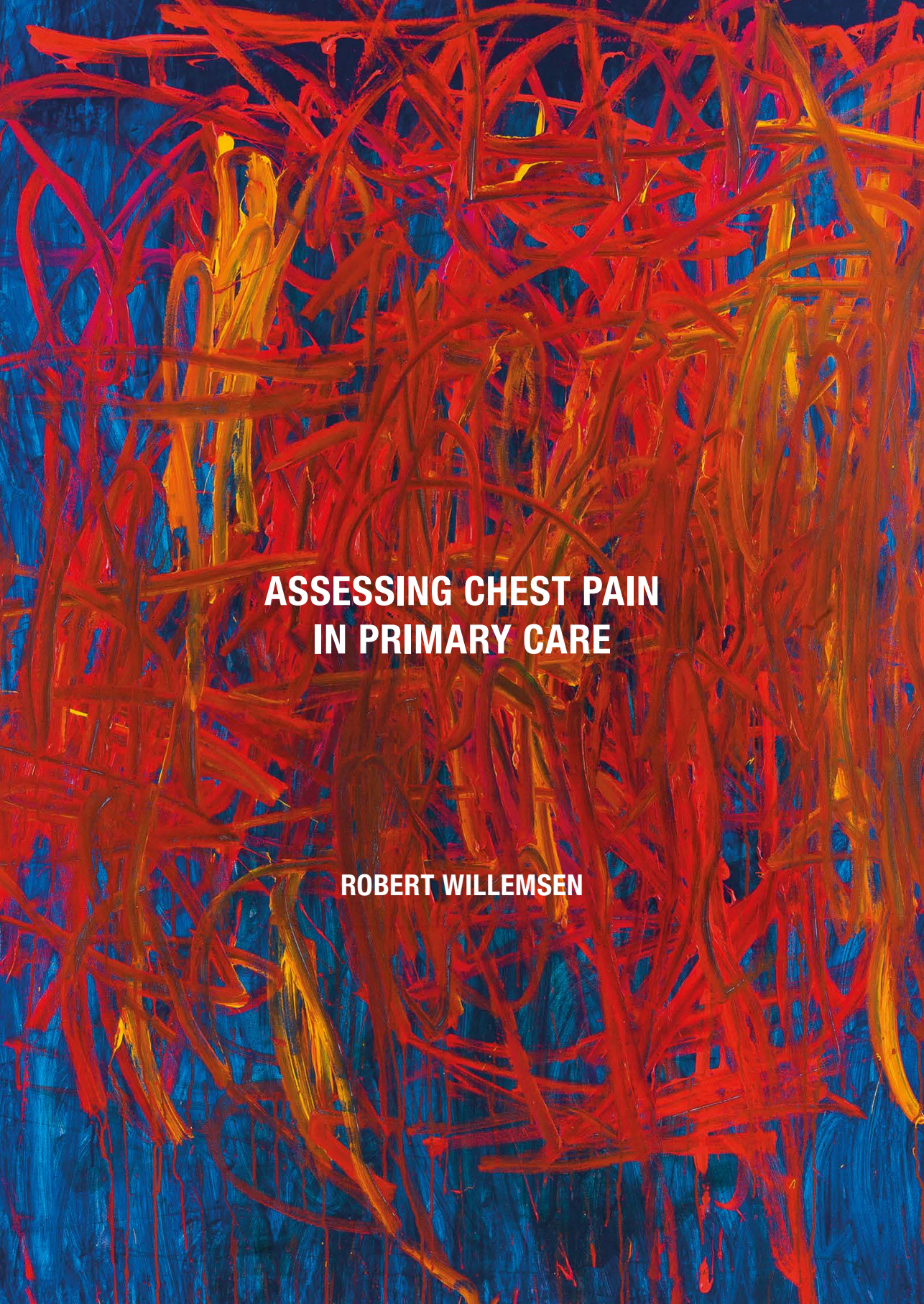

ASSESSING CHEST PAIN IN PRIMARY CARE

ROBERT WILLEMSEN

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Promotores:
Prof. dr. G.J. Dinant
Prof. dr. F. Buntinx
Prof. dr. J.F.C. Glatz

Beoordelingscommissie:
Prof. dr. J.A. Knottnerus (voorzitter)
Dr. A. van den Bruel (University of Oxford, United Kingdom)
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Dr. S.J.R. Meex

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abbrevia-tions

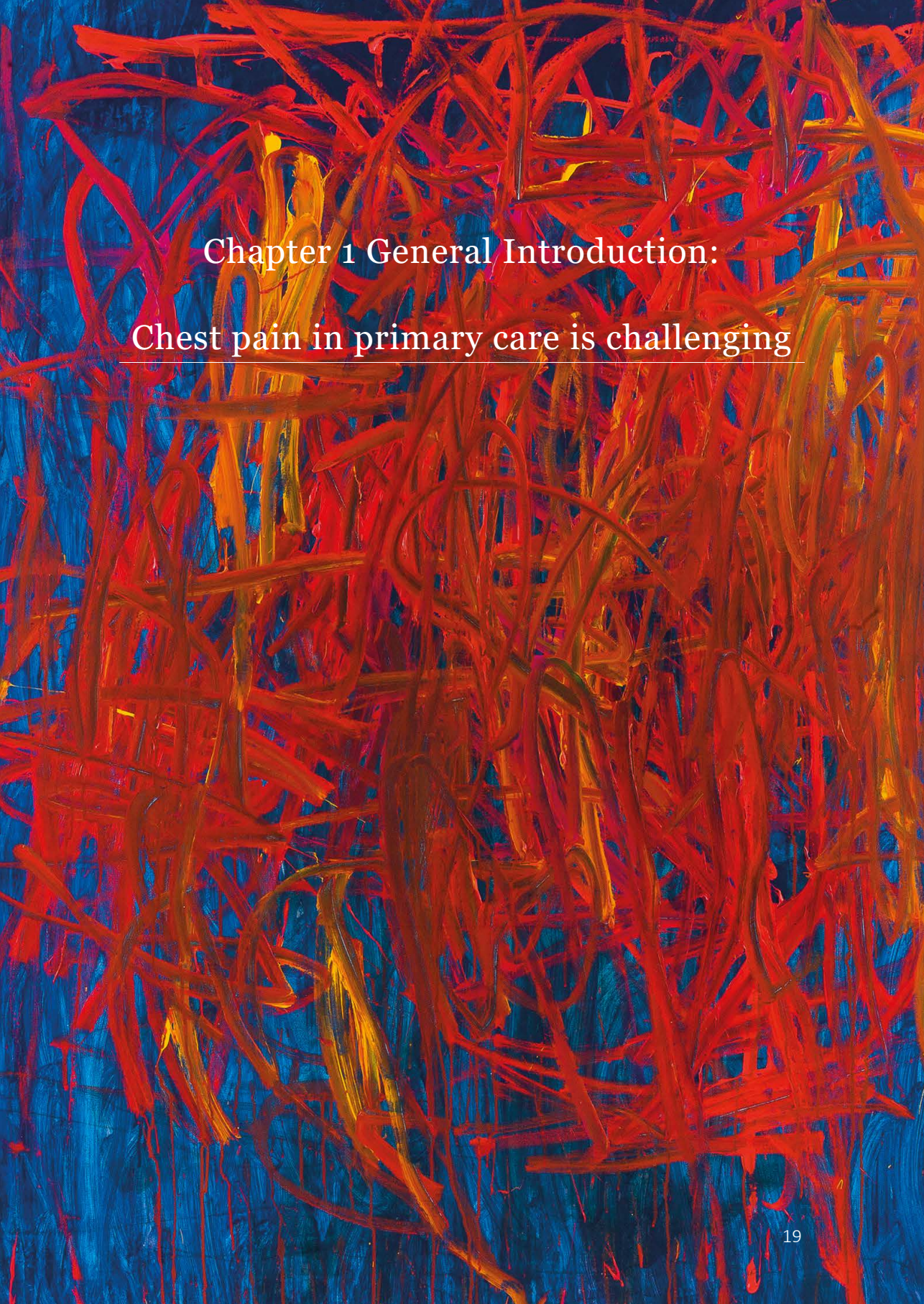
Abbreviations

95%CI	95% confidence interval
ACS	acute coronary syndrome
AMI	acute myocardial infarction
AUC	area under (receiver operating characteristic (ROC)) curve
B	Belgium
BMI	body mass index
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CAG	coronary angiography
CAN	Canada
CCTA	cardiac CT angiography
CCU	coronary care unit
CDR	clinical decision rule
CE	European conformity quality mark
CHD	coronary heart disease
CI	confidence interval
CK	creatine kinase
CK-MB	creatine kinase MB
CMP	cardiomyopathy
CMR	continuous registration of morbidity
COPD	chronic obstructive pulmonary disease
CRF	case report form
CRP	c-reactive protein
cTn	cardiac-specific troponin
cTnI	cardiac-specific troponin I
cTnT	cardiac-specific troponin T
CH	Switzerland
CV	coefficient of variance
CVD	cardiovascular disease
D	Germany
DM2	type 2 diabetes mellitus
dpt	department
DV	discriminator value
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EP	expert panel
ER	emergency room

ESC	European Society of Cardiology
FN(s)	false negative(s)
FP(s)	false positive(s)
FR	full range
GERD	gastro-esophageal reflux disease
gi	gastro-intestinal ICPC-diagnosis
GP	general practitioner
h	hour(s)
H-FABP	heart-type fatty acid-binding protein
HOCM	hypertrophic obstructive cardiomyopathy
hs-cTn	high-sensitive cardiac-specific troponin
hs-cTnI	high-sensitive cardiac-specific troponin I
hs-cTnT	high-sensitive cardiac-specific troponin T
IC	Iceland
ICPC	international classification of primary care
ICS	inhaled corticosteroid
IQR	interquartile range
LAB	laboratory
LABA	long acting β-2 agonist
LOD	limit of detection
MACE	major adverse cardiac event
MHS	Marburg Heart Score
MI	myocardial infarction
min	minute(s)
ml	mililiters
mnm	minimum
mxm	maximum
MYO	myoglobin
n / N	number
NL	the Netherlands
NPV	negative predictive value
NR	not reported
NS	non significant
NSTEMI	non ST-Elevated Myocardial Infarction
NT-proBNP	N-terminal B-type natriuretic peptide
OOH-service	primary care out of hours service
PAC	premature atrial contraction
PoC(T)	point of care test
PPV	positive predictive value
PSA	probabilistic sensitivity analysis
psychol	psychological ICP- diagnosis

pat	patients
pt	point
PVC	premature ventricular contraction
RAPIDA	RAPid test for Investigating complaints possibly Due to Acute coronary syndrome
RCA	right coronary artery
resp	respiratory ICPC-diagnosis
ref	referral
RfE	reason for encounter
ROC	receiver operating characteristic
RUO	research use only
S	significant
one- / two way SA	one- / two-way sensitivity analysis
SA(P)	stable angina (pectoris)
sens	sensitivity
spec	specificity
SPECT	single-photon emission computed tomography
SST2	soluble suppression of tumorigenicity 2
STEMI	ST-elevated myocardial infarction
SVT	supraventricular tachycardia
SW	Sweden
TN(s)	true negative(s)
TP(s)	true positive(s)
UA(P)	unstable angina (pectoris)
UK	United Kingdom
US	United States of America
YRS	years

1



Chapter 1 General Introduction:

Chest pain in primary care is challenging

1.1 The general practitioner as a 'diagnostic instrument'

General practitioner (GP) residents are taught to ask themselves '*why*, is *this patient* coming *to me* at *this moment*'. It's one useful strategy to find out what is really bothering the patient. It might turn out not to be the back pain, but the conflict with the chief at work or the worries about an adolescent child. However, on a (rare) moment of weakness, in the middle of the winter's viral epidemic and on one of these days the waiting room lacks sufficient seating capacity, a GP might tend to rephrase the question into: 'why are *all these* patients with a viral nose obstruction coming to me at this moment'. Still, GPs rarely complain about this issue, humbled by the experience of the challenging epidemiology of their work. Since after all, although patients in primary care mostly have self limiting mild diseases, pulmonary embolism might come disguised as one of those flu patients and the tenth patient in a row presenting with abdominal pain, might be suffering from a leaking abdominal aneurysm.

Exploring patient and family context, as well as distinguishing mild from severe diseases are a GP's 'core business'. A GP is a diagnostic instrument that integrates history, physical examination, intuition, gut feeling, knowledge of patient context, and experience to interpret signs and symptoms beyond the standard clinical picture as explained in textbooks.[1-6] Positioned in a field where (severe) disease is frequently absent and possibly life threatening disease can be in an early - not directly alarming - stage, a high accuracy is demanded.[7] In general, a GP differentiates between severe and mild disease with high accuracy, safely guarding the gate of healthcare and thereby increasing patient comfort and decreasing health costs.[8-12] Thus, a GP plays an important role in reassuring patients if possible and referring or treating them if necessary.

Whereas in secondary care, diagnostic tests are part of larger workups and protocols, in primary care the GP often is the sole instrument, making his or her task challenging. However, a GP is vulnerable as well, since misjudgment is usually closer to a feeling of personal failure than of test failure. Mostly, a GP judges a case of disease as positive (true positive (TP) result) while the absence of disease is judged as negative (true negative (TN)result). Still, a diagnostic instrument without a certain failure rate is nonexistent.[13] In medicine, missing a case (a false negative (FN) result) can lead to undertreatment. On the other hand, suspecting severe disease in cases of mild or absent disease (a false positive (FP) result) can lead to patient discomfort, exposure to unnecessary tests and high healthcare costs. The performance of a test, expressed in TP, TN, FP and FN tests is best visualised in a classic two-by-two table (see table 1.1). Calculations to measure diagnostic performance (sensitivity, specificity, positive and negative predictive value (PPV and NPV, respectively)) are explained in the legend of table 1.1.

Table 1.1: Classic two-by-two table in diagnostic clinical reasoning

	Disease + (total = A + C)	Disease - (total = B + D)
Test + (total = A + B)	True positive test results = A	False positive test results = B
Test - (total = C + D)	False negative test results = C	True negative test results = D

Several calculations usually further illustrate a test's capacity. **Test sensitivity** is defined as the probability of a positive test result in case the index disease is present. It's calculated by assessing the proportion of TP test result among all cases where disease is present (A / (A +C) in table 1.1). The higher the sensitivity, the lower is the proportion of FN test results. **Test specificity** is defined as the probability of a negative test result in case the index disease is absent. It is calculated by assessing the proportion of TN test result among all cases where disease is absent (D / (B +D) in table 1.1). The higher the specificity, the lower is the proportion of FP test results. Since usually a test result, rather than the presence of disease, is the point of departure, the **positive and negative predictive values** (PPV and NPV) are of added value. These are defined as the probability of disease in cases of a positive test result (PPV, A / (A + B) in table 1.1) and the probability of the absence of disease in cases of negative test results (D / (C + D) in table 1.1). A large proportion of true positive results is associated with high sensitivity and high PPV, whereas a high proportion of true negative test result leads to high specificity and high NPV.

1.2 Chest pain

In daily practice, one of the reasons for encountering a GP that places the highest burden on a GP's diagnostic efficiency, is chest pain.[14] From the point where the underlying cause is identified, treatment is clearly defined.[15-19] However, until the cause is diagnosed, a wide variety of mild and severe diseases can be considered in the differential diagnosis.[20,21] Throughout the years, GPs have learned to work with low thresholds for referring chest pain patients to an emergency cardiology department. In literature, referral rates up to 73% are described.[22] This 'better safe than sorry' strategy is the only way of safely dealing with the fact that among a majority of chest pain patients with mild underlying disease (78-98.5%), a number of patients suffer from acute myocardial infarction (AMI) or other life threatening conditions such as pulmonary embolism or thoracic aortic aneurysm, that would require immediate treatment (1.5-22%).[22-26] By referring a high number of these patients, false negativity rate (or rate of 'missed cases') is low.[27] However, a significant number of patients undergo stressful and expensive examinations in secondary care facilities, whereas the final diagnosis frequently is reassuring the patient (e.g. 'chest wall complaints' or 'esophageal reflux disease').[28-30]

1.3 Diagnostic means

In chest pain patients, history, physical examination and assessing patient context - the basic tools of GPs - lack sufficient specificity to guarantee a low number of false positive results, leading to a high referral rate in primary care.[31-35] Ruling out ACS by means of a negative ECG is hampered by an insufficient negative predictive value of the ECG for

AMI.[36,37] Measurement of biomarkers of myocardial injury in venous blood is the cornerstone of AMI diagnosing in secondary care (**figure 1.1**).[16] Such cardiac markers are sometimes available for measurement already in primary care, but not directly at the point of care. Therefore, transport of a blood sample and measurement of this sample in external laboratory facilities are necessary and results are available only one to three hours after first assessment by the GP. This strategy is unsafe in case of any suspicion of AMI.

Decision rules such as the HEART-score (History, ECG, Age, Risk factors, Troponin) and GRACE-score (Global Registry of Acute Coronary Events), integrating several diagnostic instruments, cannot rule out AMI in primary care.[38] Validation in primary care is lacking and both scores are partly based on biomarker measurements not directly available in primary care. Although promising, implementation of the Marburg Heart Score (MHS) is hampered by a lack of validation.[39] Moreover, original data are compromised by an unclear distinction between stable and unstable complaints and final diagnoses were not determined with gold standard diagnostic strategies. Imaging techniques (e.g. coronary angiography, coronary artery CT, ultrasound) are not (directly) performed in primary care.

Criteria myocardial infarction

A Clinical signs of myocardial infarction:
- appropriate signs and symptoms, and/or
- appropriate ECG abnormalities, and/or
- proof of loss of contractile myocardial tissue on imaging, and/or
- an intraluminal thrombus upon coronary angiography



B Furthermore, a plasma biomarker - preferably troponin - must be elevated above the 99th percentile of a normal reference population (for hs-cTnT: >14 ng/L). This elevation is measured at least once from two samples taken at least 3 hours apart. A rise or fall of troponin must be observed between measurements.

Figure 1.1: Third universal definition of myocardial infarction[16]

In cases of ST-elevation (as reflected in the ECG-detail), an (ST-elevated) myocardial infarction (STEMI) is clearly present. In absence of ST-elevations, presence or absence of a non-ST-elevated myocardial infarction (NSTEMI) is assessed using the other criteria outlined above.

To summarize, diagnostic means available in primary care are useful only when utilized with low thresholds for referral , thereby losing specificity. Diagnostic means that can be seen as elementary steps in ruling in and ruling out AMI (biomarker measurement, (non)invasive imaging techniques) are currently safely applicable only in secondary care facilities (**figure 1.2**).

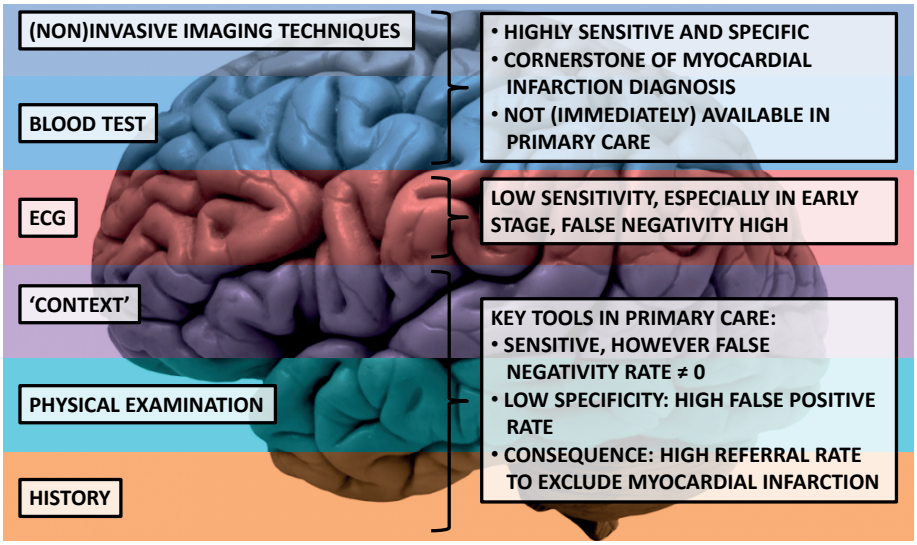


Figure 1.2: Diagnostic instruments concerning chest pain in primary care

The physician's brain is aided by several diagnostic instruments to rule in or rule out acute myocardial infarction (AMI). Those available in primary care are insufficient to safely rule out AMI. The gold standard for diagnosing and excluding AMI (biochemical approach and imaging techniques) are not available without an unacceptable delay, or not available at all in primary care.

1.4 Biomarkers

In cases of myocardial cell damage, cell contents, including proteins usually exclusively present within the myocardial cell, are released into the circulation. These proteins therefore are useful as indicators - or 'biomarkers' - of myocardial cell damage. Cardiac troponin, nowadays usually 'high sensitive cardiac troponin' (hs-cTn), is the most frequently used biomarker in this context. An elevated hs-cTn value, i.e. above the 99th percentile of a normal reference population, is a strong indicator of myocardial injury and has a very low false-positivity for myocardial cell damage. However, myocardial cell damage is not exclusively caused by coronary ischemic events ('acute coronary syndromes' (ACS), such as AMI). Severe pneumonia, myocarditis, pulmonary embolism, etcetera, can lead to a certain degree of myocardial cell damage - and thus hs-cTn release into the circulation - as well. Therefore, hs-cTn is highly specific for myocardial cell damage, and slightly less specific for ischemia caused by coronary artery obstruction.

For the purpose of early rule out of ACS in primary care, when symptoms are often less typical and mild, biomarkers that are released into the circulation in this early stage are needed. The NPV of modern hs-cTn tests is as high as 98-99%.[19] Early rule out of myocardial infarction in secondary care is becoming more and more achievable with hs-cTn.[40-42] In primary care, the role of hs-cTn remains unclear. Existing literature on tro-

ponin in primary care is scarce and performed with older, less accurate, troponin tests.[43] Point-of-care (PoC) devices based on *high sensitive* cTn are not available yet. Therefore, other biomarkers with a quick release pattern after onset of myocardial injury, and available in a PoC device, are interesting as well. In this light, heart-type fatty acid binding protein (H-FABP) is an interesting biomarker of myocardial cell injury.[44,45]

1.5 Aim of this thesis

In brief, the main theme of this thesis is the GP's diagnostic approach of chest pain. The principal questions of this thesis were:

1. How are diagnostic dilemmas expressed in daily practice?
2. What are the quantitative aspects (incidence, number of tests performed, referral rate, working and final diagnoses) of chest pain in primary care?
3. What are the qualitative aspects (GPs' perception of possible alterations in chest pain presentation, GPs' considerations when assessing patients, GPs' habits in dealing with uncertainty) of chest pain in primary care?
4. What cost reduction is achievable in the diagnostic approach of chest pain in primary care, after the introduction of future diagnostic tools?
5. What is the optimal cut-off value for a point-of-care (PoC) Heart-type fatty acid binding protein (H-FABP) test in patients presenting with chest pain?
6. How does a PoC H-FABP test with a low cut-off value perform in chest pain patients in primary care?
7. What signs and symptoms - besides H-FABP testing - are of added value to assess patients with chest pain in primary care?

Several aspects and developments in the GP's diagnostic approach of chest pain are addressed in the chapters of this thesis. In chapters 2 and 3, main question 1 is elaborated. The clinical perspective is exemplified by means of four cases. Several diagnostic problems are illustrated and contemporary difficulties in chest pain assessment in primary care are determined. In chapters 4 and 5 quantitative and qualitative aspects of chest pain in primary care are described (regarding main questions 2 and 3, respectively). Incidence, referral rates, diagnostic means used by GPs and cardiologists, final diagnoses, trends and GP perceptions are explored. In chapter 6, main question 4 is addressed. Estimations are presented on future cost reduction if referral rate of chest pain patients is safely reduced by usage of efficient diagnostic instruments.

From chapter 7 onwards, focus is on improvement of triage of chest pain patients by GPs. Main questions 5, 6 and 7 are elaborated. As explained earlier in this introduction, biomarkers play a key-role in ruling in and out myocardial infarction. Besides, development of point of care (PoC) techniques to measure blood markers directly during the

assessment of a patient are promising.[46,47] Therefore, it is expected that enhancement of diagnostic strategies by GPs should be accomplished by availability of reliable PoC devices measuring biomarkers of myocardial cell damage. In chapters 7 and 8, the background, optimal cut-off value and future clinical perspectives of such a biomarker, Heart-type fatty acid binding protein (H-FABP), are outlined. H-FABP is a biomarker detectable early after onset of myocardial injury.[44] H-FABP is available in a sensitive PoC device, enabling usage in primary care. In the main study, specified in chapters 9 and 10, this device is tested in a primary care population of patients with chest pain. Diagnostic parameters of the device are assessed and useful signs and symptoms to improve triage of chest pain patients are derived. In chapter 11, the general discussion, all findings are put into a future perspective for clinicians and researchers.

1.6 References

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2

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'Twijfelen aan diagnose is goed'

Robert TA Willemsen, Erik CF Stolper, Yvonne van Leeuwen

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Chapter 2 A case from the heart:

Doubt and diagnosis go together

2.1 Introduction

A 44-year old, non-smoking male is working in construction and performs endurance sports. He trains on a regular basis with his friends on a mountain bike. In 2004, a pulmonologist had diagnosed him with exercise-induced asthma. For a short time, inhalation medication was prescribed. No other disease is reported in his medical history. The patient appears healthy and rarely visits his general practitioner (GP).

In August 2011, the patient visits his GP for regular coughing and production of green sputum. These complaints have been present during the last 1.5 years. He is short of breath during exercise and describes the feeling “his airways are never really open”. The GP considers worsening of his exercise-induced asthma as a possible explanation. Spirometry and chest X-ray are performed; both tests are without abnormalities. On August 31st, results are reported to the patient. On the same day, the patient tells the GP that his chest complaints are painful. He is afraid of "getting a heart attack", especially while cycling at the front of his cycling group, which is physically more demanding.

2.2 Pain in the lungs

The working diagnosis of exercise-induced asthma is maintained. The combination of fluticasone with salmeterol, an inhaled corticosteroid (ICS) combined with a long acting beta-receptor agonist (LABA) is prescribed. On September 22nd, the patient reports that his shortness of breath has decreased after starting the medication. On October 4th, however, he reports an increase of sputum and pain in the lungs during a telephone discussion with his GP. A pulmonologist is subsequently consulted that month. Asthma is diagnosed. The patient’s history is consistent with this diagnosis and spirometry reveals a light degree of pulmonary obstruction. Upon provocation testing with histamine, bronchial hyperreactivity is found. The patient reports a reduction in symptoms when using his fluticasone/salmeterol, however now reports pharyngeal pain. The pulmonologist substitutes his medication for another ICS-LABA containing formoterol/beclometasone. Nystatin, an oral antimycotic agent, is also prescribed to treat a suspected oropharyngeal mycotic infection due to the ICS.

On November 23rd, the formoterol/beclometasone is stopped due to persisting pain in the throat and hoarseness. Treatment with nystatin is repeated. The patient's throat complaints improve significantly, and salmeterol without an ICS is restarted. At the end of December, the patient visits the GP once more with complaints of a feeling of pressure on the chest during exercise and recurrence of throat complaints. Advice for training with exercise-induced asthma is given, and a referral is provided for consultation with an ear, nose and throat physician.

In January, the patient collapses during mountain biking. Basic and advanced life support efforts are futile. Upon autopsy, a hypertrophic obstructive cardiomyopathy (HOCM) is found, as well as an atherosclerotic and 90% stenosed left anterior descending coronary artery (LAD). No infarction is found in the myocardial tissue. Ventricular fibrillation in the ischemic and pathologically reshaped left ventricle is the assumed cause of death. In retrospect, a symptomatic LAD stenosis as well as left ventricular outflow tract obstruction due to HOCM, seem to have resulted in the clinical picture of dyspnea and chest and throat pain in the four months before death occurred. The original diagnosis of exercise-induced asthma seems to have contributed to a minor extent only.

2.3 Diagnostic process

Ten to fifteen percent of our diagnoses are estimated to be incorrect.[1] Most of these errors are corrected in time. However, errors that are not rectified may lead to serious consequences, such as those described in this case. The attending GP has asked the authors to write a report of this case in order to offer colleagues an opportunity to learn. In the remainder of this article, we will formulate several learning points. First however, we will outline some characteristics of the diagnostic process.

A GP's main source of information is the patient's history, which is considered to be more important than physical examination.[2] Diagnostic processes are chiefly guided by analytical thinking and rely on classical lists of symptoms. However, this routine is sometimes troubled by variable or early presentations of diseases that are not in accordance with typical descriptions in textbooks.[3] Additionally, analytical thinking processes are often curtailed by recognition of disease patterns, termed 'scripts', that are consistent with the patient's set of symptoms.[4] Recognition of these scripts increases efficiency, however, as scripts lead to shortcuts in diagnostic reasoning, diagnostic errors occasionally result.

There are additional indicators beyond analytical assessment that are valuable for patient diagnosis, and should also be considered by the physician. For example, gut feelings can be of significant value, and are used by physicians to aid diagnosis.[5] A GP's as well as parents' gut feelings are important predictors for a severe course of infectious diseases in childhood: gut feelings were demonstrated to be equally predictive as classical alarm signs such as drowsiness and tachypnea in diagnosing serious infections.[6] GPs also incorporate patient context in their diagnostic reasoning by increasing their knowledge of patients' social environments and psychological state.[7] Furthermore, diagnostic mistakes in the past influence a GPs' decision making. Finally, doctor-patient interaction also influences diagnostic processes, as a sound doctor-patient relationship contributes to timely recognition of signs and symptoms.[8]

2.4 Preventing errors

Although the diagnostic process has been reasonably well investigated in the past, measures to prevent diagnostic errors have proved to be only modestly successful.[1,9] In 2012, prevention of medical errors was addressed in a paper by Klein and Van de Meerendonk. The central theme was the prevention of fast and incorrect script recognition.[10] The authors presented a checklist to avoid several mistakes in diagnostic thinking, including bias, that leads to misdiagnosis. In application to this case study, the list is helpful to identify the factors that contributed to the GP exclusively interpreting the patient's symptoms as pulmonary. In this case, a final conclusion was drawn too fast and the GP did not consider new pertinent information that could have led to re-examining the working diagnosis. Further investigation by a specialist and the patient's temporary relief from medication supported the misdiagnosis. The GP demonstrated what is known as 'confirmation bias', where information that confirms the hypothesis is received and other information that is equally valid is not given the same consideration. Whether usage of the checklist of bias by Klein and Van de Meerendonk reduces clinical mistakes, has not been studied yet. The checklist may be useful for preventing clinical mistakes, however its usage during all diagnostic reasoning is impracticable. The list should be referred to in cases of doubt about a patient's diagnosis. However, it is important to be noted that it is the *absence* of doubt that usually contributes to adhering to an incorrect working diagnosis.

2.5 A sportsman

After conversation with the GP in this case, several conclusions can be drawn in respect to his diagnostic reasoning. First, the GP adhered to the assumed pattern of asthma. As a consequence, cardiac causes were not considered, despite complaints of pain in the chest and throat. The GP didn't question the diagnosis since the focus remained on the patient's coughing and sputum production, the pulmonologist's findings were in agreement, and the patient's symptoms were relieved from medication. Second, the GP regarded this patient as a healthy sportsman, suffering from no more than 'a little asthma'. Afterwards, the GP remembered to think at one moment during a consultation of this patient: "If I didn't know better, I would assume this patient has a cardiac disease". Third, after speaking to the patient's family, this patient's profile was that of a man, reluctant to speak his thoughts. Thus, he may not have communicated the extent of his physical distress to the GP. The GP recognised this phenomenon in his own personality as well. In the contact with this particular patient, space for expressions of distress and discourse of (perception of) complaints was probably insufficient. The patient also seemed to copy the GP's pulmonary explanation, where initially he spoke of 'fear for a heart attack', but instead later described 'pain in the lungs'. Thus, a mutual understand-

ing of the patient's true symptoms and underlying thoughts may not have been clear between the patient and GP.

2.6 Admission of doubts

In retrospect, where could this erroneous diagnostic thinking have been turned? Several essential elements of diagnostic reasoning - e.g. ignoring the initially reported patient's fear of a heart attack - are part of an automatic and subconscious process. Therefore, recognition of these steps is not obvious. However, this case illustrates the fact that the consequences of faulty diagnostic reasoning may be easier to identify. For example, there was a high frequency of patient-GP contact over several months, there was only a modest result of pharmacotherapy and the clinical evolution was slow or absent. These clues did not fit the working hypothesis and could have been regarded as an indication for the GP to doubt the working diagnosis and re-examine the patient. On the one hand, noticing these signs is compromised by the tunnel vision that was present throughout this case. On the other hand, such consequences of a faulty diagnosis may be more easily recognisable than abstract erroneous thoughts as 'this sportsman is not a candidate for a heart attack'.

Looking back, the GP declared he did somehow notice the patient's ongoing help seeking behavior and the marginal results of the therapy. He felt somehow irritated by this and asked himself why the burden of the patient's complaints was so high, considering the diagnosis of exercise-induced asthma. Recognition of such elements not fitting the working diagnosis could have led the GP to reconsider the diagnosis. A certain degree of doubt can form a helpful diagnostic instrument, and allow consideration of alternative diagnoses. To help prevent misdiagnosis, 'diagnoses that definitely should not be missed' could be introduced in the differential diagnosis process, or a colleague could be consulted. The GP involved in this case summarised his thoughts as follows: "Before this incident, experience and certainty were synonymous to me. Now, experience rather equals the ability to give things a second thought."

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'Diagnosing Acute Coronary Syndrome: A Challenge for General Practitioners and Cardiologists'

Robert TA Willemsen, Bastiaan L Kietselaer, Ron Kusters, Frank Buntinx, Jan FC Glatz, Geert Jan Dinant

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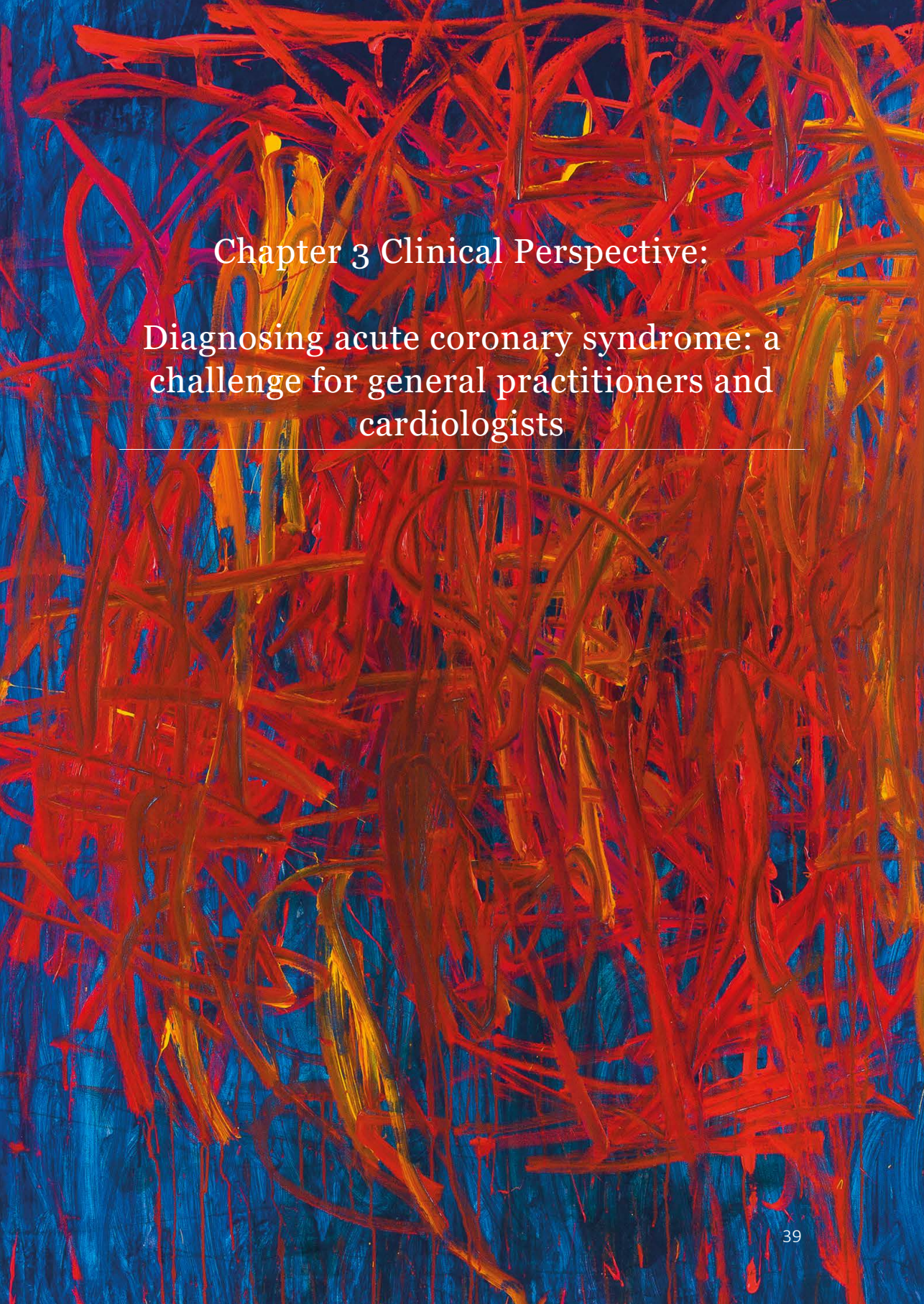

Chapter 3 Clinical Perspective:

Diagnosing acute coronary syndrome: a challenge for general practitioners and cardiologists

Abstract

Three patients present with chest pain to their general practitioner. In all three cases, the patient is suspected of acute coronary syndrome (ACS). In the first case, a coronary artery disease causing the complaints is ruled out since troponin levels remain within the normal range. In the second case, troponin is elevated due to non ST- elevated myocardial infarction. In the third case, troponin is elevated due to cardiac cell damage in severe pneumonia (i.e. cardiac damage is not caused by a coronary artery occlusion).

In cardiology, diagnostic tools for ruling ACS in or out are becoming increasingly sensitive. In general practice, diagnostic means to discriminate between ACS and less severe causes of chest complaints remain poor. Both situations challenge physicians working in their respective fields. Cardiologists must deal with a decrease in testing specificity due to the increasing analytical sensitivity of high-sensitivity troponin, and face the dilemma of whether or not to perform invasive coronary angiography in cases of doubt. General practitioners are still lacking adequate diagnostic tools. These difficulties are illustrated in three cases where patients' present chest complaints in primary care and are eventually referred to a cardiologist. Notwithstanding the presence of the aforementioned dilemmas, combining clinical reasoning with current definitions of ACS and myocardial infarction leads to an unambiguous diagnosis in all three cases.

3.1 Introduction

Patients presenting with new or altered chest pain remain a challenge to diagnose. Acute coronary syndrome (ACS) is a serious condition and one possible cause of the chest pain, but in a majority of cases, other less demanding causes are diagnosed. To distinguish between ACS and other causes is important for general practitioners (GPs) in order to correctly refer patients with ACS to a cardiologist and treat less severe causes in primary care. In secondary care, troponin tests are becoming more and more sensitive. Cardiac damage is therefore easier to detect, however, positive test results in marginal cardiac damage caused by conditions other than coronary artery disease are more common. Thus, interpreting elevated levels of high sensitive cardiac specific troponin (hs-cTn) can be difficult. Moreover, the gold standard test (coronary angiography – CAG) is not without risk. Possibly, non-invasive imaging techniques could play a role in these cases of doubt. In three case descriptions, we illustrate these dilemmas and in the discussion we eventually evaluate modern diagnostic tools in ACS.

3.2 Three cases

Patient A is a 53 years old male with a history of asthma and heavy smoking (35 pack-years). He consults his GP because of chest pain, a tense feeling in his left arm, shortness of breath, burping and fatigue. These complaints started five days before consultation. The chest pain is persistent but occasionally aggravates, for instance, during his work as a house painter. Vegetative symptoms are absent. Auscultation of the heart and lungs is normal. Blood pressure is 145/80 mmHg, pulse is 70/min and regular. The GP administers 300 mg of carbasalate calcium and immediately refers the patient to hospital due to suspected ACS. During the waiting period for the ambulance, an ECG is recorded in order to accelerate triage in case of an ST-elevated myocardial infarct (STEMI). However, this ECG reveals no abnormal findings.

Upon arrival at the coronary care unit (CCU), plasma high sensitive cardiac specific troponin T (hs-cTnT) is 9 ng/L (reference value <14 ng/L). Administration of sublingual nitroglycerine does not alleviate the patient's complaints. The complaints are considered as being typical for ACS and the patient is hospitalised. An exercise tolerance test does not reveal abnormalities. In view of the maintained low plasma hs-cTnT – the result is unchanged upon measurement 6 hours after the initial measurement – the complaints are regarded as not being of cardiac origin. Therefore, CAG is not performed. The patient’s complaints cease spontaneously and he is discharged. Within a week, he will visit his GP for primary prevention.

Patient B is a 54 year old male and visits his GP with complaints in both his left shoulder and left hand, accompanied by nocturnal tingling. These complaints have persisted for

three weeks. He has suffered from shoulder complaints for several years, and a cervical hernia nuclei pulposi (HNP) at level C5-C6 seven years earlier, which at the time was treated conservatively. He does not smoke. The complaints show no relation with physical exercise and the patient has no chest pain. Physical examination of the neck, shoulder and arm (inspection, palpation, mobility) is normal. The patient has oppressive pain ventrally on the upper arm and dorsally on the hand. Strength in the upper extremities is normal. The GP makes a working diagnosis of brachialgia, possibly caused by a recurrence of HNP, and prescribes analgesics. He asks the patient to return if the complaints remain.

Ten days later the patient returns with the same complaints and in addition, a sore throat. Two years ago he had been seen at a CCU because of chest and neck complaints; cardiac analysis was negative at this time. A physical examination does not reveal new findings. Inspection of the throat and auscultation of the heart remain without abnormalities. Blood pressure and pulse are normal; the patient is not ill and shows no vegetative signs. The GP considers a cardiac origin of the present complaints, mainly due to the unexplained neck pain, and makes an ECG recording which shows no abnormalities. He decides that the patient should be seen by a cardiologist. In order to determine whether acute referral is needed, he performs a hs-cTnT test via the hospital laboratory. Two hours later plasma hs-TnT is found to be elevated (29 ng/L), at which time the patient is sent to the cardiologist immediately.

At the CCU, plasma hs-cTnT is still elevated to the same level (29 ng/L). In view of the instability of the chest pain complaints, the patient is hospitalised, and is subjected to a cardiac CT-angiography (CCTA) as part of an ongoing trial. On the basis of the CCTA, both dissection of the aorta and lung embolism can be excluded. However, a stenosis of 90-99% of the right coronary artery (RCA) is observed. The patient subsequently undergoes a CAG which reveals the stenosis to obstruct the mid part of the RCA between 70-90%. Together these findings lead to the diagnosis non ST-elevated myocardial infarction (NSTEMI). The intervention cardiologist inserts a drug-eluting stent at the level of the stenosis. The patient's complaints dissipate and plasma hs-cTnT normalises soon thereafter. Medication aimed at secondary prevention is prescribed with sublingual nitroglycerine if deemed necessary.

Patient C is a 73 year old female, suffering from hypertension and diabetes mellitus for which she takes amlodipine 5 mg once daily, hydrochlorothiazide 12.5 mg once daily and metformin 500 mg twice daily. The patient visits the GP with complaints of pain on the left chest that started that same day. At the time of visit these complaints have persisted for 4.5 hours. The pain has spread over the entire left chest from armpit to the lower ribs. There is no pressure pain and no relation with physical exercise or use of the upper extremities. The patient began smoking at the age of 16. Auscultation of

heart and lungs is normal. Blood pressure is 132/82 mmHg with a regular pulse of 94/min. There is no fever.

The patient is known to visit her GP seldomly, apart from the preventive check-ups. The GP is unable to interpret the complaints as originating from the chest wall. He administers carbasalate calcium and calls an ambulance to refer the patient to the cardiologist due to complaints suggesting ACS. The ECG shows no abnormalities. At the CCU, plasma hs-cTnT is found to be elevated (32 ng/L). Administration of nitroglycerine sublingually provides no relief. The patient is subsequently hospitalised for further observation. One hour later, the chest pain decreases, but the patient develops a fever and become progressively ill. At recurrent measurements plasma hs-cTnT remains 31 ng/L, while plasma C-reactive protein (CRP) is 268 mg/L (reference value <5 mg/L). An X-ray of the thorax reveals a small infiltration at the periphery of the right upper lobe, and the patient is treated with antibiotics intravenously. Two days later the patient is sicker and short of breath. A repeat X-ray of the thorax shows pleural effusion on the right side. Thorax drainage is initiated and complaints are relieved that day. Twelve days later the patient leaves the hospital with no more than post infectious fatigue.

3.3 Discussion

If the cause of chest pain is clear, for example, myocardial infarction with or without ST elevations on ECG, (un)stable angina, pericarditis or a non-cardiac cause, adequate therapy is well defined (table 3.1).[1-5] Before this point is reached, GPs and cardiologists are faced with several dilemmas:

3.3.1 GP: ACS or no ACS?

When there is suspicion of ACS, referral to a cardiologist is evident.[6] However, for every patient with a coronary problem, four patients with similar complaints but not life-threatening causes present to the GP.[7] Nevertheless, 73% of these patients presenting with chest pain are referred.[7] As ACS cannot be ruled out in most cases by history taking and physical examination, it is not possible for the GP to simply refer fewer patients.[8] While typical and atypical chest complaints can be caused by ACS, they can also arise from other conditions such as gastro-intestinal or psychogenous disorders. An ECG is unable to rule out ACS at an early stage, and decision rules such as the HEART-score (History, ECG, Age, Risk factors, Troponin) and GRACE-score (Global Registry of Acute Coronary Events) cannot rule out ACS in primary care. Both scores are validated in secondary, but not in primary care.

Moreover, these scores are partly based on biomarker- measurements that are not available at the point of care (PoC) in primary care.[3,4] In primary care, measuring bi-

omarkers in a laboratory setting when PoC tests are not available as in the case of hs-cTnT is impracticable due to transport and measuring time. Only in incident cases, when chest complaints are present for several days and there is doubt as to the urgency by which a patient should be referred, a laboratory troponin test can be performed as illustrated above in our case description of patient B.

In future, PoC devices measuring relevant biomarkers might contribute to a more efficient referral process by GPs. Such devices can be based on biomarkers as troponin, heart-type fatty acid-binding protein (H-FABP), copeptin, soluble suppression of tumorigenicity 2 (sST2), amino-terminal pro brain natriuretic peptide (NT-proBNP) or on combinations of two or more of these promising markers.[2,9-12] The first study aiming at such a PoC test (based on H-FABP) in primary care, revealed an insufficient negative predictive value (NPV).[7] Future research is aimed at improving such PoC devices, as the potential cost reduction of a more effective triage is noteworthy.[13]

3.3.2 'High sensitive' troponin in diagnosing cardiac ischaemia

The NPV of contemporary fifth generation hs-cTn tests has increased to 98-99%.[5] Thus, evidence is growing that cardiac ischaemia can be ruled out within three hours after onset.[14] Moreover, unstable angina (UA) seems to be diagnosed less because of the increasing sensitivity of hs-cTn.[5] In new onset or altered chest pain where hs-cTn is negative, (severe) stable coronary artery disease is becoming increasingly diagnosed instead of UA. Conversely, in cases where hs-cTn is slightly positive, NSTEMI is diagnosed according to the third universal definition of myocardial infarction (**figure 1.1 in chapter 1**). An elevated hs-cTn value, i.e. above the 99th percentile of a normal reference population, is a strong indicator of myocardial damage and has a very low false-positivity.

Ischaemia is not the sole cause of myocardial damage, however. Several other diseases also lead to myocardial damage, including pneumonia, pericarditis and left ventricular stress. Using older generation troponin assays, 30% of patients testing positive had no coronary occlusion.[15] With the current high-sensitivity assays, this percentage is probably even higher. To solve this issue, in the third universal definition of myocardial infarction, AMI is diagnosed when, besides an elevated plasma hs-cTn, a change over time is measured.[2] When such a change is detected, a coronary cause of the cardiac damage is likely (**figure 1.1 in chapter 1**). The magnitude of the change that is indicative of acute coronary occlusion is still open to debate. In the lower range of troponin results, an absolute change of 7 ng/L between two measurements is probably indicative of acute coronary disease, whereas in the higher range, a relative change of 20% is needed.[16]

Table 3.1: Appearances of coronary artery disease[1-5]

Definitions and characteristics of manifestations of coronary artery disease
Stable angina pectoris (SA) **Definition:** 'predictable' chest pain occurring at a certain degree of exercise for a long time. **Cause:** myocardial ischaemia caused by stable stenosis in a coronary artery without local thrombotic activity. Collateral circulation often compensates for diminished perfusion through the affected coronary artery. **Treatment:** only medication, aiming at secondary prevention of cardiovascular disease. Invasive intervention is sometimes indicated when severe complaints or increased mortality risk are present.
Acute coronary syndrome (ACS) **Definition:** clinical description of complaints suspicious for a cardiac ischaemic cause. Those are new or worsened complaints when compared to an earlier, stable phase. To distinguish between ACS and other cardiac or non-cardiac causes, plasma troponin measurement is necessary unless ST -elevations on ECG are seen. In those cases, ST-elevated myocardial infarction (STEMI) is present. In case of an ACS, unstable angina or myocardial infarction is present.
Unstable angina pectoris (UA) **Definition:** chest pain of new onset or chest pain occurring at lower intensities of exercise than in the recent past. **Cause:** most often caused by acute plaque rupture in a coronary artery, activating local thrombotic activity. **Diagnosis:** UA is a clinical diagnosis; myocardial ischaemia is present, but plasma troponin levels remain normal. **Treatment:** invasive intervention may be necessary on a short term.
Acute myocardial infarction (AMI) **Definition:** near-complete occlusion of a coronary artery, most often caused by plaque rupture and local thrombotic activity in consequence. **Diagnosis:** myocardial damage is present, troponin is released from the damaged myocardial cells. ST-elevations can be present (STEMI) or absent (non-STEMI or NSTEMI). **Treatment:** STEMI: immediate coronary angiography, unless contra-indicated. NSTEMI: coronary angiography within 24 hours in high-risk patients and within 74 hours in other patients [1]. (Percutaneous coronary intervention (PCI) or bypass surgery is performed depending on the results of coronary angiography). **Prognosis:** depends on magnitude of myocardial cell loss, however not better for NSTEMI than for STEMI.

Definitions and characteristics of stable and unstable presentations of coronary artery disease.

3.3.3 Non-invasive imaging techniques

Using CT-scanning, coronary artery disease, aortic dissection and pulmonary embolism can be excluded simultaneously. Using cardiac MRI-scanning, diverse causes of myocardial damage can be visualised, among which are infarction, cardiomyopathy and myocarditis. Due to the high NPV of fifth generation hs-cTn assays, cardiac imaging for diagnosing acute coronary occlusions is often unnecessary.[17] In ongoing research, the role of non-invasive imaging techniques as a safe alternative to CAG is being studied in patients presenting with chest pain of recent onset and marginally elevated hs-cTn when there is doubt that ACS is the cause of myocardial damage.[18] The ability of non-invasive techniques to diagnose other causes of myocardial damage seems advantageous.

3.3.4 Back to our patients

Patient A had typical chest pain complaints. The GP referred him immediately. The pre-test probability for ACS at the moment of referral was approximately 20%. Given the period of complaints of several days, one negative hs-cTnT result could sufficiently rule out ACS. The prognosis is favorable.[19] Moreover, complaints were self-limiting and exercise testing was negative.

Patient B was suspected of coronary artery disease by his GP. The GP decided to refer him to a cardiologist within a few weeks, as complaints were present for a significant time. However, since a typical stable pattern was absent, such as pain aggravating on exercise and decreasing while resting, the GP measured a hs-cTn value to rule out ACS. The hs-cTnT turned out to be elevated and the patient was referred immediately. Initially, hs-cTnT was stable over time and criteria of the third universal definition were not met at that time (figure 1.1 in chapter 1). On the other hand, an alternative diagnosis explaining the hs-cTnT result - for example, pericarditis, renal insufficiency or infection - was lacking. On non-invasive cardiac imaging, NSTEMI was diagnosed. The sub-acute course possibly leads to a stable, not rising or falling, plasma hs-cTnT. After stenting, the patient was free of complaints and hs-cTnT returned to normal values. It is currently being studied whether CAG can be safely omitted in similar cases, where hs-cTnT results are difficult to interpret but CT scanning reveals no signs of acute coronary artery disease.

In some patients, further emergency-based analysis reveals an alternative cause of hs-cTn elevation, as is the case in patient C. This case illustrates that marginal elevations of hs-cTn are not on any account pathognomonic for myocardial infarction.

3.4 Synopsis

Based on three cases, we have shown that diagnosing coronary artery disease is becoming less ambiguous; however, both GP and cardiologist are still facing several bottlenecks. In primary care, new diagnostic means are needed to ensure the correct referral of ACS-positive patients and safely eliminate referral of ACS-negative patients. Using contemporary plasma hs-cTnT testing, a cardiologist is able to safely rule out ACS three hours after onset of complaints. Due to the high sensitivity of hs-cTn, unstable angina is being diagnosed less, since in most cases severe stable disease or NSTEMI is present, based on hs-cTn results. The disadvantage of the high sensitivity test is the increasing number of patients with slight elevations of hs-cTn due to causes of myocardial damage other than coronary artery disease. Non- invasive imaging techniques seem to be increasingly valuable when hs-cTn measurements are inconclusive.

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'Frequency of chest pain in primary care, diagnostic tests performed and final diagnoses'

Beatrijs BN Hoorweg*, Robert TA Willemsen RTA*, Lotte E Cleef, Tom Boogaerts, Frank Buntinx , Jan FC Glatz, Geert Jan Dinant

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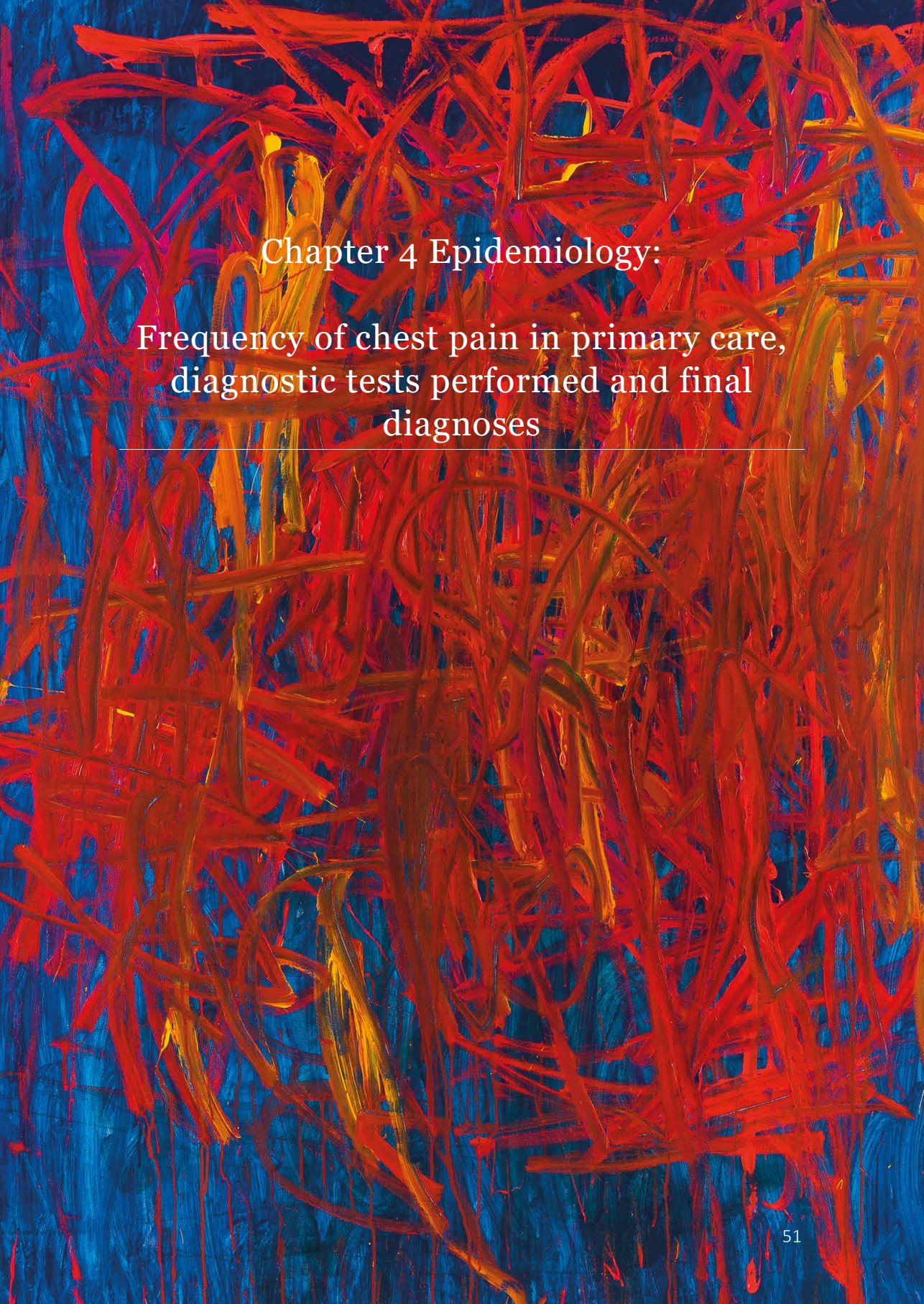
* contributed equally



Chapter 4 Epidemiology:

Frequency of chest pain in primary care, diagnostic tests performed and final diagnoses

Abstract

Objective: Observational study of chest pain patients in primary care: determination of incidence, referral rate, diagnostic tests and (agreement between) working and final diagnoses.

Methods: 118 general practitioners (GPs) in the Netherlands and Belgium recorded all patient contacts during two weeks. Furthermore, patients presenting with chest pain were registered extensively. A follow-up form was filled in after 30 days.

