BIOMARKERS FOR THE DIAGNOSIS OF ACUTE CORONARY SYNDROME

STUDIES IN PRIMARY CARE

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BIOMARKERS FOR THE DIAGNOSIS OF ACUTE CORONARY SYNDROME

STUDIES IN PRIMARY CARE

Cardiale markers voor de diagnostiek van acuut coronair syndroom
Onderzoek in de eerste lijn
(met een samenvatting in het Nederlands)

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Contents

CHAPTER 1

General introduction

A medical doctor's account:

"It was my sister who phoned to tell me that my mother was ill. She had been in bed for several days now. I visited her, not professionally of course, and found her lying in bed. She normally would have got up when visitors came along, but she stayed in bed. Some days earlier she suddenly felt a very severe pain in her back. Phoning her son was not her style, but she had insisted on asking for the general practitioner. It was not her own physician who came but a replacement, who examined her and said it was her spine. Three days later she died. My mother was obese, diabetic, used insulin, had high blood pressure, and was on antihypertensive medication. How could we simply have neglected all this high risk information, and have not recognised that the pain was high in the back region more between the shoulder blades, a phenomenon we learned from the textbooks can be the sole symptom of a myocardial infarction?"[1]

It is the difficult task of physicians to adequately interpret a patient's complaints and make a correct diagnosis. Based on this diagnosis, a patient can be informed about his or her condition (and its prognosis) and the correct treatment can be initiated. Especially in primary care, diagnosing can be a major challenge, since general practitioners (GPs) are often the first physicians to be confronted with a patient, at a moment when the patient's disease is often still in an early phase (and may therefore be less easily recognized), in a setting where diagnostic facilities are limited, many complaints are temporary and many diseases are self-limiting.

An acute coronary syndrome (ACS) is a potentially life-threatening disease that, if left untreated, causes serious morbidity and carries a high mortality. In some patients the clinical presentation will be typical, prompting a GP to take immediate action and urgently refer the patient to hospital. In many patients however, the signs and symptoms of ACS will be atypical and medical history taking and physical examination are inconclusive. As a result, ACS is quite often considered as one of the possible diagnoses in patients with atypical complaints, such as chest discomfort, 'stomach' ache or pain between the shoulder blades. In many European countries, patients with chest pain, or other symptoms (somewhat) suggestive of ACS will present to a GP first, especially when a patient (or his/her relatives) interpret the complaints as being of minor severity. There is an urgent need for more diagnostic tools to safely and accurately assess such patients suspected of ACS, especially for the GP, whose diagnostic tools consist of history taking and physical examination and, only occasionally, an electrocardiogram (ECG).

Epidemiology of acute coronary syndrome

Coronary heart disease is the second leading cause of death in both men and women in Europe, accounting for 21 and 22% of all deaths, respectively [2]. ACS refers to a spectrum of diseases ranging from unstable angina pectoris (with reversible myocardial damage), to transmural acute myocardial infarction (AMI) (with extensive, irreversible myocardial damage). The most common cause of ACS is atherosclerotic coronary artery disease. The rupture of an unstable atherosclerotic plaque causes acute thrombosis inside the coronary vessel, resulting in partial or total occlusion of the artery by the blood clot, leading to cardiac ischaemia and eventually cardiac necrosis [3].

The diagnostic challenge

The diagnostic challenge is *not* the 69-year-old former banker with a medical history of hypertension and type 2 diabetes who, while reading his book, suddenly experiences a pressing chest pain that radiates to his left arm and jaw, and who on physical examination appears pale, sweating and out of breath. The diagnostic challenge is represented by the patient introduced at the beginning of this chapter, presenting with atypical complaints and another possible explanation for these complaints. Or by the 50-year old woman who upon physical examination may not appear unwell, but nevertheless complains about a sharp pain at the right side of her chest, a feeling of fatigue (but a reorganization is currently taking place at her work), some back pain (but not all the time) and nausea.

A GP is often confronted with such patients suspected of ACS. Of the new complaints seen by a GP 0.7-7% involves chest pain, with ischaemic heart disease diagnosed in only 8-22% of patients [4-7].

Diagnostic tools in primary care

The first steps in the diagnostic process of a patient suspected of ACS are history taking and physical examination. While certain elements, such as chest-wall pain upon palpation, can make ACS less likely, history taking and physical examination by itself do not provide enough information to confidently diagnose or safely exclude ACS [8,9]. A second step may be an ECG, provided the GP has facilities to record and interpret an ECG in his or her practice or at the patient's home, using portable ECG equipment [10]. However, in patients with ACS the initial ECG can be normal in up to one third of cases [11,12]. Attempts have been made, also in a primary care setting, to develop a clinical decision rule, combining items from history taking and physical examination, with [13] or without [14] ECG analysis, into an overall diagnostic score. Although these decision rules are a complementary tool for the GP, their diagnostic accuracy still is far from

perfect and they have not been widely adopted. The third step in diagnosing ACS is the measurement of serum cardiac biomarkers. In contrast to the hospital setting, biomarkers, such as troponin, are only rarely used in primary care.

Definition and redefinition of acute coronary syndrome

Acute coronary syndrome comprises unstable angina and acute myocardial infarction (AMI). The diagnosis of AMI is based on clinical symptoms, ECG-criteria and a rise in serum cardiac biomarkers above the decision limit (typically exceeding the 99th percentile of a healthy reference population). Unstable angina is currently defined as symptoms of chest pain and ECG changes suggestive of ischaemia, but without elevation of biomarkers such as troponin and creatine kinase myocardial band (CK-MB) above the decision limits [11,18].Over the years, more sensitive and cardiac-specific biomarkers have become available and the accuracy of detecting AMI has changed. Until 2000, the widely accepted standard for diagnosing AMI was the World Health Organisation (WHO) definition of ischaemic heart disease [15]. This definition included CK-MB as cardiac biomarker. In 2000, a joint committee of the European Society of Cardiology and the American College of Cardiology (ESC/ACC) published a new definition of AMI, and troponin was officially introduced as the preferred biomarker to detect myocardial necrosis [16]. In comparison with CK-MB, troponin is a more sensitive biomarker and therefore able to detect smaller size myocardial infarctions, while also cardiac specificity is higher for troponin than for CK-MB. As could be expected, the introduction of the new ESC/ACC guideline has led to an increase in the diagnosis of AMI: some patients that would have been classified as unstable angina according to the WHO guideline (because CK-MB did not reach the threshold), are now classified as having AMI when the blood troponin level raises above the decision limit. In the next few years, even smaller myocardial infarctions could become detectable with the development of more sensitive and cardiac-specific biomarkers and assays to detect these markers, such as the very recently developed high-sensitive troponin assay [17]. This has the additional advantage of facilitating earlier detection of cardiac ischaemia, which is crucial to initiate timely interventions and improve prognosis.

Initial management of ACS in primary care

In patients with typical anginal complaints and other symptoms highly suggestive of ACS, immediate referral will follow. Primary care guidelines recommend pain relief with nitrates or opioids, a single loading dose of aspirin and, in case of hypoxia, oxygen therapy in these patients [19,20]. Although treatment should start as soon as possible, it should not delay transfer to hospital.

Of the larger group of suspected ASC patient with atypical symptoms, most will be referred to hospital for additional testing, as advocated by current guidelines [11,21]. A minority of these suspected patients actually suffer from ACS, indicating that many patients, retrospectively, could be considered as unnecessarily referred. From the patient's perspective this leads to unnecessary anxiety for both the patient and its relatives and can even lead to the unnecessary exposure to potentially harmful therapeutic interventions. From a health care perspective this leads to unnecessary hospital admissions, expensive diagnostic follow-up procedures and overuse of cardiac care facilities.

Objective and outline of the thesis

The research described in this thesis focuses on the early diagnosis of ACS in the primary care setting and on the potential value of early cardiac biomarkers. Cardiac biomarkers have become the cornerstone in the diagnosis of ACS in the hospital setting. The introduction of rapid point-of-care, or 'bedside' tests that can be performed by the GP during consultation with test results within 15 minutes, make it possible to test for cardiac biomarkers in primary care. In **chapter 2** an overview is provided of the diagnostic accuracy of currently available point-of-care tests to detect four cardiac biomarkers (troponin, CK-MB, myoglobin and heart-type fatty acid-binding protein). In **chapter 3** we further explore the diagnostic potential of heart-type fatty acid-binding protein, one of the biomarkers elevated early, with increased blood levels as soon as one hour after onset of symptoms, by performing a meta-analysis of 16 diagnostic studies involving this marker. The design of a large diagnostic study on the value of a bedside test for heart-type fatty acid-binding protein in the diagnosis of ACS in primary care is presented in **chapter 4**, while the results of this study are presented in **chapter 5**. The choice of the cardiac biomarker to be measured strongly depends on the time interval since the start of symptoms in which patients are seen by the physician. Some markers for instance, are only consistently elevated in blood after 6-9 hours of ischaemia. Currently, there is little information on the time interval in which patients suspected of ACS are seen by the GP. In **chapter 6** we studied patient and doctor delay in suspected ACS patients, as well as gender differences in symptom presentation of ACS. In **chapter 7** we discuss the possible barriers that physicians may experience in using a clinical decision rule for the diagnostic assessment of a patient suspected of ACS. We made a direct comparison between the risk assessment by a clinical decision rule and the judgment of the GP. Finally, in **chapter 8**, the general discussion, we discuss barriers for performing research in a primary care setting and, using our large diagnostic study as an example, provide possibilities to overcome these barriers. Also, the challenges for future research on the use of cardiac biomarker point-of-care tests in primary care are addressed.

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Based on:

Point-of-care tests in suspected acute myocardial infarction: a systematic review
MHE Bruins Slot, GJMG van der Heijden, AW Hoes, FH Rutten

Submitted

CHAPTER 2

Point-of-care tests in suspected acute myocardial infarction: a systematic review

Abstract

Background

The currently preferred biomarker in suspected acute myocardial infarction (AMI), troponin, is not consistently elevated within the first 6 hours of symptom onset, while approximately 60% of patients present themselves in these first hours. The measurement of earlier biomarkers, with test results within 15 minutes and performed at the 'point of care' could help to minimize this time frame of uncertainty and prove useful in primary care, for ambulance personnel and in the emergency department. This review describes currently available point-of-care (POC) tests for cardiac biomarkers in suspected AMI, with a focus on test performance within 6 hours after the start of symptoms.

Methods

We performed a literature search of the PubMed database to identify studies that used a POC test for a cardiac biomarker in patients suspected of AMI. The characteristics of the studies and biomarkers were systematically collected.

Results

36 studies investigated POC tests for one or more cardiac biomarkers. A POC test for troponin was investigated in 24 studies, creatine kinase- myocardial band (CK-MB), myoglobin and heart-type fatty acid-binding protein (H-FABP) in 17, 17 and 12 studies, respectively). In 10 studies (1827 patients) results were presented or could be recalculated for test results within 6 hours of symptom onset.

A POC troponin test can be used to diagnose AMI within 6 hours, but not to exclude AMI, because of a too low negative predictive value in these early hours (range 57 to 86%). CK-MB and H-FABP performed well within the first 6 hours, but again the negative predictive values were not high enough (range 64 to 92% for CK-MB and 40 to 97 for H-FABP) to safely exclude AMI. Myoglobin had only a moderate diagnostic value as a single marker and should only be used in combination with troponin, CK-MB or H-FABP.

Conclusion

The ideal POC test for the early diagnosis of AMI does not yet exist. Future studies should be performed in a multivariate way to investigate the added diagnostic value of a POC biomarker test when it is used in combination with information readily available from medical history taking and also (depending on the setting) electrocardiography.

Introduction

Diagnosing acute myocardial infarction (AMI), poses a dilemma for physicians as few other diseases do. The reason is clear: the mortality of untreated ACS is high, while effective interventions such as thrombolysis, percutaneous coronary intervention or coronary artery bypass graft reduce mortality rates and improve prognosis. These interventions should be performed as early as possible after the onset of ischaemia ('time is muscle'). In the last two decades, cardiac biomarkers have become an indispensable tool in the assessment of myocardial necrosis and the definitive diagnosis of AMI is determined by the presence of symptoms suggestive of AMI in combination with elevation of cardiac troponin I or T (cTnI or cTnT) or creatine kinase myocardial band (CK-MB) if troponin is not available [1]. A major disadvantage of these cardiac biomarkers is that they are not consistently elevated within the first 6 hours after symptom onset, while in Europe approximately 60% of patients already contact a doctor, usually a primary care physician, an average of 1-3 hours after the start of symptoms [2,3]. Also, the patient is usually presented at the hospital, (through self-referral or direct transport by an ambulance) within 6 hours, with a median of 4 hours after the onset of symptoms [4]. Therefore, there is an ongoing search for sensitive, cardiac-specific biomarkers to resolve the diagnostic uncertainty in the early hours of a possible AMI. A point-of-care (POC) test for such a cardiac biomarker, with measurements on-site giving a test result during consultation, could help to minimize the time-frame of uncertainty about presence or absence of AMI and could prove useful for primary care physicians, ambulance personnel and in the emergency department.

Several early cardiac biomarkers have been addressed in recent guidelines for the diagnosis of AMI, such as troponin, CK-MB, myoglobin and heart-type fatty acid-binding protein (H-FABP). The aim of this systematic review is to provide an overview of studies assessing the value of available POC tests for these cardiac biomarkers in detecting AMI within 6 hours after symptoms onset.

Methods

We performed a systematic search of the literature from January 1st 1990 to April 1st 2010 using the PubMed database. The search terms were 'acute coronary syndrome' and synonyms such as 'ischaemic heart disease' combined with 'troponin', 'myoglobin', 'creatine kinase myocardial band OR CK-MB' and 'fatty acid-binding protein OR FABP'. Additionally, to identify studies that used a POC test we used the search terms 'point of care test OR bedside test OR office test OR near patient test'.

We screened title and abstract of all studies for relevance. Full-text publications were retrieved for original articles written in English. We selected studies that used POC tests for cardiac biomarkers in patients suspected of AMI, reporting diagnostic accuracy data. We excluded studies that reported only on prognosis and studies in which accuracy data of biomarkers were obtained by comparing confirmed AMI patients with healthy controls (a 'diagnostic case-control study'). These latter types of studies are not performed in a clinically relevant patient domain, that is, patients suspected of AMI. For all relevant publications the records retrieved with the 'related articles' link in PubMed were screened and reference lists were checked for other relevant studies.

We systematically collected characteristics of the selected studies and their biomarkers on a standardized case record form. The collected items were: number of patients included, patient domain, prevalence of the outcome and the type of reference test, time intervals of biomarker measurement, diagnostic accuracy parameters (such as predictive values, sensitivity and specificity) of the biomarkers and the percentage of failed POC tests.

In the current joint guideline of the European Society of Cardiology and the American College of Cardiology (ESC/ACC), the definition of AMI is based on a typical rise of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit in combination with evidence of myocardial ischaemia, i.e. at least one of the following: symptoms of ischaemia, ECG changes indicative of new ischaemia (new ST-T changes or new left bundle branch block, development of pathological Q waves), imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Until 2000, the widely accepted standard for diagnosing myocardial infarction were the WHO criteria for diagnosis of ischaemic heart disease [5]. These criteria consisted of a clinical history of chest pain (typical or atypical) with unequivocal ECG changes and/or unequivocal serum enzyme (typically CK and CK-MB) changes, where the pattern of rise and fall should be consistent with time of symptom onset. The major difference between both definitions of AMI is that troponin is much more sensitive than CK-MB and thus able to detect smaller myocardial infarctions. Introduction of the ESC/ACC guideline has led to an increase in the diagnosis of AMI.

There are several ways to present diagnostic test accuracy. Commonly used parameters are sensitivity and specificity, indicating the probability of a positive test in diseased and the probability of a negative test in non-diseased, respectively. Obviously, when the clinician performs the test it is unclear whether the patient is

diseased or non-diseased. Therefore, it is more informative for decision making in clinical practice to present a test's positive predictive value (PPV) and negative predictive value (NPV), which can be derived from the same 2 by 2 table. The PPV and NPV refer to the probability of the presence of disease given a positive test and the absence of disease given a negative test. However, in clinical practice a biomarker test is never used as a stand alone diagnostic assessment, but is always combined with other diagnostic information, typically obtained through medical history taking, physical examination. To determine the added value of a biomarker test beyond other readily available clinical parameters, a multivariate analysis should be performed, including receiver operating characteristics curve (ROC) analysis [6].

Results

Our search yielded 71 studies assessing the diagnostic accuracy of a POC test for one or more cardiac biomarkers (TnI or TnT, CK-MB, myoglobin and H-FABP) in the diagnostic assessment of AMI (Table 1). We excluded 35 studies for the following reasons: inclusion of only confirmed AMI patients (n=21, 60%), prognostic study (n=5, 14%), accuracy data not reported (n=5, 14%), patient data already presented in a previous article (n=3, 8.6%), use of a laboratory instead of a POC test (n=1, 2.9%).

Of the 36 studies that we included in this review (Table 2), 14 (39%) used the WHO criteria as a reference standard, 20 (56%) used the ESC/ACC definition and in 2 studies (5.6%) the reference test applied was unclear. In 17 studies (47%), a single biomarker was tested (TnI or TnT in 7 studies, H-FABP in 9 studies and CK-MB in one study), while the other studies tested 2 to 4 biomarkers simultaneously. Table 3 shows the different POC tests that were used and their test characteristics. Only four studies (11%) were performed in a pre-hospital setting [7-10]. A multivariate analysis was performed in 2 studies (5.5%). In one study (2.8%) [11] (using a H-FABP POC test), unclear test results were reported.

Table 1. Characteristics of biomarkers of potential value in suspected acute coronary syndrome.

Cardiac biomarker	Weight (kDa)	Cardiac specificity	Elevated after (hours)	Reaches peak at (hours)	Duration of elevation (days)
Troponin I	23.5	+++	4-10	16	4-7
Troponin T	37	+++	4-10	16	10-14
CK-MB	85	++	3-4	16	2-3
Myoglobin	18	-	1-3	6	0.5-1
H-FABP	15	++	<2	6	1-1.5

Table 2. Studies on point-of-care tests for different cardiac biomarkers. Study characteristics and predictive value of the biomarkers tested.

Marker	First author	Year	N	Point-of-care test (reference)	Domain	Prevalence of outcome (%)	Time of testing	Positive predictive value (%)	Negative predictive value (%)	Test Failures (%)
Troponin	Collinson	1996	203	CardiacT	Pts with suspected ACS presenting to hospital	44 (WHO)	?	87	85	Not reported
	Gerhardt	1997	487	CardiacT	Pts with suspected AMI admitted to hospital	18 (WHO)	< 72h	69	100	Not reported
	Sylven	1998	151	TropT	Pts with chest pain suggestive of AMI admitted to CCU	34 (WHO)	?	44	83	Not reported
	Luscher	1998	92	CardiacT	Pts with chest pain admitted to hospital	38 (≈WHO)	< 12h	97	97	Not reported
	Panteghini	1998	101	CardiacT	Pts with chest pain admitted to CCU	74 (≈WHO)	< 12h	100	29	Not reported
	Newman	1999	87	rapid TnT assay	Pre-hospital by emergency service, pts with typical cardiac chest pain	33 (unclear ref.)	?	100	71	Not reported
	Schuchert	1999	158	CardiacT	Pre-hospital by emergency service, pts with chest pain classified as emergency	25 (WHO)	?	21	74	Not reported
	Apple	1999	192	Triage Cardiac Panel	Pts with symptoms of AMI admitted to hospital	31 (≈WHO)	7h (median)	100	86	Not reported
	Heeschen	1999	412	Stratus	Pts with chest pain suggestive of ACS presenting to hospital	15 (WHO)	< 12h	Not given	Not given	Not reported

	Hsu	2000	51	Stratus	Pts with suspected ACS and non-diagnostic ECG admitted to hospital	?	< 12h	?	? (sensitivity 95)	Not reported
	v Domburg	2000	286	CardiacT	Pts with chest pain suggestive of AMI admitted to CCU	54 (WHO)	?	94	73	Not reported
	Apple	2000	369	Alpha Dx	Pts with chest pain presenting to hospital	24 (≈WHO)	< 24h	83	98	Not reported
	McCord	2001	817	Triage Cardiac Panel	Pst suspected of AMI presenting to hospita	8 (≈WHO)	?	20	99	Not reported
	Ng	2001	1,285	Triage Cardiac Panel	Pts with symptoms of cardiac ischaemia presenting to hospital	5.1 (WHO)	?	82	99	Not reported
	Svensson	2003	511	Cardiac STATus	Pre-hospital by emergency service, pts with chest pain or other symptoms suggestive of ACS	31 (WHO and Tn)	< 6h	?	? (sensitivity 12)	Not reported
	Goldmann	2004	741	TnT myo	?	?	4h (median)	?	?	Not reported
	Di Serio	2005	30	Evidence Investigator	Pts with chest pain admitted to hospital	20 (ESC/ACC)	?	92	72	Not reported
	Ooi	2006	152	rapid TnT assay	Pts suspected of AMI presenting to hospital	50 (WHO)	3h (median)	100	57	Not reported
	Mion	2007	132	Evidence Cardiac Panel	Pts with chest pain suggestive of AMI presenting to hospital	32 (ESC/ACC)	3.8h (median)	92	82	Not reported
	Ecollan	2007	108	Triage Cardiac Panel	Pre-hospital by mobile intensive care unit, pts with ischaemic type chest pain	77 (positive TnI test <24h)	< 3h	100	57	Not reported

