symptom duration at time of testing (median in hours, IQR)	3.1 (1.5–7.1)
Referred to hospital	218 (73)
Positive H-FABP test	30 (10)
Inconclusive H-FABP test	34 (11)
Acute coronary syndrome	66 (22)
Unstable angina pectoris	14 (21)
Non ST-elevation Myocardial infarction	34 (52)
ST-elevation myocardial infarction	18 (27)

SD: standard deviation, AMI: acute myocardial infarction, PCI: primary coronary intervention, IQR: interquartile range, and H-FABP: heart-type fatty acid-binding protein.
[a] Current smoker, diabetes, hypertension (documented in primary care or hospital chart), and hypercholesterolemia.

Table 2
Final diagnosis of participants as determined by outcome panel.

Final diagnosis	Number (%)
Acute coronary syndrome	66 (22)
Unstable angina	14
Non ST-elevation myocardial infarction	34
ST-elevation myocardial infarction	18
Other cardiovascular diseases	51 (17)
Angina pectoris	30
Heart failure	3
Arrhythmias	15
Pericarditis	3
Noncardiovascular diseases	59 (20)
Myalgia	20
Anxiety/hyperventilation	11
Pulmonary embolism	4
Gall stones	8
Gastric reflux/ulcer	16
Other	16 (5)
Cause of complaints unknown	106 (36)

Table 3
Diagnostic accuracy of the H-FABP test per time interval with 95% confidence interval and original accuracy tables.

	0–6 h			0–24 h		
PPV	72 (55–84)			65 (50–78)		
NPV	83 (77–88)			84 (80–88)		
Sensitivity	43 (31–57)			39 (29–51)		
Specificity	94 (89–97)			94 (90–96)		
Likelihood +	7.5 (3.7–15.2)			6.53 (3.6–11.8)		
Likelihood −	0.60 (0.47–0.76)			0.65 (0.53–0.79)		
Accuracy tables	0–6 h	ACS	No ACS	0–24 h	ACS	No ACS
	H-FABP +	23	9	H-FABP +	26	14
	H-FABP −	30	147	H-FABP −	40	218

PPV: positive predictive value, NPV: negative predictive value, ACS: acute coronary syndrome, H-FABP: heart-type fatty acid-binding protein.

H-FABP bedside test in a primary care setting. Reported differences may therefore be due to differences in patient domain, severity of disease, variation in ACS prevalence (which ranged from 13-64% in the above mentioned studies) and the amount of test failures (reported in only 2 studies [17,16], respective failure rate 14 and 17%). Also, no multivariate analysis was performed in these earlier studies. In addition, the added value of the test (by comparing two diagnostic models, with and without the H-FABP test) was not studied, while in daily practice such a test will always be used in combination with other clinical tests, typically history taking.

Our study shows that the H-FABP test can be of use for GPs, when taking into account some important limitations. Using the test leads to more diagnostic certainty in the diagnosis of ACS in patients suspected of ACS, as was seen in the increased area under the ROC curve after adding H-FABP to our diagnostic model for ACS. However, for a condition carrying a high morbidity and mortality such as ACS, the H-FABP rapid test that we used in our study is by no means an ideal test. For instance, a false negative test result was seen in 40/298 (13%) of patients in our study, a percentage of 'missed patients' that is unacceptably high. Therefore, in our opinion, the H-FABP test should not be used for ruling out ACS. On the other hand, it could be used to provide more diagnostic certainty in diagnosing ACS. Of the patients with a positive test results, 65% have an ACS. Compared with a 22% a priori chance of ACS, this is a substantial gain in diagnostic certainty. Moreover, when used in the patient group considered at low risk for ACS (<15% chance based on our diagnostic model with only clinical parameters, otherwise not referred to hospital by the GP) still 43% of patients with a positive test are diagnosed with ACS. When using this test, GPs will be able to make a better informed referral decision in these low-risk patients by referring patients with a positive H-FABP rapid test to a specialized cardiologic intervention centre directly, instead of to a general hospital that may lack these facilities. In patients that are considered by the GP at an intermediate or high risk for ACS (requiring hospital referral) however, the use of f the H-FABP test cannot ne recommended. A negative test should not change the referral decision of the GP (false negatives), and a positive test will also not change the management decision of the GP: these patients should all be referred to hospital for additional diagnostic testing and, if necessary, treatment.

The second aim of this study was to assess the feasibility of the H-FABP rapid test. We found an initial unclear test result in 21% of patients and after repeated testing, an unclear result remained in 11%. This may partly be due to the set-up of our study in out-of-hour GP practices, where many different GPs performed the test and many of them performed a H-FABP test only once during the inclusion period. Consequently, there was little learning effect for those GPs performing the test. Also, the interpretation of the test result was dependent on the subjective judgement of the coloured control line and H-FABP line by the physician performing the test. This indicates that physicians planning to use the bedside test in their daily practice should be well informed on how to perform and read the test. To facilitate adequate interpretation of the test an automated reading device that has now become available could be of use.

