MASTER THESIS

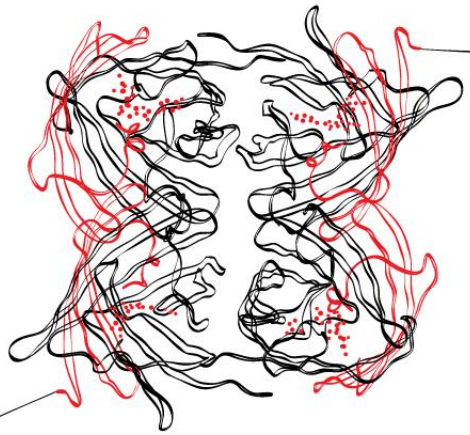
DECREASING TIME TO DIAGNOSIS IN PATIENTS WITH ACUTE CHEST PAIN

The incremental cost-effectiveness of implementing a multiple biomarker assay for early exclusion of NSTEMI

Michelle M.A. Kip

Supervisors:
Dr. L.M.G. Steuten
Prof. dr. G.C.M. Kusters

University of Twente
School of Management and Governance
Department of Health Technology and Services Research



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Name	Michelle M.A. Kip
Student number	s1089048
Supervisors	dr. L.M.G. Steuten prof. dr. G.C.M. Kusters
Institute	University of Twente School of Management and Governance Department of Health Technology and Services Research
Postal address	P.O. Box 217 7500 AE Enschede
Visiting address	Building Ravelijn (on the campus, no. 10 on the map) Drienerlolaan 5, 7522 NB Enschede Room RA 5244 (secretariat)
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UNIVERSITY OF TWENTE.

Jeroen Bosch Ziekenhuis

ABSTRACT

PURPOSE Because of the increasing pressure on healthcare budgets, it is desirable to investigate the incremental cost-effectiveness of new diagnostic opportunities prior to their implementation in practice. A likely waste of resources in healthcare, is assumed to occur at cardiology departments. Patients presenting with chest pain at the coronary pain unit (CPU), without elevation of the ST-segment on an ECG, are considered at risk of having an acute myocardial infarction (AMI), specifically a non ST-elevation myocardial infarction (NSTEMI). However, only a small proportion of these patients ultimately receive this clinical diagnosis. Because serial blood measurements are currently necessary to exclude NSTEMI, the majority of patients stay at the CPU several hours before being discharged. Since one day admission at the CPU costs €1241, research should aim at decreasing admission times. This study will examine whether implementing a multimarker assay, consisting of a myeloperoxidase (MPO), copeptin, and high-sensitive troponin measurement, is cost-effective compared to the current serial high-sensitive troponin measurement in patients presenting with chest pain at the CPU.

METHOD Semi-structured interviews with four cardiologists were performed to analyze the extent to which their decision making is influenced by a patient's troponin result. Then, the performance of a high-sensitive troponin assay only, as well as the multimarker assay were estimated based on a systematic review of the available literature. These performances were used as input for a closed-ended questionnaire. Cardiologist were provided a range of analytical performances, reported as sensitivity, and the percentage of false negative results. Subsequently, ten cardiologists were asked to estimate the influence of a multimarker assay, with higher analytical performance than the current high-sensitive troponin assay, on their decision making. This influence considers the estimated percentages of patients discharged at each time point, and the number of (diagnostic) activities performed. The incremental cost-effectiveness ratio (ICER) was calculated for three different implementation strategies of the multimarker assay, each divided in three scenarios according to the analytical performance of the assays. Incremental cost-effectiveness of each scenario was illustrated using a cost effectiveness plane. Following this, one-way sensitivity analysis and best worst case analyses were performed to examine the robustness of the model for differences in input variables.

RESULT Interviews revealed three issues with the current troponin assay. First, the consequence of a high-sensitive assay is that minor elevations in troponin can be observed in patients without NSTEMI. Secondly, serial measurements are therefore required to determine a change in troponin level, which is indicative of NSTEMI. Third, biomarkers are only of limited importance in setting the diagnosis, relative to a patient's clinical symptoms and ECG findings. Results of the questionnaire indicate that implementing a multimarker assay, with a sensitivity and negative predictive value (NPV) of both 99%, combined with additional troponin measurements after two and six hours, might result in cost savings of €191.18 per patient, and 130 earlier patient discharges. Assuming both a lower sensitivity (90 or 95%) and NPV (96 or 98%), this specific multimarker strategy remains dominant compared to the current serial troponin measurement. Sensitivity analysis revealed that the variation in cost of the multimarker assay strongly influence the ICER. However, in case of a multimarker assay with a sensitivity and NPV of 99%, combined with two additional troponin measurements, costs of MPO and copeptin together may raise up to €200.63 (including AMI-patients), to retain an equally cost-effective strategy as the current serial troponin measurement.

CONCLUSION Because this study concerns an early economic evaluation, involving relatively much uncertainty in input variables, results have to be interpreted cautiously. However, assuming that the multimarker has a higher analytical performance than a high-sensitive troponin measurement only, we recommend the implementation of this multimarker assay with additional troponin measurements after two and six hours.

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1. INTRODUCTION

1.1 BACKGROUND

Cardiovascular disease is a global health issue. Approximately one-third of all persons in the world die of cardiovascular disease. 80% of these deaths occur in developing countries, indicating an increasing problem. In industrialized countries it is already a leading cause of death[1, 2]. Coronary artery disease (CAD) is the most prevalent type of cardiovascular disease, and is associated with high morbidity and mortality[2-4].

CAD is the result of atherosclerosis, which involves the accumulation of lipoproteins on the wall of the artery. Subsequently, their modification triggers an inflammatory immune response, causing the development of atherosclerotic plaques[5]. Over time, the fibrous cap of these plaques might deteriorate and become prone to rupture[6]. A ruptured plaque might induce acute thrombosis, causing an abrupt and critical reduction in blood flow[7]. Insufficient blood supply to the heart is called ischemia, with chest pain as a typical symptom. This situation is referred to as acute coronary syndrome (ACS), which is defined as "any constellation of clinical symptoms that are compatible with acute myocardial ischemia". It encompasses both acute myocardial infarction (AMI) and unstable angina (UA). A patient is diagnosed with stable angina pectoris when chest pain develops during exertion and resolves at rest. UA, however, is mostly associated with a worse prognosis, and is referred to when symptoms of chest pain arise unexpectedly and also in periods of rest[3]. UA might progress to AMI or sudden death, and is associated with different degrees of coronary obstruction, thereby disturbing myocardial oxygen supply. AMI, however, is often associated with complete coronary obstruction, resulting in severe ischemia with the major consequence of myocardial cell death[8, 9]. Since rapid reperfusion can decrease myocardial damage, early diagnosis is crucial to facilitate rapid treatment[2, 3, 10, 11].

1.1.1 DIAGNOSING AMI

Patients with chest pain represent a very large proportion of all acute hospitalizations in medical centers in Europe. However, it remains a diagnostic challenge to distinguish those patients who really have AMI[3]. The World Health Organization (WHO) defined AMI as typical symptoms, abnormalities on the electrocardiogram (ECG), and elevation of sensitive and specific cardiac enzymes in circulation[12]. AMI encompasses both ST-segment elevation myocardial infarction (STEMI), and non-ST-segment elevation myocardial infarction (NSTEMI)[4]. ST-segment elevation on an electrocardiogram (ECG) is a typical characteristic of myocardial infarction, although it might be observed in other conditions as well. However, almost 70% of all patients with ACS tend to have UA or NSTEMI, making only an ECG insufficient for diagnosing AMI[4, 13-15]. Because a subset of NSTEMI patients has a total occlusion of one of the coronary arteries, setting this diagnosis is crucial. This occlusion mostly involves the circumflex artery, and often remains unseen on an ECG[16]. Therefore, besides a patient's clinical symptoms and ECG, biomarkers are essential in setting the diagnosis[2, 3].

1.1.2 BIOMARKERS IN THE DETECTION OF AMI

Although NSTEMI patients do not have the typical ST-segment elevation, release of cardiac biomarkers can be observed[4]. Over the years, cardiac troponins have developed into key biomarkers for patients with acute chest pain, offering high diagnostic value for AMI[2, 3, 17-19]. The underlying principle of these assays is the detection of myocardial necrosis[2, 11]. The detection of a rise and/or fall of troponin levels with at least one value above the 99th percentile in a reference population is recommended to be used as a discriminatory value for diagnosing AMI[2]. However, the standard troponin assays are limited in their diagnostic value by the fact that the increase in circulating levels of troponin is delayed, indicating low sensitivity within the first hours after chest pain onset[2, 17, 20, 21]. Consequently, excluding

AMI requires monitoring the patient for 6 to 12 hours and serial blood sampling[13]. However, only a small proportion of all patients who present at the emergency department (ED) with a normal or non-diagnostic ECG, and variable clinical features, will ultimately be diagnosed with AMI[22]. Therefore, this prolonged monitoring and subsequent blood sampling probably indicates a substantial overuse of healthcare resources.

Recently, a new generation of high-sensitive cardiac troponin assays has been introduced[19, 21, 23, 24]. Research by Reichlin et al, 2009, indicates that these high-sensitive assays can substantially improve the early diagnosis of AMI, especially in patients with a recent onset of chest pain and no ST-segment elevation[13]. Although increased accuracy of these assays compared with the conventional troponin assay has been confirmed, recent studies have expressed their concerns about possible deficits in specificity[13, 17, 25-27]. The main reason for this deficiency is that elevated troponin levels indicate the presence of myocardial injury, but not the underlying mechanism. Besides ischemia however, myocardial damage can have a variety of other causes, varying from congestive heart failure to end-stage renal disease[28-33].

Although myocardial necrosis is a typical feature of AMI, myocardial ischemia and inflammation occur prior to necrosis[34]. Besides, since inadvertent discharge of a patient with AMI may have serious consequences, the use of multiple biomarkers has been advocated by many researchers[14, 35, 36]. Two additional markers that might be helpful for the rapid exclusion of AMI, in addition to the current high-sensitive troponin measurement, are myeloperoxidase (MPO), and copeptin (figure 1).

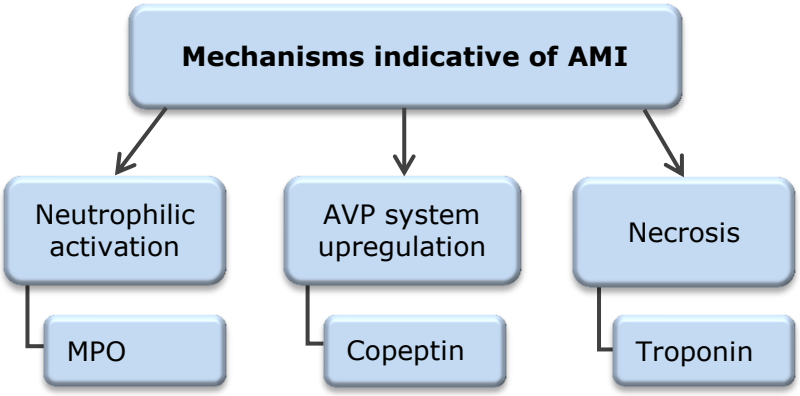

Figure 1: *using multiple biomarkers which can detect several mechanisms indicative of heart failure might improve the rapid exclusion of AMI.*

MPO is an enzyme which is released from leukocytes which are activated and involved in the process of forming atherosclerotic plaques[37-39]. Previous studies have shown that MPO is elevated and active in vulnerable plaques, indicating the potential usefulness of this marker in early detection of AMI[39, 40]. Research by Rudolph et al, 2009, reports significantly higher MPO-levels in patients with AMI compared to patients without AMI[40].

In addition, copeptin, the C-terminal portion of the hormone vasopressin, has also shown to increase very rapidly in AMI patients[41-43]. This hormone is part of the arginine-vasopressin system and is involved in regulating the endogenous stress response[44]. According to recent studies, measurement of copeptin in addition to a high-sensitive troponin assay, might improve the detection of AMI, and thereby obviate the need for prolonged monitoring and serial blood sampling[42, 43, 45].

Therefore, the combined detection of three different mechanisms indicative of AMI, named the multimarker assay, might facilitate rapid exclusion of this diagnosis, which might contribute to both earlier treatment and discharge[34]. Currently, many hospitals have specialized coronary pain units (CPUs), for diagnosing patients suspected of ACS. This term will therefore be used

throughout this report. Because ST-elevation is often sufficient for diagnosing STEMI, more sensitive biomarkers will not offer added value, and therefore the greatest benefit of this multimarker assay is expected to occur in the process of excluding NSTEMI.

In 2006, a study by Forberg et al was published, reporting that almost 40% of the total costs of chest pain patients attending the ED, was spent on patients not having ACS. Also, admission time accounted for about two third of the total costs for these patients. Because of these findings, and because of the large size of this patient category, correct management decisions at the CPU are also of great economic importance[13, 43, 46, 47].

Furthermore, it is argued that efforts to decrease costs for patients with suspected ACS should primarily be aimed at reducing the length of hospital stay. According to these researchers, the ideal diagnostic strategy is "one performed immediately in the ED, without the need for CPU or hospital admission"[47]. Therefore, a multimarker approach which reduces the time to exclusion of NSTEMI, might substantially reduce the costs that occur in this patient category. However, as these advanced diagnostics inevitably come at an additional cost to the healthcare system, who's budgets are increasingly scarce, research into the cost-effectiveness of diagnostic opportunities is highly necessary[48, 49].

As shown in figure 1, combining a copeptin, MPO, and high-sensitive troponin measurement, might improve the rapid exclusion of NSTEMI in patients presenting at the CPU with symptoms suggestive of ACS. Besides, more rapid exclusion might result in a shorter hospital stay for patients without NSTEMI, and less (diagnostic) activities that are performed. Consequently, the multimarker assay might be a cost-effective method for excluding NSTEMI compared to serial high-sensitive troponin measurement, if the additional costs of implementing the multimarker are offset by downstream savings in healthcare resource use.

1.2 RESEARCH QUESTION

Although previous research indicates that, generally, more early exclusion of NSTEMI might be cost-effective, and that multimarker testing might facilitate this rapid exclusion, the cost-effectiveness of this specific multimarker assay has not been investigated previously.

Therefore, this study will examine the incremental cost-effectiveness of adding a MPO- and copeptin measurement to the current high-sensitive troponin assay, to rapidly rule out NSTEMI in patients presenting with symptoms suggestive of ACS at the CPU. Consequently, the main research question that will be addressed in this paper is:

What is the incremental cost-effectiveness of adding a copeptin- and MPO measurement, to the conventional high-sensitive troponin assay, for early exclusion of NSTEMI in patients who present with symptoms suggestive of ACS, without ST-segment elevation, at the CPU?

1.2.1 SUBQUESTIONS

To answer this research question, several subquestions have been formulated:

- *What is the relative impact of the multimarker assay on the clinical pathway that is followed in patients who present with symptoms suggestive of ACS at the CPU?*
- *What is known in literature about the analytical performance of high-sensitive troponin, copeptin, and MPO, or about a combination of these markers?*
- *What is the relative impact of the multimarker assay on the time until a patient is discharged, the number of exercise ECGs that are performed, the amount of medication that is administered, and the number of catheterizations that are performed?*
- *From an allocative efficiency perspective, can it be recommended to either replace the serial high-sensitive troponin measurement by this multimarker assay (measured at the time of a patient's entrance at the CPU), or to implement these two laboratory analyses in addition to serial troponin measurement?*

2. METHODS

2.1 SETTING

This study is designed and coordinated in collaboration with the Jeroen Bosch Hospital (JBZ). This is a 730 bed institution located in Den Bosch, the Netherlands. It serves a population of circa 635,000. The hospital has a specialized CPU (named 'Eerste Hart Hulp'), providing ten beds for continuous heart monitoring. Percutaneous coronary intervention (PCI) is available 24 hours/day[50].

2.2 STUDY POPULATION

Although this study will not include real patient data, the theoretical study population is defined as patients presenting at the CPU with acute chest pain, or other symptoms suggestive of ACS, and:

(1) No ST-elevation on the ECG (which is diagnostic of STEMI);
(2) An onset of symptoms in the last twelve hours;
(3) Not presenting at the CPU with cardiac arrest requiring immediate reperfusion;
(4) The availability of a patient's blood samples for measurement of cardiac enzymes.

These four criteria are recommended to be used for a future study concerning the analytical performance of the multimarker assay. Because this study aims to evaluate the impact of this assay on excluding NSTEMI, only patients with the final clinical diagnosis of not having NSTEMI should be included, indicating that a retrospective study design is most suitable.

2.3 STUDY DESIGN

This study will evaluate the influence of the multimarker assay on the process and outcome of excluding NSTEMI at the CPU, considering both the patient flow and use of resources. The outcome of this report will involve the direct hospital costs that occur in patients suspected of ACS attending the CPU, without ST-elevation on the ECG, with the final discharge diagnosis of not having NSTEMI. The focus will be on the economic consequences of decisions made by the cardiologists concerning whether or not to discharge these patients, and to perform one or more (diagnostic) activities.