Marker	First author	Year	N	Point-of-care test (reference)	Domain	Prevalence of outcome (%)	Time of testing	Positive predictive value (%)	Negative predictive value (%)	Test Failures (%)
	Straface	2008	5,201	Triage Cardiac Panel	Pts with chest pain admitted to hospital	3 (chart review)	?	89	99	Not reported
	Hamilton	2008	432	Triage Cardiac Panel	Pts with ischaemic type chest pain presenting to hospital	14 (positive TnT at 12h)	< 24h	80	97	Not reported
CK-MB	Sylven	1998	151	TropT	Pts with chest pain suggestive of AMI admitted to CCU	34 (WHO)	?	86	92	Not reported
	Luscher	1998	92	CardiacT	Pts with chest pain admitted to hospital	38 (≈WHO)	< 12h	100	98	Not reported
	Apple	1999	192	Triage Cardiac Panel	Pts with symptoms of AMI admitted to hospital	31 (≈WHO)	7h (median)	79	90	Not reported
	Apple	2000	369	Alpha Dx	Pts with chest pain presenting to hospital	24 (≈WHO)	< 24h	73	96	Not reported
	Hsu	2000	51	Stratus	Pts with suspected ACS and non-diagnostic ECG admitted to hospital	?	< 12h	?	? (sensitivity 90)	Not reported
	McCord	2001	817	Triage Cardiac Panel	Pts suspected of AMI presenting to hospital	8 (≈WHO)	?	20	99	Not reported
	Ng	2001	1,285	Triage Cardiac Panel	Pts with symptoms of cardiac ischaemia presenting to hospital	5.1 (WHO)	?	54	99	Not reported
	Svensson	2003	511	Cardiac Status	Pre-hospital by emergency service, pts with chest pain or other symptoms suggestive of ACS	31 (WHO and Tn)	< 6h	?	? (sensitivity 18)	Not reported
	Di Serio	2005	30	Evidence Investigator	Pts with chest pain admitted to hospital	20 (ESC/ACC)	?	81	79	Not reported

	Ecollan	2007	108	Triage Cardiac Panel	Pre-hospital by mobile intensive care unit, pts with ischaemic type chest pain	77 (positive TnI test <24h)	< 3h	88	64	Not reported
	Mion	2007	132	Evidence Cardiac Panel	Pts with chest pain suggestive of AMI presenting to hospital	32 (ESC/ACC)	3.8h (median)	81	87	Not reported
	Hamilton	2008	432	Triage Cardiac Panel	Pts with ischaemic type chest pain presenting to hospital	14 (positive TnT at 12h)	< 24h	66	70	Not reported
Myoglobin	Sylven	1998	151	Cardiac STATus	Pts with chest pain suggestive of AMI admitted to CCU	34 (WHO)	?	37	77	Not reported
	Luscher	1998	92	CardiacT	Pts with chest pain admitted to hospital	38 (≈WHO)	< 12h	75	96	Not reported
	Apple	1999	192	Triage Cardiac Panel	Pts with symptoms of AMI admitted to hospital	31 (≈WHO)	7h (median)	56	87	Not reported
	Apple	2000	369	Alpha Dx	Pts with chest pain presenting to hospital	24 (≈WHO)	< 24h	58	93	Not reported
	Hsu	2000	51	Stratus	Pts with suspected ACS and non-diagnostic ECG admitted to hospital	?	< 12h	Not given	Not given (sensitivity 75)	Not reported
	McCord	2001	817	Triage Cardiac Panel	Pst suspected of AMI presenting to hospital	8 (≈WHO)	?	20	98	Not reported
	Ng	2001	1,285	Triage Cardiac Panel	Pts with symptoms of cardiac ischaemia 98 presenting to hospital	5.1 (WHO)	?	16		Not reported
	Svensson	2003	511	Cardiac STATus	Pre-hospital by emergencyservice, pts with chest pain or other symptoms suggestive of ACS	31 (WHO and Tn)	< 6h	?	? (sensitivity 12)	Not reported
	Di Serio	2005	30	Evidence Investigator	Pts with chest pain admitted to hospital	20 (ESC/ ACC)	?	80	73	Not reported

Marker	First author	Year	N	Point-of-care test (reference)	Domain	Prevalence of outcome (%)	Time of testing	Positive predictive value (%)	Negative predictive value (%)	Test Failures (%)
	Ecollan	2007	108	Triage Cardiac Panel	Pre-hospital by mobile intensive care unit, pts with ischaemic type chest pain	77 (positive TnI test <24h)	< 3h	64	67	Not reported
	Mion	2007	132	Evidence Cardiac Panel	Pts with chest pain suggestive of AMI presenting to hospital	32 (ESC/ ACC)	3.8h (median)	69	89	Not reported
	Hamilton	2008	432	Triage Cardiac Panel	Pts with ischaemic type chest pain presenting to hospital	14 (positive TnT at 12h)	< 24h	51	96	Not reported
H-FABP	Seino	2004	129	Rapicheck	Pts with chest pain or acute dyspnoea visiting cardiologist	24 (WHO)	< 6h (< 6h)	50 (n=55)	97 (< 6h)	Not reported
	Di Serio	2005	30	Evidence Investigator	Pts with chest pain admitted to hospital	20 (ESC/ ACC)	?	80	100	Not reported
	Alhashemi	2006	64	Cardiodetect	Pts with chest pain presenting to hospital	64 (ESC/ ACC)	< 4h	100	50	Not reported
	Ecollan	2007	108	Cardiodetect	Pre-hospital by mobile intensive care unit, pts with ischaemic type chest pain	77 (positive TnI test <24h)	< 3h	86	88	Not reported
	Mad	2007	280	Cardiodetect	Pts with acute chest pain or dyspnoea presenting to hospital	39 (ESC/ ACC)	< 6h (n=112)	62	74	39/280 (14%)
	Mion	2007	132	Evidence Investigator	Pts with chest pain suggestive of AMI presenting to hospital	32 (ESC/ ACC)	3.8h (median)	85	92	Not reported
	Valle	2008	419	Cardiodetect	Pts suspected of ACS presenting to hospital	35 (ESC/ ACC)	< 3h	72	80	Not reported
	Liao	2009	74	Cardiodetect	Pts with acute chest pain or dyspnoea presenting to hospital	73 (ref. unclear)	< 3h	76	40	Not reported

	Naroo	2009	791	Cardiodetect	Pts with typical chest pain, without ST elevation	13 (positive Tn, erial testing)	< 12h	78	97	Not reported
	Charpentier	2010	677	Cardiodetect	Pts with chest pain suspected of ACS, without ST elevation	27 (ESC/ACC)	< 6h	47	74	Not reported
	Li 2010	227	HFABP kit		Pts suspected of AMI presenting to hospital	50 (ESC/ACC)	< 12h	91	93	Not reported
Multiple markers:										
Tn, CK-MB, myo	Caragher	2002	205	Stratus	Pts with chest pain presenting to hospital	16 (retrospective chart review)	?	97	100	Not reported
Tn, CK-MB, myo	Svensson	2003	511	Cardiac STATus	Pre-hospital by emergency service, pts with chest pain or other symptoms suggestive of ACS	31 (WHO and Tn)	< 6h	60	66	Not reported
Tn, CK-MB, myo	MacDonald	2008	100	Triage Cardiac Panel	Pts suspected of ACS admitted to the hospital	6 (positive TnT at 12h)	< 24h	33	100	Not reported
CK-MB myoglobin	Panteghini	1998	101	CardiacT	Pts with chest pain admitted to CCU	74 (≈WHO)	< 12h	89	50	Not reported
Tn, CK-MB, myo	Straface	2008	5,201	Triage Cardiac Panel	Pts with chest pain admitted to hospital	3 (chart review)	?	92	100	Not reported

Abbreviations
N: number of patients, Pts: patients, ACS: acute coronary syndrome (comprising unstable angina and acute myocardial infarction), AMI: acute myocardial infarction, WHO: World Health Organisation, CCU: coronary care unit, ref: reference, ECG: electrocardiogram, ESC: European Society of Cardiology, ACC: American College of Cardiology, CK-MB: creatine kinase-myocardial band, Tn: troponin, H-FABP: heart-type fatty acid-binding protein, Myo: myoglobin

Troponin POC test

Troponin (Tn) is the currently preferred biomarker for diagnosing AMI, due to its high specificity for myocardial tissue and sensitivity in detecting small areas of myocardial necrosis. It takes 4 to 10 hours after the onset of symptoms for Tn to appear in serum, depending on the size of infarction. A peak is reached after 16 hours and levels return to normal after 4 to 7 days (TnI) and 10 to 14 days (TnT)[12].

Our search yielded 24 studies (12,303 patients) on a POC test for Tn; 15 studies on TnI and 9 studies on TnT (see Table 2). In 13 studies (54%) the diagnosis of acute

Table 3. Characteristics of the point-of-care tests studied in the diagnosis of acute coronary syndrome.

Test	Biomarker measured	Type of test	Run time (minutes)	Specimen
AlphaDx	TnI, Ck-MB, Myoglobin	Quantitative, fluorescence immunoassay	20	Serum, whole blood
Cardiac STATus	TnI, CK-MB, Myoglobin	Qualitative, particle immunoassay	15	Whole blood, plasma serum
Evidence cardiac panel	Tn, Ck-MB, Myoglobin	Quantitative, biochip immunoassay	60	serum
Stratus CS	TnI, Ck-MB, Myoglobin	Quantitative, particle immunoassay	14-22	Whole blood (hep)
Triage cardiac panel	TnI, CK-MB, Myoglobin	Quantitative, fluorescence immunoassay	15	Whole blood, plasma
Cardiac T test	TnT	Quantitative, particle immunoassay	12	Whole blood (hep)
TROPT	TnT	Qualitative, particle immunoassay	15	Whole blood (hep)
Cardiodetect	H-FABP	Qualitative, particle immunoassay	15	Whole blood, serum, plasma
Rapicheck	H-FABP	Qualitative, particle immunoassay	15	Whole blood

Adapted from [38, 39]

Abbreviations: Tn: troponin, CK-MB: creatine kinase-myocardial band, hep: heparinized, H-FABP: heart-type fatty acid-binding protein

myocardial infarction was based on the WHO definition, in 2 studies (8.3%) the reference standard was in accordance with the ESC/ACC criteria, 2 studies (8.3%) used a retrospective chart review (including Tn measurements), in 3 studies (13%) Tn measured by laboratory assay at 12 or 24 hours was the reference standard and in 3 studies (13%) the reference test that was applied was not mentioned. In three of the 24 studies (586 patients) [10,13,14] results were provided or could be recalculated for POC measurements of Tn within 6 hours. This resulted in a PPV ranging from 94 to 100% and a NPV ranging from 57 to 86% for predicting presence or absence of AMI. Four studies [7-10] were performed in a pre-hospital setting by trained emergency personnel who performed a Tn POC test either at the patient's home or in the ambulance. In one study [9], only sensitivity (12%) was mentioned as a measure of accuracy and predictive values could not be calculated. In the other three studies [7,8,10] the PPV ranged from 21 to 100% and the NPV from 57 to 74%. The remaining 17 studies were performed in a hospital setting and the performance of the POC test within 6 hours could not be calculated separately. In these studies the PPV ranged from 45 to 100% and the NPV from 70 to 100% over the undefined time-frames. Finally, one single study performed multivariable analysis and investigated the added value of TnI beyond medical history taking, ECG and CK-MB [15]. Patients suspected of acute myocardial infarction (typical or atypical chest pain, acute pulmonary oedema or acute heart failure) were included on average 3 hours after the onset of complaints and the WHO criteria were used as the reference. Adding Tn to a multivariate model with a history of chest pain, ECG and CK-MB, increased the AUC from 0.89 to 0.94, with an independent value of Tn for the diagnosis of AMI.

The overall impression of POC tests using TnI or TnT given by these 24 studies is that in the early hours (within 6 hours after the onset of symptoms) a rapid test may be used to definitely confirm the diagnosis of AMI, but not to safely exclude AMI, because this would require the NPV to be very close to 100%. An important problem when evaluating the POC tests for Tn is that in the studies using the WHO criteria for AMI, with CK-MB as biomarker, the POC test for Tn is likely to outperform the reference test, but by definition cannot perform better than that test. This will lead to an underestimation of the predictive values of the POC Tn test.

Creatine kinase-myocardial band POC test

CK-MB is predominantly found in the myocardium. It is also present in skeletal muscles, however, in lower concentrations. It begins to rise 3 to 4 hours after the onset of AMI symptoms, reaches a peak after 16 hours and falls to normal levels after 48 to 72 hours.

We found 16 studies (9,677 patients) that assessed a POC test for CK-MB. Six studies used the WHO reference standard, the remaining 10 studies the ESC/ACC guideline. In three studies (675 patients) test results within 6 hours after the onset of symptoms were provided or could be recalculated [9,10,16]. One study (77 patients) was performed in a pre-hospital setting and found a PPV of 88% and a NPV of 64% when CK-MB was measured very early; within 3 hours after the onset of complaints10. In a study in patients with chest pain suggestive of acute myocardial infarction admitted to a coronary care unit, the PPV of CK-MB was 86% and the NPV 92% [17]. Another study performed in similar patients [18] yielded a PPV of 81% and a NPV of 79%. Overall, the PPV for CK-MB ranged from 80 to 97% and the NPV from 65 to 100% and was similar when a multi-marker approach (combining CK-MB with myoglobin and/or Tn) was used. None of the studies applied multivariable analyses to determine the added value of CK-MB POC tests.

The results of these 17 studies indicate that CK-MB has reasonable predictive values for the diagnosis and exclusion of acute myocardial infarction, used as a single marker, or in combination with other biomarkers in the time frame 0 to 6 hrs after onset of symptoms.

Myoglobin POC test

Myoglobin is a small (18 kDa) heme protein involved in oxygen transportation in the myocardial cell. Within 1 to 3 hours after the onset of AMI symptoms it is released into the circulation, reaches a peak value at 6 hours, and returns to normal values within 12 to 24 hours. Myoglobin is also found in high concentrations in skeletal muscle, making it a non-specific marker for myocardial necrosis. It has retained its value in daily practice due to its early release in AMI, and is mostly used in combination with more specific markers.

Our search yielded 16 studies (9,677 patients) that examined the diagnostic properties of a POC test for myoglobin. In all studies myoglobin was measured simultaneously with other biomarkers (CK-MB, Tn and sometimes H-FABP) and the studies are therefore identical to the studies that describe the performance of CK-MB. Two studies (619 patients) that measured myoglobin within 6 hours in a pre-hospital setting10 yielded a PPV of 64% and NPV of 67% for myoglobin alone [9,10] and a PPV of 60% and a NPV of 66% using a multimarker approach (myoglobin, TnI and CK-MB) [9]. A large retrospective study (5,201 patients) in an emergency room setting [19] examined the combined use of TnI, CK-MB and myoglobin. Positive myoglobin was defined as doubling in myoglobin levels between two consecutive measurements. The PPV for diagnosing acute myocardial infarction was 92% and the NPV was 100% [19]. The

prevalence of the outcome was exceptionally low (2.9%) for a hospital setting, making generalisability of the findings questionable. Another study (192 patients) used the same POC test and the same combination of biomarkers, and prospectively included patients suspected of AMI in an emergency department setting [13]. This study yielded lower predictive values of 56% (PPV) and 87% (NPV). Overall, the PPV ranged from 40 to 80% and the NPV ranged from 65 to 85% when myoglobin was used as the only marker for AMI while a multimarker approach with combinations of myoglobin with Tn, CK-MB or H-FABP resulted in higher predictive values.

Summarizing, POC myoglobin tests have moderate diagnostic qualities as a single test for detecting acute myocardial infarction, while in combination with other markers the predictive values are better. Whether myoglobin has additional value in combination with medical history taking and physical examination remains unclear since a multivariate analysis was not included in any of the studies.

Heart-type fatty acid-binding protein POC test

H-FABP is a small (15kDa) unbound cytoplasmic protein involved in intracellular lipid transport in the myocardial cell. Within 2 hours after the onset of symptoms it is released into the circulation, reaches a peak value at 6 hours and returns to normal values within 24 to 36 hours. H-FABP is also found in skeletal muscle cells, but in much lower concentrations (10-30% of concentrations in myocardium) [20].

We found 11 studies (2,931 patients) that tested a POC test for H-FABP. One study (9%) used the WHO definition as reference test, 7 studies (64%) used the ESC/ACC guideline, two studies (18%) used serial Tn measurements and one study (9%) did not report which reference test was used [21]. In 6 studies (720 patients) the accuracy for testing within 6 hours was separately provided or could be calculated [10,11,21-24]. In one of the larger studies [11] 280 patients suspected of AMI (symptoms of chest pain or dyspnoea lasting for at least 20 minutes) were included in an emergency department. In this study, 112 patients (40% of the total number of patients) were included within 6 hours after the onset of symptoms. The PPV in these patients was 62% and the NPV was 74% for the outcome AMI. Results were roughly similar for the outcome acute coronary syndrome (comprising AMI and unstable angina). Another study using the same POC test yielded a PPV of 86% and a NPV of 88% in 77 patients who were visited at home within 3 hours of symptom onset by a mobile intensive care unit (pre-hospital setting) [10]. The same study also evaluated pre-hospital POC tests for CK-MB, TnI and myoglobin, and found that the NPV for the H-FABP test was higher than those of all the other POC assays. One study performed in an emergency department used a combination of TnT with H-FABP, which yielded a significantly higher NPV

for the combination of markers (95%) than for TnT alone (75%) [25]. Overall, the PPV and NPV varied between the different studies, ranging from 47 to 100% and 40 to 97% respectively, with large differences in the prevalence of the outcome, ranging from 20-64%. In one study a multivariate analysis was performed to assess the added value of the H-FABP POC test [24]. In this study performed in an emergency room setting, patients with chest pain and without ST-elevations on their ECG were included. Two diagnostic models for the determination of non-ST elevation AMI were constructed; the first including clinical and laboratory parameters (including ECG and troponin results) and the second with the results of the H-FABP test in addition to these previous variables. For both models the AUC was 0.87, indicating that there is no added value in using the H-FABP test in diagnosing AMI.

The results of these 12 studies indicate that a POC test for H-FABP has fairly good predictive values for diagnosing acute myocardial infarction within 6 hours. In a multivariate analysis, no additional value of H-FABP when combined with ECG analysis and Tn measurements was observed.

Discussion

This overview of different POC tests for troponin (Tn), creatine kinase myocardial band (CK-MB), myoglobin and heart-type fatty acid-binding protein (H-FABP) shows that currently available POC tests for all four cardiac biomarkers have moderate to good predictive values. The PPV for Tn POC measurement ranges from 94 to 100% and NPV ranges from 57 to 86% when it is measured within 6 hours after the onset of complaints. For CK-MB, myoglobin and H-FABP the PPV ranges from 81 to 88%, 40 to 80% and 62 to 86% respectively, while the NPV ranges from 64 to 92%, 65 to 85% and 40 to 79% respectively. In none of the POC biomarkers tests the NPV approaches 100%, indicating that there are false negative test results (and hence missed AMI patients). Myoglobin shows only moderate diagnostic qualities when it is used as a single biomarker, but diagnostic accuracy improves when it is used in combination with CK-MB and/or Tn.

Several studies have demonstrated that the use of POC tests for cardiac biomarkers results in the earlier availability of test results, an earlier diagnosis, better patient outcome and a reduction in costs [26-30]. Furthermore, POC tests could be adopted in emergency departments of hospitals in which the central laboratory lacks adequate facilities for delivering biomarker results within one hour [31]. An ideal cardiac biomarker would be rapidly released into the circulation after the onset of symptoms of ischaemia, provide a quantitative (and not a dichotomous result) and would have high positive and negative predictive values.

When interpreting the results of the individual diagnostic studies included in this review, three important methodological aspects should be emphasized: studies were performed in different settings, used different POC tests and different reference standards to define AMI; the latter two being unavoidable with the regular publication of updated guidelines and with new biomarkers becoming available over time. When used in different settings, diagnostic test characteristics may change. Contrary to what is often believed, sensitivity and specificity are not fixed test characteristics, but they may differ when a diagnostic test is used in different patient groups [32]. In addition, inherent differences in the prevalence of the outcome in different settings will lead to differences in the PPV and NPV. In a secondary care setting, prevalence rates are higher than in a primary care setting, due to the selection process of referral, and in secondary care more advanced disease stages with higher levels of diagnostic markers will be presented6. It is therefore to be expected that in a secondary care setting, the PPV (and sensitivity) is higher, while in a primary care setting the NPV (and specificity) will be higher. Secondly, one may wonder whether the differences found in diagnostic test accuracy are caused by the use of different biomarkers, or by the use of different POC tests for the measurement of these biomarkers. Different POC tests for the same biomarker may use different cut-off levels for a positive test leading to different diagnostic accuracies of the tested biomarker. To truly compare the value of a biomarker, studies should be grouped according to the used POC test, but in this overview this resulted in too few studies per POC test. Thirdly, the used reference test is especially important in determining the diagnostic accuracy of the Tn POC test. Some studies found a PPV as low as 21% for a POC Tn test, but it may well be that Tn POC tests considered as 'false' positive actually outperform the reference standard in detecting myocardial infarction. In the older studies, the WHO criteria are used, in which CK-MB is the preferred biomarker for diagnosing acute myocardial infarction. CK-MB is less sensitive in detecting small areas of myocardial necrosis than Tn. Several studies have shown that with the use of the newer ESC/ACC guideline for acute coronary syndrome, in which troponin is the reference biomarker, more patients are diagnosed with AMI than by applying the WHO criteria [33-35].

A drawback of this systematic review is that our literature search was based only on the Pubmed database and cross-checking of references and that data abstraction was performed by one author only. Also, it is likely that there was publication bias, although we did not perform an analysis to assess this. It is probable however that the estimations for diagnostic accuracy as given in the included studies are overestimations.

Future research

There is an ongoing search for other possible biomarker candidates for the early detection of cardiac ischaemia. A recent study investigating the diagnostic performance of four new, sensitive cardiac troponin assays found promising results[36]. The study was conducted in patients suspected of AMI in an emergency room setting (34% prevalence AMI, 17% prevalence AMI). The NPV in diagnosing AMI ranged from 95 to 100%, the PPV ranged from 50 to 83%. Overall, the sensitive cardiac troponin assays showed a higher diagnostic accuracy than that of the standard troponin assay. If these sensitive cardiac troponin assays become available as a POC test, the early diagnosis of AMI may be considerably improved. A second promising biomarker is Ischaemia Modified Albumin (IMA), which is also not yet available as a POC test. IMA can detect myocardial ischaemia within minutes after the onset of symptoms. A meta-analysis of 8 studies found a pooled NPV of 91% for IMA, which was superior to ECG and Tn analysis[37].