Results: 22,294 patient contacts were registered. In 281 (1.26%), chest pain was a reason for consulting the GP (mean age men 54.4 / women 53 years). In this cohort of 281 patients, in 38.1% of patients ACS was suspected at least temporarily during consultation, 40.2% of patients were referred to secondary care, and 512 diagnostic tests were performed by GPs and consulted specialists. Musculoskeletal pain was the most frequent working (26.1%) and final diagnosis (33.1%). Potentially life-threatening diseases as final diagnosis (such as myocardial infarction) accounted for 8.4% of all chest pain cases. In 23.1% of cases, a major difference between working and final diagnosis was found, in 0.7% a severe disease was initially missed by the GP.

Conclusion: Chest pain was present in 281 patients (1.26% of all consultations). Final diagnoses were mostly non life-threatening. Nevertheless, in 8.4% of chest pain patients, life-threatening underlying causes were identified. This seems reflected in the magnitude and wide variety of diagnostic tests performed in these patients by GPs and specialists, in the (safe) overestimation of life-threatening diseases by GPs at initial assessment and in the high referral rate we found.

4.1 Introduction

In primary care, general practitioners (GPs) are faced with a considerable number of patients presenting with chest pain of recent onset (0.7 - 2.7% of all GP consultations).[1-3] Underlying causes vary widely. Life-threatening conditions as acute coronary syndrome (ACS) are identified as a cause in chest pain populations in primary care in 1.5 (unselected chest pain patients) to 22% (in chest pain patients suspected of ACS) of all cases.[4,5] However, these severe diseases are outnumbered by minor conditions with an advantageous course (mild respiratory, gastrointestinal, musculoskeletal or psychiatric causes).[6] For GPs, distinguishing life-threatening causes from mild conditions, in order to minimize both over-referrals ánd missed cases, is of main importance.[7,8] However, distinction between mild and life threatening disease is challenging in primary care, due to overlapping signs and symptoms and early or atypical presentations.[9-13]

In literature, several studies have presented final diagnoses of chest pain in patients presenting in primary care.[4] However, less serious final diagnoses fail to reflect potential doubts by GPs earlier in the diagnostic process. By means of a registry study, we aimed (1) to examine the current incidence of chest pain in primary care in the Netherlands and Belgium. Moreover, we aimed to describe several other aspects of chest pain that are meaningful to GPs, secondary care physicians and researchers in the field: (2) the relative number of cases where ACS is at least temporarily considered by the GP during consultation, (3) number and types of diagnostic tests performed, (4) the overall referral rate, (5) the working diagnoses at presentation, (6) the final diagnoses after 30 days and (7) comparison of working and final diagnosis.

4.2 Methods

We performed a prospective registry study on the occurrence of chest pain in primary care in the Netherlands and Belgium. GPs were invited by email to participate. During the registration period, participating GPs registered numbers of *all patient contacts* (consultations, home visits and telephone consultations) in the daytime during a two-week period between August and December 2015 (Belgium), and April and June 2016 (the Netherlands). For the proportion of *patients with a new episode of chest pain* – defined as a painful, uncomfortable, stuffy or tight sensation on the sternum or anterior chest wall, with allowance of inclusion of new episodes of chest pain in patients with a history of coronary artery disease and without specific limitation for duration of complaints – the following additional issues were registered upon first assessment by their GP: type of contact, consideration of ACS, additional diagnostic tests at or directly after assessment, working diagnosis and referral policy. After 30 days, GPs registered: final diagnosis, diagnostic tests performed after first assessment, (duration of) hospitalisa-

tion and death. All individual patients were included only once. Data were registered on case report forms with multiple-choice answers to all studied issues. GPs were instructed by email and the registration form was self explanatory.

Working and final diagnoses were classified by the authors (RW and TB) using the international classification of primary care (ICPC) coding system. For each diagnosis, the system provides a unique combination of a capital letter (to indicate the organ tract specific main category) and a number (to indicate the specific diagnosis), e.g. K75.00 for 'cardiac: myocardial infarction'. In our study, working and final diagnoses were both registered as a complete ICPC-coded diagnosis (capital letter and number) as well as an organ tract specified diagnosis only (capital letter only, e.g. K for cardiac, R for respiratory, D for gastro-intestinal, P for psychogenic, L for musculoskeletal diagnoses). (Dis)agreement between working and final diagnosis was classified in each case as 'equal' (identical ICPC-code for working and final diagnosis), 'minor difference' (minor difference in ICPC-code) or 'major difference' (difference in ICPC-code with expected consequences for the diagnostic and/or therapeutic course of the patient).

Besides, all diagnoses were classified either as life-threatening disease or non-life-threatening disease. A life-threatening disease was defined as cardiac ischemic disease, pulmonary embolism, aortic aneurysm, pneumothorax, major hemorrage, acute life-threatening abdominal disease and ventricular rhythm disorders. Both working and final diagnoses regularly consisted of more than one optional diagnosis. In these cases, only the first disease was used for classification, except in cases where life-threatening diseases were mentioned among further (working) diagnoses. In that case, the life-threatening disease was used. All statistical analyses were calculated using SPSS 23. Differences in proportion between groups were verified using the X^2-test or Fisher's exact test if appropriate. Differences were considered significant if the p-value was below 0.05.

This study was approved by the Ethical Review Boards of University Hospital Leuven and Maastricht University. Regular care was not affected by the study. Signed consent was not required.

4.3 Results

4.3.1 Patient numbers, incidence

(Types of) contacts

1613 GPs were invited to participate, 134 GPs (8.3% of all invited GPs) agreed, accounting for 0.5% of all registered GPs in the Netherlands and Belgium. Nationwide, 118 GPs (71 Dutch and 47 Belgian) returned the registration form and recorded 22,294 patient

contacts during the two-week period. The mean number of patient contacts per GP was 189 (209 per Dutch and 158 per Belgian GP). Types of contacts of all consultations were only registered by the Dutch GPs. The 14,862 Dutch patient contacts consisted of 10,477 consultations (70.5%), 908 home visits (6.1%) and 3,477 telephone consultations (23.4%)

Chest pain: incidence

Chest pain as reason for encounter or at least substantial topic during the encounter occurred in 281 of 22,294 contacts (in the Netherlands 160 patients, in Belgium 121 patients; 249 were consultations (88.6%), 23 were home visits (8.2%) and 8 were telephone contacts (2.8%), one type of contact was unknown). The incidence of chest pain as a reason for encounter overall was 1.26% (1.08% in the Netherlands and 1.63% in Belgium, $p<0.0005$). Incidence of chest pain per GP varied from 0.0 to 6.62% of total consultations per GP. Mean incidence per GP was 1.32 (+/- SD 1.20, standard error of mean 0.11), median 0.95 (table 4.1). Chest pain occurred more ($p=0.03$) in females (158/279 cases (56.6%), mean age 54.4 years) than in males (121/279 (43.4%), mean age 53.0 years). In 2 cases sex was unknown (figure 4.1).

Table 4.1: Frequency (in absolute numbers) of different incidences of chest pain per general practitioner (n=118).

Incidence of chest pain	Number of GPs (n=118)
0%	22
0-1% (larger than 0%)	39
1-2%	31
2-3%	15
3-4%	6
4-5%	4
5-6%	0
6-7%	1

Incidence of chest pain per GP varied from 0.0 to 6.62% of total consultations per GP (mean incidence per GP 1.32 (+/- SD 1.20), median 0.95).

Abbreviations: GP = general practitioner; n = number.

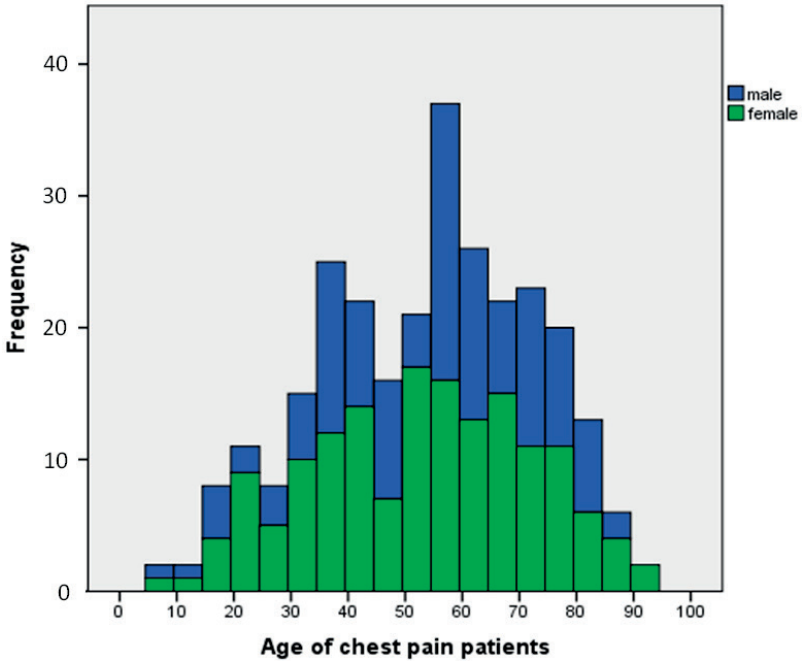


Figure 4.1: Frequency histogram of age and sex among chest pain patients (n=279, two cases missing).

Of all 281 chest pain patients, 121 (43.1%) were male (mean age 54.4 years), 158 (56.2%) were female (mean age 53.0 years), in 2 cases sex was unknown.

4.3.2 GPs' first assessment at presentation

Consideration of ACS

Only the Dutch GPs registered whether or not they at least temporarily considered ACS during assessment (independently of their working diagnosis). This issue was stated positive in 61 (38.1%) of 157 Dutch cases (three missing registrations on this topic).

Working diagnosis

GP's working diagnoses in most cases were of musculoskeletal origin (26.1%), followed by psychological complaints including hyperventilation syndrome (17.0%), cardiac ischemic disease (14.5%) and gastro-intestinal origin (11.2%) (table 4.2). The most frequent specific – ICPC-coded – working diagnoses were L04 'chest wall related complaints' (16.7%), R98 'hyperventilation syndrome' (7.1%), suspicion cardiac disease not further specified (6.8%), L99.06 'costochondritis' (6.0%), D84 'reflux/oesophagitis', K74 'ischaemic heart disease', K74.01 'unstable angina' and psychological disorder not further specified (each 5%). All ICPC-coded working diagnoses are available in addendum 4.A. There was no working diagnosis noted for 5 cases of chest pain.

Life-threatening working diagnoses
48 working diagnoses (17.1%) were labeled as life-threatening. Of these, 7 cases (2.5%) concerned suspected pulmonary embolism and 40 (14.2%) were of cardiac ischemic origin (6 were labeled as stable, in 34 cases suspected unstable cardiac disease or myocardial infarction was registered). In 23 cases, working diagnoses were insufficiently specified to assess a life-threatening nature.

Additional diagnostic tests by GPs
In 123/281 cases of chest pain (43.8%), one or more additional diagnostic tests (total of 164 tests) were performed by the GP at or directly after first assessment. These tests were: 81 (28.8%) ECGs, 59 (21.0%) venous blood samples, 8 (2.8%) point of care (PoC) tests (2 CRP, 1 D-dimer, 3 Troponin PoC tests and 2 CRP and D-dimer PoC tests combined), 7 direct access chest X-rays, 1 chest CT-scan, 3 direct accessible exercise tests, 2 24-hours blood pressure tests and 1 abdominal ultrasound. In 2 cases sublingual nitroglycerin was used as a diagnostic test (see **figure 4.2** and **table 4.2** for more details).

Referrals by GPs
113/281 (40.2%) patients witch chest pain were referred after initial assessment by the GP. 16/281 (5.7%) were referred to a coronary care unit and 24/281 (8.5%) to another emergency department. 60/281 patients (21.4%) were referred to secondary care for assessment not the same day. 13/281 were referred to an unknown destination (**table 4.2**). Belgian GPs (49%) had a higher referral rate than Dutch GPs (34%, p = 0.01)

4.3.3 Follow-up after at least 1 month

Final registration was completed in 263 of 281 chest pain cases.

Hospitalization and death
32/263 patients (12.2%) were hospitalized (in 13 cases, hospitalization was less than 24 hours). In 18 cases, hospitalization was not registered appropriately. 1 patient died, 18 days after initial assessment. This patient was directly referred to an emergency setting by the GP upon presentation, working as well as final diagnosis was myocardial infarction.

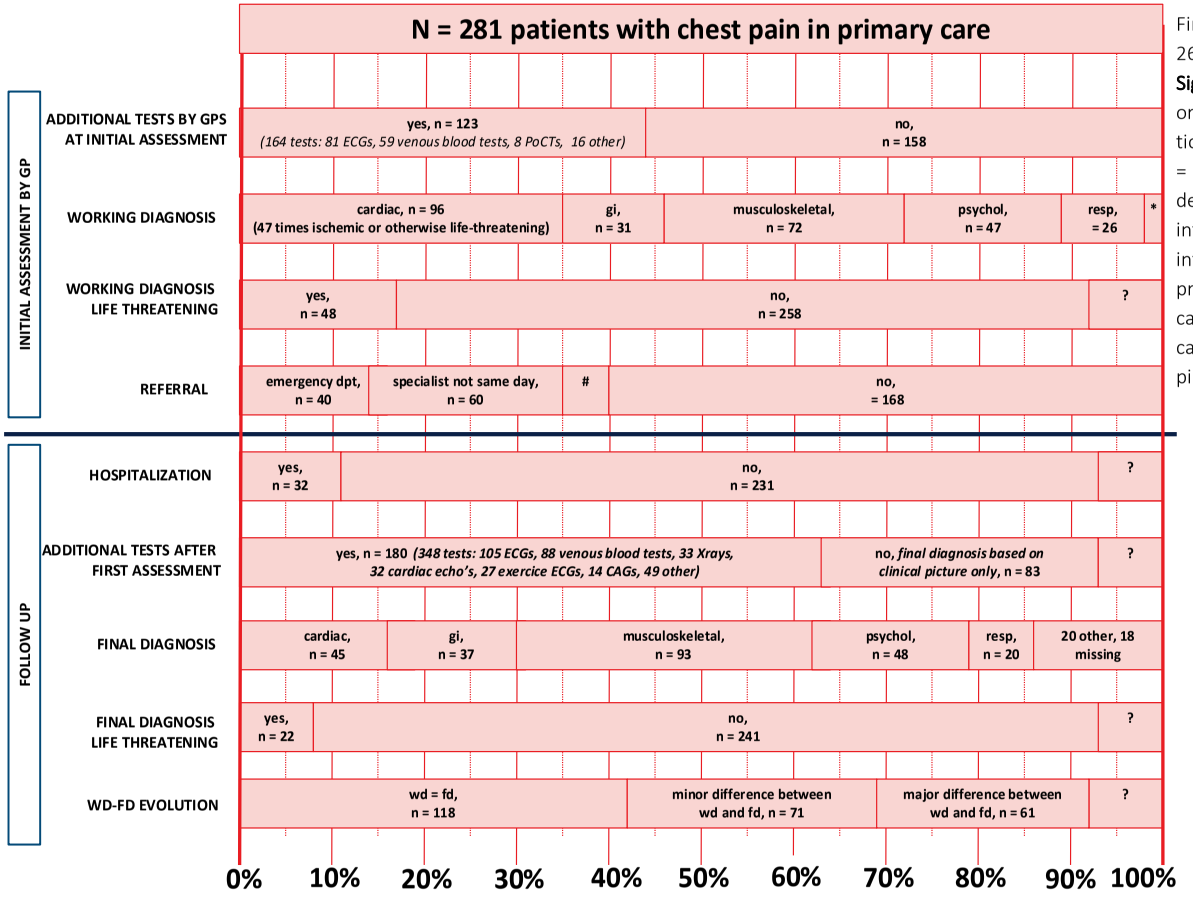
Table 4.2: Occurrence (in absolute numbers) of working and final diagnosis categorised per organ system, distribution (in percentages) of referral directions for each organ diagnosis and number of diagnostic tests at initial assessment by the GP and during follow up after initial assessment by the GP.

		Referral rates (% of all patients, n = 281)					Number of tests	
		Not referred by GP	Specialist, not the same day	Coronary care unit	Emergency department otherwise	Unknown	Total number of tests at initial assesment (tests per patient)	Total number of tests during follow up time (tests per patient)
Absolute and relative numbers of organ specific WORKING DIAGNOSIS (working diagnosis known in 276 of 281 cases)								
cardiac life threatening	n = 49 (17.7%)	10.2%	38.8%	12.2%	30.6%	8.2%	41 (0.84)	125 (2.55)
cardiac non life threatening	n = 48 (17.4%)	40.0%	35.4%	16.7%	6.3%	2.1%	33 (0.69)	79 (1.65)
respiratory disease	n = 26 (9.4%)	69.2%	11.5%	0%	7.7%	11.5%	27 (1.04)	29 (1.12)
gastro-intestinal disease	n = 31 (11.2%)	83.9%	16.1%	0%	0%	0%	14 (0.45)	29 (0.94)
musculoskeletal disease	n = 72 (26.1%)	76.4%	11.1%	1.4%	4.2%	6.9%	23 (0.32)	43 (0.60)
psychological disease	n = 47 (17.0%)	85.1%	12.8%	2.1%	0%	0%	25 (0.53)	42 (0.89)
other or mild unspecified	n = 3 (1.1%)	100%	0%	0%	0%	0%	1 (0.33)	1 (0.33)
all	n = 281	59.8%	21.4%	5.7%	8.5%	4.6%	164 (0.58)	348 (1.24)
Absolute and relative numbers of organ specific FINAL DIAGNOSIS (final diagnosis known in 263 of 281 cases)								
cardiac life threatening	n = 22 (8.4%)	18.2%	40.9%	13.6%	22.7%	4.5%	12 (0.55)	53 (2.41)
cardiac non life threatening	n = 23 (8.7%)	43.4%	30.4%	13.0%	13.0%	0%	17 (0.74)	33 (1.43)
respiratory disease	n = 20 (7.6%)	55%	20%	0%	5%	20%	19 (0.95)	32 (1.60)
gastro-intestinal disease	n = 37 (14.1%)	67.6%	18.9%	8.1%	5.4%	0%	20 (0.54)	42 (1.14)
musculoskeletal disease	n = 93 (35.4%)	70.0%	10.8%	6.5%	4.3%	8.6%	59 (0.63)	103 (1.11)
psychological disease	n = 48 (18.3%)	75%	18.8%	2.1%	4.2%	0%	24 (0.50)	47 (0.98)
other or mild unspecified	n = 20 (7.6%)	60%	20%	0%	0%	20%	13 (0.65)	38 (1.90)
all	n = 281	59.8%	21.4%	5.7%	8.5%	4.6%	164 (0.58)	348 (1.24)

Registration of working diagnosis was available in 276 of the total number of 281 chest pain patients. Registration of final diagnosis was completed in 263 of the total number of 281 chest pain patients. Hyperventilation - although a respiratory diagnosis in the ICPC coding system - was included in 'psychological disease'. Of all 281 patients, 59.8% were not referred by their GP. The majority of the referred patients were referred for further assessment not the same day. 14.2% of patients were referred for direct assessment in a (cardiac) emergency setting. On the right side, the distribution of the 164 diagnostic tests at initial assessment by the GP and the 348 tests after initial assessment by the GP is shown per working, respectively final organ specific diagnosis.

Abbreviations: ICPC = international classification of primary care; GP = general practitioner; n = number.

Figure 4.2: Diagnostic process in 281 chest pain patients.



Final registration completed in 263 patients.

Signs and abbreviations: * other or unknown; # referred, destination unknown; ? unknown ; CAG = coronary angiography ; dpt = department; gi = gastrointestinal ICPC-diagnosis; ICPC = international classification of primary care; PoCT = point of care test; psychol = psychological ICPC- diagnosis; resp = respiratory ICPC-diagnosis.

Additional diagnostic tests during follow up time

In 83/263 patients (31.6%), final diagnosis was based on 'clinical picture' and follow up only. In the remaining 180 patients, a total of 348 additional diagnostic tests were performed: 105 (39.9%) ECG's, 88 (33.4%) blood tests, 33 (12.5%) chest X-rays, 32 (12.2%) cardiac echo's, 27 (10.3%) exercise ECG's, 14 (5.3%) coronary angiographies, 10 (3.8%) coronary artery CT-scans, 7 (2.7%) CT-scans aimed at pulmonary embolism, 7 (2.7%) ambulant rhythm registrations (holter monitoring) and 6 (2.3%) gastroscopies (see figure 4.2 and table 4.2 for more details). Furthermore, 8 other types of imaging techniques, 4 initiations or alterations of medication with a diagnostic purpose, 2 psychiatric tests, 2 abdominal ultrasound examinations, 1 single-photon emission computed tomography (SPECT) scan and 2 spirometries were performed. Tests directly performed at initial assessment by the GP are not included here (these are described above in section 2 of the results).

Final diagnoses

In accordance with the working diagnoses, most final diagnoses were of musculoskeletal origin (33.1% of cases), followed by psychological complaints including hyperventilation syndrome (17.1%) and gastro-intestinal disease (13.2%) (table 4.2). The most frequent specific - ICPC-coded - final diagnoses were: L04 'chest wall related complaints' (25.6%), R98 'hyperventilation syndrome' (8.2%), D84 'reflux/oesophagitis' (6.4%) and L99.06 'costochondritis' (5.0%). All ICPC-coded working diagnoses are available in addendum 4.B. In 18 cases no final diagnosis could be obtained.

Life-threatening final diagnoses

Final diagnoses were considered life-threatening in 22 out of 263 cases where final diagnoses were registered (8.4%). Of these, 1 case of pulmonary embolism was registered (0.38%) and the remaining 21 life-threatening cases were cardiac ischemic (of which 5 patients were diagnosed with myocardial infarction). However, 4 cases were labeled as stable coronary artery disease. Therefore 17 cases (6.5%) of possible unstable cardiac disease or myocardial infarction were found (overal incidence 17/22,294 = 0.76 ‰).

4.3.4 Extent of similarity between working and final diagnosis

In 258 cases, working ánd final diagnoses were complete (in 23 cases working or final diagnosis were missing). In 68.7% of cases, the ICPC-coding of working and final diagnosis was exactly equal ór ICPC-coding differed minimally without diagnostic consequences. There was a major difference between the working- and final diagnosis in 65 (23.1% of) cases (table 4.3). Of these, in *41 cases*, there was a (life-threatening) cardiovascular diagnosis suspected and a mild final diagnosis was reported (leading to 21 referrals to an emergency service, 11 referrals to a specialist at a later time and 9 cases where GPs

performed one or more diagnostic test without referral). In *21 cases* working and final diagnosis differed, but were all non life-threatening diseases. In *1 case* working and final diagnosis differed, but were all life-threatening diseases. In *2 cases* (0.7% of all chest pain patients) a mild working diagnosis was suspected whereas the final diagnosis was a life-threatening cardiovascular diagnosis. The working, respectively final diagnoses in these two patients were atrial fibrillation, ischemic heart disease in the first and pneumonia, acute myocardial infarction in the second case. Both were not referred at initial assessment.

Table 4.3: the extent of similarity between working and final diagnosis.

Working and final diagnosis compared	Frequency	Percentage (%)
Equal	118	42.0
- working and final diagnosis non life-threatening	104	
- working and final diagnosis life-threatening	14	
Minor difference	75	26.7
- working and final diagnosis non life-threatening	70	
- working and final diagnosis life-threatening	5	
Major difference	65	23.1
- (life-threatening) cardiovascular diagnosis suspected, final diagnosis mild	41	
- working and final diagnosis non life-threatening	21	
- working and final diagnosis life-threatening	1	
- non life -threatening disease suspected, final diagnosis life-threatening cardiovascular diagnosis	2	
Missing working or final diagnosis	23	8.2
Total	281	100

Working diagnosis was the GP's diagnosis at initial assessment, final diagnosis is the diagnosis after at least 30 days of follow-up, based on the clinical picture and, when appropriate, additional tests and specialists' correspondence. Terminology: 'Equal': same ICPC-code for working and final diagnose. 'Minor and major difference': ICPC-code not equal, without respectively with diagnostic consequences. In slightly more than 1 out of 5 cases (23.1%), working and final diagnosis differed notably.

Abbreviations: ICPC = international classification of primary care; GP = general practitioner.

4.4 Discussion

In our current survey, we found that 1.26% of all GP's consultations, home visits and telephone contacts during office hours, were related to chest pain. This is comparable with earlier presented data on incidence of chest pain (estimated to be 0.7–2.7%).[1-3] Therefore, our random survey appears to be representative, the standard error of the mean (0.11) was consistently low. In 48 cases, a life-threatening disease was suspected as a working diagnosis after complete assessment by the GP. The final diagnosis was labelled as life-threatening in 22 patients, 17 of which considered unstable cardiac disease or myocardial infarction, corresponding with an incidence rate of 0.76 per 1,000 contacts in primary care. All together, 40.2% of patients were referred to secondary care facilities as a consequence of their visiting the GP for chest pain.

4.4.1 Causes of chest pain

Most frequently found working and final diagnosis was 'chest wall related complaints'. Other regularly diagnosed underlying causes of chest pain were hyperventilation syndrome, reflux or oesophagitis, and costochondritis. Life-threatening diseases are found in 8.4% of chest pain patients in primary care. An ACS as a final diagnosis occurred in 6.5%. All these findings were in agreement with international literature although the percentage of ACS was slightly higher than the 1.5–3.6% recently published in a meta-analysis.[4,14-18]

4.4.2 Patient numbers

The low incidence of unstable cardiac ischemic conditions of 6.5% as reported, probably reflects the low risk selection of chest pain patients faced by GPs. However, absolute numbers of chest pain patients with severe underlying causes are relevant. For example, in the Netherlands, an annual number of consultations of 68.5 million is carried out by GPs (see www.cbs.nl). Therefore, our data suggest that every year in the Netherlands, 863,100 consultations (1.26%) are about chest pain. During 328,841 consultations (38.1%), ACS is at least briefly considered as an underlying cause. After 122,560 consultations (14.2%), referral to an emergency department is made. In 72,500 consultations (8.4%), a life-threatening disease is diagnosed and in 790,560 consultations (91.6%), the final outcome is not life-threatening. In 56,102 consultations (6.5%), an unstable cardiac ischemic disease is the final outcome. Thus, among the frequently occurring conditions where urgent intervention is not demanded, severe cardiac disease is far from impossible.

4.4.3 How do GPs assess patients with chest pain?

The awareness of a possible severe cause of chest pain seems to be reflected in the way chest pain patients are approached by GPs. The ratio between referral to secondary care (40.2%) and a life-threatening outcome (8.4%) is approximately 5:1. The complex distinction between a mild and a severe underlying cause of chest pain is further illustrated by the 512 additional tests performed at initial assessment and during follow-up time in our population of 281 chest pain patients. These tests covered a wide variety of diagnostic means, however recording an ECG was the most used diagnostic test (186 times).

In 23.1% of all chest pain cases, a major difference was found between the working and final diagnosis, in most cases due to a mild final diagnosis following a severe working diagnosis. However, two life-threatening final diagnoses were initially assessed as non life-threatening. This percentage of 23.1% is relatively high when compared to 8% found in a previous study.[19] However, our classification 'major difference' was not only used in cases were a relevant diagnosis was missed by a GP. It was also used in cases where a working diagnosis lead to additional diagnostic tests to rule out certain conditions.

4.4.4 Strengths and weaknesses

This study is performed in primary care, which is the major strength. A participating GP recorded on average 95 patient contacts per week, including consultations in the office, home visits and telephone contacts. This is in line with the expected number, as a result we assume that the registration was approximately complete. Moreover, this study examined a part of chest pain in primary care where little is known about, namely the diagnostic steps taken by the GP. Therefore, this study contains information about the working diagnosis, final diagnosis and the process in between. However, information on 18 final diagnoses of chest pain patients (6.4%) were missing. Besides, our registry did not cover a full year. As a result, not all seasons (and associated possible fluctuations in incidence of chest pain) were covered representatively. 0.5% of all Belgian and Dutch GPs participated, providing a reliable survey, however larger studies would be of added value, in order to further address geographic and other variation between GP practices.

In cases where a GP did not refer a patient initially and where during the follow up no additional contact took place, working and final diagnosis were both assessed by the GP. We cannot exclude possible missed cases of ischemic cardiac disease among these patients, since no expert panel using troponin measurements as a gold standard was part of the study protocol. However, our aim was to observe the clinical course in chest pain patients in primary care, rather than detect subclinical cases of ischemia.

4.4.5 Conclusions

A significant number of patients with chest pain primarily contact their GP. On the one hand one could say that in 91.6% of these cases, a life-threatening condition is absent and the pre-consultation probability of an unstable ischemic cardiac disease in case of chest pain is no more than 6.5%. On the other hand, the overall occurrence and burden of chest pain patients in primary care is of important clinical significance. This is illustrated by the numbers and percentages we found as an answer to the 7 issues we described in our introduction as the aim of this study. First, (1) 1,26% of consultations in primary care is about chest pain. Furthermore, concerning the population of 281 chest pain patients (2) ACS is at least temporarily suspected in 38.1%, (3) 512 diagnostic tests are performed, (4) 40.2% are referred for assessment in secondary care facilities, (5) working diagnosis are life-threatening diseases in 17.1%, (6) final diagnoses are life-threatening diseases in 8.4%, and (7) GP's tend to take severe diseases in account at initial assessment, probably to be on the safe side and rule out disease directly after assessment, rather than miss life-threatening diagnoses. In the future, GPs might benefit from safe prediction rules and / or fast accessible tests to enhance efficiency in this demanding area of primary care.

4.5 References

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Addendum 4.A

Addendum 4.A. Frequency (in absolute numbers) of ICPC-coded working diagnoses at initial assessment by the GP.

ICPC-coded diagnosis	Frequency	Percent
B82 anaemia unspecified	1	0.4
D suspicion gastro-intestinal disease not further specified	12	4.3
D12 constipation	1	0.4
D84 reflux and/or oesophagitis	14	5.0
D87 gastritis / stomach disorder	3	1.1
D98 cholecystitis/cholelithiasis	1	0.4
K suspicion cardiac disease not further specified	19	6.8
K04 palpitations	6	2.1
K05 bradycardia	1	0.4
K06 vena cava superior syndrome	1	0.4
K24 fear of heart attack	1	0.4
K70 pericarditis	2	0.7
K74 ischaemic heart disease	14	5.0
K74.01 unstable angina	14	5.0
K74.02 stable angina	6	2.1
K75 acute myocardial infarction	6	2.1
K77 heart failure	3	1.1
K78 atrial fibrillation / -flutter	4	1.4
K79 paroxysmal tachycardia	8	2.8
K80 ectopic beats	2	0.7
K86 (symptomatic) hypertension	2	0.7
K93 pulmonary embolism	7	2.5
L suspicion musculoskeletal disease not further specified	1	0.4
L04 chest wall related symptom / complaint	47	16.7
L08 schoulder symptom / complaint	1	0.4
L76.05 rib fracture	3	1.1
L76.06 vertebral fracture	1	0.4
L81.02 ribcontusion	2	0.7
L99.06 costochronditis	17	6.0
other nos	1	0.4
P suspicion psychological disease not further specified	14	5.0
P01 anxiety nos	6	2.1
P02 acute stress reaction	5	1.8
P74.01 panic disorder	2	0.7
R suspicion respiratory disease not further specified	2	0.7
R74 acute upper respiratory infection	3	1.1
R78 acute brochi(oli)tis	8	2.8
R80 influenza(-like illness)	1	0.4

	ICPC-coded diagnosis	Frequency	Percent
	R81 pneumonia	4	1.4
	R82 pleuritis all forms (except TB)	2	0.7
	R83.02 sarcoidosis	1	0.4
	R84 malignant neoplasm lung	1	0.4
	R96 asthma	4	1.4
	R98 hyperventilation syndrome	20	7.1
	S70.01 herpes zoster	1	0.4
	X11 menopausal symptom	1	0.4
	Total	276	98.2
Missing	99	5	1.8
Total		281	100.0

Registration of working diagnosis was available in 276 of the total number of 281 chest pain patients.
Abbreviations: CMP cardiomyopathy; GP general practitioner; ICPC international classification of primary care; LVH left ventricular hypertrofy; nos not otherwise specified; TB tuberculosis.

Addendum 4.B

Addendum 4.B. Frequency (in absolute numbers) of ICPC-coded final diagnoses after a follow-up time of at least 30 days.

ICPC-coded diagnosis	Frequency	Percent
A05 malaise	1	0.4
A13 concerns about medical treatment	1	0.4
B80 iron deficiency anaemia	1	0.4
D06 abdominal pain localised other	4	1.4
D12 constipation	1	0.4
D73 gastric flu	1	0.4
D84 reflux and/or oesophagitis	18	6.4
D84.05 oesophageal stenosis	1	0.4
D87 gastritis / stomach disorder	11	3.9
D93 irritable bowel	1	0.4
final diagnosis mild, unspecified	9	3.2
K04 palpitations	5	1.8
K70 pericarditis	3	1.1
K74 coronary spasms	1	0.4
K74 ischaemic heart disease	9	3.2
K74.01 unstable angina	2	0.7
K74.02 stable angina	4	1.4
K75 acute myocardial infarction	5	1.8
K77 heart failure	1	0.4
K78 atrial fibrillation / -flutter	6	2.1
K79 paroxysmal tachycardia	5	1.8
K80 ectopic beats	2	0.7
K84.03 heart disease other including CMP and LVH	1	0.4
K86 (symptomatic) hypertension	1	0.4
K93 pulmonary embolism	1	0.4
L04 chest wall related symptom / complaint	72	25.6
L08 schoulder symptom / complaint	1	0.4
L76.05 rib fracture	2	0.7
L81.02 ribcontusion	4	1.4
L99.06 costochronditis	14	5.0
N76 neoplasm nervous system unspecified	1	0.4
N94.03 thoracic outlet syndrome	1	0.4
P01 anxiety nos	12	4.3
P02 acute stress reaction	8	2.8
P29 psychological complaint other	3	1.1
P74.01 panic disorder	1	0.4
P74.02 anxiety disorder	1	0.4
R74 acute upper airway tract infection	1	0.4

	ICPC-coded diagnosis	Frequency	Percent
	R74 acute upper respiratory infection	4	1.4
	R78 acute brochi(oli)tis	7	2.5
	R81 pneumonia	4	1.4
	R96 asthma	4	1.4
	R98 hyperventilation syndrome	23	8.2
	S70.01 herpes zoster	1	0.4
	T83 overweight	1	0.4
	T85 hyperthyroidism	1	0.4
	X18 mastodynia	1	0.4
	Z04.03 loneliness	1	0.4
	Total	263	93.6
Missing	99	18	6.4
Total		281	100.0

Registration of final diagnosis was available in 263 of the total number of 281 chest pain patients.
Abbreviations: CMP cardiomyopathy; ICPC international classification of primary care; LVH left ventricular hypertrofy; nos not otherwise specified.

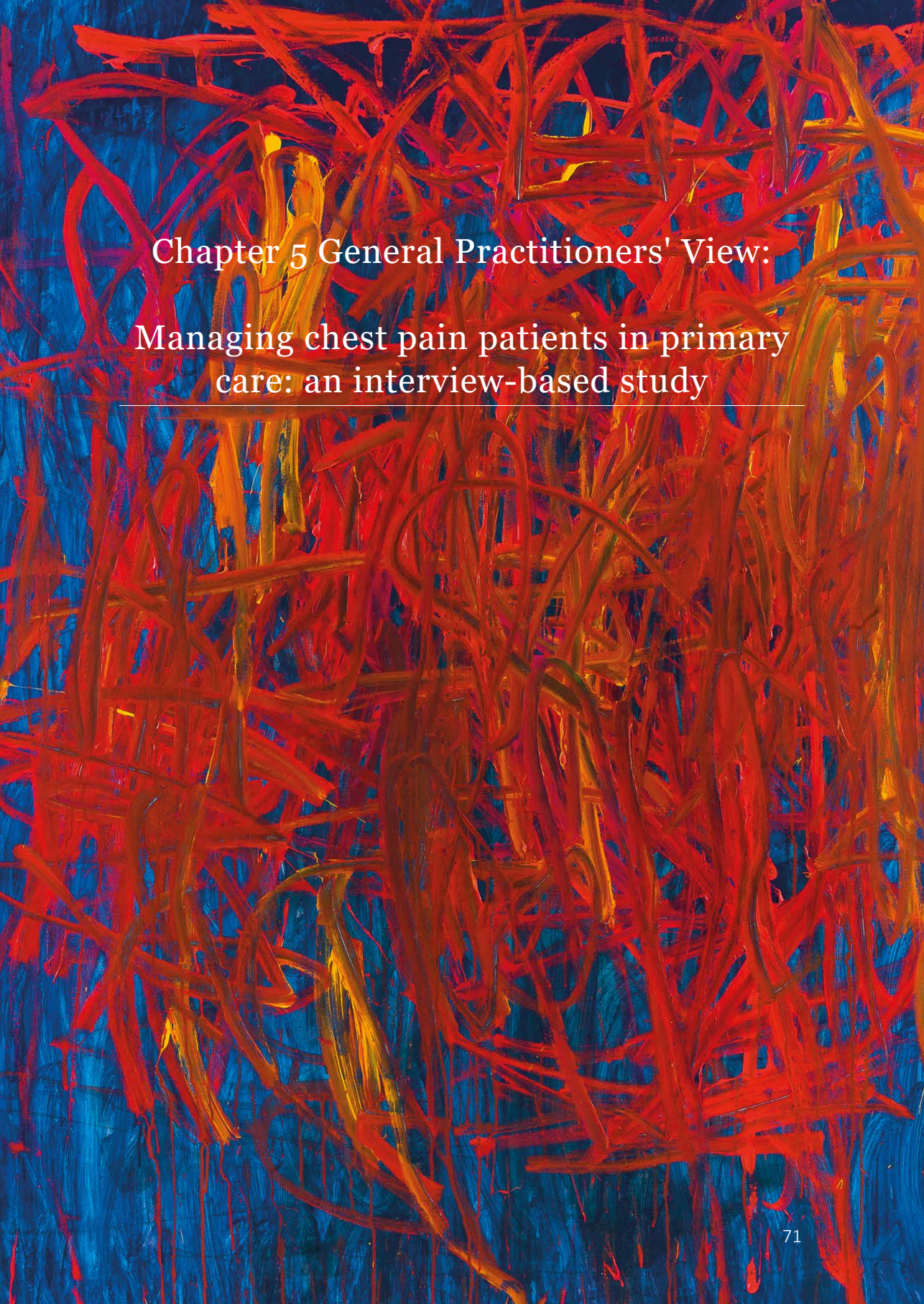
5

submitted as:

'Managing chest pain patients in primary care: an interview-based study'

Leen Biesemans*, Lotte E Cleef*, Robert TA Willemsen*, Beatrijs BN Hoorweg, Walter S Renier, Frank Buntinx , Jan FC Glatz, Geert Jan Dinant

* contributed equally



Chapter 5 General Practitioners' View:

Managing chest pain patients in primary care: an interview-based study

Abstract

Background. Assessment of chest pain in primary care is challenging. General practitioners (GPs) often feel uncertainty when dealing with chest pain. The role of new diagnostic tools is yet unclear.

Objectives. To learn (1) whether or not GPs experience a change in incidence and presentation of chest pain, (2) how GPs deal with uncertainty, and (3) which thoughts, demands and doubts concerning new diagnostic tools occur.

Methods. Semi-structured, face to face interview based study, aiming at six main subjects: experienced changes in prevalence of chest pain, the management of chest pain patients, dealing with uncertainty, the GPs' approach in referring chest pain patients, GPs' attitude towards 'unnecessary' referrals, and the GPs' suggestions for improving the management of chest pain patients.

Results. 145 GPs in Belgium and the Netherlands were invited to participate, 27 (15 Flemish and 12 Dutch) GPs were interviewed. Data saturation was reached. The number of patients having an acute coronary syndrome among chest pain patients is decreasing, whereas the presentation of atypical complaints increases, together leading to more uncertainty. GPs rely on their own judgment above all, and desire new diagnostic tools only when these tools are of proven added value.

Conclusion. The incidence of chest pain in primary care is not decreasing according to the GPs. However, the presentation of chest pain is changing. GPs feel relatively comfortable with referring a considerable number of chest pain patients without ACS, as over-referral is safe. Uncertainty is regarded as a substantial element of their profession. New diagnostic tools are awaited with cautiousness.

5.1 Background

5.1.1. Chest pain in primary care

In primary care, chest pain as a reason for encounter is common (prevalence 1–3%) and differential diagnosis is broad.[1,2] Yet, in only a minority, an acute life threatening disease is concerned. Severe diseases as acute coronary syndrome (ACS) , pulmonary embolism or thoracic aortal dissection are outnumbered by non-urgent causes as gastro-esophageal reflux disease (GERD) or thoracic wall pain.[1,3,4] However, discriminating between ACS and less severe causes of chest pain, based on clinical findings or electro-cardiography, is difficult.[5-8]

5.1.2 The challenge of (not) referring patients with chest pain

Most guidelines clearly state that general practitioners (GPs) should refer every patient suspected of an ACS to secondary care facilities as soon as possible, or GPs should even be bypassed to prevent loss of time and, consequently, myocardial cell necrosis.[9] However, for every chest pain patient with a life threatening disease as ACS, a GP encounters 11 patients with chest pain of a non severe cause.[1] Therefore, clinical judgement and triage by GPs remains inevitable to prevent unnecessary referrals and to keep the burden on secondary care facilities acceptable.[3,10] To reach this goal, GPs compromise between adequate detection of severe disease on the one hand and reassurement in cases of worried patients with no or mild underlying disease on the other hand.[6,11,12] Over time, GPs seem to have found an optimum. They refer only a minority of chest pain patients, thereby adequately maintaining their gatekeeping role. Still, a considerable number of patients with chest pain (approximately 20%-40%) are referred for safe exclusion of ACS, whereas only one out of five of these referred patients suffer from severe disease.[1,13,14] Besides classical clinical findings, GPs use gut feeling and background knowledge of their patients to make these challenging referral decisions.[15]

5.1.3 Uncertainty when dealing with chest pain

Notwithstanding this strategy to work with low thresholds for referral to maintain the number of missed cases of ACS low, uncertainty among GPs has been a part of dealing with chest pain in primary care for decades.[16-18] GPs regard guidelines as only partially solving their dilemmas in assessing chest pain patients and as suboptimally answering their questions whether or not to refer these patients.[16] As a possible consequence, guidelines do not integrally lead to behavioural change.[19] Besides, referring patients without consultation – for example based on a typical pattern presented in a phone call, as is advertised in cases of suspected stroke – is impracticable in cases of chest pain due to the broad differential diagnosis.[20] Cautious GPs that are anxious about the consequences of missing severe disease refer more often to secondary care facilities, espe-

cially when working in out of office hours services.[21,22] Especially during consultations during out of office hours, maintaining a threshold for referral is challenging.[17]

5.1.4 Developments in the field of chest pain in primary care

Several developments in the field of chest pain in primary care have been described. First, an altering presentation of ACS in primary care has been reported, whether or not due to sex differences in presentation.[5,23-25] Second, incidence of ACS among chest pain patients in primary care seems to be declining over the years (from approximately 20% to less than 10%), mortality has decreased strongly, and prognosis has improved.[1,26,27] Besides absolute data on this topic addressed in quantitative studies, a GP's perception of a possible changing incidence of ACS is important, since a GP's estimation of the probability of an ACS when assessing patients presenting with chest pain (the 'pre-test probability') is influenced by this perception.[28] Third, several diagnostic studies have recently evaluated the role of new diagnostic tools – e.g. clinical decision rules (CDRs) and point-of-care tests (PoCTs) – in managing chest pain patients. GPs in Europe desire a PoCT especially in the field of patients presenting with chest pain.[29] However, a CDR safely reducing referrals is lacking.[30]

5.1.5 Objectives

Studies on GPs' contemporary perceptions, attitudes and experiences in dealing with chest pain patients regarding uncertainty and developments in presentation, incidence and diagnostic tools as described above are mainly dealing with specific diseases, are focussing on out of office hours working situations or are lacking.[16,17,31] Therefore, in our study, we aimed to explore the following topics:

(1) Do GPs experience a changing incidence and presentation of chest pain and / or ACS in daily practice, and if so, is their course of action influenced by such alteration?
(2) Which considerations are important to GPs and how do they deal with uncertainty (regarding referrals of patients without a life threatening disease as well as missed cases of severe disease) in the management of chest pain patients?
(3) Which thoughts, demands and doubts concerning new diagnostic tools can be extracted from GPs' reflections on managing patients with chest pain? (This final question was addressed only in the Dutch interviews, since most Flemish GPs have no experience with such tools).

5.2 Methods

5.2.1. Inclusion

We invited 15 Flemish GPs by phone and 30 per e-mail. 100 Dutch GPs were invited per e-mail and were phoned shortly afterwards to inquire possible participation. We included general practitioners willing to participate, with at least 5 years of working experience. No further selection criteria were used.

5.2.2. Interview

The semi-structured face-to-face interview, composed by the Flemish researchers, consisted of five main subjects to answer the objectives of the study: (1) recently experienced changes in the prevalence of chest pain and ACS, (2) management of chest pain patients in daily practice, (3) dealing with uncertainty, (4) the GPs' approach in referring chest pain patients, and (5) their attitude towards - in the light of the final diagnosis - 'unnecessary' referrals. An additional subject was added in the Dutch interview: (6) the GP's own suggestions for improving the management of chest pain patients in primary care. The interview protocol was piloted with a Flemish and a Dutch GP who both had over 25 years of working experience. Flaws were discussed by the researchers and two GPs, which resulted in an adapted version of the interview. The pilot interviews were not included in the final research sample. The main questions, used as starting points of different phases of the interview are given in addendum 5.A. Additional questions were not predefined, further answers and themes were initiated by the GPs themselves.

5.2.3 Data collection

Data were collected through face-to-face interviews. Flemish interviews were carried out by LB, as part of her research thesis completing her GP education, between June and October, 2015. Dutch interviews were carried out by LC and BH, both fulfilling their research internships during the master phase of their medical school, between April and June, 2016. All interviews were audio-recorded and transcribed verbatim. Data were collected until saturation was achieved. Saturation was defined as the identification of no new nodes in the last two interviews in the Belgian, or the Dutch part of the study, respectively.

5.2.4 Data analysis

Thematic analysis was used to bring forth answers to the main objectives of this study. All Flemish interview transcripts were analysed independently by two researchers in a process of inductive line-by-line coding. LB coded all transcripts, and four GP residents and one anesthesiology resident coded three transcripts each. Afterwards, differences were discussed and further analysis was assisted by FB and WR. Thereafter, the initial

codebook was established, which was adjusted after every four interviews. In a second step the codes were refined, resulting in the development of descriptive themes. Finally, a thematic analysis was performed by all researchers to generate new analytical themes.

Each Dutch interview was analysed and coded independently using the Flemish codebook by LC and BH. Conflicts were solved by discussion. During the analysis of subsequent interviews, the initial code list was further refined by adding new codes under the pre-existing themes, when confronted with relevant data that could not be linked to an existing code. Finally, a framework analysis was performed by LC, BH, and RW to generate new hypotheses. Ultimately, Flemish and Dutch results were independently analysed by LB, LC and RW to uncover similarities and differences in outcomes. Subsequently, these findings were discussed in order to document the final results.

5.2.5 Ethics

All participants were informed about the aims of the study and the recording of the interviews. The study was approved by the Medical Ethical Committees of the University of Leuven and of Maastricht University.

5.3 Results

145 (45 Flemish, 100 Dutch) GPs were invited to participate, 27 GPs (15 Flemish and 12 Dutch) were interviewed. The main reason for declining our invitation was a lack of time. GP characteristics are presented in table 5.1. During the interviews, all GPs commented extensively on the questions concerning this study's main three objectives. All interviews lasted 45 to 60 minutes, incidentally an interview lasted 75 minutes.

Table 5.1. Characteristics (gender, age, years of experience, type and area of practice) of the participating GPs.

Gender	
Male	18
Female	9
Age groups	
35 - 39	3
40 - 44	4
45 - 49	4
50 - 54	3
55 - 59	7
59 – 65	5
> 65	1
Years of experience	
All GPs (N=27)	24 (2.5 – 40) *

Type of practice	
Single	8
Duo	9
Group	10
Area of practice	
Urban	14
Rural	13

Through purposive sampling we aimed to attain a heterogeneous group, including both female and male GPs, GPs working in both rural and urban regions and in single, duo and group practices. One participating GP had only 2,5 years of experience. Yet the data derived from this interview were maintained, since these were in line with the data from the more experienced GPs. Single, duo, group practices refer to GP practices managed by respectively one, two and more GPs.

Signs and abbreviations: * Mean followed by the range in brackets; GP = general practitioner; N = number.

5.3.1 Incidence and presentation of chest pain in primary care (objective 1)

Most GPs stated that they are confronted with chest pain at least once every week. Chest pain can have a wide variety of causes, of which the majority is not of cardiac origin.

> *"Hm, I think we are confronted with this complaint weekly, maybe even multiple times a week."* [NL GP 12]
>
> *"Yes, the lion's share here, of people presenting with chest pain, is not of cardiac origin."* [NL GP 8]

Although some Dutch GPs experienced an evident increase in the prevalence of chest pain in their practice, the majority of GPs did not experience a change in frequency over time. However, most GPs experienced a change in the clinical spectrum of chest pain. GPs claimed to encounter less cases of ACS, due to improved cardiovascular risk management in primary care, and more atypical thoracic complaints, due to a growing awareness on chest pain in the general population. The anxiety accompanying this awareness, combined with the continuously available health care in large out-of-hours primary care facilities, lower the threshold to consult a GP.

> *"Then I think it is more or less the same … if you don't only count cardiac but also other types of chest pain like respiratory infections or indeed psychosomatic symptoms. Then I think it [the frequency of chest pain] is comparable to before."* [BE GP 4]
>
> *"I think that the frequency with which we see a grave acute infarction nowadays is a lot lower than it was twenty years ago."* [BE GP 7]

Most GPs believed raising awareness in the general population on the possible consequences of chest pain is important. However, Dutch GPs stated it can result in an increase in patient anxiety, leading to more uncertainty and consultation of a GP.

> *"Of course raising public awareness is helpful, but it can also cause more unnecessary consultations. Not everyone is good at assessing their own situation. And people are worried when they feel something."* [NL GP 12]

Especially in out-of-hours primary care facilities in the Netherlands, new triage guidelines with a low threshold for directly sending out an ambulance in case of chest pain, are causing Dutch GPs to encounter less chest pain patients. Some Flemish GPs stated that recently more patients go directly to the emergency room, especially in urban areas with a high number of immigrants.

> *"Outside office hours people often call, saying: "I experience an acute severe pressure on my chest", and according to the current guidelines, the ambulance will leave for this patient. In such case we don't assess the patient ourselves."* *[NL GP 8]*
>
> *"We have a varied patient population here. We are on the verge of a rural area where most people still obediently go to the GP. On the other hand, in the city of Mechelen e.g., the citizens – and certainly the immigrants – go to the emergency department much easier and will thus pass us by."* *[BE GP6]*

5.3.2 Assessment of chest pain and dealing with uncertainty (objective 2)

When confronted with a chest pain patient, GPs quickly attempt to distinguish between acute and non-acute pathology. The most important tools in assessing chest pain are history taking, clinical evaluation and gut feeling. The language used by GPs suggests a feeling of responsibility.

> *"Yes, you first try to determine in which framework the pain fits. (…) Are the lungs causing the problems, or is it the heart or is it something less serious? So that's what you try to assess first and foremost."* [BE GP10]
>
> *"But I taught myself, if I have a certain gut feeling that something isn't right, yes, then I just refer them. I'm not going to take the risk behind the patient's back."* [NL GP 11]

Most GPs questioned the value of diagnostic tools such as ECG or troponin in ruling out ACS at first assessment. However, a few GPs felt confident enough to not refer a patient based on a negative ECG. In non-acute situations, these diagnostic tools are mostly used to take away any doubt, experienced by the GP, and to reassure the patient. GPs regard personal judgment, not advanced diagnostic tools, as the main instrument to rely on.

> *"Especially because you have to assess the value of an ECG. I mean that an ECG can be negative despite the fact that the clinical presentation is very suspicious. Then you have to follow your clinical judgment. The technicalities can be an affirmation of your clinical assessment but not vice versa."* [BE GP8]

> *"It also helps to reassure people that are not expected to have a serious condition, then you'll have an additional confirmatory tool [ECG]."* [NL GP 12]

When a patient is suspected of ACS, GPs immediately refer them to the emergency department, transported by ambulance with the highest level of urgency.

> *"But when someone has acute chest pain suspected of ACS, that goes with getting picked up by an ambulance with the highest urgency."* [NL GP 8]

Some GPs considered it acceptable for a patient to leave for the hospital on their own, if the patient is in a stable condition. However, they should never drive themselves.

> *"Or it is a semi-acute problem and the person can go to the hospital by their own means of transportation, transported by someone else. They shouldn't drive themselves."* [NL GP 2]

Before the ambulance arrives, some GPs administer medication and accomplish intravenous access. However, a few Flemish GPs felt insecure about their knowledge on acute interventions and their necessity in urgent situations.

> *"Imagine if you had to suddenly give an injection urgently: (...) If you haven't done any of that in twenty years, or haven't received any information about it anymore, you won't start doing it again that easily, right?"* [BE GP10]

When patients call their GP because of chest pain and their situation seems to be unstable, it depends on the amount of time available, whether the GP heads to the patient himself, sends an ambulance directly, or does both.

> *"Unless I have to drive for fifteen minutes, some of our patients live quite far off, and I am really busy with other obligations. But in principle I do both [send an ambulance and leave for the patient]."* [NL GP 2]

In non-urgent cases patients are referred to the hospital cardiology department for a consultation on a following day.

To GPs, the greatest difficulties in the assessment of chest pain are atypical symptoms, expressed – according to Dutch GPs – mainly by women.

> *"Because a woman often has atypical complaints regarding cardiovascular conditions. You have to be more careful, which means you maybe have to look a little closer."* [NL GP 7]

Some GPs feel the need to refer anxious patients, for their own and the patient's peace of mind.

> *"I think when people keep consulting you with a certain complaint, not just chest pain, even if they have already consulted you about this complaint earlier, that's an indication to refer the patient anyway."* [NL GP 2]

In urgent cases, most GPs feel no insecurity in choosing to refer a patient or not. However, when GPs experience uncertainty, it is mainly due to doubt as to which condition is causing the chest pain, sometimes leading to more referrals.

> *"But my rule is: when I'm uncertain, I always refer the patient."* [NL GP 10]

In less urgent cases some GPs try to perform most diagnostics themselves, start a test treatment, or opt for the approach of watchful waiting, to make a more targeted referral.

> *"Yes, I try to rule out some things myself, those things that are really easy to rule out. (…) And subsequently, because of these possibilities, you refer less often."* [NL GP 10]

To diminish uncertainty, GPs stated they could consult colleagues or a cardiologist. However, not all GPs feel the need to do so. Mainly Flemish GPs stated they rarely ask for advice on managing chest pain patients.

> *"I think that we are in a luxury position because we work here with three GPs in a group. There is always someone you can immediately ask for a second opinion. That helps a lot. A short discussion is often enough to be able to make a decision."* [BE GP5]

Sometimes, uncertainty remains after a consultation with a chest pain patient. To reduce this uncertainty, some GPs tend to refer more patients.

> *"Yes, if you have a feeling that you've made a mistake somewhere or that you've misjudged something it certainly keeps…lingering in your head for a while, keeps bothering you for a while."* [BE GP14]

Afterwards, some GPs like to debrief cases they were uncertain about, both on medical and personal aspects, either through the cardiologist's letters or through discussion with colleagues. However, some Flemish GPs find it difficult to find a safe environment to talk about their uncertainty.

> *"It helps me that I can debrief about it … eh … in a safe environment. I think that that is one of the most important things a GP – and actually any doctor – can attain: safe situations. I've been working now for twenty years and I have finally*

found safety. (…) I think that that's important for every doctor, that he has the opportunity to talk about his uncertainties with his peers." [BE GP1]

Nonetheless, all GPs believed that insecurity and mistakes are part of their profession and that GPs must learn to handle these situations. Most GPs believed they became more confident in assessing chest pain during their career, due to experience and development of their gut feeling, causing them to refer less patients unnecessarily. Still, GPs stated they refer quite a large part of chest pain patients because they do not want to risk missing ACS. Looking back after obtaining the final diagnosis, some of these referrals were unnecessary. However, GPs believed this is due to a lack of diagnostic tools to initially rule out ACS. Critical incidents of missing ACS cause GPs to be more cautious, either temporarily or permanently. GPs judge their referral decisions as right or wrong in the light of a final diagnosis. This is remarkable, since a referral decision based on considering a severe disease can essentially not be wrong.

"I think the experience and the development of the gut feeling plays a role in becoming more confident. So, I think that I was more insecure 15 years ago, and because of that I may have referred more patients wrongly." [NL GP 2]

"It is like that, when you get a claim or you think: "Oops, did I miss that?" then you will pay more attention to those complaints for a period of time. Absolutely." [NL GP 5]

"Sometimes you have to make a risk assessment. Sometimes you are right and sometimes you are wrong. But there's no dishonour in that. I would rather refer one patient too many than one too few. Because then you are going to have to come up with a really good explanation." [BE GP3]

Referrals of patients that eventually appear to have no severe disease can be unfavourable, leading to high health care costs, an overload of the hospital staff and a stressful experience for patients. However, some GPs never let their referral decision depend on such possible thresholds. Others stated they try to prevent medicalisation and somatisation in low-risk patients. GPs sometimes get criticised on their referral decisions by hospital physicians. Most GPs claim not to be affected by this criticism, however, their language to express their feeling of making autonomous referral decisions is rather strong. Thus, GPs seem to define their position in a difficult field where colleagues and patients might judge the GP's decisions.

