Point-of-care testing for heart-type Fatty Acid Binding Protein

Horizon Scan Report 0039
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Clinical Question:

In patients presenting to primary care or the Emergency Department (ED) with acute chest pain, what is the accuracy and utility of a point-of-care test for heart-type Fatty Acid Binding Protein (H-FABP) in diagnosing acute myocardial infarction (AMI), compared to routine clinical practice?

Background, Current practice and Advantages over Existing Technology:

When blood flow to the myocardium is acutely obstructed, a person will typically suffer more prolonged chest pain of recent onset; this is referred to as acute coronary syndrome (ACS). When the obstruction leads to myocardial necrosis (cell death), this results in an acute myocardial infarction (AMI) or 'heart attack', and the release of a series of biomarkers from myocytes into the bloodstream. The most well-known and widely tested of these is cardiac troponin (cTn), composed of 3 subunits, C, T and I. A wide range of other biomarkers exist, such as myoglobin, creatine kinase MB isoenzyme (CK-MB), copeptin, and heart-type Fatty Acid Binding Protein (H-FABP). H-FABP has become of particular interest in recent years because its concentration in the plasma rises much sooner after an AMI than troponin (within 3 hours, compared to 6-8 hours). The myocardial tissue content of FABP is about five-fold lower than that of myoglobin, but the reference plasma concentration of FABP is about 15-fold lower than that of myoglobin. The differences in amounts of myoglobin and FABP in heart and skeletal muscles and their simultaneous release upon muscle injury allow also the plasma ratio of myoglobin/FABP to be applied for discrimination of myocardial (ratio 4–5) from skeletal muscle injury (ratio 20–70). AMI can be subdivided into ST segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI) based on electrocardiograph (ECG) findings. Non-ST segment elevation myocardial infarctions (NSTEMI) occur when the infarction is either brief or affects only a small part of the myocardium.

A temporary obstruction of the blood flow to the myocardium does not lead to myocardial necrosis, in which case the clinical syndrome is termed unstable angina. In contrast to AMI, unstable angina is not associated with an elevation of markers of myocardial necrosis. Current practice in the UK is that assessment of chest pain of recent onset is based on a combination of history, physical examination, electrocardiography (ECG) and cardiac markers, usually a cTn taken on arrival in hospital and then again 10-12 hours after the onset of symptoms [1].

When it comes to AMI, time is of the essence, with a rapid reduction in salvageable myocardium over time, and a shorter time to treatment being strongly linked to better survival [1]. Point-of-care blood tests reduce the time taken to get a result compared to laboratory blood tests, allowing definitive treatment to be commenced sooner [2].

Both false positive diagnosis and false negative diagnosis of AMI are an issue. One study found the rate of missed diagnosis in the ED to be 2% [3]. If AMI can be ruled in using a point-of-care test (POCT) reliably and cheaply with a short turnaround time when people first present to primary care or the ED with suspicious symptoms, then the rates of delayed and of missed diagnoses could potentially be reduced. Equally, there is a cost burden for the health service and a psychological burden for the patient when AMI is diagnosed but is not present. If a POCT could effectively rule out AMI earlier in the clinical pathway, unnecessary referrals and resultant anxiety and costs could be avoided.

Data from UK Emergency Departments show that 6% of attendances were for chest pain [4] and a presenting complaint of chest pain makes up 1% of all UK primary care consultations [5].

Details of technology:

Available POCTs for testing for the presence of H-FABP in whole blood are listed in Table 1. We have identified six POC tests for H-FABP, all but one use finger-prick whole blood samples and take from 2 to 15 minutes to produce a result. Two of these are CE marked, but none currently have FDA approval. Tests are qualitative (existing as an individual cassette with a strip which becomes coloured if the test is positive), but for the CardioDetect the test results can be quantified, using an external 'reader' device to calculate the concentration of H-FABP present in the sample.

Table 1. Point-of-care H-FABP tests

Product (Company, Country)	**Volume**	**Time (mins)**	**Test threshold (ng/mL)**	**Quantitative/ Qualitative readout?**	**FDA/CE approval**
H-FABP True Rapid Test (Fabpulous, Netherlands)	1 drop (~20-30 µl)	2-5	4	Qualitative	CE
CardioDetect (Rennesens GmBH, Germany – now marketed by Renesa, Germany)	4 drops (100-120µl)	15	7	Qualitative and quantitative*	CE
Rapicheck (DaiNippon, Japan)	150µl	15	6.2	Qualitative	N/A
H-FABP Kit (Wuhan Easydiagnosis Medicine, China)	Finger prick	10	7	Qualitative	N/A
QuickSens H-FABP (8sens.biognostic GmbH, Germany)	Finger prick	15	N/A	Qualitative	N/A
H-FABP Diagnostic Kit (Harbin TDR Medical, China)	Finger prick	N/A	N/A	Qualitative	N/A

N/A =not available

* Requires CardioDetect quant, a desktop reader which quantifies H-FABP concentration in the sample by reading the intensity of the result line of the rapid test strip.