Sound diagnostic studies should be performed to test the accuracy of POC tests for these novel cardiac biomarkers. In this overview, most included studies investigated the diagnostic accuracy of the POC test by univariate analysis, as if the POC test was used as a stand-alone diagnostic test to diagnose AMI. Future research should be performed in a multivariable way, assessing the diagnostic value that a POC test may have in addition to other diagnostic tests (medical history taking and, usually in a secondary care setting, ECG analysis), since this in accordance with the use of the test in clinical practice. Also, most studies did not specifically address the diagnostic test accuracy of the investigated biomarker within the first 6 hours after the onset of symptoms, while most patient present themselves to either a primary care physician or hospital within this time interval. It is important to address this particular time interval in future studies.

In conclusion, the ideal POC test for the diagnosis of AMI does not yet exist. Future studies should be performed to identify novel early biomarkers for the diagnosis of AMI that have high predictive values, are rapidly released into the circulation after AMI symptom onset and are available as easy to perform and accurate POC tests. It is important to establish the additional value of such a POC test in the appropriate domain when it is used in combination with currently available diagnostic tests.

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Based on:

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

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In revision: Heart

CHAPTER 3

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

Abstract

Background

The introduction of early and safe biomarkers could lead to a large reduction in unnecessary hospital referrals of suspected patients *without* acute myocardial infarction (AMI) and an earlier start of treatment in patients *with* AMI. Aim of this systematic review is to determine the accuracy of heart-type fatty acid-binding protein (H-FABP) as a new and early cardiac biomarker in the early diagnosis of AMI.

Methods

Studies including consecutive patients suspected of AMI were included in the meta-analysis. A summary estimate for sensitivity and specificity was calculated using the bivariate random effects approach and covariate analysis was used to examine sources of heterogeneity between studies.

Results

A systematic search yielded 16 studies (3709 patients, prevalence of AMI range 13 to 74%, male gender range 49 to 84%, median age range 64 to 76 years). The summary estimate was 84% (95% confidence interval (CI) 0.76 to 0.90) for sensitivity and 84% (95% CI 0.76 to 0.89) for specificity. Covariate analyses revealed that the use of troponin in the reference standard for AMI (as opposed to CK or CK-MB) had a significant impact on sensitivity.

Conclusion

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

Introduction

Timely diagnosing acute coronary syndrome (ACS, comprising unstable angina and acute myocardial infarction) is crucial as this allows earlier initiation of adequate treatment and improves patient outcome. According to recent guidelines1 the diagnosis of ACS is based on a combination of history taking, electrocardiographic (ECG) findings and the presence in serum of at least one biomarker for myocardial damage, preferably cardiac Troponin I or T (cTnI or cTnT). A major limitation of troponin is its low sensitivity in detecting myocardial infarction in the early hours: depending on the infarction size, troponin is elevated in serum 6-8 hours after the onset of symptoms. This means that myocardial infarction may go undetected during these first hours, since history taking, physical examination, ECG and current biomarker tests are often inconclusive [1,2].

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

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

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

Box 1. Used search terms.

Pubmed search terms:

(("ischaemic heart disease"[tw] OR "ischemic heart disease"[tw] AND "ischaemic heart diseases"[tw] OR "ischemic heart diseases"[tw]) OR heart[tw] OR "chest pain"[tw] OR "angina pectoris"[tw] OR "angina, unstable"[tw] OR ("acute coronary syndrome"[tw] OR ACS[tw]) OR "coronary artery disease"[tw] OR "coronary disease"[tw] OR CAD[tw] OR (myocyte[tw] OR myocytes[tw]) OR myocardial[tw] OR myocardium[tw] OR "heart"[MeSH Terms] OR "cardiovascular diseases"[MeSH Terms] OR "cardiovascular disease"[tiab] OR "cardiovascular diseases"[tiab]) AND (h-fabp[tw] OR fabp[tw] OR "fatty acid binding protein"[tw] OR "heart fatty acid binding protein"[tw] OR "heart type fatty acid binding protein"[tw] OR "heart type cytoplasmic fatty acid binding"[tw]) AND (("1950/01/01"[PDat]: "2009/09/01"[PDat]))

Embase search terms:

(heart:ab,ti OR 'chest pain':ab,ti OR 'angina pectoris':ab,ti OR 'angina, unstable':ab,ti OR ('acute coronary syndrome':ab,ti OR acs:ab,ti) OR 'coronary artery disease':ab,ti OR 'coronary disease':ab,ti OR cad:ab,ti OR (myocyte:ab,ti OR myocytes:ab,ti) OR myocardial:ab,ti OR myocardium:ab,ti OR ('cardiovascular disease':ab,ti OR 'cardiovascular diseases':ab,ti OR (('cardiovascular disease'/exp OR 'cardiovascular disease') OR ('cardiovascular disease'/exp OR 'cardiovascular disease')) OR (('heart'/exp OR 'heart') OR ('heart'/exp OR 'heart')))) AND ('h-fabp':ab,ti OR fabp:ab,ti OR 'fatty acid binding protein':ab,ti OR 'heart fatty acid binding protein':ab,ti OR 'heart type fatty acid binding protein':ab,ti OR 'heart type cytoplasmic fatty acid binding':ab,ti) AND [embase]/lim AND [01-01-1965]/sd NOT [01-09-2009]/sd

Methods

Literature search

We performed a systematic electronic search of the PubMed and EMBASE databases for original articles published until September 1st 2009. Used search terms were 'acute coronary syndrome' and synonyms such as 'ischaemic heart disease' combined with 'heart-type fatty acid-binding protein'. Box 1 displays the exact search terms used. For all relevant publications the records retrieved with the 'related articles' link in PubMed were screened, reference lists were checked for other relevant studies and finally experts in the field were consulted to complement our electronic search.

Selection of publications

We screened title and abstract of all studies for relevancy. Full-text publications were retrieved for relevant articles written in English, Dutch, German or French. Studies were selected on the basis of (1) the included population i.e. adults suspected of an ACS, (2) outcome: ACS (unstable angina and/or myocardial infarction) (3) index test: quantitative or qualitative measurement of H-FABP (4) reference test: clear description of the used reference test (i.e. 'gold standard'), and (5) completeness of data: availability of absolute numbers of true positive (TP), false positive (FP), true

negative (TN) and false negative (FN) H-FABP results to allow for reconstruction of the diagnostic 2 by 2 table.

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

Methods appraisal and data extraction

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

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

Data analysis

From each included study we aimed to extract the number of patients with a true positive (TP), false positive (FP), false negative (FN) and true negative (TN) test result either directly or through recalculation based on reported measures of accuracy in combination with the prevalence and sample size of a study. Sensitivity and specificity together with 95% confidence intervals were calculated for each study based on the two-by-two table. Graphically, we plotted the individual study's points of sensitivity and specificity in the same receiver operating characteristic (ROC) curve, together with a ROC point summarizing all studies. In a ROC curve sensitivity on the y-axis is plotted against 1-specificity on the x-axis.

The bivariate random effects approach was used to analyze our data. The bivariate approach uses a random effects approach for both (logit transformed) sensitivity and

specificity within a single model, thereby incorporating any (negative) correlation that might exist between these measures. The random effects approach estimates and incorporates the amount of between-study variability in both sensitivity and specificity. The within-study variability (i.e. precision) was accounted for by using the binomial distribution. This means that more weight is given in the estimation of sensitivity to studies having more patients with ACS, whereas the weighting for specificity is linked to the number of patients without ACS. We extended the basic bivariate model with covariates to assess the impact of study level covariates on sensitivity or specificity or both. The bivariate model produces summary estimates for sensitivity and specificity based on a random effects approach [5]. The interpretation of summary estimates is most straightforward when the amount of between-study variation is small to moderate. We examined whether differences in study population, in index test properties, or in design could explain the observed heterogeneity in results by adding these factors as covariates to the bivariate model. These factors included: the use of a point of care test, the use of a reference standard incorporating troponin, the prevalence of the outcome, the used cut-off value of the H-FABP test. We used Stata Statistical Software Release 10 (College Station, TX: StataCorp LP) and SAS Statistical Software (SAS Institute 9.2, Cary, USA) for all meta-analytical analyses and SPSS 15.0 for all other analyses.

Results

Of the 1395 articles that we identified by our electronic literature search 16 unique studies were eventually included in our systematic review (Figure 1). Main reasons for exclusion were duplicates between the Pubmed and EMBASE database, use of an inappropriate patient domain (e.g. established AMI patients vs. healthy controls), use of an inappropriate outcome (e.g. heart failure), multiple reporting of the same data and reporting of insufficient data to allow for reconstruction of the 2 by 2 table.

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

Patient characteristics

Overall, the selected 16 studies included 3709 patients suspected of ACS. The study size ranged from 30 to 791 patients (median: 149, IQR 102-352). The proportion of males ranged from 49% to 84% (median: 71%; IQR: 64-76). The mean or median age of patients in the included studies ranged from 54 to 69 years (median: 63 years;

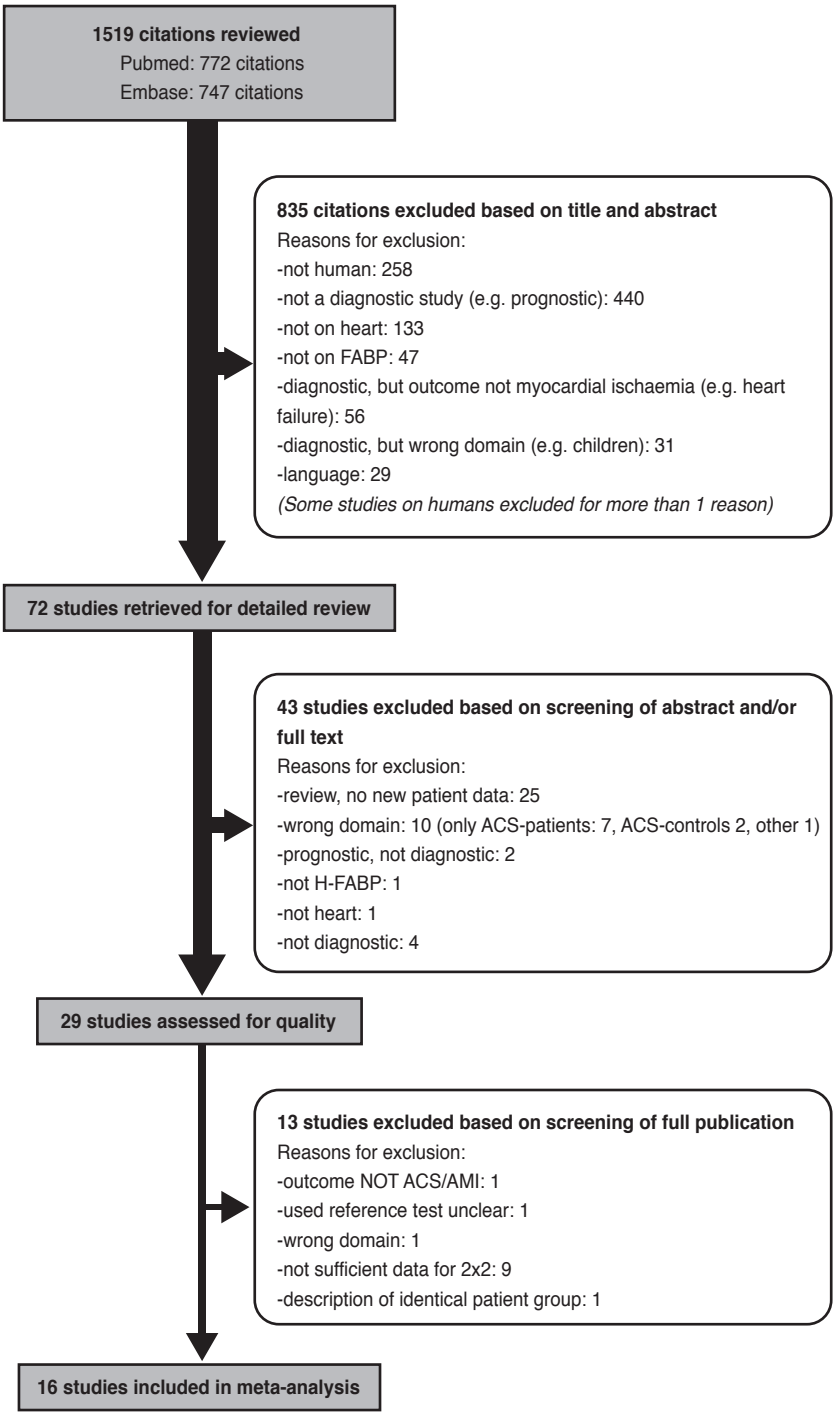

Figure 1. Flowchart of in- and excluded studies.

Table 1. Methods appraisal of included studies.

	Performance of same reference standard in all patients	Index test interpreted independently of reference test (yes/no)	Withdrawals reported	Cut-off value index test determined without bias (yes/no)	Valid reference (ESC/ACC criterial)	Unclear test results reported
Lefevre	●	●	●	●	●	●
Mad	●	●	●	●	●	●
Ilva	●	●	●	●	●	–
McCann	●	●	●	●	●	–
Naroo	●	●	●	●	●	○
Valle	●	●	●	●	●	○
Alhashemi	●	●	○	●	●	○
Di Serio	●	●	⁎	○	●	–
Mion	●	●[1]	⁎	○	●	–
Ecollan	●	○[1]	⁎	●	●	○
Seino - '04	●	●[1]	⁎	●	○	○
Okamoto	●	●[1]	⁎	●	○	–
Seino - '03	●	⁎	●	●	○	○
Chen	●	●[1]	●	●	○	–
Haastrup	●	●	○	●	○	–
Ishii	●	●	○	●	○	–

● *yes,* ○ *no,* ⁎ *unclear,* – *not applicable (did not use immunochromatographic test)*
ESC: European Society of Cardiology, ACC: American College of Cardiology
[1]*: simultaneous measurement of troponin rapid test*

IQR: 61-67). In two studies using a mobile intensive care unit patients were included outside the hospital [6,7] while in the remaining studies patients were included in a hospital setting (Table 1). The median duration of symptoms at the time of testing was 3.8 hours (IQR 2.8-5.0). The median prevalence of ACS in the 16 included studies was 36% (range 13-74%).

For nine studies a separate diagnostic 2 by 2 table could be reconstructed including a subgroup of patients tested for H-FABP within 6 hours after onset of complaints only [7-13].

H-FABP assay

An ELISA laboratory assay for H-FABP was used in 6 studies, giving a quantitative result of H-FABP levels. In 3 studies, the value that offered the maximal predictive accuracy was taken as the cut-off levels for a positive H-FABP test [8,9,11], while 3 studies used healthy controls or previously published decision limits [7,10,12]. The cut-

off values used by these different studies ranged from 5.0 to 16.8 ng/ml. Two studies [14,15] used the Evidence Cardiac Panel, which is a biochip cardiac panel measuring not only H-FABP but also other cardiac biomarkers (including troponin and CK-MB). This Evidence Cardiac Panel is performed in a laboratory setting by applying a serum blood sample (obtained through venipuncture) onto a biochip, adding a chemiluminescent reagent and measuring the strength of the light signal -using a special camera- which is then converted into a marker concentration.

In the remaining 8 studies two different point of care tests were used: Cardiodetect [6,13,16-19] and Rapicheck [20,21]. The Cardiodetect test is a rapid chromatographic immunoassay that is performed by applying 3 drops of whole blood (capillary blood from the patient's finger or venipuncture) onto a test strip. After 15 minutes the qualitative test result can be read as the appearance of one or two red strips in the test card window. One red strip (control; test performed correctly) is a negative test result and two red strips (control and H-FABP; test performed correctly and H-FABP

Table 2. Study characteristics and population of included studies. AMI: Acute myocardial infarction, ELISA: Enzyme-linked immunosorbent assay, ESC: European Society of Cardiology, ACC: American College of Cardiology, WHO: World Health Organisation.

Author	Year	Number of included patients	H-FABP test	Point of care test	Prevalence of AMI overall (%)	Overall symptom-duration (minutes)	Cutoff (ng/ml)	Reference standard
Alhashemi	2006	64	Cardiodetect	Yes	64	390	7	ESC/ACC
Chen	2004	93	ELISA	No	34	not known	16.8	WHO
Di Serio	2005	30	Evidence	No	20	204	6.4	ESC/ACC
Ecollan	2006	108	Cardiodetect	Yes	51	139	7	≈ESC/ACC
Haastrup	2000	130	ELISA	No	16	168	8	WHO
Ilva	2008	293	ELISA	No	46	282	10.4	ESC/ACC
Ishii	1997	165	ELISA	No	60	229	12	≈ WHO
Lefevre	2007	100	Cardiodetect	Yes	36	354	6.2	ESC/ACC
Mad	2007	280	Cardiodetect	Yes	35	180	7	≈ESC/ACC
McCann	2008	415	ELISA	No	48	300	5	≈ESC/ACC
Mion	2007	132	Evidence	No	32	228	6.02	ESC/ACC
Naroo	2009	791	Cardiodetect	Yes	13	not known	7	≈ESC/ACC
Okamoto	2000	189	ELISA	No	74	not known	6.2	WHO
Seino	2003	371	Rapicheck	Yes	49	not known	6.2	WHO
Seino	2004	129	Rapicheck	Yes	24	not known	6.2	WHO
Valle	2008	419	Cardiodetect	Yes	35	74	7	ESC/ACC

present in sample) represents a positive test result. The Cardiodetect test used by Lefevre et al. [17] has a detection limit for H-FABP of 6.2 ng/ml, while the Cardiodetect test used in the remaining studies uses a cut-off value for a positive test of 7 ng/ml [6,13,16,18]. The Rapicheck test is a similar point of care chromatographic immunoassay test, also providing one or two red lines that can be judged by the physician after 15 minutes. The cutoff value for a positive Rapicheck test is 6.2 ng/ml.

Definition of myocardial infarction

Until 2000 the widely accepted definition ofmyocardial infarction was based on the WHO criteria for diagnosis of ischemic heart disease [22]. These criteria consist of a clinical history of chest pain (typical or atypical) with unequivocal ECG changes and/or unequivocal serum enzyme changes (pattern of rise and fall consistent with time of symptom onset; typically CK and CK-MB were used). Six studies included in this review [8,9,11,12,20,21] published between 1997 and 2004 used these WHO criteria or criteria based thereon. The remaining ten studies used the criteria published in 2000 in a consensus document by the European Society of Cardiology (ESC) and American College of Cardiology (ACC) [23] or the criteria proposed in the 2007 expert consensus document1 as the universal definition of acute myocardial infarction. These diagnostic criteria also encompass a typical clinical history and, ECG changes and serum enzyme changes of a cardiac biomarker, but in this case preferably cardiac troponin, which should be measured upon the first assessment and 6-9 hours later.

Diagnostic value of H-FABP

The overall pooled sensitivity of all studies was 0.84 (95% CI 0.76-0.90) and overall pooled specificity was 0.84 (95% CI 0.76-0.89). However, between studies variation was substantial and attributable to heterogeneity, rather than chance, as indicated by an I-square of 91% for sensitivity results and 96% for specificity results. Also, there was evidence for publication bias as we found funnel plot asymmetry, indicating significant small study bias (p=0.09): Smaller studies finding high estimates of sensitivity and specificity are more likely to be published than large studies with more modest results. The estimates of sensitivity and specificity of all included studies are shown in a ROC curve, together with the summary ROC point (pooled sensitivity against 1-(pooled specificity)). We also plotted the 95% confidence region (precision of estimation of pooled sensitivity and specificity) and the 95% prediction region (likely range of values for a new study) (Figures 2A and 2B).

Covariate analysis

Adding the covariate whether troponin was part of the reference standard to the bivariate model had a significant impact on sensitivity, indicating that it is an important

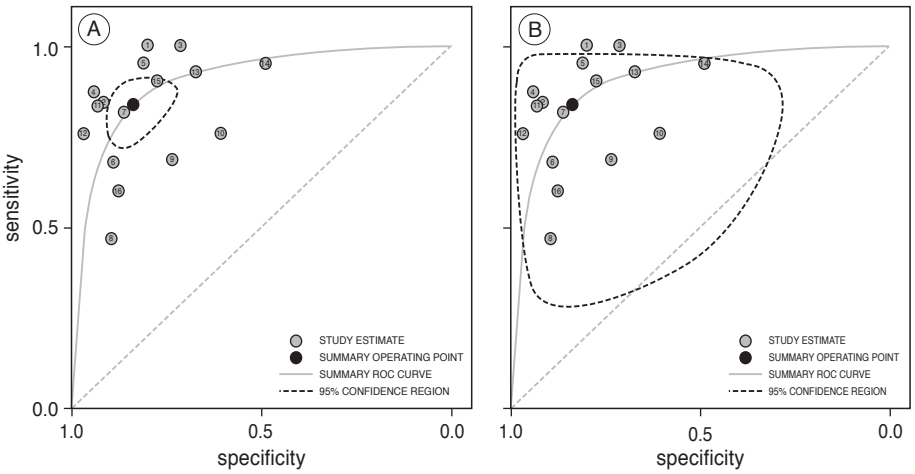

Figure 2. Summary ROC curve for all included studies: with 95% confidence interval for overall pooled sensitivity and specificity (A) and with 95% prediction region (B).

source for heterogeneity between studies. We found that studies using a reference standard including troponin yielded a lower sensitivity of H-FABP (0.76, 95% CI 0.67-0.84) than studies that did not use troponin as part of their reference standard (0.91, 95% CI 0.84-0.95). Also, the prevalence of the outcome had a significant impact on specificity: studies with a lower prevalence (20%) had a higher specificity than studies with a higher prevalence (40%), specificity 0.90, 95% CI 0.82-0.95 vs. 0.84, 95% CI 0.77-0.89 respectively.

To explain heterogeneity in results we also added other factors to the bivariate model, (i.e. the use of a point of care test and the used cut-off value for the H-FABP test), but these factors had no significant impact on either sensitivity or specificity (Table 3).