"I have assessed the patient, so I have to take responsibility and I have to make the decision on my own." [NL GP 1]

"That is your autonomous decision. He wasn't there at the moment you called. And if you say in that moment 'I want an emergency doctor here', then it has to be there, end of story! Ten minutes later, the situation is different, the insight is

different, the patient is different and so on. And then maybe the decision would be different. But they can never judge you for that!" [BE GP 1]

5.3.3 Thoughts, demands, and doubts concerning new diagnostic tools (objective 3)

Most GPs stated they are satisfied with the current diagnostic options for chest pain patients in primary care and some believe that clinical assessment will remain the most important tool in assessing chest pain patients. Others do believe an additional diagnostic tool such as a biomarker PoCT would be useful. Yet, usability strongly depends on indications and diagnostic accuracy. A few Dutch GPs suggested to combine such test with a clinical decision rule. In general, new diagnostic tools are considered to be of a certain degree of added value, with a remaining central role for clinical judgment by the GP.

"Look, if you just… Independently of what it says, and I think the patient's situation is not looking good based on the clinical assessment, then I'll refer him anyway. Then I don't let it depend on a biomarker." [NL GP 12]

"It [PoCT] might contribute something in case of doubt. Then of course it also depends on the sensitivity and the cost price. You have to be quite sure when you use such a thing and it comes out positive, that you won't make big effort which in the end turns out to be futile." [BE GP8]

"If a clinical decision rule will be designed (...) those are really helpful. You count the points and then you get yes, no, or an intermediate. Yes, if you add a troponin test to that (...) then I think it will contribute of the quality of health care." [NL GP 8]

5.4 Discussion

5.4.1 Summary of main findings

First, when suspecting an ACS, GPs base their suspicion mainly on history taking and gut feeling. Second, recent findings in literature are endorsed by the interviewed GPs: chest pain is still a common reason for consulting a GP, the relative number of ACS patients among chest pain patients seems decreasing, whereas the presentation of atypical complaints increases, leading to more uncertainty. Third, GPs compensate for the experienced feeling of uncertainty by referring patients, performing additional tests or discussing cases with colleagues. Besides, GPs regard uncertainty as a substantial part of their profession and they feel more certainty when working experience increases. Still, some GPs use strong language to express their certainty, possibly reflecting an ongoing struggle to keep patients and colleagues in secondary care satisfied. Overall, GPs feel

relatively comfortable with a certain degree of over-referral of chest pain patients, as over-referral is regarded as a safe strategy in dealing with a potentially life threatening condition. An ongoing and substantial role for clinical judgment by the GP is expected. Fourth, new diagnostic tools in primary care are anticipated with cautiousness. Proper clinical embedding of such tools is obligatory according to the interviewed GPs.

5.4.2 Strenghts and limitations of the study

Before interviewing the GPs, an extensive tryout of the interview with an experienced GP, observed by another experienced GP, was carried out. Two pilot interviews were performed. All Belgian interviews were carried out by LB, a GP in training. Her own experience from working in primary care might have had an impact on the interviews. There might have been bias due to her own opinion on subjects that were discussed. On the other hand, her own learning process as a GP might have lead to a curious attitude. The Dutch interviews were carried out by LC and BH, both master's students in medicine. They had no experience in managing chest pain patients themselves, possibly leading to a certain degree of open-mindedness although the lack of experience could have prevented them from thinking of all possible in-depth questions.

The population of interviewed GPs contained a good variety in area, type of practice and age (table 5.1). They might represent a selection of GPs more than averagely interested in chest pain, although we did not find any evidence for such selection bias. Moreover, a selection of interested GPs would lead to an underestimation of experienced uncertainty, rather than an overestimation. Our study population consisted of more men (n=18) than women (n=9). However, differences of the answers between sexes or years of experience as a GP were not observed. All participating GPs seemed motivated to respond extensively to our questions. Theoretical data saturation was reached in the Flemish and Dutch interviews separately.

5.4.3 Further findings and comparison to existing literature

The incidence of chest pain in primary care has not changed remarkably. However, most GPs do experience a change in the clinical spectrum of chest pain, encountering less cases of ACS, and in its presentation. These findings are in line with various epidemiological studies, although data of these studies were partially obtained in a hospital setting.[26,27] The GPs attribute these changes primarily to better prevention and treatment strategies. Additionally, GPs find that there are more atypical presentations of chest pain, due to the growing awareness of the possible causes of chest pain in the general population. This causes chest pain patients to worry and consult their GP more often. Dutch GPs state that the prevalence of atypical chest pain in women has increased over the years, possibly due to the growing awareness on this subject, and find the management of these patients challenging. Women indeed present with atypical chest pain

more often than men, but more research on the possibly different pathophysiology in women and men is needed, in order to reveal the relevance of the differences in presentation.[25] Both Dutch and Flemish GPs reported that, in recent years, more patients go directly to the emergency room.

GPs' judgment of chest pain is based mainly on history, physical examination and gut feeling. Indeed, it is known that GPs use additional tools for assessment, such as background knowledge about patients and gut feeling.[15,32] Most GPs question the value and applicability of currently available diagnostic tools such as ECG and troponin in the assessment of chest pain. However, some GPs do use them to take away doubt or to reassure the patient. When there is a strong suspicion of ACS, GPs immediately refer the patient to the emergency department. Although most GPs agreed that transportation by ambulance with the highest level of urgency is appropriate, some GPs send stable patients to the hospital by their own means of transport, which is debatable.[33] Before the ambulance arrives, GPs sometimes administer medication and accomplish intravenous access. However, several Flemish GPs are reluctant to do this, doubting their ability to perform these interventions. Studies on this subject are scarce. A cross-sectional study from 2008 showed that a training program for GPs on interventions for ACS could improve the pre-hospitalization care of these patients.[34]

GPs sometimes experience uncertainty in the management of chest pain patients, during or after the consultation. GPs tend to reduce this uncertainty by easily referring patients or performing additional tests. Some GPs consult their colleagues or a cardiologist to diminish uncertainty, though mainly Flemish GPs rarely ask for advice on managing chest pain. When uncertainty persists after the consultation, most GPs seek confirmation either through the cardiologist's letters or through discussion with colleagues. GPs overall become more confident in assessing and managing chest pain patients during their career.

GPs mainly feel comfortable with their diagnostic assessment, management and possible over-referral of chest pain patients, stating that sometimes referral is necessary to get confirmation of the diagnosis. For most GPs the unfavourable consequences of 'unnecessary' referrals and criticism by secondary care physicians are not influencing their decisions. Several studies indeed indicate that GPs' clinical judgment is quite accurate and that they succeed in managing chest pain patients well.[35] However, the strong language used when describing their feeling of certainty suggests that GPs are aware of underlying phenomena. These phenomena might be reflections of their strong feeling of responsibility when dealing with possibly life threatening disease and / or might be a consequence of the feeling of being judged by patients or colleagues for correctly referring.

Though most GPs agree that clinical assessment will remain the most important tool in diagnosing chest pain patients, some GPs think that reliable new diagnostic tools (such

as PoCTs) could be a useful addition to improve diagnostic accuracy. The general attitude towards such tools seemed more conservative than in recent questionnaire based studies.[29,36] GPs pointed out that such tools should be reliably embedded in clinical care and is regarded as an additional tool rather than an alternative one making clinical judgments unneeded in the future. Moreover, dilemmas in assessing chest pain patients are thought to partially persist, regardless of future developments.

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Addendum 5.A: Semi-structured interview

Steps before start interview:

- Introduction of interviewer(s)
- Explanation of procedure, purpose, anonymous analysis, recording of interview.
- Informed consent procedure.
- Explain: explorative interview, no right or wrong answers, chest pain is broader than ACS alone.
- Register GP's age, sex, region, practice type, years of experience, specific areas of interest, post academic education

Interview:

***A** Epidemiology*

Main question 1:

The interview is about chest pain of all kinds. Have you got an idea how frequently you are confronted with chest pain in your practice? Does the frequency of chest pain seem altered lately?

***B** Imagine a chest pain patient...*

Main question 2:

Imagine you're assessing a chest pain patient at this very moment. What factors determine whether or not you decide to refer the patient?

***C** Uncertainty*

Main question 3:

The differential diagnosis of chest pain is broad, some of the possible causes demand early recognition and action, e.g. ACS. It is imaginable that GPs are in doubt when faced with pain about their diagnosis and actions to take. How are your experiences on this topic?

***D** Actions*

Main question 4:

If you decide to refer a patients with chest pain, which further actions do you take?

Main question 5:

We know from studies that GPs tend to refer a fair number of patients that turn out to not suffer from any serious conditions, in order to miss only few of such severe diseases. However, this leads to a high number of referral of patients not suffering from severe conditions? How do you see this?

***E** Future tools*

Main question 6:

How, to your opinion, can diagnostic assessment of chest pain patients in primary care be improved in the future?

After the main interview: We have reached the end of the main interview. Have you got any questions, remarks or additions concerning the interview?

Whenever you have any questions or requests, please feel free to contact us..
Have you got any tips for us?

We will send you a copy of out paper once we have completed it.

Thank you very much for time and effort to participate in our study.

Addendum 5.A: the semi-structured interview used in the study

Six main questions were predefined as a starting point. Further questions were not predefined. The conversation on the six main topics was primarily lead by the GPs' answers. Additional questions were asked when appropriate. GPs were given free space to talk about other issues, whenever applicable.

Abbreviations: ACS = acute coronary syndrome; GP = general practitioner.

6

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'Early health technology assessment of future clinical decision rule aided triage of patients presenting with acute chest pain in primary care (a model based economic evaluation).'

Robert TA Willemsen, Michelle Kip, Hendrik Koffijberg, Ron Kusters, Frank Buntinx , Jan FC Glatz, Geert Jan Dinant

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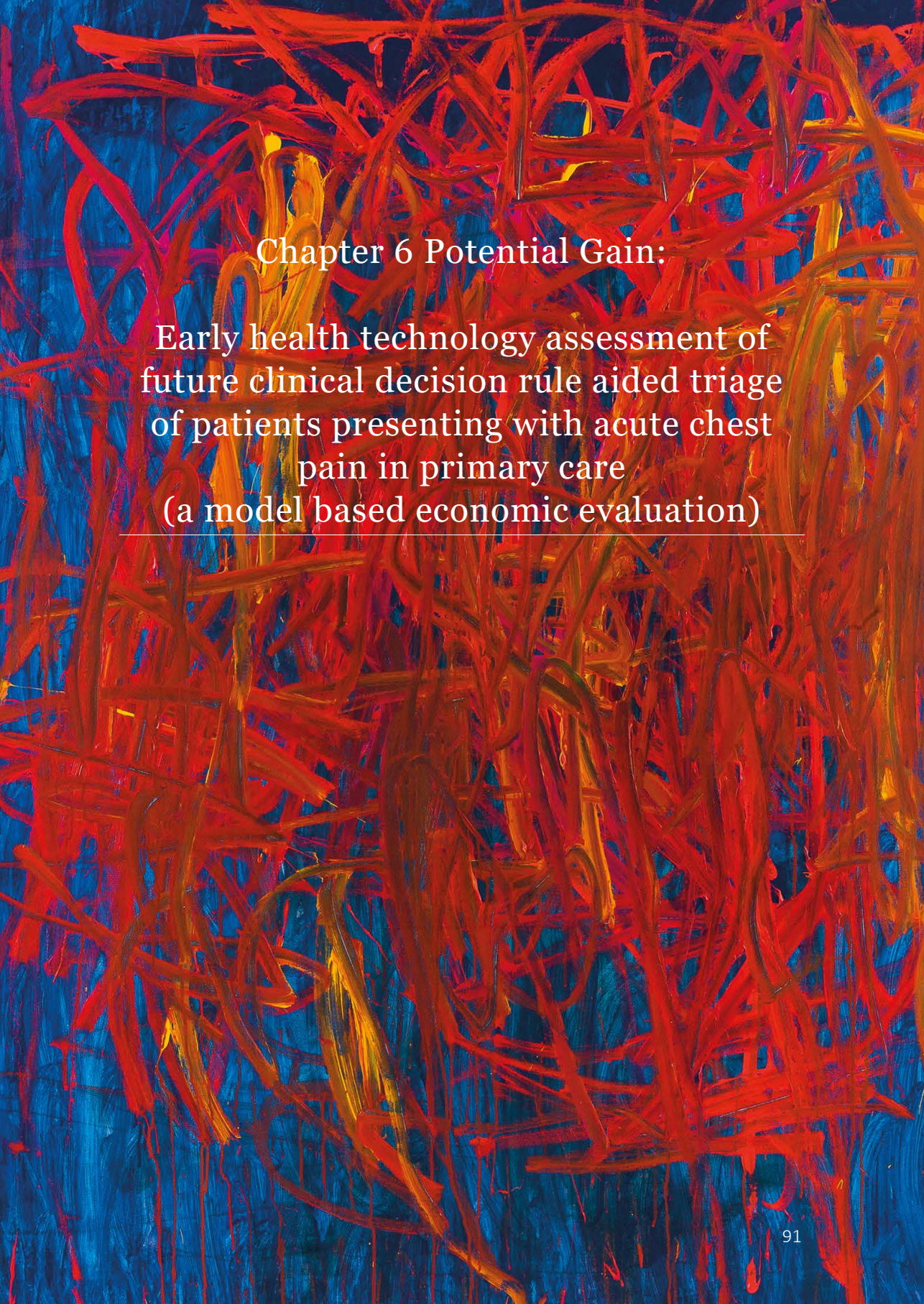

Chapter 6 Potential Gain:

Early health technology assessment of future clinical decision rule aided triage of patients presenting with acute chest pain in primary care (a model based economic evaluation)

Abstract

Objective: To estimate the number of patients presenting with chest pain suspected of acute coronary syndrome (ACS) in primary care and to calculate possible cost effects of a future clinical decision rule (CDR) incorporating a point-of-care test (PoCT) as compared to current practice.

Methods: The annual incidence of chest pain, referrals and ACS in primary care was estimated based on a literature review and on a Dutch and Belgian registration study. A health economic model was developed to calculate the potential impact of a future CDR on costs and effects (i.e. correct referral decisions), in several scenarios with varying correct referral decisions. One-way, two-way, and probabilistic sensitivity analyses were performed to test robustness of the model outcome to changes in input parameters.

Results: Annually, over one million patient contacts in primary care in the Netherlands concern chest pain. Currently, referral of eventual ACS negative patients (false positives, FPs) is estimated to cost €1,448 per FP patient, with total annual cost exceeding 165 million Euros in the Netherlands. Based on 'international data', at least a 29% reduction in FPs is required for the addition of a PoCT as part of a CDR to become cost-saving, and an additional €16 per chest pain patient (i.e. 16.4 million Euros annually in the Netherlands) is saved for every further 10% relative decrease in FPs. Sensitivity analyses revealed that the model outcome was robust to changes in model inputs, with costs outcomes mainly driven by costs of FPs and costs of PoCT.

Conclusion: If PoCT-aided triage of patients with chest pain in primary care could improve exclusion of ACS, a CDR including PoC testing could lead to a considerable reduction in annual healthcare costs as compared to current practice.

6.1 Introduction

6.1.1 Background

A clinical decision rule (CDR) based on history and physical examination to safely rule out acute coronary syndrome (ACS) in primary care is not available.[1-5] Therefore, in primary care, up to 73% of patients with new or altered chest pain are immediately referred by the general practitioner (GP) to the emergency department.[6] However, only a minority of those patients (up to 26% in literature) are subsequently diagnosed with an acute life threatening disease, e.g. ACS ('true referrals' or 'true positives' (TPs)).[6-10] Patients that were referred and were found to be ACS negative ('false referrals' or 'false positives' (FPs)) were diagnosed with alternative diseases with advantageous courses.[8,9] In this context, the term 'false' is used to indicate a referral in absence of ACS afterwards. The referral itself however is undisputed, as it is the result of a GP unable to exclude a potentially life threatening disease. On the other hand, incidentally, *ACS is present in patients that were initially not referred* ('false non-referrals' or 'false negatives'(FNs)).[8,9]

ACS negative referrals (FPs) pose a significant burden on healthcare resources, and reduction of FPs can lead to increased patient comfort, while decreasing costs.[11-13] Therefore, specificity of a future CDR for ACS should be higher - and sensitivity should at the least be *maintained - as compared to current practice that is based on a GPs' clinical judgment only*. Recently, the efficiency of similar diagnostic processes in primary care was improved by introducing a cost-effective CDR, combining point of care tests (PoCTs) with clinical findings, leading to less prescription of unnecessary antibiotics in lower respiratory tract infections and less unnecessary referral for suspected pulmonary embolism.[14-16]

The availability of a validated CDR, incorporating a PoCT measuring a biomarker of myocardial damage (e.g. high-sensitive troponin (hsTn) or heart-type fatty acid binding protein (H-FABP)) is anticipated, however not yet available.[17-21] The majority of GPs expect future PoCTs to be of added value in ruling out ACS.[22]

6.1.2 Objectives

1) to estimate the number of patients with chest pain in primary care, their referral rates and the incidence of ACS among these patients
2) to assess the minimum required reduction in ACS negative referrals (FPs) due to a future CDR, incorporating clinical findings and a PoCT, to become cost-saving, assuming that the number of non-referrals among ACS patients (FNs) equals current practice
3) to assess the impact of a relative decrease in ACS negative referrals (FPs), with decrements of 10%

4) to assess the combined impact of simultaneously varying the referrals among non-ACS patients (FPs) and the costs of the PoCT, to determine which combinations are expected to save costs

6.2 Methods

6.2.1 Estimation of patient numbers based on literature

International data and a Dutch registration study were used as separate sources to estimate numbers of true and false referrals (referred to as true and false positives respectively (TPs and FPs)) as well as true and false non-referrals (referred to as true and false negatives respectively (TNs and FNs)) in primary care in the Netherlands.[23] The international data were obtained through an extensive literature search. Those data will be referred to as 'international data', and will be used as the base case scenario in the remainder of this paper. However, as registration studies are rare, it was expected that part of the data were to be derived from studies describing relevant data that were primarily designed to meet other objectives.

Therefore, we searched PubMed and Embase from January 1989 to May 2017 for chest complaints in primary care (see figure 6.1 for an overview of the literature search and strategy). Articles assumed relevant based on title / abstracts were read in order to select all studies supplying relevant data on the incidence of chest complaints in primary care, referral rates, and final diagnoses (when available). Additional relevant articles were identified from the references in these selected papers. Besides these sources, we used Dutch registry data (governmental data, data from the Dutch Heart Foundation and data from the Dutch Central Statistics Agency).[24-31] Data from the literature review as well as from the Dutch registries were pooled and mean values with 95% confidence intervals (95%CI) were calculated.

In most cases, the included studies did not describe all probabilities in the patient pathway (for example, the set of studies that described the percentage of patients that is referred to secondary care, differed from the set of studies that described the proportion of ACS positive cases among those referred patients). Therefore, the sample sizes of the pooled estimates differed across the different parameters. Eventually, the pooled international data were translated to estimated referral rates and incidence of ACS in the Netherlands. As a second scenario to model the patient pathway of Dutch patients with chest pain in primary care, a Dutch / Belgian registration study was used, and this scenario will be referred to as 'NL and B data'.[23]

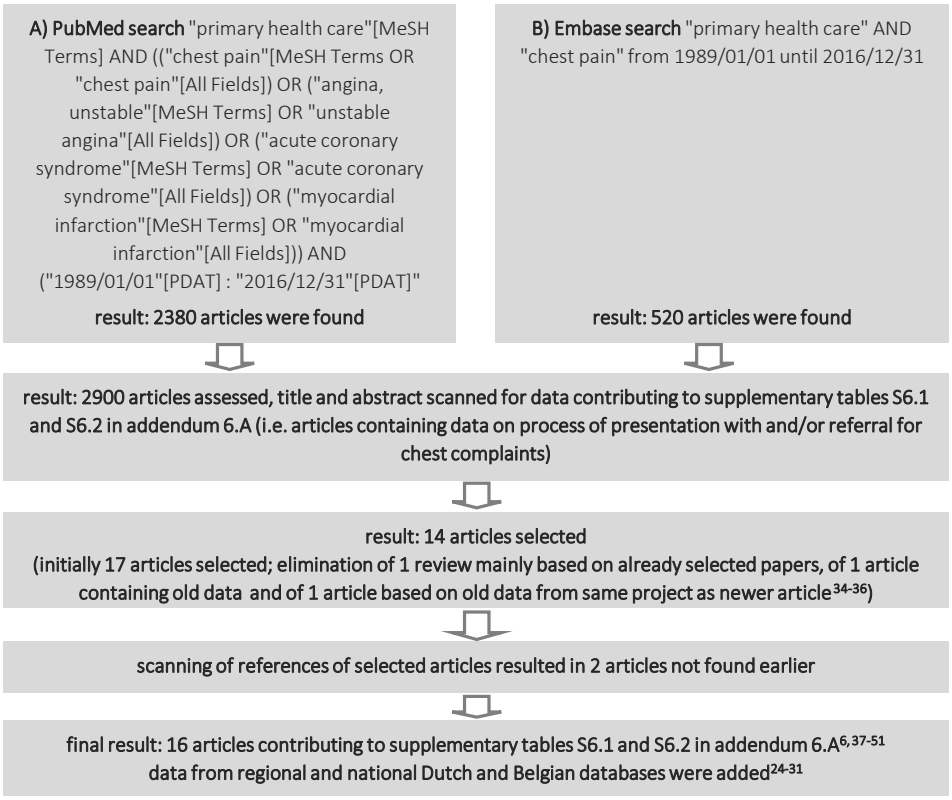

Figure 6.1 Literature search.

Visualisation of search for quantitative data on care process of chest pain in primary care, contributing to supplementary tables S6.1 and S6.2 in addendum 6.A.

6.2.2 Model diagnostic process, resource use

A health economic model was developed to estimate the costs of the full diagnostic work-up. Costs were estimated based on several sources (see **table 6.1**), and expressed in 2016 Euros.[32] The analysis was performed from a healthcare perspective, incorporating all direct medical costs that occur from the moment a patient presents with chest pain in primary care, until the patient was either referred to and diagnosed and treated in secondary care, or sent home following the GP consultation (without referral). As this time horizon is less than one year, discounting of costs and effects was not required. Calculations were performed using unit costs for assessment in primary care including PoCT testing, ambulance transport to the hospital, and assessment in secondary care. Exclusion of ACS by a GP costs €18 without PoCT, and increases to €63 when cost for usage of a PoCT of €45 is included (based on the expected price of a H-FABP PoCT which is currently in development). The cost for every patient that is assessed in a hospital for

cardiac analysis with and without the eventual presence of an underlying ACS is estimated at € 5,735 and €1,426 respectively, including hospital transport by ambulance.

Table 6.1. Model input: cost data.

Parameter	Value [95% CI]	Distribution
Consultation at tariff GP (double)*	€18.00 [€10.18 - €27.93]	Gamma
PoCT (including finger prick needle, and VAT)**	€45.00 [€26.08 - €69.52]	Gamma
Ambulance transport medium to high urgency (medical personnel A1/A2 drive, overhead costs call center, and VAT)***	€750.00 [€429.70 - €1,172.51]	Gamma
Analysis CCU, no ACS (diagnostic tests, medical personnel, hospital stay 1-2 days)****	€676.00 [€386.75 - €1,054.49]	Gamma
Analysis CCU, ACS present (diagnostic tests, medical personnel, hospital stay 3 days, PCI)****	€4,985.00 [€2,823.36 - €7,673.56]	Gamma

Cost prices for relevant events in in- or excluding ACS in The Netherlands. Cost prices are based on the following sources: double consultation price GP in The Netherlands (*), estimations from manufacturer (**), cost price requested at large ambulance service in South of The Netherlands (***), average diagnosis-treatment combination tariffs of considerable number of Dutch hospitals of varying type (small, large, academic, urban, rural) (****).
Abbreviations: *95%CI = 95% confidence interval;* ACS = acute coronary syndrome; CCU = Coronary Care Unit; GP = general practitioner; H-FABP = **Heart-type fatty acid binding protein;** PCI = percutaneous coronary intervention; PoCT = point of care test; VAT = value added tax

Table 6.2: Model input: effectiveness data for three different base cases.

	Referred		Not referred		Distribution
Scenario (estimated annual number of chest pain patients for the Netherlands [95%CI])	ACS (TP) [95% CI]	No ACS (FP) [95% CI]	ACS (FN) [95% CI]	No ACS (TN) [95% CI]	
International data[6,37-51] (N = 1,054,729 [1,047,881 - 1,061,578])	3.4% [2.8% - 4.0%]	10.8% [10.2% - 11.5%]	1.5% [0.8% - 2.2%]	84.3% [83.5% - 85.0%]	Beta
NL and B data[23] (N = 862,960)	6.1% [4.0% - 7.9%]	8.1% [6.0% - 11.1%]	0.3% [0.0% - 2.5%]	85.5% [80.6% - 89.1%]	Beta
Combined data[6,23,37-50] (N = 1,054,729 [1,047,881 - 1,068,427])	6.8% [5.5% - 7.0%]	21.9% [21.6% - 23.3%]	0.3% [0.0% - 1.7%]	71.0% [69.6% - 71.7%]	Beta

Number of chest pain patients in the Netherlands and probabilities of 'true positives' (ACS positive referrals), 'false positives' (ACS negative referrals), 'false negatives' (ACS negative non-referrals) and 'true negatives' (ACS negative non-referrals), as well as the accompanying 95%CI and the distribution applied. Numbers and distributions are presented for three different scenarios: based on pooled analysis of international literature *('international data')*, based on a Dutch / Belgian cohort study ('NL and B data') and based on a combination of sources ('combined data'). As the international data are based on the largest set of patients, those were used in the base case analysis of this article.
Abbreviations: 95%CI = 95% confidence interval; ACS = Acute coronary syndrome; B = Belgium; FN = 'false negatives'; FP = 'false positives'; NL = the Netherlands; TN = 'true negatives'; TP = 'true positives'

6.2.3 Outcome measures

The primary effectiveness measure was defined as the percentage of patients in whom ACS (including both unstable angina [UA] and acute myocardial infarction [AMI]) was correctly diagnosed or excluded when using the CDR as compared to current practice. The incremental cost-effectiveness ratio (ICER) was therefore expressed as incremental costs per patient when using a CDR (including PoCT), as compared to current practice, and divided by the difference in the number of patients in whom the correct referral decision is made in both work-ups.

6.2.4 One- and two-way sensitivity analysis

A two-way deterministic sensitivity analysis was performed to obtain insight into the combined impact of simultaneously varying the cost of the PoCT and the %FPs.[33] For subsequent analysis (i.e. one-way and probabilistic sensitivity analyses), the minimum required relative decrease in FPs to obtain a strategy that is cost-saving compared to current practice was applied in the scenarios with PoCT (while assuming that costs of the PoCT remain unaffected). Following this, to identify which individual cost parameters drive the model outcome, given fixed costs of the PoCT and the minimum required relative decrease in FPs, we conducted a one-way deterministic sensitivity analysis.[33] In the one-way sensitivity analysis, the impact of a 25% decrease and increase in all cost input parameters on the costs per patient presenting with suspected ACS in primary care was analysed. As the impact on FP referrals in the CDR + PoCT strategy was arbitrarily chosen (based on the minimum required reduction in FPs), it was decided to only incorporate the impact on costs in this one-way sensitivity analysis. In addition, this avoids double counting, as both the numerator and the denominator of the ICER are affected by a change in correct referral decisions.

6.2.5 Probabilistic sensitivity analysis

Distributions were assigned to all model parameters.[33] Subsequently, random samples were drawn for all model input parameters simultaneously. An overview of the type of distribution used for each input parameter, as well as the accompanying 95% confidence intervals (95% CI) is provided in table 6.1 and table 6.2. A probabilistic sensitivity analysis (PSA) based on Monte Carlo simulation with 10,000 samples was performed to determine the effect of joint uncertainty in all model input parameters on model outcome.

6.3 Results

6.3.1 Estimation of relevant patient numbers

In our literature search, 1,900 articles were assessed. The majority of articles were not considered relevant after screening the title and abstract. Of the remaining 17 articles, three additional articles were eliminated after full text evaluation, since no relevant data were obtainable from these papers.[34-36] Two articles reported as references in the remaining 14 articles were added, resulting in a final number of 16 articles that were included (figure 6.1). [6,37-51] In addition, data from regional and national Dutch and Belgian databases were used.[24-31] In supplementary table S6.1 in addendum 6.A, all relevant data representing parts of the patient flow of patients with chest complaints, found in the selected articles and databases, are presented. All data were converted to absolute patient numbers in the Netherlands (supplementary table S6.2 in addendum 6.A). Numbers of TPs, FPs, TNs and FNs were calculated (see table 6.2).

Besides the estimated patient numbers based on the two previously defined data sets (i.e. base case 'international data' and the 'NL and B data'), a third scenario (referred to as 'combined data') was defined. This dataset was based on the international data, although one article was excluded because the health system and time setting in which this study was performed were considered not comparable to the current health system in the Netherlands.[51] In addition, in this scenario the incidence of FNs was based on the 'NL and B data', as the incidence of FNs in the base case 'international data' seemed higher than observed in Dutch daily practice .[23] All analyses were performed for each of these three scenarios, with the international data used as base case, as these data are based on the largest set of patients. The main results based on the 'NL and B data' and the 'combined data' are also presented in the text of this paper, the accompanying figures can be found in addendum 6.B.

6.3.2 Patient flow, GP's sensitivity and specificity in current practice

The results of the literature review indicate that annually in primary care in the Netherlands, 1,054,729 [95%CI 1,047,881-1,061,578] patients consult a GP for chest pain. The referral rate among these patients was found to be 14.2% [95%CI 14.0-14.4]. Sensitivity and specificity of a GPs judgment in the current setting (not aided by a CDR), are 69% and 89% for the 'international', 95% and 91% for 'NL and B', and 96% and 76% for the 'combined data', respectively.

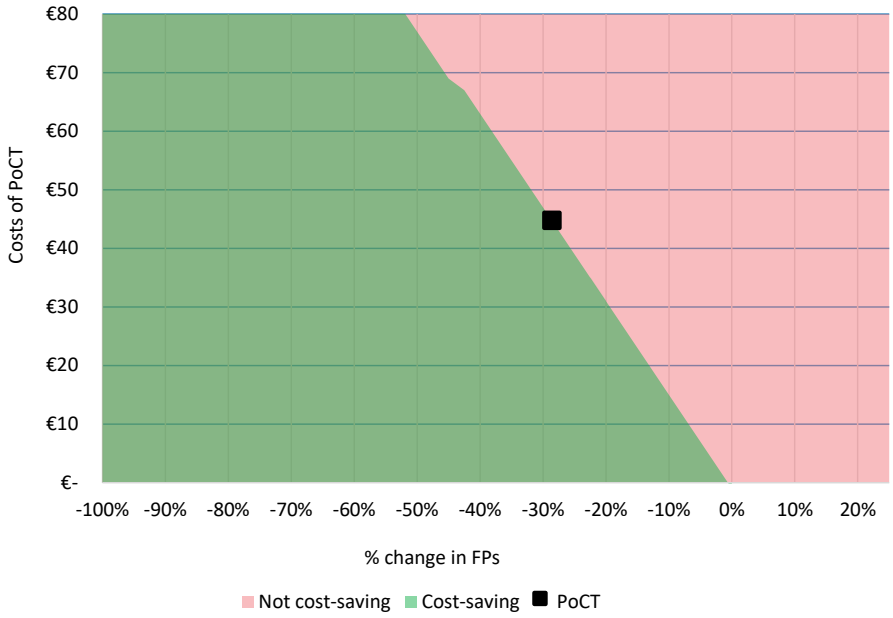

Figure 6.2:. Two-way SA for 'international data'.

Deterministic two-way SA showing the combined effect of a relative reduction in ACS negative referrals (FPs, on X-axis), and of a variation in costs of a PoCT (on y-axis), on the difference in total costs between PoCT and current practice (i.e. without PoCT). The analysis was performed based on the 'international data'. When assuming that PoCT would only impact the %FPs and incur costs of the PoCT test (and leave all other model input parameters unaffected), a relative reduction of at least 29.0% in FPs is required to make the PoCT strategy become cost-saving (as represented by the black square, assuming a cost price of a PoCT test of €45,00).

Abbreviations: ACS = Acute Coronary Syndrome; FPs = 'false-positives'; PoCT = point of care test; two-way SA = two-way sensitivity analysis

6.3.3 Required reduction of ACS negative referrals (FPs) due to a future CDR, effect of further reduction of FPs

When the cost price of a future PoCT is set at €45, the minimum required relative reductions in FPs for the PoCT strategy to become cost-saving are 29.0%, 39.5%, and 14.5% for the 'international data', the 'NL and B data', and the 'combined data', respectively (see **figure 6.2** and supplementary **figures S6.1** and **S6.2** in **addendum 6.B**). In **table 6.3**, the impact of a further relative reduction in FP rates on costs is shown for all three scenarios. For every additional absolute 10% reduction in %FPs, average additional cost savings per patient are €16 when using 'international data', €12 for 'NL and B data' and €31 for 'combined data' per chest pain patient.

Table 6.3: Effect of a stepwise reduction of ACS negative referrals (FPs) on costs.

	International data Base case without POC: € 366.57 Base case with POC: €411.71		NL and B data Base case without POC: € 485.01 Base case with POC: € 530.14		Combined Base case without POC: €722.46 Base case with POC: €757.59	
Change in %FPs	Effect on costs	% effect	Effect on costs	% effect	Effect on costs	% effect
-100%	€ -110.20	-30.1%	€ -71.93	-14.8%	€ -286.05	-39.6%
-90%	€ -94.66	-25.8%	€ -60.22	-12.4%	€ -236.73	-32.8%
-80%	€ -79.13	-21.6%	€ -48.52	-10.0%	€ -205.41	-28.4%
-70%	€ -63.60	-17.4%	€ -36.81	-7.6%	€ -174.09	-24.1%
-60%	€ -48.07	-13.1%	€ -25.10	-5.2%	€ -142.77	-19.8%
-50%	€ -32.53	-8.9%	€ -13.40	-2.8%	€ -111.46	-15.4%
-40%	€ -17.00	-4.6%	€ -1.69	-0.3%	€ -80.14	-11.1%
-30%	€ -1.47	-0.4%	€ 10.01	+2.1%	€ -48.82	-6.8%
-20%	€ 14.07	+3.8%	€ 21.72	+4.5%	€ -17.50	-2.4%
-10%	€ 29.60	+8.2%	€ 33.43	+6.9%	€ 13.81	+1.9%
0% (base case)	€ 45.13	+12.3%	€ 45.13	+9.3%	€ 45.13	+6.2%

This table shows the impact of steps of a 10% relative decrease in FP referrals (deterministic). At the top of the table, the costs for each of the base case scenarios is shown, depending on whether the PoCT is used. Absolute and relative effects are given for all three scenarios ('international data', 'NL and B data' and 'combined data' respectively). If no reduction in FPs is achieved (0% change = base case for all three scenarios where the PoCT is used) costs in all three scenarios will rise with the cost of a PoCT (€ 45.13), as compared to current daily practice where a PoCT is not used.

Abbreviations: ACS = acute coronary syndrome; B = Belgium; FP = 'false positives'; NL = the Netherlands; PoCT = point of care test

6.3.4 Impact on health outcomes and costs

The minimum required relative decrease in %FPs, as obtained from the two-way SA, was used as input into the PSA, while assuming that costs of the PoCT would remain unchanged (i.e. €45). The results of this analysis on the average total costs (both per patient as well as the total costs in the Netherlands), are shown in **table 6.4**. To visualize the constitution of those total costs, results are split up into costs that are attributable to TPs, FPs, FNs and TNs, and as the corresponding fraction of total costs. The result of the 10,000 Monte Carlo simulations is shown in **figure 6.3** for the 'international data', whereas results for the 'NL and B data' and 'combined data' are shown in supplementary **figure S6.3** and **S6.4** of **addendum 6.B**, respectively.

Table 6.4: Costs per patient, converted to patient numbers in the Netherlands.

	Referred				Not referred				Costs per patient	Total costs in the Netherlands
	ACS (TP)		No ACS (FP)		ACS (FN)		No ACS (TN)			
	Costs	%	Costs	%	Costs	%	Costs	%		
Scenario: international data[6,37-51]	€194.00 (€116.35 - 293.90)	52.9%	€157.22 (€108.36 - €215.09)	42.9%	€0.28 (€0.12 - €0.50)	0.1%	€15.25 (€8.71 - €23.66)	4.2%	€366.71 (€268.07 - €483.72)	€385,736,500 (€282,739,424 - €510,189,897)
Scenario: NL and B data[23]	€338.82 (€182.95 - €546.32)	71.3%	€120.88 (€72.67 - €184.89)	25.4%	€0.12 (€0.00 - €0.47)	0.0%	€15.40 (€8.76 - €23.87)	3.2%	€475.27 (€296.30 - €712.19)	€400,543,692 (€255,691,986 - €614,595,666)
Scenario: combined data[6,23,37-50]	€371.23 (€224.78 - €559.47)	52.5%	€322.99 (€221.85 - €445.24)	45.7%	€0.08 (€0.00 - €0.33)	0.0%	€12.79 (€7.31 - €20.00)	1.8%	€707.07 (€518.55 - €936.05)	€767,833,684 (€546,928,106 - €987,276,217)

This table presents where the average costs per patient are composed of, by splitting up those average costs into costs that are attributable to ACS positive referrals (TPs), ACS negative referrals (FPs), ACS positive non-referrals (FNs), and ACS negative non-referrals (TNs), as well as the accompanying percentage. Costs are given for all three base case scenarios ('international data', 'NL and B data' and 'combined data' respectively, without using PoCT), and based on the results of the probabilistic analysis.

Abbreviations: ACS = Acute coronary syndrome; B = Belgium; FN = 'false negatives'; FP = 'false positives'; NL = the Netherlands; PoCT = point of care test; TN = 'true negatives'; TP = 'true positives'

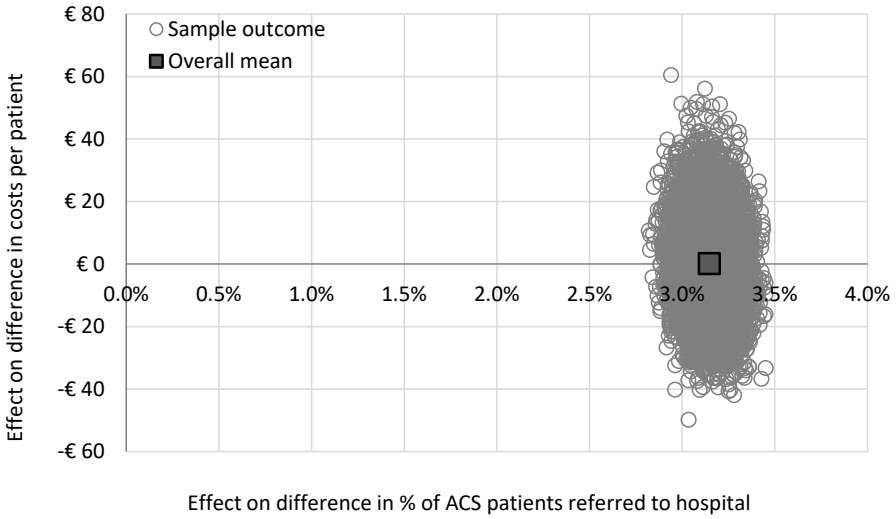

Figure 6.3: Incremental cost-effectiveness plane based on 'international data'.

This figure shows the result of 10,000 model simulations (PSA), and the mean value, based on the international data. Costs of a PoCT are set at € 45, and reduction of ACS negative referrals (FPs) is assumed to be 29.0% (cost-neutral as compared to current practice, see figure 1).

Abbreviations: ACS = Acute coronary syndrome; FPs = 'false positives'; PoCT = point of care test; PSA = probabilistic sensitivity analysis

6.3.5 Sensitivity of model outcome to changes in cost input parameters

The sensitivity of the model outcome to changes in individual cost input parameters, was measured using a one-way sensitivity analysis. The results are shown in tornado

diagrams (see figure 6.4 for 'international data' and supplementary figure S6.5 and S6.6 of addendum 6.B for 'NL and B data' and 'combined data'). Results indicate that the model outcome (expressed as cost per patient) is robust to changes in input parameters in all three scenarios. In addition, in all three scenarios, the model outcome is most sensitive to changes in costs of the PoCT, while it is less sensitive to changes in costs of ambulance transportation to the hospital and costs of analysis at the coronary care unit (CCU) among FPs. As each patient is assumed to undergo one consultation at the GP, and because the probability of correctly diagnosing ACS was assumed not to be affected by the PoCT, the model outcome was not affected by changes in those input parameters.

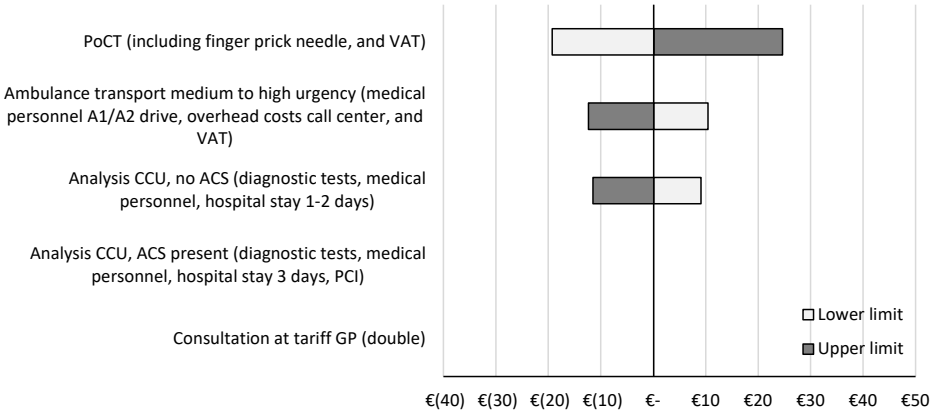

Figure 6.4: Tornado diagram of one-way SA's for 'international data'.

Tornado diagram showing the impact of changes in input parameters on the difference in costs, based on 'international data'. Costs of a PoCT are set at € 45, and the reduction of ACS negative referrals (FPs) is assumed to be 29.0% (cost-neutral situation as compared to current practice, see figure 1). All input parameters were varied with 25% below and above the mean value.

Abbreviations: ACS = Acute coronary syndrome; CCU = Coronary Care Unit; FPs = 'false positives'; GP = general practitioner; PCI = percutaneous coronary intervention; one-way SA = one-way sensitivity analysis; PoCT = point of care test; VAT = value added tax

6.4 Discussion

6.4.1 Summary of main findings

We estimated that in the Netherlands (population 17 million) annually approximately 1 million patient contacts with GPs are about chest pain. In 14% of these contacts, direct referral to a cardiologist is made. Eventually, no more than a quarter of these referred patient is diagnosed with ACS (3.4% of all chest pain patients). As a result, 10.8% of all chest pain patients are referred while they eventually are diagnosed as not having ACS

(FP). The estimated annual number of FPs in the Netherlands is 113,911, representing an economic burden of 162 million Euros. Improving triage of patients presenting with chest complaints to their GP could lead to a considerable reduction of FPs and thus to a reduction in both direct healthcare costs and patients' distress.

We estimated the impact of a CDR incorporating a PoCT in this diagnostic process, on the accompanying costs and effects (i.e. number of patients in whom the correct referral decision is made). When using an estimated cost price of a PoCT of €45, introduction of such test would be cost-saving if a relative reduction in FPs of at least 29% is achieved. This would imply a reduction in percentage of unnecessary referred patients from 10.8% to 7.7%. Such decrease would account for a cost saving of €47,106,755. Besides, *f*or every 10% further reduction in %FPs, beyond the reduction of 29% where cost neutrality was reached, €16 per chest pain patient - referred or not referred - is saved, accounting for an annual saved amount of approximately 16 million Euros in the Netherlands.

In the two alternative scenarios, a required reduction in %FPs of 39.5% for the 'NL and B data' and 14.4% for the 'combined data' was found. Such a reduction of FPs seems achievable when compared to results of similar studies in the field of suspected pulmonary embolism.[16] Yet, a lower cost price of a PoCT can attenuate the required reduction in FPs. Halving a PoCT's cost price to €22.50 leads to a minimum required reduction of FPs of only 14.5% for the PoCT to become cost-saving, when based on the 'international data'. Although the effect of preventing ACS negative referrals on societal costs has not been included in the current analysis, including those costs for both patients (and family or caregivers) would likely have increased the estimated cost savings that can be achieved by implementation of a PoCT aided CDR.

6.4.2 Sensitivity analysis

In the one-way model-sensitivity analysis, the model outcome proved to be robust for varying the model input parameters with -25% and +25% from the base case value. However, the starting point for variation in costs was based on a cost price for the PoCT of €45, which was based on the cost prognosis of a PoCT H-FABP test in development, and results may have been different when differently priced or different cardiac marker based PoCTs (for example PoCT troponin) would have been used. Therefore, a wider range of costs was applied in the two-way sensitivity analysis, as this allows to apply the model to a wider range of PoCT cardiac markers for use in primary care.

6.4.3 Strength & weakness

A strength of this study is that, to our knowledge, this study is the first to describe the possible financial benefit of a CDR incorporating a PoCT in chest pain patients presenting in primary care. We synthesized all available and relevant evidence, from different

studies and countries, to make the best possible estimation of prevalence of chest complaints and referral rates in primary care. Moreover, we repeated the analysis using three different data sets for patient numbers of chest pain patients in primary care in the health economic model. As the base case model outcome is based on several international studies, it is likely that the results regarding the effectiveness can be generalized to other countries. However, as costs may differ strongly between countries, country-specific cost estimates are required to make reliable per-country calculations.

In our analyses it was assumed that the test is performed in all patients. However, when a CDR is already positive after only scoring a patient's clinical findings by the GP, the patient will most likely be immediately referred without performing a PoCT. Therefore, as the use of PoCT will likely be more sophisticated in daily clinical practice, the costs of PoCT have (conservatively) been overestimated in the current analysis. On the other hand, wide availability of a validated PoCT in the future could lower the threshold for using this test in daily practice, as expected based on previous research.[22]

Still, some uncertainties remain. Despite the fact that patient numbers and referral rates are based on a thorough review of available literature, the number of studies that could eventually be included was limited for some model input parameters. In addition, some of those studies were relatively small. Although it might have been most straightforward to use a Dirichlet distribution to estimate all four probabilities (TP, FP, TN, and FN) simultaneously, this would have required to use a small number of patients across this distribution, thereby largely overestimating the uncertainty in model outcomes. Therefore, a Beta distribution was used instead, which allows a two-step approach. First, the probability of a patient being referred was estimated (which was based on a large number of patients), followed by estimating the probability of being either TP or FP (among referrals), or TN or FN (among non-referrals). As we assumed that the number of patients with and without ACS had to remain constant, patients could only switch from TP to FN, and from TN to FP (and vice versa). Consequently, we could not simultaneously incorporate uncertainty in the number of patients that either have or do not have ACS. However, as the result of Monte Carlo simulations shows that the uncertainty in costs is expected to be limited, and because the analysis has been performed for three different scenarios, we consider it unlikely that incorporating this uncertainty would have changed the conclusions.

Furthermore, a validated CDR does not yet exist and until such a diagnostic tool is available, the actual diagnostic performance of a CDR incorporating a POCT remains uncertain. In addition, an issue that could not be included in the current model (as it was considered too complex for the scope of this analysis), is the possible presence of other severe diseases causing chest pain in patients where ACS is excluded. However, in recent studies, nearly all FPs are diagnosed with not life threatening diseases.[6,23] Another possible limitation may be caused by the fact that the number of FNs was assumed to

remain constant in the current analysis. In current practice, patients that are initially not referred but are eventually diagnosed as having ACS (in the following days after assessment by a GP) might be under registered. Moreover, a PoCT could reduce FN referrals, which likely leads to health gain. In addition, those FN rates were found to be relatively high in our 'international data' set, but appear to be much lower in recent studies[23], and based on the authors' experience in daily clinical practice. Therefore, the 'combined' dataset is assumed to provide an estimate better reflecting current practice in The Netherlands, and in many other countries with similar health care systems. However, because of the assumptions that had to be made, the 'international' data were conservatively chosen as base case scenario in the current analysis.

6.4.4 Conclusion

If the use of a CDR including a PoCT can reduce unnecessary referrals of chest pain patients to secondary care, this could considerably reduce healthcare costs. Our study provides insights in the minimum requirements (regarding the relative reduction in FPs, as well as the costs of the PoCT) for the CDR strategy including a PoCT to become cost-saving.

6.5 References

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Addendum 6.A: supplementary tables S6.1-S6.2

Table S6.1: Webtable on literature search results.

Source	Country	Year	Population	Outcome	Weighted average of estimated patient numbers and percentages, with 95%CI between [ ] when appropriate and estimations of variation (multiplication of more than one 95% CI) between [[ ]]	Estimated patient number for the Netherlands 2013, as used in figure 2, with 95%CI between [ ] when appropriate and estimations of variation (multiplication of more than one 95% CI) between [[ ]]
a] Population in the Netherlands						
CBS[24-27]	NL	2013	All inhabitants of the Netherlands	Total population: N = 16,779,575 Population aged 20-79: N = 12,205,982	-	-
b] Number of annual GP consultations						
CBS[24-27]	NL	2013	All inhabitants of the Netherlands	Population visiting GP at least once: N = 12,015,601 Total number of GP consultations: N = 68,488,928	-	-
c] Incidence of chest pain as RfE GP						
CMR Nijmegen[28]	NL	1995-2008	All 35,000 registered patients of selected GPs	Incidence of chest pain or pressure as reason for encountering a GP: 10.9/1000/yr	pooled data: 61,039 cases of chest pain in 3,964,274 consultations, weighted average of incidence of chest pain 1.54% [1.53-1.55] (after exclusion of Rosser[51] 60,052 cases among 3,892,749 consultations, weighted average of incidence of chest pain 1.54% [1.53-1.56]	annual number of consultations for chest pain, NL 2013: 1.54% of 68,488,928 consultations = 1,054,729 [1,047,881-1,061,578] (value C) (after exclusion of Rosser[51] 1,054,729 [1,047,881-1,068,427] (value C')
Soler et al[37]	NL	1995-2005	All 15,318 registered patients of selected GPs	Incidence of chest pain or pressure as reason for encountering a GP: 30.6/1000/yr		
Ruigómez et al[38]	UK	1996	All 3,000,000 registered patients of appr. 1500 GPs	Incidence of new-onset chest pain as reason for encountering a GP: 15.5/1000/yr		
Nilsson et al[39]	SW	1998-2000	All 16,152 registered patients of selected GPs, aged 20-79	Incidence new onset chest pain 19.6/1000 patients aged 20-79/yr		

Bösner et al[40]	D	2005-2006	All 190,000 consultations done by 74 participating GP's	Prevalence chest pain in patients aged ≥ 35 among all patients visiting GP: 0.7%		
Verdon et al[41]	CH	2001	24,620 patients seen by 59 GPs	Prevalence new-onset chest pain among patients aged ≥ 16 among all patients visiting a GP: 1.8%		
Svavarsdottir[47]	IC	1989-1990	5470 patients registered in one GP practice, making 28,050 consultations in 2 years	Percentage of GP consultations where chest pain is RfE: 0.68%		
Frese[49]	D	1999-2000	8877 consultations in primary care	Percentage of GP consultations where chest pain is RfE: 3.0%		
Frese[49]	NL	1985-2003	597,312 consultations in primary care	Percentage of GP consultations where chest pain is RfE: 1.7%		
Rosser[51]	US/CAN	1985	registration of 71,525 consultations in primary care	Percentage of GP consultations where chest pain is RfE: 1.38%		
d] Number of patients with ACS in primary care						
Verdon et al[41]	CH	2001	442 patients presenting new-onset chest pain	Incidence ACS among patients presenting with chest pain in primary care 1.5% (diagnosis set after 1 year follow up)	pooled data: 84 cases of ACS among 3,012 cases of chest pain	number of patients with ACS in primary care, NL 2013: 2.79% of 1,054,729 chest pain consultations (value C x value D) = 29,427 [[23,473-36,731]] (after exclusion of Rosser[51] (value C' x value D) 29,427 [[23,473-36,968]]
Bösner et al[40]	D	2005-2006	1,212 patients ≥ 35, presenting with chest pain in primary care	Incidence ACS among patients presenting with chest pain in primary care: 3.6% (diagnosis set after 6 months follow up)	weighted average of incidence of ACS among cases of chest pain in primary care: 2.79%	
Klinkman[46]	US	1994	399 episodes for chest pain in primary care	Incidence ACS among patients presenting with chest pain in primary care: 1.5%	[2.24-3.46] (value D)	
Haasenritter[50]	D	2009-2010	844 patients with chest pain in primary care	Incidence ACS among patients presenting with chest pain in primary care: 2.5% (diagnosis set after 6 months follow up)		

Andersson[48]	SW	2009-2011	115 patients with chest pain in primary care	Incidence ACS among patients presenting with chest pain in primary care: 5.2% (diagnosis set after 1 month follow up)		
e] Absolute and relative number of referrals among all patients presenting chest pain to a GP.						
CMR Nijmegen[28]	NL & SW	1995-2008	All 35,000 patients presenting with chest complaints to a GP.	Relative number of patients that are immediately referred by the GP: 29%	pooled data: 15,266 referrals among 107,284 cases of chest pain	number of patients with chest pain in primary care directly referred to secondary care, NL 2013:
Nilsson et al[39]	SW	1998-2000	Patients presenting with new-onset chest pain (exclusion of those suspected of stable coronary disease), N = 317	Relative number of patients that are immediately referred by the GP: 12%	weighted average of referral rate among cases of chest pain in primary care: 14.2% [14.0-14.4] (value E) (after exclusion of Rosser[51] 10,259 referrals among 35,759 cases, weighted average of referral rate among cases of chest pain in primary care: 28.7% [28.2-29.2]) (value E')	14.2% of 1,054,729 chest pain consultations (value C x value E) = 149,772 [[146,703-152,867]] (value E") (after exclusion of Rosser[51] (value C' x value E') 302,707 [[295,502-311,981]] (value E''')
Verdon et al[41]	CH	2001	442 patients presenting new-onset chest pain	Percentage of patients presenting with chest complaints to a GP, that are immediately referred by the GP: 16%. (Percentage suspected of severe acute disease: 20%)		
Rosser[51]	US/CAN	1985	registration of 71,525 consultations in primary care	Percentage of patients presenting with chest complaints to a GP, that are immediately referred by the GP: 7%		
f] Referral rate among patients presenting with chest pain to a GP who are suspected of ACS						
Bruins Slot et al[6]	NL	2006-2008	Selection of patients presenting with chest complaints to a GP *that are suspected for ACS by the GP*. N = 298.	Relative number of patients that are immediately referred by the GP: 73%	referral rate among cases of chest pain in primary care where ACS is suspected: 73.2% [67.7-78.0]	

g] Absolute and relative number of patients presenting with chest pain in primary care where ACS / severe disease is considered						
based on e] and f] in this table				In the total population presenting with chest pain to a GP, mean referral rate is 14.2% (see row e] in this table). Referral rate in the population of patients presenting chest pain to a GP who are suspected of ACS is 73% (see row f] in this table). Since the group of patients suspected of ACS in both populations is the same, the population of patients with chest pain suspected of ACS is assumed to be 14.2/73 = 19.5% of the total population of patients with any chest pain, either suspected or unsuspected of ACS.	percentage of patients where ACS / severe disease is considered among patients presenting with chest pain in primary care: 20% (value G)	number of patients presenting with chest pain in primary care where ACS / severe disease is considered, NL 2013 (value C x value G): 210,946 [209,576-212,316] (after exclusion of Rosser[51] (value C' x value G): 210,946 [209,576-213,685]
Verdon et al[41]	CH	2001	442 patients presenting new-onset chest pain	Percentage of patients with new presentation of chest pain suspected of severe acute disease: 20%		
h] Absolute and relative number of ACS among referred patients						
Nilsson et al[39]	SW	1998-2000	65 patients immediately referred by GP after presenting with new-onset chest pain	Percentage of ACS, resp AMI among patients with chest complaints that are referred by a GP, 29% resp 11% (outcome set 3 months after presentation)	pooled data: 67 cases of ACS among 283 referred patients weighted average of true referrals among referred patients with chest pain in primary care: 23.7% [18.9-29.1] (value H)	number of ACS among referred patients presenting with chest pain in primary care ('true referrals'), NL 2013 (value E'' x value H): 35,496 [[27,727-44,484]] (after exclusion of Rosser[51] (value E''' x value H) 71,742 [[55,850 - 90,786]])
Bruins Slot et al[6]	NL	2006-2008	Selection of study population that was referred by GP, N = 218	Percentage of ACS, resp AMI: 22% resp 17%,		

i] Absolute and relative number of ACS among patients initially not referred						
Nilsson et al[39]	SW	1998-2000	281 patient with new onset chest pain where ACS was not suspected by GP	Percentage of ACS among patients with chest complaints that were initially not suspected of ACS by a GP: 1.8% (outcome set 3 months after presentation)	ACS rate among non-referred patients with chest pain in primary care: 1.8% [0.7-4.3] (value I)	number of ACS among not referred patients presenting with chest pain in primary care ('false non referrals'), NL 2013 (value I x (value C - value E")): 16,289 [[6,279-39,257]] (after exclusion of Rosser[51] (value I x (value C' - value E'")): 13,536 [[5,151 - 33,236]]
j] Number of patients with chest pain at ER						
Data from Academic Hospital Maastricht[29]	NL	2013	199,411 inhabitants of a region in the South-East of the Netherlands	incidence of visiting cardiologic emergency department with chest pain (either referred by GP, brought by ambulance or self- referred): 12,54/1000 pts/year	Incidence of chest pain presentation at ER: 1.25 [1.21-1.30]	Number of patients with chest pain at ER, NL 2013: 209,745 [203,033- 218,134]

Data on numbers and referral rates of patients presenting with chest complaints in primary care are presented. Sources are presented and all numbers and rates are converted into absolute numbers in The Netherlands in the year 2013.These converted numbers are used in Figure 2, means are used in Figure 2 when more than 1 source is available.

Abbreviations: 95%CI = 95% confidence interval; ACS = Acute coronary syndrome; AMI = Acute myocardial infarction; B = Belgium; CAN = Canada; CH = Switzerland; CMR = continuous registration of morbidity; D = Germany; ER = emergency room; GP = general practitioner; IC = Iceland; MI = myocardial infarction; N = number; NL = the Netherlands; RfE = reason for encounter; SW = Sweden; UK = United Kingdom; US = United States of America

Table S6.2: Overview of three base cases based on various estimations of incidence of chest pain, referral rates and 'true and false (non-) referrals'.