This study aims to estimate the incremental cost-effectiveness of either implementing a multimarker assay, existing of both a copeptin, MPO, and high-sensitive troponin measurement, or retaining the current strategy of serially measuring high-sensitive troponin. In the new strategy, the multimarker will be measured at the time of a patient's entrance at the CPU (t0). In the conventional method however, troponin is measured at t0, and repeated after two and six hours (t2 and t6, respectively).

This study will adopt the hospital perspective on costs and effects, indicating that only direct costs and effects as these occur within the hospital are analyzed. Because the decision whether or not to implement two additional laboratory analyses will be made by the hospital decision makers (who are primarily accountable for hospital budgets), this perspective best reflects the actual decision making context. Although the impact of myocardial infarction on societal cost is also very important – especially because of the economic burden and disability caused by it – this falls outside the scope of this first economic evaluation of the multimarker assay. This analysis will take the form of a cost-effectiveness analysis (CEA), because benefits are measured in natural (health) units – whether or not the diagnosis NSTEMI is excluded earlier – rather than in terms of money (as in cost-benefit analysis). The time horizon of this analysis is the time from the patient entering the CPU, up to hospital discharge.

2.3.1 Outcome measures

Effectiveness of both high-sensitive troponin measurement only and the multimarker assay is defined as the number of patients in whom NSTEMI is excluded at either t0, t2, t6, or after overnight admission. Because laboratory results are available after approximately one hour, discharge following the laboratory results at t0, t2, and t6, is assumed to occur after one, three, and seven hours respectively. Cost is defined as direct hospital costs (in 2012 Euros), that occur from the moment a patient enters the CPU, until the patient is discharged from the hospital.

The main outcome measure of this economic evaluation is the incremental cost-effectiveness ratio (ICER). The ICER is defined as the difference in cost divided by the difference in effectiveness between competing strategies[51]. In this analysis, the ICER is defined as:

The incremental cost per additional patient in whom NSTEMI is excluded at t0, t2, t6, or after overnight admission, using either serial high-sensitive troponin measurement, or the multimarker assay.

2.3.2 Overview study design

To identify the issues cardiologists experience with the current high-sensitive troponin assay, this evaluation will start with analyzing the available literature. To validate the occurrence of these issues in daily practice, and to identify potential other issues arising, observations and semi-structured interviews at the cardiology department of the JBZ will be performed. Following this, the most important cost components involved in excluding NSTEMI at the CPU will be identified. Subsequently, a systematic review of the literature will be performed, to estimate the analytical performance of both the multimarker assay and serial high-sensitive troponin measurement. These results are used as input for the questionnaire. Using hospital registrations and by studying literature, unit costs of the cost components occurring in either intervention are determined. Subsequently, cardiologists are asked to fill out a questionnaire, to identify resource use (considering the time of a patient's discharge and the activities performed). Data about unit costs and resource use are combined, following the principle of Activity Based Costing, to obtain the total costs of each intervention. The ICER is determined by dividing the difference in costs by the difference in effects of both interventions, as displayed in figure 2.

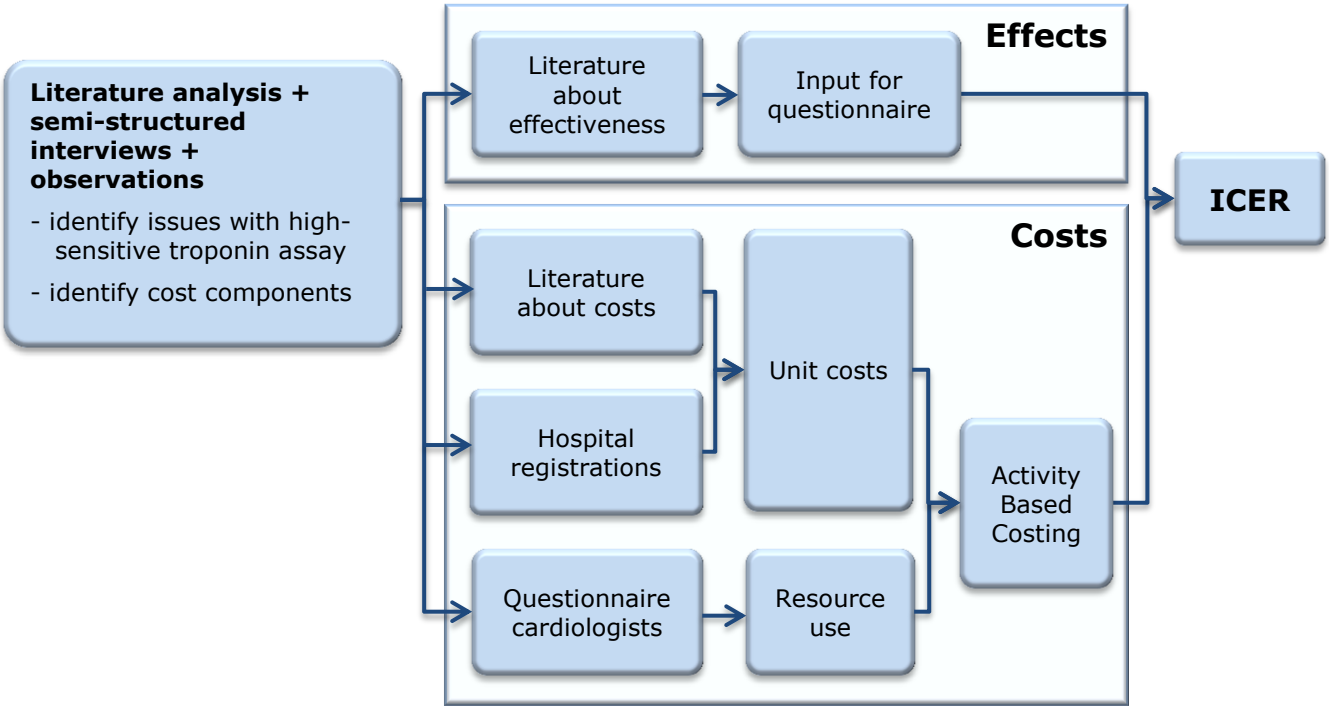

Figure 2: *flow chart visualizing the subsequent steps that are taken in this cost-effectiveness analysis.*

2.4 CLINICAL PATHWAY

Following a literature analysis and observations at the JBZ, the clinical pathway of excluding NSTEMI at the CPU is established. To visualize how the multimarker might change this pathway, both the current clinical pathway, and the suggested pathway using the multimarker assay, are illustrated in figure 3. The green fields represent the exclusion of NSTEMI based either on the current serial troponin measurement, or on the multimarker assay at t0.

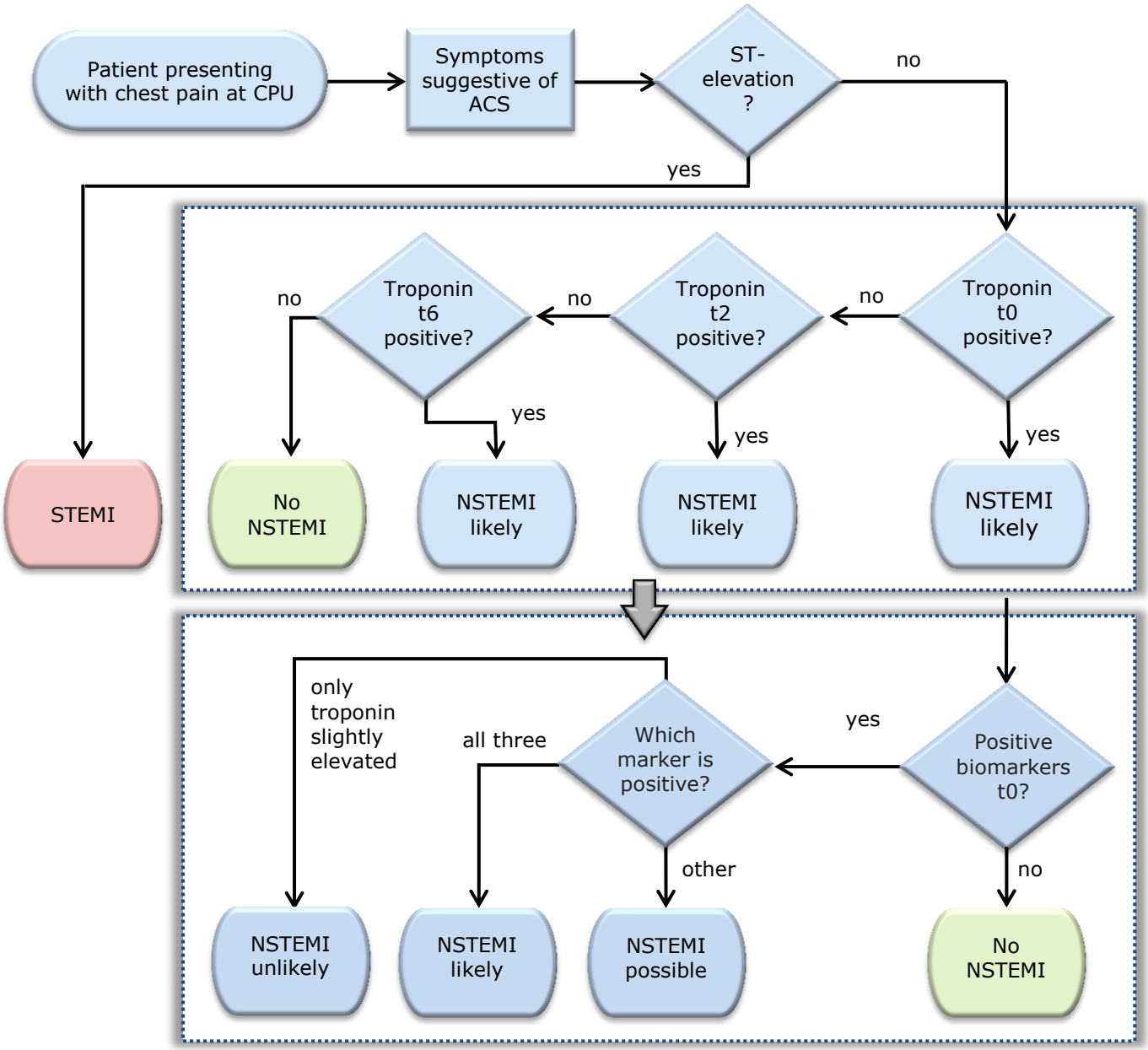

Figure 3: *the current clinical pathway that is followed in patients presenting with symptoms suggestive of ACS at the CPU, involving serial high-sensitive troponin measurement (above), and the multimarker assay (below). This figure illustrates how the multimarker assay might contribute to earlier exclusion of NSTEMI at the CPU.*

2.5 DECISION-ANALYSIS: POTENTIAL STRATEGIES

Although the flow chart in figure 3 illustrates how the multimarker might contribute to more early exclusion of NSTEMI, namely based on a negative result of the multimarker at t0, it might not be realistic in practice to assume that cardiologists would discharge all patients based on laboratory results at t0. Therefore, the incremental cost-effectiveness will be examined for three potential strategies of implementing the multimarker assay in a theoretical population of patients attending the CPU with symptoms suggestive of ACS:

I) The multimarker assay at t0, compared to serial troponin analysis;
II) The multimarker assay at t0, combined with one additional troponin analysis at t2, compared to serial troponin analysis;
III) The multimarker assay at t0, combined with additional troponin analyses at t2 and t6, compared to serial troponin analysis.

For all three strategies, a decision-analytic model is developed, resulting in the decision tree as shown in figure 4 on the next page. However, along with the laboratory assay, an exercise ECG can be of diagnostic value as well. Therefore, a distinction is made between patients in whom an exercise ECG is performed, and in whom not. Therefore, all three strategies will be assessed twice, both for patients who underwent an exercise ECG, and for patients who did not.

2.6 SYSTEMATIC REVIEW PERFORMANCE LABORATORY ASSAYS

To estimate the probabilities for each of the branches in the decision analytical model to occur, the expected performance of both the conventional troponin measurement and the multimarker assay needs to be determined. The performance of each of the markers is also required for cardiologists in order to estimate how a more sensitive laboratory assay would change their decision making (section 2.7). Considering troponin, the performance is based on the specific type of troponin that is measured at the JBZ, which is troponin I. Although this marker is measured using the Troponin I LOCI assay, insufficient information was available about the analytical performance of this relatively new assay. Therefore, the performance was estimated based on the Troponin I Ultra Assay, which is also a relatively new high-sensitive troponin I assay produced by the same manufacturer (Siemens). Considering copeptin, the analytical performance is based on the BRAHMS Copeptin assay. For MPO however, the available literature is limited, and therefore this performance is not based on an analysis from a specific manufacturer. To obtain an accurate estimation of the performances of all three markers, a systematic review of the available literature is carried out. The PubMed database is searched for relevant articles about the analytical performance of troponin, MPO, and/or copeptin. The following combinations of terms are searched in title or abstract of published papers: *copeptin* OR *pro-terminal vasopressin* OR *MPO* OR *myeloperoxidase* OR *high-sensitive troponin* OR *high sensitive troponin* OR *hsTn* AND (*acute coronary syndrome* OR *ACS* OR *acute myocardial infarction* OR *AMI*) AND *sensitivity* AND *specificity*. The search is further limited to articles published after 2006 and in English or Dutch. Exclusion criteria are: 1) articles not reporting both the sensitivity, specificity, and negative predictive value (NPV) of either high-sensitive troponin, copeptin and/or MPO; 2) articles not reporting the performance of the markers specifically to diagnose AMI; 3) articles using another assay than the Siemens ADVIA Centaur Ultra I assay to measure high-sensitive troponin I; 4) articles focusing on the prognostic value of biomarkers instead of the diagnostic value; and 5) articles which cannot be obtained from the university library or open access databases. Relevant articles are initially selected based on the title and abstract. Additional articles are obtained from the reference lists of the selected articles. After that, full texts are reviewed to assess whether the papers meet the inclusion and exclusion criteria. The literature search is performed in April 2012.

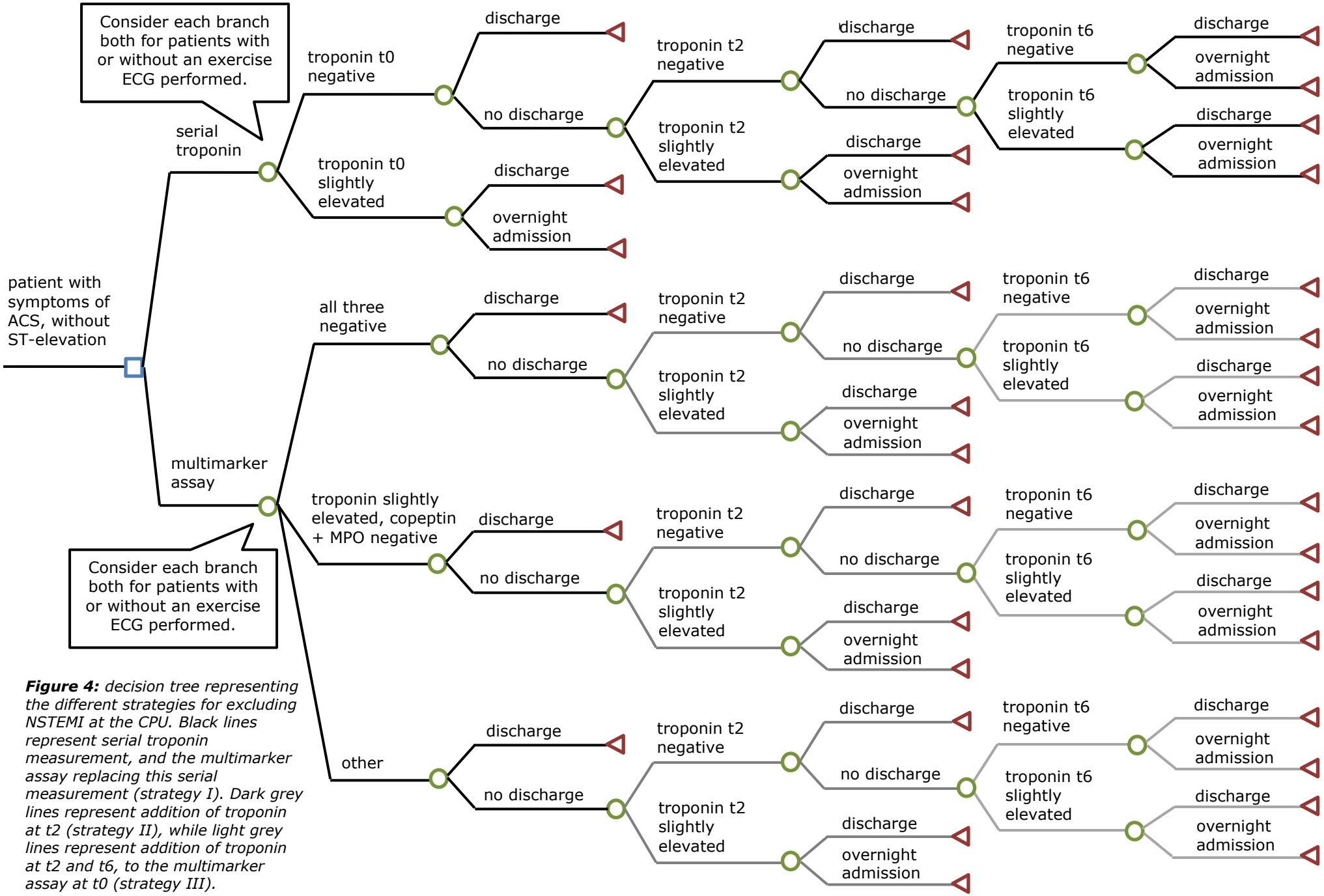

Figure 4: *decision tree representing the different strategies for excluding NSTEMI at the CPU. Black lines represent serial troponin measurement, and the multimarker assay replacing this serial measurement (strategy I). Dark grey lines represent addition of troponin at t2 (strategy II), while light grey lines represent addition of troponin at t2 and t6, to the multimarker assay at t0 (strategy III).*

2.7 QUESTIONNAIRE

As described previously, the multimarker assay might influence both the length of a patient's hospital stay, as well as the (diagnostic) activities that are performed. To evaluate this impact, a questionnaire is used to obtain expert estimations concerning the influence of the analytical performance of a laboratory assay on excluding NSTEMI. To obtain sufficient response for the analysis, the questionnaires were handed both to cardiologists of the JBZ, and to cardiologists of 'Medisch Spectrum Twente', MST, located in Enschede, the Netherlands. Because the questionnaire is performed at two different locations, both the specific troponin assay used in each hospital (troponin I or T), as well as the accompanying cut-off values, are adapted prior to handing the questionnaires to the cardiologists. Because the exact performance of the combination of copeptin, MPO and high-sensitive troponin is unknown, a range of expected analytical performances is presented in the questionnaire. The complete questionnaire, as conducted at the JBZ, is enclosed in appendix III.