Discussion

To our knowledge this is the first systematic review and meta-analysis to determine the diagnostic performance of the early cardiac biomarker H-FABP in the diagnosis of AMI. Potentially, the introduction of safe and early biomarkers could lead to a considerable reduction in unnecessary hospital referrals of patients without AMI and an earlier start of treatment in patients with AMI. Using the bivariate random effects approach we found a summary estimate of 84% for sensitivity and 84% for specificity, indicating that the use of H-FABP would lead to a false negative test result in 16% of patients with AMI and to a false positive test result in 16% of patients without AMI. For a potentially fatal condition such as AMI this percentage of missed patients

Table 3. Results of subgroup analyses and covariate analysis.

Covariate		Number of studies	Sensitivity (95% CI)	Specificity (95% CI)
Point of care test	yes no	8 8	0.81 (0.69-0.90) 0.86 (0.75-0.93) p=0.47	0.85 (0.74-0.92) 0.84 (0.73-0.91) p=0.89
Reference standard with troponin	yes no	10 6	0.76 (0.67-0.84) 0.91 (0.84-0.95) p<0.005	0.88 (0.81-0.93) 0.78 (0.64-0.88) p=0.11
Impact of prevalence of outcome	20% 40%	All	0.82 (0.65-0.92) 0.84 (0.76-0.90) p=0.71	0.90 (0.82-0.95) 0.84 (0.77-0.89) p<0.05
Impact of cut-off value	5 7 14	All	0.85 (0.73-0.92) 0.84 (0.76-0.90) 0.82 (0.58-0.94) p=0.82	0.80 (0.69-0.88) 0.83 (0.76-0.89) 0.91 (0.78-0.97) p=0.20

is unacceptably high, making H-FABP unsuitable for use as a stand-alone test in a primary care setting. In a hospital setting, patients with a false positive test will be unnecessary subjected to coronary interventions or aggressive thrombolytic therapy, with associated risks.

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

Some other methodological and technical issues must also be addressed. First, the interpretation of the summary estimates of sensitivity and specificity that we provide is not straightforward, since we found marked heterogeneity between the included

studies. This heterogeneity was illustrated in the summary ROC curve, which had a very wide prediction ellipse, indicating that future studies on H-FABP could yield widely differing results, ranging from a test result with a very high sensitivity and specificity to test results which are neither very sensitive nor specific. Covariate analysis revealed that the use of a reference test with troponin was an important explanation for the differences in sensitivity found between the studies: studies that did not use troponin in their reference standard for AMI found a higher sensitivity of H-FABP. This finding is explained by the fact that troponin is considerably more sensitive than CK or CK-MB in detecting even small areas of myocardial infarction. Thus, the use of troponin categorizes more patients as having suffered myocardial infarction, that would have been diagnosed with angina pectoris or unstable angina using the less sensitive markers CK and CK-MB [24]. Compared to the older biomarkers, H-FABP performs better, showing higher sensitivity, while in comparison with troponin, H-FABP's sensitivity for detecting myocardial infarction will be lower. Also, covariate analysis revealed that the prevalence of the outcome significantly influences the specificity of H-FABP. Studies with a lower prevalence of the outcome found a higher specificity, apparently because of a selection of less severely ill patients and hence a higher amount of true negative test results.

We also added two other factors (use of a point of care test and the cut-off value of the H-FABP test) to the covariate analysis, but these did not explain the heterogeneity. Due to the limited number of studies in this meta-analysis we restricted the covariate analysis to these four factors, which we pre-specified because they were the most likely cause for variation between the studies.

Obviously the strength of a meta-analysis depends on the methodological strength of the included studies. In our quality assessment we found that both withdrawals from the study and, in the case of qualitative tests, unclear test results were poorly reported. Also, there were several studies in which the cutoff point for the index test was derived from the same study data. Poor-quality studies tend to overestimate the diagnostic performance of a test [25] and data driven determination of the cutoff point leads to an overestimated sensitivity and specificity. Furthermore, we found evidence for small sample size effects and publication bias as the test for asymmetry of the funnel plot showed a significant result. Also, the asymmetry could be caused by an inadequate search strategy. Although we performed a very sensitive search in multiple databases and for multiple languages, we did not search for unpublished data, because diagnostic studies, unlike trials, are usually not recorded in research registries [26]. The potential effect of publication bias is therefore unknown, but it is probable that the reported estimates for sensitivity and specificity are overestimations.

In point of care testing different test interpretations may lead to threshold effects in diagnostic test properties. The point of care tests used in the studies included in this meta-analysis are judged positive or negative by the physician performing the test according to the appearance of one (control) or two (control and H-FABP) red lines. A vague line by some physicians will be judged as absence of a line, while others will judge this a positive test. The (implicit) use of different thresholds for a positive test leads to a trade off between sensitivity and specificity: lowering the threshold in general leads to an increase in sensitivity, but a decrease of specificity [27]. This is a problem that could be solved by using an automated point of care test reader to measure the intensity of the result line made by the chromatographic immunoassay test.

A major strength of this systematic review is that we included only studies addressing the relevant patient domain, i.e. patients suspected of AMI. We did not include several diagnostic studies on the performance of H-FABP in diagnosing AMI because they were set up as diagnostic case-control studies (performance of the test in a group patient already known to have the target disease and a group of healthy controls, without the target disease). These studies will yield overestimated results of diagnostic accuracy [25].

Conclusion

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

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Based on:

Heart-type Fatty acid-binding protein in Acute Myocardial infarction Evaluation (FAME): background and design of a diagnostic study in primary care
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CHAPTER 4

Heart-type Fatty acid-binding protein in Acute Myocardial infarction Evaluation (FAME): background and design of a diagnostic study in primary care

Abstract

Background

Currently used biomarkers for cardiac ischaemia are elevated in blood plasma after a delay of several hours and therefore unable to detect acute coronary syndrome (ACS) in a very early stage. General practitioners (GPs), however, are often confronted with patients suspected of ACS within hours after onset of complaints. This ongoing study aims to evaluate the added diagnostic value beyond clinical assessment for a rapid bedside test for heart-type fatty-acid binding protein (H-FABP), a biomarker that is detectable as soon as one hour after onset of ischaemia.

Methods

Participating GPs perform a blinded H-FABP rapid bedside test (Cardiodetect ®) in patients with symptoms suggestive of ACS such as chest pain or discomfort at rest. All patients, whether referred to hospital or not, undergo electrocardiography (ECG) and venapunction for a plasma troponin test within 12-36 hours after onset of complaints. A final diagnosis will be established by an expert panel consisting of two cardiologists and one general practitioner (blinded to the H-FABP test result), using all available patient information, also including signs and symptoms. The added diagnostic value of the H-FABP test beyond history taking and physical examination will be determined with receiver operating characteristic curves derived from multivariate regression analysis.

Conclusions

Reasons for presenting the design of our study include the prevention of publication bias and unacknowledged alterations in the study aim, design or data-analysis. To our knowledge this study is the first to assess the diagnostic value of H-FABP outside a hospital-setting. Several previous hospital-based studies showed the potential value of H-FABP in diagnosing ACS. Up to now however it is unclear whether these results are equally promising when the test is used in primary care. The first results are expected in the end of 2008.

Introduction

For a general practitioner (GP), diagnosing or excluding acute coronary syndrome (ACS; comprising unstable angina (UA) and acute myocardial infarction (AMI)) often poses a diagnostic dilemma. On the one hand, missing an ACS may lead to excess morbidity and mortality that could have been prevented with optimal treatment. Guidelines therefore recommend immediate hospital referral in patients suspected of ACS, even when suspicion is relatively low [1,2]. On the other hand, unjustified referral of patients without ACS increases workload in the emergency department and causes unnecessary anxiety in both patients and their relatives. Consequently, adequate diagnostic assessment, correctly identifying ACS patients, while limiting unnecessary referral of non-ACS patients is desirable, but may be difficult to achieve.

Although some patients with chest pain or other symptoms suggestive of ACS will contact emergency services directly, the majority of patients will consult a GP first. Typically, the GP will assess these patients using history taking and physical examination only. With these limited tools it is notoriously difficult to accurately rule out or rule in ACS, notably in women and elderly patients in whom signs and symptoms of ACS can be rather atypical [3]. An electrocardiogram (ECG) may provide additional diagnostic information in the assessment of ACS, but is often not available in primary care. Moreover, the initial ECG of a patient with AMI does not always reveal ST-segment elevation or Q-wave changes, indicative of infarction [4]. Alternatively, biomarkers of myocardial damage could be useful as these, after their appearance in plasma, show 100% sensitivity. Currently, troponin is the biomarker of choice according to European and American guidelines on myocardial infarction. Unfortunately, troponin is elevated only 6-9 hours after onset of ischaemia [5-7], while most patients with symptoms suggestive of ACS present themselves to the GP between 1 and 3 hours after symptom onset [8-10]; hours before troponin can be used to accurately exclude or confirm AMI.

Recent studies in laboratories and the emergency department have shown that heart-type fatty acid-binding protein (H-FABP), a more recently developed cardiac biomarker, is able to detect myocardial damage as soon as one hour after onset of ischaemia and, therefore, is regarded the earliest plasma marker available [11-13]. A bedside test for H-FABP, providing results within 15 minutes [14],could potentially reduce diagnostic uncertainty for patients suspected of ACS in primary care. We therefore sought to determine the diagnostic accuracy and feasibility of a rapid bedside test for H-FABP in patients suspected of ACS in primary care.

Objectives

This study aims to assess the diagnostic value of a rapid bedside test for H-FABP, in addition to history taking and physical examination in primary care patients suspected of ACS. In addition, the balance between costs and effects of applying the H-FABP bedside test in primary care will be evaluated.

Methods

Study design and data collection

The study design is depicted in Figure 1. Patients are primarily recruited by GPs working at one of three participating out-of-hours GP services in the region of Utrecht, The Netherlands (1 urban and 2 semi-urban). Additionally, 25 GPs from group practices will recruit patients during daytime hours. Diagnostic assessment during the initial GP consultation includes standardised history taking and physical examination and rapid H-FABP testing (see below). To allow for a definitive decision whether ACS is present ('gold' or reference standard) an ECG is recorded and a venous blood sample is collected in all patients (for measurement of currently preferred biomarkers including troponin, creatinin kinase (CK) and creatinin kinase-myocardial band (CK-MB)), irrespective of whether or not they are referred to hospital. In patients who are referred to hospital these measurements are performed as part of routine care. Patients who are not referred to hospital are visited at home by qualified GP laboratory service personnel to perform the above mentioned tests. Blood samples are obtained between 12 to 36 hours after onset of complaints in order to allow for a definitive diagnosis of AMI. Using this time interval we adopt a safe margin for a troponin rise to become detectable in the blood.

The study protocol was approved by the Medical Ethics Committee of the University Medical Center Utrecht, The Netherlands.

In- and exclusion criteria

All patients with symptoms suggestive of ACS who present themselves to a GP are eligible for inclusion in the study. Presenting symptoms will typically include chest pain or discomfort at rest, but also atypical 'vague' complaints such as abdominal discomfort, dizziness or sudden onset of dyspnoea.

Excluded are patients with complaints lasting more than 24 hours, as H-FABP levels usually return to normal 24-36 hours after onset of myocardial ischaemia [15,16]. Also excluded are patients who require instant hospital referral and those patients in whom no written informed consent is obtained.

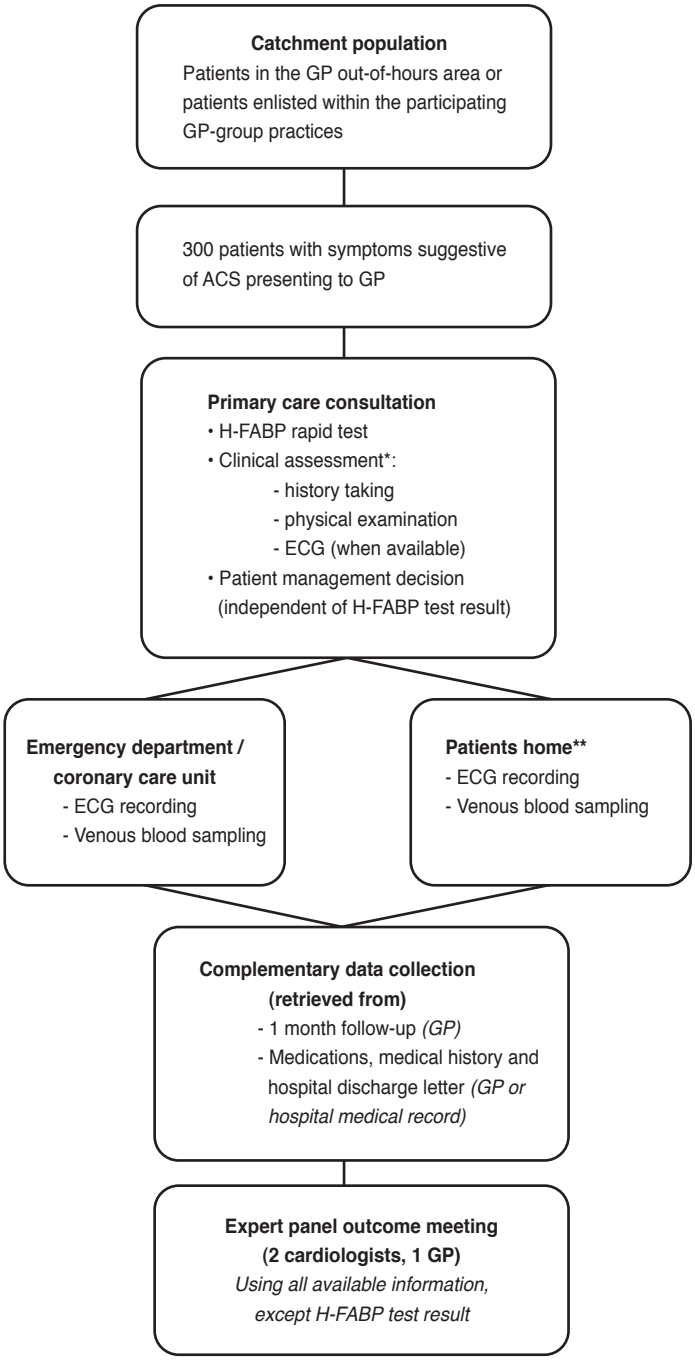

Figure 1. Study design. Abbreviations: GP = general practitioner, ACS = acute coronary syndrome, H-FABP = heart-type fatty acid-binding protein, ECG = electrocardiogram.*The clinical score is based on ref. 17. **Measurements are performed by qualified GP laboratory personnel.

H-FABP test and clinical score

The H-FABP bedside test (Cardiodetect® Rennesens GmbH, Berlin) can easily be performed by the GP by drawing four drops of capillary whole blood from the patient's finger and applying them onto the test-strip. Within 15 minutes the H-FABP test result (elevated or non-elevated plasma FABP) is available. For study purposes the result is concealed by a blinding-strip. The test is de-blinded by the GP after he/she has made the referral decision. Test results are documented on a standardized case record form, together with findings from history taking and physical examination. Other items on the form include age, gender, prior AMI and treatment for AMI (bypass surgery or percutaneous coronary intervention). Also recorded are patient delay and doctor delay and a probability estimate by the GPs (prior to the H-FABP test result) that a patient has ACS, their decision about referral to hospital and the result of the H-FABP test.

A previous study by Grijseels et al provided a pre-hospital decision rule based on items from history taking and physical examination for patients suspected of ACS [17]. We will validate the diagnostic accuracy of this clinical score and estimate the added value of the H-FABP bedside test.

Outcome

An expert panel consisting of two cardiologists and one GP will establish the final diagnosis using all available patient information, including signs and symptoms, ECG and biomarker levels (troponin-T or -I, CK and CK-MB). These results are available for all patients, including patients that are not referred to hospital, as they are visited at home by qualified GP laboratory personnel for performance of ECG and laboratory tests.

AMI will be defined in accordance with guidelines from the European Society of Cardiology and the American College of Cardiology [18,19]. The diagnosis of AMI is established when patients have suggestive symptoms (such as chest pain) and a maximal concentration of troponin T or I exceeding the decision limit (99th percentile of the values for a reference control group) within the first 36 hours after the onset of complaints and/or CK-MB values greater than two times the upper reference limit on at least one occasion during the same time frame. The presence of ST- and T-wave changes on the ECG, notably ST elevations and Q-waves, can further confirm AMI. Unstable angina (UA) is defined as symptoms of chest pain and ST- and/or T-wave changes on the ECG suggestive of ischaemia, without elevation of troponin or CK-MB above the decision limits [20,21].

Patient management

As already mentioned, every GP will decide about referral to hospital in accordance with daily practice, using only history taking and physical examination and, when available, ECG. This decision is made without using the H-FABP test result. For safety reasons an exception is made for patients with a positive H-FABP test result in whom the GP initially decided not to refer. In these cases, the GP is instructed to change his initial management decision in favor of hospital referral.

Statistical analyses

Using 2 by 2 tables the diagnostic value of the H-FABP test alone and in combination with the clinical score will be assessed, using AMI as the outcome, and positive and negative predictive values, sensitivity and specificity will be calculated with 95% confidence interval.

Multivariable regression analysis with receiver operating characteristic (ROC) curves will be used to determine whether the H-FABP test provides added diagnostic value beyond history taking and physical examination (summarized in a clinical score). Two diagnostic models will be tested: one using only the clinical score, the other one consisting of the clinical score together with the H-FABP test result. This will lead to 2 different areas under the ROC-curve (AUC), where the difference in AUC presents the added value of the H-FABP test.

As AMI is notoriously difficult to diagnose in women and the elderly we will perform subgroup analyses in these specific patient categories[22].

Sample size and power calculation

A frequently used 'rule of thumb' recommends that for each diagnostic determinant included in a multivariable logistic regression analysis at least 10 events (in this case AMI) are necessary[23,24]. Our study includes 2 diagnostic determinants (clinical score and H-FABP test result). Thus, a population in which at least 20 patients with AMI is required. Although available estimates vary, Dutch studies show that in more than 10% of patients suspected of AMI by the GP the diagnosis is confirmed[2,25]. Therefore, 200 patients with suspected AMI need to be included in our study. We will include 300 patients to allow for subgroup analyses.

Design issues

Blinding

In diagnostic prediction research the physician ideally should be blinded to the results of the test under study in order to prevent bias in the ascertainment of the disease. In

this study, the H-FABP test result may influence the inferences drawn from medical history and physical examination, and thereby influence the referral decision of the GP, especially since it is notoriously difficult to decide about the presence or absence of an ACS based on clinical assessment only.

There are however two important reasons why a fully blinded H-FABP test is not feasible in our study. Firstly, previous hospital based studies showed that the H-FABP bedside test has a positive predictive value of well above 80% [26-29]. We therefore instructed the GPs to decide on the referral before de-blinding the test result, but for safety reasons we also instructed them to refer patients with a positive H-FABP test result to hospital irrespective of their initial referral decision. Secondly, in the hours following application of the test, discoloration of the test-strip occurs which negatively influences the interpretation and thereby the accuracy of the test results. Therefore the test has to be read shortly after its performance.

Informed consent
It is neither very realistic nor feasible to ask written informed consent to study participation from a patient in an acute life threatening situation, such as with symptoms suggestive for ACS. Therefore the Medical Ethics Committee agreed to ask verbal consent from patients for taking the H-FABP test by the GP. Subsequently patients are given the opportunity for written informed consent after having read an information letter at a more convenient moment. Patients may also decide to withdraw their consent then or at any time thereafter. Only patients who return a written informed consent are included in our study.

Recruitment
We have chosen for a phased introduction of our study in 3 different GP out-of-hour services (weekdays from 5 pm - 8 am and weekends). Participating centers are notified of the study progress by a monthly overview of the number of participants and a 2-monthly newsletter with background information on the study, frequently asked questions and tips and tricks, for instance on how to draw the required amount of capillary blood. We anticipate including 300 patients within 36 months.

Preliminary results
In March 2006 we started enrollment of patients. In September 2007, 172 patients were included; i.e. monthly enrollment of about 12 patients. Conclusion of enrollment is anticipated before the summer of 2008. Baseline characteristics of the first participants are summarized in Table 1.

Table 1. Preliminary patient baseline characteristics (N=172).

Characteristics	Number (%)
Demographics	
Age (years, mean ± SD)	66 ± 14
>75 years	57 (33)
Female	88 (51)
Risk factors (N=114)	
Current smoker	21 (22)
Diabetes mellitus	24 (21)
Hypertension	51 (45)
Hyperlipidemia	36 (32)
Prior ischemic heart disease	34 (30)
Presenting symptoms	
Chest pain	157 (91)
Radiation of chest pain	109 (64)
Vagal symptoms*	97 (57)
Patient referred to hospital	126 (73)
Duration of symptoms (hours)**	3.0 (IQR 1.4-7.0)

** Including nausea, sweating, pallor*
*** From symptom onset until time of testing, IQR = interquartile range*

Discussion

The presentation of the design of our study provides the reader the opportunity to get informed about our study in an early stage. Moreover, publishing the design of a study independently of its results allows for a reflection on the design of a study. It helps to reduce publication bias and unacknowledged alterations in the study aims, the study design or data-analysis during its conduct. Finally, this article can be seen as an announcement of upcoming study results that may have an impact on the guidelines on acute coronary syndrome currently used in primary care.

Our study on H-FABP as a new cardiac biomarker is noteworthy as patients are recruited outside a hospital setting. The, few, previous studies on H-FABP have been performed in the emergency room or by ambulance personnel [28,30-35], representing an entirely different domain of patients than those seen by the GP. This is also illustrated by the difference in prevalence of AMI in these populations. Hospital-based studies reported a prevalence of AMI around or above 50% in those suspected of AMI [28,36-40], with the exception of one study that reported a prevalence of 16% [33]. Studies performed in primary care observed prevalences as low as 5 or 8% [41,42]. By definition this difference in prevalence has an important impact on the added diagnostic value of the novel rapid bedside test.

Many (earlier) diagnostic studies focus on the performance of a single test, ignoring the information obtained from history taking and physical examination. Based on symptoms and signs however, the likelihood of ACS may increase or decrease, thereby potentially altering the added value of the test. Moreover, single test research is not according to clinical practice, where a diagnosis is established after multiple tests performed in a hierarchical way, starting with simple, non-invasive and inexpensive tests, such as signs and symptoms [43]. Therefore a clinical score based on history and physical examination is included in our diagnostic model and the added value of the H-FABP bedside test will be calculated.