Source	Used in base case	Country; year	Population, background	Outcome [estimation for variation, 95% CI when applicable]	Translation to (estimated) patient numbers, NL 2013 [estimation for variation, 95% CI when applicable]
a] Population in the Netherlands					
CBS[24-27]	'international data' and 'NL and B'	NL; 2013	All inhabitants of the Netherlands	Total population: N = 16,779,575 Population aged 20-79: N = 12,205,982	N = 16,779,575 N = 12,205,982
b] Number of annual GP consultations					
CBS[24-27]	'international data' and 'NL and B'	NL; 2013	All inhabitants of the Netherlands	Population visiting GP at least once: N = 12,015,601 Total number of GP consultations: N = 68,488,928	N = 12,015,601 N = 68,488,928
c] Incidence of chest pain as RfE GP					
Dutch cohort study[23]	'NL and B'	NL, B; 2015-2016	Registration of 22,294 consultations in primary care	Percentage of GP consultations where chest pain is RfE: 1.26%	N = 862,960
Pooled data international studies[6, 37-51]	'international data'	NL, UK, SW, D, Ch, Ic, US, Can; 1989-2008	Pooled data: 61,039 cases of chest pain in 3,964,274 consultations	Percentage of GP consultations where chest pain is RfE: 1.54% [1.53-1.55]	N = 1,054,729 [1,047,881-1,061,578]
Combination Dutch data and selected international data[6,23,37-50]	'combined data'	NL, UK, SW, D, Ch, Ic, US, Can; 1989-2008	Pooled data: 60,052 cases of chest pain in 3,892,749 consultations,	Percentage of GP consultations where chest pain is RfE: 1.54% [1.53-1.56]	N = 1,054,729 [1,047,881-1,068,427
d] Number of patients with ACS in primary care					
Dutch cohort study[23]	'NL and B'	NL, B; 2015-2016	281 patients with chest pain in primary care	Incidence ACS among patients presenting with chest pain in primary care: 6.45%	N = 55,654
Pooled data international studies[6, 37-51]	'international data'	SW, D, Ch, US; 1994-2011	Pooled data: 84 cases of ACS among 3,012 cases of chest pain	Incidence of ACS among patients presenting with chest pain in primary care: 2.79% [2.24-3.46]	N = 29,427 [23,473-36,731]

Source	Used in base case	Country; year	Population, background	Outcome [estimation for variation, 95% CI when applicable]	Translation to (estimated) patient numbers, NL 2013 [estimation for variation, 95% CI when applicable]
Combination Dutch data and selected international data[6,23,37-50]	'combined data'	NL, UK, SW, D, Ch, Ic, US, Can; 1989-2008	Pooled data: 84 cases of ACS among 3,012 cases of chest pain	Incidence of ACS among patients presenting with chest pain in primary care: 2.79% [2.24-3.46]	N = 29,427 [23,473-36,731]
e] Absolute and relative number of referrals among all patients presenting chest pain to a GP.					
Dutch cohort study[23]	'NL and B'	NL, B; 2015-2016	281 patients with chest pain in primary care	Relative number of patients that are immediately referred by the GP: 14.2%	N = 122,540
Pooled data international studies[6, 37-51]	'international data'	NL, SW, CH, US, CAN; 1985-2008	Pooled data: 15,266 referrals among 107,284 cases of chest pain	Relative number of patients that are immediately referred by the GP: 14.2% [14.0-14.4]	N = 149,772 [146,703-152,867]
Combination Dutch data and selected international data[6,23, 37-50]	'combined data'	NL, UK, SW, D, Ch, Ic, US, Can; 1989-2008	Pooled data: 10,259 referrals among 35,759 cases of chest pain,	Relative number of patients that are immediately referred by the GP: 28.7% [28.2-29.2]	N = 302,707 [295,502-311,981]
g] Absolute and relative number of patients presenting with chest pain in primary care where ACS / severe disease is considered					
Dutch cohort study[23]	'NL and B'	NL, B; 2015-2016	281 patients with chest pain in primary care	Percentage of patients with new presentation of chest pain suspected of ACS: 38.1%	N = 328,788
Pooled data international studies[6, 37-51]	'international data'	NL, SW, CH, US, CAN; 1985-2008		Percentage where ACS / severe disease is considered among patients presenting with chest pain, primary care: 20%	N = 210,946 [209,576-212,316]
Combination Dutch data and selected international data[6,23, 37-50]	'combined data'	NL, UK, SW, D, Ch, Ic, US, Can; 1989-2008		Percentage where ACS / severe disease is considered among patients presenting with chest pain, primary care: 20%	N = 210,946 [209,576-213,685]

Source	Used in base case	Country; year	Population, background	Outcome [estimation for variation, 95% CI when applicable]	Translation to (estimated) patient numbers, NL 2013 [estimation for variation, 95% CI when applicable]
h] Absolute and relative number of ACS among referred patients					
Dutch cohort study[23]	'NL and B'	NL, B; 2015-2016	281 patients with chest pain in primary care	Percentage of ACS among patients with chest complaints that are referred by a GP ('true referrals'): 43% (outcome set at least 30 days after presentation)	'True referrals' (ref+, ACS+): N = 52,692 'False referrals' (ref+, ACS-): N = 69,848
Pooled data international studies[6, 37-51]	'international data'	NL, SW; 1998-2008	Pooled data: 67 cases of ACS among 283 referred patients	Percentage of ACS among patients with chest complaints that are referred by a GP ('true referrals'): 23.7% [18.9-29.1]	'True referrals' (ref+, ACS+): N = 35,496 [27,727-44,484] 'False referrals' (ref+, ACS-): N = 114,276 [105,288-122,045]
Combination Dutch data and selected international data[6,23, 37-50]	'combined data'	NL, UK, SW, D, Ch, Ic, US, Can; 1989-2008	Pooled data: 67 cases of ACS among 283 referred patients	Percentage of ACS among patients with chest complaints that are referred by a GP ('true referrals'): 23.7% [18.9-29.1]	'True referrals' (ref+, ACS+): N = 71,742 [55,850 - 90,786] 'False referrals' (ref+, ACS-): N = 230,965 [211,921-246,857]
i] Absolute and relative number of ACS among patients initially not referred					
Dutch cohort study[23]	'NL and B'	NL, B; 2015-2016	281 patients with chest pain in primary care	Percentage of ACS among patients with chest complaints that were initially not suspected of ACS by a GP ('false non-referrals'): 0.4% (outcome set at least 30 days after presentation)	'False non-referrals' (ref-, ACS+): N = 2,962 'True non-referrals' (ref-, ACS-): N = 737,458
Pooled data international studies[6, 37-51]	'international data'	NL, SW; 1998-2008	Pooled data: 9 cases of ACS among 361 not referred patients	Percentage of ACS among patients with chest complaints that were initially not suspected of ACS by a GP ('false non-referrals'): 1.8% [0.7-4.3]	'False non-referrals' (ref-, ACS+): N = 16,289 [6,279-39,257] 'True non-referrals' (ref-, ACS-): N = 888,668 [865,700-898,678]

Source	Used in base case	Country; year	Population, background	Outcome [estimation for variation, 95% CI when applicable]	Translation to (estimated) patient numbers, NL 2013 [estimation for variation, 95% CI when applicable]
Combination Dutch data and selected international data[6,23, 37-50]	'combined data'	NL, B; 2015-2016	281 patients with chest pain in primary care	Percentage of ACS among patients with chest complaints that were initially not suspected of ACS by a GP ('false non-referrals'): 0.4% (outcome set at least 30 days after presentation)	'False non-referrals' (ref-, ACS+): N = 3,008 [2,971 - 3,037] 'True non-referrals' (ref-, ACS-): N = 749,014 [748,985-749,051]

The first base case ('NL and B') is based on the results of a Dutch cohort study.[23] The second base case ('international data') is based on a pooled analysis of international studies on incidence of chest pain, incidence of ACS and referral rates in primary care. The third base case ('combined data') is based on a combination of base cases 'NL and B' and 'international data', using the international data set after exclusion of one reference because of a non comparable health care system in the study.[50] Moreover, in this third base case ('combined data'), the incidence of ACS positive non-referrals ('false non-referrals') was based on the Dutch and Belgian cohort study since it was considered more representative on this issue.[23] All three base cases were analysed separately in our model for cost efficiency (see remainder of article). All numbers and rates are converted into absolute numbers in the Netherlands in the year 2013.

Abbreviations: 95%CI = 95% confidence interval; ACS = Acute coronary syndrome; B = Belgium; CAN = Canada; CH = Switzerland; CMR = continuous registration of morbidity; D = Germany; GP = general practitioner; Ic = Iceland; N = number; NL = the Netherlands; Ref = referral; RfE = reason for encounter; SW = Sweden; UK = United Kingdom; US = United States of America

Addendum 6.B: supplementary figures S6.1-S6.6

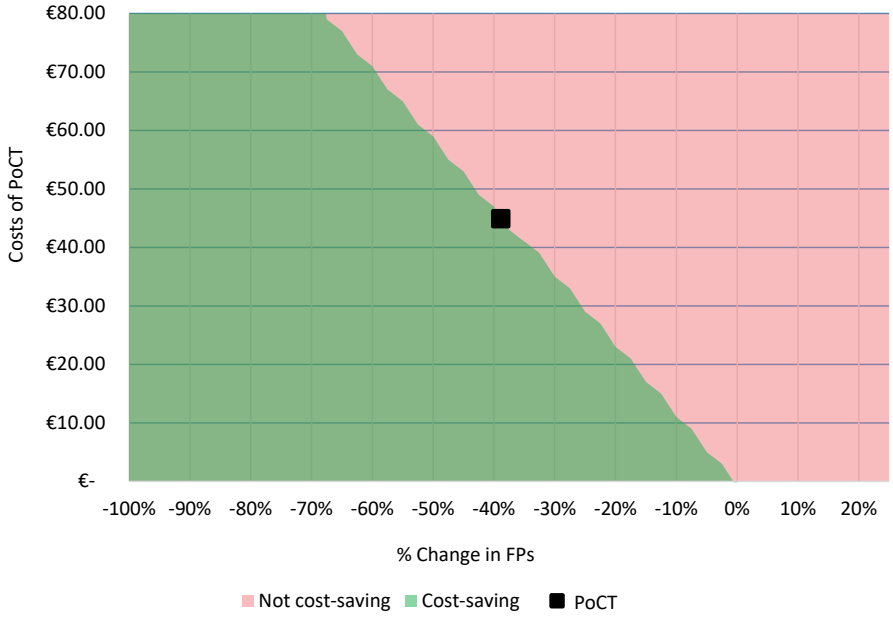

Figure S6.1: Two-way SA for 'NL and B data'.

Deterministic two-way SA showing the combined effect of a relative reduction in ACS negative referrals (FPs, on X-axis), and of a variation in costs of a PoCT (on y-axis), on the difference in total costs between PoCT and current practice (i.e. without PoCT). The analysis was performed based on the 'NL and B data'. When assuming that PoCT would only impact the %FPs and incur costs of the PoCT test (and leave all other model input parameters unaffected), a relative reduction of 39.5% in FPs is required to make the PoCT strategy cost-neutral (as represented by the black square, assuming a cost price of a PoCT test of €45,00).

Abbreviations: ACS = Acute Coronary Syndrome; FPs = 'false-positives'; PoCT = point of care test; two-way SA = two-way sensitivity analysis

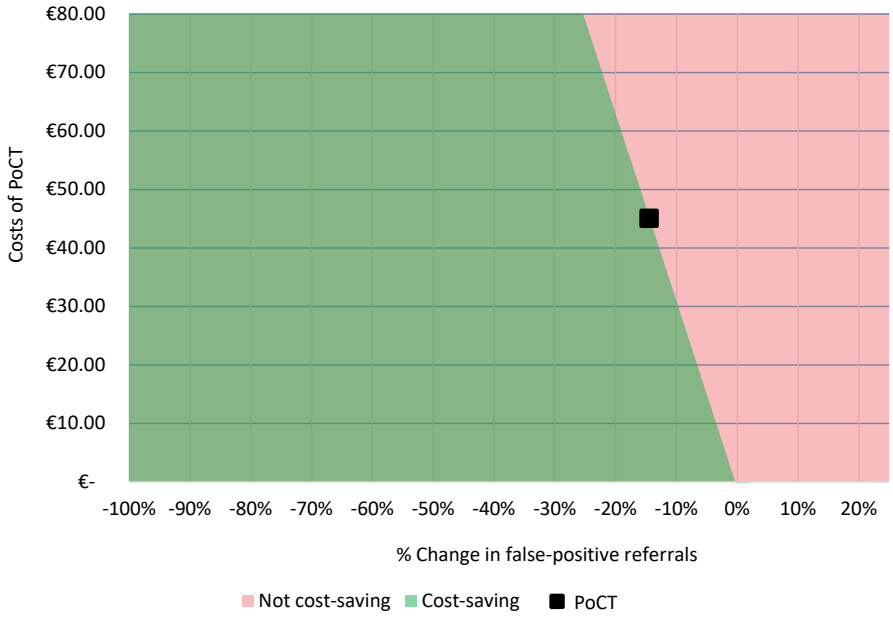

Figure S6.2*:* Two-way SA for 'combined data'.

Deterministic two-way SA showing the combined effect of a relative reduction in ACS negative referrals (FPs, on X-axis), and of a variation in costs of a PoCT (on y-axis), on the difference in total costs between PoCT and current practice (i.e. without PoCT). The analysis was performed based on the 'combined data'. When assuming that PoCT would only impact the %FPs and incur costs of the PoCT test (and leave all other model input parameters unaffected), a relative reduction of 14.5% in FPs is required to make the PoCT strategy cost-neutral (as represented by the black square, assuming a cost price of a PoCT test of €45,00).

Abbreviations: ACS = Acute Coronary Syndrome; FP = 'false-positives'; PoCT = point of care test; two-way SA = two-way sensitivity analysis

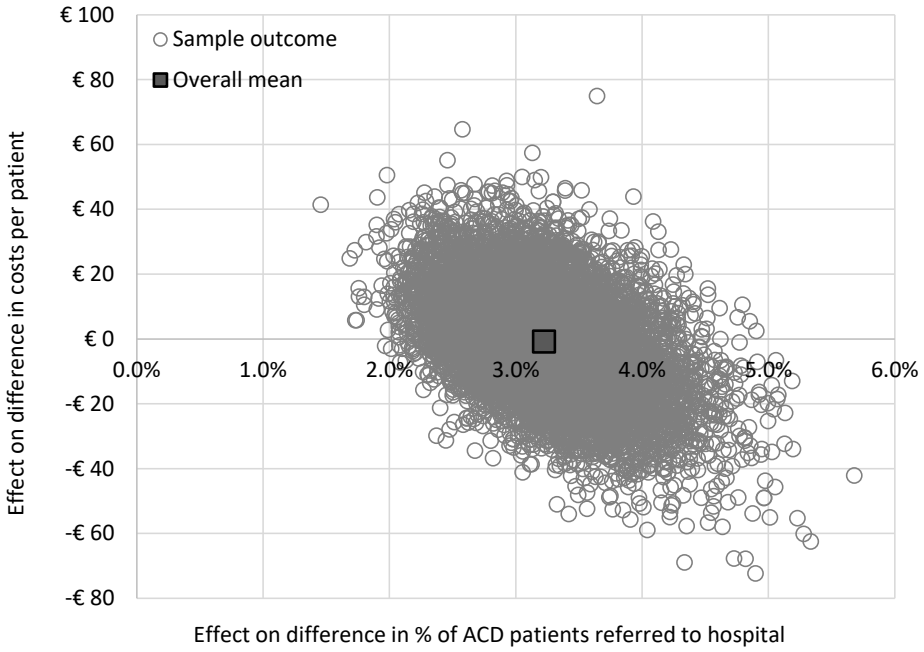

Figure S6.3: Incremental cost-effectiveness plane, based on 'NL and B data'.

This figure shows the result of 10,000 model simulations (PSA), and the mean value, based on the 'NL and B' data. Costs of a PoCT are set at € 45, and reduction of ACS negative referrals (FPs) is assumed to be 39.5% (cost-neutral as compared to current practice, see figure S2).

Abbreviations: ACS = Acute coronary syndrome; FPs = 'false positives'; PoCT = point of care test; PSA = probabilistic sensitivity analysis

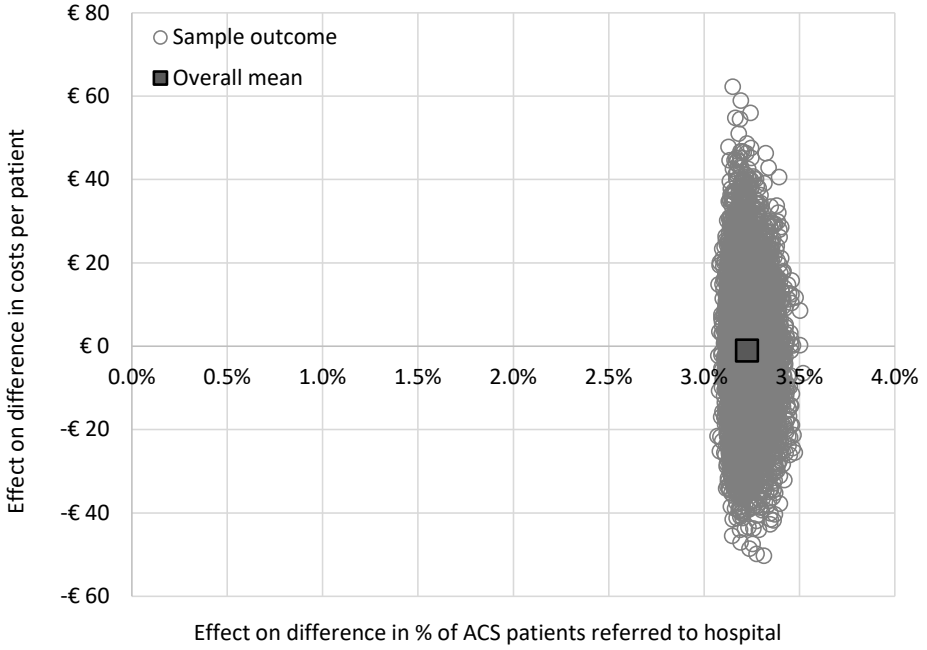

Figure S6.4: Incremental cost-effectiveness plane based on 'combined data'.

This figure shows the result of 10,000 model simulations (PSA), and the mean value, based on the 'combined data'. Costs of a PoCT are set at € 45, and reduction of ACS negative referrals (FPs) is assumed to be 14.5% (cost-neutral as compared to current practice, see figure S5).

Abbreviations: ACS = Acute coronary syndrome; FPs = 'false positives'; PoCT = point of care test; PSA = probabilistic sensitivity analysis

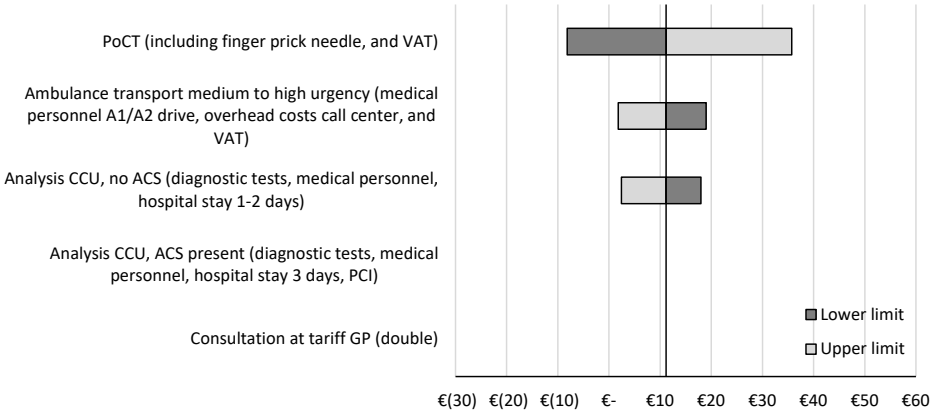

Figure S6.5: Tornado diagram of one-way SA's for 'NL and B data'.

Tornado diagram showing the impact of changes in input parameters on the difference in costs, based on the 'NL and B' data. Costs of a PoCT are set at € 45, and the reduction of ACS negative referrals (FPs) is assumed to be 39.5% (cost-neutral situation as compared to current practice, see figure S2). All input parameters were varied with 25% below and above the mean value.
Abbreviations: *ACS = Acute coronary syndrome;* CCU = Coronary Care Unit; FPs = 'false positives'; GP = general practitioner; PCI = percutaneous coronary intervention; one-way SA = one-way sensitivity analysis; PoCT = point of care test; VAT = value added tax

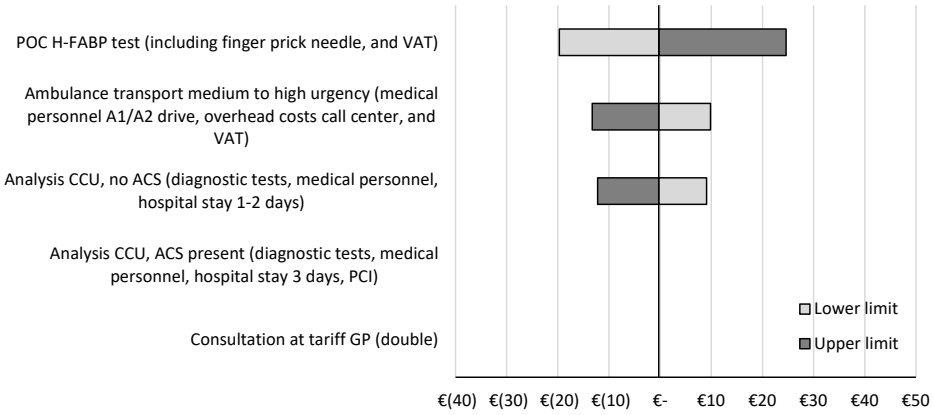

Figure S6.6: Tornado diagram of one-way SA's for 'combined data'.

Tornado diagram showing the impact of changes in input parameters on the difference in costs, based on the 'combined data'. Costs of a PoCT are set at € 45, and the reduction of ACS negative referrals (FPs) is assumed to be 14.5% (cost-neutral situation as compared to current practice, see figure S5). All input parameters were varied with 25% below and above the mean value.
Abbreviations: ACS = Acute coronary syndrome; CCU = Coronary Care Unit; FPs = 'false positives'; GP = general practitioner; PCI = percutaneous coronary intervention; one-way SA = one-way sensitivity analysis; PoCT = point of care test; VAT = value added tax

7

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'Biomarkers of Myocardial Cell Damage: Heart-Type Fatty Acid Binding Protein (H-FABP) for the Early Evaluation of Suspected Acute Coronary Syndrome'

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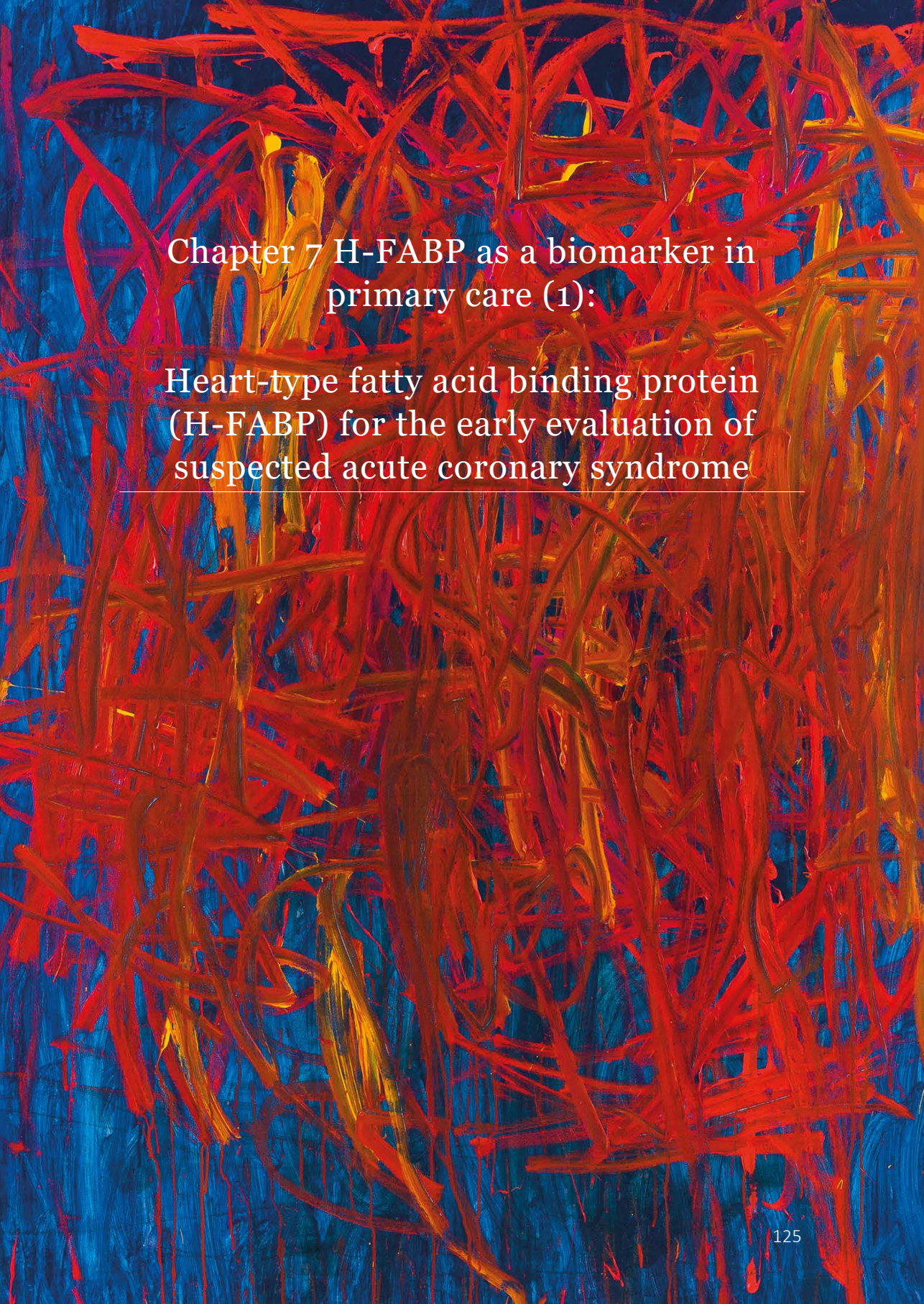

Chapter 7 H-FABP as a biomarker in primary care (1):

Heart-type fatty acid binding protein (H-FABP) for the early evaluation of suspected acute coronary syndrome

Abstract

Suspected acute coronary syndrome (ACS) represents a substantial healthcare problem and is responsible for a large proportion of emergency department admissions. Better triaging of patients with suspected ACS is needed to facilitate early initiation of appropriate therapy in patients with acute myocardial infarction and to exclude low-risk patients who can safely be sent home thereby limiting healthcare costs. Heart-type fatty acid-binding protein (H-FABP) is established to be the earliest available plasma marker for myocardial injury. In this chapter, the clinical utility of H-FABP for suspected ACS is evaluated. H-FABP shows added value in addition to cardiac troponin, especially in the early hours after onset of symptoms. Moreover, H-FABP identifies patients at increased risk for future cardiac events. It is concluded that measuring H-FABP along with troponin shortly after onset of symptoms improves risk stratification of patients suspected of having ACS in a cost-effective manner.

7.1 Introduction

7.1.1 H-FABP and ACS

In an earlier publication, heart-type fatty acid-binding protein (H-FABP) has been extensively reviewed.[1] Referral is made to this chapter for a basic, mainly biochemical approach with elaborate references. In this present chapter, H-FABP is reviewed in a rather clinical perspective, to underline the future perspectives of H-FABP in dealing with acute coronary syndrome (ACS) in primary and secondary care.

7.1.2 A Major healthcare problem: suspected ACS

Cardiovascular diseases remain the leading cause of death in industrialized countries with coronary artery disease being the most prevalent manifestation.[2] The clinical presentations of this include stable angina pectoris, unstable angina pectoris (UAP), myocardial infarction (MI), heart failure, manifestations of silent ischemia, and sudden death. Marked improvements in clinical treatment during the previous decades have resulted in increased survival of patients with acute coronary syndrome (ACS, i.e., MI or UAP). In contrast, diagnostic means have remained poor, especially in an early stage of acute coronary artery disease when patients may need immediate clinical treatment. While chest pain is the main symptom of chronic coronary artery disease and ACS, early assessment is hampered by the large number of patients presenting with chest pain of another, less severe, cause.

7.1.3 Dilemma in chest pain: ACS or alternative cause?

ACS represents a life-threatening manifestation of atherosclerosis causing a sudden and critical reduction in coronary blood flow due to intraluminal thrombosis. The therapeutic objective is to achieve rapid, complete, and sustained reperfusion by primary angioplasty or fibrinolytic therapy. Therefore, rapid triaging of patients presenting with chest pain is needed to facilitate early initiation of appropriate treatment in patients with acute MI. At the same time, low-risk patients who can safely be sent home without further expensive diagnostic analysis should be identified as well. The latter group currently represents up to 80 % of patients with suspected ACS.[3-5] Therefore, adequate ruling out of MI and of UAP is important in view of not only patient burden but also the large costs involved, which may include ambulance transfer, extensive diagnostic procedures, and hospital stay.

Thus, one of the main demands in the diagnostic process of coronary artery disease is to distinguish chest pain caused by coronary obstruction from chest pain with a benign course (thoracic wall pain, gastroesophageal reflux disease, etc.).[6] In the former situation, urgent specialist care is needed, which is rarely the case in the latter situation. Therefore, in a patient presenting with chest pain to primary or secondary care facili-

ties, the presence or absence of ACS should be crystal clear as soon as possible in order to design the most cost-effective diagnostic strategy in patients presenting with chest pain suggestive of MI. Among the most promising tools to reach this goal are biomarker tests that deliver immediate results at the point of care.

7.1.4 High sensitive troponin and additional biomarkers

As a sensitive biomarker of cardiac injury, high-sensitive troponin (hs-cTn) is of great importance in the current diagnostic strategy in suspected ACS. Using hs-cTn, acute MI can be ruled out based on a negative test result in an emergency setting as early as 3 h after onset of symptoms.[7] However, extension of these diagnostic rule-out strategies could lead to further cost reduction and more convenience for patients. Besides, time of onset of complaints can be uncertain. Altogether, in this field of increasing rule-out capacity, additional biomarkers that appear in plasma at an earlier point in time after MI can be of interest.

In the following paragraphs, the specific demands of ruling out ACS in primary care and at an early moment in secondary care are made explicit. Furthermore, it is described how available evidence indicates that heart-type fatty acid-binding protein (H-FABP, also designated FABP3) fulfills the criteria to be useful for triaging patients with acute chest pain particularly in the early hours after onset of symptoms. In this chapter, therefore, the clinical utility of H-FABP for the early evaluation of suspected ACS is depicted. Other biomarkers representing different aspects of an evolving acute MI such as markers for vascular stress (copeptin, N-terminal B-type natriuretic peptide or NT-proBNP), oxidative stress (myeloperoxidase), or plaque instability (placental growth factor) are not discussed in this chapter, since their diagnostic value is not well defined or considered not useful.[8,9]

7.2 ACS in primary care

Because a large number of patients with symptoms suggestive of MI will first be presented to primary care physicians, often during out-of-office hours, the general practitioner (GP) plays a crucial role in the early diagnosis and referral of these patients.[3-5] In case of suspected ACS, patients will be urgently referred to a secondary care facility, since early treatment of ACS markedly increases survival and quality of life.[10,11] The majority of patients presenting with chest pain to a physician (either in primary or in secondary care), however, do not suffer from an acute cardiac condition at all. In specialized care facilities such as coronary care units, only 50 % of patients presenting with chest pain are diagnosed with ACS, whereas in primary care, ACS is diagnosed in no more than 1.5–22 % of cases.[3,5,12]

In the remainder of cases, chest pain is mostly caused by a condition with beneficial outcome (e.g., gastroesophageal reflux disease, thoracic wall pain, etc.). Given the high prevalence of noncardiac chest pain, expenses to exclude severe disease in such patients result in a significant societal burden.[13] Moreover, even after expensive diagnostic research, reassuring patients is challenging.[14] Referring every patient with chest complaints would overwhelm secondary care facilities; however the GP is faced with serious diagnostic dilemmas since milder diseases with beneficial outcome can mimic ACS and vice versa.[15] To distinguish chest pain caused by ACS from chest pain of another cause therefore remains challenging.

7.2.1 ACS in primary care: diagnostic means

Contemporary diagnostic means are insufficient to overcome the difficulties in distinction between chest pain due to ACS and thoracic complaints due to alternative causes. This is caused by several reasons with two common factors: all tools are of limited availability in general practice or lack acceptable negative predictive value (NPV) and sensitivity. A few points, partly based on current literature and partly based on experience in daily practice, can be made.

First, literature confirms that symptoms and signs vary widely in chest pain possibly due to ACS, from none (in circa 25 %) to severe, and thus have limited diagnostic value in a significant amount of cases.[15-17] Second, validated decision rules for general practice to rule out AMI or ACS have been developed, but evidence for superiority of using these decision rules above the GP's judgment without these rules is lacking.[18,19] Third, the value of electrocardiography is limited, since only about 50–65 % of patients with ischemic cardiac disease have classic electrocardiogram (ECG) findings in the first time period after start of the complaints, while an ECG is sometimes not even available in general practice.[20] Fourth, since the definition of AMI is for an important part based on biomarker levels and AMI can in a significant amount of cases not be ruled out otherwise, blood analysis, especially measurement of the concentration of troponin, is a cornerstone in diagnosing as well as ruling out AMI. Venous blood samples, obtained in general practice, however cannot be analyzed on the spot, and adequate monitoring of the patient in expectation of the results is impossible. Moreover, serial measurement of plasma hs-cTn is the cornerstone in diagnosing as well as ruling out MI.[21,22] However, such a time consuming procedure is impossible to safely perform in primary care. This impairment could partly be overcome by usage of point-of-care (PoC) tests. Unfortunately, contemporary PoC troponin tests are less accurate due to detection limits higher than the widely used cutoff values for a positive test, usually set at the 99th percentile of a healthy population.[23]

7.2.2 Ruling out ACS in primary care: specific demands

Since diagnostic means accessible for GPs lack potency to safely rule out ACS, a low threshold for referring patients with possible ACS is maintained. Although ACS is present in the minority of cases, a majority is referred to a cardiologist to rule out ACS. In a Dutch cohort of such patients, 27 % of patients were not referred, in 8 % of whom ACS was diagnosed in a later stage, leading to a false-negativity rate of 2 %. Seventy-three percent of patients were referred, 75 % of whom were not diagnosed with ACS (false-positivity rate or "unnecessary referral rate" 54.8 %).[3,24] Patients that were referred and appeared to be ACS negative were diagnosed with alternative diseases with advantageous courses. Thus, over-referral of patients presenting with chest pain in primary care leads to a low number of missed cases of ACS but is an (expensive) burden to secondary care facilities.[25] Since unnecessary referral considerably outnumbers missed cases in the triaging of patients with suspected ACS in primary care, focus is rather on ruling out ACS and other urgent medical conditions as early as possible. Thus improvement of diagnostic tools aims at making referral unnecessary, without missing more cases of ACS, enabling limitation of overall healthcare costs. Besides, anxiety in patients undergoing unnecessary diagnostic procedures is reduced.

A PoC test with a high negative predictive value for ACS that delivers a clear result within several minutes is needed to reach this goal. Notably, such a PoC test is among the most demanded future tests by GPs.[26] An improved triage of patients with signs and symptoms suggestive of ACS would reduce unnecessary referral and associated cost and anxiety. Therefore, to enrich the diagnostic tools of a GP in thoracic symptoms and to reduce unnecessary referral in cases of clinical doubt, novel, immediately measurable biomarkers with strong potency to rule out myocardial infarction in single measurements are needed. Combined with signs and symptoms, such tools should be able to safely rule out ACS in a significant number of otherwise referred patients, without a rise in missed cases of ACS. Importantly, this would lead to a significant cost reduction. The number of referred patients would decrease, and in the remaining patients who are referred, ACS could be confirmed or ruled out as is common in secondary care.

In the field of pulmonary embolism and respiratory tract infections, diagnostic tools combining clinical signs and symptoms with the result of a PoC test have recently been introduced. Both increased efficiency by reducing unnecessary referral (in cases of suspected pulmonary embolism) or unnecessary treatment (in respiratory tract infections).[27-29] For ACS, a similar procedure has not yet been defined.

7.3 ACS in secondary care

Various marker proteins are known to be released into plasma after MI, each showing a distinct tissue specificity and unique release pattern (table 7.1). Of these, the cardiac troponins, i.e., troponin T (cTnT) and troponin I (cTnI), are more specific and, as measured by the latest generation of troponin tests, more sensitive than the traditional cardiac enzymes, such as creatine kinase (CK) and its isoenzyme creatine kinase MB (CK-MB), and therefore have become the standard in establishing a diagnosis and stratifying risk.[22] In patients with MI, plasma troponins initially rise about 3–4 h after symptom onset and remain elevated for up to 2 weeks due to slow proteolysis of the contractile apparatus in damaged cardiac myocytes.

There is no fundamental difference between cTnT and cTnI. The NPV of contemporary fifth-generation hs-cTn tests in an emergency care department has increased to 98–99 %.[30] Thus, evidence is growing that cardiac ischemia can be ruled out within 3 h after onset.[7] Moreover, UAP seems to be diagnosed less because of the increasing sensitivity of hs-cTn.[30] In new onset or altered chest pain where hs-cTn is negative, (severe) stable coronary artery disease is becoming increasingly diagnosed instead of UAP. Conversely, in cases where hs-cTn is slightly positive, MI is diagnosed according to the third universal definition of MI.[22] An elevated hs-cTn value, i.e., above the 99th percentile of a normal reference population, is a strong indicator of myocardial cellular damage and has a very low false positivity.

Ischemia is not the sole cause of myocardial injury, however. Several other diseases also lead to myocardial cellular damage, including pneumonia, pericarditis, and left ventricular stress. Using older-generation troponin assays, 30 % of patients testing positive had no coronary occlusion.[31] With the current high-sensitivity assays, this percentage is probably even higher. To solve this issue, in the third universal definition of MI, AMI is diagnosed when, besides an elevated plasma hs-cTn, a change over time is measured. When such a change is detected, a coronary cause of the cardiac injury is likely.[22] The magnitude of the change that is indicative of acute coronary occlusion is still open to debate. In the lower range of troponin results, an absolute change of 7 ng/L between two measurements is probably indicative of acute coronary disease, whereas in the higher range, a relative change of 20 % is needed.[32]

Table 7.1: Characteristics of plasma biomarkers for acute myocardial infarction

Marker protein	Molecular mass (kD)	First elevation in plasma after AMI* (h)	Peak plasma concentration (h)	Normalisation of plasma level** (days)
H-FABP	14.5	1 – 2	6 – 12	1 – 1.5
Myoglobin	17.8	2 – 3	6 – 12	1 – 2
Cardiac troponin I	22.5	3 – 8	12 – 24	7 – 10
Cardiac troponin T	37.0	3 – 8	12 – 24	7 – 10
Creatine Kinase MB	86	2 – 6	12 – 24	2 – 3

Several characteristics (molecular mass, first elevation in plasma after acute myocardial infarction (AMI), peak plasma concentration, and normalization of plasma level) of several widespread used biomarkers of cardiac ischemia.

* First elevation above the upper reference level of the marker protein.

** Dependent on (time of) reperfusion of the occluded vessels

7.3.1 Ruling out ACS in secondary care: specific demands

Further improvement of the care process could be realized if patients presenting with chest pain of acute onset in secondary care – either after referral by a GP or otherwise – would undergo rule-out as soon as possible. Ideally such rule-out would occur within 1 h after onset of complaints. Furthermore, rule-out would ideally be based on a solitary measurement, while positive results due to other causes of myocardial injury should be limited as far as technically possible.

7.4 Ruling out ACS in primary and secondary care

As expounded above, main demands for ruling out ACS in primary as well as secondary care are early rule-out using a highly sensitive test with a high NPV for ACS. Such test could be an algorithm combining signs, symptoms, and a biomarker result. Moreover, especially in primary care, results should be available for assessment within several minutes. However, time to assessment is of significance in secondary care too, when definitive rule-out is demanded as early as possible (within 1 h). Key words in the field of future diagnostic means in ACS therefore are *point-of-care devices* and *high negative predictive value*. In the next subheadings, both requirements for efficient triaging are depicted.

7.4.1 Point-of-care tests

Contrary to pharmaceuticals, the legislation for diagnostic tests in general, and point-of-care tests in particular, is very limited. PoC tests may enter the European market after receiving no more than a CE certificate, which includes several fundamental, mostly technical, and laboratory aspects of the test. Proven reliability and diagnostic accuracy

in daily clinical care do not belong to CE certification requirements. Consequently, primary care professionals took the initiative to start listing criteria to which PoC tests in their view should apply, and they simultaneously performed studies in daily clinical care, on the performance of relevant PoC tests.[33,34]

In primary care, PoC tests can be divided over (1) tests for (home) monitoring of patients who are unable to visit their GP; (2) tests for screening purposes, mostly as a service toward (future) patients; and (3) tests for ruling out particular diseases in patient presenting with symptoms possibly representing an underlying serious disease, like ACS. Preferably, all tests belonging to one or more of the above indications are fast, meaning they produce a test result within the duration of one consultation (i.e., 10 min). Furthermore, a PoC test for primary care must be reliable in the hands of non-laboratory trained personnel, it must have a better diagnostic accuracy than existing alternatives, its diagnostic accuracy must be investigated with the new PoC test as part of existing and accepted diagnostic algorithms, test results must adequately steer treatment or referral decisions, the test should be cost effective, costs of PoC testing must be properly reimbursed, PoC tests must be appreciated by both medical professionals and patients, and, last but not the least, a PoC test must be easy to implement in both the daily work-up of a GP and existing (laboratory) facilities of a particular clinic. Very few of currently in primary care used PoC tests apply to all requirements.[35]

Infectious diseases and ACS belong to the relatively small group of (potentially) life-threatening diseases presented in daily primary care, needing PoC tests, like H-FABP, for quickly reaching accurate diagnostic conclusions and referral decisions. But before deciding on a definite introduction of H-FABP in primary care, the above listed criteria must be evaluated in daily general practice circumstances.

7.4.2 Early diagnosis of ACS: plasma marker requirements

The "ideal" plasma marker to be used for evaluation of myocardial injury in patients presenting with chest pain suggestive of acute coronary syndromes in primary or secondary care would need to meet three criteria, i.e., (i) show absolute *myocardial specificity* and (ii) be *instantaneously released into the circulation* upon myocardial injury, while (iii) a test should be available that allows the accurate and *rapid (minutes) assessment* of its elevated concentration in plasma so as to permit the use of the test result in triaging of the patient. Unfortunately, such an "ideal" marker does not exist:[36]

i Cardiac specificity

Although the troponins show virtually absolute cardiac specificity and therefore have been adopted as primary marker for ACS diagnostics to be included in both the US and European guidelines for the management of ACS they appear in plasma only 3–8 h after onset of myocardial injury which in a substantial number of cases is too late to influence

the initial triaging process.[6] Hence, in cases where MI is not revealed on ECG, echocardiogram, or other imaging techniques, patients will be monitored up to 9–12 h to rule in or rule out an MI based on an elevated plasma troponin. For those patients that turn out not to have MI, the latter procedure involves a marked financial burden that should be avoided when possible.

ii Early release into plasma

H-FABP is the earliest marker to be elevated in plasma following myocardial injury and yet does not show absolute cardiac specificity because an elevation of plasma H-FABP could also be due to skeletal muscle injury. However, in view of the presence of H-FABP only in red (oxidative) skeletal muscle fibers and only in minute amounts (i.e., < 5 % of that in the myocardium), a significant release of H-FABP from skeletal muscle takes place merely in specific cases such as eccentric exercise.[37] In addition, in reported studies on the use of H-FABP for MI diagnostics to our knowledge, no such cases have been described in which plasma H-FABP was falsely elevated due to skeletal muscle injury.

iii Rapid test result

The availability of an appropriate test that allows the rapid assessment of elevated marker concentrations in plasma is crucial to aid in the diagnosis of MI. Because H-FABP nor the troponins show enzymatic activity, such test has to be based on immunochemical detection of the protein. For both markers tests are available for use in the hospital emergency room or chest pain unit. For instance, Randox has developed a turbidimetric H-FABP assay that provides a quantitative result with a range of 2.5–120 ng/ml in serum in 14 min (table 7.2). Tests for cTnT and cTnI have been developed and marketed by most diagnostic companies, yet not all provide a high-sensitive test that complies with the requirements of current standard definition.[22] To meet these requirements, high-sensitivity or ultrasensitive troponin assays (hs-cTnT and hs-cTnI) are needed. The limit of detection of these assays is 10 to 100-fold lower than that of the conventional troponin assays. This suggests their application for diagnosing smaller MIs otherwise undetected or for identifying MI earlier when abnormal troponin levels are below detection by conventional assays. Recently, PoC tests have become available for both H-FABP and the troponins; these will be discussed in a separate paragraph.

Table 7.2: Overview of H-FABP assays in plasma.

H-FABP assay	Test principle	Sample type	Detection limit (ng/ml)	Time to result (min)	Regulatory status (RUO/CE)	Reference
Laboratory immunoassays						
Random Evidence Investigator Cardiac Array	biochip	serum / plasma	0.15	20	CE	www.randox.com
Randox H-FABP immunoturbidimetric	turbidimetry	serum / plasma	0.75	14	CE	www.randox.com
Roche Diagnostics H-FABP	turbidimetry	serum / plasma	1.1	8	NR	
Markit-M FABP (Dainippon Pharmaceutical)	elisa	serum / plasma	1.25	75	RUO	www.bmassay.com
Hycult biotechnology H-FABP	elisa	serum / plasma / urine	0.1	50-120	RUO	www.hycultbiotech.com
Oxis Research H-FABP	elisa	serum	NR	90	RUO	www.oxisresearch.com
Point-of-care (bedside) tests *						
Rapicheck (Dainippon Pharmaceutical)	lateral flow	whole blood	6.2	15	CE	www.bmassay.com
CardioDetect (8sens.biognostic)	lateral flow	whole blood	7	15-20	CE	www.biognostic.de
QuickSens H-FABP (8sens.biognostic)	lateral flow	plasma / whole blood	0.6	15-20	CE	www.biognostic.de
H-FABP True Rapid Test (FABPulous)	lateral flow	whole blood	4	5	CE	www.fabpulous.com

Several characteristics (test principle, sample type, detection limit, time to result, regulatory status and reference) of currently available point of care and laboratory assays for testing heart-type fatty acid-binding protein.

* Rapicheck, CardioDetect, and H-FABP True Rapid Test are qualitative tests; QuickSens H-FABP uses a reader providing a quantitative test result

Abbreviations: CE= European conformity quality mark; H-FABP = Heart-type fatty acid-binding protein; NR =not reported; RUO = research use only

7.4.3 H-FABP as a plasma marker of cardiac injury

The cytoplasmic protein FABP has a relatively small size (14.5 kDa) and functions as an intracellular fatty acid carrier in parenchymal cells, thus supplying essential substrates for energy production in the myocytes.[38] It comprises as much as 1–2 % of total cardiac cytosolic proteins, making it one of the most abundant cytosolic proteins. H-FABP is also found in small amounts in (slow-twitch oxidative) skeletal muscle, in distal tubule cells of the kidney, and in some parts of the brain.[39] The potential of H-FABP to be used as plasma marker of myocardial injury was suggested first in 1988.[40] Its cytosolic occur-

rence, cardiac tissue abundance, and small size make that, upon myocardial cellular damage, H-FABP is released rapidly and in appreciable amounts to the interstitial space, from where it escapes through the endothelial clefts into the vascular space. While larger cytosolic proteins such as CK-MB (86 kDa, i.e., five times larger than H-FABP) appear in the interstitium simultaneously with H-FABP, these larger proteins are delayed in their plasma appearance because the speed of reaching the plasma compartment is governed by the permeability of the endothelial barrier (which is dependent on protein size) and by lymph drainage.[41] The troponins also appear in plasma markedly later than H-FABP, despite their relative small size (troponin T, 37 kDa, i.e., three times larger than H-FABP; troponin I, 22 kDa, i.e., 1.5 times larger than H-FABP). This is due to the fact that following cellular damage the troponins first need to be proteolytically cleaved from the contractile matrix.

As a result, H-FABP is the earliest available plasma marker of cardiac injury.[42,43] Release of H-FABP from injured myocardium is essentially complete, indicating that infarct size can be estimated from the cumulative release of H-FABP into plasma.[44,45] Because the subsequent clearance of H-FABP from plasma occurs via the kidneys, renal insufficiency could hamper such estimation.[46] Renal clearance of small proteins such as H-FABP is rapid and thus contributes markedly to maintaining a relatively low plasma reference concentration. In apparently healthy subjects, the plasma H-FABP concentration is between 1 and 2 ng/ml.[47-51] This is less than 0.0001 % of the tissue content (estimated at 170 µmol/L which is equivalent to 2500 µg/ml).[52] As a result, there is a steep gradient of H-FABP from myocardial cells to plasma which adds to the high sensitivity of this marker for tissue injury detection. Circulating levels of H-FABP are somewhat higher in males (ca. 1.9 ng/ml) than in females (ca. 1.5 ng/ml) and slightly increase with age, especially after 50 years, which most likely is explained by the decrease in renal function in elderly people.[46,51]

7.4.4 H-FABP, troponin: sensitive markers of myocardial injury

Representative mean plasma release curves of H-FABP and cTnT and, for comparison, myoglobin are shown in **figure 7.1**. These curves were recorded for 15 patients with MI, treated with reperfusion therapy, from whom blood samples were obtained frequently during the first 24 h of hospitalization.[43,53] Peak plasma concentrations of FABP and myoglobin are reached at about 4 h after onset of symptoms, whereas for cTnT this takes about 15 h (**figure 7.1**) and for CK-MB about 12 h (data not shown). Plasma FABP and myoglobin return to their respective reference values already within 24 h after MI, indicating the usefulness of both markers particularly for the assessment of a recurrent infarction.[54] This might be missed by CK-MB or the troponins as these markers return much slower to their normal plasma value. Importantly, for MI patients not treated with thrombolytics, H-FABP peaks after approximately 8 h and remains elevated up to 24–36 h after chest pain onset.[54] This latter finding indicates that the so-called diagnostic win-

dow of H-FABP for detection of myocardial injury in patients presenting with chest pain stretches to 24–36 h after onset of symptoms.

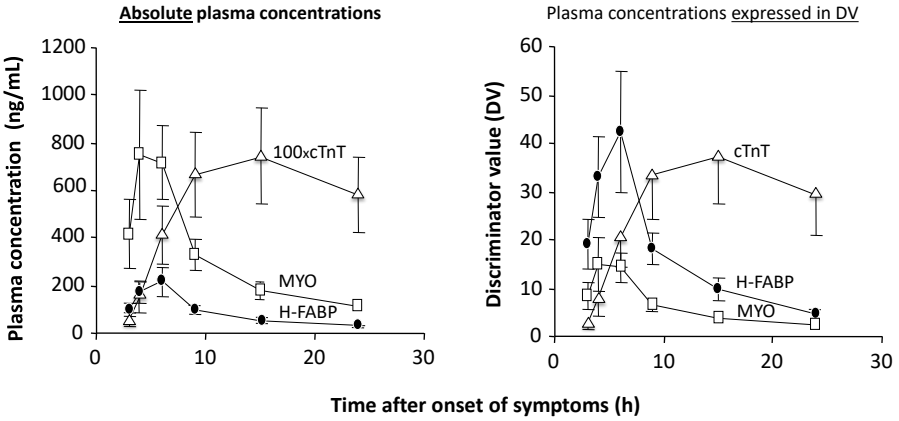

Figure 7.1: Plasma release curves for three cardiac marker proteins.

Mean plasma concentrations of heart-type fatty acid-binding protein (H-FABP) (●), myoglobin (MYO) (□) and cardiac troponin T (cTnT) (△) as a function of time after acute myocardial infarction for 15 patients who were treated successfully with reperfusion therapy and from whom serial blood samples were obtained up to 24 h after onset of symptoms. The data are presented as plasma concentrations in ng/mL (left panel) or relative to the upper reference limit for H-FABP (6 ng/mL), MYO (60 ng/mL) and cTnT (0.1 ng/mL) (right panel). Data refer to mean ± S.E.M. Adapted from Glatz et al, 2002, with permission.[43] Abbreviations: cTnT = cardiac troponin T; DV = discriminator value; h = hours; H-FABP = heart-type fatty acid-binding protein; MYO = myoglobin.

When expressed relative to the upper reference limit (or discriminator value) of each marker protein, it is clear that the rise in plasma concentrations is highest for H-FABP, closely followed by cTnT, and is much lower for myoglobin (figure 7.1, right panel). This difference is explained mainly by the markedly lower relative plasma reference concentrations of H-FABP and cTnT when compared to myoglobin. Taken together, the sensitivity of H-FABP and cTnT for cardiac injury detection markedly outperforms that of myoglobin (figure 7.1), as well as that of CK-MB (data not shown).

In more recent years, the performance of H-FABP for acute MI diagnosis has been centered on its comparison with cTnT/cTnI and/or hs-cTnT/hs-cTnI, thereby focusing on early exclusion of MI. Table 7.3 lists the larger and more recent clinical studies that have directly compared H-FABP and troponin applying quantitative assays that are currently in use. Quantitative tests are independent of the cutoff level that is chosen and thus allow a proper evaluation of the markers. In contrast, the performance of a qualitative test (such as a PoC test) depends on the assigned cutoff (see discussion below).

The emerging overall picture is that the area under the receiver operating characteristic (ROC) curve (AUC) for H-FABP is similar to that for the conventionally analyzed tro-

ponins (table 7.3, upper part). However, when analyzed with high-sensitivity assays, troponin exhibits a significantly greater AUC than H-FABP (table 7.3, lower part). Irrespective of the assay format used, the overall specificity is higher for troponin than for H-FABP; however the overall sensitivity is lower for troponin than for H-FABP. When distinction is made for patients seen early after onset of symptoms (e.g., within 3–4 h) versus patients admitted to the emergency room at a later point in time, the performance of H-FABP is significantly better in the first hours after MI.[55-58]. This finding is illustrated in the report by Haltern et al. (2010), who evaluated patient groups according to symptom duration (figure 7.2).[56] Sensitivity of H-FABP at presentation was more than twofold higher than that of conventional cTnT when symptom duration was less than 2 hours and increased to 100 % in the group with symptom duration of 2–4 hours. In this latter group, the sensitivity of cTnT was only 55 %. For patients admitted after having had symptoms for more than 4 hours, the sensitivity of the two markers switched: the sensitivity of cTnT reached 100 %, while that of H-FABP decreased significantly (figure 7.2). The data reported by McMahon et al. (2012) (table 7.3) reveal a similar bell-shaped curve for the sensitivity of H-FABP as a function of the admission delay.[57] The corollary is that combining H-FABP and cTnT (i.e., either marker elevated) provides a significant improvement in sensitivity for patients presenting less than 4 hours after symptom onset while being maintained at 100 % for patients presenting more than 4 hours after symptom onset (figure 7.2). These data indicate the usefulness of combining H-FABP and troponin for improved early diagnosis of ACS. In conclusion, each of the biomarkers has its own characteristics, with H-FABP being the preferred marker to diagnose AMI in the early hours after onset of symptoms and (hs-)cTnT or (hs-)cTnI the preferred marker from 3 to 4 h onward after presentation.

7.4.5 Combining H-FABP and troponin for ruling out ACS

As discussed above, especially in the early hours after onset of symptoms, H-FABP shows a superior sensitivity to troponin, even when high-sensitivity troponin tests are used. However, published data indicate that measurement of H-FABP alone cannot enable a safe rule-out of AMI at presentation, i.e., NPV > 97–98 % (see table 7.3, and references therein). This is illustrated by the results of a meta-analysis of 16 studies including 3,709 patients with suspected AMI, which reported for H-FABP a pooled sensitivity of 84 % (95 % confidence interval (CI) 76–90 %) and a pooled specificity of 84 % (95 % CI 76–89 %).[59] As mentioned above, combining H-FABP and cardiac-specific troponin (cTn) significantly improves the diagnostic sensitivity (figure 7.2), especially when using hs-cTnT or hs-cTnI assays. A systematic review by Carroll et al. (2013) on four clinical studies (total of 1,598 patients) on combinations of quantitatively assessed H-FABP and cTn versus cTn alone at presentation, revealed that the addition of H-FABP to cTn increased sensitivity from 42–75 % to 76–97 % but decreased specificity from 95–100 % to 65–93 %.[55,56,60-62]

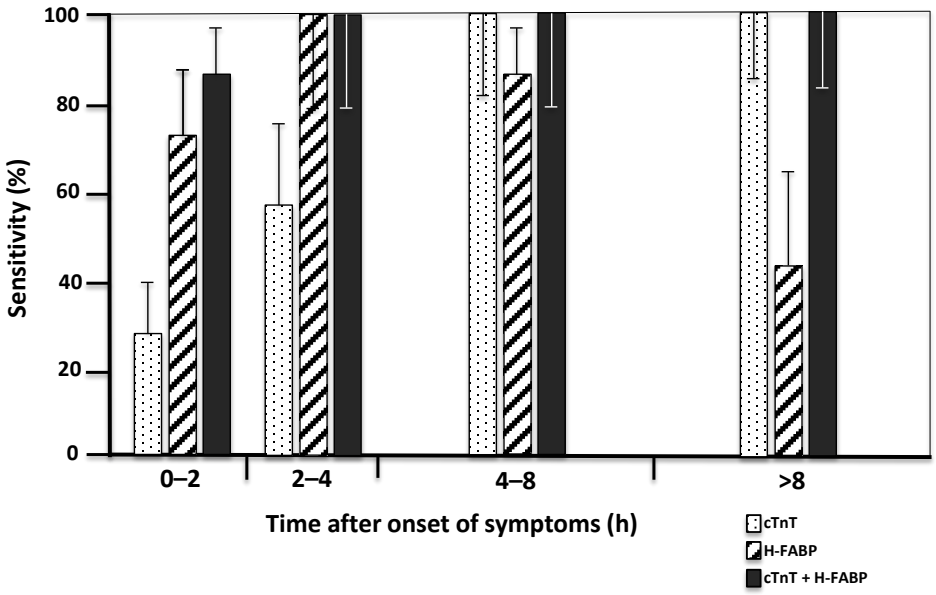

Figure 7.2: Diagnostic performance of plasma heart-type fatty acid-binding protein (H-FABP) and cardiac troponin T (cTnT) as a function of time after onset of symptoms suggestive of acute coronary syndrome.