Patient Group and use:

- Patients presenting with acute chest pain suspicious of myocardial infarction. .

Importance:

Coronary heart disease (CHD), which is the leading cause of AMI, is a common and important clinical problem leading to considerable mortality and morbidity: 3.5% of the population in the UK, or 2.3 million people, were thought to have CHD in 2012 [6]. It was the largest cause of death in the UK in 2012, and it was estimated that in that year CHD cost the UK £1.8bn, or 1% of the total NHS budget, in healthcare costs alone [6]. Further economic costs include those of production losses from death and illness in those of working age (£3bn) and of informal care (£1.7bn).

An H-FABP POCT could have roles in different points in the various clinical pathways depending on the setting [7]. For example, it could be used in combination with (or instead of) troponin in the existing clinical pathway to aid early diagnosis, as indicated in a meta-analysis of studies on the combination of H-FABP and high sensitivity troponin, which showed an increased sensitivity (0.73 for troponin alone versus 0.80 for the combination; p=0.02), although at the expense of lower specificity (0.94 vs 0.82, p=0.001) [8], or H-FABP could aid in triage of patients into high, moderate and low risk groups, who could then be referred to different secondary care departments (for example, lower risk patients could be sent to a rapid access chest pain clinic rather than straight to the ED). However, well-designed research studies would be required to establish the optimal role(s) of this test.

Previous research:

Accuracy compared to existing technology:

A total of 20 studies evaluated H-FABP POCTs: 15 of these looked at the CardioDetect device, including the only two studies carried out pre-hospital, one of which was in primary care and the other in a mobile intensive care unit. Of the remainder, two examined the Rapicheck, and one each for the FABPulous, H-FABP kit, and QuickSens H-FABP. A summary of the findings of the studies is presented in Table 2. Where the results were subdivided according to time since onset of symptoms, this is indicated.

All studies evaluated the diagnostic value of the H-FABP POC test for acute myocardial infarction and/or acute coronary syndrome. The reference standards for the POCT in these studies were either the Combined European Society for Cardiology and American College of Cardiology (ESC/ACC) diagnostic criteria for ACS or AMI [9], which consist of a history of chest pain or other symptoms consistent with ACS, typical electrocardiography (ECG) changes and troponin measurements exceeding the 99th percentile of a reference control group within 36 hours of symptom onset, or those of the World Health Organisation (WHO), consisting of a history of prolonged chest pain, ECG changes (development of a new Q wave following ST elevation, or prolonged ST-segment depression or T-wave inversion) and characteristic elevation of serum creatine kinase (more than twice the upper limit) and creatine kinase–MB fraction (more than 10% of total creatine kinase or more than

twice the upper limit) [10]. In four studies, a positive troponin test alone was used as a reference test [11-14]. Three studies excluded patients who had known renal impairment, or who had had recent skeletal muscle trauma, as both can falsely elevate the blood H-FABP concentration [15-17].

The Dutch study using the CardioDetect POCT in primary care enrolled 298 patients presenting to their GP with chest pain or other symptoms prompting the GP to consider ACS as a diagnosis [11]. The ESC/ACC criteria were used as a reference standard. For H-FABP, performed within 24h after symptom onset, sensitivity was 39% (29%–51%) and specificity 94% (90%–96%), with a positive predictive value (PPV) of 65% (95% CI: 50%–78%) and negative predictive value (NPV) of 85% (95% CI 80%–88%), respectively. 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 using an established clinical score based only on history taking (including radiation of chest pain, nausea/sweating, the presence of prior cardiovascular disease and gender), led to an increase in the area under the receiver operating curve (AUC) from 0.66 (95% CI 0.58–0.73) to 0.75 (95% CI 0.68–0.82).