Previous studies with H-FABP in the hospital-setting showed the potential value of this novel cardiac biomarker in assessing patients suspected of ACS. Since GPs are confronted with patients suspected of an acute coronary syndrome at a very early stage, mostly without the availability of an ECG, the impact of a novel cardiac biomarker on the diagnostic assessment is potentially much higher in general practice than in the emergency room. To answer the question whether H-FABP has (additional) diagnostic value in the diagnosis of ACS in the primary care setting, the test needs to be studied before its introduction in that specific setting.

Application of an early biomarker potentially reduces diagnostic uncertainty in patients suspected of an ACS. On the one hand this may lead to a reduction of unnecessary hospital referrals, patient burden, hospital work load and health care costs. On the other hand, a diagnosis of ACS can be established much earlier than with troponin which may result in earlier initiation of treatment, including revascularization interventions.

To our knowledge, our study is the first to assess the (added) diagnostic value of H-FABP in patients with chest pain or other complaints suggestive of ACS in primary care.

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Based on:

Diagnostic value of a heart-type fatty acid-binding protein (H-FABP) bedside test in suspected acute coronary syndrome in primary care

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Submitted

CHAPTER 5

Diagnostic value of a heart-type fatty acid-binding protein (H-FABP) bedside test in suspected acute coronary syndrome in primary care

Abstract

Background

Biomarkers for myocardial ischaemia could improve the early diagnosis of acute coronary syndrome (ACS). The aim of this study was to determine the diagnostic accuracy of a rapid heart-type fatty acid-binding protein (H-FABP) bedside test in patients suspected of ACS in primary care, in addition to clinical findings.

Methods

We conducted a prospective multicenter study, in which consecutive patients suspected of ACS were included by the general practitioner (GP). The H-FABP bedside test (Cardiodetect©, cutoff 7 ng/ml) was performed within 24 hours after symptom onset. The final diagnosis ACS was determined by an outcome panel in accordance with international guidelines.

Results

The H-FABP bedside test (Cardiodetect©, cutoff 7 ng/ml) was performed a median of 3.1 hours (IQR 1.5 to 7.1) after symptom onset. 66 patients (22%) were diagnosed with ACS. The PPV of H-FABP was 65% (95%CI 50 to 78) and the NPV was 84% (95%CI 80 to 88). Within 6 hours after symptom onset, PPV and NPV were 72% (55 to 84) and 83% (77 to 88) respectively. Adding H-FABP to a diagnostic model of signs and symptoms led to an increase in the area under the receiver operating curve (AUC) from 0.66 (95%CI 0.58 to 0.73) to 0.75 (95%CI 0.68 to 0.82).

Conclusion

The H-FABP rapid test provides additional diagnostic certainty in combination with clinical findings when it is performed in patients suspected of ACS in primary care. However, the test cannot be used to safely exclude ('rule out') ACS. We only recommended use of the test to diagnose ('rule in') ACS in patients that were otherwise not referred to hospital by the GP, as an extra precaution not to miss ACS.

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 hours after the onset of ischaemia [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 hours 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 ischaemia and elevated levels have been detected already from one hour onwards [8-10]. Especially in a primary care setting, a bedside test for H-FABP, providing results within 15 minutes [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.

Methods

The design and methods of this study have been described extensively elsewhere [12]. In short, patients suspected of an acute coronary syndrome by the GP 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 hours 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 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 minutes 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 hours 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 hours 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 ischaemia, 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.

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

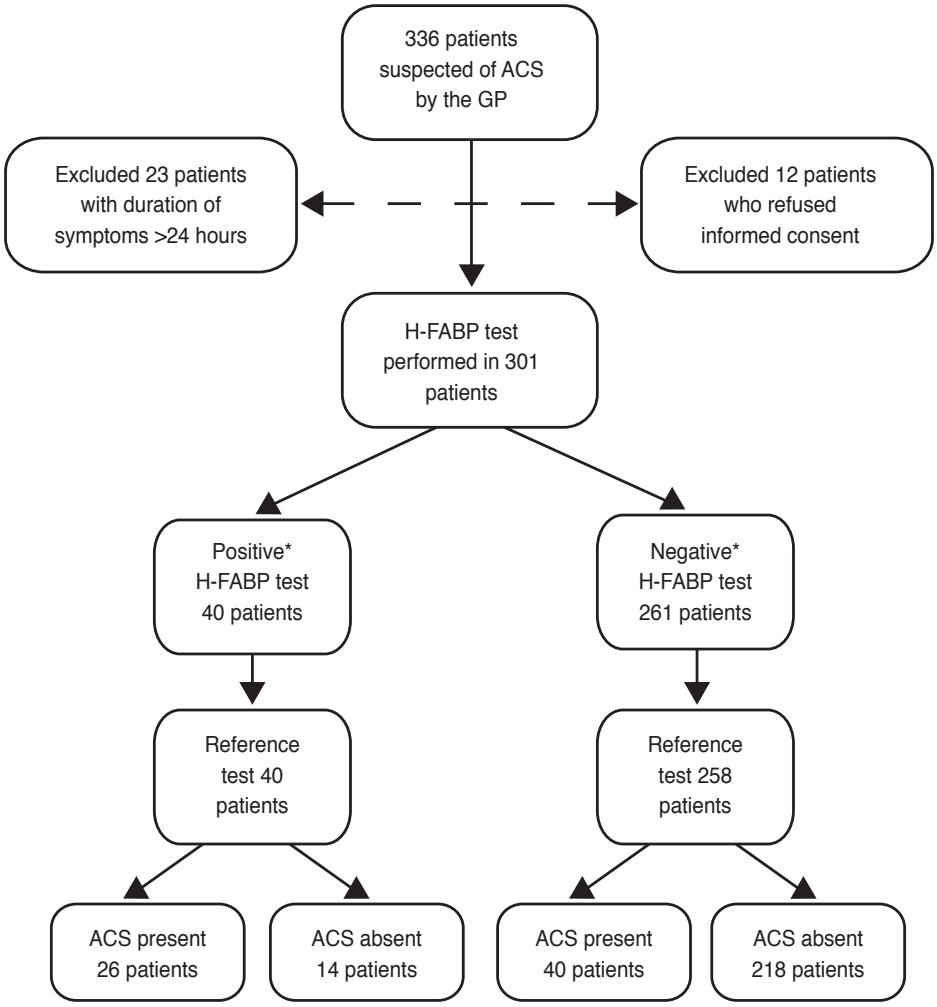

Figure 1. Patient flow diagram. ACS: acute coronary syndrome, GP: general practitioner, H-FABP: heart-type fatty acid-binding protein. *Unclear test results (34 cases (11%)) were imputed.

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.

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

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

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*	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)

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

(11%). Of these, 12 refused informed consent, 23 had symptoms suggestive of ACS for more than 24 hours at the time of testing, and three patients had an undetermined final diagnosis. These last three patients were not referred to 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 (Figure 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 six hours 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).

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)**

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 hours 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) (Figure 2). Calibration of both models was good (Figure 3).

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

	0-6 h			0-24 h		
PVV	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)		
	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

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 to 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%.

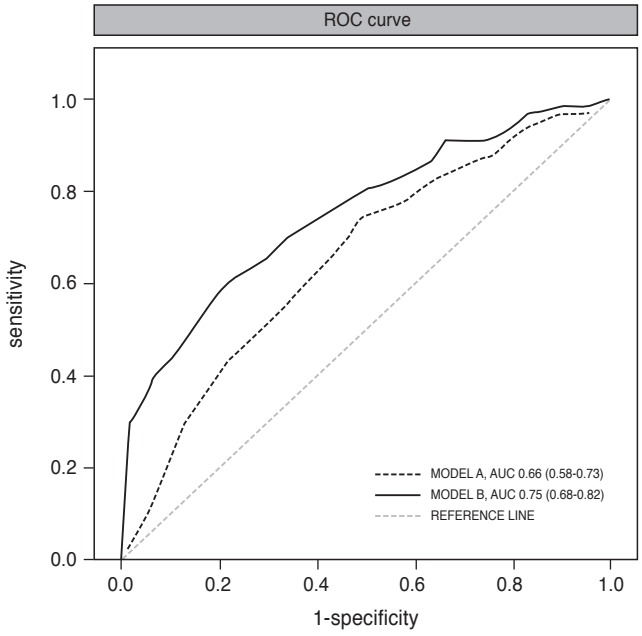

Figure 2. Receiver operating characteristic (ROC) curve analyses with AUC (area under the curve) with 95% confidence interval for two diagnostic models. Model A: clinical parameters. Model B: clinical parameters and H-FABP rapid test result.

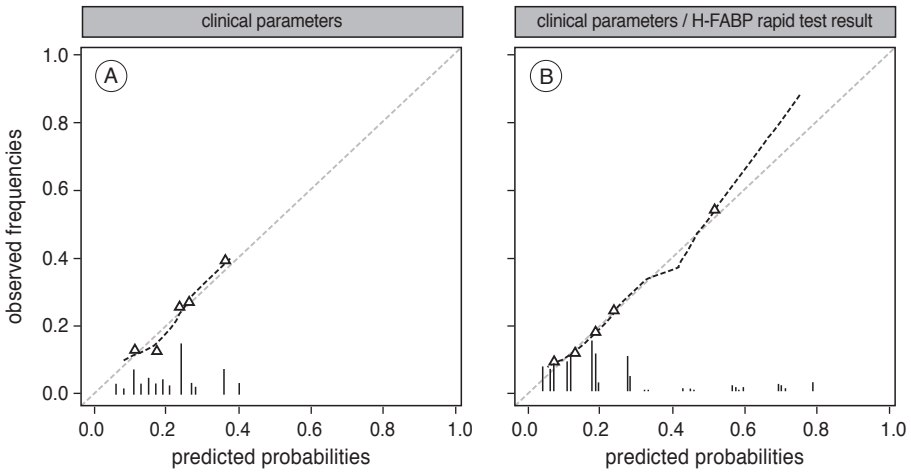

Figure 3. Calibration plots of the two diagnostic models. Model A: clinical parameters. Model B: clinical parameters and H-FABP rapid test result.

Clinical feasibility of the bedside test

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

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.

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 was 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 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 to 64% in the above mentioned studies) and the amount of test failures (reported in only 2 studies [16,17], respective failure rate 14 and 17%). Also, no multivariate analysis was perfomed 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 can not 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 H-FABP test and many of them performed the 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 ischaemia severe enough to cause sufficient myocardial damage to release detectable quantities of a cardiac biomarker into the circulation, whereas in unstable angina there is ischaemia without a measurable amount of a cardiac biomarker in the circulation [4,20]. 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 ischaemia in unstable angina detected by H-FABP will by definition not be detected by the reference standard that we used (troponin). However, an analysis taking acute MI as the outcome yielded similar results. 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 can not 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.

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Based on:

Gender differences in pre-hospital time delay and symptom presentation in patients suspected of acute coronary syndrome in primary care

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Submitted

CHAPTER 6

Gender differences in pre-hospital time delay and symptom presentation in patients suspected of acute coronary syndrome in primary care

Abstract

Background

Early recognition of an acute coronary syndrome (ACS) greatly improves prognosis, but information on gender differences and pre-hospital delay times and symptom presentation in patients suspected of ACS in primary care is lacking.

Methods

298 consecutive patients suspected of ACS (52% female, mean age 66 years, 22% eventually diagnosed with ACS according to international guidelines) were included by the general practitioner (GP). Time intervals were prospectively recorded by the GP together with patient and symptom characteristics (age, sex, previous medical history, chest pain, radiation of chest pain, nausea/sweating).

Results

Median doctor delay (defined as time from call for help until GP consultation) was 33 (interquartile range (IQR) 20-55) minutes in men and 45 (IQR 26-72) minutes in women (p=0.01). Median patient delay (defined as the time from onset of symptoms until call for help) was 108 (IQR 39-348) minutes in women and 180 (IQR 48-396) minutes in men (p=0.20). Women reported radiation of chest pain more often than men (57% versus 68%). Presence of chest pain and nausea/sweating did not differ between men and women. Women diagnosed with ACS were older than men (mean 75 years versus 65 years, p<0.001).

Conclusion

In patients suspected of ACS in primary care doctor delay was longer in women than in men, while presenting symptoms of ACS were similar, or even more typical, in women. Both physicians and patients should be aware that women are not at a lower risk for developing ACS, but women have ACS at an older age.

Introduction

Coronary heart disease is the second leading cause of death in both men and women in Europe, accounting for 21 and 22% of all deaths, respectively [1]. In the case of acute coronary syndrome (ACS, comprising acute myocardial infarction and unstable angina) early recognition is of paramount importance, since a timely intervention (e.g. percutaneous coronary intervention, anti-thrombotic therapy or bypass surgery) will reduce the severity of infarction and improve patient outcome. In both primary and secondary care, the early diagnosis of ACS presents a diagnostic challenge for physicians, as signs and symptoms of ACS can be atypical and causes of chest pain may vary widely. Biomarkers, especially troponin, have become the cornerstone for the diagnosis of ACS. It is important to measure cardiac biomarkers in the correct time interval, because of their specific pattern of rise and fall. For instance, troponin reaches the threshold for acute myocardial infarction 6-9 hours after the onset of symptoms [2]. It is therefore important to establish the time frame in which physicians are confronted with patients suspected of ACS, since this influences the choice and interpretation of the biomarker to be measured.

Previous studies on the time delay in ACS have been conducted within a hospital setting, often retrospectively, and typically included patients with confirmed ACS only. Information about time delay in a primary care setting is scarce, as is knowledge of the delay of those with suspected ACS who are not referred to hospital and/or did not eventually showed to have an ACS. It is especially important to determine time delays in patients presenting with ACS in primary care since in many European countries, including the Netherlands, many patients suspected of ACS will contact a general practitioner (GP) first.

Some studies suggest that there are gender differences in symptom presentation of ACS. Women have been reported to present atypical complaints, such as back pain, neck or jaw pain and nausea and shortness of breath more often, while men are more likely to present with chest pain and diaphoresis [3-7]. Other studies however could not support these gender differences [8,9] and reviews on the subject confirm that study results are conflicting and conclude that further research systematically investigating gender differences in the presentation of ACS is needed [10,11].

We therefore assessed gender differences in pre-hospital delay times and in symptom presentation in suspected ACS patients in the primary care setting.

Methods

The pre-hospital components of delay were divided into patient delay and doctor delay. We defined patient delay as the time from onset of (chest pain) symptoms until the patient's call for help to a GP. We defined doctor delay as the time from the first call for help until the actual GP consultation. Overall delay was defined as the time from symptom onset until the GP consultation. All time intervals were prospectively recorded on a case record form. Also recorded by the GP were patient characteristics (age, sex, previous medical history) and presenting symptoms (presence of chest pain, radiation of pain, nausea/sweating).

The present study was embedded within a large diagnostic study in suspected ACS patients. The design of this study was presented in detail elsewhere [12]. In short, consecutive patients suspected of ACS were included. Three out-of-hours GP services (one urban and two semi-urban) in the region of Utrecht, The Netherlands, participated in the study, and 25 GPs from group practices recruited patients during daytime hours on week days. We excluded patients with complaints lasting more than 24 hours and patients who required instant hospital referral, as judged by the GP, to prevent any delay with questions as part of our study.

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 signs and symptoms, ECG and biomarker levels (troponin, CK and CK-MB), specialist letters in those who had been referred to hospital and follow-up results up to one month after the event. ACS was defined in accordance with guidelines from the European Society of Cardiology and the American College of Cardiology [13,14]. AMI was diagnosed based on the presence of symptoms suggestive of cardiac ischaemia in combination with a rise of a cardiac biomarker, preferably troponin, above the decision limit for AMI with or without typical ECG changes indicative of myocardial ischaemia. Unstable angina was diagnosed when there were typical symptoms and ECG changes indicating cardiac ischaemia, without the elevation of cardiac biomarkers above the decision limit.

Data analyses

We examined the differences in median time delay between men and women suspected of ACS using the Mann-Whitney U-test. Gender differences in patient characteristics and symptom characteristics were compared using the chi-square or Fisher's exact test (categorical variables) and t-test (continuous variables). We performed a subgroup analysis in patients with an established diagnosis of ACS. SPSS version 16.0 (SPSS, Inc., Chicago Il, USA) was used for all statistical analyses.

Results

298 patients suspected of ACS by their GP were included in the study. The baseline characteristics of the patients and their symptoms are presented in Table 1. There were 155 (52%) females and the mean age of the participants was 66 years (SD 14). The panel established ACS in 66 (22%) patients: 38 (13%) men and 28 (9%) women.

Table 1. Patient and symptom characteristics according to gender of patients suspected of acute coronary syndrome (in percentages).

	Study participants suspected of ACS by GP			
Patient characteristics (%)	**Overall %** ***(N=298)***	**Men** ***(N= 143)***	**Women** ***(N=155)***	**p-value**
Age (mean, years)	66 *(SD 14)*	63 *(SD 13)*	68 *(SD 14)*	*<0.001*
History of AMI, bypass, PCI, angina pectoris	36	37	36	*0.81*
Current smoker	23	31	16	*<0.05*
Diabetes	23	20	26	*0.20*
Hypertension	49	45	52	*0.20*
Hyperlipidemia	31	32	30	*0.74*
Presence of cardiovascular risk factors [1]	79	76	82	*0.23*
Symptom characteristics (%)				
Chest pain	93	91	96	*0.12*
Radiation of pain	63	58	68	*0.06*
Nausea / sweating	58	59	57	*0.77*
Time of presentation (%)				
Morning (6.00 a.m. - 11.59 a.m.)	16	15	18	*0.10*
Afternoon / evening (12.00 a.m. - 11.59 p.m.)	22	26	18	*0.43*
Night (12.00 p.m. - 5.59 a.m.)	62	59	64	*0.43*
Weekend [2]	34	34	34	*0.99*
Referred to hospital (%)	73	76	71	*0.38*
Outcome acute coronary syndrome (%)	22	27	18	*0.08*
Unstable angina pectoris	21	18	25	*0.88*
Non-ST Myocardial infarction	52	53	50	*0.18*
ST myocardial infarction	27	29	25	*0.25*

ACS: acute coronary syndrome, GP: general practitioner

[1] Current smoker, diabetes, hypertension, hypercholesterolemia

[2] Friday 00:00 p.m. - Sunday 00:00 p.m.

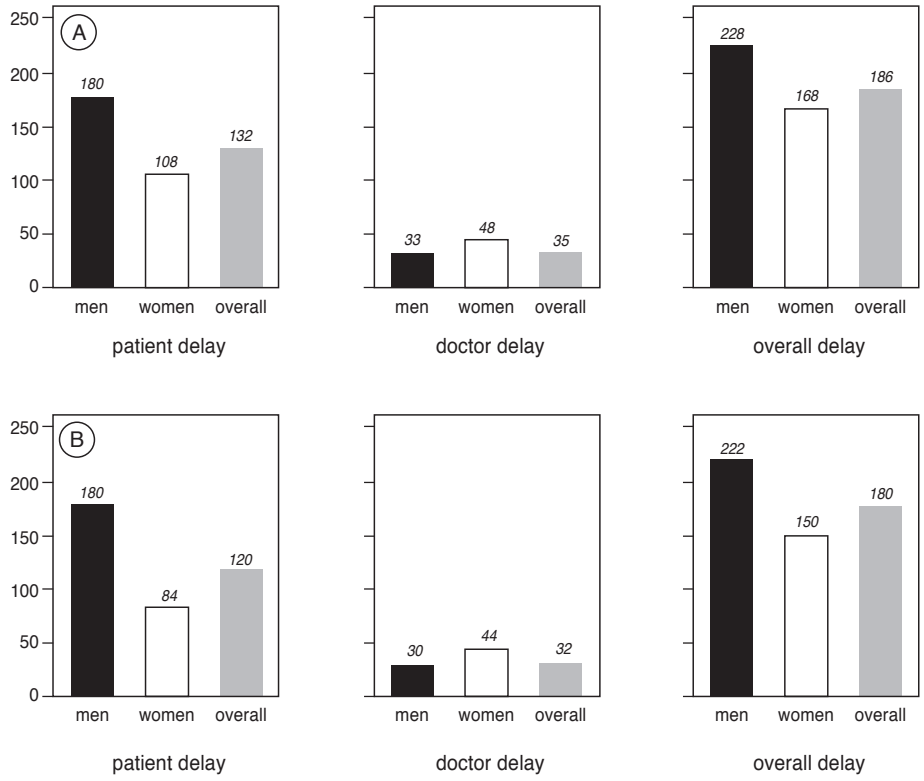

Figure 1. Duration of pre-hospital delay (in minutes) according to gender in all participants (A) and in patients diagnosed with ACS (B).

Time delay

Median patient delay in patients suspected of ACS was 108 (interquartile range (IQR) 39-348) minutes in women and 180 (IQR 48-396) minutes in men (p=0.20). Doctor delay in women suspected of ACS was 45 (IQR 26-72) minutes versus 33 (IQR 20-55) minutes in men (p=0.01). Overall, pre-hospital delay in women suspected of ACS was 168 (IQR 90-408) minutes, in men this was 228 (IQR 90-480) minutes (Figure 1).

In a subgroup analysis in patients who were diagnosed with ACS patient delay in women was 84 (IQR 40-210) minutes versus 180 (34-330) minutes in men (p=0.33). Doctor delay in women was 44 (IQR 25-90) minutes in women and 30 (IQR 15-58) minutes in men (p=0.04). Overall pre-hospital delay in this subgroup was 150 (102-240) minutes in women and 222 (IQR 72-366) minutes in men.

The majority of patients (209, 70%) was seen by the GP within six hours after onset of symptoms.

Patient characteristics and symptom presentation

Women suspected of ACS in primary care had a mean age of 63 (SD 14) years versus a mean age of 68 (SD 13) years for men (p<0.001). Women were less likely to smoke than men (16% versus 31%, p<0.01). Diabetes tended to be more prevalent in women than men (26% presence in women versus 20% in men). Other risk factors for coronary heart disease such as hypertension, hyperlipidemia and a previous history of coronary heart disease did not differ appreciably between men and women. Women reported radiation of chest pain more often than men (57% versus 68%, p 0.06). Other symptoms, such as the presence of chest pain and nausea/sweating did not differ between men and women. There were no differences in the time of presentation (morning, afternoon/evening or night) between men and women and also the management decision of the GP (hospital referral or not) was similar for both sexes.

