# MASTER THESIS

ASSESSING THE COST-EFFECTIVENESS OF POINT-OF-CARE TESTING FOR PRIMARY CARE PATIENTS WITH SYMPTOMS SUGGESTIVE OF ACUTE CORONARY SYNDROME

A THRESHOLD ANALYSIS

**Marco J. Moesker**

**Examination committee**

Prof. dr. G.C.M. Kusters
Prof. dr. M.J. IJzerman
Dr. L.M.G. Steuten
Michelle M.A. Kip MSc

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

UNIVERSITY OF TWENTE.

19-11-2014

**Title:**

# Assessing the cost-effectiveness of point-of-care testing for primary care patients with symptoms suggestive of acute coronary syndrome

*A threshold analysis*


| | |
|---|---|
| **Name** | Marco J. Moesker |
| **Supervisors** | Prof. dr. G.C.M. Kusters<br>Dr. L.M.G. Steuten<br>Michelle M.A. Kip MSc |
| **Institute** | University of Twente<br>School of Management and Governance<br>Department of Health Technology and Services Research |
| **Postal address** | P.O. Box 217<br>7500 AE Enschede |
| **Visiting address** | Building Ravelijn (on the campus, no. 10 on the map)<br>Drienerlolaan 5, 7522 NB Enschede<br>Room RA 5244 (secretariat) |
| **Date** | 19 November, 2014 |

# Abstract

**Background**

Chest complaints such as pain and pressure are challenging to interpret in primary care and have extensive differential diagnoses. Patients as well as their general practitioners (GPs) are often concerned whether these symptoms are indicative of acute coronary syndrome (ACS). Because of the severity of this condition, GPs are advised to refer patients presenting with those symptoms to the emergency department (ED). However, in only 14-16% of the annual 156.000 patients presenting to the GP, cardiac origin is causing the symptoms, resulting in a burden on ED's resources and the Dutch healthcare budget. Point of care testing (POCT) of cardiac markers might improve the certainty with which ACS can be ruled out in the GPs office and influence referral rates of those patients. To assess if POCT can play a role in ACS diagnostics in primary care, a threshold analysis is performed to estimate the minimum required diagnostic performance for the GP's assessment combined with POCT, to be cost-effective compared with GP assessments without POCT.

**Methods**

A patient-level health economic model, reflecting a hypothetical cohort of the Dutch population aged >35 years consulting their GP with chest complaints, was developed. The analysis included all direct and indirect medical costs, and productivity losses. Health benefit was expressed as patient's life expectancy, adjusted for the health-related quality of life; the so-called Quality Adjusted Life Year (QALY). Input data come from an extensive literature search. Quality of life estimates are based on published quality of life weights for patients with ACS and heart failure. Cost estimates come from literature and open access healthcare declaration data. Costs and health benefits are considered over a life-long time horizon. Primary outcome parameters include: a) the incremental cost-utility ratio (ICUR) of the GP's assessment combined with POCT vs. GP's assessment alone, and b) the minimum required performance of the GP's assessment combined with POCT to be considered a cost-effective treatment option compared with GP assessment only. Secondary outcome parameters include differences in mortality and new heart failure cases between the two strategies.

**Results**

The sensitivity and specificity for a GP in diagnosing ACS are 88% and 72% respectively. The minimum required sensitivity of the GP's assessment combined with POCT should be 91%, the minimum specificity should be 82%. However, a higher sensitivity allows for lower specificity and still be cost-effective. A sensitivity of 91% and specificity of 82% results in a median cost saving for society of € 8.365 (IQR: € 4.788 - € 13.741) for one extra QALY. The number of false-positive referrals will reduce with an estimated median of 1872 (IQR: 1854-1911), while the number of missed diagnoses (false-negatives) will reduce with a median of 20 (IQR: 16-24) per 20.000 patients. Median risk ratios for mortality and heart failure are 0,987 (IQR: 0,971-01,015) and 0,964 (IQR: 0,948-0,982) respectively for the POCT strategy compared with non-POCT strategy.