The other study carried out pre-hospital with the CardioDetect device was in 108 patients who dialled the emergency number in France complaining of chest pain and who were subsequently assessed in a specialised ambulance [13]. Within 3 hours of symptom onset, the study reported a sensitivity of 86% (95% CI 72%-95%), a specificity of 93% (95% CI 80%-99%), when compared with the ESC/ACC criteria for diagnosing ACS. In patients presenting with both a negative pre-hospital cTnI and no ST-elevation on their 18-lead ECG, sensitivity was 83% (95% CI 59%-96%), and specificity was 93% (95% CI 82%-99%).

The sensitivities for the CardioDetect device used in the Emergency Department in the shortest time period since symptom onset measured in each of the 13 studies ranged widely from 8.7% to 98%, with a median value of 71% [12, 14-25]. It should be noted that the study reporting sensitivity of 8.7% restricted its population to patients presenting with chest pain and non-ST segment elevation. Ten studies used a clinical diagnosis of AMI or ACS (i.e. including ECG and cTn) as a reference standard (ESC/ACC, WHO, or unspecified), while three used laboratory troponin T values only. Specificities ranged from 30-100% (median 88%), PPV from 40-100% (median 78%), and NPV from 40-97% (median 78%). Where quoted, likelihood ratios ranged from 1.2 to ∞ for LR+ (median 3.4) and 0.26 to 0.95 for LR – (median 0.5).

The study looking at the FABPulous device in diagnosing AMI was an ED-based study acting as a pilot to one currently being carried out in primary care, and only reported sensitivity values: with 57% at 3 hours, increasing to 75% overall [26, 27]. The reference standard was not quoted.

The H-FABP kit had a reported sensitivity of 84% (95% CI 69%-94%), and a NPV of 86% (95% CI 72%-95%) compared to ESC/ACC diagnostic criteria of AMI in one Chinese study of patients presenting to hospital within 3 hours of onset of chest pain [28]. This increased to 100% (95% CI 89%-100%) for both sensitivity and NPV in patients tested between 6 and 12 hours after symptom onset.

The large Swiss study using the QuickSens H-FABP device looking at 1074 ED patients presenting with chest pain suggestive of ACS reported a sensitivity of 72% (95% CI 65%-89%), a specificity of 80% (95% CI 77%-82%), a PPV of 41% (95% CI 35%-47%) and a NPV of 94% (95% CI 92%-95%) for the diagnosis of AMI compared to the ESC/ACC criteria [29].

Finally, in the two studies (both from the same research group), one of patients presenting to a cardiac ED with acute onset of chest pain (within 36h) [30] and one of patients with chest pain or dyspnoea presenting to cardiology offices (clinics) [31] the Rapicheck device was reported to have sensitivities of 89% (95% CI 74%-97%) within 2 hours of symptom onset and 100% (95% CI 60%-100%) within 3 hours of symptom onset compared to the WHO criteria for AMI diagnosis [30, 31]. Specificities were 52% (95% CI 32%-71%) and 63% (95% CI 43%-83%). The PPV and NPV for the test within 3 hours of symptom onset were reported in the cardiology office study as 44% (95% CI 19%-70%) and 100% (95% CI 77%-100%), respectively.

Many of the studies also compared the accuracy of H-FABP to other cardiac markers, such as cTn, CK-MB and myoglobin. The full details can be seen in Table 2, but in general H-FABP was either significantly more sensitive than or comparable to other biomarkers compared to the same reference standard in the first few hours after symptom onset.

A number of the studies also explored the additional effect of risk factors for cardiovascular disease on accuracy of the H-FABP POCT. One study which reported the overall positive likelihood ratio to be 5.4, noted that it was 9.2 in patients who had hypertension, 9.1 in patients who had hypertension and diabetes, and 3.9 in patients who had diabetes alone; though it is surprising that this is lower than the overall value for the study considering diabetes is an independent risk factor for CHD [17]. However, confidence intervals were not provided, therefore these results should be interpreted with caution. Another study found a more modest increase from 1.2 to 1.8 in those with hypertension, and from 1.2 to 1.5 in those with diabetes [22]. Two studies also evaluated accuracy in different age groups. For patients 55 years or older, sensitivities were 80.0% (95% CI 65.4%–90.4%) and 77.9% (95% CI 66.2%–87.1%), and specificities of 47.1% (95% CI 23.0%–72.1%) and 61.5% (95% CI 51.0%–71.2%). For patients under 55 years sensitivities were 55.6% (95% CI 21.4%–86.0%) and 53.7% (95% CI 37.4%–69.3%), and specificities were 66.7% (95% CI 11.6%–94.5%) and 89.3% (95% CI 80.1%–95.3%) [17, 23].