In a subgroup analysis of patients diagnosed with ACS, women were again significantly older than men (mean age 75 (SD 14) years and 65 (SD 13) years respectively, p < 0.001). Although women tended to have a previous history of coronary heart disease more often than men (46% versus 37% respectively) and also suffered from diabetes more often (39% of women versus 24% of men) these differences were not statistically significant. Overall however, women more often had one or more cardiovascular risk factors than men (93% versus 74%, p<0.05). No gender differences were found for time of presentation and the management decision of the GP in this subgroup analysis.

Discussion

To our knowledge, this is the first study to assess gender differences in patient and doctor delay in patients suspected of ACS in a primary care setting. We found that women, after the start of symptoms, called for a GP a median of 80 minutes before men did. Doctor delay, defined as the time from the patients call for help until the actual GP consultation, was more than ten minutes longer in women suspected of ACS than in men (median doctor delay 45 and 33 minutes respectively). However, the overall delay time, from start of symptoms until GP consultation, was one hour shorter for women than for men (median overall delay 168 and 228 minutes respectively). In the subgroup of patients that was eventually diagnosed with ACS we found similar results. Women reported radiation of chest pain more often than men, but other symptoms such as the presence of chest pain or nausea/sweating were similar for both sexes.

The longer doctor delay we observed in women, is not easy to explain, since we also found that men and women are equally likely to present with chest pain, that women more often have radiation of chest pain (considered a typical symptom) and that women more often have risk factors for coronary heart disease (which should trigger a physician to considering ACS). One explanation may be the misconception, shared by both patients and physicians, that women are at a lower risk for developing coronary heart disease than men. An experimental case study found that physicians assigned women to a lower risk category for coronary vascular disease than men, despite a similar calculated risk [15]. Also, in two reviews for gender differences in ACS presentation women were found to experience chest pain less often than men [11,10] and present with more atypical complaints [11], which would indeed explain a longer delay in the diagnosis. Nevertheless, these findings were not supported by our study.

Although we found a longer doctor delay in women than in men, overall pre-hospital delay was shorter in women. Previous studies on pre-hospital delay yielded opposite results: women arrived 10 to 45 minutes later in hospital than men [16-18]. These studies however included only patients with proven myocardial infarction and were all performed in a hospital setting. The 'conflicting' results could therefore be caused by a different setting and patient type. It has been shown that the more serious the ACS (for instance STEMI patients versus unstable angina patients) the shorter the pre-hospital delay time [19,20]. In our study, more low-risk patients were included, as patients at high risk of ACS are more likely to contact the emergency room or cardiologist directly, thereby bypassing the GP. This may also explain why the men in our study delayed longer in calling for help than women: included in our study are men with a lower risk for ACS and hence longer delay times. A previous hospital-based study reported the opposite: women with AMI delayed longer than men in calling for help after the start of symptoms (76 minutes for women, 65 minutes for men) [9].

Our study illustrates that delay times in a primary care setting differ from those found in a hospital setting. Patients presenting with symptoms suggestive of ACS in primary care are notoriously difficult to assess, because they present early after symptom onset and the GP has limited diagnostic facilities (mostly only medical history taking and physical examination, sometimes ECG analysis) to accurately diagnose or exclude ACS [21]. More diagnostic certainty in the primary care setting is needed and biomarker testing may play an important part, also in primary care, in the diagnosis of ACS in the future. The choice of the biomarker to be measured strongly depends on the time interval in which patients are seen. Troponin for instance, is positive for myocardial infarction 6-9 hours after the onset of symptoms [2]. The results of our study indicate that troponin is not a suitable biomarker for measurement in a primary care setting,

since most patients were seen within six hours. A negative troponin result can therefore not exclude myocardial infarction, since in many instances it will be false negative.

Some methodological issues need to be addressed. One of the weaknesses of our study is the small number of patients diagnosed with ACS. Thus, the findings of especially the subgroup analysis should be viewed with caution and further studies are needed to confirm our results. Also, not included in our study are patients that required instant hospital referral according to the participating GP, because this would lead to an unacceptable delay in patients requiring instant medical attention. We also excluded patients with complaints lasting more than 24 hours, since in this study we simultaneously evaluated and early biomarker for ACS that had to be measured within 24 hours. However, the most challenging group of patients are those presenting within 24 hours, because this is the time interval in which most complications of ACS occur. Regarding gender differences in symptom presentation, it is a drawback that on the case record form that was used, symptoms were not separately specified, but clustered into broad categories. We therefore had no information on the exact location of the chest pain or the radiation pattern, nor did we assess the type of chest pain (e.g. sharp pain, pressure, tightness).

A major strength of our study is that the data on time delay was prospectively recorded by the participating GPs, as opposed to many other studies in which these time delays were obtained by interviewing of the patient or retrospective chart review, with possible recall bias and missing information. Also, the patients that we included in our study (suspected of ACS) are highly representative of the actual patient spectrum that the GP will encounter. Most studies included only patients diagnosed with ACS, but in actual clinical practice, GPs will not know whether or not a patient is suffering ACS. We deliberately included patients from this diagnostically challenging domain, since this is most in accordance with clinical practice.

Conclusion

In patients suspected of ACS in a primary care setting, we found a longer doctor delay in women than in men, while presenting symptoms of ACS are similar or even more typical in women. Women suspected of and diagnosed with ACS were older than men. Both physicians and patients should be aware that women are not at a lower risk for developing ACS: they just do so at an older age. Women with symptoms suggestive of ACS should therefore be just as rapidly evaluated by the GP as their male counterparts and if necessary a prompt hospital referral for additional diagnostic testing and adequate treatment should be ascertained.

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Based on:

Diagnosing acute coronary syndrome in primary care: comparison of the physician's risk estimation and a clinical decision rule

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In revision: Family Practice

CHAPTER 7

Diagnosing acute coronary syndrome in primary care: comparison of the physician's risk estimation and a clinical decision rule

Abstract

Background

Diagnosing acute coronary syndrome (ACS) in a primary care setting poses a diagnostic dilemma for physicians. We directly compared the diagnostic accuracy of a clinical decision rule (CDR) in suspected acute coronary syndrome with the risk estimates of the attending primary care physician.

Methods

In a prospective multicentre study in primary care patients suspected of acute coronary syndrome (ACS) were included by the general practitioner (GP). GPs were asked to estimate the probability (0%-100%) of the presence of ACS. GPs collected patient data, but they were not aware of the CDR and did not score the patient accordingly.

Results

298 patients were included (52% female, mean age 66 years, 22% ACS). The area under the ROC curve was 0.75 (95% confidence interval (CI) 0.68-0.82) for the GP risk estimate and 0.66 (95%CI 0.58-0.73) for the CDR. There was concordance between the risk estimation of the general practitioner and a CDR in 51% of patients suspected of ACS. The prevalence of ACS in predefined low-, intermediate- and high-risk groups was similar for the GP and CDR estimates. In the low risk group according to the GP, four patients (8.2%) suffered an ACS. These four patients were all identified by the CDR as high risk.

Conclusion

The GP classified patients as ACS or no ACS more adequately than the CDR, judged by the area under the ROC curve. However, we recommend the use of the CDR in patients that are considered at low risk for ACS (<10%) by the GP, since this will further reduce the amount of missed myocardial infarctions.

Introduction

Diagnosing or excluding acute coronary syndrome (ACS, comprising acute myocardial infarction and unstable angina) is a challenge for primary care physicians, because signs and symptoms may be atypical and other diagnostic tools, such as cardiac biomarker testing or electrocardiography are often lacking. There is no generally accepted clinical decision rule (CDR) for ACS, although several attempts have been made to develop and validate such a rule [1-3].

In a CDR, patient characteristics and findings from history taking, physical examination and often other additional diagnostic tests (typically laboratory testing or imaging techniques) are combined to give an overall score, which is related to the absolute probability of the presence (or absence) of a certain disease and often guides the further diagnostic work-up. A CDR, for example the Ottawa ankle rule for the use of radiography in ankle injuries4, is generally developed to improve the efficacy, quality and efficiency of health care [5-7]. For instance, introduction of the Ottawa ankle rule led to a relative reduction in ankle radiography of 28%, reduction in costs and emergency room waiting times, without increasing the number of missed fractures [8].

Many CDRs have had limited effect on physicians behavior, and several barriers for adherence to a decision rule have been described [9,10,7]. These barriers range from unpractical use of the rule itself or lack of awareness of existence of the rule, to disagreement with the rule. In general, physicians view CDRs as oversimplified and not applicable to their specific practice population. Moreover, physicians often perceive CDRs as a reduction of their professional autonomy and they argue that their clinical judgment is superior10. Physicians will be more likely to use a CDR if they are convinced that it has additional value to their own clinical judgment in estimating risks.

In this study we directly compared the diagnostic accuracy of a clinical decision rule in suspected ACS with the risk estimates of the attending primary care physician.

Methods

Data was collected within a large diagnostic accuracy study in which the diagnostic value of a rapid cardiac biomarker, in addition to a decision rule, was determined. The design of this study has been published previously [11]. From March 2006 until September 2008, 298 consecutive patients suspected by the general practitioner (GP) of acute coronary syndrome were enrolled. Presenting symptoms were most

often chest pain, but also sudden dyspnoea or any other symptom prompting a GP to consider ACS as a possible diagnosis, could lead to inclusion in this study. We excluded patients with complaints lasting more than 24 hours and patients requiring instant hospital referral, as judged by the GP.

Participating GPs systematically collected data on the patient's presenting signs and symptoms and history taking. The GPs were asked to make a management decision based on their own judgment. For the purpose of the present study, GPs were explicitly instructed to estimate the probability of the presence of ACS on a scale from 0% to 100% after they finalized medical history taking and physical examination.

Using multivariate regression analysis, we developed a CDR using the same clinical items as in a diagnostic model previously developed by Grijseels et al. [12]. The clinical items included in the CDR are: sex, radiation of chest pain, nausea/sweating and the presence of prior coronary artery disease. We (internally) validated this new model with bootstrapping techniques to correct for over-optimism. Although GPs did collect patient data, they were not aware of the CDR and were not asked to score the patient accordingly.

ACS was defined in accordance with guidelines from the European Society of Cardiology and the American College of Cardiology [13,14]. An expert panel consisting of two cardiologists and one GP established a final diagnosis in each patient. The panel used all available patient information, including signs and symptoms, ECG and biomarker levels (troponin, CK and CK-MB), specialist letters in those who had been referred to hospital and follow-up results up to one month after the event.

The study protocol was approved by the Medical Ethics Committee of the University Medical Center Utrecht, The Netherlands. All patients provided written consent.

Data analysis

First, we compared the abilities of the CDR and the GP judgment in discriminating patients with a low risk of disease from patients with a high risk, using receiver operating characteristic (ROC) curve analysis. An area under the ROC curve (AUC) of 0.5 indicates no discrimination, whereas an AUC of 1.0 indicates perfect discrimination [15]. Then, we constructed a calibration plot to separately examine the agreement between the predicted probabilities of the decision rule with the observed outcome ACS and we constructed a similar calibration plot for the predicted probabilities of the GP. Perfect predictions should lie on the 45-degree line for agreement with the outcome in the calibration plot [16]. Finally, we divided patients into different risk groups

Table 1. Clinical decision rule for acute coronary syndrome in a primary care setting.

Clinical item	Score
Sex (male)	5 points
Presence of radiation of chest pain	8 points
Presence of nausea/sweating	5 points
History of coronary artery disease	2 points

and constructed a classification table to quantify the concordance between the risk estimation based on the CDR and by the GP. We made a division into low, intermediate and high risk groups according to the expected probability of the outcome based on the CDR and also according to the expected probability of the outcome based on the GPs risk estimation. No previously determined threshold exists for such a division into risk categories of ACS patients and we therefore used values that seemed clinically plausible and resulted in a sufficient number of patients in each risk category: a <10% chance of ACS as low risk, a 10% to 20% chance to indicate intermediate risk and a probability exceeding 20% chance to indicate high risk.

Statistical analyses were performed using SPSS version 16.0 for Windows, Chicago, USA.

Results

Patient characteristics

The mean age of the 298 patients suspected of ACS by the GP was 66 (SD 14) years, 52% was female and 66 (22%) were diagnosed with ACS by the expert panel. The majority of patients (75%) had one or more cardiovascular risk factors (current smoker, diabetes, hypertension, hyperlipidemia), while 36% of all patients had a history of coronary artery disease. The presenting symptoms involved chest pain in 278 patients (93%). The median ACS risk estimation according to the GP was 47.5% (interquartile range (IQR) 20.0-70.0%) and 23.2% (IQR 13.8-27.6%) according to the CDR. Of the suspected ACS patients, 73% was referred to hospital by the GP for further diagnostic testing and/or treatment (Table 2).

The AUC for the GP risk estimate was 0.75 (95% confidence interval (CI) 0.68-0.82) and for the CDR this was 0.66 (95%CI 0.58-0.73) (Figure 1), indicating that the GP categorised patients with and without ACS more accurately than the CDR. Calibration of the GP risk estimate showed that the GP generally overestimated the risk for ACS. For example, when the GP estimated a risk of 60% the actual risk was around 25%. Calibration of the CDR showed good agreement between predicted and observed probabilities (Figures 2A and 2B).

Table 2. Demographic and clinical characteristics of included patients suspected of acute coronary syndrome by the general practitioner (numbers and (percentages)).

Characteristic	N=298
Demographics	
Age (mean, years)	66 (SD 14)
Sex (male)	143 (48)
Cardiovascular risk factors	
Presence of any of the following cardiovascular risk factors	236 (79)
History of AMI, bypass, PCI, angina pectoris	108 (36)
Current smoker	69 (23)
Diabetes	68 (23)
Hypertension	145 (49)
Hyperlipidemia	91 (31)
Symptoms	
Chest pain	278 (93)
Radiation of pain	189 (63)
Nausea / sweating	174 (58)
Referred to hospital	218 (73)
Outcome	
Acute coronary syndrome	66 (22)
Unstable angina pectoris	14 (21)
Myocardial infarction	52 (79)

AMI: acute myocardial infarction, PCI: primary coronary intervention

GPs estimated 49 (16%) patients as low risk for ACS and 209 (70%) as high risk; 8.2 and 27% of these groups, respectively, had an ACS according to the expert panel. According to the decision rule 24 (8.1%) of patients had a low risk and 162 (54%) were high-risk; the prevalence of ACS in these groups was 8.3 and 30% respectively. The risk estimation by the GP and the decision rule showed concordance in 153 (51.3%) cases. In 27 (9.1%) cases there was major discordance. Importantly, the prevalence of ACS in the low-, intermediate- and high risk groups according to the GP and CDR estimations was similar, but of the 19 patients estimated as low risk according to the GP and high risk according to the decision rule 4 patients (21%) suffered an ACS. Of the 8 patients with a low risk according to the decision rule and a high risk according to the GP, 2 patients (25%) suffered an ACS (Table 3a and 3b). Of the patients that were estimated as low or intermediate risk by both the GP and the CDR none had an ACS.

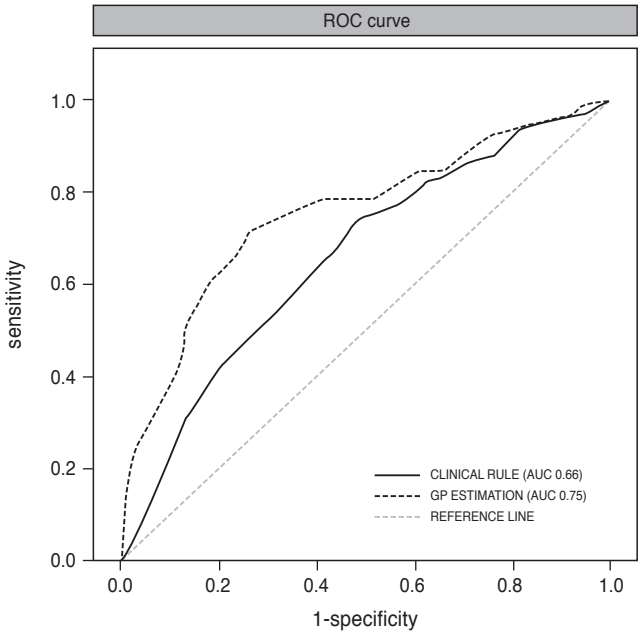

Figure 1. Receiver operating characteristics curve for the GP risk estimation and for the clinical decision rule for acute coronary syndrome.

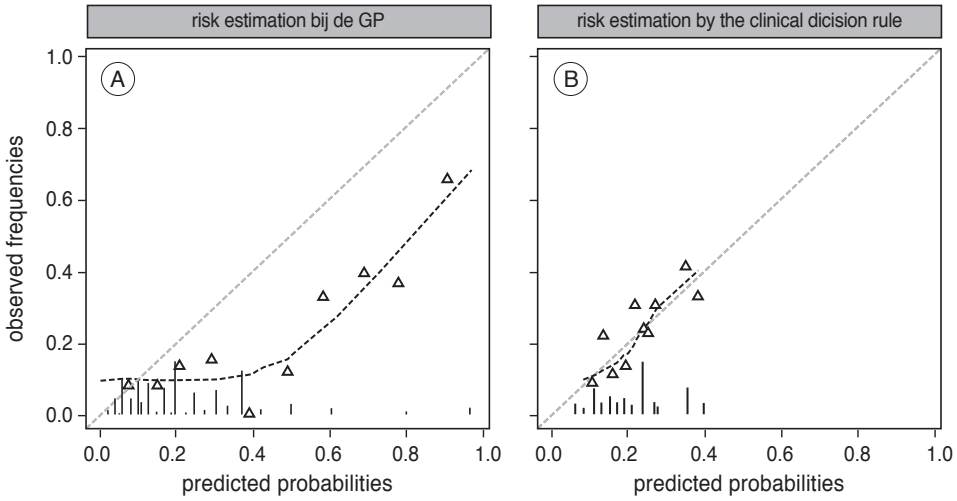

Figure 2. Calibration plots of risk estimation by the GP and the clinical decision rule.

As a sensitivity analysis we constructed the same classification table using the lowest and highest quintiles for the GP estimation and the CDR. For the GP estimation this yielded thresholds of <15% for low risk and >76% for high risk and for the CDR this was <13.2% for low risk and >28.2% for high risk. Concordance between the GP estimation and the CDR was similar for these new thresholds (157, 52.7%), major discordance was less prevalent (14, 4.7%).

Table 3a. Comparison of the risk estimation by the general practitioner and the clinical decision rule with the actual outcome.

	GP risk estimate				Clinical decision rule			
	Number (%)	Outcome ACS			Number (%)	Outcome ACS		
		N	% within risk group	% from total		N	% within risk group	% from total
Low risk	49 (16)	4	8.2	1.3	24 (8)	2	8.3	0.7
Intermediate risk	40 (13)	6	15	2.0	112 (38)	15	13.4	5.0
High risk	209 (70)	56	27	19	162 (54)	49	30	16
Total	298 (100)	66	-	22	298 (100)	66	-	22

GP: general practitioner, ACS: acute coronary syndrome

Table 3b. Concordance of the estimations of the general practitioner and the clinical decision rule with absolute number of patients with acute coronary syndrome (in grey italics).

		Clinical decision rule			
		Low risk	Medium risk	High risk	Total
Risk estimation GP	Low risk	10 *0*	20 *0*	19 *4*	49 (16) *4*
	Medium risk	6 *0*	17 *4*	17 *2*	40 (13) *6*
	High risk	8 *2*	75 *11*	126 *43*	209 (70) *56*
	Total	24 (8.1) *2*	112 (38) *15*	162 (54) *49*	298 (100) *66*

Discussion

To our knowledge, this is the first direct comparison of a physician's judgment with a clinical decision rule for patients suspected of ACS in primary care. Comparing the AUC of the GP estimate and the CDR revealed that the GP more adequately classified patients as ACS or no ACS than the CDR. Calibration plots showed that the GP tends to systematically overestimate a patients risk for ACS. Furthermore, in a classification table for three different risk categories (low, intermediate and high) there was a 51% concordance between the risk estimation of the GP and the decision rule. In the 49 patients judged as low risk by the GP, four patients (8.2%) suffered an ACS. These four patients with ACS were all identified by the decision rule as high risk.

Based on our findings we conclude that an adequate CDR for the triage of patients suspected of ACS in primary care is still lacking. Interestingly however, even the use of our moderate discriminative CDR for ACS would increase the safety and efficiency in the diagnostic work-up of patients suspected of ACS if it is used as follows: the GP performs his or her usual diagnostic work-up of a patient suspected of ACS, which leads to a certain management decision. If the GP judges the patients to be at low risk for ACS, than, as an extra precaution, the clinical decision rule for ACS could be performed. Patients estimated as high risk by the decision rule should than still be referred to hospital. This will decrease the number of missed ACS patients in a primary care setting.

Widely accepted decision rules for the diagnosis of ACS do not exist and available prediction rules for ACS have major methodological limitations, as was shown in a systematic review on the diagnostic accuracy of clinical prediction rules for excluding ACS in an emergency room setting [17]. These limitations included verification bias (failure to use the same reference standard ('gold standard') in all patients), lack of blinding and lack of external validation of the CDR, which all could have led to overestimation of diagnostic performance of the CDR.

It is important to realize that the CDRs that were developed in a secondary care setting cannot be applied uncritically to the primary care setting, even when performed in patients in whom the same diagnostic problem exists. In primary care, the prevalence of ACS is lower as compared to secondary care (because only the medium and high risk patients are referred to hospital) and in primary care patients present at in an earlier stage after symptom onset. Patient characteristics and symptoms will therefore differ and it is possible that an item that provides considerable diagnostic information in secondary care will be of little additional value for a CDR in a primary care setting.

In general, in diagnostic research, the positive predictive value of a diagnostic test is higher in secondary care while on the other hand the negative predictive value will be higher in primary care.