Sensitivities for myocardial infarction of the markers separately and a combined approach (either one positive) are presented with varying symptom durations. Adapted from Haltern et al, 2010, with permission[56]. Abbreviations: cTnT = cardiac troponin T; h = hours; H-FABP = heart-type fatty acid-binding protein.

In a subsequent review, Lippi et al. (2013) analyzed eight studies (totaling 2,735 patients), including four studies applying qualitative H-FABP tests, to observe that the addition of H-FABP to cTn increased pooled sensitivity from 73 % to 91 % which however was counterbalanced by a decreased pooled specificity from 94 % to 82 %.[63] These reviews did not include the earlier extensive study (1,818 patients) described by Keller et al. (2011), combining quantitative H-FABP and hs-cTnI.[8] These investigators reported that the addition of H-FABP to hs-cTnI increased sensitivity from 73 % to 85 %, decreased specificity from 95 % to 91 %, and decreased positive predictive value (PPV) from 66 % to 60 % but increased the NPV from 95.9 % to 97.6 %.[8] The latter indicates that the NPVof the combined test fulfills the diagnostic requirements for application as a rule-out parameter. In this study, the time between chest pain onset and admission to the emergency room (first blood sample) was 4.3 h (range 2.0–13 h). It was not examined whether the performance of the combined markers is dependent on the time of presentation of the patient.

Table 7.3: Diagnostic performance of heart-type fatty acid binding protein (H-FABP) and cardiac troponin (cTn) for acute myocardial infarction.

Reference, number of participants	Admission time (h)*	H-FABP				cTn (cTnT of cTnI)			
		Cut-off (ng/ml)	AUC	Sensitivity	Specificity	Cut-off (ng/ml)	AUC	Sensitivity	Specificity
Conventional cTn tests									
Mion 2007[61], n = 132	3.8 (FR 1.5-13)	5.8	0.92	0.83	0.93	0.032 cTnI	0.75	0.55	0.98
McCann 2008[55], n = 415	0-4	5.0	0.77	0.73	0.71	0.03 cTnT	0.78	0.55	0.95
	5.3 (IQR 2.7-8.9)		0.74	0.76	0.61		0.88	0.75	0.94
Haltern 2010[56], n = 94	0-4	7.3	0.76	0.86	0.66	0.03 cTnT	0.71	0.42	1.00
	4 (CI 3-6)		0.71	0.71	0.65		0.87	0.74	1.00
Alhadi 2010, n = 100	<6	5.0	NR	0.80	0.92	0.032 cTnI	NR	0.56	0.81
Gururajan 2010, n = 485	<6	17.7	0.97	0.87	0.93	0.032 cTnI	0.77	0.54	0.95
Kurz 2011, n = 94	6.0 (IQR 2.5-15)	6	0.81	0.89	0.62	0.03 cTnT	0.72	NR	NR
Body 2011[62]	3.5 (IQR 1.8-7)	58	0.86	0.75	0.89	0.055 cTnI	0.70	0.42	0.96
Keller 2011[8], n = 1,818	4.3 (IQR 2.0-13)	5.8	0.89	NR	NR	0.032 cTnI	0.92	0.79	0.95
McMahon 2012[57], n = 1,128	0-3	5.2	0.84	0.64	0.84	0.037 cTnT	0.76	0.50	0.93
	3-6		0.89	0.85	0.89		0.85	0.68	0.94
	6-12		0.94	0.90	0.94		0.90	0.81	0.94
	12-24		0.97	0.90	0.91		0.98	0.96	0.94
	24-48		0.91	0.63	0.91		0.98	0.97	0.95
	>48		0.87	0.66	0.91		0.94	0.88	0.94
Ruff 2013[64], n=343	8.7 (IQR 5-14)	5	0.78	0.63	0.79	0.10 cTnI	0.91	0.77	0.97

Reference, number of participants	Admission time (h)*	H-FABP				cTn (cTnT of cTnI)			
		Cut-off (ng/ml)	AUC	Sensitivity	Specificity	Cut-off (ng/ml)	AUC	Sensitivity	Specificity
High sensitive (hs-) cTn tests									
Kurz 2011, n = 94	6.0 (IQR 2.5-15)	6	0.81	0.89	0.62	0.014 hs-cTnT	0.82	0.82	0.76
Keller 2011[8], n = 1,818	4.3 (IQR 2.0-13)	5.8	0.89	NR	NR	0.030 hs-cTnI	0.99	0.82	0.92
Eggers 2012, n = 360**	<8	5.8	0.71	0.39	0.95	0.014 hs-cTnT	0.74	0.79	0.75
Kagawa 2013, n = 114	NR	6.2	0.59	0.78	0.22	0.028 hs-cTnI	0.89	0.81	0.79
Reiter 2013[58], n = 1,074**	<3	4.2	0.85	NR	NR	0.014 hs-cTnT	0.92	NR	NR
	<12		0.84	0.72	0.80		0.94	0.93	0.77
Ruff 2013[64], n = 343	8.7 (IQR 5-14)	5	0.78	0.63	0.79	0.040 hs-cTnI	0.96	0.92	0.92
Cappellini 2013[76], n = 67	<8	3.5	0.84	1.00	0.39	0.014 hs-cTnT	0.81	0.81	0.56
Collinson 2014[83], n = 838	3.7 (IQR 2.6-5.8)	3	0.84	0.65	0.94	0.040 hs-cTnT	0.92	0.78	0.96
Bank 2015, n = 453	3.0 (IQR 1.8-6.8)	7	0.73	0.54	0.81	0.014 hs-cTnT	0.88	0.71	0.90
Jacobs 2015[82], n = 584	3.0 (IQR 1.8-5.1)	4	0.81	0.60	0.86	0.045 hs-cTnI	0.88	0.68	0.96

Comparison of recent clinical trials using quantitative tests of H-FABP and cTn and acute myocardial infarction as an outcome. Cut-off level (being the 99th percentile upper reference level used), area under the curve, sensitivity and specificity are given for both H-FABP and cTn.

* Median time from symptom onset to admission, with full range (FR), 95% confidence interval (CI), or interquartile range (IQR).** Non-STEMI patients only.

(Abbreviations: AUC = area under receiver operating characteristic (ROC) curve; CI = 95% confidence interval; cTn = cardiac specific Troponin; cTnI = cardiac specific Troponin I; cTnT = cardiac specific Troponin T; FR = full range; h = hours; H-FABP = Heart-type fatty acid-binding protein; hs-cTnI = high sensitive cardiac specific Troponin I; hs-cTnT = high sensitive cardiac specific Troponin T; IQR = interquartile range; non-STEMI = non ST-elevated myocardial infarction; NR = not reported)

In a study by Ruff et al. (2013), similar data were found.[64] The addition of H-FABP to a conventional cTnI assay significantly enhanced both the sensitivity (from 77 % to 92 %) and NPV (from 92 % to 97 %) of MI diagnosis. When H-FABP was added to hs-cTnI, the overall diagnostic accuracy was not improved when compared to the performance of hs-cTnI alone, but in early presenters (less than 6 hours after onset of symptoms) the combination did improve both sensitivity and NPV (each to 100 %).[64] In contrast, in the recent study by Reiter et al. (2013), no synergistic performance of H-FABP and hs-cTnT was reported, but in this study patients with ST-segment elevation in the initial ECG were excluded.[58]

7.4.6 Minimal myocardial injury

Patients with a clinical diagnosis of UAP often show an elevated plasma concentration of H-FABP.[65,66] Analysis of serial plasma samples after onset of symptoms has revealed that, also in these patients, there is a characteristic rise and fall of plasma markers reminiscent of their release from injured myocardium (figure 7.3).[43] This reflects the sensitivity of the marker H-FABP for myocardial cell injury and should not be labeled as false positive. Patients with such minimal (or minor) myocardial injury – also referred to as subclinical myocardial injury – may have a prognosis as serious as do patients with definite MI and therefore may benefit from similar medical treatment.[67] Interestingly, H-FABP has also been applied as plasma marker to identify minimal myocardial injury in nonalcoholic fatty liver disease.[68]

7.4.7 H-FABP and kidney function

H-FABP is cleared by glomerular filtration in the kidneys, and thus, H-FABP values can be elevated in case of severe kidney damage (eGFR < 30 ml/min). After myocardial injury, H-FABP is eliminated by renal clearance and values return to normal after 24–36 h. Therefore, it can be used up to 24 h after onset of complaints.

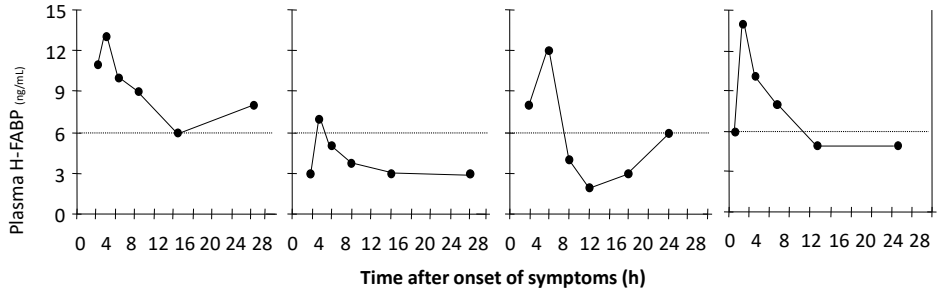

Figure 7.3: Plasma release curves of heart-type fatty acid-binding protein (H-FABP) for patients with unstable angina pectoris.

Examples of individual patients clinically diagnosed as having unstable angina pectoris. In each case plasma H-FABP was elevated above its discriminator value (of 6 ng/mL; dashed line) and shows a typical "rise and fall" pattern suggesting the occurrence of minor myocardial injury. Data obtained from the EuroCardi multicenter trial. Adapted from Glatz et al, 2002, with permission.[43] Abbreviations: h = hours; H-FABP = heart-type fatty acid-binding protein.

7.5 Primary care: extension of diagnostic strategies in ACS and potential role of H-FABP

Because in primary care the median period between onset of symptoms of MI and diagnostic assessment by the GP in most countries is 2–3 h and only in rural areas will be longer, the troponins cannot be used as the lead parameter for stratification of patients.[69] Furthermore, as stated above, although troponin levels are of high importance in ruling out AMI in a secondary care setting, unacceptable practical limitations are faced in using troponin in a primary care setting. Therefore, attention is drawn to alternative biomarkers. Of the biomarkers studied to date, H-FABP is placed among the earliest of plasma markers.[70] In case of AMI, elevation of plasma H-FABP can be detected within the first 1–2 h after onset of complaints.[42,71] Venous levels are increased to concentrations up to 40-fold the normal concentration.[53] Especially in cases of AMI, H-FABP levels correspond impressively to hs-cTnT levels.[12] Therefore, H-FABP may have meaningful potential in improving the triage of patients suspected of AMI.

The main requirement for any biomarker test in primary care is the possibility to measure and obtain a result within several minutes at the point of care, combined with a potency to rule out AMI with a high NPV that should be higher than 97–98 %. The NPV largely depends on sensitivity of the test and prevalence of the disease and less on specificity. At this moment, studies reviewing early PoC markers are characterized by methodological imperfections.[72] The function of H-FABP and other early markers combined with signs and symptoms in risk classification in a low-prevalence setting such as primary care is still to be determined.[58,73,74] When H-FABP testing is combined with signs and symptoms in a *diagnostic algorithm*, NPV hypothetically improves, and thus the number of patients that are referred by a GP, but turn out to have no ACS, could be reduced. Even with a moderate amount of false-positive results, such an algorithm could improve daily practice since currently the majority of patients without underlying ACS are referred to secondary care facilities.

A primary care study evaluating a PoC test on H-FABP did not lead to implementation of PoC testing in daily practice. Limiting test characteristics in this study were insufficient sensitivity (using a test cutoff point for H-FABP of 7 ng/ml), robustness (11 % invalid results), and a time to result of 15–20 min that is considered too long for acute situations in general practice. However, the PoC device for H-FABP used in this study used a cutoff value of 7 ng/ml, which is above the 99th percentile of 5.7 ng/ml as found in a

normal reference population.[51] Retrospective measurement of plasma H-FABP values revealed added value of H-FABP, although insufficient to reach a NPV of 98 % or more.

Reported 99th percentile values for H-FABP range from 5.2 to 7.3 ng/ml.[47-51,56] However, when derived from ROC curves, optimal cutoff levels for H-FABP at presentation to discriminate AMI from other causes of chest pain generally are lower, ranging from 3.3 ng/ml to 4.4 ng/ml.[58,75] Similarly, in a recent study of 218 consecutive patients with new-onset chest pain seen by a GP, the ROC-derived optimal cutoff for H-FABP was 4.0 ng/ml.[12] Improved diagnostic performance of H-FABP using such lower values has been documented and advocated.[60,64,76]

As a consequence, recently, a new PoC H-FABP test was designed to overcome the earlier mentioned limitations, by lowering the cutoff value to 4 ng/ml in a secondary care population, where 50 % of patients were diagnosed with AMI.[12] This is below the 99th percentile of H-FABP – in a normal reference population determined by the manufacturer in a healthy reference population of blood donors between 40 and 70 years of age.[51] Setting the cutoff value at 4 ng/ml leads to a diagnostic performance equaling that of hs-cTn. Thus, H-FABP has the same properties as hs-cTn with the generally used cutoff value of 14 ng/ml for high-sensitive troponin T, used as gold standard for AMI, whereas the earlier used PoC H-FABP test with a cutoff point of 7 ng/ml correlates to high-sensitive troponin T with a cutoff point of 50 ng/ml (table 7.4). Calculated NPV in a primary care population (with an incidence of ACS of 20 % or less) would reach 88.3 % in patients with a duration of complaints of less than 3 h and 97.9 % in patients with a duration of complaints of 3–24 h. Currently this PoC H-FABP test is studied in primary care.[77] At the cutoff point of 4 ng/ml, this PoC H-FABP test is regarded as positive by its users in 95 % of cases, and coefficient of variance (CV) is < 10 %. Furthermore, decrease of invalid results to an amount of less than 2 % has improved robustness, and a time to result of 5 min increases usability in an acute setting.

7.6 Secondary care: extension of diagnostic strategies in ACS and potential role of H-FABP

In secondary care, where safe rule-out based on one measurement would be preferable above several measurements with a given time interval, ongoing studies focus on the potency of hs-cTn as well as the potency of other biomarkers to be combined with a single hs-cTn measurement. cTnT or cTnI measurement has become the cornerstone of diagnosing MI in secondary care.[6,22] Adding copeptin or H-FABP to troponin in an early phase in emergency room settings increases sensitivity for ACS, but so far the combination has failed to safely rule out ACS in an early stage.[62,78] Until recently, troponin assays have gained sensitivity due to usage of highly sensitive techniques (resulting in hs-cTn measurements). The additional value of H-FABP testing besides hs-cTn in some studies

is small or unclear.[60,63,79,80] Several studies however have described an added value of H-FABP when measured besides troponin in an emergency room setting in an early phase.[57,60,81,82] As a solitary rule-out test at admission, hs-cTnT outperforms H-FABP slightly, but H-FABP tested in addition to hs-cTnT leads to an increase of sensitivity compared to hs-cTnT alone.[83] Recently, promising results were published of hs-cTn measurement combined with H-FABP measurement, ECG findings, and several clinical findings in early rule-out of severe underlying disease in patients presenting with chest pain.[84,85]

Table 7.4: Diagnostic values of H-FABP and hs-cTnT at different cut-off points.

Biomarke	Cut-off value	Sensitivity, depending on duration of complaints	Specificity, depending on duration of complaints	Expected NPV in primary care, (prevalence of AMI 17%), depending on duration of complaints
H-FABP	4 ng/ml	0-3 h 56,1% 3-24 h 91,5%	0-3 h 67,5% 3-24 h 80,7%	0-3 h 88,3% 3-24 h 97,9%
hs-cTnT	14 ng/ml	0-3 h 56,3% 3-24 h 91,5%	0-3 h 70% 3-24 h 68,4%	0-3 h 88,7% 3-24 h 97,5%
H-FABP	7 ng/ml	0-3 h 20,8% 3-24 h 76,3%	0-3 h 95% 3-24 h 91,2%	0-3 h 85,4% 3-24 h 94,9%
hs-cTnT	50 ng/ml	0-3 h 14,6% 3-24 h 78%	0-3 h 92,5% 3-24 h 94,7%	0-3 h 84,1% 3-24 h 95,5%
hs-cTnT	100 ng/ml	0-3 h 8,3% 3-24 h 72,9%	0-3 h 100% 3-24 h 98,2%	0-3 h 84,2% 3-24 h 94,6%

Sensitivity, specificity and negative predictive value (NPV) for acute myocardial infarction of H-FABP and hs-cTnT at different cut off points are given. Patients with an estimated glomerular filtration rate below 30 ml/min were excluded. NPV is calculated using a prevalence of AMI of 17%, as has been reported among patients presenting with chest pain in primary care (Willemsen et al, 2015 extended data).[12]

Abbreviations: AMI = acute myocardial infarction; h = hours; H-FABP = Heart-type fatty acid-binding protein; hs-cTnT = high sensitive cardiac specific Troponin T; NPV = negative predictive value.

7.7 Concluding remarks

Twenty-five years after the first report on the potential use of H-FABP as a plasma biomarker for myocardial injury, a large number of clinical studies performed by a variety of researchers applying a multitude of assay formats have now documented that H-FABP:

(i) is rapidly released from injured myocardium to be the earliest available plasma marker after an ischemic insult;
(ii) shows a sensitivity for cardiac injury detection that is similar to that of cTn and markedly better than that of all other known cardiac marker proteins;
(iii) for AMI diagnosis or exclusion shows added value on top of the recommended markers cTnT or cTnI, even when these are determined by high-sensitivity assays,

with the added value being larger for patients presenting early (less than 4 hours) after onset of symptoms;

(iv) in early (less than 4 hours after symptom onset) presenters may be suited as stand-alone diagnostic test for safely ruling out AMI. This is relevant especially for primary healthcare and would markedly increase cost-effectiveness of AMI diagnosis but awaits appropriate prospective trials.

H-FABP also is established to be a robust early predictor of future cardiovascular events or mortality independent of other cardiac risk factors including plasma troponin. As a result, the clinical utility of H-FABP both as early marker for the evaluation of suspected ACS and as prognostic marker is undisputed, especially when it is part of a diagnostic assessment combining several early findings.[53,84-89]

7.8 Future perspective

Despite the strong data available for H-FABP on its performance as biomarker for early triaging of patients with chest pain, FABP has not (yet) gained widespread use. Likely this will change in the near future, when more PoC tests (that employ optimal cutoff levels) and tests for clinical chemistry analyzers will become available. This would hold especially for tests that would give results within the time of a typical primary care consultation of 7–10 min. H-FABP then may be adopted as "early" plasma marker to be applied alone or beside a "late" marker such as cTnT or cTnI. In emergency care diagnostics, the future focus will be on very early exclusion of AMI. H-FABP could be excellently suited for this purpose especially when measured in combination with several other early findings in patients presenting with chest pain. In this way, a major reduction of costs otherwise spent on hospitalization and extensive diagnostic follow-up of non-AMI patients is enabled.[84,85] There is a large number of patients who present with chest pain (for instance, in Germany more than 750,000 annually).[90] Therefore, due to its diagnostic accuracy and due to the reliability of contemporary PoC tests, H-FABP may well become part of a new golden standard for improving quality yet reducing cost of care.

7.8.1 Potential applications to prognosis

Besides its (future) use as a biomarker for acute ischemic heart disease, H-FABP has been reported to be valuable as a prognostic marker to assess future risks on major cardiac events in patients. H-FABP is an early and independent predictor of future cardiovascular events and thus may help to improve long-term risk stratification of patients with acute chest pain.[91-95] Increased plasma H-FABP is a robust predictor of major cardiac events (such as death or MI) within 2 years in patients with chest pain and remained significant in a multivariate analysis that included both various plasma biomarkers and

echocardiographic assessment of cardiac morphology and function.[58,91-93] The NPV regarding 1-year and 2-year mortality was 99% (CI 98–100) and 98 % (CI 96–99), respectively, for plasma H-FABP < 2.7 ng/ml.[64] H-FABP plasma concentration identifies patients at risk for death and major cardiac events even when troponin and/or NT-proBNP are not elevated.[58,91,92] These findings are consistent when H-FABP is compared to troponin values obtained with hs-cTnT assays.[58,95] These findings confirm H-FABP to be a rapidly released and sensitive biomarker of minor myocardial injury as caused by ongoing and recurrent myocardial ischemia.

7.8.2 Potential applications to other diseases or conditions

In patients with congestive heart failure, plasma H-FABP identifies those at high risk for future cardiac events, independent of cTnT.[96,97] In patients undergoing coronary artery bypass grafting (CABG), H-FABP is a superior independent predictor of postoperative mortality and ventricular dysfunction.[98] H-FABP appears a promising early biomarker also for risk stratification of normotensive patients with acute pulmonary embolism and was found to perform markedly better than either plasma cTnT or right ventricular dysfunction.[99-102] In case of a negative H-FABP test, these patients had an excellent prognosis regardless of echocardiographic findings, while patients with an elevated plasma H-FABP had a complication rate of 23 %. In sepsis, H-FABP appears to be an independent prognostic factor for 28-day mortality.[103,104] Finally, an elevated H-FABP concentration measured during the follow-up of MI (median of 20 days post-MI) predicted longterm all-cause mortality and readmission for heart failure significantly better than did plasma cTnT, for a time interval up to 5 years post-MI.[105] In conclusion, when plasma H-FABP is elevated, a decreased clinical outcome can be expected in patients with chest pain, congestive heart failure, and pulmonary embolism, in patients after CABG, and in post-MI patients.

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'Heart-type fatty acid-binding protein (H-FABP) in patients in an emergency department setting, suspected of acute coronary syndrome: optimal cut-off point, diagnostic value and future opportunities in primary care.'

Robert TA Willemsen, Evie van Severen, Pieter M Vandervoort, Lars Grieten, Frank Buntinx, Jan FC Glatz, Geert Jan Dinant

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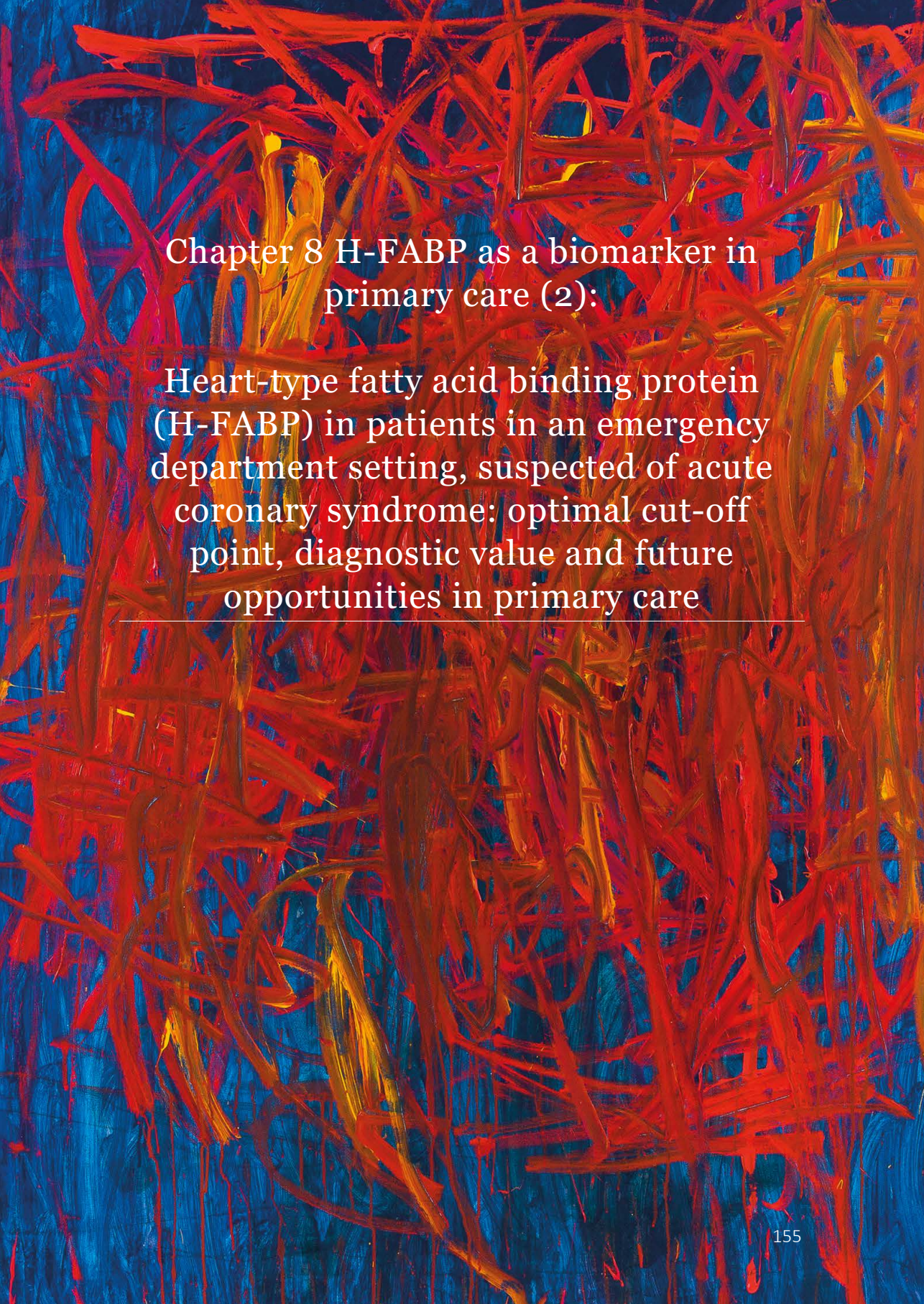

Chapter 8 H-FABP as a biomarker in primary care (2):

Heart-type fatty acid binding protein (H-FABP) in patients in an emergency department setting, suspected of acute coronary syndrome: optimal cut-off point, diagnostic value and future opportunities in primary care

Abstract

Background: Most patients presenting chest complaints in primary care are referred to secondary care facilities, whereas only a few are diagnosed with acute coronary syndrome (ACS).

Objective: The aim is to determine the optimal cut-off value for a point-of-care heart-type fatty acid binding protein (H-FABP) test in patients presenting to the emergency department and to evaluate a possible future role of H-FABP in safely ruling out ACS in primary care.

Methods: Serial plasma H-FABP (index test) and high sensitivity troponin T (hs-cTnT) (reference test) were determined in patients with any new-onset chest complaint. In a receiver operating characteristic (ROC) curve, the optimal cut-off value of H-FABP for ACS was determined. Predictive values of H-FABP for ACS were calculated.

Results: For 202 consecutive patients (prevalence ACS 59%), the ROC curve based on the results of the first H-FABP was equal to the ROC curve of hs-cTnT (AUC 0.79 versus 0.80). Using a cut-off value of 4.0 ng/ml for H-FABP, sensitivity for ACS of the H-FABP (hs-cTnT) tests was 73.9% (70.6%). Negative predictive value (NPV) of H-FABP for ACS in a population representative for primary care (incidence of ACS 22%) thus could reach 90.8%.

Conclusion: In patients presenting chest pain, plasma H-FABP reaches the highest diagnostic value when a cut-off value of 4 ng/ml is used. Diagnostic values of an algorithm combining point-of-care H-FABP measurement and a score of signs and symptoms should be studied in primary care, to learn if such an algorithm could safely reduce referral rate by GPs.

8.1 Introduction

8.1.1 Background

Patients with symptoms possibly due to acute coronary syndrome (ACS) frequently contact their general practitioner (GP) first. In case of suspected ACS, patients will be urgently referred to a secondary care facility since early treatment of ACS markedly increases survival and quality of life.[1,2] In primary care, however, differential diagnosis of chest complaints is broad, and ACS is present only in a minority of patients.[3] In addition, signs or symptoms decisively distinguishing ACS (with a low prevalence) from high prevalent diagnoses with an advantageous course have not been described earlier.[4,5] Furthermore, an electrocardiogram (ECG) reveals no signs of ischaemia in a significant number of patients.[6] Therefore, diagnostic means accessible for GPs lack potency to safely rule out ACS and a low threshold for referring patients with possible ACS is maintained. In literature, incidence of ACS among patients presenting symptoms suspected for ACS, is at most 22% and incidence of acute myocardial infarction (AMI) 17%.[7,8] In a Dutch cohort of such patients, 27% of patients were not referred, in 8% of whom ACS was diagnosed at a later stage, leading to a false negativity rate of 2%. A total of 73% of patients were referred, 75% of whom were not diagnosed with ACS (false positivity rate or 'unnecessary referral rate' 54.8%).[7,9] For a safer and more cost-effective referral policy by GPs, new diagnostic means should become available.

Serial measurement of plasma high sensitivity cardiac specific troponin (hs-cTn), the cornerstone in diagnosing as well as ruling out AMI, is impossible to perform in primary care.[10,11] Furthermore, current point-of-care troponin tests are less accurate due to detection limits higher than the widely used cut-off values for a positive test, usually set at the 99th percentile of a healthy population.[12] Heart-type fatty acid binding protein (H-FABP) is a small sized protein (molecular mass 15 kD).[13] Therefore, in case of AMI, elevation of plasma H-FABP can be detected within the first one–two hours after onset of complaints.[14-16] Several studies have described an added value of H-FABP when measured besides troponin in an emergency room setting in an early phase.[17,18] As a solitary rule-out test at admission, high sensitivity cardiac specific troponin T (hs-cTnT) outperforms H-FABP slightly but H-FABP tested in addition to hs-TnT leads to an increase in sensitivity compared to hs-TnT alone.[19] The value of H-FABP as a solitary marker in a primary care setting with a typical low prevalence of ACS has been studied once using a point-of-care H-FABP test. Prevalence of ACS was 22% in this study.[7] Safe implementation of this test in daily care was opposed by excessive false negative results. This was possibly caused by the relatively high cut-off value for H-FABP (7 ng/ml) of the point-of-care test and a high number of early presenters (presenting within three hours after onset of symptoms) included in this study. In daily general practice, however, a point-of-care test facilitating early rule-out of ACS and reducing unnecessary referral to secondary care facilities would improve the interface between primary and sec-

ondary care. It would add to an evidence-based approach of unselected and early presented problems that GPs are faced with and it would increase efficient use of diagnostic facilities in primary care. Thus, several main goals, as formulated by the European General Practice Research Network in the research agenda for general practice/family medicine and primary health care in Europe (http://www. egprn.org) are met.

8.1.2 Objectives

The main objectives of this study are twofold. First, the intention to determine the optimal cut-off value for a point-of-care H-FABP test. Second, to evaluate H-FABP as a potential marker for early triage of patients presenting complaints possibly due to ACS in primary care. Therefore, in an emergency department setting, plasma H-FABP and high sensitivity troponin T (hs-cTnT) levels were compared in an early phase after onset of chest complaints. This study is part of a larger project focusing on point-of-care H-FABP testing in suspected ACS in primary care.

8.2 Methods

8.2.1 Study design

A delayed type cross-sectional diagnostic study was performed in the emergency department of Ziekenhuis Oost-Limburg (ZOL), a large academic hospital in Genk, Belgium.

8.2.2 Patient selection and informed consent

Patients consecutively presenting with cardiac symptoms (presence of acute pain, discomfort or pressure in either chest, epigastric, neck, jaw or arm) or atypical symptoms suspected of cardiac origin (fatigue, nausea, vomiting, diaphoresis, faintness and back pain, without apparent non-cardiac source like a trauma) after triage by an emergency department physician were included. Excluded were patients from whom no informed consent could be obtained and patients with symptoms lasting more than 24 h (H-FABP levels return to baseline 24–36 h after onset of myocardial ischaemia).[13] Patients visited the emergency department on their initiative or they were brought in by an emergency service after referral by a GP or after contacting the emergency service themselves. All patients received routine care considering rule in and rule out of ACS and subsequent treatment. Treating physicians were blind to H-FABP results. A flowchart summarizing patient numbers and the process of inclusion is presented in figure 8.1.

Obtaining patients' written informed consent in an acute life-threatening situation was considered inconvenient. Furthermore, all medical acts were part of usual care, including blood sampling, except for the additional determination of H-FABP. Patients were, therefore, asked for written informed consent at a later stage. They could decide to withdraw

their consent then or at any time after. Only H-FABP results and clinical data of patients who returned a written informed consent were included in the study. The study protocol was in agreement with the WMA Declaration of Helsinki for Ethical Principles for Medical Research Involving Human Subjects and was approved by the Ethical Review Board of ZOL that specifically agreed on the solution for the consent procedure as described above.

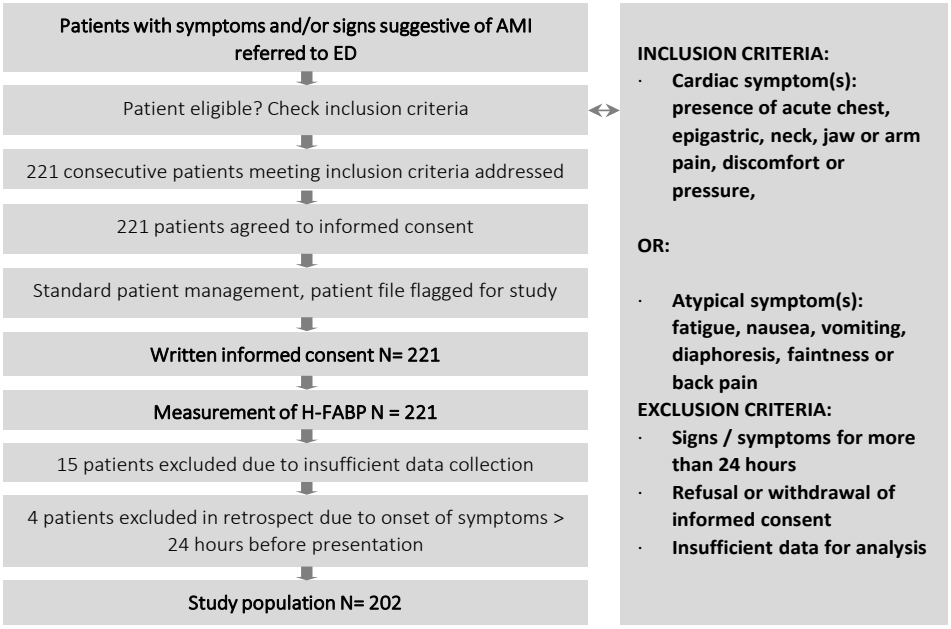

Figure 8.1: Study flow chart as executed in the emergency service of the hospital of Genk, Belgium.

Abbreviations: AMI = Acute Myocardial Infarction; ED = Emergency Department; H-FABP = Heart-Fatty Acid Binding Protein; N = number of patients

8.2.3 Measurements

Presence of the inclusion criteria, symptoms, ECG-findings, time of onset of symptoms, time of drawing the initial blood sample and all laboratory test results were documented. The initial blood samples to measure H-FABP and hs-cTnT were collected by the ambulance staff immediately upon arrival at the patient's site or arrival in our hospital. Routinely, in all venous blood samples—at presentation and any time later during the evaluation at the emergency department—plasma creatinine and hs-cTnT (using Elecsys Cobas fifth-generation hs-cTnT assay by Roche Diagnostics) were measured. Estimated glomerular filtration rate (eGFR) was measured in order to determine the influence of renal clearance on H-FABP and hs-cTn test results. Additionally, a quantitative H-FABP measurement was performed using an H-FABP assay developed by FABPulous BV (limit of detection: 0.5 ng/ml; 99th percentile in a healthy reference population: 5.3 ng/ml).[20]

8.2.4 Outcomes and (statistical) analysis

To allow for a final (gold standard) diagnosis, an ECG was recorded and serial venous blood samples to determine hs-cTnT—used as the reference standard—were analysed. Final diagnoses were established by propounding all data available after an in hospital follow-up of at least 12 h to an expert panel of one independent GP and one independent cardiologist. The expert panel had access to all clinical data including, if performed, the results of coronary angiography. In cases of disagreement, two extra cardiologists and GPs were consulted to determine the final diagnosis unanimously. The expert panel based all decisions on definitions of final diagnoses that were unambiguous and determined beforehand according to current guidelines.[10,11,21-24] The expert panel thus utilized the following possible diagnoses: acute myocardial infarction (AMI) with or without ST elevations on ECG (STEMI or NSTEMI), unstable angina (UA), stable angina, no coronary disorders. See **table 8.1** for complete definitions.

Table 8.1: Outcome definitions

Diagnosis	Definition as used by expert panel
AMI	Clinical presence of ACS with ECG-changes, hs-cTn results or results of imaging techniques supporting myocardial infarction. Exact cut-off values of hs-cTn were defined using the 99th percentile of the upper reference limit in a normal reference population, as is widely accepted.[10,11] In all cases of AMI, distinction was made between STEMI and non-STEMI.
Non-STEMI	A situation of complaints indicative for ACS combined with at least one measurement of hs-ctn above the 99th percentile and thereby a change between two measurements of at least 20%, without ST elevations on ECG recordings.[21]
STEMI	Complaints indicative for ACS combined with ST elevations on ECG recordings.[23]
UA	Clinical presence of ACS based on typical and recently developed or altered symptoms of myocardial ischemia without changes in ECG or hs-ctn indicative for AMI.[21]
SA	Angina pectoris occurring in a patient in predictable situations for months, without a recent change in severity or amount of exertion that is needed for angina pectoris to occur.[22]
No coronary disorder	No coronary disorder was diagnosed when AMI, SA and UA were excluded

Outcome definitions as used by the expert panel.

Abbreviations: ACS = acute coronary syndrome; AMI = acute myocardial infarction; hs-cTn high sensitive cardiac specific Troponin; NSTEMI = non ST elevated myocardial infarction; SA = stable angina; STEMI = ST elevated myocardial infarction; UA = unstable angina

Receiver operating characteristic (ROC) curves have been used to find the mathematical optimal cut-off point of the venous H-FABP-test for ACS as well as to compare H-FABP to the reference test, hs- cTnT. We used exact tests for comparisons between two areas under the curve (AUC).[25] Sensitivity, specificity, positive and negative likelihood ratios (PLR and NLR) for AMI and ACS of H-FABP (cut-off value between positive and negative: greater or equal to 4 ng/ml) and hs-cTnT (cut-off value between positive and negative: above 14 pg/ml) were determined, using outcomes of the expert panel as undisputed diagnoses. Potential negative and positive predictive value (NPV and PPV) in a primary care setting were calculated using Bayes' theorem. SPSS statistics version 21 and MedCalc were used for the statistical analyses. Before the start of the study, a power calculation revealed that 100 AMI patients were required to compare properly the performance of the plasma biomarkers.

8.3 Results

Agreement to the study consent was given by 221 consecutive patients. Four patients appeared to have complaints for more than 24 hours. For 15 patients, data collection was insufficient. Therefore, data of 202 patients meeting the inclusion criteria was analysed. Patient characteristics are displayed in **table 8.2**. Duration of the complaints ranged between 15 min and 23.3 hours. Median duration of complaints was 3 hours and 54 minutes. Of the 202 admitted patients, 119 (59%) were diagnosed with ACS among whom 111 (55% of the total population) had an AMI. A total of 157 patients were males, 93 (59%) of whom had an AMI. Of 45 female patients, 18 (40%) had an AMI. Median age was 62 years (range 26 – 93 years) and ages of AMI and non-AMI patients overlapped. The duration of the complaints at first contact was 0 – 3, 3 – 6, 6 – 12, and 12 – 24 hours in 82, 40, 56, and 24 patients, respectively. There was no relation between duration of the complaints and AMI risk (P= 0.11; Mann – Whitney). In 193 (96%) patients, the eGFR was > 30 ml/min.

Table 8.2: Patient characteristics

		All	AMI (%)	No AMI (%)
Number		202	111 (55)	91 (45)
Gender	male	157	93 (59)	64 (41)
	female	45	18 (40)	27 (60)
Age group	> 65 years	84	43 (51)	41 (49)
	≤65 years	118	68 (58)	50 (43)
Duration complaints at presentation	0-3 hours	82	46 (56)	36 (44)
	3-6 hours	40	23 (58)	17 (43)
	6-12 hours	56	29 (52)	27 (48)
	12-24 hours	24	13 (54)	11 (46)
eGFR	≥ 30	193	108 (56)	85 (44)
	< 30	9	3 (33)	6 (67)

Abbreviations: AMI = Acute Myocardial Infarction; eGFR = estimated glomerular filtration rate (using modification of diet in renal disease (MDRD) - formula

ROC curves based on the results of the first H-FABP and hs-cTnT tests, using ACS as outcome measure, were similar with an area under the curve (AUC) of 0.80 (95% CI: 0.735 – 0.856) for hs-cTnT and 0.79 (95% CI: 0.728 – 0.851) for H-FABP (**figure 8.2**). The optimal cut-point for H-FABP, based on inspection of the curve, was at 4.0 ng/ml, resulting in a sensitivity for ACS of 74.8% and a specificity of 71.1%. Additionally, in **table 8.3**, sensitivity and specificity of H-FABP for ACS at adjacent cut-off values are shown. Sensitivity of H-FABP is strongly related to time between sample taking and the first complaints. Sensitivity for AMI was 63, 88, 96, 83% for patients presenting 0– 3, 3– 6, 6– 12, 12– 24 h after onset of symptoms (**table 8.4**). During the first six hours after onset of complaints, sensitivity of H-FABP tended to be higher than that of hs-cTnT, without reaching statistical significance. However, within the first three hours after onset of

complaints, sensitivity of H-FABP is lower than sensitivity of H-FABP at a time interval of 3 – 24 hours after onset of complaints. Sensitivity for ACS (UA and AMI) is lower than sensitivity for AMI only (table 8.5).

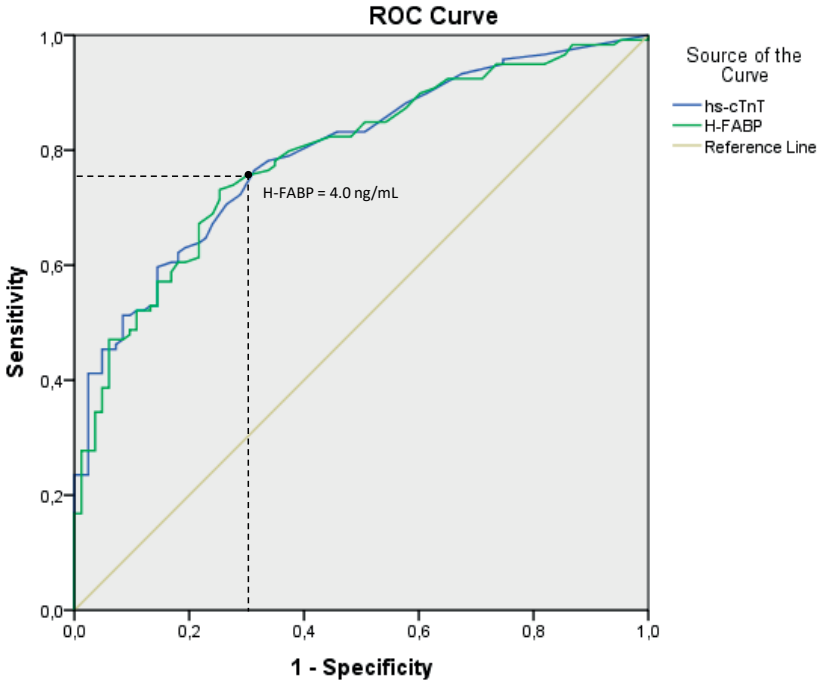

Figure 8.2: Receiver operating characteristic (ROC) curve of high sensitive Troponin and H-FABP, optimal cut-off point for H-FABP using ACS as outcome.

Abbreviations: ACS = acute coronary syndrome; H-FABP = Heart-type Fatty Acid Binding Protein; hs-cTnT high sensitive cardiac specific Troponin T; ROC curve = receiver operating characteristic curve

The overall sensitivity and specificity of H-FABP for AMI at presentation using a cut-off value of 4 ng/ml were 77.5% and 71.4% respectively. In a population of patients presenting chest complaints representative for primary care, with an incidence of AMI of 17%, NPV of H-FABP using a cut-off between positive and negative of 4 ng/ml would reach 93.9% for all patients and 97.1% for patients presenting complaints with a duration of at least three hours. For ACS, an overall sensitivity of 73.9% and a specificity of 71% was found. With an incidence of ACS in primary care among patients presenting chest complaints of 22%, NPV would reach 90.8% (table 8.6). If only data of patients presenting complaints with a duration of more than three hours are regarded, NPV would amount 94.8%. Referral is made to table 8.3 for NPVs of H-FABP at other cut-off values. Furthermore, negative and positive likelihood ratios as well as odds ratios — all independent of the incidence of ACS — are given in table 8.6.

Table 8.3: Sensitivity and specificity of H-FABP for ACS at different cut-off values between positive and negative.

cut-off value (ng/mL)	interval onset complaints – presentation 0-24h			interval onset complaints – presentation (h) 3-24		
	spec	sens	NPV	spec	sens	NPV
3.0	43.5	85.7	91.5	45.7	94.2	96.5
3.5	60.9	79.0	91.1	65.2	88.4	95.2
4.0	71.7	73.9	90.7	73.9	85.5	95.8
4.5	78.3	66.4	89.2	82.6	84.1	94.9
5.0	78.3	58.8	87.1	82.6	79.7	93.5
hs-cTnT	73.9	70.6	89.9	67.4	88.4	95.4

Sensitivity and specificity of H-FABP for ACS at different cut-off values are given for all patients presenting complaints with a duration of 0-24 hours and for all patients presenting complaints with a duration of 3-24 hours at presentation. NPV is estimated for a population representative for primary care (incidence of ACS = 22%). Sensitivity, specificity and NPV for hs-cTnT with a cut-off of 14 pg/mL is given for comparison.

Abbreviations: ACS = acute coronary syndrome; h = hours; H-FABP = Heart-type Fatty Acid Binding Protein; hs-cTnT = high sensitive cardiac specific Troponin T; NPV = negative predictive value; sens = sensitivity; spec = specificity

Table 8.4: Sensitivity and specificity of hs-cTnT and H-FABP.

interval onset complaints – presentation (h)	0-3		3-6		6-12		12-24		0-24	
	sens	spec	sens	spec	sens	spec	sens	spec	sens	spec
hs-cTnT	54.9	75.7	83.3	56.3	91.7	77.8	91.7	63.3	73.0	71.4
H-FABP	62.7	70.3	87.5	56.3	95.8	81.5	83.3	72.7	77.5	71.4
n	51	37	24	16	24	27	12	11	111	91

Sensitivity and specificity of hs-cTnT (cut-off 14 pg/mL) and H-FABP (cut-off 4 ng/mL) for AMI at different time intervals after onset of complaints

Abbreviations: h = hours; H-FABP = Heart-type Fatty Acid Binding Protein; hs-cTnT = high sensitive cardiac specific Troponin T; n = number of patients; sens = sensitivity; spec = specificity

If H-FABP was used as a stand-alone test at presentation, in this population of 202 patients among whom 119 patients were diagnosed with ACS, 31 patients (25 AMI, 6 UA) would test false negative (i.e., H-FABP < 4 ng/ml at presentation in an eventual case of ACS). Using only hs-cTnT at presentation, 35 patients would be missed (30 AMI, 5 UA). Among 24 false positive cases (i.e., H-FABP at or above 4 ng/ml in eventually ACS negative patients as based on serial hs-cTnT measurements and clinical judgment), 15 patients were diagnosed with either a non-cardiac mild disease or with stable angina, whereas 9 cases related to moderate to severe alternative cardiac diagnoses needing acute treatment. H-FABP and hs-cTnT values were compared in patients with an eGFR at or above 30 ml/min versus below 30 ml/min according to their ROC curves and AUC. There was no significant difference between both markers in both subgroups and for each marker the 95% confidence intervals overlapped with both renal function groups. However, only 9 patients with an eGFR below 30 ml/min were included.

Table 8.5: Sensitivity of hs-cTnT and H-FABP.

final diagnosis	STEMI		NSTEMI		AMI		UA		ACS	
interval onset complaints – presentation (h)	0-24	3-24	0-24	3-24	0-24	3-24	0-24	3-24	0-24	3-24
n	55	39	56	26	111	65	8	4	119	69
sens hs-cTnT	78.2	94.9	67.9	84.6	73.0	90.8	37.5	50.0	70.6	88.4
sens H-FABP	80.0	92.3	75.0	84.6	77.5	89.2	25.0	25.0	73.9	85.5
median plasma concentration hs-cTnT [25th, 75th percentile]	129 [15;2140]	502 [49;3740]	24 [13;114]	88 [18;325]	45 [13;490]	194 [31;2140]	6 [3;15]	3 [3;15]	40 [13;325]	163 [31;1830]
median plasma concentration H-FABP [25th; 75th percentile]	13.6 [4.3;24.9]	19.1 [10.0;25.6]	5.2 [3.9;11.3]	5.8 [4.2;11.7]	7.1 [4.1;18.4]	12.9 [5.4;21.6]	2.3 [2.2;3.5]	2.3 [2.3;3.1]	6.4 [3.9;18.1]	11.9 [4.9;21.2]

Sensitivity and median plasma concentrations [25th; 75th percentile] of hs-cTnT (cut-off 14 pg/mL) and H-FABP (cut-off 4 ng/mL) for STEMI, NSTEMI, all AMI (STEMI and NSTEMI), UA and all ACS (AMI and UA) at presentation, for all patients presenting complaints with a duration of 0-24 hours and 3-24 hours resp.

Abbreviations: ACS = acute coronary syndrome; AMI = acute myocardial infarction; h = hours; H-FABP = Heart-type Fatty Acid Binding Protein; hs-cTnT high sensitive cardiac specific Troponin T; n = number of patients; NSTEMI = non ST elevated myocardial infarction; sens = sensitivity; STEMI = ST elevated myocardial infarction; UA = unstable angina

Table 8.6. Predictive values and likelihood ratios.

		PPV		NPV		PLR		NLR		OR	
interval onset complaints – presentation (h)		0-24	3-24	0-24	3-24	0-24	3-24	0-24	3-24	0-24	3-24
hs-cTnT	AMI	34.3	39.5	92.8	97.3	2.55	2.94	0.38	0.13	6.75	22.0
	ACS	42.9	47.6	89.9	94.8	2.66	3.22	0.40	0.16	6.65	20.2
H-FABP	AMI	35.7	40.1	93.9	97.1	2.71	3.27	0.32	0.15	8.60	22.1
	ACS	42.9	48.6	90.8	94.8	2.67	3.36	0.36	0.20	7.41	17.2

PPV and NPV of hs-cTnT (cut-off 14 pg/mL) and H-FABP (cut-off 4 ng/mL) for AMI and ACS at time intervals of 0-24 hours and 3-24 hours after onset of complaints in a primary care setting with an incidence of AMI of 17% and ACS of 22%. PLR, NLR and OR of hs-cTnT (cut-off 14 pg/mL) and H-FABP (cut-off 4 ng/mL) for AMI and ACS at time intervals of 0-24 hours and 3-24 hours after onset of complaints.

Abbreviations: ACS = acute coronary syndrome; AMI = acute myocardial infarction; h = hours; H-FABP = Heart-type Fatty Acid Binding Protein; hs-cTnT high sensitive cardiac specific Troponin T; NLR = negative likelihood ratio; NPV = negative predictive value; OR = odds ratio; PLR = positive likelihood ratio; PPV = positive predictive value

8.4 Discussion

8.4.1 Main findings

The main objectives of this study were to determine the optimal cut-off point of H-FABP and to assess the possible diagnostic potency of plasma H-FABP in patients presenting with chest pain to the GP. The cut-off value for ACS of H-FABP, where sensitivity and specificity reached optimal values, is 4.0 ng/ml. Using this cut-off value for H-FABP, sensitivity for AMI of the H-FABP (hs-cTnT) tests was 77.5% (73.0%) for all patients at presentation and the sensitivity for ACS was 73.9% (70.6%). Based on the results of this study, H-FABP with a cut-off value of 4.0 ng/ml could reach an overall NPV for AMI of 93.9% and for ACS of 90.8% in an unselected primary care population (estimation based on a prevalence of ACS of 22%).

8.4.2 Strengths and limitations

The strength of this study is its performance in a population of consecutive patients presenting to an emergency setting covering the broad spectrum of referred and non-referred patients, complying with usual care for chest pain bridging primary and secondary care. The outcome measurement complied with recent evidence-based guidelines.[11] Besides, with our emergency department based data in a high prevalence setting of ACS, estimations for an NPV in an unselected primary care setting with a lower prevalence could be made. These estimations are limited by the fact that data was not gathered in a true primary care population, where sensitivity and specificity could differ slightly, as it is known that these parameters are influenced by different characteristics of a given population.[26] Thus, further research in primary care has to be carried out to evaluate the actual role of H-FABP in assessing patients who present complaints possibly due to ACS. All the more since in this study laboratory testing was used, whereas point-of-care testing in the field could be susceptible to more user error.

Compared to recent literature, a higher incidence of AMI was found in these patients of 55%. This is probably due to the presence of an emergency doctor that performs triage of patients before consultation by a cardiologist if necessary. Furthermore, using hs-cTnT combined with criteria meeting contemporary international guidelines, incidence of NSTEMI rises, while incidence of UA falls (only 4% in this population), as is described in current literature.[27]

8.4.3 Interpretation, implications for future research

H-FABP as a stand-alone test seems unable to rule in and out ACS, especially in early presenters (< 3 h) and in case of UA. However, the estimated NPV of 90.8% in a primary care population could be further improved if signs and symptoms are added to point-of-care H-FABP measurement in a clinical decision rule (CDR). False positivity of H-FABP

alone would be 29% for ACS, whereas currently 54.8% of patients presenting chest complaints to their GP are referred without an underlying ACS. Actual effect on referral decisions of a CDR combining signs, symptoms and point-of-care H-FABP testing in primary care merits further study. We, therefore, intend to test the incremental diagnostic value of a recently launched point-of-care H-FABP test with a cut-off value of 4.0 ng/ml combined with signs and symptoms in primary care.[28]

8.4.4 Conclusion

In patients presenting chest pain at an early stage, H-FABP and hs-cTnT have the similar diagnostic potency. The optimal cut-off value for H-FABP is 4 ng/ml. Possibly, H-FABP could be of value in reducing referrals by GPs of eventually ACS negative patients and in reducing missed cases of ACS in primary care. Thus, in future studies performed by GPs, the diagnostic value of a CDR, combining signs, symptoms and point-of-care H-FABP testing—using 4.0 ng/ml as a cut-off value—in a true primary care population should be studied.

8.5 References

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'The value of signs, symptoms and plasma heart-type fatty acid-binding protein (H-FABP) in evaluating patients presenting with symptoms possibly matching acute coronary syndrome: background and methods of a diagnostic study in primary care'

Robert TA Willemsen, Frank Buntinx, Bjorn Winkens, Jan FC Glatz, Geert Jan Dinant - the 'RAPIDA'-study team ('RAPIDA': RAPid test for Investigating complaints possibly Due to Acute coronary syndrome)

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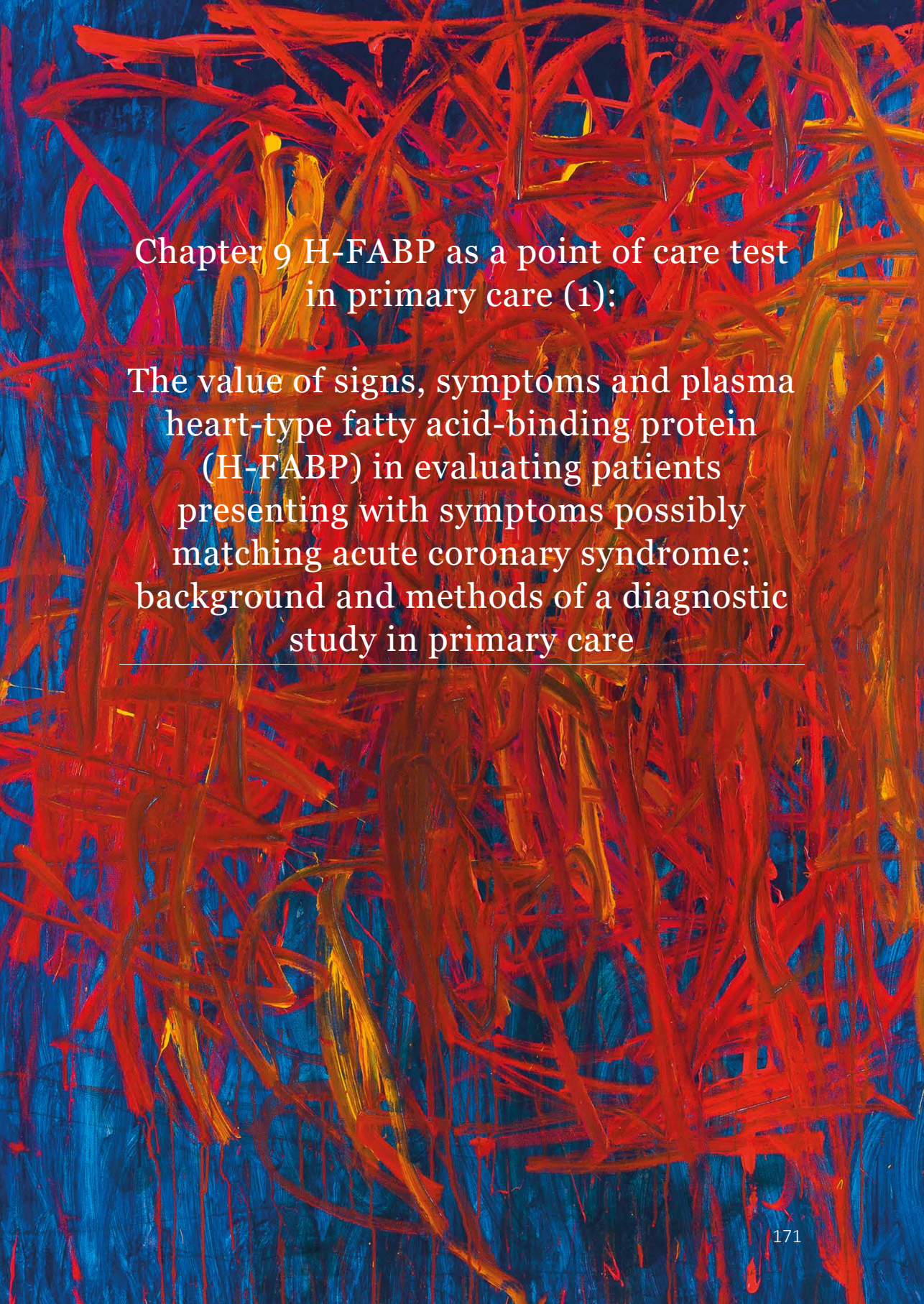

Chapter 9 H-FABP as a point of care test in primary care (1):

The value of signs, symptoms and plasma heart-type fatty acid-binding protein (H-FABP) in evaluating patients presenting with symptoms possibly matching acute coronary syndrome: background and methods of a diagnostic study in primary care

Abstract

Background: Chest complaints presented to a general practitioner (GP) are frequently caused by diseases which have advantageous outcomes. However, in some cases, acute coronary syndrome (ACS) is present (1.5-22% of cases). The patient's signs, symptoms and electrocardiography results are insufficient diagnostic tools to distinguish mild disease from ACS. Therefore, most patients presenting chest complaints are referred to secondary care facilities where ACS is then ruled out in a majority of patients (78%). Recently, a point of care test for heart-type fatty acid-binding protein (H-FABP) using a low cut-off value between positive and negative of 4 ng/ml has become available. We aim to study the role of this point of care device in triage of patients presenting chest complaints possibly due to ACS, in primary care. Our research protocol is presented in this article. Results are expected in 2015.