The questionnaire contains 14 questions, which are structured in three sections. The first section focuses on the importance of laboratory results in diagnosing both STEMI and NSTEMI, and the problems experienced with the current troponin assay (seven questions). In the second section, a range of analytical performances of the multimarker assay is presented, in the form of sensitivities and accompanying false negative rates. Cardiologists are asked to estimate the percentage of patients they would discharge based on the information that is provided (following the laboratory result at t0, t2, t6, or after overnight admission). The third section analyzes the number of activities that are performed in patients attending the CPU with symptoms of ACS (catheterizations, exercise ECG, and administering medication). Again, a range of performances of both the high-sensitive troponin assay and the multimarker assay are presented (three questions). The percentages cardiologists can choose from in section two and three of the questionnaire include values ranging from 0 up to and including 100%, with steps in between of 25% each. In the last question, there is room for comments.

The questionnaire consists of both open-ended and closed-ended questions. It contains three statements for which a 5-point Likert-scale is used whereby respondents can indicate their degree of agreement. The questionnaire is pre-tested by one cardiologist and one epidemiologist at the department cardiology of the JBZ, to prevent misinterpretations and to optimize the questionnaire. The questionnaires are filled out by the cardiologists, after the purpose has been introduced and explained by means of a short presentation. To evaluate the importance of an exercise ECG relative to laboratory assays in excluding NSTEMI, cardiologists are asked to answer each question both for a patient group with no result of an exercise ECG available, and for patients with a negative result of this exercise ECG. When filling out the questionnaires, no interaction between experts was possible.

2.8 EFFECT OF THE MULTIMARKER ASSAY ON DIRECT HOSPITAL COSTS

After examining the expected impact of the multimarker assay regarding a patient's discharge and the activities that are performed, the possible impact on costs is estimated.

2.8.1 ACTIVITY BASED COSTING

Direct hospital costs will be estimated using Activity Based Costing (ABC), from the moment a patient presents with symptoms suggestive of ACS at the CPU, until this patient is discharged from hospital. ABC is an advanced cost technique used for cost calculation, which allocates resource costs to products, based on resource consumption. ABC is a bottom up costing approach, which might provide greater visibility into organizational processes and their cost drivers, and might thereby make improvements possible in the efficiency of the current process of excluding NSTEMI[52-55]. In this analysis, all unit cost are first multiplied by the volume used. Following this, by adding up the costs of the various elements that comprise each scenario, the overall costs of each branch in the decision analytic model are calculated.

2.8.2 DATA SOURCES

Unit costs for medical treatment are obtained from www.medicijnkosten.nl (heparin, metoprolol, clopidogrel, and carbaspirin calcium). Costs for the current laboratory assays, including the accompanying tariff order, as well as unit costs for diagnostic procedures (catheterizations and exercise ECGs) are obtained from the Dutch Health Authority (Nederlandse Zorg Autoriteit, NZA).

Unit costs for medical admission are obtained from two different data sources. First, the costs of one overnight admission at the CPU are based on the costs for one night hospital admission, plus additional costs for medical specialists, derived from the cost manual by Hakkaart-van Roijen, 2010[56]. Because costs for hospital admission are assumed not to be evenly distributed over the period of hospital stay, an additional data sources is used to estimate the costs of earlier discharge from the hospital, based on the laboratory results at t0, t2, or t6. Because laboratory results are available one hour after the blood sample has been taken, patients can be discharged after one, three, or seven hours respectively. Costs which occur in the first hour following hospital admission are estimated based on the costs manual by Hakkaart-van Roijen (2010), reporting the unit cost of a consultation at the ED[56]. Because this unit cost does not include costs for food and overhead, these additional costs are derived from Financial Statistics 2009 ("Financiële Statistiek 2009")[57]. Because the costs manual by Hakkaart-van Roijen was published in 2010, and the document Financial Statistics was published in 2009, all obtained unit costs are discounted by the annual discount rate to obtain costs in 2012 Euros.

Costs of three and seven hours hospital stay are estimated as the costs from one hour hospital stay (as described in the previous paragraph), plus additional costs including costs for food and overhead, nurses, and medical specialists, which occur in the additional two or six hours hospital stay. These costs are estimated based on the discounted costs derived both from Financial Statistics 2009, and from the costs manual by Hakkaart-van Roijen[56, 57].

The direct costs of each strategy are estimated by summing its constituent elements, and the probability of each element occurring. Because all effects are observed within 24 hours, these values are not discounted.

2.9 ASSUMPTIONS

Several general assumptions are made in the decision analytic model. First, for each patient entering the CPU with symptoms suggestive of ACS, either the multimarker assay or conventional troponin measurement(s) will be performed to exclude NSTEMI. If the diagnosis NSTEMI is not excluded following the result of the final laboratory assay, it is assumed that a patient will remain at the CPU for 24 hours (overnight admission), after which discharge will follow. What is named the 'final' laboratory assay depends on the three different strategies, being either at t0, t2, or at t6. Because only patients without NSTEMI are included in this analysis, troponin results >0.099 ng/mL are not included, because it is assumed that these laboratory results are only observed in patients who are having a myocardial infarction.

Also, some assumptions are made related to event probabilities. Specifically concerning the result of the multimarker assay, three categories are distinguished in the model:

- First, there is the probability of a negative result for both MPO, copeptin, and high-sensitive troponin. This category is included in the questionnaire.
- The second category involves a slightly elevated troponin level combined with a negative copeptin and MPO result. This category is also included in the questionnaire.
- However, the third category is named 'other', involving any other outcome than the two mentioned above. For all patients in this category, it is assumed that the cardiologists will not discharge a patient based on the laboratory result at t0, and therefore the patient will either stay for one or two additional troponin

measurements, or stay overnight. Concerning the activities that are performed in this category, two subgroups are distinguished:

- One group consists of patients who have a negative troponin level combined with a positive MPO and/or copeptin. For this subgroup it is assumed that the probabilities of activities that are performed will be the same as in case of a negative troponin level with the conventional troponin measurement at t0.
- The other subgroup however, involves a slightly elevated troponin level combined with a positive MPO and/or copeptin. Concerning the activities that are performed, it is assumed that these probabilities will be the same as in case of a slightly elevated troponin level in the conventional troponin analysis.

Furthermore, if one troponin result is positive, it is assumed that any subsequent troponin measurement will be positive as well. Also, the decision to discharge patients, as well as the activities performed, will be the same regardless whether troponin is positive at t0, t2 or t6. Also, discharge rates after additional troponin measurements at t2 and t6 are assumed to be the same regardless of former laboratory analyses. Furthermore, it is assumed that there is no difference in the number of ECGs that are assessed for either analysis. Therefore, the assumption is made that, independent of the laboratory assay conducted, one ECG is assessed for each patient.

Concerning the costs of laboratory analyses, the costs of a MPO and copeptin measurement are both assumed to be the same as a troponin measurement. Furthermore, because the initial approach of the analysis is that the addition of a copeptin and MPO assay will replace two additional troponin measurements, it is assumed that the two new assays will not require an increase in capacity of the laboratory equipment and/or personnel. This indicates that, besides possible extra costs for the required reagents, no extra costs will be made for implementing these two analyses.

2.10 ANALYSIS OF THE RESULTS

Statistical analyses are conducted using Microsoft Office Excel (2010), and SPSS software version 18.0 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics are used to report numbers, means and percentages. 95% confidence intervals will be determined for the percentages obtained from the questionnaire. The result of the cost-effectiveness analysis will be illustrated using a cost-effectiveness plane.

As stated by Meltzer (2001), "one of the main challenges faced by medical cost-effectiveness analysis has been the question of how to perform these analyses in the presence of uncertainty about the benefits and costs of medical interventions[58]". Therefore, the robustness of the model to changes in one variable, will be estimated by changing each variable individually over its range. This univariate sensitivity analysis is performed to estimate the influence of either variations in analytical performance of the biomarkers, variations in the percentage of patients that is discharged, variations in resource use, as well as variations in cost units on direct hospital costs, on the accompanying ICER.

Following this, a best and worse-case scenario will be constructed to advice the hospital on whether or not to implement the multimarker assay, about the best strategy, and about the risks involved with this decision. Also, because the costs of the two additional laboratory assays are uncertain, the maximum costs of both analyses will be determined to remain equally cost-effective as the current serial troponin analysis.

3. RESULTS

3.1 OBSERVATIONS AND SEMI-STRUCTURED INTERVIEWS

A literature analysis revealed three major issues with the current troponin assay. To validate these issues, observations at the JBZ and semi-structured interviews with four cardiologists are performed. The results of this problem identification are described in the following section.

3.1.1 THE NECESSITY OF SERIAL BLOOD SAMPLING

First, although the high-sensitive troponin assays should be able to detect AMI earlier (both STEMI and NSTEMI), serial blood monitoring remains a necessity before this diagnosis can be excluded[59, 60]. Consequently, discharge of a patient from the CPU often takes up to seven hours. This was confirmed by both observations and semi-structured interviews at the JBZ. The interviews revealed that the strong risk-averse approach in making decisions in healthcare is an important factor. This implies that, if NSTEMI cannot be excluded with almost complete certainty, a patient will not be discharged from hospital. A multimarker analysis with high analytical performance might therefore improve the exclusion of NSTEMI at the CPU.

3.1.2 TROPONIN ELEVATIONS IN PATIENTS WITHOUT AMI

Second, a slightly elevated troponin level is associated with an increased risk of death and recurrent cardiovascular events, but might also be due to other conditions than myocardial infarction[28, 30-32, 61, 62]. The semi-structured interviews indicate that a patient with only a slightly elevated troponin level will therefore not be discharged from hospital, because this implies that NSTEMI cannot be excluded with certainty. Sequential troponin measurements are required to detect a rise or fall in a patient's troponin level. This issue has also been described extensively in literature[60, 63]. Therefore, by detecting multiple mechanisms indicative of a myocardial infarction, the multimarker assay might allow cardiologists to distinguish NSTEMI from other causes of elevated troponin levels.

3.1.3 THE LIMITED DIAGNOSTIC IMPORTANCE OF LABORATORY MARKERS

Third, the interviews revealed that a patient's troponin level is only 'a tiny piece of the puzzle', in patients who are suspected of having a myocardial infarction. Mainly a patient's clinical presentation, and other diagnostic strategies, like an exercise ECG, are of great diagnostic importance[33, 64, 65]. Semi-structured interviews confirmed that mainly a patient's clinical symptoms are essential in setting a diagnosis and making treatment decisions. The interviews made clear that, if a patients presents without an elevated troponin level but with very typical symptoms of NSTEMI, cardiologists might decide to perform a catheterization without waiting for additional troponin measurements. Therefore, in the current setting, the importance of laboratory assays in excluding NSTEMI is limited.

3.2 ANALYTICAL PERFORMANCE OF THE LABORATORY MARKERS

As described in section 2.6, a systematic review of the available literature was performed to estimate the analytical performance of both high-sensitive troponin, and the multimarker. The search strategy initially resulted in 1,120 articles. Based on the title and abstract, this resulted in 64 potentially relevant articles. Based on the exclusion criteria, 57 articles were excluded, and 1 relevant article was included based on the reference lists of the included articles. The main reasons for exclusion involved first the use of a high-sensitive troponin assay other than the Siemens Advia Centaur I Ultra, and secondly because articles assessed the prognostic performance of a laboratory assay instead of the diagnostic performance.

Of the 9 remaining articles, four assessed the analytical performance of high-sensitive troponin I (HsTnI) using the Siemens Advia Centaur I Ultra assay, three assessed the performance of MPO (using different assays), and two assessed the performance of copeptin, using the BRAHMS Copeptin assay. Figure 5 shows an overview of the selection process.

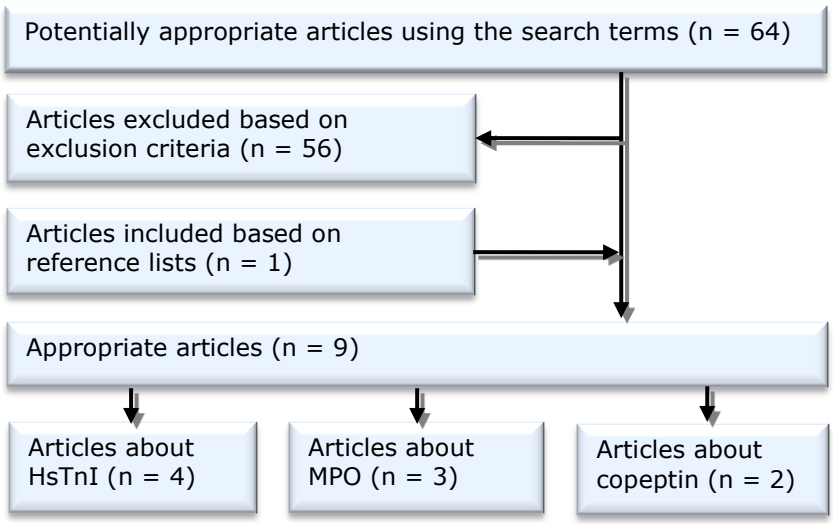

Figure 5: *selection process for the articles reviewed.*

These nine studies, and the reported sample sizes, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are listed in table 1.

Table 1*: result of the systematic review, involving the sensitivity, specificity, PPV, and NPV of the different biomarkers in each of the studies (n.a. = data not available).*

Study	Marker	Sample size (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Keller et al, 2009[17]	HsTnI	1,818	90.7%	90.2%	76.7%	94.6%
Keller et al, 2010[42]	HsTnI	1,386	86.7%	92.4%	80.6%	95.0%
Kelly et al, 2011[66]	HsTnI	952	76.7%	93.6%	n.a.	96.3%
Reichlin et al, 2009[13]	HsTnI	718	89%	92%	68%	98%
Cheng et al, 2008[67]	MPO	77	74.0%	90.6%	91.9%	70.6%
Esporcatte et al, 2008[68]	MPO	140	92.3%	40.2%	13.6%	98.1%
Inoue et al, 2011 [69]	MPO	432	57.4%	72.6%	52.2%	76.6%
Chenevier-Gobeaux et al, 2011[45]	Copeptin	317	81%	53%	21%	95%
Lotze et al, 2011[70]	Copeptin	142	69.2%	47.3%	11.7%	93.9%

These results are used to determine the range of sensitivities and NPVs of the multimarker assay reported in the questionnaire, and to estimate the specificities for each of the branches in the decision tree. To obtain these values, the performance of each marker (sensitivity, specificity and NPV) is first multiplied with the sample size of that study. After summing the results from the individual studies, a weighted average of the performance is obtained.

Consequently, the sensitivity of high-sensitive troponin I measurement only (on admission) was estimated to be slightly higher than 86%, forming the input for the lower limit of analytical performance as reported in the questionnaire. The upper limit for this range was set at 99%, which is estimated based on the study by Keller et al, 2010, reporting a sensitivity of 98.3% and a NPV of 99.0% for the combination of HsTnI and copeptin only in the diagnosis of AMI[42]. Therefore, the range of sensitivities in the questionnaire was set from 85% (for the current high-sensitive troponin analysis), to 90, 95, and 99% for the multimarker assay. For

simplicity, each step indicates a 5% increase in sensitivity. However, since achieving a sensitivity of 100% is not a realistic assumption, the upper limit was set at 99%. Following this, the estimated NPVs corresponding to these sensitivities were calculated as a linear correlation, resulting in NPVs of 95, 96, 98 and 99% respectively.