Some limitations of our study deserve further discussion. A drawback of our study is that the decision rule that we developed in this study was not externally validated in a different patient set. ROC curve analysis shows that the discriminative power of the CDR that we used in our study was moderate. This is explained because we only included signs and symptoms in our CDR, and no additional diagnostic information such as ECG or biomarker testing. It is notoriously difficult to diagnose ACS based on clinical parameters only [14,18]. A previous study that derived and validated a clinical prediction score to rule out coronary heart disease in primary care found an AUC of 0.75 upon external validation using a CDR with 8 signs and symptoms [1]. Although we did not externally validate our CDR, so-called 'overfitting' of the CDR for ACS that we derived is less likely, because we used pre-specified items that were previously used in another CDR for ACS in primary care, not items that we derived from our own data [12,19]. The original decision rule that formed the basis of the presented CDR also included abnormal electrocardiographic examination at the time of patient presentation. In our study, no ECGs at the time of presentation to the GP were available, however. An ECG was performed later (but within 24 hours), on arrival in hospital or at the patient's home in case of non-referral. We therefore only included the clinical items of the original decision rule which may also explain the CDR's restricted performance. On the other hand, in daily clinical practice GPs often do not have (portable) facilities to record an ECG in their practice, or at the patients home in case of a house call.

Another limitation of our study is that one can argue whether we chose the correct threshold for low, intermediate and high risk groups. No established thresholds for such risk stratification exists and we chose thresholds of 10% and 20%, since they seemed reasonable thresholds given the average ACS risk of 22% in our population. To test for the validity and robustness of our findings we performed a sensitivity analysis using the lowest and highest quintiles as thresholds. This analysis yielded similar results with respect to overall concordance and unjustified low risk estimations by the GP.

Conclusion

Judged by the area under the ROC curve, the GP more accurately classified patients as with or without ACS than the CDR. There was concordance between the risk estimation of the general practitioner and a clinical decision rule in 51% of patients suspected of ACS and the prevalence of ACS in predefined low-, intermediate- and high-risk groups was similar for the GP and CDR estimates. However, we recommend the use of the CDR in patients that are considered at low risk for ACS (<10%) by the GP, since this will further reduce the amount of missed myocardial infarctions.

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CHAPTER 8

General discussion

Introduction

General practitioners (GPs) are regularly confronted with patients presenting with chest pain or other symptoms suggestive of acute coronary syndrome (ACS). Patients with typical angina symptoms will be referred to hospital without delay, but there are many patients with vague, atypical complaints in whom the GP considers ACS rather unlikely to be the underlying diagnosis, but where the possibility of cardiac ischaemia cannot be completely ruled out with the diagnostic tools, typically history taking and physical examination, available in primary care. In such patients, additional diagnostic tests could be instrumental to reduce diagnostic uncertainty.

The studies described in this thesis focused on the potential role of cardiac biomarkers in the early detection of acute coronary syndrome (ACS) in a primary care setting. We provided an overview for currently available point of care tests for cardiac biomarkers and performed a meta-analysis including 16 studies on a potentially very useful marker, reported to be detectable within the first few hours after cardiac ischaemia: heart-type fatty acid-binding protein (H-FABP). In addition, we assessed the diagnostic accuracy of H-FABP in a large diagnostic study in which an H-FABP point-of-care (or 'bedside') test was performed in patients suspected of ACS in the primary care setting. Although this study showed that the H-FABP bedside test can be a complementary tool for the general practitioner (GP) in addition to history taking and physical examination, the investigated test is by no means the ideal test for diagnosing ACS in this setting, since the number of false-negative tests was too large. For a condition carrying a high morbidity and mortality such as ACS, that is unacceptable. Sound diagnostic studies on novel point of care tests for new cardiac biomarkers are needed, and will hopefully provide GPs the additional diagnostic certainty that is required to adequately and safely manage patients with suspected ACS in primary care.

In this general discussion, we will first discuss some general barriers for performing diagnostic research in a primary care setting, using our large diagnostic study as an example. Secondly, we will address the implementation of our results into clinical practice as well as the challenges for future research on the use of cardiac biomarker point of care tests in primary care. We will finish our discussion with some final comments on the studies presented in this thesis.

Performing research in primary care

When assessing the value of a bedside test in suspected ACS, it is tempting to perform such a study in an emergency room, or coronary care unit. In these settings,

a high concentration of suspected ACS patients can be found, due to the selection of patients by GPs and ambulance personnel. This facilitates the inclusion of many eligible patients in a short time period, reducing the length of duration of a study, and thereby its costs. It should be emphasized, however, that test results found in a secondary care setting cannot be applied uncritically to the primary care setting, even when the test is performed in patients in whom the same disease is suspected [1]. In primary care, the prevalence of ACS is lower as compared to secondary care (because only the medium and high risk patients are referred to hospital). In general, in diagnostic research, the positive predictive value of a diagnostic test will be higher in secondary care, while the negative predictive value will be higher in primary care. Also, in primary care, patients present at an earlier stage of their disease. Disease symptoms will therefore differ (and are often less typical) and diagnostic marker levels are likely to be lower. This will lead to a different test accuracy, since sensitivity and specificity are not fixed test characteristics (as is still often wrongly believed) but may vary according to the severity of disease [2,3]. It is therefore essential that sound (diagnostic) research is performed in a primary care setting, even when a similar study has already been performed in another domain, such as the hospital setting. Valid diagnostic research will help GPs to make evidence based health care decisions and provides an answer to the diagnostic dilemmas encountered in every day practice [4,5]. To be of use in clinical practice, it is also important that a diagnostic study follows the steps in the diagnostic process that physicians take in daily practice, i.e. first history taking, then physical examination, followed by easily available additional tests and finally more complicated, expensive and patient-burdening tests (the latter mostly requiring referral) [1].

Fortunately, in the last decades there has been a strong increase in diagnostic research in primary care with an impressive development in the number of publications in the field.

To recruit patients: first recruit physicians

Diagnostic research in primary care obviously requires the participation of GPs. For practicing physicians there is a delicate balance between active research participation and efficient clinical practice and an often heard reason not to participate in a study is that the GP is simply too busy, that workload in practice is too high already, and that participation would be too burdensome, involving too much paperwork [6-9]. Other reasons for not cooperating in a study may be that a practice is already involved in other studies [6,7], the negative impact that a study may have on the physician-patient relationship according to the GP [10,11] and the belief that evidence-based medicine is 'incompatible' with 'personalized' primary care [9]. Factors associated with successful

recruitment of physicians to participate in research are the involvement of physicians in the recruitment of other physicians [12-14], personal close contact or friendship between the researcher and the physician [14-16], clinical relevance of the research question or interest of the GP in the research topic [15-17] and financial incentives [7], although several other studies concluded that financial incentives had no effect [6,12].

How to make participating physicians actually recruit patients (and how not to)
Often, there is a discrepancy between the number of physicians that agree to participate in a study, and the number that actually start recruiting patients [11,16]. In a survey among 78 Dutch studies determinants of recruitment success and failure were evaluated. The study characteristics most consistently associated with success were the recruitment of prevalent cases (identified by searching the electronic medical record), the GP not having to be alerted during consultations and inviting the patient by mail [18]. In a study requiring incident cases, that is, direct patient recruitment during the consultation of patients presenting with complaints for the first time, much more effort is required from the GP: the GP has to be aware of the study during the consultation, the GP has to inform the patient and invite him/her to participate, often involving a written consent procedure. This means that there clearly is an extra workload associated with the project and that inclusion of a patient will disrupt the regular consultation schedule [18]. Overall, a median of 87% of planned patients was eventually included in the 78 studies, but to achieve this, almost half of projects needed extension of the recruitment period). Additional factors associated with successful recruitment of patients by participating GPs are delegation of research logistics to research nurses or practice assistants [7,8,13,16], providing clear instructions [6,16], establishing regular contact with participating physicians and monitoring of recruitment to address and solve possible barriers that physicians encounter during the study [6,13,16].

A clinical example

Recruiting physicians
The diagnostic study we performed as part of this thesis involved the active participation of more than 150 GPs working in 3 out-of-hours GP practices and in 9 GP group practices. The out-of-hours GP practices are large scale non-profit organizations in which GPs take turns being on duty during out-of-office hours for the patient population of all participating GPs in a certain region, supported by nurses and chauffeurs. Two practising GPs and one GP in training were part of our research group. They contacted GPs of group practices and managers of the out-of-hour GP practices in the region of Utrecht that previously participated in research performed by our academic research centre, or GPs who were known to one of the members of the research group. GPs were first contacted by telephone, then received a letter

containing more detailed information about the study protocol and, if they were interested in participation, were visited at their practice.

Retaining physician recruitment
In our study, patients suspected of ACS by the GP were included during regular consultations at the GP practice and during house calls. As explained previously, including incident cases requires study awareness and increased effort by the participating GP, but to reduce the extra effort to a minimum we constructed a case record form of one page only, that could partly be completed by the nurse. Furthermore, at the time of inclusion, patients were asked for verbal consent to participate in our study only, since it is neither very realistic nor feasible to ask written informed consent to study participation from a patient who may have a potentially life threatening acute condition, such as ACS. Written consent was obtained at a later stage, but this did not require interference of the GP. This procedure was approved by the Ethics Committee of the University Medical Center Utrecht.

To keep GPs actively involved in including patients for our study we used several methods, most of which were aimed at keeping a regular contact with all participating centres, by telephone, by practice visits (also to collect used tests and deliver new tests) and a bimonthly newsletter. We also provided a small financial incentive (15 euro) for the GP for every included patient.

Overcoming barriers
The recruitment period was anticipated to be 1.5 years, but an additional 12 months were needed to successfully complete recruitment. We expected the initial recruitment rates of a centre to be high (>15 patients for out-of-hour practices and >3 patients for group practices each month), and this was indeed the case, but after several weeks, recruitment rates declined, apparently because of a loss of interest in the study or the blood test and also possibly because of unsatisfactory experiences with the use of the test (there was a relatively high amount of test failures in our study). Although intensified contact with the practice could often improve recruitment rates temporarily, they never reached the initial rates again (Figure 1). We would therefore advise researchers to continuously attract new GP practices for their research, thereby keeping overall patient inclusion at a steady rate.

To improve patient inclusion in the out-of-hours GP practices we first started with providing a incentive not only for the GPs, but also for the GP practice personnel for every included patient. Later, we also increased the financial incentive that was given to GPs (Figure 2). Apparently, GP participation does not critically depend on

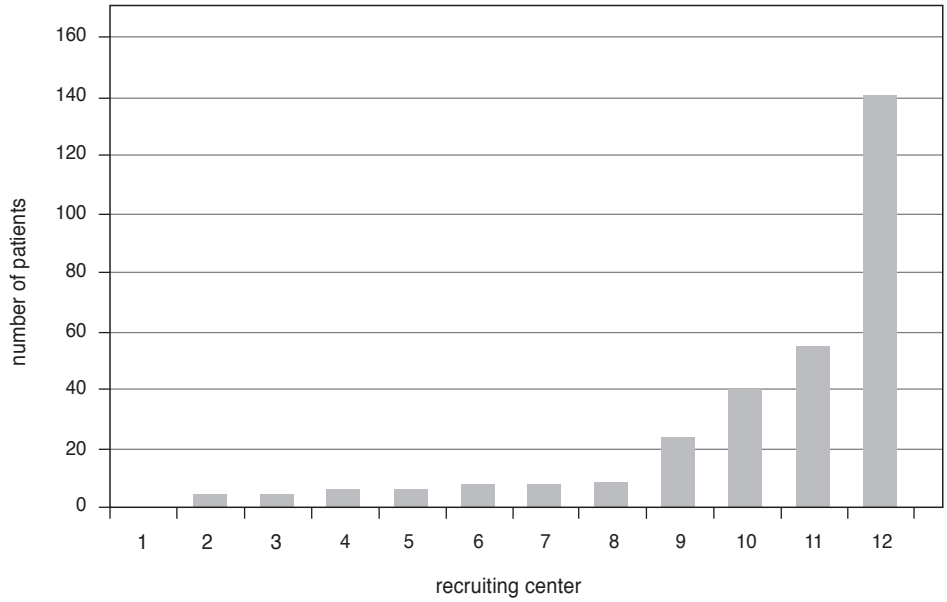

Figure 1. Number of patients included per participating centre.

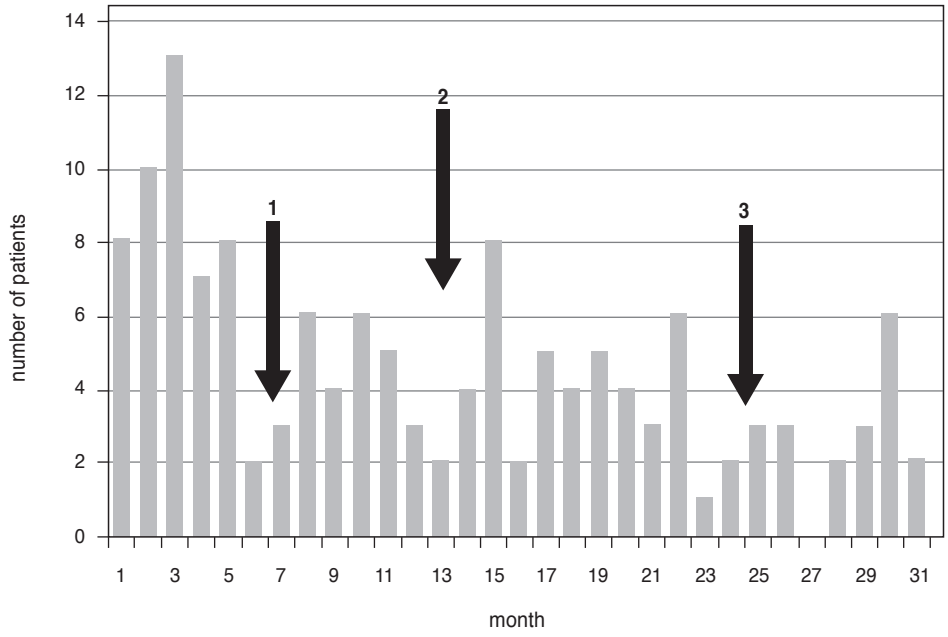

Figure 2. Number of patients recruited in one of the participating out-of-hours general practitioners practices and interventions to improve recruitment. Month 1: March 2006. Black arrows: intervention 1 (start bimonthly newsletter), intervention 2 (start incentive per included patient for general practice personnel), intervention 3 (increase in financial incentive given to general practitioners).

incentives, but more on the GP's motivation and the clinical relevance of the research topic, which is in line with the conclusions of others [6]. The fact that suspected ACS is considered by many GPs a major diagnostic challenge no doubt played a role in their willingness to participate. The importance of an appealing research topic and the relative ease by which diagnostic evidence can be implemented in daily primary care practice was also apparent from several other large diagnostic studies from our group, for example in suspected deep vein thrombosis [19,20].

Implementation of our findings in clinical practice

In the diagnostic study assessing the diagnostic accuracy of an H-FABP bedside test we also examined whether the test provides useful diagnostic information for the GP when it is used in combination with history taking and physical examination, following the natural hierarchy of diagnostic testing in clinical practice. We concluded that performance of the test can be useful in those patients in whom the risk of ACS is (very) low according to the GP, as an extra precaution not to miss ACS. Use of the test in all suspected ACS patients may lead to missed myocardial infarctions, assuming that GPs will tend to refrain from referring patients with a negative test result. The overall negative predictive value of the H-FABP bedside test used in our study is 84%, indicating that of those patients with a negative test, still 16% will suffer an ACS. In our view, this selected use of the test in low risk patients only should be cautiously conveyed to the GPs, since misuse of the 'myocardial infarction test' in all suspected ACS patients may be tempting. With the ongoing search for early and more sensitive biomarkers [21,22], and with the increased interest in point-of-care testing [23-25], it is to be expected that in the forthcoming years, new bedside tests for diagnosing ACS will become available that outperform the H-FABP bedside test used in our study. Also, it may be that alterations will be made in the cut-off value for a positive H-FABP test, leading to different predictive values. A lower cut-off value will lead to a better NPV (and higher sensitivity). Until that time however, safe and adequate diagnostic tools for the early diagnosis of ACS in primary care will remain scarce. It may therefore be helpful to examine if the use of the H-FABP bedside test influences decision making behaviour of GPs and if the use of a new diagnostic rule incorporating the result of an H-FABP test improves patient outcomes. Ideally, such a diagnostic impact study would involve GP group practices or out-of-hours services randomly allocated to either the use of the diagnostic rule with the bedside H-FABP test or usual care [26]. Another step towards successful implementation of a new diagnostic rule into clinical practice could be the strategy that we described in chapter 7, in which we directly compared the physician's judgment with our clinical decision rule for patients suspected of ACS (without the results of the H-FABP bedside test). The rationale behind this direct comparison was that physicians often perceive decision rules as a

reduction of their professional autonomy, arguing that their own clinical judgment is superior in individual cases [26]. Actually comparing results of a decision rule with the physician's judgment may be one way to convince physicians that sometimes a rule indeed outperforms their judgment [27].

Future research on point of care testing for ACS biomarkers

Promising biomarkers

There is an ongoing search for new biomarker candidates in the early detection of cardiac ischaemia. A recent study investigating the diagnostic performance of four new, sensitive cardiac troponin assays found promising results [21]. The study was conducted in patients suspected of ACS presenting to an emergency room within 12 hours after symptom onset (34% suffered ACS, half of these (17%) had acute myocardial infarction (AMI)). The negative predictive value in excluding AMI ranged from 95 to 100%, the positive predictive value ranged from 50 to 83%. Overall, the sensitive cardiac troponin assays showed a higher diagnostic accuracy, also in the early hours, than the standard troponin assay, as determined by receiver operating characteristic (ROC) curve analysis. If these sensitive cardiac troponin assays become available for testing in primary care, they could improve the early diagnosis of AMI. A major drawback however, for the use in primary care, is that the accuracy for detecting unstable angina with these sensitive assays was low to moderate (NPV ranged from 77 to 82%, PPV not provided). The authors state that further research is needed to identify biomarkers for the detection of myocardial ischaemia without necrosis.

Ischaemia modified albumin (IMA) is a biomarker that detects ischaemia without necrosis. IMA is increased within a few minutes after the onset of myocardial ischaemia and continues to increase for 6 to 12 h, suggesting that it could be used to detect myocardial ischaemia before it progresses to myocardial necrosis [28]. In a meta-analysis of 8 studies in 1812 patients suspected of ACS a negative IMA in combination with a negative troponin and an ECG without signs of ischaemia was 97% [22].

Also interesting is the development of biomarkers for the detection of inflammatory activity, such as C-reactive protein, serum amyloid A, myeloperoxidase or interleukin-6 [29]. The elevation of inflammatory markers may be a manifestation of the focal inflammatory process that takes place inside the coronary vessel when an atherosclerotic plaque becomes unstable. This would mean that even before the occurrence of actual myocardial damage, caused by the rupture of an unstable plaque, an ACS could be predicted and hence, possibly prevented.

Confirming or excluding ACS?

In primary care, a major diagnostic challenge for the GP is to balance the risk of missing a diagnosis of ACS against the risk of unnecessary hospital referral (and associated patient and health care burden) in patients without ACS. Clearly, there is a need to accurately and safely exclude ACS in suspected patients in the early hours (within 6 hours) after the onset of symptoms of ischaemia, to reduce the number of unnecessary hospital referrals. Important diagnostic characteristics of a biomarker for this purpose should be a high negative predictive value and high sensitivity for detecting myocardial necrosis (AMI) or even better, not just myocardial necrosis, but also myocardial ischaemia (unstable angina), for all patients suspected of ACS in a primary care setting.

Clinically relevant diagnostic research

Many diagnostic studies have been performed, and no doubt are currently underway, to address the diagnostic value of newly developed biomarkers in suspected ACS. Our overview of available point of care tests in the diagnosis of ACS and our meta-analysis on the diagnostic accuracy of H-FABP, clearly show that in many studies the clinical usefulness of the results are questionable, because studies were not performed in the relevant patient domain, but, for example in diagnosed AMI patients only, or in combination with healthy patients not even suspected of ACS. Moreover, research performed in the primary care setting was lacking. Furthermore, a multivariate analysis was hardly ever performed, and therefore, at present, information is lacking on the value of cardiac biomarker tests beyond the GP's clinical assessment (notably signs and symptoms) [1]. Introduction of the STARD (STAndard for Reporting of Diagnostic accuracy) initiative has led to some improvement in the quality of reporting diagnostic accuracy studies [30,31]. Hopefully, there will be increasing awareness amongst (primary care) researchers to target their diagnostic studies at providing answers to the diagnostic dilemmas of practicing GPs, performing studies at the relevant patient domain and quantifying the added value of a new test.

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CHAPTER 9

Summary

Samenvatting

In many European countries, patients with chest pain, or other symptoms suggestive of an acute coronary syndrome (ACS) will present to a general practitioner (GP) first. Patients with typical angina symptoms will be referred to hospital without delay, but there are many patients with vague, atypical complaints in whom the GP considers ACS unlikely to be the underlying diagnosis, but where the possibility of cardiac ischaemia cannot be completely ruled out with the diagnostic tools available in primary care, typically history taking and physical examination. In such patients, additional diagnostic tests, performed during the GP consultation, could be instrumental to reduce diagnostic uncertainty and support the GP in his or her management decision. The research described in this thesis focuses on the potential value of early cardiac biomarkers in the diagnosis of ACS in the primary care setting, with special attention for point-of-care tests.

The introduction of rapid point-of-care, or 'bedside', tests (performed by the GP and giving test results within 15 minutes) facilitates testing for cardiac biomarkers in primary care. An overview of the diagnostic accuracy of currently available point-of-care tests to detect four cardiac biomarkers (troponin, creatine kinase myocardial band (CK-MB), myoglobin and heart-type fatty acid-binding protein (H-FABP)) is given in **chapter 2**. A literature search of the PubMed database yielded 36 studies on a point-of-care test for one or more biomarkers. In 10 studies (1827 patients) results were presented or could be recalculated for early test results (measurement within 6 hours of the start of symptoms). Point-of-care tests for troponin, CK-MB and H-FABP performed moderate to good within the first 6 hours, but for none of the tests the negative predictive value (NPV) approached 100%, indicating that there were false negative test results (and hence missed ACS patients). Myoglobin had a moderate diagnostic value as a single marker and should only be used in combination with troponin, CK-MB or H-FABP. The ideal point-of-care test for the early diagnosis of ACS clearly does not yet exist.