Methods/Design: Participating GPs will register signs and symptoms in all patients presenting chest complaints possibly due to ACS. Point of care H-FABP testing will also be performed. Our study will be a derivation study to identify signs and symptoms that, combined with point of care H-FABP testing, can be part of an algorithm to either confirm or rule out ACS. The diagnostic value for ACS of this algorithm in general practice will be determined.

Discussion: A safe diagnostic elimination of ACS by application of the algorithm can be of significant clinical relevance. Improved triage and thus reduction of the number of patients with chest complaints without underlying ACS, that are referred to secondary care facilities, could lead to a substantial cost reduction.

Trial registration: ClinicalTrials.gov, NCT01826994.

9.1 Background

9.1.1 Daily practice

Patients presenting with chest complaints caused by acute coronary syndrome (ACS) need urgent transport to a specialist setting.[1,2] In these situations, favourable outcome is inversely related to the time interval between onset of complaints and vascular rescue treatment. However, in daily practice, most patients experiencing chest complaints primarily apply to a general practitioner (GP). Within this population, benign conditions such as thoracic wall complaints, gastric disease or psychiatric and somatoform disease, largely outnumber cases of ACS.[3-5] In specialised care facilities such as coronary care units, 50% of patients presenting with chest pain are diagnosed with ACS, whereas in primary care, ACS is diagnosed in no more than 1.5-22% of cases.[6-8] Referring every patient with chest complaints would overwhelm secondary care facilities, however the GP is faced with serious diagnostic dilemmas since milder diseases with beneficial outcome can mimic ACS and vice versa.[9] Safe exclusion, rather than inclusion, is the main task of a GP in assessing chest complaints.

In primary care, where clearly circumscribed diseases with specific symptoms are embedded in a broad scope of illness and mild disease with less typical appearance, discriminative signs are usually scarce. This applies in particular to ACS, where history, physical examination and electrocardiography notoriously lack sensitivity and specificity as has been extensively surveyed.[10-12] With regard to chest pain, only few signs and symptoms, for example, the absence of pain on chest palpation or presence of pain on exertion, generate discriminative strength in diagnostic studies, although to a limited extent.[9,13,14] Altogether, clinical signs and symptoms are inappropriate for ruling out ACS or lack additive value above the clinical judgment by the GP, which on itself is correct in a majority of cases.[6] Weighing more abstract factors (e.g. contextual patient factors and altered presentation in time) probably leads to this fairly adequate clinical judgment of GPs.[15-17]

Because of these diagnostic problems in primary care, most patients presenting complaints possibly matching ACS are still referred to a cardiologist.[18] A low threshold for referring patients with chest complaints to secondary care is an effective strategy for the GP to avert missed cases of ACS.[19] In the Netherlands, this strategy results in 78% of referred patients that are ACS negative in the emergency room (positive predictive value (PPV) is 22%), whereas ACS is present in 5% of patients that are not referred (negative predictive value (NPV) is 95%) and the outcome is probably not severely affected by initially not referring (specificity and sensitivity of clinical assessment by GP: 55%, resp 81%)[6,20] To enhance triage by a GP and reduce patient burden in secondary care, new diagnostic tools should become available.[21] Combined with signs and symptoms, such tools should be able to safely rule out ACS in a significant number of otherwise

referred patients, without a rise in missed cases of ACS. Importantly, this would lead to a significant cost reduction. The number of referred patients would decrease and in the remaining patients who are referred, ACS could be confirmed or ruled out as common in secondary care.

In the field of pulmonary embolism and respiratory tract infections, diagnostic tools combining clinical signs and symptoms with the result of a point of care (PoC) test have recently been introduced. Both increased efficiency by either reducing unnecessary referral (in cases of suspected pulmonary embolism) or treatment (in respiratory tract infections).[22-24] For ACS, a similar procedure has not yet been defined.

9.1.2 Biomarkers and point of care testing in primary care

Cardiac troponin T or I (cTnT or cTnI) measurement has become the cornerstone of diagnosing acute myocardial infarction (AMI).[25-29] Some promising novel biomarkers have featured in recent literature, for example, copeptin and heart-type fatty acid-binding protein (H-FABP).[30-32] Adding measurements of these markers to troponin in an early phase in emergency room settings increases sensitivity for ACS, but so far the combination has failed to safely rule out ACS in an early stage.[33,34] Until recently, troponin assays have gained sensitivity due to usage of highly sensitive techniques, referred to as high sensitive cardiac troponin (hs-cTn). The additional value of H-FABP testing besides hs-cTn is unclear.[35,36] At this moment, studies reviewing early PoC markers are characterised by methodological imperfections.[37] The function of H-FABP and other early markers combined with signs and symptoms in risk classification in a low prevalence setting such as primary care is still to be determined.[38-40]

An earlier study in primary care evaluating a PoC-test on H-FABP did not lead to implementation of PoC-testing in daily practice because of a lack of NPV.[20] However, the PoC device for H-FABP used in this study used a cut-off value of 7 ng/ml, which is above the 99th percentile of 5.7 ng/ml as found in a normal reference population.[41] Retrospective measurement of plasma H-FABP values revealed added value of H-FABP, although insufficient to reach a NPV of 98% or more. Recently, a potential gain in sensitivity for PoC-testing has been found by lowering the cut-off value to 4 ng/ml in a secondary care population, where 50% of patients were diagnosed with AMI.[8] Setting the cut-off value at 4 ng/ml leads to a diagnostic performance equalling that of hs-cTn. Calculated NPV in a primary care population (with an incidence of ACS of 20% or less) would reach 88.3 % in patients with a duration of complaints of less than 3 hours and 97.9% in patients with a duration of complaints of 3–24 hours.

When H-FABP-testing is combined with signs and symptoms in a *diagnostic algorithm*, NPV hypothetically improves and thus the number of patients that are referred by a GP but turn out to have no ACS, could be reduced. Even with a moderate amount of false positive results, such an algorithm could improve daily practice since currently, the

majority of patients without underlying ACS are referred to secondary care facilities. Thus, our hypothesis is that net reduction of referral rate – without an increase in missed cases of ACS – in patients presenting chest complaints to their GP could be accomplished by the aforementioned algorithm including PoC H-FABP-testing. Therefore a PoC H-FABP-device meeting the demand of a lower cut-off value of 4 ng/ml has recently been developed by FABPulous B.V. We intend to study the diagnostic value of this device in primary care. The methodology of the study is presented in the remainder of this article in order to inform colleagues in the same research field, to anticipate forthcoming results of our study and to prevent publication bias or violation of the protocol during the running time of the study.

9.1.3 Study design and objectives

This current study is a derivation study to identify signs and symptoms that, combined with point of care heart-type fatty acid-binding protein (PoC H-FABP) testing, can be part of an algorithm to confirm or rule out ACS (meaning AMI and unstable angina (UA)) and AMI alone in a population of patients with complaints possibly due to myocardial ischaemia in general practice. Thus, stage 2 of the 6 major stages in the development and testing of a clinical decision rule as defined by Stiell and Wells will be studied.[42] The diagnostic value of the algorithm will be studied and compared to regular assessment by a GP without PoC H-FABP testing using a delayed type cross-sectional diagnostic model. Both ACS and AMI as a subgroup of ACS will be analysed as final diagnosis. The cost-effectiveness of the test will also be evaluated. The study commenced in November 2013 and will run for two years. External validation of the algorithm derived from this study needs to be performed in future studies.

9.2 Methods

9.2.1 Recruitment. Inclusion and exclusion criteria

Two hundred and ten GPs in four regions in the South and Southeast of the Netherlands and the Northeast of Belgium, including both urban and rural areas, will be informed by e-mail of our study and given the opportunity to respond. The first 60 GPs that decide to participate will receive a detailed training in using the test and performing all relevant research activities in order to include ten successive eligible patients, making a total of 600 patients. Inclusion will take place at any time during the day and night, including either during consultation in a primary care facility or during home visits by participating GPs. During evaluations in the study period with participating GP's, adherence to the protocol and actual recruitment of consecutive cases will be checked and reported.

Patients presenting to the GP with any new-onset chest pain or pressure (ventral, dorsal and/or lateral), any left or right upper arm pain or any pain in the epigastric, neck or jaw region, at time of presentation not lasting for more than 24 hours, that is considered to be of possible cardiac origin by the GP will be included. Patients presenting burning sensation on the chest not typical for gastric reflux or anxiety with referral to the chest region are also eligible.

Patients presenting other, less specific complaints possibly matching ACS (dyspnoea, nausea, fatigue, etc.) will only be included if at least one of the above mentioned complaints of pain is co-presenting. Patients will be excluded if an obvious emergency is present (haemodynamic instability, otherwise severely ill patient, etc.). Patients will be excluded if symptoms are present for more than 24 hours, if written informed consent is refused during presentation or withdrawn afterwards, if a traumatic cause is present, if complaints are presented that can be regarded as a recurrence of earlier complaints with clear diagnosis (hyperventilation, stable angina) or in case of death of unidentified cause.

9.2.2 Data collection

Eligible patients will be evaluated by the GP using the following work up schedule:

1. The GP asks written informed consent using a short version of the consent document in the Netherlands or oral informed consent in Belgium.
2. The GP uses the standardised case report form (CRF-HA) for documentation of history and physical examination. If available and if considered as indicated by the GP, an electrocardiogram (ECG) is performed and documented by the GP.
3. The GP is instructed to fill out the presumptive diagnosis together with the decision whether or not to refer to a cardiologist, *before* performing the H-FABP test.
4. The GP obtains one drop of blood from the patient's finger and starts the PoC H-FABP test. While the test is running, the GP replaces the test in its cardboard package.
5. At this moment, the GP should wait for no less and no longer than 5 minutes before taking the device out of the package again and reading the result. If the GP is still working on point 1–3 as mentioned above in the 5 minutes waiting time, he cannot be influenced by discolouration of the test.
6. Five minutes after starting the test the result is read. The result has to be added to the CRF-HA directly.

By filling out the presumptive diagnosis together with the decision whether or not to refer to a cardiologist on the CRF-HA before reading the result of the PoC H-FABP-test, the regular decision by the GP whether or not to refer to a cardiologist, which is not influenced by the test result, will be formally recorded. Thus, we will be able to compare this regular care with an algorithm using standardised signs and symptoms with

PoC H-FABP-testing. This procedure is seen as the next-best option after complete blinding participating GPs for the test result, which is impossible to realise as test results must be read at the point of care within 5 minutes.

GPs will be instructed to base their referral decisions on the current guidelines on ACS, as is common in the Netherlands and Belgium.[43] Participating GPs will be informed that the PoC H-FABP test is currently under study and that the test results should not influence their decision to refer. Only in the few cases that a PoC H-FABP test is positive after an initial decision not to refer, referral policy will be different from usual care since in that rare occasion, the GP is advised to refer. By following the registration work up as mentioned above, we can still conclude that principally, a referral wouldn't have been made.

Patients that are not referred to secondary care will be instructed and facilitated to have a venous blood sample drawn within the interval between three hours to three days after onset of complaints. Test results will be primarily used to exclude AMI in non-referred patients based on hsTn analysis. However, the GP is instructed to take notice of the result. If the troponin value is elevated, referral to a cardiologist must take place. Furthermore, renal function, based on creatinine and glomerular filtration rate using MDRD-formulas, will be determined. Collected samples will be preserved for a maximum of 15 years for possible future analysis when relevant.

9.2.3 Final diagnosis

The participating GP will send the CRF-HA (and ECG, if present) to the research team. The research team will contact the GP and, if referral has taken place and if necessary, the hospital, 30 days after inclusion to collect all relevant patient data. Final diagnosis will be established by an expert panel of one independent GP and one independent cardiologist, based on the outcome definitions. If agreement is not reached within the panel, extension will automatically take place to a panel of two cardiologists and two GPs. The expert panel will be blinded to the PoC H-FABP test performed at initial presentation, but will be given access to all other data. This kind of delayed-type reference standard using an expert panel is considered a reasonable alternative, especially in a low-prevalence setting if the definite reference standard (for example, serial troponin measurements or coronary angiography) is reasonably unavailable for reasons of patient risk, cost, etc.[44] In cases where final diagnosis of our expert panel appears to be different from the clinical diagnosis made by the treating clinicians, we will follow the diagnosis made by our expert panel.

The definitions of cardiac ischaemic situations – 'stable angina' (SA), 'unstable angina' (UA), 'acute myocardial infarction' (AMI) and 'heart-related sudden death' – will be standardised for this study based on current literature and have been settled during a panel discussion with two cardiologists, one GP, an ethicist and two researchers before

the trial started. SA will be defined as angina pectoris occurring in a patient in predictable situations for months, without a recent change in severity or amount of exertion that is needed for angina pectoris to occur, whereas UA will be defined as new or altered chest pain due to ischaemia without myocardial cell damage reaching a level where significant changes in myocardial damage-markers can be measured.[45,46] AMI will be defined according to the third universal definition of AMI.[29] This definition is mainly based on the combination of clinical evidence and a rise or fall in biomarker values, preferably hsTn. Exact cut-off values for hsTn will depend on the 99th percentile as is widely accepted. Further judgement on whether STEMI (*ST-segment elevation myocardial infarction*) or NSTEMI (*non-ST-segment elevation (non-Q wave) myocardial infarction*) has occurred will depend on the presence of ST-elevations on the ECG.

The classification 'none of these' will refer to complaints that are caused by other than cardiac diseases, or by cardiac, non-ischaemic diseases. Those conditions can be described by 'atypical thoracic complaints' or, when available, by the clinical diagnosis (e.g. 'gastric reflux', 'pericarditis', etc.). Acute death of identified cause will refer to any case of death occurring in a patient that meets the inclusion criteria for the study and dies after diagnostic evaluation has reached a point where cause of death can reasonably be determined, or death occurring in a patient before evaluation is done but where post-mortem research is performed to identify cause of death. In all other cases of acute death, the outcome will be defined as acute death of unidentified cause.

9.2.4 Primary and secondary outcome

The most important feature of the algorithm of signs and symptoms combined with PoC H-FABP testing will be to adequately categorise all patients as either positive or negative for ACS. The ability of the algorithm to rule in UA in the ACS group is important, since UA is a condition that does not give a rise in biomarkers and diagnosis depends exclusively on signs and symptoms.

Primary outcome: using multivariate analysis of our data, signs and symptoms that have diagnostic value in an algorithm to predict or exclude ACS and AMI will be identified. The primary outcome measures of the study will be sensitivity, specificity, positive and negative predictive value of an algorithm of those relevant signs and symptoms combined with PoC H-FABP testing for ACS and AMI, in patients with thoracic complaints of new onset in general practice. To determine influence of sex, age, duration of the complaints, and kidney function on clinical performance of H-FABP-testing, subgroup analyses within our study population will be performed.[47,48]

Secondary outcome: an economic evaluation by means of an incremental cost-effectiveness ratio (ICER) will be performed. This evaluation will be performed by determination of the ratio between the difference in medical costs and the difference in benefits between the two strategies that are observed in this study, being the usual

reference policy of the GP and the reference policy that could be created using a determined algorithm consisting of a clinical score and PoC H-FABP-testing. The benefits will be described as reduction in number of referred patients versus missed diagnoses if the algorithm is used.

9.2.5 Data management. Withdrawal or missing data

Data will be stored confidentially and anonymously on the research computer. Researchers obtaining patient data 30 days after study inclusion will work with decoded data. Afterwards, coding will be restored. All data will be held for 15 years after closure of the study. Handling of personal data will comply with the Dutch Personal Data Protection Act and the Belgian privacy legislation (http://wetten. overheid.nl/BWBR0011468/geldigheidsdatum_30-10-2013). Collected blood samples will be preserved for a maximum of 15 years. These samples will only be used for analyses that could contribute to our current field of research.

Should patients refuse informed consent after initial agreement on inclusion, they will be withdrawn from the study and their data abolished. If final diagnosis is impossible due to insufficient data, calculations will be made artificially regarding all patients with missing data as having an ACS, as well as regarding them as having no cardiac ischaemic cause for their initial complaints.

9.2.6 Sample size, power calculation. Statistical analysis

An incidence of ACS of 22% would generate 132 patients with ACS and 468 patients without ACS in a study population of 600 patients. To create a usable algorithm consisting of signs, symptoms and H-FABP, the sensitivity of this algorithm should reach 85-90% and specificity should reach 80-85%. In a worst case scenario, where sensitivity would be 85% and specificity would be 80%, combined with the incidence of ACS of 22%, PPV of the algorithm of signs, symptoms and H-FABP for ACS would be 54% (95% C.I. 47-61%) and the NPV 95% (95% C.I. 93-97%). These diagnostic values with their 95% C.I. would be of significant interest, since PPV based on clinical judgment only is 22% and NPV is 95%. Therefore, a sample size of 600 generates adequate precision to find clinically relevant improvement of PPV, as compared to the current situation, and NPV that is at least not diminishing.

Receiver Operating Characteristic (ROC) curves have been used in an earlier stage to find the optimal cut-off point of the venous H-FABP-test.[8] Using 2 × 2 tables and multivariate analyses, including CART analysis, multiple logistic regression, or both, the diagnostic value of the H-FABP-test in combination with clinical findings for ACS and AMI will be assessed.[49,50] Our analysis will result in PPVs and NPVs, sensitivity and specificity and their 95% confidence intervals. Additionally, C-statistics will be presented to quantify overall prediction quality of the models.

9.2.7 Ethical considerations. Informed consent. Incentives

The outcome of the test will be subject to this diagnostic study and can therefore have no clinical consequence on the GP's decision. Patients willing to take part in this study will mainly be treated as usual. Only a finger prick blood analysis for H-FABP will be added to the normal procedure and venous blood sampling will be added in patients that are not referred to secondary care facilities. This study will be in agreement with the current version of the WMA Declaration of Helsinki and will be in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO, http://wetten.overheid.nl/BWBR0009408/geldigheidsdatum_29-10-2013).[51] An independent expert will be available in both countries throughout the study and contact data of this expert will be given to all participating patients. This study protocol has been approved by the ethical review board of Maastricht University for the Netherlands and by the ethical review board of KU Leuven for Belgium. Full research procedures are registered on www.clinicaltrials.gov, NCT01826994.

All GPs including patients for our study will have a liability insurance themselves or via the centre they work for. Maastricht University and KU Leuven have an insurance covering damage to research subjects through injury or death caused by the study, that becomes apparent within 4 years after the end of the study.

In a short time window of only one consultation, inclusion in our study and performance of the PoC H-FABP test will take place. The majority of the procedure can be categorized as regular care. Therefore the ethical review board was asked to agree on asking oral consent (Belgium) and short written consent (The Netherlands) from patients for taking the PoC H-FABP-test and (if required) the venous blood sample by the GP on initial consultation. This short content contains the four basic principles as stated in article six of the Dutch law for scientific research concerning humans. Subsequently, within one to seven days from initial consultation, patients will be given the opportunity for complete 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 short and complete informed consent will be included in our study.

All GPs will receive €40 per included patient as a compensation for their extra workload.

9.2.8 Publication policy

All data, results of analyses and conclusions by the study team, either favourable or unfavourable to using PoC H-FABP testing will be disclosed by offering our work for publication in (a) medical journal(s). Our report will follow the international STROBE guideline.

9.3 Discussion

Our study, which commenced in November 2013, will focus on deriving factors to be included in an algorithm of signs and symptoms combined with PoC H-FABP testing (stage 2 of the aforementioned stages of Stiell and Wells).[42] All criteria for a methodologically correct stage 2 (definition of outcomes and predictor variables, generalisability of subject selection, several statistical and methodological demands) are present in this study, except the inter-observer reliability for the clinical findings, which is difficult to measure in the acute setting in primary care. This study, and subsequent studies aiming to validate, implement and calculate cost-effectiveness (stages 3–6 of Stiell and Wells) in a new clinical setting will possibly enable formulation of a clinical decision rule meeting the current criteria for an effective decision rule.[52] The focus will be on substantially changing clinical behaviour and thus safely reducing the number of referred patients by GPs to secondary care facilities without underlying ACS. An improved triage of patients presenting with chest complaints possibly due to ACS can lead to a substantial cost reduction.

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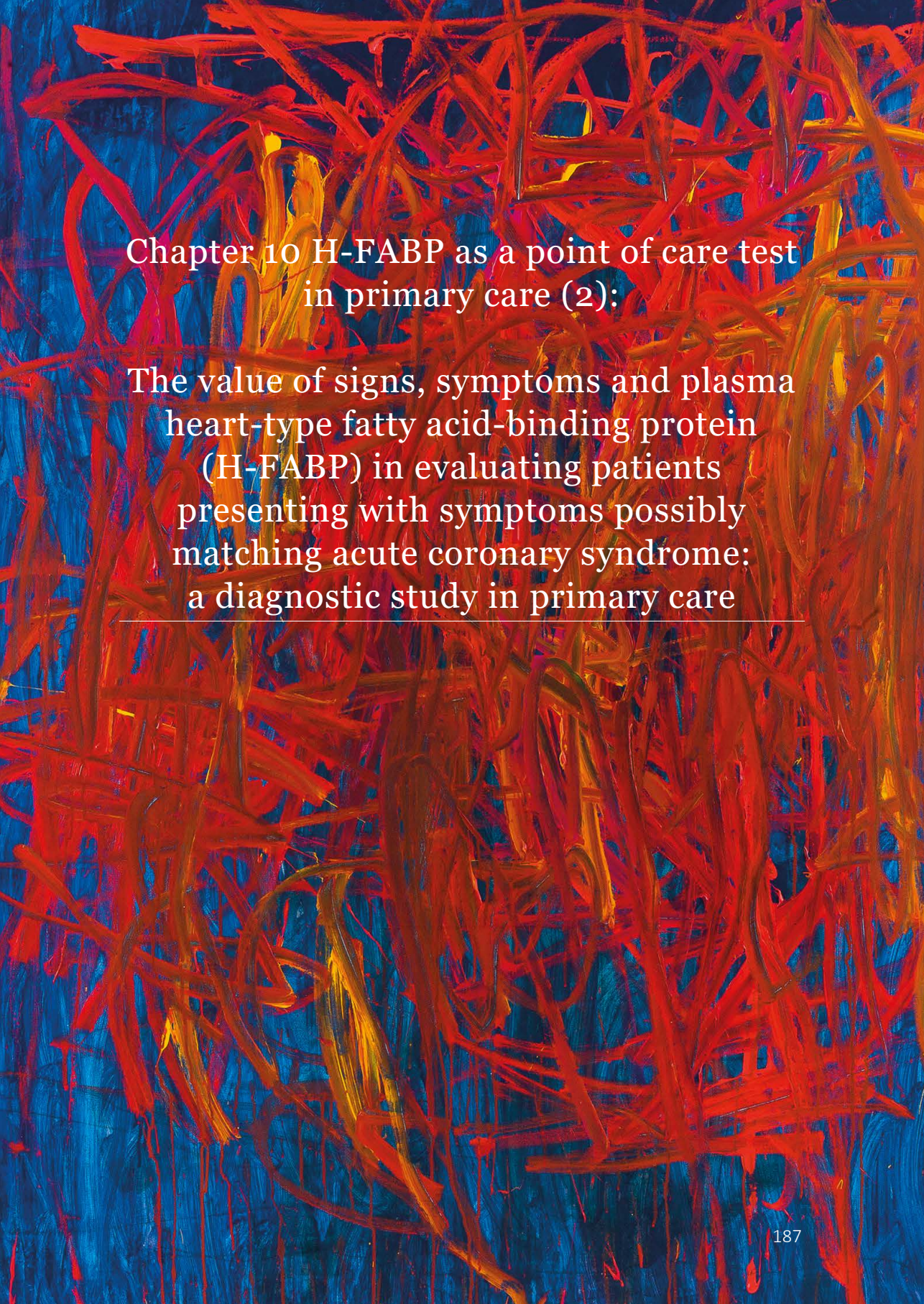
submitted as:

'The value of signs, symptoms and plasma heart-type fatty acid-binding protein (H-FABP) in evaluating patients presenting with symptoms possibly matching acute coronary syndrome: a diagnostic study in primary care.'

Robert TA Willemsen, Frank Buntinx, Jan FC Glatz, Bjorn Winkens, Ron Kusters, Geert Jan Dinant - the 'RAPIDA'-study team ('RAPIDA': RAPid test for Investigating complaints possibly Due to Acute coronary syndrome)



Chapter 10 H-FABP as a point of care test in primary care (2):

The value of signs, symptoms and plasma heart-type fatty acid-binding protein (H-FABP) in evaluating patients presenting with symptoms possibly matching acute coronary syndrome: a diagnostic study in primary care

Abstract

Background: To distinguish acute coronary syndrome (ACS) from the large group of patients presenting with chest pain in primary care without a life threatening disease, is challenging. Point of care biomarker testing, embedded in a clinical decision rule (CDR) could be helpful to the general practitioner (GP). Heart-type fatty acid binding protein (H-FABP) seems a promising early marker for myocardial cell damage.

Objectives: To derive signs and symptoms that have diagnostic value in a clinical decision rule (CDR) and to assess the diagnostic value of a point of care (PoC) H-FABP test alone and combined with a CDR, in order to predict or exclude ACS and acute myocardial infarction (AMI) in primary care.

Methods/Design: GPs recruited patients presenting with chest pain in primary care. Regular care was provided . A H-FABP PoC test was performed. Final diagnosis was assessed by an expert panel, at least 30 days after initial presentation. Logistic regression analysis was used to define signs and symptoms predicting AMI or ACS and contributing to a CDR. Diagnostic values of the PoC H-FABP test alone and combined with a CDR were determined.

Results: 303 patients were included in the study, ACS was found in 32 (10.6%)patients, whereas 75.2% of all patients suffered from non-cardiac disease. For ACS, sensitivity and negative predictive value (NPV) of the PoC H-FABP test was 25.8%, 91.6% respectively for all patients, and 36.8%, 92.7% respectively for patients with a duration of complaints > 3 hours. Area under the receiver operating curve of a CDR combining presence of ST-depressions, ST-elevations, dyspnea, a feeling of pressure on the chest, absence of left sided lateral chest pain and PoC H-FABP test result was 0.78 for ACS. As compared to a GP's unaided judgment, the false negativity count for ACS was lower, whereas the false positivity count was higher when using the CDR.

Discussion: Sensitivity of the current H-FABP PoC test as a stand-alone test is poor. The efficiency of using a CDR derived from these results is doubtful: the CDR could be of use in reducing the number of ACS cases missed by the GP, however as a consequence, more ACS negative patients would be referred. Additional studies should focus on large primary care populations presenting with chest pain to validate future PoC tests and to derive signs and symptoms predicting ACS.

10.1 Background

10.1.1 Introduction

In primary care, 1.26% of all consultations are about chest pain.[1] Among these patients, cases of acute coronary syndrome (ACS) are largely outnumbered by less severe causes of chest pain such as thoracic wall complaints.[1-4] However, history taking, physical examination and electrocardiography (ECG), lack reliability to distinguishing ACS from less urgent causes in chest pain patients.[5-8] Since in urgent conditions as ACS, safe exclusion is the main task of a general practitioner (GP), GPs tend to refer a majority of chest pain patients, knowing that ultimately, only a minority will be diagnosed with an acute life threatening disease as ACS.[1,9,10] To lower referral percentages and thus reduce the patient burden in secondary care, advanced diagnostic tools should become available.[11] Such tools could be based on biomarkers of myocardial cell damage such as high sensitive cardiac troponin (hs-cTn) or heart-type fatty acid-binding protein (H-FABP).[12-19] Combined with signs and symptoms, such tools should enable GPs to safely rule out ACS in a significant number of otherwise referred patients, without a rise in missed cases of ACS. Importantly, this would lead to a significant cost reduction.[3] The added value of H-FABP and other early markers combined with signs and symptoms in risk classification in a low prevalence setting such as primary care is still to be determined.[20-23] Besides, an essential condition for using such tool is its availability in point of care (PoC) format. We earlier found a potential role for H-FABP PoC testing using a cut-off value of 4 ng/ml, in an emergency department setting.[24]

10.1.2 Study design

We performed a derivation study to identify signs and symptoms that, combined with PoC H-FABP testing, can be part of a clinical decision rule (CDR) to confirm or rule out ACS (i.e., acute myocardial infarction (AMI) or unstable angina (UA)) and AMI alone in a population of patients presenting with chest pain suspected of ACS in primary care. Thus, stage 2 of the 6 major stages in the development and testing of a clinical decision rule (CDR) as defined by Stiell and Wells was studied.[25] The diagnostic value of the PoC H-FABP test alone, and as a part of a CDR were studied and compared to regular assessment by a GP using a delayed type cross-sectional diagnostic model.[26]

10.1.3 Objectives

1. To assess the diagnostic value (sensitivity, specificity, positive predictive value and negative predictive value) of a PoC H-FABP test for the outcome AMI, ACS and life threatening causes (i.e. ACS,acute heart failure, pulmonary embolism, aortic dissection, acute death), respectively.

2. Derivation of signs and symptoms that have diagnostic value in an algorithm (i.e., a CDR including PoC H-FABP testing) to predict or exclude ACS and AMI.
3. Calculation of sensitivity, specificity, positive predictive value and negative predictive value of a CDR including PoC H-FABP testing for ACS and AMI within our study population (internal validation).

For an extended background of this study and its rationale, and full details on the methodology, referral is made to our earlier published research protocol and case reports.[27,28]

10.2 Methods

10.2.1 Recruitment, inclusion and exclusion criteria

As earlier announced, our purpose was to let 60 GPs in the southeast of the Netherlands and the Northeast of Belgium include 10 patients with chest pain each. For inclusion criteria, see figure 10.1. However, GPs faced difficulties in performing the necessary study procedures (e.g. informed consent, venous sampling) while urgently being consulted for chest pain of recent onset. Therefore, the study was extended to several out of hours (OOH) primary care facilities where incidence of chest pain is higher and specialised nurses are available to aid with study procedures.

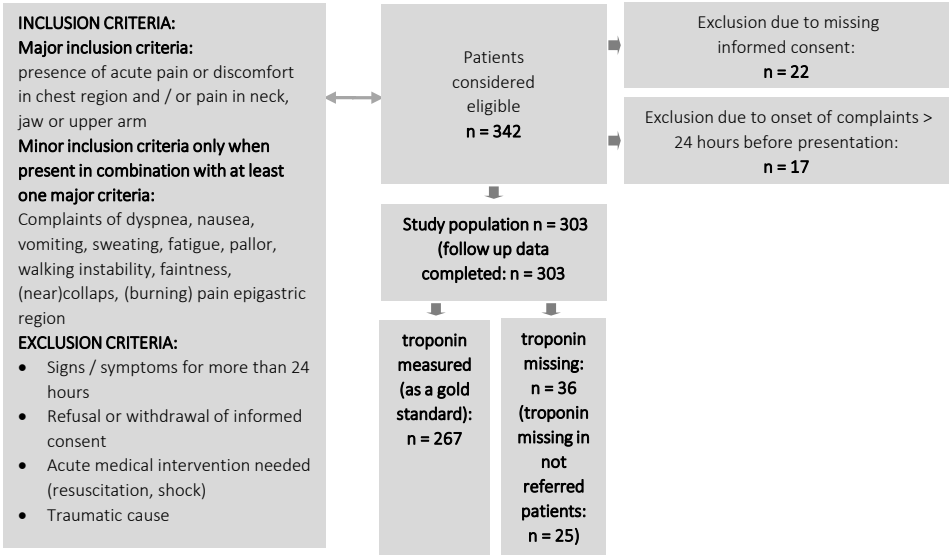


Figure 10.1: Study flow chart, showing in- and exclusion criteria and eligible participants.

Abbreviations: n = number of patients

10.2.2 Data collection

After obtaining oral informed consent (Belgium) or a short version of the written informed consent (the Netherlands) the standardised case report form (CRF-HA) was completed by the GP by registration of history, physical examination, ECG if performed and the presumptive diagnosis together with the original decision whether or not to refer to a cardiologist. Then, a PoC H-FABP test with a cut-off value of 4 ng/ml (manufactured by FABPulous BV) was performed. Five minutes after starting the test, the result was read and reported on the CRF-HA. Afterwards, the original GP's decision is followed, unless a decision not to refer a patient is followed by a positive H-FABP test. In those cases, GPs were instructed to overrule their original decision and refer the patient, based on the positive test result. Patients who were not referred to secondary care were instructed to have a venous blood sample drawn for measurement of hs-cTn (as a gold standard to rule out AMI in non-referred patients), creatinine and estimated glomerular filtration rate, within the interval between three hours to three days after onset of complaints. Within seven days from the initial consultation, patients were given the opportunity for complete written informed consent after having read an information letter at a more convenient moment.

10.2.3 Final diagnosis, study outcomes

After 30 days, all available patient data were collected by the study team. Final diagnoses were established by an expert panel of one independent GP and one independent cardiologist. The expert panel was blinded to the PoC H-FABP test result. The expert panel had access to all other patient data, including troponin measurements. The final diagnosis was based on these results, including the gold standard troponin test results, if available. All outcome diagnoses were determined following current definitions of conditions as cardiac (ischemic) disease, stable angina (SA), UA, AMI and ACS, as extensively explicated in our published research protocol.[27] Diseases labeled as life threatening were: ACS (i.e., UA and AMI), acute heart failure, pulmonary embolism, aortic dissection, acute death. Main study outcomes were: cardiac (ischemic) causes, life threatening causes, ACS and AMI.

10.2.4 Statistical analysis

Univariate analyses of our data was used to assess predictive parameters for the outcomes (cardiac (ischemic) causes, life threatening causes, ACS and AMI). Using 2 × 2 tables and multivariate analysis (multiple logistic regression), a CDR (consisting of a H-FABP-test in combination with clinical findings) was formulated. The diagnostic value of the CDR for the study outcomes were assessed.[29,30] Additionally, C-statistics were determined to quantify overall prediction quality of the models. Data were processed

using SPSS software version 23, chi-square tests were used unless indicated otherwise, differences with p-values lower than 0.05 were considered significant.

10.2.5 Data management, ethical approval

All data will be preserved for 15 years after closure of the study. Handling of personal data will comply with the Dutch Personal Data Protection Act and the Belgian privacy legislation. Collected blood samples will be preserved for a maximum of 15 years. These samples will only be used for analyses that could contribute to our current field of research. Our study is in agreement with the current version of the WMA Declaration of Helsinki and is in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO).[31] This study protocol has been approved by the ethical review board of Maastricht University for the Netherlands and by the ethical review board of KU Leuven for Belgium. Full research procedures are registered on www.clinicaltrials.gov, NCT01826994. All GPs and OOH-services received €40 per included patient as a compensation for their extra workload.

10.3 Results

10.3.1 Patient characteristics

342 patients were selected for inclusion by the participating GPs. 39 patients were excluded (in 22 cases no final informed consent was obtained, in 17 cases complaints were present > 24 hours). Thus, 303 patients were included in the study. Patient characteristics are shown in table 10.1.

10.3.2 Final diagnoses

ACS was found in 32 (10.6%) of the included patients, and other life threatening disease was found in three additional patients (all diagnosed with heart failure). Two patients (0.7%) died shortly after assessment by the GP. Of all chest pain patients, 75.2% suffered from non-cardiac disease. All final diagnoses as assessed by the expert panel are displayed in table 10.2.

10.3.3 Study objective 1: diagnostic value of the PoC H-FABP test

Test failure was reported in 12 out of 303 cases (4.0%). The PoC H-FABP test was positive in 16 cases (5.3%). In five of these cases, the GP had no intention to refer before testing. Following the study protocol, all five patients were referred. In one of these cases, an ACS was found as a final diagnosis. In the remaining four cases, no cardiac diagnosis was identified. The H-FABP PoC test was positive in 8 out of 32 cases of ACS (25%). See figure 10.2 for details on referral policy and test results. Diagnostic parame-

ters for all patients, patients presenting within 3 hours after onset of complaints and patients presenting 3-24 hours after onset of complaints for several outcomes of the PoC H-FABP as a stand-alone test, without considering additional signs and symptoms, are given in **table 10.3**. For ACS, sensitivity of the PoC H-FABP test was 25.8%. Negative predictive value (NPV) for ACS was 91.6%. Even when complaints were present for more than 3 hours, the test missed a considerable number of cases of ACS (sensitivity 36.8 for complaints > 3 hours). All 2x2 tables for all patients, patients presenting with chest pain ≤ 3 hours after onset of complaints and patients presenting with chest pain 3-24 hours after onset of complaints, with outcomes ACS or other life threatening disease, ACS, AMI, NSTEMI respectively are given in **addendum 10.A**. Additional comments and details on false positive and false negative test results are given in **addendum 10.B**.

10.3.4 Study objective 2: derivation of a CDR, univariate and multivariate analyses

Correlations between signs and symptoms and outcome measures were tested in a univariate analysis, see **table 10.4**. For ACS, significant correlations were found for age, absence of left-sided lateral chest pain, a feeling of pressure on the chest, pain in right arm or throat, palor or sweating upon physical examination, several ECG-abnormalities and a positive H-FABP PoC test. No influence was seen for the parameters 'duration of complaints', 'seen by own GP / seen at OOH-service', 'sex' and 'history of cardiovascular disease (CVD)' or 'history of type 2 diabetes mellitus (DM2)'.

In a multivariate regression analysis of all signs and symptoms revealing significant predictive value in the univariate analysis, five highly significant predictors for acute coronary syndrome (ACS) and acute myocardial infarction (AMI) were found: ST-depressions, ST-elevations, dyspnea, a feeling of pressure on the chest and absence of left sided lateral chest pain. Different combinations of signs and symptoms (with and without PoC H-FABP testing) were combined in possible CDRs (**table 10.5**).

10.3.5 Study objective 3: diagnostic value of the CDR

Rule in and rule out characteristics for the different CDRs and area under the receiver operating curves (AUC) were calculated (**table 10.5**). Possible relevance of a CDR in ruling in or ruling out ACS or AMI was defined as an increase in probability of presence, respectively absence of disease after using the particular CDR. AUC for ACS was highest for CDR 1 (0.78). Compared with a GP's clinical judgment (regular care), no significant difference in NPV, PPV or sensitivity was found. False negativity count for CDR 1 (4 cases) was lower than the false negativity count of a GP's judgment only (8 missed cases). However, specificity of CDR 1 was significantly lower than the specificity of a GP's clinical judgment, leading to 48% more false positive test results and thus ACS negative referrals.

Table 10.1: Patient and population characteristics of study population (n = 303).

Variable		Frequency absolute number (relative number)	Remarks
Gender	Male	148 (48.8%)	-
	Female	155 (51.2%)	
Age categories (in years)	Age ≤ 30	15 (5.0%)	Mean age in years (range): 58.3 (17-100)
	30 < age ≤ 40	25 (8.3%)	
	40 < age ≤ 50	47 (15.5%)	
	50 < age ≤ 60	78 (25.7%)	
	60 < age ≤ 70	74 (24.4%)	
	70 < age ≤ 80	43 (14.2%)	
	Age > 80	21 (6.9%)	
Type of contact (missing: n = 1)	Consultation daytime own GP	139 (46.0%)	150 patients (49.7%) seen by their own GP during office hours, 152 patients (50.3%) seen by GP on call at out of hours service
	Home visit daytime own GP	11 (3.6%)	
	Consultation OOH service	146 (48.3%)	
	Home visit OOH service	6 (2.0%)	
Past history	No DM2 or prior CVD	179 (59.1%)	-
	DM2	22 (7.3%)	
	Prior CVD	90 (29.7%)	
	DM2 and prior CVD	12 (4.0%)	
Duration complaints at presentation (in hours) (missing: n = 6)	0 < duration ≤ 1	32 (10.8%)	-
	1 < duration ≤ 3	83 (27.9%)	
	3 < duration ≤ 6	62 (20.9%)	
	6 < duration ≤ 12	52 (17.5%)	
	12 < duration ≤ 24	68 (22.9%)	
eGFR (in ml/min) (missing: n = 49)	eGFR ≤ 30	3 (1.2%)	-
	30 < eGFR ≤ 60	42 (16.5%)	
	eGFR > 60	209 (82.3%)	
ECG performed (missing: n = 1)	No	50 (16.6%)	-
	Yes, no abnormalities	152 (50.3%)	
	Yes, abnormalities	100 (33.1%)	
Referral policy	No referral	167 (55.1%)	Overall referral percentage: 44.9% Overall direct referral percentage: 37.0% Overall referral percentage at later time: 7.9%
	Direct referral upon presentation to cardiologist	107 (35.3%)	
	Direct referral upon presentation other	5 (1.7%)	
	Referral at later time during follow up cardiologist	20 (6.6%)	
	Referral at later time during follow up other	4 (1.3%)	
Troponin available	Troponin available (all patients)	267 (88.1%)	
	Troponin available (not referred patients)	171 (87.2%)	
	Troponin available (referred patients)	96 (89.7)	

Abbreviations: CVD = cardiovascular disease; DM2 = type 2 diabetes mellitus; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; GP = general practitioner; h = hours; min = minutes; ml = mililiters; mnm = minimum; mxm = maximum; n = number; OOH-service = primary care out of hours service

Table 10.2: Frequencies of final diagnoses as established by the expert panel, after reviewing all available patient information including history, diagnostic tests when applicable, specialist letters when applicable, and 30 days follow up period.

Frequencies of expert panel's final diagnoses in all patients (n=303)					
Main category	Subcategory 1	Subcategory 2	Specific diagnosis	Absolute number	Relative number
Cardiac ischemic disease n=56 (18.5%)	Stable angina n=24 (7.9%)	Stable angina n=24 (7.9%)	Stable angina	24	7,9%
	ACS n=32 (10.6%)	Unstable angina n=5 (1.7%)	Unstable angina	5	1,7%
		AMI n=27 (8.9%)	STEMI	10	3,3%
			NSTEMI	16	5,3%
			AMI and acute death	1	0,3%
Cardiac non-ischemic disease n=18 (6.0%)	Heart failure n=3 (1.0%)		Heart failure due to CMP	1	0,3%
			Heart failure due to hypertensive heart disease	1	0,3%
			Heart failure due to diastolic failure	1	0,3%
	Other n=15 (5.0%)		Pericarditis	3	1,0%
			Atrial fibrillation or other SVT or PAC / PVC	11	3,6%
			Bradycardia	1	0,3%
Non cardiac disease n=228 (75.2%)	Chest wall / locomotory tract related n=172 (56.8%)		Related to locomotory tract	19	6,3%
			Thoracic wall pain	13	4,3%
			Atypical thoracic complaints	140	46,2%
	Other n=56 (18.5%)		Astma or COPD exacerbation	1	0,3%
			Cholelithiasis	3	1,0%
			Oesophagitis or gastritis	21	6,9%
			Panick attack	24	7,9%
			Pleuritis	1	0,3%
			Pneumonia	3	1,0%
			Primary hyperventilation	3	1,0%
Other n=1 (0.3%)			Acute death unknown cause	1	0,3%

Abbreviations: ACS = acute coronary syndrome; AMI = acute myocardial infarction; COPD: chronic obstructive pulmonary disease; CMP = cardiomyopathy; n = number; NSTEMI = non ST elevated myocardial infarction; PAC = premature atrial contraction; PVC = premature ventricular contraction; STEMI = ST elevated myocardial infarction; SVT = supraventricular tachycardia

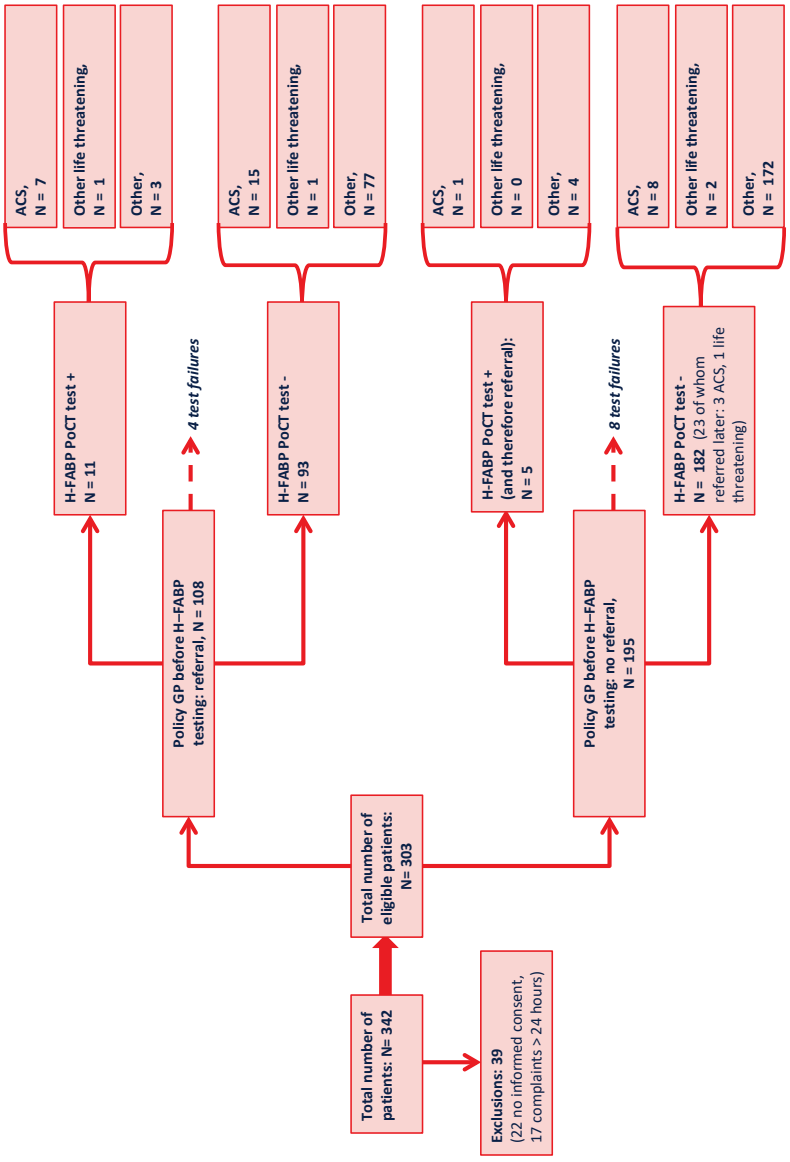


Figure 10.2: Patient flow chart of all included patients (N=303), referral decisions before H-FABP PoCT testing, H-FABP PoCT test results and final outcomes.

Other life threatening disease: acute heart failure, pulmonary embolism, aortic dissection, acute death.

Abbreviations: ACS = acute coronary syndrome; H-FABP = Heart-type Fatty Acid Binding Protein; NSTEMI = non ST elevated myocardial infarction; PoCT = point of care test; STEMI = ST elevated myocardial infarction

Table 10.3: Diagnostic parameters of PoC H-FABP as a stand-alone test.

	outcome: ACS or other life threatening disease			outcome: ACS			outcome: AMI			outcome: NSTEMI		
interval onset complaints – presentation (h)	0-24	0-3	3-24	0-24	0-3	3-24	0-24	0-3	3-24	0-24	0-3	3-24
number of patients	291*	106**	179**	291*	106**	179**	291*	106**	179**	291*	106**	179**
sens H-FABP PoCT (95% CI)	25.7% (13.1-43.6%)	8.3% (0.44-40.2%)	36.4% (18.0-59.2%)	25.8 (12.5-44.9%)	9.1% (4.8-42.9%)	36.8% (17.2-61.4%)	26.9% (12.4-48.1%)	10.0% (0.52-45.9%)	40.0% (17.5-67.1%)	18.9% (5.0-46.3%)	0% (0-48.3%)	33.3% (9.0-69.1%)
spec H-FABP PoCT (95% CI)	97.3% (94.2-98.8%)	98.9% (93.4-99.9%)	96.2% (91.5-98.4%)	96.9% (93.8-98.6%)	98.9% (93.4-99.9%)	95.6% (90.8-98.1%)	96.6% (93.4-98.3%)	99.0% (93.5-99.9%)	95.1% (90.3-97.7%)	95.3% (91.9-97.4%)	98.0% (92.3-99.7%)	93.5% (88.4-96.6%)
NPV H-FABP PoCT (95% CI)	90.5% (86.3-93.6%)	89.4% (81.5-94.3%)	91.5% (85.9-95.1%)	91.6% (87.6-94.5%)	90.4% (82.6-95.0%)	92.7% (87.4-96.0%)	93.1% (89.2-95.7%)	91.3% (83.8-95.7%)	94.5% (89.6-97.3%)	95.3% (91.9-97.4%)	94.2% (87.4-97.6%)	96.4% (91.9-98.5%)
PPV H-FABP PoCT (95% CI)	56.3% (30.6-79.2%)	50.0% (26.7-97.3)	57.1% (29.6-81.2%)	50.0% (25.5-74.5%)	50.0% (26.7-97.3%)	50.0% (24.0-76.0%)	43.8% (20.8-69.4%)	50.0% (26.7-97.3%)	42.9% (18.8-70.4%)	18.9% (5.0-46.3%)	0% (0- 80.2%)	21.4% (5.7-51.2%)

Sensitivity, specificity, negative and positive predictive values of PoC H-FABP for all patients, patients presenting within 3 hours after onset of complaints and patients presenting 3-24 hours after onset of complaints for several outcomes, being: (1) life threatening disease (i.e. composite of acute heart failure, pulmonary embolism, aortic dissection, acute death, ACS), (2) ACS (i.e. UA, NSTEMI, STEMI), (3) AMI (i.e. NSTEMI and STEMI) and (4) NSTEMI only).

*12 test failures among 303 included patients

** In 6 cases, patients presented within 24 hours after onset of complaints, however registration of duration of complaints was incomplete. These patients are not included in the tables representing subgroups of patients presenting with chest pain within 3 hours or 3-24 hours after onset of complaints.

Abbreviations: 95% CI = 95% confidence interval; ACS = acute coronary syndrome; AMI = acute myocardial infarction; h = hours; H-FABP = Heart-type Fatty Acid Binding Protein; n = number of patients; NPV = negative predictive value; NSTEMI = non ST elevated myocardial infarction; PoC = point of care; PPV = positive predictive value; sens = sensitivity; spec = specificity; STEMI = ST elevated myocardial infarction; UA = unstable angina

Table 10.4: Univariate analysis of all variables (signs, symptoms and additional tests) for different outcome values.

Univariate analysis of all variables (signs, symptoms and additional tests) for different outcome values					
	Outcome value (number of positive findings)				
	All cardiac disease (n=74)	Cardiac ischemic disease (n = 56)	Life threatening disease (n = 36)	ACS (n = 32)	AMI (n = 27)
Age > 50 yrs	**S (p < 0.001)**	**S (p < 0.001)**	**S (p < 0.001)**	**S (p = 0.001)**	**S (p = 0.003)**
Age > 60 yrs	**S (p < 0.001)**	**S (p = 0.03)**	NS	NS	NS
Age > 70 yrs	**S (p < 0.001)**	**S (p < 0.001)**	**S (p = 0.001)**	**S (p = 0.004)**	**S (p = 0.03)**
Sex	NS	NS	NS	NS (male more probable, P=0.10)	NS
Seen by own GP*	NS	NS	NS	NS	NS
History of DM2	**S (p = 0.02)**	**S (p = 0.03)**	**S (p = 0.03)**	NS	NS
History of CVD	NS (p = 0.09)	NS	NS	NS	NS (p = 0.08)
Duration of complaints > 3 hours	NS	NS	NS	NS	NS
Central chest pain	NS	**S (p = 0.04)**	NS	NS	NS
Absence of lateral chest pain left	**S (p < 0.001)**	**S (p < 0.001)**	**S (p = 0.03)**	**S (p = 0.02)**	**S (p = 0.04)**
Lateral chest pain right	NS	NS	NS	NS	NS
Dorsal chest pain	NS	NS	NS	NS	NS
A feeling of pressure on the chest	**S (p = 0.02)**	**S (p = 0.02)**	NS (p = 0.06)	**S (p = 0.02)**	NS (p = 0.07)
Tightening around chest	NS	NS	NS	NS	NS
Chest discomfort	NS	NS	NS	NS	NS
Anxiety	NS	NS	NS	NS	NS
Dyspnea	NS	NS	NS (p = 0.10)	NS	NS
Burning sensation around sternum	NS	NS	NS	NS	NS
Pain left arm	NS	NS	NS	NS (p = 0.11)	**S (p = 0.02)**
Pain right arm	NS (p = 0.06)	**S (p = 0.006)**	**S (p = 0.006)**	**S (p = 0.002)**	**S (p < 0.001)**
Pain throat	NS	NS	**S (p = 0.002)**	**S (p = 0.003)**	NS (p = 0.08)
Pain jaw	**S (p = 0.04)**	NS (p = 0.051)	NS	NS	NS
Epigastric pain	NS	NS	NS	NS	NS
Sweating in history	NS	NS	NS	NS	NS
Nausea	NS	NS	NS	NS	NS
Vomiting	NS	**S (p = 0.05)**	NS	NS	NS
Sudden fatigue	NS	NS	NS	NS	NS
Palor in history	NS	**S (p = 0.02)**	NS	NS	NS
Weakness upon standing	NS	NS	NS	NS	NS (p = 0.08)
Collaps	NS	NS	NS	NS	NS
Feebleness/Near-collaps	NS	NS	NS	NS	NS

Univariate analysis of all variables (signs, symptoms and additional tests) for different outcome values

	Outcome value (number of positive findings)				
	All cardiac disease (n=74)	Cardiac ischemic disease (n = 56)	Life threatening disease (n = 36)	ACS (n = 32)	AMI (n = 27)
Pulse irregularity	**S (p = 0.02)**	NS	NS	NS	NS
Palor upon physical examination	**S (p = 0.003)**	**S (p = 0.001)**	**S (p = 0.001)**	**S (p = 0.001)**	**S (p = 0.001)**
Sweating upon physical examination	**S (p = 0.007)**	**S (p = 0.006)**	**S (p = 0.002)**	**S (p = 0.005)**	**S (p = 0.008)**
Visible anxiety	NS	NS	NS	NS	NS
Pain not reproducable upon chest palpation	**S (p = 0.001)**	**S (p = 0.02)**	NS	NS	NS
Cardiac murmur	NS	NS (p = 0.058)	NS	NS	NS
Abnormal heart sounds	NS	NS	NS	NS	NS
ECG abnormalities yes versus no (n = 252)	**S (p < 0.001)**	**S (p < 0.001)**	**S (p < 0.001)**	**S (p < 0.001)**	**S (p = 0.005)**
ST-elevations on ECG	**S (p =0.02)**	**S (p < 0.001)**	**S (p < 0.001)**	**S (p < 0.001)**	**S (p < 0.001)**
ST-depressions on ECG	**S (p < 0.001)**	**S (p = 0.001)**	**S (p < 0.001)**	**S (p < 0.001)**	**S (p < 0.001)**
Negative T on ECG	**S (p = 0.03)**	**S (p = 0.006)**	**S (p = 0.005)**	**S (p = 0.001)**	**S (p = 0.003)**
Bradycardia	NS (p = 0.09)	NS	NS	NS	NS
Positive H-FABP PoCT	**S (p < 0.001)**	**S (p < 0.001)**	**S (p < 0.001)**	**S (p < 0.001)**	**S (p < 0.001)**

For every variable as registered on the CRF's in the study, significance or non significance for different outcome values is given. Outcome values are: any cardiac disease as final outcome determined by the expert panel, cardiac ischemic disease as final outcome determined by the expert panel (i.e. SAP or ACS), a life threatening disease as final outcome determined by the expert panel (i.e. ACS,acute heart failure, pulmonary embolism, aortic dissection, acute death), ACS as final outcome determined by the expert panel (i.e. AMI or UAP), AMI as final outcome determined by the expert panel. In cases of (near) significance, P-values are given between brackets.

* Incidence of ACS, nor test results of PoCT H-FABP, were dependent of the variable 'seen by own GP'.

Abbreviations: ACS = acute coronary syndrome; AMI = acute myocardial infarction; CRF = case report form; CVD = cardiovascular disease; DM2 = type 2 diabetes mellitus; ECG = electrocardiogram; GP = general practitioner; H-FABP = Heart-type Fatty Acid Binding Protein; NS = non significant; PoCT = point of care test; S = significant; SAP = stable angina pectoris; UAP = unstable angina pectoris; yrs = years

Table 10.5: sensitivity and specificity of possible clinical decision rules (CDRs) based on multivariate analyses of our study data. Number of chest pain patients analysed: N = 303. Number of patients with ACS: 32 (10.6%). Number of patients with AMI: 27 (8.9%).