3.3 INCREMENTAL EFFECTIVENESS OF THE MULTIMARKER ASSAY

Because it is assumed that, in patients presenting with ST-elevation, treatment is initiated immediately without waiting for the laboratory results, the current analysis only focuses on excluding NSTEMI at the CPU. To evaluate whether this assumption is correct, and to estimate the importance of laboratory assays in patients suspected of NSTEMI, cardiologists are asked to indicate their degree of agreement with the following two statements:

- *If a patients presents at the CPU with symptoms suggestive of ACS, and ST-segment elevation on the ECG, I do not consider it necessary to wait for the laboratory results before initiating treatment.*
- *If a patients presents at the CPU with symptoms suggestive of ACS, but without ST-segment elevation on the ECG, I do not consider it necessary to wait for the laboratory results before initiating treatment.*

Reactions were recorded using a 5-point Likert scale, with answer options ranging from completely agree, to completely disagree (figure 6a and b). Considering the first statement, all cardiologists agree not to wait for the laboratory results in patients presenting with ST-segment elevation (figure 6a). Therefore, it can be assumed that it is correct to focus only on patients without ST-elevation. The same Likert scale was used for the next statement. As displayed in figure 6b, this question shows much more variance in the answers reported. However, because five cardiologists report not to agree with this statement, this indicates the potential benefit of an improved laboratory assay in this patient category.

To evaluate whether cardiologists frequently encounter slightly elevated troponin levels in patients without AMI, the same 5-point Likert scale was used to measure their response to the following statement:

- *The current troponin assay frequently gives slightly elevated troponin results in patients who do not have an acute myocardial infarction.*

The response to this question is shown in figure 6c. These results show that, although there is some disagreement, the majority of cardiologists agree with the statement, also indicating the usefulness for an improved laboratory assay.

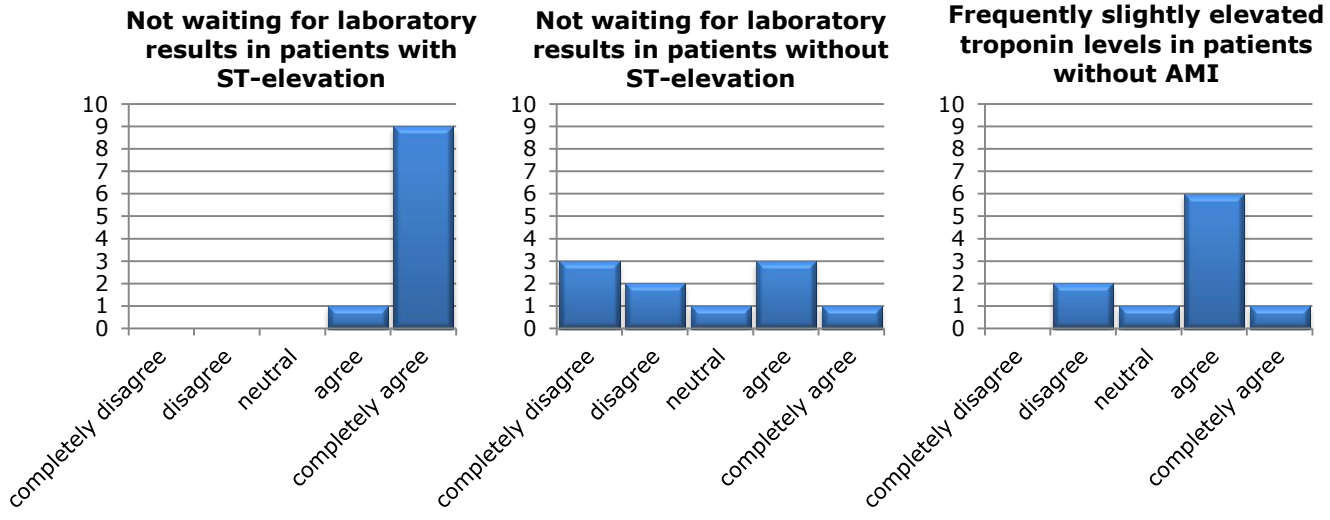

***Figure 6a-c**: bar graphs showing the number of respondents answering to wait for laboratory results in patients with or without ST-elevation on the ECG (6a-b), and the frequency of elevated troponin levels in patients without AMI (6c).*

3.3.1 IMPACT OF MULTIMARKER ASSAY ON TIME OF DISCHARGE

The following section describes the effectiveness of the multimarker compared to serial troponin measurement. As described previously, effectiveness is defined as the number of patients who are discharged following the laboratory result of either t0, t2, or t6. Remaining patients are discharged after overnight admission. The following table represents the number of patients that is discharged at each point in time, using the conventional troponin assay (gray bars) or using a multimarker assay with increasing analytical performance (green bars).

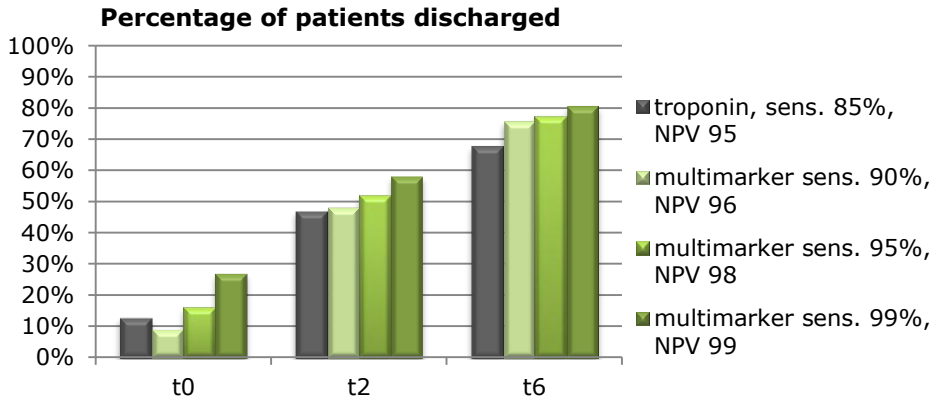

Figure 7: *effect of both serial troponin analysis (gray bars), and of each of the analytical performances of the multimarker assay (green bars) on time to discharge, showing the percentage of patients that is discharged following the available laboratory results, as estimated by the cardiologists.*

This figure illustrates how the multimarker assay might result in an increase in the percentage of patients that is discharged compared to serial troponin measurement. At t0, the decision whether or not to discharge a patient is based either on the troponin measurement, or on the result of the multimarker assay, with varying analytical performance. At t2 and t6, the decision to discharge a patient is based on additional troponin measurements.

3.4 INCREMENTAL COSTS OF THE MULTIMARKER ASSAY

The following section evaluates the incremental costs of the multimarker assay compared to conventional troponin measurement. First, the effect of the multimarker assay on the number of (diagnostic) activities that are performed will be shown. Following this, the total costs of each strategy are presented in table 2.

3.4.1 IMPACT OF MULTIMARKER ASSAY ON DIAGNOSTIC ACTIVITIES

This figure displays the impact of the multimarker assay on the number of (diagnostic) activities that are performed. This illustration indicates the decrease in both the number of exercise ECGs and catheterizations, and the amount of medication administered, as the analytical performance of the multimarker increases.

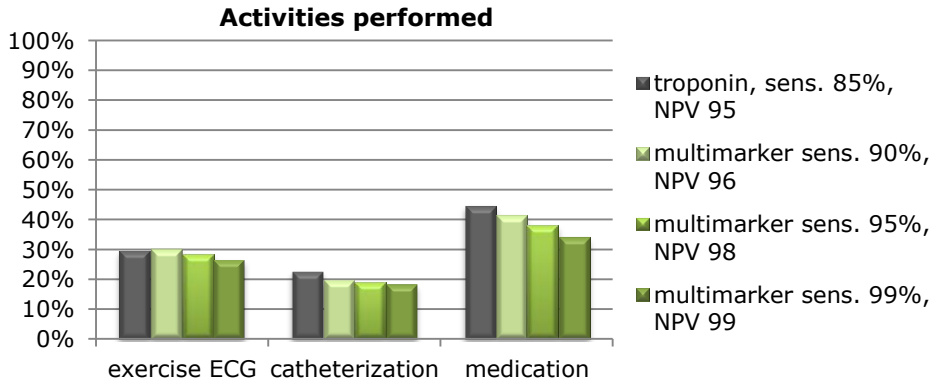

Figure 8: *in-hospital resource use as estimated by cardiologists, showing the percentage of patients in whom a catheterization or an exercise ECG is performed, and in whom medication is administered.*

3.4.2 IMPACT OF MULTIMARKER ASSAY ON DIRECT HOSPITAL COSTS

The table below lists the direct hospital costs (in 2012 Euros) for each of the three different strategies, subdivided according to the range of analytical performances, resulting in nine possible implementation scenarios. In the remaining chapters of this report, sensitivities of 90, 95, and 99% always correspond to NPVs of 96, 98, and 99% (as explained in section 3.2). First, results show decreasing costs as the analytical performance of the multimarker increases. Results also show that cost savings can be achieved when the multimarker (with a sensitivity of 99%), is implemented in addition to one additional troponin analysis at t2 (strategy II), and that more costs can potentially be saved when additional troponin analyses are performed at both t2 and t6 (strategy III).

Table 2: *costs of each treatment strategy, showing first the costs of serial troponin analysis, followed by the costs of replacing the serial troponin analysis for one multimarker assay at t0 (strategy I), the costs of the multimarker analysis with one additional troponin analysis at t2 (strategy II), and the costs of the multimarker analysis with additional troponin analyses at both t2 and t6 (strategy III).*

			Multimarker assay								
			Strategy I			Strategy II			Strategy III		
Cost driver	**Unit cost**	**Serial troponin analysis**	Sens. 90	Sens. 95	Sens. 99	Sens. 90	Sens. 95	Sens. 99	Sens. 90	Sens. 95	Sens. 99
Exercise ECG + assessment	€ 115.65	€34.36	€ 36.96	€ 35.06	€ 32.71	€ 36.96	€ 35.06	€ 32.71	€ 36.96	€ 35.06	€ 32.71
Medication	€ 9.09	€ 3.95	€ 4.01	€ 3.70	€ 3.33	€ 4.18	€ 3.87	€ 3.49	€ 4.31	€ 3.99	€ 3.58
ECG assessment	€ 17.91	€ 17.91	€ 17.91	€ 17.91	€ 17.91	€ 17.91	€ 17.91	€ 17.91	€ 17.91	€ 17.91	€ 17.91
Catheterization	€ 789.35	€ 179.72	€ 168.08	€ 161.88	€ 155.68	€ 179.62	€ 173.11	€ 164.24	€ 189.19	€ 181.25	€ 169.57
Conventional laboratory analysis t0	€ 56.65	€ 56.65	€ 0.00	€ 0.00	€ 0.00	€ 0.00	€ 0.00	€ 0.00	€ 0.00	€ 0.00	€ 0,00
Laboratory analysis multimarker t0	€ 73.23	€ 0.00	€ 73.23	€ 73.23	€ 73.23	€ 73.23	€ 73.23	€ 73.23	€ 73.23	€ 73.23	€ 73.23
Follow up troponin analysis t2 and/or t6	€ 23.78	€ 27.88	€ 0.00	€ 0.00	€ 0.00	€ 21.57	€ 19.94	€ 17.33	€ 31.44	€ 29.14	€ 25.38
Hospital stay		€ 668.51	€ 1142.61	€ 1069.45	€ 952.55	€ 786.01	€ 741.36	€ 666.53	€ 550.70	€ 522.68	€ 475.50
- 1 hour	€ 176.83										
- 3 hours	€ 335.66										
- 7 hours	€ 647.31										
- overnight	€1241.37										
Total		€ 988.98	€ 1442.80	€ 1361.24	€ 1235.41	€ 1119.48	€ 1064.48	€ 975.43	€ 903.66	€ 863.18	€ 797.80

3.5 INCREMENTAL COST-EFFECTIVENESS OF THE MULTIMARKER ASSAY

Following the costs and effectiveness of each scenario, the incremental cost-effectiveness ratio of each can be calculated. Therefore, first the number of patients that is discharged at either t0, t2, or t6 using either assay, is determined, followed by calculating the incremental effectiveness. After that, the incremental direct hospital cost of each strategy of the multimarker assay compared to serial troponin analysis are determined. Dividing the difference in costs by the difference in effectiveness of the competing interventions, results in the incremental cost-effectiveness ratio as reported in table 3. Strategy I, involving a multimarker assay at t0 (with a sensitivity of 90%), is dominated by the conventional troponin measurement.

Table 3: *incremental cost-effectiveness for each of the nine scenarios of the multimarker assay, compared to serial troponin measurement.*

			Effectiveness (# of patients discharged)		Incremental effectiveness	Costs (€)	Incremental costs	ICER
Serial troponin analysis			t0:	130	-	€ 988.98	-	-
			t2:	471				
			t6:	678				
Multimarker assay	**Strategy I**	Sens. 90%	t0:	93	-37	€ 1442.80	€ 453.82	-12.335
		Sens. 95%	t0:	161	32	€ 1361.24	€ 372.26	11.658
		Sens. 99%	t0:	271	142	€ 1235.41	€ 246.43	1.738
	Strategy II	Sens. 90%	t2:	485	14	€ 1119.48	€ 130.50	33.167
		Sens. 95%	t2:	522	51	€ 1064.48	€ 75.50	7.289
		Sens. 99%	t2:	586	115	€ 975.43	- € 13.56	- 2.150
	Strategy III	Sens. 90%	t6:	758	80	€ 903.66	- € 85.32	- 5.683
		Sens. 95%	t6:	776	98	€ 863.18	- € 125.80	- 3.793
		Sens. 99%	t6:	808	130	€ 797.80	- € 191.18	- 1.902

3.6 COST-EFFECTIVENESS PLANE

A cost-effectiveness plane shows the relationship between costs and effects of a new intervention compared to a standard intervention[71]. Figure 9 represents the cost-effectiveness of each of the nine scenarios of implementing the multimarker assay, compared to conventional serial troponin measurement is shown.

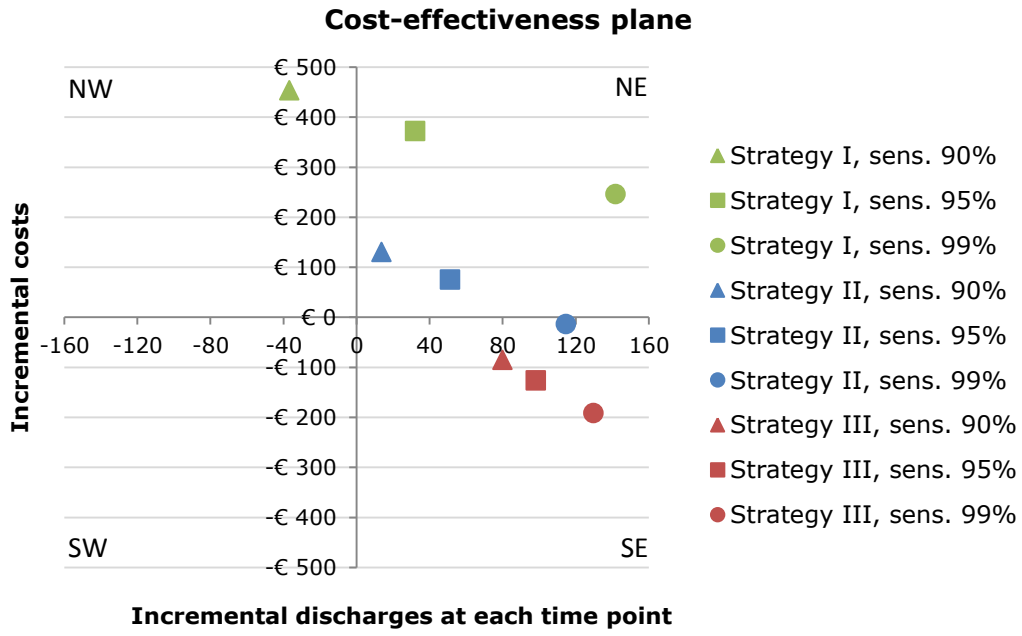

Figure 9: *cost-effectiveness plane showing the ICER of each of the nine scenarios.*

The cost-effectiveness plane is often employed for decision making under uncertainty and is divided into four quadrants. Scenarios that fall into one of the two quadrants on the right side of the y-axis indicate increasing effectiveness, meaning that more patients are discharged at an earlier time point, while a less effective strategy will fall in the left halve of this plane. Similarly, an intervention that comes at additional cost falls above the x-axis, while an intervention with lower costs will fall below this axis. Consequently, a strategy that is more effective but comes at additional costs will fall in the northeast quadrant (NE). Also, a strategy that is both more effective and cost-saving, lies in the southeast quadrant (SE), and is named a 'dominant' scenario compared to the competing intervention[71].