Since H-FABP is one of the earliest biomarkers to be detected, with increased blood levels as soon as one hour after the onset of symptoms, we further explored the diagnostic potential of this protein. A meta-analysis of 16 diagnostic studies (3709 patients) on H-FABP, is described in **chapter 3**. Studies including consecutive patients suspected of ACS were eligible for the meta-analysis. In the included studies, the prevalence of ACS ranged from 13 to 74%, male gender ranged from 49 to 84%, median age ranged from 64 to 76 years. The summary estimate, calculated using the bivariate random effects approach, was 84% (95% confidence interval (CI) 76-90%) for sensitivity and 84% (95%CI 76-89%) for specificity. Concluding, H-FABP did not fulfil the requirements needed for a safe and early diagnosis of ACS when it was tested as a stand-alone test.

Most previous studies on H-FABP have been performed as if H-FABP was used as a stand-alone diagnostic test for ruling in or ruling out ACS. A more clinically directed approach would be to investigate the added value of H-FABP when it is used in combination with findings from medical history taking, physical examination and, if available, ECG analysis. In **chapter 4** the design of a large diagnostic study on the value of a bedside test for H-FABP in the diagnosis of ACS in primary care is presented. To our knowledge, this study was the first to determine the additional diagnostic value of H-FABP in primary care. The results of this study are presented in **chapter 5**. Three out-of-hours general practitioner (GP) services and 9 GP group practices participated in the study. In 298 consecutive patients suspected of ACS by the GP the H-FABP bedside test (Cardiodetect©, cutoff 7 ng/ml) was performed within 24 hours after symptom onset (median 3.1, IQR 1.5-7.1). ACS was determined by an outcome panel in accordance with international guidelines and was present in 66 patients (22%). The overall PPV of H-FABP was 65% (95%CI 50-78) and the NPV was 84% (95%CI 80-88), sensitivity was 43% (95%CI 31-57) and specificity 94% (95%CI 89-97). Within 6 hours after symptom onset, PPV and NPV were 72% (95%CI 55-84) and 83% (95%CI 77-88) respectively. Multivariate analysis was used to determine the value of H-FABP beyond clinical findings. Adding H-FABP to a diagnostic model of signs and symptoms 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). Thus, the H-FABP bedside test did provide additional diagnostic certainty in combination with clinical findings. However, the test cannot be used to safely exclude ACS. We recommend use of the test to confirm ACS in patients who were otherwise not referred to hospital by the GP, since the test can be used as an extra precaution not to miss ACS.

Currently, there is little information on the time interval in which patients suspected of ACS are seen by the GP. The choice of which cardiac biomarker to use however, strongly depends on the time interval since the start of symptoms in which patients are seen by the physician. Some markers for instance, are only consistently elevated in blood after 6 to 9 hours of ischaemia. In **chapter 6** we studied time intervals and patient and doctor delays in 298 patients suspected of ACS, as well as gender differences in symptom presentation of ACS. Within our diagnostic study, time intervals were prospectively recorded by the GP, together with patient and symptom characteristics (age, sex, previous medical history, chest pain, radiation of chest pain, nausea/sweating). Median patient delay (defined as the time from onset of symptoms until call for help) was 132 minutes (interquartile range (IQR) 44-360 minutes). This was 108 (IQR 39-348) minutes in women and 180 (IQR 48-396) minutes in men (p=0.20). Median doctor delay (defined as time from call for help until GP consultation) was 33 (IQR 20-55) minutes in men and 45 (IQR 26-72) minutes in women (p=0.01). Women

reported radiation of chest pain more often than men (68% versus 57%). Presence of chest pain and nausea/sweating did not differ between men and women. Women diagnosed with ACS were older than men (mean 75 years versus 65 years, p<0.001). Thus, in patients suspected of ACS in primary care doctor delay was longer in women than in men, while presenting symptoms of ACS were similar, or even more typical, in women. When interpreting these results, it is important to bear in mind the modest number of patients included. The findings of especially the subgroup analysis in diagnosed ACS patients should therefore be viewed with caution and other studies performed in primary care should confirm these results.

In **chapter 7** we directly compared the diagnostic accuracy of a clinical decision rule (CDR) in suspected ACS with the risk estimates of the attending GP. GPs were asked to estimate the probability (0-100%) of the presence of ACS within our large diagnostic study comprising 298 suspected ACS patients. Comparing the area under the receiver operating curve of the GP estimate and the CDR revealed that the GP more adequately classified patients as ACS or no ACS than the CDR (AUC 0.75 (95%CI 0.68-0.82) and 0.66 (95%CI 0.58-0.73)) respectively. In a classification table for three predefined categories, that is, low, intermediate and high risk (<10%, 10 to 20% and >20%) there was a 51% concordance between the risk estimation of the GP and the decision rule. In the 49 patients judged as low risk by the GP, four patients (8.2%) suffered an ACS. These four patients with ACS were all identified by the decision rule as high risk. We therefore recommend the use of an externally validated CDR in patients that are considered at low risk for ACS (<10%) by the GP, since this will further reduce the amount of missed myocardial infarctions.

Finally, in **chapter 8** we discussed barriers for performing research in a primary care setting, using our large diagnostic study as an example. GPs will be more likely to take part in a research project when they are invited to participate by one of the practicing physicians of the research group (and not by a non-physician), when there is personal contact between the researcher and the GP and when the clinical relevance of the research question is high or the research topic has the special interest of the GP. We used several methods to stay in a regular contact with the GPs in participating centres and attracted new GP practices during the inclusion period to keep overall patient inclusion at a steady rate.

In the general discussion we furthermore addressed the implication of our findings for clinical practice and conclude that performance of the H-FABP bedside test can be useful in those patients in whom the risk of ACS is (very) low according to the GP, as an extra precaution not to miss ACS. Use of the test in all suspected ACS patients

may lead to missed myocardial infarctions, assuming that GPs will tend to refrain from referring patient with a negative test result. It is to be expected that in the forthcoming years, new bedside tests for new biomarkers for the diagnosis of ACS will become available that outperform the H-FABP bedside test used in our study. Until that time however, diagnostic tools for the early diagnosis of ACS in primary care will remain scarce. Future research into new promising biomarkers, such as high sensitive troponin assays, should focus on the value of a biomarker used in combination with currently available diagnostic tools and, to be of use for the GP, should also be investigated in primary care.

In veel Europese landen gaan patiënten met pijn op de borst, of andere klachten passend bij een acuut coronair syndroom (ACS), als eerste naar een huisarts. Sommige patiënten hebben klachten die zo typisch zijn voor ACS dat de huisarts hen direct per ambulance zal verwijzen naar het ziekenhuis. Er zijn echter ook patiënten bij wie de klachten meer atypisch, of 'vaag' zijn en bij wie de huisarts op grond van de anamnese en het lichamelijk onderzoek ACS weliswaar onwaarschijnlijk acht, maar bij wie niet geheel is uit te sluiten dat de klachten tóch veroorzaakt worden door cardiale ischemie. In deze gevallen zou het gebruik van een extra diagnostische test, die de huisarts tijdens het spreekuur of de visite kan verrichten, van grote waarde zijn. De diagnostische twijfel die nu vaak bestaat zou afnemen en de huisarts zou meer gesteund worden in zijn of haar beleid. De studies in dit proefschrift beschrijven de potentieel aanvullende waarde van vroege cardiale markers voor de diagnostiek van ACS in de eerste lijn en in het bijzonder het gebruik van sneltesten daarbij.

Sneltesten zijn eenvoudig uit te voeren door de huisarts en geven een testuitslag binnen enkele minuten tot een kwartier. Een sneltest maakt het dus mogelijk om ook in de huisartsenpraktijk een cardiale marker te meten. **Hoofdstuk 2** geeft een overzicht van de op dit moment beschikbare sneltesten voor vier cardiale markers (troponine, creatine kinase iso-enzym MB (CK-MB), myoglobine en cardiaal vetzuur bindend eiwit (H-FABP)). Een literatuurstudie van artikelen uit de PubMed database leverde 36 studies op waarin een sneltest voor één of meer cardiale markers werd onderzocht. Voor 10 studies (1827 patiënten) waren ook gegevens beschikbaar voor een vroege meting (binnen 6 uur na het ontstaan van de klachten) van de cardiale marker. Sneltesten voor troponine, CK-MB en H-FABP presteren matig tot goed in deze eerste 6 uur, maar de negatief voorspellende waarde (NVW) van de sneltesten benaderde nooit de 100%, wat betekent dat er fout-negatieve uitslagen zijn (en dus gemiste ACS patiënten). Myoglobine presteert slechts matig wanneer het als enige marker gebruikt wordt en zou alleen in combinatie met troponine, CK-MB en H-FABP gebruikt moeten worden. Het is duidelijk dat de ideale sneltest voor een cardiale marker voor de diagnostiek van ACS op dit moment nog niet bestaat.

Omdat H-FABP een van de vroegste cardiale markers is (één uur na het ontstaan van de klachten is er al een stijging meetbaar in het bloed) onderzochten wij de diagnostische eigenschappen van deze marker verder. **Hoofdstuk 3** beschrijft de resultaten van een meta-analyse van 16 diagnostische studies (3709 patiënten) over H-FABP. Alleen studies waarin opeenvolgende patiënten verdacht van ACS werden ingesloten kwamen in aanmerking voor de meta-analyse. In de verschillende studies varieerde de prevalentie van ACS van 13 tot 74%, was 49 tot 84% van de patiënten man en hadden patiënten een mediane leeftijd van 64 tot 76 jaar. Wij gebruikten

de bivariate random effects methode om een gemiddelde schatting te geven van de sensitiviteit en specificiteit van H-FABP. Deze waren respectievelijk 84% (95% betrouwbaarheidsinterval (BI) 76-90%) en 84% (95%BI 76-89%). Deze waarden zijn niet hoog genoeg om op een veilige manier ACS aan te tonen dan wel uit te sluiten en wij concluderen dan ook dat H-FABP alléén niet geschikt is om ACS te diagnosticeren.

Veel studies naar H-FABP onderzoeken de marker alsof deze als enige test gebruikt wordt voor het aantonen of uitsluiten van ACS. In de praktijk zal de test echter altijd als aanvulling gebruikt worden op andere diagnostische onderzoeken zoals anamnese, lichamelijk onderzoek en in sommige gevallen zelfs ECG-diagnostiek. Het zou meer overeenkomen met de klinische praktijk als de toegevoegde waarde van de test bepaald werd in combinatie met deze onderzoeken. In **hoofdstuk 4** wordt de studieopzet beschreven van een grote diagnostische studie naar de toegevoegde waarde van een H-FABP sneltest (Cardiodetect©, afkapwaarde voor een positieve test 7 ng/ml) voor de diagnose ACS in de huisartsenpraktijk. Voor zover wij weten is een dergelijke studie nooit eerder uitgevoerd in de huisartsenpraktijk. De resultaten van de studie worden gepresenteerd in **hoofdstuk 5**. In 3 huisartsenposten en 9 gezondheidscentra werden 298 opeenvolgende patiënten verdacht van ACS ingesloten door deelnemende huisartsen. Alle patiënten ondergingen binnen 24 uur na het ontstaan van hun klachten de H-FABP sneltest (mediaan 3,1 uur, interkwartiel range 1,5-1,7 uur) en nadien werden zij besproken in een consensusbijeenkomst waarin volgens internationale richtlijnen getoetst werd of er wel of niet sprake was van ACS op het moment van de testafname. 66 patiënten (22%) hadden een ACS. De positief voorspellende waarde (PVW) van de H-FABP sneltest was 65% (95%BI 50-78%) en de NVW was 84% (80-88%). Met een multivariabele analyse werd de toegevoegde waarde van de H-FABP test aan anamnese en lichamelijk onderzoek bepaald. Het diagnostische model met de H-FABP test had een groter oppervlak onder de receiver operating characteristic (ROC) curve dan het model dat alleen uit klinische items bestond (0,75; 95%BI 0,68-0,82 versus 0,66; 95%BI 0,58-0,73). Er is dus inderdaad een toegevoegde waarde voor het gebruik van de H-FABP sneltest in de diagnose van ACS in de eerste lijn. ACS uitsluiten op grond van een negatieve test is echter niet veilig. Wij raden aan de test alleen te gebruiken bij patiënten die niet verwezen worden naar het ziekenhuis, als een extra voorzorgsmaatregel om geen ACS te missen.

Er zijn nauwelijks gegevens uit de eerste lijn over de duur van de klachten bij mensen verdacht van ACS. Dit is echter wel van belang bij het meten van cardiale markers in de huisartsenpraktijk: sommige markers zijn pas 6 tot 9 uur na het ontstaan van de klachten meetbaar in het bloed en daarvóór niet bruikbaar. **Hoofdstuk 6** geeft de resultaten van een studie in de huisartsenpraktijk waarbij de tijdsintervallen

('delay') worden bekeken van het moment van ontstaan van klachten tot het eerste (telefonische) contact met de huisarts (patient delay) en vanaf dat moment tot het consult met de huisarts (doctor delay). Ook onderzochten wij in deze studie man-vrouw verschillen in de klachtenpresentatie van ACS. De gegevens werden verzameld binnen de grotere diagnostische studie. De huisarts registreerde de verschillende delay-tijden op het moment dat een patiënt ingesloten werd in de studie, tegelijk met enkele kenmerken van de patiënt en diens klachten (leeftijd, geslacht, medische voorgeschiedenis, aanwezigheid van pijn op de borst, uitstralende pijn, misselijkheid/zweten). De mediane 'patient delay' was 132 minuten (interkwartielrange (IKR) 44-360 minuten). Dit was 108 minuten (IKR 39-348 minuten) bij vrouwen en 180 minuten (IKR 48-396 minuten) bij mannen (p=0,20). Mediane 'doctor delay' was 33 minuten (IKR 20-55 minuten) bij mannen en 45 minuten (IKR 26-72 minuten) bij vrouwen (p=0,01). Vrouwen presenteren zich vaker met uitstralende pijn dan mannen (68% versus 57%). Er waren geen man-vrouw verschillen in klachten van pijn op de borst en misselijkheid/zweten. De vrouwen die een ACS hadden waren ouder dan de mannen met ACS (gemiddeld 75 versus 65 jaar, p<0,001). Concluderend is het 'doctor delay' bij vrouwen verdacht van ACS in de eerste lijn groter dan bij mannen. De klachten bij presentatie bij de huisarts zijn voor mannen en vrouwen gelijk, of zelfs meer typisch voor ACS bij vrouwen dan bijmannen. Een kanttekening bij deze studie is het bescheiden aantal patiënten, vooral in de subgroep van patiënten bij wie een ACS werd vastgesteld. Nieuwe studies uitgevoerd in de eerste lijn zijn daarom gewenst voor bevestiging van deze resultaten.

In **hoofdstuk 7** vergelijken wij de diagnostische eigenschappen van een klinische beslisregel voor patiënten verdacht van ACS met de kansschatting van de huisarts. De huisarts werd gevraagd een schatting te geven (0-100%)voor de aanwezigheid van ACS in 298 patiënten, op het moment dat ze werden ingesloten in onze grotere diagnostische studie. De oppervlakte onder de ROC curve was 0,75 (95%BI 0,68-0,82) voor de huisartsenschatting en 0,66 (0,58-0,73) voor de klinische beslisregel, waarbij de huisarts dus beter in staat blijkt een onderscheid te maken tussen patiënten met en zonder ACS. In 51% van de gevallen kwam de schatting van de huisarts overeen met de beslisregel: hiervoor zetten wij de huisartsenschatting uit tegen de beslisregel in een classificatietabel met vooraf vastgestelde groepen van laag, midden en hoog risico op ACS (<10%, 10-20% en >20%). Van de 49 patiënten met volgens de huisarts een laag risico op ACS, hadden vier patiënten (8,2%) in werkelijkheid wél een ACS. Deze vier patiënten werden allen door de beslisregel als hoog-risico herkend. Het gebruik van een extern gevalideerde klinische beslisregel zal waarschijnlijk leiden tot minder gemiste myocardinfarcten en kan met name nuttig zijn bij patiënten die door de huisarts als laag-risico worden ingeschat.

Tot slot worden in **hoofdstuk 8** de hindernissen bij het verrichten van onderzoek in de huisartsenpraktijk besproken, met als voorbeeld de diagnostische studie die wij verricht hebben. Huisartsen zullen sneller hun medewerking verlenen aan een studie wanneer zij door een collega-(huis)arts gevraagd worden, er persoonlijk contact is tussen de onderzoeker en de huisarts, de klinische relevantie van het onderzoek groot is en het onderwerp van de studie de deelnemende huisarts aanspreekt. Wij hebben op verschillende manieren geprobeerd om regelmatig contact te houden met deelnemende huisartsenposten en gezondheidscentra en hebben gedurende de uitvoering van de studie voortdurend nieuwe centra geworven om het tempo van patiënteninclusie constant te houden. Daarnaast bespreken wij in dit hoofdstuk de implicaties van onze onderzoeksresultaten voor de klinische praktijk. De H-FABP sneltest kan gebruikt worden bij die patiënten die volgens de huisarts een (zeer) laag risico hebben op het bestaan van ACS, als een extra voorzorgsmaatregel om geen ACS te missen. Wanneer de test gebruikt wordt in alle patiënten verdacht van ACS leidt dit mogelijk tot gemiste myocardinfarcten, omdat het waarschijnlijk is dat een huisarts een patiënt met een negatieve test minder snel zal verwijzen naar het ziekenhuis.

De komende jaren zullen er ongetwijfeld nieuwe sneltesten ontwikkeld worden die betere diagnostische prestaties leveren dan de H-FABP sneltest die gebruikt is in onze studie. Tot die tijd echter zijn er weinig diagnostische middelen die de huisarts kan inzetten voor het vaststellen of uitsluiten van ACS. Toekomstige studies naar nieuwe veelbelovende cardiale markers, zoals 'high sensitive' troponine, zouden expliciet moeten kijken naar de toegevoegde waarde van een dergelijke marker in combinatie met de op dit moment al beschikbare diagnostische onderzoeken. Daarnaast is het van belang dat ook in de huisartsenpraktijk wordt onderzocht wat de diagnostische waarde van deze nieuwe cardiale markers is. Vanwege de verschillen in patiëntpopulaties kunnen resultaten uit de tweedelijn niet zomaar doorgetrokken worden naar de eerste lijn.

Dankwoord

Curriculum vitae

Mijn eerste dank gaat uit naar u, voor het lezen van mijn proefschrift. En u bent als ik: als eerste leest u het dankwoord! Toch hoop ik dat ik u ook kan verleiden tot het lezen van de andere hoofdstukken van mijn proefschrift, waarin een aantal mooie studies beschreven staan. Of leest u in elk geval hoofdstuk 9, de samenvatting, die ik voor uw gemak in het Nederlands geschreven heb.

Het begin van dit proefschrift was in 2004: Onno van der Spoel, huisarts in Wijk bij Duurstede, zocht contact met het Julius Centrum om een nieuwe biomarker voor hartschade te onderzoeken, heart-type fatty acid-binding protein (H-FABP). Prof. dr. Arno Hoes, hoogleraar Klinische epidemiologie en Huisartsgeneeskunde, werd de leider van het project, waarin een H-FABP sneltest in de huisartsenpraktijk zou worden onderzocht. Hij werd mijn promotor. Prof. dr. Jan Glatz, hoogleraar Metabole aspecten van hart- en vaatziekten bij het Cardiovascular Research Institute Maastricht (CARIM), ontdekte in de jaren tachtig het H-FABP eiwit. Hij werd mijn tweede promotor. Dr. Geert van der Heijden, universitair hoofddocent en klinisch epidemioloog en Dr. Frans Rutten, onderzoeker en huisarts te Rhenen, werden mijn co-promotoren.

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Tot slot: u hebt aan het begin van dit proefschrift kunnen lezen dat het tot stand gekomen is dankzij enkele sponsors, maar de hoofdsponsor werd daarbij nog niet genoemd. De BV is uitgegroeid tot een multinational met vestigingen in Nederland, Noorwegen en Frankrijk en een tijdelijk kantoor in Oostenrijk. De afgelopen jaren is het personeelsbestand bijna verdubbeld en werd besloten ook niet-roodharige 'werknemers' toe te laten. De BV levert materiële ondersteuning, maar nog veel belangrijker: zij voorziet in onvoorwaardelijke liefde, acceptatie en grenzeloos vertrouwen. Pap, mam, Karsten, Katarina, Peer en Birk: daarom gaan mijn laatste woorden van dank uit naar jullie.

Madeleine

Madeleine Bruins Slot was born on leap day, February 29th, 1980 in Hengelo (O). In 1998 she obtained her gymnasium diploma at the Baudartius College in Zutphen and started her medical training at the University of Groningen. As a student, she was involved in several research projects with varying subjects (ranging from sedation of children in diagnostic procedures (supervisor professor J.M.K.H. Wierda, department of anesthesiology) to carcinoid tumours (supervisors professor E.G.E. de Vries and dr. A.N.M. Wymenga, department of internal medicine)). Additionally, she followed electives in law and philosophy. For her doctoral thesis she worked 3 months in the Toronto General Hospital under supervision of professor F. Wong, and 3 months in the University Medical Center of Groningen, under supervision of professor C.H. Gips, both from the department of internal medicine.

After her graduation in 2004 she worked as a resident at the department of Internal Medicine in Deventer Hospital. In 2006 she started her vocational training at the department of General Practice in Utrecht, as well as the doctoral research described in this thesis, which she performed at the Julius Center for Health Sciences and Primary Care under supervision of professor A.W. Hoes, professor J.F.C. Glatz (Maastricht University), dr. G.J.M.G. van der Heijden and dr. F.H. Rutten.

At present, she is in her third and final year of vocational training. She is board member of the Dutch association of General Practice Trainees (LOVAH) and a delegate in the body of members of the Dutch College of General Practitioners (NHG Verenigingsraad). She is involved in the revision of the Dutch general practice guideline (NHG-standaard) on acute coronary syndrome and angina pectoris.