	CLINICAL DECISION RULE (CDR) BASED ON...						CDR / DECISION CHARACTERISTICS			RULE OUT CHARACTERISITICS			RULE IN CHARACTERISITICS				AUC		RULE IN/OUT*
	ST-depressions	ST-elevations	dyspnea	feeling of pressure chest	absent lateral chest pain left	PoCT H-FABP result	maximum score	considered negative if	patients with a negative, resp. positive score	sens resp. NPV for ACS [95% CI]	n of FNs for ACS (% of all)	n of TNs for ACS (% of all)	sens resp. NPV for AMI [95% CI]	spec resp PPV for ACS [95% CI]	n of FPs for ACS (% of all)	n of TPs for ACS (% of all)	spec resp PPV for AMI [95% CI]	AUC for CDR, outcome ACS	AUC for CDR, outcome AMI	
CLINICAL JUDGMENT GP	/	/	/	/	/	/	/	GP did not refer	191 negative 112 positive	sens 75.0 [56.2-87.9]; NPV 95.8 [91.6-98.0]	8 (2.6%)	183 (60.4%)	sens 70.4 [49.7-85.5]; NPV 95.8 [91.6-98.0]	spec 67.5 [61.6-73.0]; PPV 21.4 [14.5-30.4]	88 (29.0%)	24 (7.9%)	spec 66.3 (60.4-71.8]; PPV 17.0 [10.8-25.5]	/	/	Rule in, out ACS. Rule in, out AMI.
CDR VARIANT 1	1	1	1	1	1	1	6	≤ 1	145 negative 158 positive	sens 87.5 [70.1-95.9]; NPV 97.2 [92.6-99.1]	4 (1.3%)	141 (46.5%)	sens 88.9 [69.7-97.1]; NPV 97.9 [93.6-99.5]	spec 52.0 [45.9-58.1]; PPV 17.7 [12.3-24.8]	130 (42.9%)	28 (9.2%)	spec 51.4 [45.4-57.5]; PPV 15.2 [10.2-22.0]	0.782	0.781	Rule in, out ACS. Rule in, out AMI.
CDR VARIANT 2	1	1	1	1	1	/	5	≤ 1	147 negative 156 positive	sens 81.2 [63.0-92.1]; NPV 95.9 [90.9-98.3]	6 (2.0%)	141 (46.5%)	sens 81.5 [61.3-93.0]; NPV 96.6 [91.8-98.7]	spec 52.0 [45.9-58.1]; PPV 16.7 [11.4-23.7]	130 (42.9%)	26 (8.6%)	spec 51.4 [45.4-57.5]; PPV 14.1 [9.2-20.8]	0.754	0.756	Rule in, out ACS. Rule in, out AMI.
CDR VARIANT 3	/	/	1	1	1	1	4	≤ 1	157 negative 146 positive	sens 78.1 [60.0-90.0]; NPV 95.5 [90.7-98.0]	7 (2.3%)	150 (49.5%)	sens 77.8 [57.3-90.6]; NPV 96.2 [91.5-98.4]	spec 55.4 [49.2-61.3]; PPV 17.1 [11.6-24.4]	121 (39.9%)	25 (8.3%)	spec 54.7 (48.6--60.7]; PPV 14.4 [9.3-21.4]	0.722	0.705	Rule in, out ACS. Rule in, out AMI.
CDR VARIANT 4	/	/	1	1	1	/	3	≤ 1	161 negative 142 positive	sens 68.8 [49.9-83.3]; NPV 93.8 [88.6-96.8]	10 (3.3%)	151 (49.8%)	sens 66.7 [46.0-82.8]; NPV 94.4 [89.3-97.2]	spec 55.7 [49.6-61.7]; PPV 15.5 [10.2-22.7]	120 (39.6%)	22	spec 55.1 (49.0-61.0]; PPV 12.7 [7.9-19.6]	0.665	0.644	Non decisive.

In a multivariate regression analysis, five highly significant predictors for acute coronary syndrome (ACS) and acute myocardial infarction (AMI) were found: ST-depressions, ST-elevations, dyspnea, a feeling of pressure on the chest and absence of left sided lateral chest pain. Different combinations of signs and symptoms (with and without point of care Heart-type fatty acid binding protein (PoC H-FABP) testing) were combined in possible CDRs. Sensitivity and specificity with 95% confidence intervals (95% CIs) of these combinations were calculated.

* A CDR is considered as possibly relevant for rule in when the pre-test probability (based on the prevalence in the study population) of presence of an AMI (8.9%), respectively ACS (10.6%), is below the lower margin of the 95% CI of the positive predictive value (PPV)of the CDR. A CDR is considered as potentially relevant for rule out when the pre-test probability of absence of an AMI (91.1%), respectively ACS (89.4%), is below the lower margin of the 95% CI of the negative predictive value (NPV).

Abbreviations: 95% CI = 95% confidence interval; ACS = acute coronary syndrome; AMI = acute myocardial infarction; AUC = area under (receiver operating characteristic (ROC)) curve; CDR = clinical decision rule; FNs = false negatives; FPs = false positives; GP = general practitioner; H-FABP = Heart-type Fatty Acid Binding Protein; n = number of patients; NPV = negative predictive value; PoCT = point of care test; pat = patients; PPV = positive predictive value; pt = point; sens = sensitivity; spec = specificity; TNs = true negatives; TP = true positives ;

10.4 Discussion

10.4.1 Summary of main findings

The first objective of the present study was to assess the diagnostic value of a PoC H-FABP test as a stand-alone test. Sensitivity (25.8%) for ACS was poor, leading to a high number of false negative test results. The second and third study objective, to derive (combinations) of factors predicting the presence of ACS and assess diagnostic values of such combinations, was elaborated in uni- and multivariate tests. An algorithm of a feeling of pressure on the chest, absence of left lateral chest pain, dyspnea, ST depressions, ST elevations and H-FABP PoC test result (CDR 1) predicted the outcome of ACS reasonably well (sensitivity 87.5%, NPV 97.2%). However, the gain as compared to a GP's clinical judgment was limited to a rather small reduction of missed cases of ACS (a relative reduction of the false negativity rate of 50%, absolute reduction of 1.3%) at a price of a considerable increase in over-referral of eventually ACS negative cases ánd the necessity to perform a PoC test and an ECG as part of the CDR in all chest pain patients.

10.4.2 Strengths and limitations

This study was performed in daily primary care, with primary care patients. The H-FABP PoC test was given to health care professionals and was tested in a representative clinical situation. The incidence of ACS (10.6%) was lower than the incidence found in a similar previous study (22%).[23] However, in several other studies with unselected chest pain patients, incidence of ACS was 1.5-5.2%.[32-36] Therefore an incidence of approximately 10% in patients suspected of possible ACS is reasonable.

We focused on deriving factors to be included in an algorithm of signs and symptoms combined with PoC H-FABP testing, predicting ACS (stage 2 of the aforementioned stages of Stiell and Wells).[25] All criteria for a methodologically correct stage 2 (definition of outcomes and predictor variables, generalisability of subject selection, several statistical and methodological demands) are present in this study, except the inter-observer reliability for the clinical findings, which is difficult to measure in an acute setting. Signs and symptoms with predictive value for the outcome of AMI or ACS were combined in several CDRs that were internally validated. External validation has not yet been performed.

Problems were faced regarding inclusion of sufficient patients. Therefore, extension of the study from day care in primary care to OOH-services was necessary. GPs embraced the study with enthusiasm, but faced serious barriers when actually including patients. The fact that patients with chest pain are usually unannounced, and therefore not scheduled, leads to expiration of consultations hours. In addition, the possible life threatening underlying disease seemed to limit inclusion into the study. Moreover,

study procedures as obtaining a (temporary) written informed consent were seen as thresholds. However, in Belgium, oral consent was sufficient and inclusion did not meet our expectations either. Finally, although we aimed to include 600 patients, 303 patients were included.

10.4.3 Expected versus actual performance of stand-alone PoC H-FABP test and CDR

In an earlier study, based on a PoC H-FABP test with a cut-off value of 7 ng/ml, performance of the test in clinical situations was insufficient.[23] In this present study, we worked with a new PoC H-FABP test, with a cut-off value of 4 ng/ml based on a clinical study with chest pain patients in a secondary care emergency setting.[24] Based on this study, expected specificity, sensitivity of this test for ACS was 71.7%, 73.9%. In a population of chest pain patients in primary care with an incidence of ACS of 22% as earlier described, NPV was expected to be 90.7%.[23,24] In this present study however, specificity, sensitivity of the PoC H-FABP test as a stand-alone test was 96.9%, 25.8%. NPV was 91.6%. Although specificity and NPV are reasonably high, partially due to a lower incidence of ACS in our population of 10.6%, sensitivity was poor, leading to 24 negative test results in 32 cases of ACS. Several causes could be underlying.

First, in these ACS patients, a plasma rise of H-FABP could be absent (***underperformance of the marker***). This is not in accordance with earlier research.[24] A comparison between the H-FABP PoC test result and the absolute H-FABP concentration to be measured by ELISA in stored plasma samples obtained from a selection of patients is planned and should provide further insight into this matter. Including patients with UA - a usually biomarker-negative condition - possibly compromises the marker performance. However, subgroup analyses with only AMI patients revealed similar results and in primary care, ruling out strategies should aim at ACS, not AMI alone. Second, the test signal could be insufficient, for example, the discoloration of the test could take place at higher cut-off values than the cut-off of 4 ng/ml (***underperformance of the PoC test***). However, test calibration by the manufacturer suggests high accuracy of the test. Third, slight discoloration of the PoC test might have been under-detected by care providers participating in the study (***underperformance of the test operator***). However, in this study we were testing the PoC H-FABP performance as a clinical tool and if under-detection of the test was a problem, the test should be improved to augment usability. Moreover, caregivers never complained about the usability of the test.

CDR 1 performed reasonably well. When compared to regular care, based on the GP's clinical judgment, in 1.3% of all chest pain patients a missed case of ACS was prevented. However, an ECG and a PoC test are necessary to carry out CDR 1. Moreover, 13.9% of all chest pain patients change from a true negative estimate based on the GP's clinical judgment to a false positive state due to CDR 1, leading to more over-referral. Annually,

a Dutch GP at least briefly suspects approximately 35 patients with chest pain of ACS.[1] For every GP using CDR 1, in two years time, one missed case of ACS would be prevented. However, in the same two years, 70 ECGs and 70 PoC tests would be necessary, and 30 instead of the usual 20 ACS negative patients are referred to secondary care facilities to rule out ACS.

Fine-tuning of the CDR in order to reduce over referral by adding signs and symptoms to the CDR and / or value the different components of the CDR differently is desirable, as well as a better PoC test performance to further improve the CDR. Larger studies are needed to externally validate a CDR derived from this study. Judging from our experience with this study, we fear that performing such a study might be problematic.

10.4.4 Final conclusions and implications for future research

- Sensitivity of the current H-FABP PoC test as a stand-alone test (FABPulous BV, cut-off value of the test set at 4 ng/ml) is insufficient to support its use for ruling out ACS in daily practice. Future research on H-FABP PoC testing should focus on re-evaluating the cut-off value of the test, on a more operator-friendly usability of the test, or on using a combination of H-FABP and troponin.
- Several factors possibly improving in- and excluding ACS in chest pain patients were identified. A CDR, including a feeling of pressure on the chest, absence of left lateral chest pain, dyspnea, ST depressions, ST elevations and H-FABP PoC test result, was derived.
- The AUC for this CDR for ACS was 0.78. False negativity rate decreases when using the CDR, whereas false positivity rate increases as compared to a GP's clinical judgment.
- Additional studies should focus on large primary care populations presenting with chest pain and on (combinations of) biomarker PoC tests with a high sensitivity. Diagnostic algorithms as the Marburg Heart Score, the HEART-score and other CDRs as the CDR found in this study, should be compared and possibly fused into a strong tool with sufficient sensitivity and good specificity for ACS in primary care.[36-38] Thereafter, further studies should focus on validation, implementation and calculation of cost-effectiveness (stages 3–6 of Stiell and Wells) of such a tool in a new clinical setting, enabling formulation of a usable CDR in primary care, meeting the current criteria for an effective decision rule.[25,39] Thus, cases of ACS should be adequately detected and referral rates should decrease as compared to current practice, improving patient comfort and lowering societal costs.

10.5 References

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Addendum 10.A: supplementary tables S10.1-S10.12

(2 x 2 tables for all patients, patients presenting with chest pain ≤ 3 hours after onset of complaints and patients presenting with chest pain 3-24 hours after onset of complaints respectively. OUTCOME ACS OR OTHER LIFE THREATENING DISEASE (addendum 10.A1, tables S10.1-S10.3), ACS (addendum 10.A2, tables S10.4-S10.6), AMI (addendum 10.A3, tables S10.7-S10.9), NSTEMI (addendum 10.A4, tables S10.10-S10.12) respectively.)

Addendum 10.A1:

2x2 tables S10.1-S10.3 for all patients, patients presenting with chest pain ≤ 3 hours after onset of complaints and patients presenting with chest pain 3-24 hours after onset of complaints, respectively.

OUTCOME ACS OR OTHER LIFE THREATENING DISEASE.

Table S10.1: Two-by-two table displaying the relationship between H-FABP PoCT result and the presence of ACS (unstable angina, NSTEMI or STEMI) or other life threatening disease (acute heart failure, pulmonary embolism, aortic dissection, acute death) in all patients (n = 291).

	ACS or other life threatening disease +	ACS or other life threatening disease -	TOTAL
H-FABP PoCT +	9	7	16
H-FABP PoCT -	26	249	275
TOTAL	35	256	291 (12 test failures among 303 included patients)

Among 9 cases of ACS or other life threatening disease where H-FABP PoCT was positive, 8 were diagnosed with ACS, and one case of acute heart failure due to cardiomyopathy was found.
Among 27 cases of ACS or other life threatening disease where H-FABP PoCT was negative, 24 were diagnosed with ACS, two cases were diagnosed with acute heart failure (due to hypertensive heart disease and severe diastolic heart failure respectively) and in one case acute death of unknown cause was the expert panel's final diagnosis.
Test sensitivity, specifity, negative and positive predictive value (95% CI) for ACS or other life threatening disease: 25.7% (13.1-43.6%), 97.3% (94.2-98.8%), 90.5% (86.3-93.6%), 56.3% (30.6-79.2%) respectively.
Abbreviations: 95% CI = 95% confidence interval; ACS = acute coronary syndrome; H-FABP = Heart-type Fatty Acid Binding Protein; NSTEMI = non ST elevated myocardial infarction; PoCT = point of care test; STEMI = ST elevated myocardial infarction

Table S10.2: Two-by-two table displaying the relationship between H-FABP PoCT result and the presence of ACS (unstable angina, NSTEMI, STEMI) or other life threatening disease (acute heart failure, pulmonary embolism, aortic dissection, acute death) for all patients presenting with chest pain ≤ 3 hours after onset of complaints (n=106).

	ACS or other life threatening disease +	ACS or other life threatening disease -	TOTAL
H-FABP PoCT +	1	1	2
H-FABP PoCT -	11	93	104
TOTAL	12	94	106 (115 patients presented ≤ 3 hours after onset of complaints, 9 test failures)

Among 12 cases of ACS or other life threatening disease where H-FABP PoCT was negative, 11 were diagnosed with ACS and in one case acute heart failure due to severe diastolic heart failure was found.
Test sensitivity, specifity, negative and positive predictive value (95% CI) for ACS or other life threatening disease in all patients presenting with chest pain ≤ 3 hours after onset of complaints: 8.3% (0.44-40.2%), 98.9% (93.4-99.9%), 89.4% (81.5-94.3%), 50.0% (26.7-97.3%) respectively.
In 6 cases, patients presented within 24 hours after onset of complaints, however registration of duration of complaints was incomplete. These patients are not included in the tables representing subgroups of patients presenting with chest pain within 3 hours or 3-24 hours after onset of complaints.
Abbreviations: 95% CI = 95% confidence interval; ACS = acute coronary syndrome; H-FABP = Heart-type Fatty Acid Binding Protein; NSTEMI = non ST elevated myocardial infarction; PoCT = point of care test; STEMI = ST elevated myocardial infarction

Table S10.3: Two-by-two table displaying the relationship between H-FABP PoCT result and the presence of ACS (unstable angina, NSTEMI, STEMI) or other life threatening disease (acute heart failure, pulmonary embolism, aortic dissection, acute death) for all patients presenting with chest pain 3-24 hours after onset of complaints (n=179).

	ACS or other life threatening disease +	ACS or other life threatening disease -	TOTAL
H-FABP PoCT +	8	6	14
H-FABP PoCT -	14	151	165
TOTAL	22	157	179 (182 patients presented > 3 hours after onset of complaints, 3 test failures)

Among 8 cases of ACS or other life threatening disease where H-FABP PoCT was positive, 7 were diagnosed with ACS, and one case of acute heart failure due to cardiomyopathy was found.
Among 14 cases of ACS or other life threatening disease where H-FABP PoCT was negative, 12 were diagnosed with ACS, one case was attributed to acute heart failure (due to hypertensive heart disease) and in one case acute death of unknown cause was the expert panel's final diagnosis.
Test sensitivity, specifity, negative and positive predictive value (95% CI) for ACS or other life threatening disease in all patients presenting with chest pain > 3 hours after onset of complaints: 36.4% (18.0-59.2%), 96.2% (91.5-98.4%), 91.5% (85.9-95.1%), 57.1% (29.6-81.2%) respectively.
In 6 cases, patients presented within 24 hours after onset of complaints, however registration of duration of complaints was incomplete. These patients are not included in the tables representing subgroups of patients presenting with chest pain within 3 hours or 3-24 hours after onset of complaints.
Abbreviations: 95% CI = 95% confidence interval; ACS = acute coronary syndrome; H-FABP = Heart-type Fatty Acid Binding Protein; NSTEMI = non ST elevated myocardial infarction; PoCT = point of care test; STEMI = ST elevated myocardial infarction

Addendum 10.A2:

2x2 tables S10.4-S10.6 for all patients, patients presenting with chest pain ≤ 3 hours after onset of complaints and patients presenting with chest pain 3-24 hours after onset of complaints, respectively.

OUTCOME ACS.

Table S10.4: Two-by-two table displaying the relationship between H-FABP PoCT result and the presence of ACS (unstable angina, NSTEMI or STEMI) in all patients (n = 291).

	ACS +	ACS -	TOTAL
H-FABP PoCT +	8	8	16
H-FABP PoCT -	23	252	275
TOTAL	31	260	291 (12 test failures among 303 included patients)

Among all 259 cases where ACS was negative, 23 cases of stable coronary disease were reported (in 2 of these cases, H-FABP PoCT was positive, in 21 cases the H-FABP PoCT was negative). Among all 32 cases where ACS was positive, 9 cases of STEMI were present (in 3 of these cases, H-FABP PoCT was positive, in 6 cases the H-FABP PoCT was negative).
Test sensitivity, specifity, negative and positive predictive value (95% CI) for ACS: 25.8 (12.5-44.9%), 96.9% (93.8-98.6%), 91.6% (87.6-94.5%), 50.0% (25.5-74.5%) respectively.
Abbreviations: 95% CI = 95% confidence interval; ACS = acute coronary syndrome; H-FABP = Heart-type Fatty Acid Binding Protein; NSTEMI = non ST elevated myocardial infarction; PoCT = point of care test; STEMI = ST elevated myocardial infarction

Table S10.5: Two-by-two table displaying the relationship between H-FABP PoCT result and the presence of ACS (unstable angina, NSTEMI, STEMI) for all patients presenting with chest pain ≤ 3 hours after onset of complaints (n=106).

	ACS +	ACS -	TOTAL
H-FABP PoCT +	1	1	2
H-FABP PoCT -	10	94	104
TOTAL	11	95	106 (115 patients presented ≤ 3 hours after onset of complaints, 9 test failures)

Among all 93 cases where ACS was negative, 9 cases of stable coronary disease were reported (in all of these cases, H-FABP PoCT was negative).
Among all 12 cases where ACS was positive, 3 cases of STEMI were present (in all 3 of these cases, H-FABP PoCT was negative).
Test sensitivity, specifity, negative and positive predictive value (95% CI) for ACS in all patients presenting with chest pain ≤ 3 hours after onset of complaints: 9.1% (4.8-42.9%), 98.9% (93.4-99.9%), 90.4% (82.6-95.0%), 50.0% (26.7-97.3%) respectively.
In 6 cases, patients presented within 24 hours after onset of complaints, however registration of duration of complaints was incomplete. These patients are not included in the tables representing subgroups of patients presenting with chest pain within 3 hours or 3-24 hours after onset of complaints.

Abbreviations: 95% CI = 95% confidence interval; ACS = acute coronary syndrome; H-FABP = Heart-type Fatty Acid Binding Protein; NSTEMI = non ST elevated myocardial infarction; PoCT = point of care test; STEMI = ST elevated myocardial infarction

Table S10.6: Two-by-two table displaying the relationship between H-FABP PoCT result and the presence of ACS (unstable angina, NSTEMI, STEMI) for all patients presenting with chest pain 3-24 hours after onset of complaints (n=179).

	ACS +	ACS -	TOTAL
H-FABP PoCT +	7	7	14
H-FABP PoCT -	12	153	165
TOTAL	19	160	179 (182 patients presented > 3 hours after onset of complaints, 3 test failures)

Among all 160 cases where ACS was negative, 14 cases of stable coronary artery disease were reported (in 2 of these cases, H-FABP PoCT was positive, in 12 cases the H-FABP PoCT was negative).
Among all 19 cases where ACS was positive, 6 cases of STEMI were present (in 3 of these cases, H-FABP PoCT was positive, in 3 cases the H-FABP PoCT was negative).
Test sensitivity, specificity, negative and positive predictive value (95% CI) for ACS in all patients presenting with chest pain > 3 hours after onset of complaints: 36.8% (17.2-61.4%), 95.6% (90.8-98.1%), 92.7% (87.4-96.0%), 50.0% (24.0-76.0%) respectively.
In 6 cases, patients presented within 24 hours after onset of complaints, however registration of duration of complaints was incomplete. These patients are not included in the tables representing subgroups of patients presenting with chest pain within 3 hours or 3-24 hours after onset of complaints.
Abbreviations: 95% CI = 95% confidence interval; ACS = acute coronary syndrome; H-FABP = Heart-type Fatty Acid Binding Protein; NSTEMI = non ST elevated myocardial infarction; PoCT = point of care test; STEMI = ST elevated myocardial infarction

Addendum 10.A3:

2x2 tables S10.7-S10.9 for all patients, patients presenting with chest pain ≤ 3 hours after onset of complaints and patients presenting with chest pain 3-24 hours after onset of complaints, respectively.

OUTCOME AMI.

Table S10.7: Two-by-two table displaying the relationship between H-FABP PoCT result and the presence of AMI (NSTEMI or STEMI) in all patients (n = 291).

	AMI +	AMI -	TOTAL
H-FABP PoCT +	7	9	16
H-FABP PoCT -	19	256	275
TOTAL	26	265	291 (12 test failures among 303 included patients)

Test sensitivity, specifity, negative and positive predictive value (95% CI) for AMI: 26.9% (12.4-48.1%), 96.6% (93.4-98.3%), 93.1% (89.2-95.7%), 43.8% (20.8-69.4%) respectively.

Abbreviations: 95% CI = 95% confidence interval; AMI = acute myocardial infarction; H-FABP = Heart-type Fatty Acid Binding Protein; NSTEMI = non ST elevated myocardial infarction; PoCT = point of care test; STEMI = ST elevated myocardial infarction

Table S10.8: Two-by-two table displaying the relationship between H-FABP PoCT result and the presence of AMI (NSTEMI, STEMI) for all patients presenting with chest pain ≤ 3 hours after onset of complaints (n=106).

	AMI +	AMI -	TOTAL
H-FABP PoCT +	1	1	2
H-FABP PoCT -	9	95	104
TOTAL	10	96	106 (115 patients presented ≤ 3 hours after onset of complaints, 9 test failures)

Test sensitivity, specifity, negative and positive predictive value (95% CI) for AMI in all patients presenting with chest pain ≤ 3 hours after onset of complaints: 10.0% (0.52-45.9%), 99.0% (93.5-99.9%), 91.3% (83.8-95.7%), 50.0% (26.7-97.3%) respectively.

In 6 cases, patients presented within 24 hours after onset of complaints, however registration of duration of complaints was incomplete. These patients are not included in the tables representing subgroups of patients presenting with chest pain within 3 hours or 3-24 hours after onset of complaints.

Abbreviations: 95% CI = 95% confidence interval; AMI = acute myocardial infarction; H-FABP = Heart-type Fatty Acid Binding Protein; NSTEMI = non ST elevated myocardial infarction; PoCT = point of care test; STEMI = ST elevated myocardial infarction

Table S10.9: Two-by-two table displaying the relationship between H-FABP PoCT result and the presence of AMI (NSTEMI, STEMI) for all patients presenting with chest pain 3-24 hours after onset of complaints (n=179).

	AMI +	AMI -	TOTAL
H-FABP PoCT +	6	8	14
H-FABP PoCT -	9	156	165
TOTAL	15	164	179 (182 patients presented > 3 hours after onset of complaints, 3 test failures)

Test sensitivity, specifity, negative and positive predictive value (95% CI) for AMI in all patients presenting with chest pain > 3 hours after onset of complaints: 40.0% (17.5-67.1%), 95.1% (90.3-97.7%), 94.5% (89.6-97.3%), 42.9% (18.8-70.4%) respectively.

In 6 cases, patients presented within 24 hours after onset of complaints, however registration of duration of complaints was incomplete. These patients are not included in the tables representing subgroups of patients presenting with chest pain within 3 hours or 3-24 hours after onset of complaints.

Abbreviations: 95% CI = 95% confidence interval; AMI = acute myocardial infarction; H-FABP = Heart-type Fatty Acid Binding Protein; NSTEMI = non ST elevated myocardial infarction; PoCT = point of care test; STEMI = ST elevated myocardial infarction

Addendum 10.A4.

2x2 tables S10.10-S10.12 for all patients, patients presenting with chest pain ≤ 3 hours after onset of complaints and patients presenting with chest pain 3-24 hours after onset of complaints, respectively.

OUTCOME NSTEMI

Table S10.10: Two-by-two table displaying the relationship between H-FABP PoCT result and the presence of NSTEMI in all patients (n = 291).

	NSTEMI +	NSTEMI -	TOTAL
H-FABP PoCT +	3	13	16
H-FABP PoCT -	13	262	275
TOTAL	16	275	291 (12 test failures among 303 included patients)

Test sensitivity, specifity, negative and positive predictive value (95% CI) for NSTEMI: 18.9% (5.0-46.3%), 95.3% (91.9-97.4%), 95.3% (91.9-97.4%), 18.9% (5.0-46.3%), respectively.
Abbreviations: 95% CI = 95% confidence interval; H-FABP = Heart-type Fatty Acid Binding Protein; NSTEMI = non ST elevated myocardial infarction; PoCT = point of care test; STEMI = ST elevated myocardial infarction

Table S10.11: Two-by-two table displaying the relationship between H-FABP PoCT result and the presence of NSTEMI for all patients presenting with chest pain ≤ 3 hours after onset of complaints (n=106).

	NSTEMI +	NSTEMI -	TOTAL
H-FABP PoCT +	0	2	2
H-FABP PoCT -	6	98	104
TOTAL	6	100	106 (115 patients presented ≤ 3 hours after onset of complaints, 9 test failures)

Test sensitivity, specifity, negative and positive predictive value (95% CI) for NSTEMI in all patients presenting with chest pain ≤ 3 hours after onset of complaints: 0% (0-48.3%), 98.0% (92.3-99.7%), 94.2% (87.4-97.6%), 0% (0-80.2%) respectively.
In 6 cases, patients presented within 24 hours after onset of complaints, however registration of duration of complaints was incomplete. These patients are not included in the tables representing subgroups of patients presenting with chest pain within 3 hours or 3-24 hours after onset of complaints.
Abbreviations: 95% CI = 95% confidence interval; H-FABP = Heart-type Fatty Acid Binding Protein; NSTEMI = non ST elevated myocardial infarction; PoCT = point of care test; STEMI = ST elevated myocardial infarction

Table S10.12: Two-by-two table displaying the relationship between H-FABP PoCT result and the presence of NSTEMI for all patients presenting with chest pain 3-24 hours after onset of complaints (n=179).

	NSTEMI +	NSTEMI -	TOTAL
H-FABP PoCT +	3	11	14
H-FABP PoCT -	6	159	165
TOTAL	9	170	179 (182 patients presented > 3 hours after onset of complaints, 3 test failures)

Test sensitivity, specifity, negative and positive predictive value (95% CI) for NSTEMI in all patients presenting with chest pain > 3 hours after onset of complaints: 33.3% (9.0-69.1%), 93.5% (88.4-96.6%), 96.4% (91.9-98.5%), 21.4% (5.7-51.2%) respectively.

In 6 cases, patients presented within 24 hours after onset of complaints, however registration of duration of complaints was incomplete. These patients are not included in the tables representing subgroups of patients presenting with chest pain within 3 hours or 3-24 hours after onset of complaints.

Abbreviations: 95% CI = 95% confidence interval; H-FABP = Heart-type Fatty Acid Binding Protein; NSTEMI = non ST elevated myocardial infarction; PoCT = point of care test; STEMI = ST elevated myocardial infarction

Addendum 10.B

Addendum 10.B: Additional comments and details on false positive and false negative test results

	Frequency	Details
H-FABP PoCT TP for AMI	7 / 303	**3x** STEMI, **3x** NSTEMI, **1x** 'AMI and acute death'
H-FABP PoCT FP for AMI	9 / 303	• **2x** GP writes comment on CRF: "very slightly positive". hs-cTnT in the one case 16 h and 45 min and in the other 1 h and 19 min after onset of complaints negative. EP's final diagnosis: atypical thoracic complaints and locomotory tract related pain (referral to orthopaedics) respectively. • **2x** GP indicates H-FABP PoCT positive on CRF. In the one case hs-cTnT 11 h and 32 min and in the other hs-cTnI 11 h and 41 min and 16 h and 45 min after onset of complaints negative. EP's final diagnosis in both cases: SAP. • **3x** GP indicates H-FABP PoCT positive on CRF. In first case hs-cTnI the same day and 40 h after onset of complaints negative, in second case hs-cTnT 6 h and 46 min after onset of complaints negative, in third case hs-cTnI 6 h and 53 min after onset of complaints negative. EP's final diagnosis: atypical thoracic complaints (two times) and vertigo due to upper airway tract infection respectively. • **2x** GP indicates H-FABP PoCT positive on CRF. In the first case hs-cTnT 29 h and 47 min after onset of complaints eventually positive, in the second case hs-cTnT 5 h and 43 min after onset of complaints positive. EP's final diagnosis: UAP (therefore H-FABP PoCT TP for ACS) and heart failure due to non ischemic CMP respectively. Remark: eGFR 22 ml/min and 13 ml/min respectively.
H-FABP PoCT TN for AMI	256 / 303	-
H-FABP PoCT FN for AMI	19 / 303	• **3x**, the GP decided not to refer, time between onset of complaints and H-FABP PoCT was 240 minutes, 310 minutes and 'unknown, however < 24 hours', respectively. Troponin was negative, diagnosis of NSTEMI was established only several days, 17 days and 14 days respectively after first presentation. *Conclusion: false negative H-FABP PoCT result due to late diagnosis of AMI, troponin negative.* • **5x**, the GP decided not to refer, time between onset of complaints and H-FABP PoCT was 75, 120, 180, 210 minutes, 375 minutes, respectively. However troponin measured within three days after onset of complaints was elevated. Therefore the EP diagnosed NSTEMI, in one case further confirmed by findings of cardiac ultrasound. Among these, in one case eGFR was low (32 ml/min). *Conclusion: false negative H-FABP PoCT result (in 2 cases false negative result > 3 hours after onset of complaints, in 3 cases false negative result possibly due to short time between onset of complaints and presentation to GP).* • **11x**, the GP decided to refer immediately. Time between onset of complaints and H-FABP PoCT was 25, 35, 70, 95, 115, 120, 200, 225, 300, 645 and 950 minutes respectively. Troponin was elevated in 9 cases and in 6 cases a STEMI was found on ECG, therefore the EP diagnosed (N)STEMI. *Conclusion: false negative H-FABP PoCT result (in 5 cases false negative result > 3 hours after onset of complaints, in 6 cases false negative result possibly due to short time between onset of complaints and presentation to GP).*
Test failures	12 / 303	-

Abbreviations: ACS = acute coronary syndrome; AMI = acute myocardial infarction; CAG = coronary angiography; CMP = cardiomyopathy; CRF = case report form; ECG = electrocardiogram; eGFR = estimated glo-

merular filtration rate; EP = expert panel; FN = false negative; FP= false positive; GP = general practitioner; H-FABP = Heart-type Fatty Acid Binding Protein; h = hours; hs-cTnT = high-sensitive cardiac-specific troponin T; min = minute(s); NSTEMI = non ST elevated myocardial infarction; PoCT = point of care test; SAP = stable angina pectoris; STEMI = ST elevated myocardial infarction; TN = true negative; TP= true positive; UAP = unstable angina pectoris

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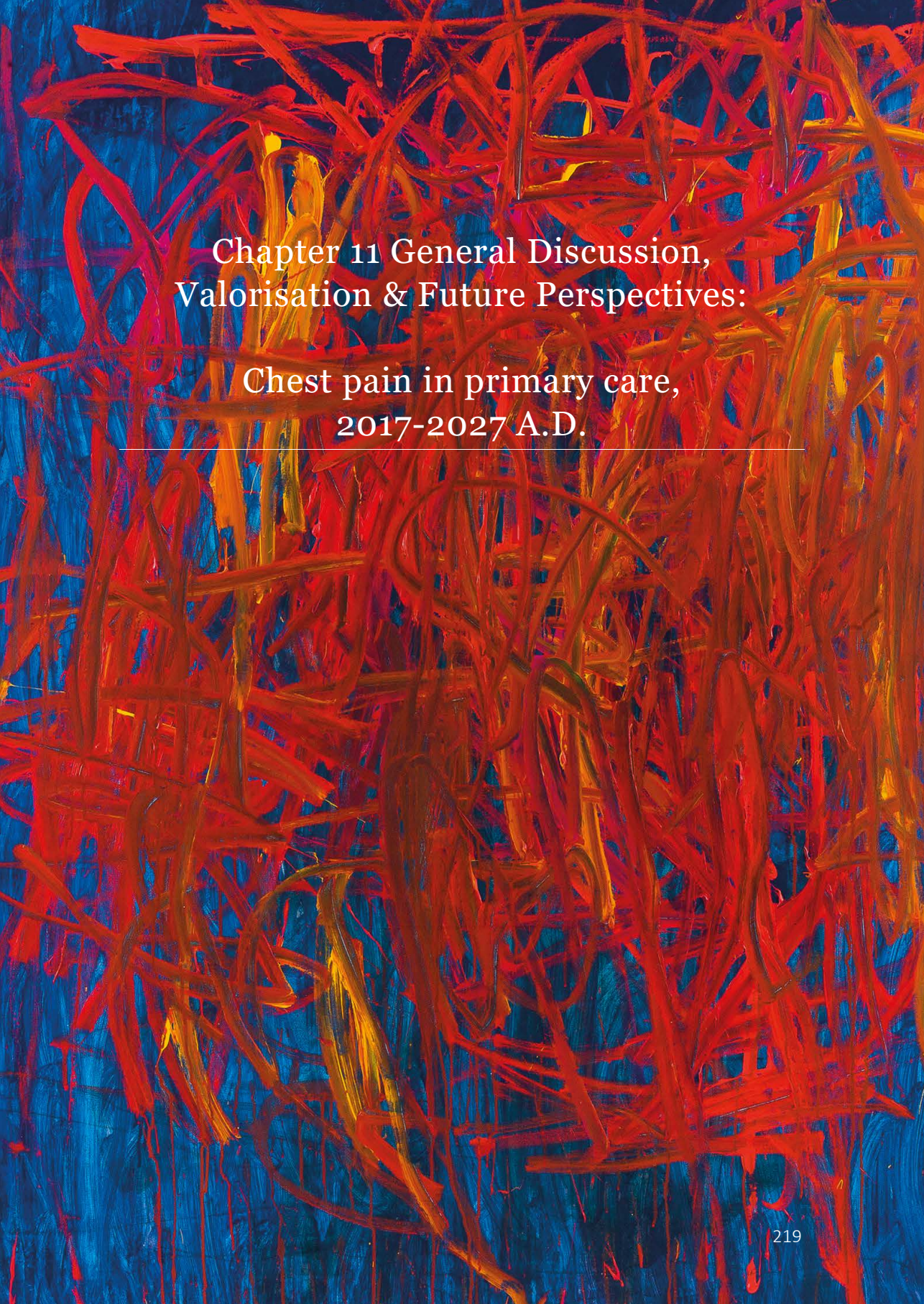

Chapter 11 General Discussion, Valorisation & Future Perspectives:

Chest pain in primary care, 2017-2027 A.D.

11.1 Introduction

When discussing chest pain in primary care, researchers and general practitioners (GPs) agree on the difficulties in patient assessment and diagnosis. Chest pain is the most common presenting complaint of acute coronary syndrome (ACS), a life-threatening condition in which patients are at risk of ventricular fibrillation and sudden death. Therefore, for decades, missing myocardial infarction is one of every doctor's worst nightmares. Yet, simply referring all patients with chest pain is impractical. Chest pain also accompanies other non-cardiac related conditions which are not medical emergencies. Thus, the GP faces the difficult decision of whether to refer the patient immediately for treatment on the suspicion of ACS, or not refer them and risk possibly missing the diagnosis with likely fatal outcomes. Although it's better to be safe than sorry, referring a 6th patient in a few weeks time, knowing that the previous five patients were diagnosed with chest wall pain and gastric reflux disease, is a hard decision.

This dilemma in chest pain is possibly best reflected in that moment that a GP tells his or her patient with moderate chest pain and no signs of shock that he or she wants to refer. The patient might agree at that point. But then, when the patient is told that he or she needs immediate ambulance transport, the patient's face is often full of disbelieve. Sometimes, a GP has to convince the patient that he or she is not allowed to go home to get a toothbrush and a set of pajamas first. After having discussed it, a paramedic that comes to the practice to transport the patient and feels free to say to the patient that he thinks it is not that bad, is not helpful, although well-meant. Neither, although understandable, is a busy cardiologist receiving the phone announcement, asking the GP the question of conscience whether it is really necessary for the patient to come immediately. Thus, after the ambulance has left, the GP will be in need for a cup of coffee - although the waiting room might be filled with patients due to the delay caused by managing the unannounced chest pain patient. Over this well deserved cup, his or her thoughts most likely are about the future availability of a decent diagnostic tool in primary care to rule out ACS.

The main goal of this thesis was to explore perspectives in assessing ACS in primary care. In this final chapter, the main findings are related to contemporary literature in **sections 11.2** to **11.7**. The conclusions from this thesis are summarised in **section 11.8: 'conclusions from this thesis and current literature'.**

In **section 11.9**, future perspectives are outlined. In **section 11.10,** a valorisation of our material is given. Throughout the main text of this **chapter 11**, fourteen points of attention for future research are **marked in bold type setting**. These points are recited and arranged by topic - not necessarily in their order of appearance in the main text **- in section 11.11**: **'fourteen points of attention for future research'**.

11.2 Clinical perspectives

In primary care, GPs act with restraint in using diagnostic tests (venous blood tests, X-rays, ECGs, etc). Testing everybody is uncomfortable for the patients, inefficient and expensive. Therefore, reducing the GP's diagnostic process to additional tests would not justify the broader picture where the GP's own judgment plays an important role. Before using any additional test, the GP has estimated the necessity of testing, watchful waiting or just remaining expectative, based on history taking, physical examination and patient context. This part of the GP's diagnostic process without additional diagnostic tests is especially demanding since GPs encounter manifestations of a wide variety of more and less typically elapsing diseases in an often early, and therefore less easily recognisable, stage. In chapter 2 and chapter 3 of this thesis, examples of different situations of chest pain in primary care are provided. In chapter 2, a typical example of the complicated process before using additional tests is illustrated, whereas chapter 3 focuses on the advantages ánd pitfalls of additional diagnostic tests that occur, once physicians have decided these tests are indicated.

The case report in chapter 2 describes an occasion where diagnosis of a severe cardiac disease was missed, resulting in fatal consequences. Although rare, most GPs will be able to recall examples of these occasions, either from their own experiences or those of colleagues. Factors that may contribute to a missed diagnosis, such as 'confirmation bias', as well as possibly more easily recognisable signs of a missed diagnosis, such as a high frequency of patient visits and little effect of initiated therapy, are listed. Given the risks of misdiagnosis, referral on the basis of possible ACS is an appropriate course of action, even on the slightest suspicion, thereby accepting a certain degree of over referral.

In chapter 3, dilemmas in evaluating chest pain in primary care are illustrated. While referring all patients with chest pain to rule out ACS will reduce chances of missed diagnoses, it is not an efficient use of time or resources, and can generate unnecessary stress for patients, given the fact that the large majority of chest pain cases are non-cardiac related. This chapter describes three different cases to illustrate the wide variety of presentations and types of chest pain in primary care. The first details a patient suspected of ACS who was referred to secondary care for biomarker testing, and a negative result was used to rule out ACS. In the second case, the patient’s pre-test probability of ACS was low, but persistent complaints and the time range of symptoms led the GP to test troponin levels and an ACS diagnosis was found. Complaints are usually more acute and therefore, there often is insufficient time to test biomarkers and wait for results in primary care. In the third case, a biomarker test returned positive but no ACS was found. This was an example of a 'false positive' result. However, the biomarker result was indicative of another severe disease . The first case highlights the current challenge for diagnostic researchers: the need for a reliable rule-out test in primary care

with a high negative predictive value (NPV) for ACS. This tool would assist GPs in screening patients with chest pain and discriminating which patients should be referred for possible ACS and which patients can be ruled out accurately and efficiently, thereby reducing the number of ACS negative referrals.

11.3 Epidemiology

In chapter 4, we studied the incidence of sudden onset chest pain and ACS in primary care. Dutch and Belgian GPs are consulted for chest pain in every 79th patient contact, which means consultation for chest pain occurs at least weekly (incidence of chest pain consultation is 1.26% of all GP consultations). ACS as an underlying cause was at least briefly considered in 2 out of 5 patients presenting with chest pain, and referral took place in 2 out of 5 cases. In most cases, the patients with suspected ACS were those with referrals to secondary care. Although most chest pain patients were finally diagnosed with mild causes, ACS was diagnosed in every 15th, and ACS or another life-threatening cause of chest pain was diagnosed in every 12th patient presenting with chest pain, emphasising the reality that a critically ill patient may walk into the GP's consulting room. The NPV of the GPs' clinical judgment for ACS was 99.6% (i.e. 99.6% of patients who were not referred, were not diagnosed with ACS within 30 days after initial assessment). However, in these non-referred patients, a gold standard test to rule out ACS was not performed. The positive predictive value (PPV) of the GPs' clinical judgment for ACS was 43% (43% of referred patients were diagnosed with ACS). Sensitivity and specificity of the GPs' clinical judgment were 94.7% and 91.3% respectively. Thus, the diagnostic value of the GPs' clinical judgment is reasonable: only one in seven patients is referred and almost every second of those referred patients is diagnosed with ACS. However, on average, almost two diagnostic tests are used per chest pain patient, illustrating the demanding diagnostic assessment of these patients.

In the Netherlands, 50,000 patients annually are referred to secondary care facilities where ACS is subsequently not diagnosed (ACS-negative patients). Thus, there is enormous value in developing a method to rule out ACS at the GP's office, reducing unnecessary time, cost, patient discomfort and resources (e.g. ambulance transportation, secondary care facilities) (point 5 in section 11.11). In international literature, the incidence of chest pain ranged from 0.7 to 3.0% of all patient consultations in primary care (weighted average 1.54%, slightly higher than the 1.26% found in chapter 4).[1-9] Moreover, predictive values of GPs' clinical judgment from international literature were slightly less favourable than we found in chapter 4: PPV was 23.7% and NPV was 98.2%.[2-17] Based on these data, it is arguable that the patient burden of referred ACS-negative patients is even higher, when compared to our data in chapter 4. Cost analyses associ-

ated with reducing the burden of ACS-negative referrals, based on our data derived from chapter 4 as well as on international literature, are presented in chapter 6.

11.4 General practitioners' view

In chapter 5, the results of interviews with 27 Dutch and Belgian GPs are summarised. Patients presenting with chest pain were encountered at least once per week. While the incidence of ACS was reported by GPs to have decreased, they did not report a change in the incidence of chest pain in general. Most reported a difference in the clinical presentations, with atypical chest pain complaints becoming more frequent. This was partially attributed to an altered presentation of chest pain in female patients. The GPs' experiences were in line with findings in literature.[18-24] Clinical judgment and referral decisions were reported to be based mainly on history taking and gut feeling. Yet, GPs emphasised the limitations of those methods and felt confident about referring patients in cases of doubt. In the language they use to justify their over-referral, expressions of a sense of responsibility and of a perceived feeling of disapproval by patients or colleagues can be recognised. Still, GPs have high confidence in history taking, following gut feeling and referring in cases of doubt.

GPs had several reservations about additional diagnostic tools to exclude ACS in primary care, such as point of care tests (PoCTs) on biomarkers of myocardial cell damage, pointing out that proper clinical embedding of such a test is crucial. The interviewed GPs thereby formulated more preservation than was seen in a questionnaire studying GPs' expectations of new diagnostic tools in chest pain.[25,26] However, the approach in this online survey study was directed at usability and potential gain, rather than an in-depth evaluation of clinical utility of the test. GPs in our interview study emphasised that a new test should be accompanied by clear instructions on when (e.g. for what indication) and how (e.g. as part of a clinical decision rule (CDR)) to use it. Furthermore, it should be clear what action should follow a certain test results (point 13 in section 11.11).

Indeed, it is known from literature that fine tuning of diagnostic tools on several levels is necessary to achieve correct and cost-effective usage, but this is not always achieved for a number of reasons.[27] First, complete clinical evaluation of a PoCT has only been covered in a minority of PoCT studies, thus the total impact on clinical care is difficult to interpret.[28] Second, correct usage of tests by optimising four essential usage conditions – management, training, quality assurance and registration – is not always guaranteed.[29-31] Third, the introduction of PoCTs in different clinics with different organisational structures, local protocols and facilities has led to marked differences in efficiency in using the PoCT: costs even increased in some clinics after a fast rule-out test for ACS was introduced.[32] Given the scope of challenges in effectively implementing a PoCT in primary care, the reservations held by GPs for new diagnostic tools is reasona-

ble. However, as has been documented in earlier studies, if all requirements can be met, GPs would be highly interested in a PoCT in primary care.[26]

11.5 Potential gain

Annually in the Netherlands, upto an estimated 1 million primary care consultations concern chest pain, as reviewed in chapter 6 (based on international data). In 14% of these consultations, direct referral takes place. For every referred case with a positive ACS diagnosis (ACS-positive referral), there are three referred cases where ACS is subsequently ruled out (ACS-negative). These ACS-negative cases account for 10.8% of all chest pain patients, costing €162 million in the Netherlands every year. With an estimated cost price of a PoCT of €45, a reduction of ACS-negative referrals from 10.8% to 7.7% of all chest pain patients would make the PoCT cost-neutral (point 7 in section 11.11). Furthermore, an additional €14.5 million would be saved for every further absolute reduction of 1% of ACS-negative referrals. The price of a PoCT is of considerable influence on its cost saving potency: if the cost price was halved to €22.50 per test, the PoCT would become already cost-neutral after a reduction of ACS-negative referrals from 10.8% to 9.2%. The economic model built for chapter 6 appeared mainly sensitive to changes in cost price of a PoCT and to variation of numbers of ACS-negative referrals.

In other words: a not too expensive PoCT fairly reducing the number of ACS negative referrals, leaving the number of ACS positive non referrals equal to current practice, 'could do the job'. A similar qualification of the health care burden of chest pain has been described from a secondary care perspective.[33] The importance of calculating cost effects of new diagnostic tools has also been described.[32] However, chapter 6 is, to our knowledge, the first model-based analysis to estimate the health-economic impact of introducing (a CDR incorporating) a PoCT into primary care for ruling out ACS-negative causes of chest pain.

11.6 Heart-type fatty acid binding protein (H-FABP) as a biomarker in primary care

In chapter 7, H-FABP as a biomarker in ischemic heart disease is reviewed. Due to its small molecular mass and cytoplasmic location, H-FABP is one of the earliest detectable markers of myocardial cell damage, and meets the main criteria of a usable marker.[34,35] H-FABP is specific and detectable early after symptom onset, and with the availability of PoC H-FABP tests such as the CARDIODETECT and the test introduced by FABPulous BV, rapid test results at the point of care can be obtained. High-sensitive troponin on the contrary also meets all these demands, except the demand for a PoCT with a low cut-off

value, which is not yet available.[36] This is a point of particular interest in PoCT devices. A considerable number of tests of questionable quality are available, since only limited quality testing is obligatory. Every test that is considered for implementation in healthcare should be rigorously validated.

In the past, an attempt to validate usage of the H-FABP PoCT with a cut-off value of 7 ng/ml (CARDIODETECT) failed due to an unacceptable number of missed cases of ACS.[10] In chapter 8, the hypothesis that H-FABP with a lower cut-off value would detect more cases of ACS in an early stage was explored. In primary care, where safe rule-out with a single test is crucial, such a low cut-off value seems promising since the NPV, and thereby safety, is increased. In analyses of venous blood samples from patients at a cardiac emergency department, H-FABP measurements were performed. In a receiver operating characteristic (ROC)-curve, the optimal cut off value of H-FABP for ACS was 4 ng/ml.[37] Indeed, this is a cut-off value even lower than the 99th percentile in a normal reference population, which seems recommendable when aiming at safe rule-out of ACS in primary care (point 3 in section 11.11).[38] The test sensitivity reached 73.9% and NPV in a population with an incidence of ACS of 22% would reach 90.8%. Thus, H-FABP performed slightly better than high sensitive troponin (sensitivity of 70.6%). Based on the earlier PoCT H-FABP studies and based on our findings in chapter 8, the FABPulous test with a cut-off value of 4 ng/ml was developed.

11.7 Heart-type fatty acid binding protein (H-FABP) as a point of care test (PoCT) in primary care

In general, less than 1% of newly discovered biomarkers find their way from bench to bedside.[39] Due to insufficient collaboration between academic, clinical, governmental and commercial parties, and due to a lacking standardisation of developmental trajectories, only few biomarkers are finally registered for clinical use.[40,41] The inefficient development of clinically usable biomarker devices was addressed by the National Biomarker Development Alliance (http://nbdabiomarkers.org). Seamless evolution of biomarker tests from 'bench' to 'bedside' should be covered in unambiguous study pathways incorporating both the experimental and the implementational phase of development (point 1 in section 11.11).[40,42] In our RAPIDA-study (RAPIDA: RAPid test for Investigating complaints possibly Due to Acute coronary syndrome), collaboration between manufacturers and researchers as well as clinical validation was guaranteed.[37,38] Furthermore, the development of a H-FABP PoCT with a low cut-off value in primary care to reduce ACS negative referrals in chest pain patients in primary care, as tested in the RAPIDA-study, meets the demands formulated in the checklist for biomarker development: an unmet clinical need is identified without an obvious other solution presently available, new developments in biomarker testing could contribute to the solution of the unmet clini-

cal need and with the availability of a PoCT with a clinically validated cut-off value, the solution seems feasible in practice.[43] **Before developing and implementing a new biomarker test, defining its clinical need should be a 'conditio sine qua non' (point 1 in section 11.11).**

Following the encouraging results of H-FABP with a cut-off value of 4 ng/ml in venous blood to rule in and rule out ACS, the actual performance of a PoC test device with a similar cut-off value was studied. In **chapter 9** (background and protocol) and **chapter 10** (results and discussion) our study on the performance of a H-FABP PoCT with a cut-off value of 4 ng/ml is described. We performed a clinical study in primary care examining the potential use of the PoCT H-FABP by testing the PoCT in chest pain patients that were assessed by GPs. After inclusion of 303 chest pain patients, the sensitivity of the H-FABP PoCT with a cut-off value of 4 ng/ml was lower than expected, based on analyses in **chapter 8**. The duration of complaints or outcome variation (ACS, acute myocardial infarction (AMI), or non-ST-elevated myocardial infarction (NSTEMI)) were of minor influence on the moderate test performance. Sensitivity was low across all subgroups. A considerably high NPV for ACS (91.6%) was calculated due to the relatively low incidence of ACS (10.6%). However, the false negativity rate of the test was unacceptably high with a sensitivity for ACS of 25%. Thus, final bedside use was hampered by a disappointing diagnostic outcome, as described in **chapter 10**.

In the RAPIDA-study, the demands for biomarker development targeting unmet clinical needs were met.[43] Yet, the promising qualities of the test, based on our pre-study with venous blood samples in an emergency department setting (**chapter 8**), were refuted by disappointing clinical validation of the PoCT in primary care. Whether or not a PoCT provides similar results to venous blood tests depends on several factors. First, test factors are of influence. For example, the performance of the test when measuring levels of H-FABP around the cut-off value (reflected by the coefficient of variance) is crucial: is the PoCT negative when a value slightly under 4 ng/ml is measured? And positive when levels are just a little above 4 ng/ml? Second, marker factors are of influence. By changing the domain for an emergency room population to a primary care population, H-FABP levels might be different too. In the near future, performance of the marker will be evaluated by measuring H-FABP concentrations in plasma samples obtained from a subset of patients shortly after their presentation to the GP (or Emergency Department). These data will provide insight whether the current PoCT requires revision.Third, operator factors influence test performance. The experience of the person performing the test and the accuracy of reading the results influences the outcome. In the RAPIDA-study, we studied the PoCT as a diagnostic test in triage of chest pain patients. Therefore, all of these aspects that influence the diagnostic value of the PoCT-device (test, marker and operator factors) were present in the RAPIDA-study and could have influenced the final results.

The unaided clinical judgment of the GP reached a sensitivity and specificity of 75%, 67.5% respectively in the RAPIDA-study. In a multivariate regression analysis of all signs and symptoms, five highly significant predictors for acute coronary syndrome (ACS) and acute myocardial infarction (AMI) were found: ST-depressions, ST-elevations, dyspnea, pressure on the chest and absence of left sided lateral chest pain. When combining these five signs and symptoms with the PoCT H-FABP result, a CDR with a sensitivity and specificity of 87.5%, 52% respectively is described. However, negative and positive predicte values of this CDR did not significantly differ from the predictive values of the GP's sole clinical judgment. When using the CDR, the number of missed cases of ACS halved. However, for every prevented missed case of ACS, 10 patients without ACS scored a positive result of the CDR and would be referred, whereas these patients were not referred when the GP's clinical judgment was decisive. Therefore, the CDR increases safety but the false positivity rate increases, thus the efficiency of the CDR is poor. Besides, in order to use this CDR, a PoC H-FABP test ánd an ECG should be performed in all chest pain patients, further lowering the efficiency of such a CDR.

Studies with larger study populations should focus on the question whether the predictive signs and symptoms for ACS as found in our study (ST-depressions, ST-elevations, dyspnea, pressure on the chest and absence of left sided lateral chest pain)could play a role in a future CDR. Possibly, combinations with predictive factors derived from other studies and used in CDRs such as the Marburg Heart Score and the HEART-score, could attribute to an efficient CDR.[17,44-47] A PoC test with better diagnostic performance than found in our RAPIDA-study could further improve such a CDR.

11.8 Conclusions from this thesis and current literature

In chapter 2 and chapter 3 we presented several patient cases, illustrating different problems and dilemmas when it comes to assessing chest pain in primary care. The clinical judgment of a GP is a complex process based on medical knowledge and gut feeling. Additional diagnostic tests can be of added value However, knowledge of the possibilities ánd restrictions of such tests is necessary. In chapter 4, our registry study revealed that annually, in the Netherlands, 863,100 consultations concern chest pain and in 328,841 consultations (38.1%), ACS is at least briefly considered as an underlying cause. In 122,560 consultations (14.2%), the patient is referred to an emergency department. In every twelfth case of chest pain (72,500 consultations; 8.4%), a life-threatening disease is diagnosed and in 11 out of 12 cases of chest pain (790,560 consultations; 91.6%), the final outcome is not life-threatening. The reflections by GPs in chapter 5 considering assessment of chest pain in primary care can be summarised in three main points: first, the incidence of chest pain in general practice is stable, however the proportion of patients with ACS is decreasing. Atypical complaints are pre-

sented more frequently lately. Second, GPs feel relatively comfortable with over-referring chest pain patients to prevent missed cases of ACS. Third, new diagnostic tools are awaited, however GPs emphasise the importance of proper clinical embedding of such a test and they expect their clinical judgment will still remain essential in the future.

In chapter 6, we calculated that a relatively small reduction of ACS-negative referrals is needed for a PoCT to become cost neutral. However, a higher specificity of a PoCT, leading to a larger reduction in ACS-negative referrals, as well as a lower cost price of the PoCT, can further improve both economic and diagnostic outcomes of introducing a PoCT in assessing chest pain patients in primary care. In chapter 7, chapter 8 and chapter 9, we explained the possible role of H-FABP as a biomarker in primary care. Using a cut-off value of 4 ng/ml, a sensitivity for ACS of 73.9% was found in a secondary care population of patients with chest pain and an estimated NPV for ACS in a primary care population could reach 90.8%. Thus, H-FABP performed equal to high sensitive troponin. Based on the earlier PoCT H-FABP studies and based on our findings in chapter 8, the FABPulous PoCT with a cut-off value of 4 ng/ml was developed and tested in primary care. We reported the results in chapter 10. Surprisingly, the test performance was insufficient. A NPV for ACS of 91.6% was found (incidence of ACS in our study population was 10.6%), however, in 3 out of 4 cases of ACS, false-negative PoCT results were found. Combining the test with signs and symptoms in a CDR increases safety since ACS positive non-referrals are halved, when compared to the GP's clinical judgment. However, using this CDR would lead to more ACS negative referrals. Besides, PoC H-FABP tests and ECGs would be obligatory in all chest pain patients.