The plane in figure 9 visualizes the desirability of each of the scenarios. First, the ICER resulting from only a multimarker analysis at t0, with a sensitivity of 90%, falls in the NW quadrant. This indicates a lower number of patients that are discharged, while resulting in higher costs. The ICERs located in the NE quadrant refer to only a multimarker analysis at t0, with a sensitivity of 95 and 99% (strategy I), and from the multimarker analysis with sensitivities of 90 and 95%, combined with one additional troponin measurement at t2 (strategy II). These ICERs indicate a higher discharge of patients, but at additional cost. However, the ICERs in the SE quadrant, refer to a multimarker analysis with both a sensitivity and NPV of 99% combined with one additional troponin measurement at t2 (strategy II), and from all expected analytical performances of the multimarker assay with additional troponin measurements at both t2 and t6 (strategy III). These four scenarios are considered dominant compared to the current serial troponin measurement.

3.7 SENSITIVITY ANALYSIS

Sensitivity analysis is a valuable tool to deal with uncertainty in the model. To estimate the robustness of the model to changes in input variables, a deterministic sensitivity analysis is performed. This analysis will involve a one-way sensitivity analysis, in which each variable at the time is changed over its expected range, and the accompanying effect is observed. Next, best and worst case scenarios are constructed to evaluate the best and worst outcome of all nine scenarios. These results are displayed in a cost-effectiveness plane. Subsequently, the influence of costs of the multimarker assay on the ICER will be evaluated. Because the costs of these two additional assays are highly uncertain, the maximum costs to achieve equal cost-effectiveness as the current troponin measurement will be determined.

3.7.1 ONE-WAY SENSITIVITY ANALYSIS

The robustness of the model to changes in one variable, is determined by individually changing each variable over its range to obtain estimates of the accompanying ICER. Concerning the estimates of discharging patients and performing activities, the lower and upper limits are obtained from 95% confidence intervals of the percentages obtained from the questionnaire. Variation in unit costs which are obtained from the Dutch Health Authority, are estimated to be 5% above or below the reported value. These consider the costs of an exercise ECG, a catheterization, an ECG assessment, the conventional laboratory assay at t0, and the costs for the follow up assay at t2 and/or t6.

Costs for medication are considered uncertain, because the exact dose as well as the exact type of medication may show variations per hospital and per patient, and are therefore considered to vary with a maximum of 50% below or above the estimated value. In addition, the costs for MPO and copeptin measurement are uncertain as well. Assuming that it is unlikely that these measurements will cost less than a troponin measurement, the lower limit was set at 95% of the cost of one conventional troponin measurement at t0. However, the maximum cost may, when the measurements require specific laboratory equipment, involve much higher cost. Therefore, it is assumed that the cost of the new analyses, especially shortly after implementation, may be twice the estimated cost. Finally, because no literature

was available about costs of several hours stay at the CPU, these values were estimated to be moderately uncertain. Consequently, the lower and upper limit were estimated to be 25% below or above the estimated unit cost. All variables and the lower and upper limits are enclosed in appendix IV.

Because implementation of the multimarker assay is expected to bring the greatest benefit when it is implemented in addition to the current troponin analysis, as visualized in the cost-effectiveness plane, only the results of strategy III are shown in the table below. Also, only the variables that show the strongest change by varying it over its range are shown. A complete overview of one-way sensitivity analysis of all variables is enclosed in appendix V.

Table 4: *results of one-way sensitivity analysis, showing the change in the ICER in Euros. The variables are divided in four categories (performance laboratory assays, costs, activities, and discharge). Red compartments indicate increasing costs compared to the current setting. Green compartments indicate lower costs. The more intense the color the greater the influence on the ICER.*

	Strategy III					
	Sensitivity 90%		Sensitivity 95%		Sensitivity 99%	
	lower	upper	lower	upper	lower	upper
Performance laboratory assays						
Specificity troponin t0 (%)	-€66,70	€10,18	-€66,69	€10,17	-€66,76	€10,18
Specificity multimarker t0 (%)	€16,28	-€15,04	€32,75	-€31,17	€59,01	-€56,91
Costs						
Costs multimarker assay t0	-€3,66	€73,23	-€3,66	€73,23	-€3,66	€73,23
Costs until hospital discharge t24	€49,12	-€49,12	€53,04	-€53,03	€59,93	-€59,94
Activities						
Exercise ECG (%), serial troponin, negative at t0	-€27,21	€27,21	-€27,21	€27,21	-€27,21	€27,21
Catheterization (%), serial troponin, negative at t0	€102,17	-€102,17	€102,17	-€102,17	€102,17	-€102,17
Catheterization (%), multimarker negative at t0	-€28,41	€28,41	-€30,64	€30,64	-€33,60	€33,59
Discharge						
Discharge (%), serial troponin, negative at t0, exercise ECG negative	-€30,67	€30,67	-€30,67	€30,68	-€30,68	€30,67
Discharge (%), multimarker, negative at t0, without exercise ECG	€23,07	-€23,07	€37,82	-€37,82	€53,51	-€53,51

As this table shows, the ICER is most strongly influenced by changes in the number of catheterizations that are performed, in this case specifically for a negative troponin analysis at t0. This indicates that, if the multimarker assay leads to a relative decrease in the percentage of catheterizations performed, large cost savings can be achieved.

Secondly, the costs of the multimarker assay at t0 are very important. Because the costs might be much higher than estimated in the current analysis, the uncertainty in costs of this variable might strongly influence the ICER in a negative way for the multimarker assay. These will be further discussed in the next paragraph.

Other variables that show much variance in this one-way sensitivity analysis are the costs until hospital discharge after 24 hours, and the specificity of both troponin and the multimarker at t0.

3.7.2 BEST WORST CASE SCENARIOS

To estimate how the incremental cost-effectiveness of each scenario might change due to changes in all variables, best and worst case scenarios are determined. First, each variable is changed individually over its range. The accompanying effect, either a fall or rise in the ICER, is determined. Subsequently, each variable is first changed for each scenario in the way that affects the ICER negatively. After that, each variable is changed in the way that affects the ICER positively. The table below shows the result of this analysis.

Table 5: *best and worst case scenarios for each of the nine implementation scenarios, showing the difference in cost, the difference in the number of patients that is discharged, and the ICER, for both the worst and best case scenarios.*

		Worst case scenarios			Best case scenarios		
Strategy	**Sensitivity (%)**	**Incremental effectiveness**	**Incremental costs**	**ICER**	**Incremental effectiveness**	**Incremental costs**	**ICER**
I	**90**	282	-€ 382,78	**-1,36**	-333	€ 1.344,88	**-4,04**
	95	412	-€ 526,67	**-1,28**	-308	€ 1.257,89	**-4,08**
	99	585	-€ 680,94	**-1,16**	-269	€ 1.219,91	**-4,53**
II	**90**	235	-€ 365,55	**-1,56**	-241	€ 886,01	**-3,68**
	95	288	-€ 443,83	**-1,54**	-222	€ 881,28	**-3,97**
	99	360	-€ 600,64	**-1,67**	-185	€ 811,36	**-4,39**
III	**90**	415	-€ 731,34	**-1,76**	-61	€ 344,21	**-5,64**
	95	349	-€ 849,14	**-2,43**	-57	€ 306,32	**-5,37**
	99	405	-€ 990,58	**-2,45**	-1	€ 231,24	**-231,24**

To visualize these results, a cost-effectiveness plane is used. Green symbols in the plane represent best case scenarios, while red symbols represent worst case scenarios.

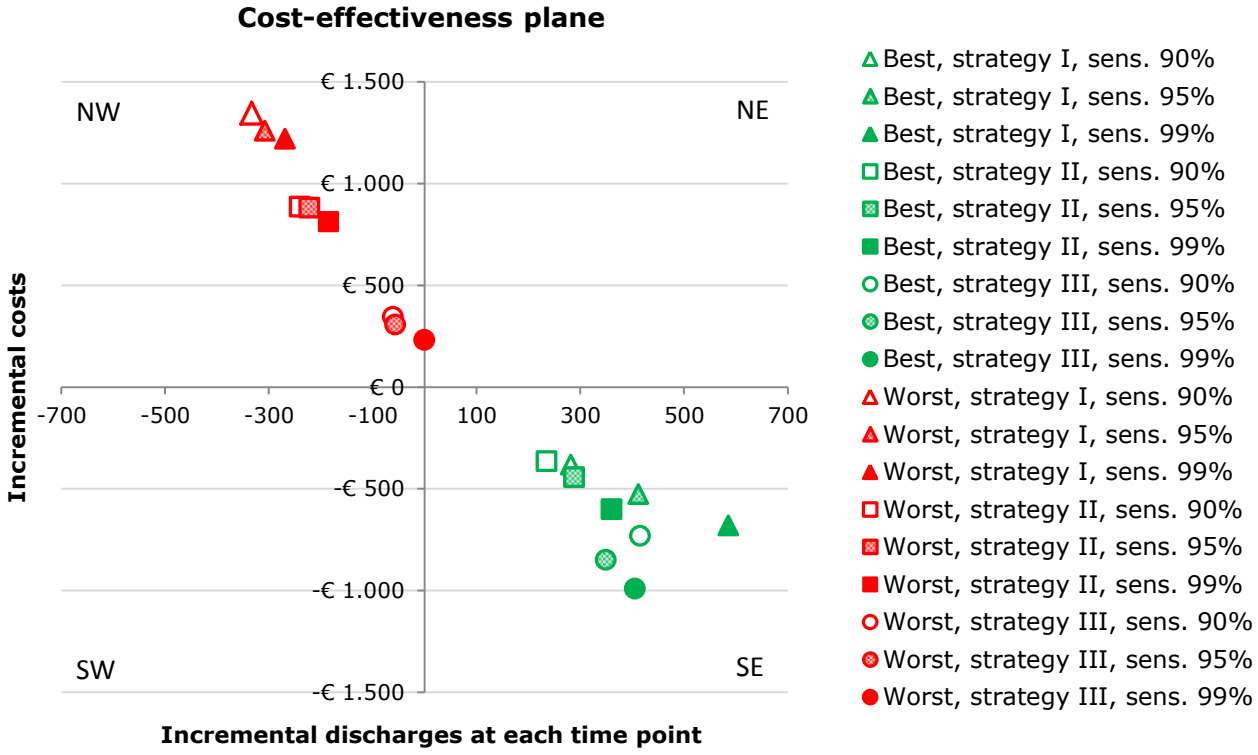

Figure 10: *cost-effectiveness plane showing the best and worst case scenarios for each nine implementation scenarios of the multimarker assay.*

The cost-effectiveness plane of the best and worst case scenarios shows two important findings. Assuming that a sensitivity and NPV of both 99% can be achieved with the multimarker assay, combined with two additional troponin measurements, this would in the best case scenario imply a cost saving of €990,58 per patient attending the CPU with symptoms suggestive of ACS. Concerning the accompanying effectiveness, this would imply that 405 out of 1000 patients are being discharged more early compared to the current work-up. In the worst case scenario, this same strategy would come at additional cost of €231.24 per patient, and a decrease in discharge with 1 patient out of 1000. As the figure illustrates, great variation is observed between the worst and best case scenarios. Furthermore, mainly the worst case scenarios show that each of the three strategies is almost independent of the sensitivity and NPV of the multimarker assay.

3.7.3 COSTS LABORATORY ASSAY

One-way sensitivity analysis showed that the costs of the multimarker assay are very influential on the ICER. Since the competing intervention in this study actually concerns the implementation of this multimarker assay, the variation that is acceptable in this variable is determined. To achieve this, it is assumed that the competing intervention will be implemented as long as the expected cost of the multimarker assay do not exceed the cost of the current serial troponin assays. Cost of the multimarker assay were raised up to the point where the difference in cost between the competing strategies equals zero. Because the third strategy of implementing the multimarker analysis in addition to the serial troponin measurement (at t2 and t6) are expected to be most cost-effective, only the three scenarios from this strategy will be evaluated.

However, both the multimarker assay and the conventional troponin measurement at t0 involve the measurement of additional laboratory markers, which are not specific to the heart. Therefore, the difference in maximum cost of the multimarker assay and the conventional measurement at t0 are determined, to obtain the maximum cost of both MPO and copeptin measurement in excluding NSTEMI.

Following this, because either the current or the new multimarker assay will be performed in all patients who present at the CPU with symptoms suggestive of ACS, patients who are diagnosed with AMI (both STEMI and NSTEMI) need to be included as well. According to Murphy et al, 2004, about 43% of people who are suspected of ACS have a discharge diagnosis of AMI[72]. Therefore, the costs for performing these analyses in patients with AMI (both STEMI and NSTEMI) are also included, to calculate the maximum cost of both MPO and copeptin measurement for excluding NSTEMI in all patients presenting with symptoms suggestive of ACS at the CPU. The results of this analysis are shown in table 6.

Table 6: *maximum cost of laboratory assays for strategy III. The second column shows the maximum cost of the complete multimarker assay. The next column shows the maximum cost of the multimarker minus the cost of conventional troponin measurement at t0. The last column shows these additional costs, including costs of laboratory assays performed in AMI patients (both STEMI and NSTEMI).*

Strategy III	Maximum cost	Additional cost (AMI patients excluded)	Additional cost (AMI patients included)
Sensitivity 90 %	€ 158.55	€ 101.90	€ 94.77
Sensitivity 95%	€ 199.03	€ 142.38	€ 135.25
Sensitivity 99%	€ 264.41	€ 207.76	€ 200.63

This table shows that costs for both MPO and copeptin measurement together, can raise up to €94.77, €135.25, and €200.63, for a multimarker analysis with a sensitivity of 90, 95, or 99% respectively, when AMI patients are included. Because such high cost for MPO and copeptin are assumed not to be realistic, especially in the long term, this indicates that cost savings are likely to be achieved by the implementation of this multimarker assay, following the third strategy.

4. DISCUSSION AND CONCLUSION

This economic analysis evaluates the incremental cost-effectiveness of a multimarker assay compared to serial high-sensitive troponin measurement, for earlier exclusion of NSTEMI at the CPU. By means of a literature analysis and semi-structured interviews, the main issues that arise with the current high-sensitive troponin assay have been determined. These issues mainly involve the need for serial troponin measurement before NSTEMI can be excluded, and the occurrence of slightly elevated troponin levels in patients without a myocardial infarction. The semi-structured interviews revealed an additional issue, which is the limited role of a troponin result in diagnosing a myocardial infarction. However, this issue might be a consequence of the two previous issues, which limit the usefulness of this laboratory assay, and thereby enhances the need for biomarkers with higher analytical performance. Therefore, the potential impact of a more sensitive assay was estimated based on a questionnaire, focusing both on the impact on resource use and a patient's discharge. Using decision tree analysis, the cost-effectiveness has been evaluated for nine scenarios. These include three implementation strategies, each involving three levels of analytical performance.

Results of the questionnaire indicate that in the current setting, 13.0% of all patients suspected of ACS are discharged from the CPU following a negative troponin result at t0. The multimarker assay could increase these discharge rate up to 27.1% (for a multimarker with a sensitivity and NPV of both 99%). Consequently, the percentage of patients without NSTEMI that is admitted overnight might decrease from 32.2% to 19.4%. Because costs of hospital stay, in the current setting, involve 67.6% of direct hospital costs, it is essential to reduce admission times to achieve cost savings. Similar findings are reported in a study by Forberg et al, 2006. They found that admission times account for two third of direct hospital costs for chest pain patients attending the ED[47]. Based on these results, we estimate that, when a sensitivity and NPV of 99% of the multimarker assay can be achieved, combined with two additional troponin assays, costs of hospital stay can decrease with 8.0%.

Although a very high sensitivity and NPV is most desirable, a small increase in analytical performance of the multimarker assay, when implemented in addition to troponin measurements at t2 and t6, is expected to be cost-effective compared to the current setting. The direct hospital costs per patient suspected of ACS at the CPU, in the current setting, are estimated to be €988.98. Due to the multimarker assay, costs could decrease to €903.66, €863.18, or €797.80, corresponding with a sensitivity of 90, 95, and 99% respectively. This indicates cost savings of respectively 8.6, 12.7, and 19.3%.

Although no studies have already reported the analytical performance of this multimarker assay, several studies have examined the diagnostic accuracy of a dual marker strategy, combining copeptin with a troponin measurement[42, 70, 73-75]. A recent study by Keller et al, reports a sensitivity of 98.3% and NPV of 99.0% for this combination in patients presenting within three hours after chest pain onset[42]. Because the current study involves the addition of a third assay (MPO), it is likely that the same sensitivity, or even higher, is a realistic expectation. Assuming this analytical performance, combined with additional troponin measurements at t2 and t6 (strategy III), this is expected to result in an additional discharge of 130 patients per 1000, with accompanying cost savings of €191.18 per patient.