While the H-FABP POCTs studied consistently outperform other cardiac biomarkers within the first hours of symptom onset in terms of accuracy, based on the sensitivity and negative likelihood ratio they are currently not accurate enough to be a fully reliable rule-out test for AMI. The most widely studied test, the CardioDetect device, had highly variable accuracy results. The Rapicheck POCT seemed to perform with the greatest accuracy. Indeed, 5 studies reported that the combination of H-FABP with troponin in a POCT device greatly increased the accuracy of the test, which would merit further investigation [20, 21, 28, 29].

Impact compared to existing technology:

The Dutch study of the CardioDetect device in 298 primary care patients also reported on its feasibility [11], and found that in 21% of cases, the result of the test was unclear, remaining unclear in 11% after a retest. It was suggested that the GP's lack of familiarity with the equipment may have been a factor in this, and adequate training or an automated reader (available for the CardioDetect device) might reduce uncertainty. The 2010 study using the CardioDetect device makes some subjective comments on the ease of use of the device in both the ambulance and ED, and states the authors are planning a cost-effectiveness study and will investigate whether this test can improve

clinical outcomes and shorten time to diagnosis compared to the currently used WHO guidelines [17].

Guidelines and recommendations:

Neither laboratory nor point-of-care testing for H-FABP explicitly appear in relevant guidelines from the National Institute for Health and Care Excellence (NICE) [1], Scottish Intercollegiate Guidelines Network (SIGN) [32], or British Cardiovascular Society (BCS) [33]. NICE has recommended further research into novel cardiac biomarkers in people with acute chest pain. In addition the joint guidelines of the American Heart Association (AHA) and AAC do not mention laboratory or point-of-care testing for H-FABP [34, 35]. Currently troponin (cTnI or cTnT) is recognised by the ESC, ACC, BCS and AHA as the biomarker of choice for diagnosing MI, with NICE recommending a blood sample for troponin should be taken on admission and then again 10-12 hours after the onset of symptoms [1].

Health Economics

The only available health economic information on use of H-FABP in the NHS is that produced by Collinson in 2013 with respect to the QALY values of combined H-FABP/cTn tests in secondary care, where it found that such a combination was cost-effective at a £20,000/QALY threshold in once and twice daily ward round scenarios on admitted patients (£14,806/QALY) [36]. We did not identify any health economic analyses with regard to the use in emergency department, paramedic or primary care settings.

Research Questions:

What is the accuracy of point-of-care H-FABP in primary care settings, including the paramedic setting and Community Emergency Care Units?

What is the accuracy and utility of combined biomarker POCTs, for example the combination of H-FABP with cTn, in the clinical pathway of acute chest pain in primary care and paramedical settings?

Where would an H-FABP POCT fit into the clinical pathway for acute chest pain – would it be most useful in complementing clinical judgment (or clinical prediction rules), or could it complement or replace existing tests such as other biomarkers or ECG. Could it assist in risk stratification, and therefore be useful for ruling out hospital referral?

What is the cost effectiveness of POC H-FABP testing (alone or in combination with other biomarkers) in primary care, paramedic or ED setting to rule out AMI in patients presenting with chest pain?

Suggested next step:

Considering the claimed faster response than cTn, HFABP would be potentially most useful in first contact settings. The paucity of research in such settings (such as primary care and other pre-hospital settings such as paramedics, out of hours services etc.) [37], suggests a need for evidence from such settings on the accuracy, clinical utility, feasibility, cost effectiveness of H-FABP with and without other cardiac biomarkers in the evaluation of adults with chest pain of acute onset. Some pre-hospital settings where there is a higher rate of acute chest pain (such as out of hours services, or paramedics) would be an ideal setting for such a study.

Expected Outcomes:

Current evidence does not suggest it is accurate enough to replace current practice and the role for this test in the clinical pathway has not been established. If rigorous further research into the use of H-FABP POCTs in primary care establish an acceptable level of accuracy for the test, and it is deemed to be acceptable and economical to introduce the test on a widespread basis, then it could be an extremely useful adjunct to clinical judgement, especially in cases where there is doubt over whether to refer a patient or not.