Some limitations of our study should be discussed. Firstly, one could argue whether we used the correct outcome in our study. According to current guidelines, AMI is characterised by ischemia severe enough to cause sufficient myocardial damage to release detectable quantities of

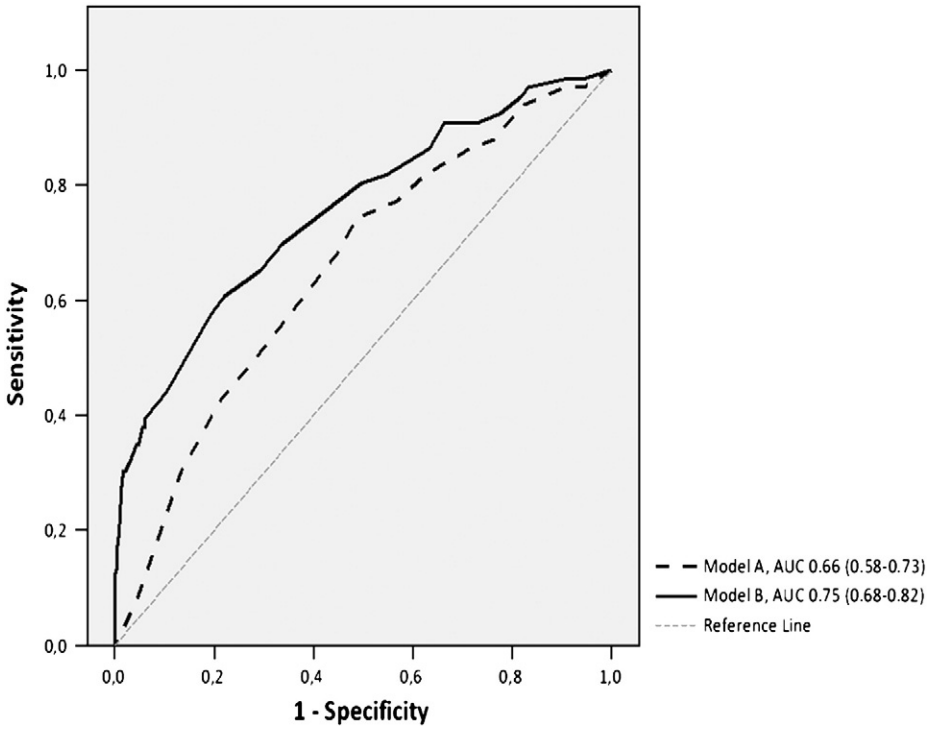

Fig. 2. Receiver operating characteristic (ROC) curve analysis with area under the curve (AUC) and 95% CI for two diagnostic models. Model A: clinical parameters. Model B: clinical parameters and H-FABP test result.

a cardiac biomarker into the circulation, whereas in unstable angina there is ischemia without a measurable amount of a cardiac biomarker in the circulation [20,4]. We used ACS as the primary endpoint in this study, because in primary care there is no difference in management decision: both AMI and unstable angina patients should be referred to hospital for further treatment. Previous studies suggest that H-FABP is a very sensitive marker for even minor myocardial injury in patients with unstable angina. Using ACS as primary outcome could therefore lead to an underestimation of the diagnostic accuracy of H-FABP in acute myocardial infarction, because the ischemia in unstable angina detected by H-FABP will by definition not be detected by the reference standard that we used (troponin). An analysis, taking acute MI as the outcome yielded similar results, however. Secondly, as we already mentioned, the H-FABP test was performed by many untrained GPs and GP practice personnel, which probably led to the relatively high number of unclear test results. Because we believe that in clinical practice after proper training there will be less unclear test results, we imputed the unclear test results.

An important strength of our study is that we performed this diagnostic accuracy study in a primary care setting, where improvement in the early diagnosis of ACS is needed most. Furthermore, we included a large number of consecutive patients suspected of ACS without adopting many exclusion criteria and thus the patient population in our study will very likely resemble the actual patients for whom the test is intended.

In conclusion, the H-FABP rapid test does provide additional diagnostic certainty in suspected ACS patients in primary care when added to general patient and symptom characteristics. Since the test cannot safely rule out ACS, however, we only recommended its use in suspected patients considered as low risk and otherwise not referred to hospital by the GP. A need remains for more adequate testing methods or alternative biomarkers for the detection of both myocardial infarction and unstable angina. It is possible that high sensitive troponin could fill that gap, but although there currently are commercial point of care tests available for high sensitive troponin, no studies have been published to evaluate its clinical effectiveness.

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