Assuming that the multimarker assay results in a sensitivity of at least 90%, we conclude that this assay combined with troponin assays at t2 and t6, is a dominant strategy compared to conventional serial troponin measurement. As expected, the scenarios with the highest analytical performance of the multimarker assay offer the greatest cost savings. Estimating that 108.000 people in the Netherlands each year present at the CPU with chest pain, costs savings could range from 5 up to almost 12 million Euros per year following the implementation of this multimarker assay[76, 77].

4.1 INTERPRETATION OF THE RESULTS

To estimate the robustness of the model to changes in input variables, both one-way sensitivity analysis and best worst case scenarios are performed. One-way sensitivity analysis indicates that the changes in the variable for which this analysis is most sensitive, is the percentage of catheterizations that are performed in the current setting, with a negative troponin result at t0. This indicates the large impact of catheterization on direct hospital costs. Therefore, a multimarker assay which can contribute to a decrease in the number of unnecessary catheterizations that are performed, could imply great cost savings.

Considering the costs of these catheterizations, some influences might not have been taken into account. First, the costs of complications due to the procedure have not been included in this analysis. However, because of the low complication rate (about 0.8%), this is unlikely to have great influence on the results[78, 79]. Moreover, because the multimarker assay is expected to decrease the number of catheterizations that are performed in patients without NSTEMI, the accompanying decrease in complications will make the multimarker assay an even more cost-effective intervention. Also, costs of antithrombotic drugs after cardiac catheterization have not been included in this analysis. However, this is expected to have a similar effect, although these costs are expected to be minimal.

Besides the changes in the number of catheterizations performed, the model is also sensitive to changes in the costs of the multimarker assay. Especially the potentially higher cost of this assay are influential on the ICER. However, results have indicated that, in the third strategy, costs of the multimarker assay can increase strongly, while still retaining a cost-effective scenario.

Another issue to keep in mind when interpreting these results, is that the analytical performance of diagnostic measures requires a trade-off between sensitivity and specificity. Consequently, if high sensitivity is desired, this mostly comes at cost of the specificity[80]. In the current analysis, the specificity in the decision model might not correlate with the sensitivity of the multimarker in the questionnaire. Because the sensitivity of the multimarker is estimated to be at least 99% (based on the study by Keller et al, 2010[42]), the lower sensitivities in the questionnaire are expected to correlate with higher specificities. Following this, because sensitivity analysis shows that an increase in specificity will strongly affect the ICER in favor of the multimarker assay, this is assumed not to be a problem.

Considering the best and worst case scenarios, results indicate that great cost savings can be achieved in all best case scenarios. Also, these are accompanied by a large increase in effectiveness. However, this plane shows strong differences in costs between the best and worst case scenarios. These are not strongly dependent on the sensitivity of the multimarker assay, but instead on the choices that are made by cardiologists. Since the percentages estimated in the questionnaire vary strongly between cardiologists, this indicates a major source of uncertainty in the model. However, the worst case scenario corresponding to a multimarker with a sensitivity and NPV of 99%, combined with two additional troponin measurements, is expected to come at higher cost, but only a minor decrease in effectiveness. This can be considered an acceptable risk to take.

4.2 STRENGTHS

A study by Twerenbold et al, 2010, evaluates the economic impact of a dual marker strategy, combining a copeptin and high-sensitive troponin measurement[81]. Recently however, a report by the Evidence Adoption Centre (EAC) has been published, in which the evidence supporting the implementation of the copeptin measurement is reviewed. This report describes that a major limitation of the study by Twerenbold et al concerns the lack of patient outcome data[82]. It is argued that the authors only assess the analytical performance of the dual marker strategy, but do not take into account how the pathway of care a patient receives is affected. However, it cannot be assumed that a better laboratory assay will automatically

impact a patient's clinical pathway. Therefore, one of the main strengths of this analysis is, that this is the first study evaluating the impact of an improved laboratory analysis on both the time until the diagnosis NSTEMI is excluded (and the patient is discharged), and the number of activities that are performed.

Another strength of this analysis is the generalizability of the results to the use of other cardiac markers. Although the principle of both copeptin and MPO has been explained to the cardiologists prior to having them fill in the questionnaires, it is likely that the results can be generalized to the use of other cardiac markers as well, because only the analytical performance of the markers was included in the questionnaire, without mentioning the specific markers. In addition, during the interviews it became clear that there is especially a high need for cardiac markers which are elevated very early after a myocardial infarction. Therefore, results of this questionnaire might also be used for other markers with similar or better performance than the ones described in this study.

In this study, the specificity of the multimarker has been calculated by multiplying the individual specificities as described by Schoenbach, 2004[80]. However, in the EAC report it is mentioned that the accuracy of two stand-alone tests is lower than the combination of these two tests[82]. Consequently, the analytical performance of the multimarker assay is likely to be higher than reported in this analysis. Following this, a higher specificity will affect the ICER in favor of implementing the multimarker assay.

4.3 LIMITATIONS

There are some practical issues with the model used in this study. First, cardiologists mentioned difficulties with filling out the questionnaire, because of the theoretical approach of this analysis. This problem was observed in the results obtained, because very large variations were observed between the estimated percentages. The main reason for this issue is that this study describes an early economic evaluation, indicating that not all input parameters could be determined with high accuracy. However, the aim of this early evaluation is primarily to give an indication whether more sensitive laboratory analyses are expected to be valuable in the early exclusion of NSTEMI. Thus, although the analysis is in favor of implementing the multimarker assay, these results shown should be interpreted carefully.

Also, it was assumed that a sensitivity of the multimarker of either 90, 95, or 99% correlates with a sensitivity of 80, 90, and 99% respectively for the combination of copeptin and MPO, in case of a slightly elevated troponin. However, there is no literature describing the combined performance of copeptin and MPO, and therefore this might not have been an accurate estimation. However, one-way sensitivity analysis shows that the variations in the analytical performance of MPO and copeptin (in case of a slightly elevated troponin), will not strongly influence the ICER. Therefore, this is unlikely to change the conclusion of this study.

One assumption of the model is that the diagnosis NSTEMI is correctly excluded in all patients, regardless of the analysis that is used. This assumption is based on the strong risk-averse approach when discharging patients suspected of ACS from the CPU, which came up during the semi-structured interviews. However, it is not certain that no patients with NSTEMI will be discharged. Also, because of this assumption, the accompanying adverse health effects that might occur, could not be investigated in this early evaluation.

One aspect that has not been included in the questionnaire, is the influence of abnormalities on the ECG other than ST-elevation. For instance, ST-depression might also be observed, and might also influence the treatment pathway of these patients. However, due to the explorative nature of this research, these aspects could not all be evaluated. Besides, cardiologists were asked what percentage of patients they would discharge based on the combined results of the laboratory analyses at t0, and the exercise ECG. However, it is unrealistic that an exercise ECG is performed before the laboratory result of t0 is available.

5. RECOMMENDATIONS

5.1 IMPLICATIONS FOR PRACTICE

Besides the expected earlier exclusion of NSTEMI, the rapid increase of MPO and copeptin compared to troponin might also contribute to earlier detection of NSTEMI[42, 43, 45, 67, 69, 70]. Thereby, the multimarker might allow earlier treatment initiation. Although not much research has been performed in this area, one study by Núñez-Gil et al, 2010, has suggested the possible more favorable outcome following early treatment of NSTEMI patients[83].

Another important implication for practice, is the extra effort of cardiologists that might be required. In 1996, Howard et al published a report in which the important role of the doctor in reassuring patients is described[84]. However, earlier patient discharge might come at the cost of properly reassuring patients that they are not having a myocardial infarction. This might imply that improperly reassured patients come back to the CPU soon, thereby raising hospital cost.

During the semi-structured interviews, it was observed that cardiologists are skeptical considering new laboratory analyses. Even after explaining the principle of both the MPO and copeptin assay, as well as the expected analytical performance, a frequent response of the cardiologists was "I don't know these new assays". This implies that they first have to experience the new markers themselves, like "seeing is believing". One cardiologist mentioned the same phenomenon shortly after the introduction of troponin. Initially, the cardiologists did not believe that troponin would be of much added value to the assays that were used at that time. By now however, troponin is included in the general guidelines for diagnosing AMI[2]. Therefore, if these two markers will be implemented in practice, it is assumed that it will take a few years before the full effect can be observed.

Also, cardiologists from both the JBZ and MST currently use the GRACE risk score in determining a patient's risk of having a myocardial infarction. This score includes many factors, in which the influence of a troponin assay is very limited. However, because the sensitivity of troponin at the time of a patient's entrance at the CPU is estimated to be about 86%, this might explain the limited relevance of this marker. On the contrary, if this multimarker assay can increase this sensitivity to 99%, the influence of cardiac markers on this risk score might need to be re-evaluated.

5.2 IMPLICATIONS FOR FURTHER RESEARCH

5.2.1 ASPECTS NOT EVALUATED IN THIS EARLY EVALUATION

Another issue that should be taken into consideration is the costs of catheterizations in case of ACS. Studies have already recommended cardiac catheterizations in some cases of ACS, because early intervention might decrease the risk of myocardial infarction[85]. This potential effect of the multimarker assay on early treatment of ACS needs to be investigated. Also, MPO is known to be an early marker of inflamed atherosclerotic plaques and UA, which might contribute to early detection of vulnerable plaques, thereby allowing earlier treatment[86]. The consequences of these two issues should be investigated in further research.

One aspect that has not been included in this study, is the effect of the addition of a MPO and copeptin measurement on the number of patients that are diagnosed with other conditions, including UA. Because this effect is difficult to estimate from literature, and because MPO and copeptin are both less specific markers for diagnosing myocardial infarction than troponin, further research is necessary to evaluate the accompanying effects of this implementation.

Another aspect that is difficult to include in this study, is the actual cost savings that are achieved following the implementation of this multimarker assay. For instance, earlier discharge of a patient is not directly going to lead to cost savings, as long as the occupancy of

the CPU will not change. As long as the capacity of the ward is not used optimally, these cost savings will not actually be achieved. Therefore, it should be evaluated how the multimarker assay might make changes in occupancy possible. However, this can only be fully evaluated after the actual implementation. Also, data regarding patient flow at the CPU are required for this estimation.

5.2.2 RECOMMENDATIONS CONSIDERING DATA COLLECTION

Another recommendation for future research is to stratify patients according to time since chest pain onset. Mainly because MPO and copeptin rise very early after a myocardial infarction, and decrease within a few hours, the multimarker assay might be more effective when implemented for patients with a recent onset of chest pain (within three hours)[40, 42, 43].

To validate the results of the questionnaire, it is recommended to interview more cardiologists from more hospitals. In this analysis, respondents were derived from both the JBZ (Den Bosch) and the MST (Enschede). However, although these hospitals both have a 24 hour cardiac catheterization unit, these coronary care units differ in size and in years of experience with these interventions. Therefore, differences in the relative importance of an exercise ECG and the laboratory assays in excluding NSTEMI are observed. Also, MST mostly uses two high-sensitive troponin T analyses to exclude NSTEMI, while the JBZ mostly uses three high-sensitive troponin I analyses. These differences might have influenced the results obtained in the questionnaire. Therefore, future research should aim at achieving a more representative group of respondents.

5.2.3 RECOMMENDATIONS FOR CLINICAL EFFECTIVENESS STUDIES

Furthermore, for determining the analytical performance of this multimarker assay in practice, it is recommended to use the combined result of the ECG, a patient's clinical characteristics, and the troponin result for setting the diagnosis, as recommended by Thygesen et al, 2007[2]. Using only troponin as gold standard might, because this marker is not 100% accurate, lead to selection bias because patients are incorrectly diagnosed.

Also, when performing such a study, the most suitable threshold values for all three markers need to be determined. Because this threshold value requires a trade-off between sensitivity and specificity, care should be taken to achieve a multimarker assay with a high NPV, because cardiologists focus on excluding NSTEMI with high certainty. Following this, if the optimal values for each marker can be determined, more specific data regarding the analytical performance of the markers can be obtained.

As described previously, Keller et al, 2010, reported that addition of copeptin to the high-sensitive troponin I assay might increase the sensitivity at t0 from about 86% to 98.3%[42]. The accompanying specificity is 63.2%. Imputing this specificity into the model of this study, and assuming a sensitivity of 99% at t0, and additional laboratory analyses at t2 and t6, results in a cost savings of €251,57, with 158 patient's being discharged more early. With the current multimarker assay, a specificity of 42.8% is achieved, with €191,18 saved and 130 patients discharged more early. Therefore, addition of the MPO measurement decreases specificity that much, that it should be considered whether it might be more cost-effective not to add this cardiac marker to the multimarker assay at t0[80].

5.2.4 RECOMMENDATIONS FOR FUTURE DEVELOPMENT OF CARDIAC MARKER ASSAYS

Another implication for further research concerns the further development of bedside (point-of-care) tests for use at the CPU. The interviews revealed that waiting one hour for the laboratory results is considered too long for patients who are at high risk of having ACS. Mainly in these patients, real improvements with better laboratory analyses can only be made when the results will be instantly available.

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APPENDIX I: LIST OF ABBREVIATIONS

Abbreviation:	Meaning:
ABC	Activity Based Costing
ACS	acute coronary syndrome
AMI	acute myocardial infarction
CAD	coronary artery disease
CEA	cost-effectiveness analysis
EAC	Evidence Adoption Centre
ECG	electrocardiogram
ED	emergency department
CPU	chest pain unit
JBZ	Jeroen Bosch Ziekenhuis
hsTnI	high-sensitive troponin I
hsTnT	high-sensitive troponin T
ICER	incremental cost-effectiveness ratio
MPO	myeloperoxidase
MST	Medisch Spectrum Twente
PCI	percutaneous coronary intervention
NICE	National Institute for Health and Clinical Excellence
NPV	negative predictive value
NSTEMI	non ST-elevation myocardial infarction
NZA	Nederlandse Zorg Autoriteit
PPV	positive predictive value
STEMI	ST-elevation myocardial infarction
UA	unstable angina
WHO	World Health Organization

APPENDIX II: MEASURES OF DIAGNOSTIC TEST PERFORMANCE

Glossary of Diagnostic Accuracy Study Terminology
(adapted from Whiting *et al.* (2004))

Simple 2 x 2 diagnostic test result table: measures of diagnostic test performance

		Disease state	
		Positive	Negative
Test result	Positive	**a**	**b**
	Negative	**c**	**d**

Glossary of terms:

Index test	The new test under investigation.
Reference standard	Best available test(s) for diagnosing the target disease. Diagnostic accuracy studies assume this is 100% accurate, and therefore the index test cannot be shown to be more accurate.
True positive	Number of people with the disease and a positive test result (a).
True negative	Number of people without the disease and a negative test result (d).
False positive	Number of people without the disease and positive test result (b).
False negative	Number of people with the disease and a negative test result (c).
Sensitivity	a/(a+c), proportion of people with the disease who have a positive test result.
Specificity	d/(b+d), proportion of people without the disease who have a negative test result.
Positive Predictive Value (PPV)	a/(a+b), probability of disease among all people with a positive test result.
Negative Predictive Value (NPV)	d/(c+d), probability of non-disease among all persons with a negative test result.

APPENDIX III: QUESTIONNAIRE

Enquête

Een multimarker analyse ten behoeve van snel uitsluiten van een acuut myocard infarct

ALLE ANTWOORDEN ZIJN VERTROUWELIJK EN ANONIEM.

De resultaten van de vragenlijst zullen worden samengevat en zullen gebruikt worden ten behoeve van de mogelijke implementatie van twee nieuwe laboratoriumanalyses voor de diagnose acuut myocard infarct op de Eerste Hart Hulp van het Jeroen Bosch Ziekenhuis.

Om een waarheidsgetrouw beeld te krijgen van de mogelijke gevolgen van de invoering van deze nieuwe laboratoriumanalyses, is het van belang dat deze enquête zo nauwkeurig mogelijk wordt ingevuld. Uw persoonlijke mening en ervaring is van belang, er zijn geen goede of slechte antwoorden. De enquête zal ongeveer 10 minuten in beslag nemen.

Michelle M.A. Kip

Student Health Sciences, Universiteit Twente

1. Wat is uw huidige functie binnen de cardiologie van het JBZ:

○ Cardioloog — Ga verder met vraag 3.

○ AIOS — Ga verder met vraag 2.

○ Anders, namelijk [ ] — Ga verder met vraag 2.

2. Hoeveel maanden ervaring heeft u met het specialisme cardiologie?

[ ] maanden

3. Wat is uw mening over de volgende stelling (vink het gekozen antwoord aan):
Indien een patiënt op de Eerste Hart Hulp binnenkomt met symptomen van ACS en ST-elevaties op het ECG, acht ik het niet noodzakelijk om op de laboratoriumuitslagen te wachten alvorens behandeling te starten.

○	○	○	○	○
geheel oneens	tamelijk oneens	neutraal	tamelijk eens	geheel eens

Alle onderstaande vragen hebben betrekking op patiënten met een ECG dat geen ST-elevaties vertoond.

4. Wat is uw mening over de volgende stelling (vink het gekozen antwoord aan):
Indien een patiënt op de Eerste Hart Hulp binnenkomt met symptomen van ACS, zonder ST-elevaties op het ECG, acht ik het niet noodzakelijk om op de laboratoriumuitslagen te wachten alvorens behandeling te starten.