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Table 2. Diagnostic accuracy of H-FABP point-of-care tests

POCT	Location	Population	n	Reference Test	Prevalence of AMI/ACS in population (%)	Time since symptom onset	Sen % (95% CI)	Spec % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR- (95% CI)	Sensitivity compared to other biomarkers	Study [ref] (country)
CardioDetect	Primary Care	Patients presenting to GP with chest pain or other symptoms prompting GP to suspect ACS	298	ESC/ACC diagnosis of ACS	ACS: 25	<6	43 (31-57)	94 (89-97)	72 (55-84)	83 (77-88)	7.5 (3.7-15.2)	0.60 (0.47-0.76)		[11] (Netherlands)
					ACS: 22 UA: 5 STEMI: 6 NSTEMI: 11	Overall (0-24)	39 (29-51)	94 (90-96)	65 (50-78)	84 (80-88)	6.53 (3.6-11.8)	0.65 (0.53-0.79)		
	Pre-hospital	Patients out of hospital who called emergency number with chest pain	108	Positive cTnI test (laboratory) anytime over first 24h, according to ESC/ACC cut-off	AMI: 47	<3	86 (72-95)	93 (80-99)		86 (73-93)			Greater than CK-MB, myoglobin and cTnI	[13] (France)
					STEMI: 31 NSTEMI: 20	Overall (0-11)	87 (76-95)	94 (84-99)		93 (82-99)				
	ED	Patients with typical chest pain, without ST elevation	791	Positive cTnT test (in line with American Heart Association cut-off)	AMI: 13	<12	76	97	78	97			Greater than cTnT and CKMB <6h	[24] (UAE)
		Patients with symptoms suggestive of MI	317	ESC/ACC diagnosis of AMI	NSTEMI: 10 STEMI: 4 UA: 3	<3	63 (41-80)	86 (80-91)	40 (25-57)	94 (89-96)			No significant difference to cTnI overall or at <3h	[20] (France)
						3-6	40 (14-73)	85 (73-92)	29 (10-58)	90 (79-96)				
						Overall	62 (47-76)	86 (82-90)	43 (31-56)	93 (89-96)				
		Patients with symptoms	200	ESC/ACC diagnosis of AMI	AMI: 54	<6	77 (68-84)	88 (80-94)	88 (79-94)	76 (67-84)	6.49 (5.6-7.6)	0.27 (0.1-0.5)	Greater on admission than cTnI and	[21] (China)

		suggestive of MI				<8	94 (88-98)	82 (72-89)	84 (76-91)	92 (84-97)	5.16 (4.6-5.8)	0.07 (0.03-0.2)	myoglobin	
		Patients with chest pain suggestive of ACS without ST elevation	677	ESC/ACC diagnosis of NSTEMI or UA	AMI : 27.3 UA : 12.7 NSTEMI :14.6	<3	8.7 (5.8-12)	96 (94-98)	47 (42-52)	74 (69-78)	2.36	0.95		[16] (France)
						>3	20 (15-24)	97 (95-99)	73 (68-78)	77 (72-81)	7.2	0.82		
						Overall	14 (11-16)	97 (95-98)	61 (57-65)	75 (72-78)	4.15	0.89		
		Patients with chest pain admitted to hospital	64	ESC/ACC diagnosis of AMI	AMI: 64	<4	63 (36-84)	100 (51.7-100)	100 (66-100)	50 (22-77)			Greater than CK and cTn <4h	[15] (Saudi Arabia)
						4-12	100 (73-100)	80 (30-99)	93 (66-100)	100 (40-100)				
						12-24	100 (20-100)	50 (9-91)	50 (9-91)	100 (20-100)				
						>24	78 (40-96)	80 (30-99)	88 (47-99)	67 (24-94)				
		Patients with acute chest pain or dyspnoea presenting to hospital	74	Diagnosis of MI (criteria not mentioned)	ACS: 73 STEMI: 53 NSTEMI: 20	<3	83 (71-92)	30 (12-54)	76	40	1.2	0.56	Positive significantly earlier than cTnT	[22] (China)
		Patients with acute chest pain or dyspnoea presenting to hospital	280	ESC/ACC diagnosis of ACS	AMI: 49	<2	65 (51-78)	78 (65-88)			3.00 (1.8-5.1)	0.44 (0.30 – 0.66)	Positive significantly earlier than cTnT	[23] (Austria)
					AMI: 32	2-6	59 (41-75)	70 (58-81)			2.0 (1.3-3.1)	0.59 (0.38-0.90)		
					AMI: 34	>6	91 (72-99)	73 (58-85)			3.4 (2.1-5.7)	0.12 (0.031-0.45)		
					ACS: 50 UA: 11	Overall	69 (59-77)	74 (66-80)	62	74	2.6 (2.0-2.5)	0.42 (0.32-		