11.9 Future perspectives

11.9.1 Lessons from this research

Patients with recently altered chest pain during the weeks before presentation should be considered unstable until proven otherwise. However, in the era of high-sensitive troponin testing, these patients are either diagnosed with urgent stable coronary heart disease (CHD) or with myocardial infarction.[48] In our RAPIDA-study we assessed patients presenting with acute chest pain (onset < 24 hours). Thus, in our population, we found an incidence of ACS of 10.6%. This is lower than the 22% found in an earlier similar study, but comparable to other primary care populations of patients presenting with acute onset chest pain.[10,24]

Primary care chest pain populations have also been assessed in other studies. These were mainly derivation studies to develop a CDR, in which patients with chest pain with a duration of up to one month were included.[17,49] The main outcome was CHD, resulting

in a variety of patients suffering from both stable and unstable coronary conditions. These two manifestations of CHD are different entities: the former is caused by stable coronary stenosis, and the latter by intraluminal thrombosis. The mixed population of stable and unstable coronary problems was reflected by a low incidence of ACS of 2.5% in these populations. Therefore, the studies were not sufficiently powered to calculate predictive factors for ACS.

The clinical problem addressed in these studies is legitimate, since in all cases of chest pain in primary care, CHD should be safely ruled out. However, to find diagnostic tools in acute chest pain suspected of ACS, patient selection should focus on including these patients and this should be reflected in an incidence of ACS of at least 10% (point 11 in section 11.11). Predicting factors possibly contributing to a CDR to discriminate ACS cases should be derived by multivariate analysis with ACS, not a heterogeneous mixture of CHD patients, as a main outcome measure (point 12 in section 11.11). Therefore, studies should be designed to include a considerable number of ACS patients, either by aiming at a population with acute chest pain or by working with a mixture of CHD cases that have a substantial subgroup of ACS patients. The latter design would require large patient numbers and thus recruitment would be difficult.

11.9.2 Challenges of this research

In order to recruit a sufficient number of suspected unstable ACS patients, we specifically focused on patients presenting with acute chest pain with a duration of less than 24 hours. However, we faced several challenges inherent in drawing from such a narrow study population, and subsequently were delayed in meeting patient recruitment targets.

Studies for derivation of signs and symptoms that are of value as part of a CDR, and in a later stage implementation of such a CDR, should take place in real-life primary care patients assessed by their GP. Therefore, we invited 60 GPs to include ten patients each. We estimated that it would take about a year for a GP to be consulted for chest pain ten times. However, we expected that a considerable number of chest pain patients actually consulting their GP would not be included, due to practical reasons or exclusion criteria. Thus, we estimated that it would take up to 2 years to recruit a total of 600 patients. When inviting GPs into the study, we received great enthusiasm and had recruited 60 GPs in the Netherlands and Belgium within a few weeks.

By now, we know from our registration study – performed with another group of GPs than the group participating in our main RAPIDA-study – that our estimation of 10 chest pain patients per year was realistic. Indeed, chest pain is encountered by GPs at least weekly and 6% of these patients are ACS-positive referrals. In our RAPIDA-study, 60 GPs had recruited a total of 150 patients over two years – an average of one patient yearly, rather than weekly. Some GPs reached higher inclusion numbers, some GPs were not

able to include a single patient. The incidence of ACS among included patients was similar to the incidence found in our registration study, suggesting that the GPs in our RAPIDA-study did not select a subgroup of patients with a higher suspicion of ACS than generally seen in chest pain patients.

Weekly inclusion targets may have not been reached because of stringent exclusion criteria such as complaints that had persisted longer than 24 hours. However, given the weekly presentation in our registration study, under-recruitment of eligible patients by GPs seems to have contributed to difficulties in reaching target numbers. For example, some GPs acknowledged they missed several inclusions, and explained that chest pain patients are mostly unscheduled and that there is not always enough time to offer study involvement in the consultation, such as obtaining written informed consent. In the Netherlands, a brief written informed consent form was one of the study activities requested by the ethical review board before inclusion, requiring additional time spent on consultation of the patient.

Additionally, GPs stated that at the moment they consulted an eligible patient, they sometimes had to refresh their knowledge on study procedures and had no time to do so. We tried to minimise these difficulties by repeatedly offering the GPs instructions and other assistance. Interest in contributing to the study remained high and was not an apparent factor in under-recruitment, as GPs emphasised their undiminished enthusiasm and willingness to include patients at each point of contact.

In our work, we have shown that minimising the time taken for GPs to enroll patients and perform study activities may help aid patient recruitment. During the final year of our RAPIDA-study, six Dutch out of hour (OOH-) services were added to our recruiting institutions. Here, all patients are routinely met by nurses performing a range of tasks prior to assessment by the GP. For the purpose of our RAPIDA-study we asked the nurses to perform all study activities that could be taken over from the GP, such as performing the PoC test and the brief informed consent procedure. The incidence of chest pain was higher at OOH-services, thus nurses had greater opportunity for patient recruitment and more experience in handling the necessary forms. Indeed, patient inclusion was considerably faster in these OOH-services, with 152 inclusions in less than one year, though given the large service areas involved with these OOH-services, again, under-recruitment must still have taken place. However, we have learned from this exercise that **patient inclusion improves when nurses take over study activities from the GP and are free to perform the necessary consent procedures to enroll patients (point 9 in section 11.11).**

Under-recruitment of eligible patients is a well-known phenomenon in medical science.[50] Recruitment of patients is inherently extra challenging in acute settings such as with ACS and other life-threatening conditions.[51] The tension between patient protection and low thresholds for inclusion is widely known.[52] We feel that under-recruitment in our study was particularly high, due to:

(1) The nature of the acute setting, where patients often presented unscheduled and immediate diagnosis and treatment is critical. Patients needed to be included at this very time, since brief informed consent was obligatory and the PoC test had to be performed at this moment;
(2) The performance of additional tasks above normal patient management required for study inclusion, such as obtaining written informed consent, completion of the case report form and performance of the test; and
(3) The need for GPs to recall and perform study procedures within the limited time available during consultations with eligible patients.
(4) The possible life threatening problem of the patient, drawing the GP's full attention.

In attempt to overcome these difficulties, we proposed to the medical ethical board in the Netherlands to take oral consent at presentation only and full written consent at a more convenient time afterwards. This procedure was accepted by the Belgian medical ethical board evaluating the Belgian study protocol. In a similar study in the Netherlands, the proposal of only oral consent at presentation was also approved.[10] In the RAPIDA-study however, the board emphasised the necessity of *written* consent at presentation. The board agreed on a brief informed consent instead of full informed consult at presentation. Full informed consent could be obtained later, at a more convenient moment. While the requirement of written consent at presentation may have been an additional barrier to patient inclusion and contributed to low inclusion rates, the Belgian study still had low study inclusion rates despite only requiring oral consent, suggesting the time taken to consent patients may not have impeded study inclusion. Nevertheless, **researchers and medical ethical boards should keep the procedures as simple as possible in studies involving acute medicine, given the challenges of recruitment in the very short time window available (point 8 in section 11.11).** Studies in these hard to reach populations are of high importance and the balance between necessary legal procedures and broad inclusion should be optimised. Besides, the patient's decision quality is only moderately related to the quality of the informed consent.[53]

11.9.3 Evolving management of chest pain in primary and secondary care: clinical decision rules (CDRs)

Several CDRs have been introduced the past years, e.g. the GRACE-, EDACS-, ACSD-, MACS-, MHS-, HEART-, TIMI-, PURSUIT-score. Most of these scores were developed to assess a patient's risk and necessary treatment after a diagnosis of myocardial infarction (mostly in cases of NSTEMI; in cases of STEMI, fast CAG without further risk assessment is indicated) was established. Few scores were primarily developed for primary care to stratify the risk for ACS. A selection of clinical scores are discussed here and summarised in **table 11.1**.

The *Manchester Acute Coronary Syndromes (MACS) score* and *the HEART-score* have the potential to aid the physician at the emergency department to rule out ACS early in a

selection of patients. [45-47,54-56] The HEART-score was compared to the *TIMI-* and *GRACE-score* in this setting and performed significantly better.[46] See **table 11.1** for details on these scores that are suited for usage in the emergency department. However, validation in primary care has not taken place. Moreover, quantitative biomarker testing is needed in these scores.

Few CDR scores have been derived from primary care studies. *Bruins Slot* studied a simple CDR consisting of four parameters. [57,58] This score however was out-performed by the clinical judgment of GPs. [57] In the *TOPIC* and the *Marburg Heart Score (MHS)* studies, a decision aid was built to rule out CHD in primary care patients presenting with chest pain.[17,44,59] External validation of this rule revealed a sensitivity for CHD of 89.1% and a specificity of 63.5%. PPV was 23.3% and NPV 97.9%.[17] The sensitivity for CHD of clinical judgment aided by MHS compared to GP's unaided clinical judgment only had a non-significantly 8.0% higher sensitivity [95% C.I. -6.9 - 23.0] and a non-significantly 5.8% higher specificity [95% C.I.: -1.6 - 13.2].[44] The strength of the MHS is its derivation and validation in a primary care setting. The value for ACS patients must be determined in future studies, as the MHS was only validated for the outcome of CHD, including stable conditions of coronary artery disease. Chest pain patients with symptoms of up to one month were included and the studies were underpowered for detection of ACS: the incidence of ACS (AMI and UA) in the validation cohort was low (21 cases among 853 patients (2.5%)). Furthermore, a gold standard rule-out for non-referred patients was absent. Final diagnosis was set by a delayed-type reference standard diagnosis and expert panel. Thus, CHD was assumed absent in case of a negative follow up at six months. This strategy is the next best after using the gold standard test, when the gold standard rule-out is impractical.[60] However, missing mild cases of ACS after first presentation is possible. Therefore, **in studies on diagnostic tools in chest pain patients in primary care, venous blood sampling in non-referred patients to rule out ACS is recommendable (point 10 in section 11.11).** To assess the usability of the MHS-score in ruling out ACS, it must be validated in a primary care setting with a sufficient incidence of ACS, preferably with a confirmation of the absence of ACS in negative cases based on gold standard biomarker testing.

The *INTERCHEST* working group recently described another algorithm incorporating several signs and symptoms derived from a meta-analysis of primary care studies.[49] In their analysis, the working group also used CHD as an outcome value. The value in ruling out ACS has yet to be determined. However, these data also seem underpowered for evaluating ACS as a primary outcome.

Altogether, CDRs and early biomarker-based rule-out strategies have provided promising results. Nevertheless, evidence of the health and economic value in using these decision aids is essential before implementation in the clinical setting.[61]

Table 11.1: Overview of clinical decision rules (CDRs) used in assessing patients with chest pain.

CDR	Score Cut-off values	Validation and additional remarks
CDR Grijseels / Bruins Slot[57,58]	Male sex: 5 points Presence of radiation of chest pain: 8 points Presence of nausea / sweating: 5 points History of CHD:2 points	CDR compared to clinical judgment by GP: the area under the receiver operating characteristic (ROC) curve (AUC) was 0.75 [95% C.I. 0.68 - 0.82] for the GP's clinical judgment and 0.66 [95% C.I. 0.58 - 0.73] for the CDR.[57]
CDR derived from Topic study[59]	Age in men ≥ 55 or in women ≥ 65: 2 points (otherwise 0 points) ≥ 1 known cardiovascular risk factor**: 2 points Known previous history of CVD: 2 points Duration of chest pain 1 to 60 minutes: 1 point Area of pain described as substernal: 2 points Precipitating with exertion: 1 point Absence of tenderness: 1 ***Low risk: score < 5***	External validation: Sensitivity for CHD 85.6% and specificity 47.2%. NPV 94.8%. Derived and validated in primary care. Inclusion of chest pain patients with presence of chest pain of up to one month. Aimed mainly at CHD. Study underpowered for detection of ACS: low incidence of AMI and UA in validation cohort (10 cases among 774 patients, among these was 1 case of AMI with a score < 5 points, i.e. false negative). Absence of gold standard rule-out in non referred patients (definitive diagnosis assessed by delayed-type reference standard and expert panel, i.e. CHD assumed absent in case of a negative follow up at six months).
MHS[17,44]	**Age** in men ≥ 55 or in women ≥ 65: 1 point (otherwise 0 points) Known previous **history of CVD**: 1 point **Patient assumes cardiac** origin of pain: 1 point Pain worse with **exercise:** 1 point Pain **not reproducible by palpation**: 1 point ***Cut-off: low risk when score < 3***	External validation: Sensitivity for CHD 89.1% and specificity 63.5%. PPV 23.3%. NPV 97.9%.[17] Clinical judgment aided by MHS compared to GP's unaided clinical judgment only: sensitivity 8.0% higher [95% C.I. -6.9 - 23.0], specificity 5.8% higher [95% C.I. -1.6 - 13.2].[44] Derived and validated in primary care. Inclusion of chest pain patients with presence of chest pain of up to one month. Aimed mainly at CHD. Study underpowered for detection of ACS: low incidence of AMI and UA in validation cohort (21 cases among 853 patients (2.5%)). Absence of gold standard rule-out in non referred patients (definitive diagnosis assessed by delayed-type reference standard and expert panel, i.e. CHD assumed absent in case of a negative follow up at six months).

CDR	Score Cut-off values	Validation and additional remarks
INTERCHEST CDR[49]	**Age** in men ≥ 55 or in women ≥ 65: 1 point (otherwise 0 points) **Physician suspected a serious diagnosis**: 1 point) **History of CHD** (+1) Pain worse with **exercise**: 1 point Pain feels like **"pressure"**: 1 point Pain **reproducible by palpation**: -1 point ***Cut-off: low risk when score < 2***	NPV 97.9%, PPV 43.0%. Outcome value CHD, not ACS. Meta-analysis providing methods to cope with heterogeneous patient groups.
MACS[54-56]	Level of **hs-TnT** Level of **H-FABP** **Ischemic ECG** **Sweating** observed by clinician **Vomiting** in association with the presenting symptoms **Systolic blood pressure < 100** on arrival **Worsening** (or crescendo) angina Pain **radiating to right arm or shoulder** ***Computer model calculates score, based on absolute biomarker levels and dichotomous input for remaining 6 variables***	Based on emergency department patients. Quantitative biomarker testing needed. MACS: NPV = 99.2% - 100%. 10.7% -17.0% of emergency department patients presenting with chest pain are categorised as '(very) low risk' and as suitable for early discharge.[54,62] Troponin only MACS (the so called T-MACS, without H-FABP testing): NPV = 99.6%. 19.8% - 40.4% of emergency department patients presenting with chest pain are categorised as low risk and as suitable for early discharge.[62,63] High NPV for ACS in subgroup of patients identified as 'very low risk' by (T-)MACS. NPV for major adverse cardiac event (MACE) slightly lower.
HEART-score[45-47]	History (higly suspicious = 2, moderately = 1, slightly = 0) Electrocardiogram (ST deviations = 2, non specific or left bundle branch block = 1, none = 0) Age (≥65 = 2, 45-65 = 1, ≤45 = 0) Risk factors* (≥3 risk factors ór history of atherosclerotic disease = 2, 1 or 2 risk factors = 1, no risk factors = 0) initial Troponin (≥ 3x normal limit = 2, 1-3x normal limit = 1, ≤ normal limit = 0) ***Cut-off: 0-3 points = early discharge, 4-6 points = observation and risk management, 7-10 points is observation, treatment, CAG.***	Qualitative biomarker testing necessary. Validated in emergency department settings. External validation in 2906 emergency department patients: 28.2% patients had a HEART-score ≤ 3, of these, 1.7% eventually were diagnosed with MACE (false negatives).[45] C-statistic of HEART-score (0.81 [95% C.I. 0.76-0.86]) not significantly different from physician's clinical judgment (0.79 [95% C.I. 0.73-0.84]) .[64] HEART-score in emergency department is safe, health-economic effect is limited due to reluctance of physicians to early discharge low-risk patients as categorised by HEART-score.[47]

CDR	Score Cut-off values	Validation and additional remarks
TIMI- % GRACE-score	GRACE-score is based on 'Killip class' to qualify the degree of congestive heart failure, on systolic blood pressure, heart rate, age, creatinin level, cardiac arrest at admission, ST-segment deviation and on elevated levels of a cardiac biomarker. TIMI-score is based on age, several potential risk factors, coronary artery disease, ST deviation, severe chest pain symptoms, aspirin-use and elevated cardiac biomarkers.	Used to assess risk and treatment *after* assessing a diagnosis of ACS. Usage of GRACE- and TIMI-scores for risk stratification of chest pain patients before diagnosis was performed recently and compared to the HEART-score.[46] The HEART-score outperformed TIMI- and GRACE-score: the AUC of GRACE-, TIMI- and HEART-score differed significantly (0.73, 0.80 and 0.86, respectively). At a set requested sensitivity of minimally 98%, GRACE-score identified 231 patients as 'low risk', missing 2.2% cases of MACE. TIMI-score identified no 'low risk' patients. HEART-score identified 381 patients as 'low risk' missing 0.8% cases of MACE.[46]

* Risk factors in HEART-score are hypercholesterolemia, diabetes mellitus, hypertension, obesity (BMI > 30), cigarette smoking, positive family history

** Risk factors in MHS are family history of CVD, diabetes, (treated) hypertension,(treated) hyperlipidemia, smoking, obesity (BMI ≥ 30)

Abbreviations: ACS = acute coronary syndrome; AMI = acute myocardial infarction; AUC = area under the receiver operating characteristic (ROC) curve; BMI = body mass index; CAG = coronary artery angiography; CDR = clinical decision rule; CHD = coronary heart disease; CVD = cardiovascular disease; GP = general practitioner; H-FABP = heart-type fatty acid binding protein; hs-TnT = high-sensitive troponin T; MACE = major adverse cardiac event; MACS = Manchester Acute Coronary Syndromes score; MHS = Marburg Heart Score; NPV = negative predictive value; PPV = positive predictive value; T-MACS = Troponin-only Manchester Acute Coronary Syndromes score; UA = unstable angina

11.9.4 Evolving management of chest pain in secondary care: biomarkers, early rule-out strategies

In general, biomarkers for myocardial cell damage are regarded as positive when measurement exceeds the 99th percentile in a healthy reference population. High-sensitive cardiac-specific troponin T (hs-cTnT) is the cornerstone of diagnosing myocardial infarction.[65] For hs-cTnT, the clinical cut-off value is usually set at 14 ng/ml. With high-sensitive troponin assays, it is possible to measure troponin accurately, with a low coefficient of variance around the cut-off value. Thus, a result slightly higher, respectively slightly lower than the cut-off value can be regarded as highly accurate. A hs-cTnT result exceeding the 99th percentile is highly suspicious for myocardial infarction, however, the gold standard is to assess a rise or fall in troponin levels in serial measurements instead of a single absolute reading.[65,66] As a consequence of this, until recently, hs-cTnT testing in an emergency department took at least 3-6 hours to rule out myocardial infarction. As a stay in an emergency department of more than three hours is automatically followed by at least one full day of hospitalisation in declaration systems of health insurances, serial measurements therefore considerably increase the cost of a referral to an emergency department to rule out myocardial infarction.[67] Reducing the duration of a patient's time in the emergency department to less than three hours will therefore significantly reduce the cost of treatment.

Several rule-out strategies that have the potential to exclude myocardial infarction in less than three hours have been studied in recent years.[68] Several of these studies tested diagnostic algorithms that could rule out myocardial infarction in less than three hours, but serial troponin measurement was still a substantial part of the algorithm.[69,70] In one study, the interval between serial measurements was reduced to one hour with a NPV of 100% (95% CI 99-100%).[71] By lowering the cut-off value, false negative results decrease, however, false positive results increase slightly.[72] Balancing these effects is the major challenge in early rule-out strategies.

Several very early rule-out strategies have also been studied.[73-76] One strategy is the limit of detection (LOD) strategy, based on an undetectable high-sensitive cardiac troponin (hs-cTn) result. The second is a single cut-off strategy based on a single-measured hs-cTn level below a cut-off value significantly lower than the 99th percentile in a healthy reference population (e.g. a result that is below the 30th percentile in a healthy reference population is used in this strategy). The third strategy is the 1-hour algorithm, combining the single cut-off strategy with a marginal 1-hour change (for example, for troponin T < 3 ng/l). The fourth is the 0/1-hour algorithm, a combination of the LOD-strategy and the 1-hour algorithm as recommended by the *European Society of Cardiology* (ESC).[77] Direct comparison of these four rule-out strategies was performed.[78] The LOD-strategy was true negative in 16% of patients presenting with chest pain to an emergency department (sensitivity reached 100%), compared to 50% for the other

strategies (sensitivity 97.1-98.4). The total number of patients was 2,828 with a 16% incidence of myocardial infarction, which is lower than found in other emergency department populations. Thus, 1 hour exclusion or, in case of an undetectable hs-cTn, direct exclusion appears safe.[78] Except for the single cut-off strategy, all strategies performed well in the challenging subgroup of patients presenting early after onset of complaints.[78] Both strategies where a change was part of the algorithm (the 1-hour and 0/1-hour strategy) showed a high value in including myocardial infarction as well. A multicenter trial (N = 2,222 chest pain patients, 9.7% incidence of myocardial infarction), testing the 0/1-hour rule-out strategy at an emergency department showed 30.6% of patients could be classified as low risk, with 0.5% false negatives.[79] A pooled analysis (N = 9,241 patients, 15.4% incidence of myocardial infarction) testing a combination of negative ECG-findings and a LOD-strategy for hs-cTnT, showed that 64.1% of patients could be classified as low risk, with 2.9% false negatives.[80] These findings lead to the question of what percentage of false negative results is acceptable. Recently, incorporation of blood glucose testing alongside cardiac biomarkers has been reported to be cost-effective in comparison to the ESC-strategy.[81]

To summarise, improvements in the performance of very early rule-out strategies could lead to implementation in the near future. This would lead to a reduction in the time needed to exclude myocardial infarction in an emergency department, making such rule-out strategies more economical. The efficiency of this fast rule-out in terms of reducing the number of patients for further analysis is yet to be determined, although in the study population the test was true-negative in approximately half of the presenting patients, except for the LOD-strategy which had considerably fewer true-negative patients. Whether PoC-devices, with a yes/no indication (qualitative test) or, alternatively, equipped with a reader to obtain a quantitative result, could reach the same level of efficiency in primary care, eliminating unnecessary referrals, is yet to be determined. Of note, PoCTs for troponin that are sensitive enough to measure LODs or low single cut-offs are not yet available.

11.10 Valorisation: how is this thesis related to a chest pain patient in primary care in 2027 A.D.?

Imagine 2027 A.D...
A 50 year old GP in the South of the Netherlands, more specifically in an old Roman city close to the Belgian border, assesses a female patient with chest pain. The patient came walking from her house, 5 minutes from the GP practice. Most probably, there is a mild underlying condition, but the GP cannot rule out ACS. This doctor has been working in general practice for 16 years now and during these years, he has assessed 650 chest pain patients. He has referred 39 patients that eventually had ACS and 52 patients that

eventually only had stomach, chest wall or stress related problems. He has failed to diagnose two cases of ACS, unfortunately in one of these two cases, the patient died after initially not having been referred. At assessment, this patient had hypoglycemia and he recovered after application of glucose.

Late in his fourth decade the GP completed a thesis on this topic. Still, the thesis is now and then seen on book shelves in academic institutions throughout the country. Nowadays, he feels more comfortable with these patients, as in the past few years, assessment of patients suspected of ACS in primary care has become easier. He tells the patient: "not too long ago, I had to refer you for assessment at the hospital during at least half a day, but these days, I can..."

Right there the imagination stops. The crucial point as to what the GP can do in ten years from now, is yet to be answered. But there will be *evolutio*n in the assessment of chest pain, perhaps even *revolution* at some point. In this section, a light is shed on the (r)evolution and the scientific conditions under which such change could be realised. In other words: where do primary and secondary care meet around the chest pain patient in the future? Notably, the search for advanced diagnostic means in primary care should be seen in the light of today's accurate rule-out capacity of the GP's clinical judgment. Given a NPV for ACS of the GP's clinical judgment of 99.6% as we found in chapter 4 and an odds ratio of the GP's judgment for correctly categorising a patient as having or not having a life threatening disease of 48 (table 4.3), improving this highly accurate clinical judgment as achieved by GPs is not a matter of course.

Subsections 11.9.3 and 11.9.4 outline the development of CDRs combining signs, symptoms and PoCTs (11.9.3), and the development of high-sensitive biomarker regimes available in highly equipped laboratories as seen in hospital settings (11.9.4). The optimal CDR or biomarker regime has yet to be determined and its economic value has to be assessed after validation. However, classical clinical assessment combined with two point biomarker tests with high interval times of up to 6 hours will be replaced by accurate and fast rule-out regimes in the near future of secondary care assessment. From a primary care perspective, one of two possible scenarios molded by the introduction of 'the ideal rule-out schedule' could become daily practice.

The first possible effect of a fast rule-out schedule in secondary care, with a strong negative predictive value for ACS within one hour after presentation, is a fast and less expensive assessment after referral to secondary care. Ambulance transport will still be necessary, however cost reductions will be realised by shorter assessment at the emergency room. For example, assessment could start in the ambulance by taking the initial blood samples.[82] Assessment could even take place outside the hospital, with experienced specialists working in outpatient clinics with lower overhead costs.[83] This type of highly efficient specialist care, positioned 'in between' primary and secondary care, is becoming more common in non-acute settings and could in the near future evolve in

acute medicine as well. An ideal environment to monitor a patient with suspected ACS, and fast access to specialist care when needed, would be close to, even perhaps within the walls of, but technically not inside the hospital. For example, primary care OOH services are often located close to, or even inside, the hospital and could provide this type of care. Thus, **the potential role of specialist care outside the hospital with lower overhead costs, using fast rule-in and rule-out tests for ACS, could be a subject of future studies (point 14 in section 11.11).** If rule-out strategies become faster and specialist care is becoming less expensive due to shorter assessment times and lower overhead costs, new workup models do not necessarily have to be established in primary care to be cost-efficient. In the Netherlands, GPs with a post academic education for both emergency medicine and cardiovascular disease are available and could possibly have a role as well as cardiologists, in the same way they are presently working outside the hospital in non-acute matters.[83]

The second possible consequence of a very fast rule-out regime (a CDR, incorporating a high sensitive biomarker-based PoCT) could be its availability in primary care directly. It seems unlikely for a CDR without incorporation of a PoCT, to gain sufficient NPV. Perhaps, even a combination of two or more different biomarkers should be tested at once to reach a high NPV, e.g. the combination of H-FABP and cTnI. Earlier work has shown that these markers identify distinct patients, so possibly their combined evaluation shows increased performance in a rule-out strategy.[84] Note that the analytical challenge to rapidly and accurately measure both H-FABP (in ng/mL) and cTnI (in pg/mL, i.e. a 1,000-fold lower concentration) has recently been overcome in a pilot study (details not yet available). Therefore, a **highly accurate CDR incorporating a single-measurement, high-sensitive PoCT device would be an effective solution to the high number of ACS-negative referrals and the incidentally occurring ACS-positive non-referrals. A combination of two or more markers in one device may be even more effective (point 6 in section 11.11).**

Biomarker tests are becoming more and more accurate. Yet, these tests thrive on high-sensitive quantitative measurements, with a low variance around the cut-off value. Performance of similar qualitative tests in an easily accessible PoCT format seems to lag behind the accurate (combinations of) biomarker tests available in laboratories, which measure the whole blood biomarker values which modern fast rule-out regimes are based on.[85] **Translating early rule-out strategies based on highly specialist laboratory measurements into easy to use PoCTs and maintaining accuracy of the laboratory tests, is challenging (point 4 in section 11.11).** Perhaps extremely low cut-off values for such easy to use PoCTs or utilisation of a combination of biomarkers in one test could gain sufficient NPV. However, in our RAPIDA-study, the cut-off value was lower than the 99th percentile and the test still failed in ruling out ACS. One of the D-Dimer PoCTs investigated in ruling out pulmonary embolism in primary care is based on a cut-off value of 80 ng/ml, which is less than 20% of the cut-off values usually used in whole blood meas-

urements of D-Dimer concentrations.[86] Theoretically, such a low cut-off value seems impractical. Such a test would rarely be negative, when looking at the usual results of 100-400 ng/ml that are obtained in whole blood measurements, where a cut-off value of around 500 ng/ml is utilised. Still, the test proved to be considerably effective in ruling out pulmonary embolism when combined with the Well's score. From this example, one could learn that **cut-off values cannot be directly translated from whole blood quantitative measurements to qualitative point of care devices (point 2 in section 11.11).**

Altogether, it is yet unclear whether a GP in 2027 tells his patient that referral has to take place for fast rule-out of ACS in a hospital or another specialist setting, or the GP rules out the ACS in his own practice. Nevertheless, rule-out will become much faster and more accurate, thereby increasing patient and doctor comfort.

11.11 Fourteen points of attention for future research

The next traveler exploring the field of chest pain in primary care could consider the following 14 points of attention:

Development of biomarker based PoC tests:

1. Seamless evolution of biomarker tests from 'bench' to 'bedside' should be covered in unambiguous study pathways incorporating both the experimental and the implementational phase of development. Before developing and implementing a new biomarker test, defining its clinical need should be a 'conditio sine qua non'.
2. Cut-off values cannot be directly translated from whole blood quantitative measurements to qualitative point of care devices.
3. The optimal cut-off value of H-FABP for AMI -and therefore for ACS in a clinical setting in primary care - was set at 4 ng/ml: a cut-off even lower than the 99th percentile in a normal reference population. This strategy seems recommendable when aiming at safe rule-out of ACS in primary care.
4. Translating early rule-out strategies based on highly specialist laboratory measurements into easy to use PoCTs and maintaining accuracy of the laboratory tests, is challenging.

Rationale of a CDR:

5. In the Netherlands, 50,000 patients annually are referred to secondary care facilities to rule out ACS that eventually is excluded. Ruling out ACS in these patients at the GP's office, thereby preventing an ambulance transport and examinations in secondary care, is valuable to both the patient and the health system at large.
6. A highly accurate CDR incorporating a single-measurement, high-sensitive biomarker based PoCT-device would be an effective solution to the high number of

ACS-negative referrals and the incidentally occurring ACS-positive non-referrals. A combination of two or more biomarkers in one device may be of added value.

7. With an estimated cost price of a PoCT of €45, a reduction of ACS negative referrals from 10.8% to 7.7% of all chest pain patients would make the test cost-neutral.

Study methods in PoC test research in primary care:

8. Researchers and medical ethical boards should keep the procedures as simple as possible in studies involving acute medicine, where the very short time window to include patients as well as the acute setting is challenging.
9. Patient inclusion improves when nurses take over study activities from the GP and are free to perform the necessary consent procedures to enroll patients (without interfering too much with the handling of the GP).
10. In studies on diagnostic tools in chest pain patients in primary care, venous blood sampling in non-referred patients - rather than a negative clinical follow-up period - to definitively rule out ACS is recommended.
11. To find diagnostic tools in acute chest pain suspected of ACS, patient selection should focus on including these patients and this should be reflected in an incidence of ACS in the study population of at least 10%.
12. Predicting factors possibly contributing to a CDR to rule in and out ACS should be derived by multivariate analysis with ACS – not a heterogeneous mixture of CHD patients – as a main outcome measure.

Future implementation:

13. A new PoC test to rule in and out ACS should be accompanied by clear instructions on when (e.g. for what indication) and how (e.g. as part of a clinical decision rule (CDR)) to use it. Furthermore, it should be clear what action should follow a certain test result.

14 The potential role of specialist care outside the hospital with lower overhead costs, using fast rule-in and rule-out tests for ACS when available, could be a subject of future studies.

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summary



Summary

For an extended summary, in relation to international literature, referral is made to chapter 11, section 11.2 - section 11.8.

In chapter 1, the general introduction of this thesis, the diagnostic dilemmas in assessing chest pain in primary care are outlined. The difficulty in distinguishing patients with acute coronary syndrome (ACS) from chest pain patients with a mild underlying problem is described. In an important part of these patients referral is needed to finally exclude ACS, leading to patient discomfort and high costs. The main themes addressed in this thesis are formulated. These are: the expression of diagnostic dilemmas in daily practice, the quantitative and qualitative aspects of chest pain in primary care, the possible cost reduction after the introduction of future diagnostic tools, the optimal cut-off value for a point-of-care (PoC) Heart-type fatty acid binding protein (H-FABP) test in patients presenting with chest pain, the performance of a PoC H-FABP test in chest pain patients in primary care and the derivation of signs and symptoms that are of added value in assessing these patients.

In chapter 2 and 3, we illustrate the diagnostic dilemmas in daily practice. In several case descriptions, the risk of missing cases of severe underlying disease, the need for biomarker testing to definitely rule out ACS, and the dilemmas following a marginally elevated troponin result are elaborated. In chapter 4, the results of an observational study of chest pain patients in primary care are discussed. For this study, we asked 118 general practitioners (GPs) in the Netherlands and Belgium to record all patient contacts during two weeks. Furthermore, patients presenting with chest pain were registered extensively and a follow-up form was filled in after 30 days. Finally, 22,294 patient contacts were registered. 281 patient contacts (1.26%) were about chest pain. In this cohort of 281 patients presenting with chest pain, in 38.1% of patients ACS was suspected at least temporarily during consultation, 40.2% of patients were referred to secondary care, and 512 diagnostic tests were performed by GPs and consulted specialists. Musculoskeletal pain was the most frequent working (26.1%) and final diagnosis (33.1%). Potentially life-threatening diseases as final diagnosis (such as myocardial infarction) accounted for 8.4% of all chest pain cases. This seems reflected in the magnitude and wide variety of diagnostic tests performed in these patients by GPs and specialists, in the (safe) overestimation of life-threatening diseases by GPs at initial assessment and in the high referral rate we found. Retrospectively looking at the differences between the working diagnose of the GP at initial assessment and the final diagnose after at least 30 days, we found a major difference between working and final diagnosis in 23.1% of chest pain cases. In only 0.7%, a severe disease was initially missed by the GP. Therefore, chapter 4 emphasises the magnitude ánd relevance of chest pain presentation in primary care.

In chapter 5, by conducting a semi-structured, face to face interview based study, we found that the 27 participating Belgian and Dutch GPs agreed about their experience

that the number of patients having an ACS among chest pain patients is decreasing, whereas the presentation of atypical complaints increases, together leading to more uncertainty. The overall incidence of chest pain in primary care is not decreasing according to the GPs. GPs stated to rely on their own judgment above all, and are willing to work with new diagnostic tools only when these tools are of proven added value. GPs do not seem afraid or reluctant to refer a considerable number of chest pain patients without ACS, as over-referral is safe and uncertainty is regarded as a substantial element of their profession.

In chapter 6, we estimated the possible cost effects of a future clinical decision rule (CDR) incorporating a point-of-care test (PoCT) as compared to current practice. We estimated the annual incidence of chest pain, referrals and ACS in primary care, based on a literature review ('international data') and on the data obtained in chapter 4 ('NL and B data') separately. We developed a health economic model to calculate the potential impact of a future CDR on costs and effects in several scenarios with varying correct referral decisions. We performed one-way, two-way, and probabilistic sensitivity analyses to test robustness of the model outcome to changes in input parameters. Currently, referral of eventual ACS negative patients (false positives, FPs) is estimated to cost €1,448 per FP patient, with total annual cost exceeding 165 million Euros in the Netherlands. Based on 'international data', at least a 29% reduction in FPs is required for the addition of a PoCT as part of a CDR to become cost-saving, and an additional €16 per chest pain patient (i.e. 16.4 million Euros annually in the Netherlands) is saved for every further 10% relative decrease in FPs. Sensitivity analyses revealed that the model outcome was robust to changes in model inputs. Costs outcomes were mainly driven by costs of FPs and costs of PoCT. We concluded that - *if* triage aided by a CDR incorporating a PoCT could improve exclusion of ACS - this CDR could lead to a considerable reduction in annual healthcare costs as compared to current practice.

In chapter 7, we describe in detail the current literature on biomarker testing in suspected ACS. Heart-type fatty acid-binding protein (H-FABP) is thought to be among the earliest available plasma markers for myocardial injury. We evaluate the clinical utility of H-FABP for suspected ACS. Reviewing current literature, H-FABP shows added value in addition to cardiac troponin, especially in the early hours after onset of symptoms. However, contemporary high-sensitive troponin assays are becoming more accurate in the first hours after onset of complaints as well. H-FABP identifies patients at increased risk for future cardiac events. We conclude that measuring H-FABP along with troponin shortly after onset of symptoms improves risk stratification of patients suspected of having ACS.

In chapter 8 we determined the optimal cut-off value for a PoC H-FABP test in patients presenting to the emergency department and we evaluated a possible future role of H-FABP in safely ruling out ACS in primary care. Serial plasma H-FABP-values (index test)

and high sensitivity troponin T (hs-cTnT) values (reference test) were determined in patients with any new-onset chest complaint. For 202 consecutive patients (prevalence ACS 59%), the receiver operating characteristic (ROC) curve based on the results of the first H-FABP was equal to the ROC curve of hs-cTnT (area under the curve (AUC) 0.79 versus 0.80).The optimal cut-off value of H-FABP for ACS was 4.0 ng/ml. Furthermore, we found that the sensitivity for ACS of the H-FABP (hs-cTnT) tests was 73.9% (70.6%). Negative predictive value (NPV) of H-FABP for ACS in primary care thus could reach 90.8%. Therefore, we concluded that PoC H-FABP measurement and a score of signs and symptoms should be studied in primary care, to learn if such an algorithm could safely reduce referral rate by GPs.

In chapter 9 and 10, we present the methodology and results of our main study. Participating GPs provided regular care when assessing patients presenting with new onset chest pain suspected of ACS. Besides, they registered signs and symptoms in all patients presenting chest complaints possibly due to ACS. Point of care H-FABP testing was performed. We derived signs and symptoms that have diagnostic value in a CDR using logistic regression analysis and we assessed the diagnostic value of PoC H-FABP testing, alone and combined with a CDR, in order to predict or exclude ACS and acute myocardial infarction (AMI) in primary care. The final diagnosis was assessed by an expert panel, at least 30 days after initial presentation. 303 patients were included in the study and ACS was found in 32 (10.6%) patients, whereas 75.2% of all patients suffered from non-cardiac disease. For ACS, sensitivity and negative predictive value (NPV) of the PoC H-FABP test was 25.8%, 91.6% respectively for all patients, and 36.8%, 92.7% respectively for patients with a duration of complaints > 3 hours. For AMI, sensitivity and negative predictive value (NPV) of the PoC H-FABP test was 26.9%, 93.1% respectively for all patients, and 40.0%, 94.5% respectively for patients with a duration of complaints > 3 hours. Area under the receiver operating curve of a CDR combining presence of ST-depressions, ST-elevations, dyspnea, a feeling of pressure on the chest, absence of left sided lateral chest pain and PoC H-FABP test result was 0.78 for ACS. As compared to a GP's unaided judgment, the false negativity count for ACS was lower, whereas the false positivity count was higher when using the CDR. Altogether, the sensitivity of the current H-FABP PoC test as a stand-alone test is poor. The efficiency of using a CDR derived from these results is doubtful: the CDR could be of use in reducing the number of ACS cases missed by the GP, however as a consequence, more ACS negative patients would be referred. Additional studies should focus on large primary care populations presenting with chest pain to validate future PoC tests and to derive signs and symptoms predicting ACS.

In chapter 11, we discuss all findings in the light of available literature. We describe the development of CDRs and potent biomarker-based rule-out regimes in secondary care facilities. Probably, these developments make assessment in secondary care faster and less expensive in the future. The question is whether these technologic innovations

become available for the GP to safely rule out ACS. Moreover, it is questionable if availability in primary care is the highest good, when very safe rule-out regimes make assessment in secondary care faster and less expensive. Furthermore, several aspects of performing acute medicine studies in primary care in general, and studies specifically focusing on biomarkers and CDRs are outlined. An effort should be made to keep such studies free from unnecessary paperwork and to guarantee seamless evolution of biomarker tests from 'bench' to 'bedside'.

samen-vatting



Samenvatting

Voor een uitgebreide samenvatting van dit proefschrift in het licht van de internationale literatuur: zie ***hoofdstuk 11, paragraaf 11.2 - 11.8***.

In **hoofdstuk 1**, de algemene introductie van dit proefschrift, zetten we de diagnostische dilemma's bij het beoordelen door de huisarts van patiënten die zich presenteren met pijn op de borst uiteen. We beschrijven hoe lastig het is om patiënten met een acuut coronair syndroom (ACS) te onderscheiden van patiënten met pijn op de borst zonder ernstige oorzaak. In een belangrijk deel van deze patiënten is verwijzing noodzakelijk om uiteindelijk ACS uit te sluiten. Dit is veelal onprettig voor de patiënt en leidt tot hoge kosten. In **hoofdstuk 1** formuleren we vervolgens de hoofdonderwerpen van dit proefschrift. Deze zijn: de diagnostische dilemmas die de huisarts ervaart bij patiënten met pijn op de borst, kwantitatieve en de kwalitatieve aspecten van de aan de huisarts gepresenteerde klacht pijn op de borst, de potentiële kostenreductie na de introductie van toekomstige diagnostische hulpmiddelen, de optimale afkapwaarde voor een point of care (PoC) sneltest gebaseerd op Heart-type fatty acid binding protein (H-FABP) bij patiënten met pijn op de borst, de diagnostische prestaties van een PoC H-FABP test bij pijn op de borst patiënten bij de huisarts en het definiëren van symptomen en bevindingen die bij de huisarts van waarde zijn voor het voorspellen van ACS .

In **hoofdstuk 2 en 3** illustreren we de diagnostische dilemma's rond pijn op de borst klachten in de dagelijkse praktijk van de huisarts en cardioloog aan de hand van een aantal casus-beschrijvingen. We gaan in op het risico van het missen van een ernstige ziekte, op de noodzaak om biomarkers (meestal troponine) te testen om een ernstige ziekte uit te sluiten en we gaan in op de dilemma's bij een marginaal verhoogd troponine. In **hoofdstuk 4** bespreken we de resultaten van een observationele studie naar patiënten die zich bij de huisarts presenteren met pijn op de borst. Voor deze studie hebben we 118 huisartsen in Nederland en België gevraagd om gedurende twee weken álle patiëntencontacten te registreren. Patiënten met pijn op de borst werden daarbij in detail geregistreerd én gevolgd tot minimaal 30 dagen na het consult. Aldus registreerden de huisartsen samen 22,294 patiëntcontacten. Tijdens 281 patiëntcontacten (1,26%) ging het om pijn op de borst. In dit cohort van 281 patiënten, dacht de huisarts in 38,1% van de patiënten op zijn minst tijdelijk aan ACS. 40,2% van de patiënten werd naar de tweedelijn verwezen en huisartsen en specialisten voerden in deze groep van 281 patiënten 512 diagnostische tests uit. Musculoskeletale pijn was de meest voorkomende werkdiagnose (26,1%) en einddiagnose (33,1%). Potentieel levensbedreigende aandoeningen als einddiagnose (zoals myocardinfarct) werden gevonden bij 8.4% van alle patiënten met pijn op de borst. Dit lijkt ook tot uiting te komen in (a) de grote hoeveelheid van - en diversiteit aan – diagnostische tests die bij deze patiënten door huisartsen en specialisten werd uitgevoerd, in (b) de (veilige) overschatting van levensbedreigende problemen door de huisarts bij de initiële beoordeling en in (c) het hoge verwijspercentage dat we vonden in deze studie. Achteraf kijkend naar de verschillen tussen de werkdiagnose door de huisarts bij de aanvankelijke beoordeling en de einddi-

agnose na minimaal 30 dagen, kunnen we vaststellen dat de werk- en einddiagnose in 23,1% van de gevallen van pijn op de borst in belangrijke mate verschilden. In slechts 0,7% van de gevallen (twee gevallen) miste de huisarts een ernstige ziekte. In **hoofdstuk 4** illustreren we aldus de omvang én relevantie van het aan de huisarts gepresenteerde probleem pijn op de bors .

In **hoofdstuk 5** constateren we na het doen van semi-gestructureerde interviews dat de 27 participerende Belgische en Nederlandse huisartsen het eens zijn over het feit dat de incidentie van pijn op de borst als reden voor consultatie van de huisarts niet afneemt. Wel geven zij aan dat ACS onder patiënten met pijn op de borst minder dan voorheen lijkt voor te komen. Omdat tegelijkertijd het percentage patiënten met 'atypische klachten' toe lijkt te nemen, neemt de diagnostische onzekerheid onder huisartsen toe. De huisartsen verklaarden vooral op hun eigen klinisch oordeel te varen. Nieuwe diagnostische middelen achten zij alleen nuttig, wanneer de diagnostische meerwaarde ervan is bewezen. Huisartsen lijken niet bang of terughoudend te zijn om een aanzienlijk aantal patiënten met pijn op de borst dat uiteindelijk geen ACS heeft, te verwijzen. Zij stellen dat over-verwijzing veilig is en dat diagnostische onzekerheid een belangrijk onderdeel van het huisartsenvak is.

In **hoofdstuk 6,** schatten we het effect van een toekomstige klinische beslisregel (KBR) - waarvan een PoC sneltest deel uitmaakt - op zorgkosten. We vergelijken daartoe een dergelijke KBR met de huidige, reguliere zorg. Gebaseerd op een literatuurstudie ('internationale data') én op de in **hoofdstuk 4** beschreven onderzoeksresultaten ('NL and B data'), hebben we de jaarlijkse incidentie van pijn op de borst als gepresenteerde klacht bij de huisarts, van verwijzingen van deze patiënten naar de tweedelijn en van de diagnose ACS in de huisartsenpraktijk geschat. We ontwikkelden een gezondheidseconomisch model om de potentiële effecten van een KBR op zorgkosten te berekenen. Daarbij hanteerden we diverse scenario's, waarin we de percentages correcte verwijsbeslissingen lieten variëren. Om het model te testen op haar robuustheid voerden we éénweg-, tweeweg- en probabilistische sensitiviteitsanalyses uit. Momenteel schatten we de gegenereerde kosten van uiteindelijk ACS negatieve patiënten met pijn op de borst (de zogenaamde 'valspositieven' of VP's) op € 1,448 per VP-diagnose, met aldus een totale jaarlijkse kostenlast van meer dan € 165 miljoen in Nederland. Wanneer we ons op de 'internationale data' baseren is er een minimale reductie van 29% aan VP-diagnoses noodzakelijk, om een KBR inclusief PoC sneltest kosteneffectief te laten zijn. Een additionele €16 per patiënt met pijn op de borst (d.w.z. € 16,4 miljoen jaarlijks in Nederland) wordt bespaard met elke verdere 10% daling aan VP-diagnoses. Sensitiviteitsanalyses toonden tevens aan dat het model robuust blijft na variaties van de ingevoerde parameters. De uiteindelijke geschatte kosten worden met name beïnvloed door de kosten van iedere VP-diagnose en door de kosten van de PoC sneltest. We concluderen dat – *mits* triage met behulp van een KBR met daarin een PoC sneltest leidt

tot het beter uitsluiten van ACS – deze KBR de jaarlijkse zorgkosten aangaande patiënten met pijn op de borst aanzienlijk reduceert ten opzichte van de huidige zorg.

In hoofdstuk 7 gaan we aan de hand van de literatuur in detail in op de diagnostische waarde van biomarkertests voor ACS. H-FABP staat bekend als één van de vroegst detecteerbare plasmamarkers bij myocardschade. We evalueren in hoofdstuk 7 de klinische bruikbaarheid van H-FABP bij een verdenking op ACS. Met name in de eerste uren na aanvang van klachten zoals pijn op de borst lijkt H-FABP van waarde voor de diagnostiek te zijn. Anderzijds komt naar voren dat hedendaagse hoog-sensitieve troponine-bepalingen tevens onderscheidend vermogen hebben in de eerste uren na aanvang van de klachten. H-FABP identificeert eveneens patiënten met een verhoogd risico op toekomstige cardiale aandoeningen (prognostische waarde). We concluderen dat het meten van H-FABP plus een troponine-bepaling kort na aanvang van acute klachten, de risicostratificatie van patiënten die verdacht worden van ACS verbetert.

In hoofdstuk 8 beschrijven we de resultaten van onze studie naar de optimale afkapwaarde van een PoC H-FABP sneltest voor myocardinfarct, bij patiënten die zich op een spoedeisende-hulpafdeling van het ziekenhuis presenteren met pijn op de borst. We evalueerden in deze studie daarmee tevens de mogelijke rol van H-FABP bij het veilig uitsluiten van een acuut myocardinfarct (AMI) of ACS in de eerstelijn. Seriële plasma H-FABP-waardes (de index test) en hoog-sensitief troponine T (hs-cTnT) waardes (de referentie test) werden bepaald bij patiënten die zich met nieuw ontstane klachten op de borst presenteerden op de spoedeisende-hulpafdeling van het ziekenhuis. Voor 202 opeenvolgende patiënten (prevalentie ACS = 59%), was de receiver operating characteristic (ROC) curve gebaseerd op resultaten van de eerste H-FABP-meting gelijk aan de ROC curve van hs-cTnT (de oppervlaktes onder de curve waren 0,79, respectievelijk 0,80). De optimale afkapwaarde van H-FABP voor ACS was 4,0 ng/ml. Voorts vonden we dat de sensitiviteit van de H-FABP (hs-cTnT) tests voor ACS 73.9% (70.6%) was. De negatief voorspellende waarde van H-FABP voor ACS in een eerstelijnspopulatie zou aldus tot 90,8% kunnen reiken. Daarom concluderen we dat PoC H-FABP meting gecombineerd met nader te bepalen specifieke symptomen en bevindingen onderzocht moet worden in de eerstelijn, om te evalueren of een dergelijk diagnostisch algoritme het aantal verwijzingen door de huisarts naar de tweedelijn veilig kan reduceren.

In hoofdstuk 9 and 10 presenteren we de methodologie en resultaten van onze hoofdstudie. Deelnemende huisartsen boden reguliere zorg aan patiënten die zich presenteerden met pijn op de borst, verdacht voor de aanwezigheid van ACS. Daarnaast registreerden de huisartsen alle relevante symptomen en bevindingen bij deze patiënten en voerden ze de PoC H-FABP test uit. Middels multivariate analyses extraheerden we symptomen en bevindingen, gecombineerd in een KBR, die een diagnostische waarde voor het aantonen en uitsluiten van AMI en ACS bij de huisarts hadden en we beoordeelden de diagnostische waarde van de PoC H-FABP test alleen en als onderdeel van

die KBR . De einddiagnose werd vastgesteld door een expert panel, minimaal 30 dagen na de initiële presentatie. We includeerden aldus 303 patiënten in deze studie. ACS werd vastgesteld bij 32 (10.6%) patiënten, terwijl 75.2% van de patiënten geen cardiale aandoening had. De sensitiviteit en negatief voorspellende waarde van de PoC H-FABP test waren 25.8%, respectievelijk 91.6% voor ACS, ongeacht de duur van de klachten (0-24 uur), en 36.8%, respectievelijk 92.7% voor patiënten waarbij de klachten 3-24 uur aanwezig waren. Voor AMI waren de sensitiviteit en de negatief voorspellende waarde van de PoC H-FABP test 26.9%, respectievelijk 93.1% voor alle patiënten en 40.0%, respectievelijk 94.5% voor patiënten met een klachtenduur van 3-24 uur. De sensitiviteit van de huidige PoC H-FABP test als een op zich zelf staande test was dus laag. De oppervlakte onder de ROC curve voor een KBR gebaseerd op aanwezigheid op het ECG van ST-depressies en/of ST-elevaties, alsmede op aanwezigheid van dyspnoe en/of een gevoel van druk op de borst, op afwezigheid van links laterale pijn op de borst en op het resultaat van de PoC H-FABP test was 0.78 voor ACS. Vergeleken met het klinisch oordeel van de huisarts zónder KBR was het aantal gemiste ACS-diagnoses met de KBR kleiner, maar het aantal vals positieven nam juist toe met de KBR. We concluderen dat de efficiëntie van het gebruik van een KBR gebaseerd op onze resultaten twijfelachtig is: de KBR kan nuttig zijn bij het verminderen van door de huisarts gemiste gevallen van ACS, maar tevens tot verwijzing van meer ACS negatieve patiënten. Nieuwe studies moeten zich richten op grote eerstelijnspopulaties bestaande uit patiënten die zich presenteren met pijn op de borst of anderszins verdacht worden van een ACS, om toekomstige PoC tests te valideren en om symptomen en bevindingen te extraheren die mede de aan- of afwezigheid van een ACS kunnen voorspellen.

In hoofdstuk 11 bediscussiëren we alle bevindingen in het licht van de internationale literatuur. We beschrijven ontwikkelingen rondom KBR's en rondom krachtige, op biomarker gebaseerde regimes om ACS uit te sluiten, zoals die in de tweedelijn gebruikt (gaan) worden. De beschreven ontwikkelingen maken de beoordeling van patiënten met pijn op de borst in de tweedelijn naar alle waarschijnlijkheid binnen afzienbare tijd sneller en goedkoper. De vraag is wél of dergelijke technologische innovaties ook beschikbaar komen voor de huisarts om veilig een ACS uit te sluiten. Bovendien kunnen we ons afvragen of bedoelde beschikbaarheid in de eerstelijn het 'hoogste goed' is, als veilige diagnostische regimes in de tweedelijn het uitsluiten van ACS snel en goedkoop maken. Verder bespreken we in hoofdstuk 11 een aantal aspecten rond het uitvoeren van studies met als algemeen thema 'acute geneeskunde' bij de huisarts en van studies die gaan over KBR's en biomarkers in het bijzonder. We concluderen dat eenieder zich zou moeten inzetten om dergelijke studies zo veel mogelijk te vrijwaren van onnodig papierwerk én om een naadloze evolutie van 'experiment' naar 'patiënt' te garanderen.

dank-woord



Dankwoord

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curricu-
lum
vitae



Curriculum vitae



Robert Willemsen werd op 25 juni 1977 geboren in Tegelen en groeide op in Reuver. Hij doorliep het gymnasium op het Bisschoppelijk College Broekhin in Roermond en slaagde in 1995 'cum laude', om vervolgens in Maastricht geneeskunde te gaan studeren. In 2001 studeerde hij 'met genoegen' af om vervolgens een aantal jaren in Heerlen en Sittard te werken, afwisselend in de interne geneeskunde, longziekten en cardiologie. In 2008 maakte hij de overstap naar de huisartsgeneeskunde. In 2011 studeerde hij af als huisarts om na een waarneemperiode terecht te komen in huisartsenpraktijk Nazareth te Maastricht. Eveneens in 2011 studeerde hij af als kaderhuisarts hart- en vaatziekten en kreeg hij de registratie voor het voeren van de titel kaderhuisarts astma en COPD. Aldus blijven cardiologie en longziekten aandachtsgebieden in het onderzoek, het onderwijs en de regionale commissies waarbij hij betrokken is. Robert Willemsen is 40 jaar en woont in Maastricht met zijn echtgenote Jonne van der Zwet en zijn drie kinderen: Timo (9), Bente (7) en Niels (3).

list of publications, contributions



List of publications, contributions

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2016 Willemsen RTA, Dinant GJ, Glatz JFC. Biomarkers of Myocardial Cell Damage: Heart-Type Fatty Acid Binding Protein (H-FABP) for the Early Evaluation of Suspected Acute Coronary Syndrome. Chapter 43 in book: 'Biomarkers in Cardiovascular Disease'. Editors: V.B. Patel, V.R. Preedy. Springer Science and Business Media, Dordrecht 2016. Print + e-book, ISBN 978-94-007-7679-1.

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Boekset. Uitgeverij Bohn Stafleu van Loghum, Houten 2017. ISBN13: 9789036817288

Supervising

Supervision of WESP-internships (four-month internship in research, including writing a research paper) of:

- Beatrijs Hoorweg & Lotte Cleef (projects: 'Chest pain in primary care: frequency, causes and trends in incidence' & 'The management of chest pain patients in general practice')
- Sterre Willems (project 'Chest pain in the ambulance')

Co-supervision of WESP-internships of:

- Sofie Compiet (project 'Competence of general practitioners in requesting and interpreting ECGs. A case vignette study')

- Joep Walraven (project 'Electrocardiography in general practice out-of-hours services: a retrospective cross-sectional study', master thesis for 'AKO' programme, education programme for physician-reseacher)
- Leonore Waagenvoort (project 'Electrocardiography in symptomatic patients in general practice')
- Niek van den Nieuwenhof (project 'Electrocardiograhy in asymptomatic patients included in cardiovascular prevention programmes in general practice')

Teaching

Coordinator 'kaderopleiding hart- en vaatziekten', a Dutch two-year educational programme for general practioners to specialise in cardiovascular medicine in primary care

Teacher cardiovascular medicine in primary care at STARtclass and quarterly education days for all Dutch general practitioner residents at SBOH (Stichting Beroepsopleiding Huisartsen), Utrecht

Teacher cardiovascular and pulmonary medicine in primary care for general practitioner residents of Maastricht University

Lecturer cardiovascular and pulmonary medicine in primary care for general practitioners, physician assistants, specialist nurses and paramedics, region Maastricht & Heuvelland and incidentally in several other regions

Contributions to guidelines / protocols

2014 Regional transmural protocol patient care for atrial fibrillation, Maastricht & Heuvelland

2014 Regional transmural protocol patient care for heart failure, Maastricht & Heuvelland

2016 Regional transmural formulary for diagnosing asthma and COPD and prescribing inhalation medication, Maastricht & Heuvelland

Committees, working groups (as a general practitioner specialised in 'cardiovascular medicine in primary care' and 'asthma and COPD in primary care')

General practitioner representative in transmural working group 'cardiovascular disease', and subgroup 'heart failure and atrial fibrillation', in behalf of general practitioners of region Maastricht & Heuvelland, united into 'ZIO' (Zorg in Ontwikkeling)

General practitioner representative in transmural working group 'asthma and COPD', including subgroup 'regional pulmonary formulary', in behalf of general practitioners of region Maastricht & Heuvelland, united into 'ZIO' (Zorg in Ontwikkeling)

General practitioner representative in transmural working group 'arterial en venous thrombosis', region Maastricht & Heuvelland

General practitioner member of working group 'acute care - myocardial infarction', uniting all care providers related to assessing and treating patients with acute myocardial infarction, region Limburg

Awards

Golden Stethoscope 2007, price assigned by medical students of Maastricht University for education during internships