○	○	○	○	○
geheel oneens	tamelijk oneens	neutraal	tamelijk eens	geheel eens

5. Wat is uw mening over de volgende stelling (vink het gekozen antwoord aan):
De huidige troponine bepaling geeft regelmatig licht verhoogde uitslagen (0.045 – 0.099 ng/mL) bij patiënten die geen acuut myocard infarct hebben.

○	○	○	○	○
geheel oneens	tamelijk oneens	neutraal	tamelijk eens	geheel eens

6. Wordt een patiënt met een licht verhoogde troponine uitslag (0.045 – 0.099 ng/mL) altijd gerapporteerd als een acuut myocard infarct?

○ Ja. Ga verder met vraag 8.

○ Nee. Ga verder met vraag 7.

7. In welk percentage van alle patiënten die zich met symptomen van ACS melden op de Eerste Hart Hulp, met minstens één licht verhoogde troponine uitslag (0.045 – 0.099 ng/mL), is naar uw schatting de uiteindelijke diagnose dat de patiënt geen acuut myocard infarct heeft?

_____ %

8. Onderstaande tabel toont troponine uitslagen op t = 0, t = 2, en t = 6 uur, bij patiënten met symptomen van ACS, zonder ST-elevatie. Probeert u in te schatten welk percentage van elk van deze patiënten u, op basis van onderstaande bevindingen, zult ontslaan of nog zal laten blijven en vink het gekozen antwoord aan.

   NB:
   - Patiënten met labuitslagen op t = 2 en/of t = 6 zijn dus patiënten die **niet** zijn ontslagen op basis van eerdere labuitslagen.
   - Licht verhoogde troponine uitslag: 0.045 – 0.099 ng/mL.

   Voorbeeld: indien u bij patiënten zonder ST-elevatie, zonder fietstest uitgevoerd, bij een negatieve troponine op t = 0 en t = 2 verwacht ongeveer 16% van deze patiënten te ontslaan, vinkt u dan in de desbetreffende kolom het rondje '0-25%' aan.

		Tijd	Uitslag	0%	0-25%	25-50%	50-75%	75-100%	100%
Geen ST-elev.	Geen fietstest	t = 0 en t = 2	Negatief	○	✓	○	○	○	○

Symptomen van ACS - geen ST-elevatie

	Resultaat troponine bepaling		Patiënten die naar aanleiding van onderstaande uitslagen ontslagen worden (%). Vink het gekozen antwoord aan.					
	Tijd (uur)	Uitslag	0%	0-25%	25-50%	50-75%	75-100%	100%
Geen fietstest uitgevoerd	t = 0	Licht verhoogd	○	○	○	○	○	○
	t = 0	**Negatief**	○	○	○	○	○	○
	t = 0 en t = 2	Negatief	○	○	○	○	○	○
	t = 0, t = 2 en t = 6	Negatief	○	○	○	○	○	○
Fietstest negatief	t = 0	Licht verhoogd	○	○	○	○	○	○
	t = 0	**Negatief**	○	○	○	○	○	○
	t =0 en t = 2	Negatief	○	○	○	○	○	○
	t = 0, t = 2 en t = 6	Negatief	○	○	○	○	○	○

9. Beantwoord de vorige vraag nogmaals, maar nu met de volgende gegevens: in de onderstaande tabel zijn (in grijs) de prestaties van de huidige troponine bepaling getoond:
   - Van 100 mensen die een acuut myocard infarct (AMI) hebben, toont de huidige troponine bepaling er 85 aan op t = 0 (zie onderstaande tabel).
   - Echter, in geval van 100 negatieve testresultaten, hebben 5 patiënten **wel** een AMI.

   Vul in de twee grijze rijen de gekozen percentages in geval van een negatieve troponine uitslag op t = 0 uit de vorige vraag in (vetgedrukt).

   Stel: er worden twee markers toegevoegd aan de huidige troponine bepaling op t = 0. Probeert u in te schatten wat het effect van de verbeterde prestaties van de combinatie van deze drie markers zal zijn op het percentage patiënten dat u op basis van onderstaande bevindingen zult ontslaan.

   Het resultaat van de drie markers op t = 0 is negatief.

   Ter vergelijking: op t = 3 uur toont de huidige troponine bepaling 98 van de 100 mensen aan die een hartinfarct hebben, en in geval van 100 negatieve testresultaten heeft 1 patiënt wel AMI.

Symptomen van ACS - geen ST-elevatie

		Prestaties markers op t = 0 uur		**Patiënten die ontslagen worden (%). Vink het gekozen antwoord aan.**					
		marker positief per 100 AMI patiënten*	aantal vals-negatief per 100 patiënten**	0%	0-25%	25-50%	50-75%	75-100%	100%
Geen fietstest uitgevoerd	**Troponine**	**85**	**5**	◯	◯	◯	◯	◯	◯
	Drie markers	90	4	◯	◯	◯	◯	◯	◯
		95	2	◯	◯	◯	◯	◯	◯
		99	1	◯	◯	◯	◯	◯	◯
Fietstest negatief	**Troponine**	**85**	**5**	◯	◯	◯	◯	◯	◯
	Drie markers	90	4	◯	◯	◯	◯	◯	◯
		95	2	◯	◯	◯	◯	◯	◯
		99	1	◯	◯	◯	◯	◯	◯

* Indien deze analyse bij 100 patiënten met AMI wordt uitgevoerd, toont de marker de in deze kolom genoemde aantallen aan (sensitiviteit).

** Indien deze analyse bij 100 patiënten wordt uitgevoerd, resulteert dit in de aantallen genoemd in de kolom met een negatief testresultaat terwijl deze patiënten wel AMI hebben (1 - negatief voorspellende waarde).

10. Beantwoord bovenstaande vraag nogmaals, maar nu met de volgende gegevens: mogelijk kunnen de twee extra markers bijdragen aan het uitsluiten van een hartinfarct in geval van een licht verhoogde troponine uitslag. De mogelijke prestaties van de twee extra markers zijn weergegeven in onderstaande tabel.
Stel: resultaten op t = 0: troponine 0.045 - 0.099 ng/mL, twee extra markers negatief.

Symptomen van ACS - geen ST-elevatie

	Prestaties twee extra markers op t = 0 uur		**Patiënten die ontslagen worden (%) (troponine 0.045-0.099 ng/mL, extra markers negatief). Vink het gekozen antwoord aan.**					
	marker positief per 100 AMI patiënten*	aantal vals-negatief per 100 patiënten**	0%	0-25%	25-50%	50-75%	75-100%	100%
Geen fietstest uitgevoerd	80	8	◯	◯	◯	◯	◯	◯
	90	3	◯	◯	◯	◯	◯	◯
	99	1	◯	◯	◯	◯	◯	◯
Fietstest negatief	80	8	◯	◯	◯	◯	◯	◯
	90	3	◯	◯	◯	◯	◯	◯
	99	1	◯	◯	◯	◯	◯	◯

* Indien deze analyse bij 100 patiënten met AMI wordt uitgevoerd, toont de marker de in deze kolom genoemde aantallen aan (sensitiviteit).

** Indien deze analyse bij 100 patiënten wordt uitgevoerd, resulteert dit in de aantallen genoemd in de kolom met een negatief testresultaat terwijl deze patiënten wel AMI hebben (1 - negatief voorspellende waarde).

11. Onderstaande tabel: troponine uitslagen op t = 0 uur. Patiënten met symptomen van ACS, zonder ST-elevatie, en een negatieve of licht verhoogde troponine (0.045 – 0.099 ng/mL) op t = 0. Probeert u in te schatten of u op basis van deze gegevens de hieronder genoemde onderzoeken en behandelingen zult toepassen, en bij welk percentage van deze patiënten, van de periode van binnenkomst op de Eerste Hart Hulp tot het moment van ontslag.

Symptomen van ACS - geen ST-elevatie

	Troponine	**Uitgevoerde handelingen per patiënt (%) Vink het gekozen antwoord aan.**					
	t = 0 uur	0%	0-25%	25-50%	50-75%	75-100%	100%
Fietstest	**Negatief**	◯	◯	◯	◯	◯	◯
	Licht verhoogd	◯	◯	◯	◯	◯	◯
Hartkathe-terisatie	**Negatief**	◯	◯	◯	◯	◯	◯
	Licht verhoogd	◯	◯	◯	◯	◯	◯
Oplaaddosis medicatie	**Negatief**	◯	◯	◯	◯	◯	◯
	Licht verhoogd	◯	◯	◯	◯	◯	◯

12. Onderstaande tabel toont patiënten met symptomen van ACS, zonder ST-elevatie.

Onderstaand zijn de prestaties van enkel troponine, en de mogelijke prestaties van de combinatie van de drie markers weergegeven op t = 0. Probeert u in te schatten of u op basis hiervan de hieronder genoemde onderzoeken en behandelingen zult toepassen, en bij welk percentage van deze patiënten, van de periode van binnenkomst op de Eerste Hart Hulp tot het moment van ontslag, indien de markers negatief zijn op t = 0.

Vul in de drie grijze rijen de gekozen percentages in geval van een negatieve troponine uitslag op t = 0 uit de vorige vraag in (vetgedrukt).

Ter vergelijking: op t = 3 uur toont de huidige troponine bepaling 98 van de 100 mensen aan die een hartinfarct hebben, en in geval van 100 negatieve testresultaten heeft 1 patiënt wel AMI.

Symptomen van ACS - geen ST-elevatie

		Prestaties markers op t = 0 uur		**Uitgevoerde handelingen per patiënt (%) Vink het gekozen antwoord aan.**					
		marker positief per 100 AMI patiënten*	aantal vals-negatief per 100 patiënten**	0%	0-25%	25-50%	50-75%	75-100%	100%
Fietstest	**Troponine**	**85**	**5**	◯	◯	◯	◯	◯	◯
	Drie markers	90	4	◯	◯	◯	◯	◯	◯
		95	2	◯	◯	◯	◯	◯	◯
		99	1	◯	◯	◯	◯	◯	◯
Hartkathe-terisatie	**Troponine**	**85**	**5**	◯	◯	◯	◯	◯	◯
	Drie markers	90	4	◯	◯	◯	◯	◯	◯
		95	2	◯	◯	◯	◯	◯	◯
		99	1	◯	◯	◯	◯	◯	◯
Oplaaddosis medicatie	**Troponine**	**85**	**5**	◯	◯	◯	◯	◯	◯
	Drie markers	90	4	◯	◯	◯	◯	◯	◯
		95	2	◯	◯	◯	◯	◯	◯
		99	1	◯	◯	◯	◯	◯	◯

* Indien deze analyse bij 100 patiënten met AMI wordt uitgevoerd, toont de marker de in deze kolom genoemde aantallen aan (sensitiviteit).

** Indien deze analyse bij 100 patiënten wordt uitgevoerd, resulteert dit in de aantallen genoemd in de kolom met een negatief testresultaat terwijl deze patiënten wel AMI hebben (1 - negatief voorspellende waarde).

13. Beantwoord bovenstaande vraag nogmaals, maar nu met de volgende gegevens:

Stel: troponine op t = 0 is 0.045-0.099 ng/mL. Twee extra markers zijn negatief, met onderstaand de mogelijke prestaties van enkel deze twee markers.

Symptomen van ACS - geen ST-elevatie

	Prestaties twee extra markers op t = 0 uur		**Uitgevoerde handelingen per patiënt (%)** (troponine 0.045-0.099 ng/mL, extra markers negatief). **Vink het gekozen antwoord aan.**					
	marker positief per 100 AMI patiënten*	aantal vals-negatief per 100 patiënten**	0%	0-25%	25-50%	50-75%	75-100%	100%
Fietstest	80	8	◯	◯	◯	◯	◯	◯
	90	3	◯	◯	◯	◯	◯	◯
	99	1	◯	◯	◯	◯	◯	◯
Hartkathe-terisatie	80	8	◯	◯	◯	◯	◯	◯
	90	3	◯	◯	◯	◯	◯	◯
	99	1	◯	◯	◯	◯	◯	◯
Oplaaddosis medicatie	80	8	◯	◯	◯	◯	◯	◯
	90	3	◯	◯	◯	◯	◯	◯
	99	1	◯	◯	◯	◯	◯	◯

* Indien deze analyse bij 100 patiënten met AMI wordt uitgevoerd, toont de marker de in deze kolom genoemde aantallen aan (sensitiviteit).

** Indien deze analyse bij 100 patiënten wordt uitgevoerd, resulteert dit in de aantallen genoemd in de kolom met een negatief testresultaat terwijl deze patiënten wel AMI hebben (1 - negatief voorspellende waarde).

14. Indien u nog opmerkingen of suggesties heeft, wordt u verzocht deze hieronder te vermelden.

Hartelijk dank voor de tijd die u genomen heeft om deze vragenlijst in te vullen.

APPENDIX IV: ESTIMATED VALUES OF VARIABLES

	Average	Lower limit	Upper limit	Source
Performance laboratory assay				
specificity (%) troponin t0	0.918	0.817	0.936	systematic review
specificity (%) troponin t2	0.904	0.786	0.922	systematic review
specificity (%) troponin t6	0.812	0.765	0.852	systematic review
specificity (%) multimarker t0	0.428	0.232	0.620	systematic review + Keller et al, 2010[42]
specificity MPO en copeptin (%) t0, combined with slightly elevated troponin	0.029	0.019	0.031	systematic review + Keller et al, 2010[42]
Discharge				
% discharge serial troponin analysis, slightly elevated at t0, without exercise ECG	0.033	0.000	0.073	questionnaire
% discharge serial troponin analysis, slightly elevated at t0, exercise ECG negative	0.163	0.000	0.360	questionnaire
% discharge serial troponin analysis, negative at t0, without exercise ECG	0.063	0.015	0.110	questionnaire
% discharge serial troponin analysis, negative at t0, exercise ECG negative	0.300	0.039	0.561	questionnaire
% discharge serial troponin analysis, negative at t2, without exercise ECG	0.400	0.121	0.679	questionnaire
% discharge serial troponin analysis, negative at t2, exercise ECG negative	0.675	0.404	0.946	questionnaire
% discharge serial troponin analysis, negative at t6, without exercise ECG	0.638	0.380	0.895	questionnaire
% discharge serial troponin analysis, negative at t6, exercise ECG negative	0.775	0.530	1.000	questionnaire
% discharge multimarker sensitivity 90%, negative at t0, without exercise ECG	0.150	0.005	0.295	questionnaire
% discharge multimarker sensitivity 90%, negative at t0, exercise ECG negative	0.350	0.084	0.616	questionnaire
% discharge multimarker sensitivity 95%, negative at t0, without exercise ECG	0.313	0.088	0.537	questionnaire
% discharge multimarker sensitivity 95%, negative at t0, exercise ECG negative	0.500	0.224	0.776	questionnaire
% discharge multimarker sensitivity 99%, negative at t0, without exercise ECG	0.575	0.279	0.871	questionnaire

% discharge multimarker sensitivity 99%, negative at t0, exercise ECG negative	0.713	0.433	0.992	questionnaire
% discharge negative MPO and copeptin sensitivity 80%, slightly elevated troponin at t0, without exercise ECG	0.038	0.000	0.081	questionnaire
% discharge negative MPO and copeptin sensitivity 80%, slightly elevated troponin at t0, exercise ECG negative	0.125	0.000	0.318	questionnaire
% discharge negative MPO and copeptin sensitivity 90%, slightly elevated troponin at t0, without exercise ECG	0.163	0.029	0.296	questionnaire
% discharge negative MPO and copeptin sensitivity 90%, slightly elevated troponin at t0, exercise ECG negative	0.288	0.049	0.526	questionnaire
% discharge negative MPO and copeptin sensitivity 99%, slightly elevated troponin at t0, without exercise ECG	0.388	0.088	0.687	questionnaire
% discharge negative MPO and copeptin sensitivity 99%, slightly elevated troponin at t0, exercise ECG negative	0.483	0.175	0.790	questionnaire
Activities				
% exercise ECG, serial troponin analysis, slightly elevated at t0	0.125	0.000	0.318	questionnaire
% exercise ECG, serial troponin analysis, negative at t0	0.313	0.088	0.537	questionnaire
% catheterization, serial troponin analysis, slightly elevated at t0	0.538	0.299	0.776	questionnaire
% catheterization, serial troponin analysis, negative at t0	0.200	0.059	0.341	questionnaire
% medication, serial troponin analysis, slightly elevated at t0	0.825	0.672	0.978	questionnaire
% medication, serial troponin analysis, negative at t0	0.400	0.162	0.638	questionnaire
% exercise ECG, multimarker sensitivity 90%, negative at t0	0.313	0.073	0.552	questionnaire
% exercise ECG, multimarker sensitivity 95%, negative at t0	0.275	0.012	0.538	questionnaire
% exercise ECG, multimarker sensitivity 99%, negative at t0	0.225	0.000	0.498	questionnaire
% catheterization, multimarker sensitivity 90%, negative at t0	0.138	0.039	0.236	questionnaire
% catheterization, multimarker sensitivity 95%, negative at t0	0.125	0.022	0.228	questionnaire
% catheterization, multimarker sensitivity 99%, negative at t0	0.113	0.005	0.220	questionnaire
% medication, multimarker sensitivity 90%, negative at t0	0.363	0.119	0.606	questionnaire
% medication, multimarker sensitivity 95%, negative at t0	0.288	0.049	0.526	questionnaire