					AMI: 39 STEMI; 26 NSTEMI:13							0.57)		
		Patients with chest pain suggestive of coronary origin presenting to ED	274	ESC/ACC diagnosis of AMI	AMI: 57	0-3h	79 (65-89)	80 (65-89)	79	80	3.87	0.26	Greater than CK-MB and cTnI at 0-3h	[17] (Hong Kong)
						3-6h	88 (77-94)	82 (66-91)	90	79	4.85	0.15		
						6-12h	93 (83-97)	90 (77-96)	93	90	9.27	0.08		
						Overall	87 (81-92)	84 (76-89)	88	83	5.37	0.15		
		Patients presenting with suspected ACS lasting less than 3h	419	ESC/ACC diagnosis of ACS	AMI: 35 UA: 20	<3 (AMI only)	60 (52-68)	88 (84-91)	72 (74-80)	80 (76-85)			Greater than cTnT (p<0.05)	[25] (Spain)
						<3 (all ACS)	47 (41-54)	94 (90-97)	91 (86-96)	56 (49-64)				
		Patients presenting with typical chest pain	67	ESC/ACC diagnosis of ACS	UA: 63 NSTEMI: 10 STEMI: 27	<1	98	39					Greater than myoglobin (p<0.05)	[12] (Turkey)
						<4	98	89						
		Patients with NSTE ACS with chest pain lasting <24h	100	cTnT performed at 3 hours from hospital admission	UA: 43 NSTEMI: 57	On admission	95	100	100	93				[14] (Poland)
						3h post admission	96	100	100	96				
		Patients with STE ACS with chest pain lasting <6h	52	cTnT performed at 6 hours from hospital admission	STEMI: 95%	<3	79		100					[19] (Poland)
					STEMI: 97	4-6	87		100					
		Patients with typical chest pain	224	WHO criteria for diagnosis of AMI	STEMI: 17 NSTEMI: 15.6 UA: 45.5	On admission	41 (30-53)	100 (98-100)			∞ (5-∞)	0.59 (0.49-0.71)		[18] (Turkey)
						2h post admission	56.0 (40.0-71.0)	99.0 (96.4-100)			56.0(7.9-397)	0.45 (0.36-0.60)		
FABPulous	ED	Patients presenting with chest pain	218	N/A	AMI: 51	<3	57						Greater than cTnT at <3 and 4-6h	[26, 27] (Belgium)
						4-6	88							
						7-12	92							
						Overall	75							

H-FABP kit	ED	Patients suspected of AMI presenting to hospital	227	ESC/ACC diagnosis of AMI	AMI: 50 UA: 12	<3	84 (69-94)			86 (72-95)			Greater than CK-MB and cTnT (p<0.0001) – overall, at 0-3h and 3-6h	[28] (China)
						3-6	96 (85-94)			94 (81-99)				
						6-12	100 (89-100)			100 (89-100)				
						Overall	93 (87-97)	84	88	93 (86-97)				
QuickSens H-FABP	ED	ED: Patients presenting with chest pain suggestive of ACS	1074	ESC/ACC diagnosis of AMI	NSTEMI: 16 UA: 11	<12h	72 (65-89)	80 (77-82)	41 (35-47)	94 (92-95)				[29] (Switzerland)
Rapicheck	ED	Patients visiting cardiac ED with acute onset of chest pain within 36h	371	WHO criteria for diagnosis of AMI	AMI: 49	<2	89 (74-97)	52 (32-71)					Greater than cTnT (p<0.001)	[30] (Japan)
						2-4	96 (87–99)	45 (30–60)						
						4-6	100 (86–100)	40 (23–56)						
						6-12	97 (82–100)	55 (41–69)						
						12-24	95 (73–100)	53 (26–79)						
		Patient with chest pain or dyspnoea visiting acute cardiologist	129	WHO criteria for diagnosis of AMI	AMI: 24 UA: 13	<3h	100 (60-100)	63 (43-83)	44 (19-70)	100 (77-100)			Greater than cTnT (p<0.05) at 0-3h	[31] (Japan)
						3-6	75 (22-99)	94 (68-100)	75 (22-99)	94 (68-100)				
						6-12	100 (46-100)	73 (39-93)	63 (23-100)	100 (60-100)				
						>12	100 (66-100)	75 (53-89)	63 (36-84)	100 (78-100)				
						Total	90 (73-97)	78 (68-85)	56 (41-71)	96 (89-99)				