% medication, multimarker sensitivity 99%, negative at t0	0.208	0.000	0.448	questionnaire
% exercise ECG, negative MPO and copeptin sensitivity 80%, slightly elevated troponin at t0	0.300	0.080	0.520	questionnaire
% exercise ECG, negative MPO and copeptin sensitivity 90%, slightly elevated troponin at t0	0.288	0.060	0.515	questionnaire
% exercise ECG, negative MPO and copeptin sensitivity 99%, slightly elevated troponin at t0	0.325	0.054	0.596	questionnaire
% catheterization, negative MPO and copeptin sensitivity 80%, slightly elevated troponin at t0	0.475	0.219	0.731	questionnaire
% catheterization, negative MPO and copeptin sensitivity 90%, slightly elevated troponin at t0	0.388	0.147	0.628	questionnaire
% catheterization, negative MPO and copeptin sensitivity 99%, slightly elevated troponin at t0	0.300	0.065	0.535	questionnaire
% medication, negative MPO and copeptin sensitivity 80%, slightly elevated troponin at t0	0.688	0.434	0.941	questionnaire
% medication, negative MPO and copeptin sensitivity 90%, slightly elevated troponin at t0	0.638	0.380	0.895	questionnaire
% medication, negative MPO and copeptin sensitivity 99%, slightly elevated troponin at t0	0.388	0.137	0.638	questionnaire
Costs				
costs exercise ECG	€115.65	€109.87	€121.43	NZA, 2012
costs catheterization	€789.35	€749,88	€828.82	NZA, 2012
costs medication	€9.09	€4.55	€13.64	medicijnkosten.nl
costs ECG assessment	€17.91	€17.01	€18.81	NZA, 2012
costs conventional laboratory assay t0	€56.65	€53.82	€59.48	NZA, 2012
costs multimarker assay t0	€73.23	€69.57	€146.46	NZA, 2012 (MPO and copeptin based on cost troponin assay)
costs follow up troponin assay at t2 and/or t6	€23.78	€22.59	€24.97	NZA, 2012
costs until hospital discharge based following the laboratory results of t0	€176.83	€132.62	€221.04	Hakkaart-van Roijen, 2010[56] + Financial Statistics 2009 [57]
costs until hospital discharge based following the laboratory results of t2	€331.66	€248.74	€414.57	Hakkaart-van Roijen, 2010[56] + Financial Statistics 2009 [57]
costs until hospital discharge based following the laboratory results of t6	€641.31	€480.98	€801.64	Hakkaart-van Roijen, 2010[56] + Financial Statistics 2009 [57]
costs until hospital discharge based following the laboratory results of t24	€1241.37	€931.03	€1551.72	Hakkaart-van Roijen, 2010[56]

APPENDIX V: RESULTS OF ONE-WAY SENSITIVITY ANALYSIS

	t0, 90		t0, 95		t0, 99		t2, 90		t2, 95		t2, 99		t6, 90		t6, 95		t6, 99	
	lower	**upper**	**lower**	**upper**	**lower**	**upper**	**lower**	**upper**	**lower**	**upper**	**lower**	**upper**	**lower**	**upper**	**lower**	**upper**	**lower**	**upper**
1	-€9,46	€4,60	-€9,46	€4,60	-€9,46	€4,87	-€14,10	€5,24	-€14,10	€5,23	-€14,10	€5,24	-€12,61	€5,03	-€12,61	€5,03	-€ 12,61	€ 5,03
2	-€49,38	€7,53	-€49,38	€7,53	-€49,38	€7,53	€2,14	-€0,32	-€2,97	€0,45	-€11,35	€1,74	-€66,70	€10,18	-€66,69	€10,17	-€ 66,76	€ 10,18
3	-€6,49	€5,52	-€6,49	€5,52	-€6,49	€5,52	-€6,49	€5,52	-€6,49	€5,52	-€6,48	€5,53	-€4,06	€3,46	-€4,42	€3,76	-€ 5,13	€ 4,37
4	€53,33	-€51,30	€87,87	-€85,14	€141,55	-€137,72	€30,72	-€29,21	€53,84	-€51,86	€90,95	-€88,21	€16,28	-€15,04	€32,75	-€31,17	€ 59,01	-€ 56,91
5	€3,86	-€0,93	€5,92	-€1,45	€8,82	-€2,16	-€0,26	€0,09	€1,25	-€0,29	€3,95	-€0,95	-€2,61	€0,67	-€1,09	€0,30	€ 1,61	-€ 0,37

Table...: *results of one-way sensitivity analysis of differences in specificity of the laboratory assays, showing the difference in costs for each of the nine strategies. Differences in costs are reported in 2012 Euros.*

1 specificity (%) troponin t = 0
2 specificity (%) troponin t = 2
3 specificity (%) troponin t = 6
4 specificity (%) multimarker t = 0
5 specificity MPO en copeptin (%) t = 0, combined with slightly elevated troponin

	t0, 90		t0, 95		t0, 99		t2, 90		t2, 95		t2, 99		t6, 90		t6, 95		t6, 99	
	lower	**upper**	**lower**	**upper**	**lower**	**upper**	**lower**	**upper**	**lower**	**upper**	**lower**	**upper**	**lower**	**upper**	**lower**	**upper**	**lower**	**upper**
1	€0,58	-€0,58	€0,89	-€0,90	€1,20	-€1,20	€0,01	€0,00	€0,33	-€0,33	€0,78	-€0,77	-€0,47	€0,47	-€0,08	€0,08	€0,51	-€0,51
2	-€0,03	€0,03	€0,12	-€0,13	€0,31	-€0,31	-€0,11	€0,11	€0,04	-€0,04	€0,24	-€0,23	-€0,18	€0,18	-€0,02	€0,02	€0,19	-€0,19
3	€2,83	-€2,83	€2,83	-€2,83	€2,83	-€2,83	€2,83	-€2,83	€2,83	-€2,83	€2,83	-€2,83	€2,83	-€2,83	€2,83	-€2,83	€2,83	-€2,83
4	-€3,66	€73,23	-€3,66	€73,23	-€3,66	€73,23	-€3,66	€73,23	-€3,66	€73,23	-€3,66	€73,23	-€3,66	€73,23	-€3,66	€73,23	-€3,66	€73,23
5	€1,39	-€1,40	€1,39	-€1,40	€1,39	-€1,40	€0,32	-€0,31	€0,39	-€0,40	€0,53	-€0,52	-€0,17	€0,17	-€0,06	€0,06	€0,13	-€0,13
6	€1,62	-€1,63	-€1,42	€1,41	-€6,27	€6,27	€1,63	-€1,63	-€1,41	€1,41	-€6,26	€6,27	€1,63	-€1,63	-€1,41	€1,41	-€6,27	€6,27
7	€28,31	-€28,32	€28,31	-€28,32	€28,32	-€28,32	-€4,18	€4,19	-€1,59	€1,58	€2,25	-€2,24	-€10,69	€10,69	-€7,62	€7,62	-€3,02	€3,02
8	€33,20	-€33,20	€33,20	-€33,20	€33,20	-€33,20	€33,20	-€33,20	€33,20	-€33,20	€33,20	-€33,19	-€10,61	€10,61	-€7,54	€7,55	-€2,40	€2,39
9	-€181,67	€181,67	-€160,34	€160,34	-€126,26	€126,26	-€60,02	€60,02	-€48,42	€48,41	-€28,68	€28,69	€49,12	-€49,12	€53,04	-€53,03	€59,93	-€59,94

Table…: *results of one-way sensitivity analysis of differences in costs of the different cost units, showing the difference in costs for each of the nine strategies. Differences in costs are reported in 2012 Euros.*

1 costs catheterization (€)
2 costs medication (€)
3 costs conventional laboratory assay t = 0
4 costs multimarker assay t = 0
5 costs follow up troponin assay at t = 2 and/or t = 6
6 costs until hospital discharge based following the laboratory results of t = 0 (€)
7 costs until hospital discharge based following the laboratory results of t = 2 (€)
8 costs until hospital discharge based following the laboratory results of t = 6 (€)
9 costs until hospital discharge based following the laboratory results of t = 24 (€)

	t0, 90		t0, 95		t0, 99		t2, 90		t2, 95		t2, 99		t6, 90		t6, 95		t6, 99	
	lower	upper	lower	upper	lower	upper	lower	upper	lower	upper	lower	upper	lower	upper	lower	upper	lower	upper
1	-€1,08	€1,66	-€1,08	€1,66	-€1,08	€1,67	€0,68	-€1,04	€0,67	-€1,05	€0,68	-€1,04	€0,11	-€0,17	€0,11	-€0,17	€0,11	-€0,18
2	-€46,88	€46,87	-€46,88	€46,87	-€46,88	€46,87	-€17,91	€17,91	-€17,91	€17,91	-€17,90	€17,91	-€27,21	€27,21	-€27,21	€27,21	-€27,21	€27,21
3	€15,43	-€15,44	€15,43	-€15,44	€15,44	-€15,44	€4,30	-€4,30	€6,20	-€6,20	€9,26	-€9,25	-€1,40	€1,40	€1,49	-€1,49	€6,26	-€6,26
4	€102,17	-€102,17	€102,17	-€102,18	€102,17	-€102,17	€102,17	-€102,17	€102,17	-€102,18	€102,18	-€102,17	€102,17	-€102,17	€102,17	-€102,17	€102,17	-€102,17
5	€0,03	-€0,03	€0,03	-€0,04	€0,03	-€0,03	-€0,05	€0,05	-€0,04	€0,03	-€0,01	€0,02	-€0,09	€0,09	-€0,07	€0,07	-€0,04	€0,03
6	€0,81	-€0,81	€0,81	-€0,81	€0,81	-€0,81	€0,81	-€0,81	€0,81	-€0,81	€0,81	-€0,81	€0,81	-€0,81	€0,81	-€0,81	€0,81	-€0,81
7	€9,97	-€9,97	€9,45	-€9,45	€2,96	-€3,59	€20,10	-€20,10	€16,98	-€16,98	€5,89	-€7,14	€10,97	-€10,97	€8,38	-€8,38	€0,98	-€1,20
8	-€33,28	€33,27	-€34,80	€34,79	-€36,32	€36,32	-€30,76	€30,76	-€32,68	€32,67	-€34,94	€34,95	-€28,41	€28,41	-€30,64	€30,64	-€33,60	€33,59
9	-€0,95	€0,94	-€0,93	€0,92	-€0,81	€0,93	-€0,87	€0,88	-€0,87	€0,87	-€0,78	€0,90	-€0,81	€0,81	-€0,82	€0,82	-€0,75	€0,86
10	-€0,14	€0,14	€0,11	-€0,12	-€0,11	€0,11	€0,53	-€0,53	€0,75	-€0,75	€0,50	-€0,49	€0,53	-€0,53	€0,75	-€0,75	€0,49	-€0,50
11	-€5,79	€5,78	-€5,44	€5,43	-€5,31	€5,31	-€0,37	€0,37	-€1,08	€1,07	-€2,22	€2,23	-€0,37	€0,37	-€1,08	€1,08	-€2,22	€2,22
12	-€0,07	€0,06	-€0,07	€0,06	-€0,07	€0,06	€0,00	€0,01	-€0,02	€0,01	-€0,02	€0,03	€0,00	€0,00	-€0,01	€0,01	-€0,03	€0,03

Table...: *results of one-way sensitivity analysis of differences in the activities performed (as estimated by the cardiologists), showing the difference in costs for each of the nine strategies. Differences in costs are reported in 2012 Euros.*

1 % exercise ECG, serial troponin analysis, slightly elevated at t = 0
2 % exercise ECG, serial troponin analysis, negative at t = 0
3 % catheterization, serial troponin analysis, slightly elevated at t = 0
4 % catheterization, serial troponin analysis, negative at t = 0
5 % medication, serial troponin analysis, slightly elevated at t = 0
6 % medication, serial troponin analysis, negative at t = 0
7 % exercise ECG, multimarker negative at t = 0
8 % catheterization, multimarker negative at t = 0
9 % medication, multimarker negative at t = 0
10 % exercise ECG, negative MPO and copeptin slightly elevated troponin at t = 0
11 % catheterization, negative MPO and copeptin slightly elevated troponin at t = 0
12 % medication, negative MPO and copeptin slightly elevated troponin at t = 0

	t0, 90		t0, 95		t0, 99		t2, 90		t2, 95		t2, 99		t6, 90		t6, 95		t6, 99	
	lower	upper	lower	upper	lower	upper	lower	upper	lower	upper	lower	upper	lower	upper	lower	upper	lower	upper
1	-€5,48	€6,51	-€5,48	€6,51	-€5,48	€6,51	-€3,10	€3,69	-€3,27	€3,89	-€3,64	€4,34	-€4,89	€5,82	-€4,96	€5,90	-€5,12	€6,09
2	-€5,71	€6,93	-€5,71	€6,93	-€5,71	€6,93	-€0,84	€1,03	-€1,49	€1,81	-€2,08	€2,54	-€4,59	€5,58	-€4,84	€5,88	-€4,99	€6,07
3	-€17,95	€17,95	-€17,96	€17,95	-€17,95	€17,95	-€17,95	€17,95	-€17,96	€17,95	-€17,95	€17,96	-€17,95	€17,95	-€17,95	€17,95	-€17,95	€17,95
4	-€30,68	€30,67	-€30,68	€30,67	-€30,68	€30,67	-€30,67	€30,68	-€30,68	€30,67	-€30,67	€30,68	-€30,67	€30,67	-€30,67	€30,68	-€30,68	€30,67
5	-€92,39	€92,39	-€92,39	€92,39	-€92,39	€92,39	€49,01	-€49,01	€40,57	-€40,58	€23,98	-€23,97	-€2,96	€2,96	-€8,52	€8,52	-€19,64	€19,64
6	-€26,45	€26,44	-€26,45	€26,44	-€26,45	€26,44	€32,43	-€32,42	€26,16	-€26,17	€19,22	-€19,21	€5,15	-€5,15	€1,54	-€1,54	-€2,50	€2,49
7	-€40,27	€40,26	-€40,27	€40,26	-€40,27	€40,26	-€40,26	€40,27	-€40,27	€40,26	-€40,26	€40,27	€11,39	-€11,38	€8,30	-€8,30	€2,24	-€2,24
8	-€7,05	€6,47	-€7,05	€6,46	-€7,04	€6,47	-€7,04	€6,47	-€7,05	€6,46	-€7,04	€6,47	€4,37	-€4,01	€3,15	-€2,89	€1,81	-€1,66
9	€45,42	-€45,42	€74,16	-€74,16	€104,52	-€104,52	€33,59	-€33,58	€54,90	-€54,91	€77,49	-€77,48	€23,07	-€23,07	€37,82	-€37,82	€53,51	-€53,51
10	€37,87	-€37,88	€34,58	-€34,59	€28,65	-€28,65	€19,56	-€19,56	€17,89	-€17,89	€14,86	-€14,85	€12,97	-€12,97	€11,90	-€11,90	€9,90	-€9,90
11	€0,80	-€0,93	€2,89	-€2,90	€6,16	-€6,16	€0,83	-€0,96	€3,20	-€3,21	€7,23	-€7,22	€0,83	-€0,97	€3,21	-€3,21	€7,23	-€7,23
12	€1,14	-€1,77	€2,09	-€2,09	€3,04	-€3,05	€1,07	-€1,64	€2,08	-€2,08	€3,24	-€3,23	€1,06	-€1,64	€2,08	-€2,08	€3,24	-€3,24

Table...: *results of one-way sensitivity analysis of differences in the number of patients discharged at each time point (as estimated by the cardiologists), showing the difference in costs for each of the nine strategies. Differences in costs are reported in 2012 Euros.*

1 % discharge serial troponin analysis, slightly elevated at t = 0, without exercise ECG
2 % discharge serial troponin analysis, slightly elevated at t = 0, exercise ECG negative
3 % discharge serial troponin analysis, negative at t = 0, without exercise ECG
4 % discharge serial troponin analysis, negative at t = 0, exercise ECG negative
5 % discharge serial troponin analysis, negative at t = 2, without exercise ECG
6 % discharge serial troponin analysis, negative at t = 2, exercise ECG negative
7 % discharge serial troponin analysis, negative at t = 6, without exercise ECG
8 % discharge serial troponin analysis, negative at t = 6, exercise ECG negative
9 % discharge multimarker negative at t = 0, without exercise ECG
10 % discharge multimarker negative at t = 0, exercise ECG negative
11 % discharge negative MPO and copeptin slightly elevated troponin at t = 0, without exercise ECG
12 % discharge negative MPO and copeptin slightly elevated troponin at t = 0, exercise ECG negative