**Conclusion/Discussion**

An increase in overall sensitivity for excluding ACS at the GP from 88% to 91%, and an increase in specificity from 72% to 82% can be considered a cost-effective strategy in diagnosing ACS at the GP. This is expected to contribute to a reduction of healthcare costs because of less false-positive referrals, as well as an improvement of the quality of care provided because of less missed ACS diagnoses. Further research is necessary to further specify the use of POCT in primary care. Implementation of a clinical decision rule is recommended to be used alongside POCT to ensure safe and (cost)-effective use of POCT in diagnosing ACS.

# Table of contents

# 1 Background

## 1.1 Ischemic heart disease

Ischemic heart disease (IHD) is in most cases a consequence of coronary artery atherosclerosis.[1] It occurs when the blood flow around the heart is insufficient to meet the demands for oxygen by the heart. Ischemic heart disease can present itself as angina pectoris, myocardial infarction, chronic congestive heart failure and sudden death of which the latter is not under study in this thesis.[1] By the *European society of cardiology* (ESC) ischemic heart diseases are named coronary artery diseases (CAD)[2] Another common used name for these conditions is coronary heart disease (CHD).

### 1.1.1 Angina pectoris

Angina pectoris typically occurs in the sub sternal portion of the chest and may radiate to the left arm, jaw, and epigastrium. It is the most common symptom of ischemic heart disease.[1] Symptoms occur only when the luminal cross-sectional area of the affected vessel is reduced by more than 75%.[1] Patients with angina pectoris often experience chest pain of limited duration, one to 15 minutes, which is relieved by reducing physical activity or by treatment with nitro-glycerine, a vasodilator.[1] Angina pectoris is not associated with anatomic changes in the myocardium as long as the duration and severity of ischemic episodes are insufficient to cause myocardial necrosis.[1] When the angina is less predictable or occurs during rest or sleep, the angina is called unstable angina pectoris (UAP). Many patients with UAP progress to myocardial infarction without intervention to open up the coronary artery.[1]

### 1.1.2 Myocardial infarction

When an (acute) myocardial infarction (AMI) occurs the flow of blood to the affected coronary vessel becomes so obstructed that ischemia occurs in the heart tissue because of a lack of oxygen. The infarcted area forms after about 20 minutes of ischemia and becomes more extensive as the period of ischemia lengthens.[1]

### 1.1.3 Chronic congestive heart failure

Because early mortality associated with acute myocardial infarction has fallen in the past decades, many patients with ischemic heart disease survive longer and eventually develop chronic congestive heart failure.[1] In more than 75% of patients with heart failure, coronary artery disease is the major cause.[1] Heart failure occurs due to contractile impairment of the heart. This often results from irreversible loss of myocardium and hypo perfusion of surviving muscle, which leads to chronic ventricular dysfunction.[1]

### 1.1.4 Clinical features

Clinical features patients experience when having an acute myocardial infarction are often sudden and comprises of severe, crushing sub sternal, or precordial pain.[1] The pain may be experienced as epigastric burning or it may extend into the jaw or down the inside of either arm. It is often accompanied by sweating, nausea, vomiting, and shortness of breath.[1] Unstable angina pectoris in some cases precedes the acute myocardial infarction for several days.[1] One fourth to one-half of all non-fatal myocardial infarctions occur without any symptoms.[1] The diagnosis of acute myocardial infarction is confirmed by electrocardiogram (ECG) and the appearance of increased levels of certain enzymes or proteins in a patient's blood.[1]

## 1.2 Acute coronary syndrome

Patients with chest pain represent a very substantial proportion of all acute medical hospitalizations in Europe.[2] It is important that patients with acute coronary syndrome (ACS) are identified within this group by the medical services. ACS comprises of unstable angina pectoris and myocardial infarction. Patients with symptoms suggestive of ACS are a diagnostic challenge, especially in individuals without clear symptoms or ECG features.[2] Myocardial under perfusion, as described before, form the basic pathophysiological mechanisms in most conditions of ACS.[2] The leading symptom that initiates the

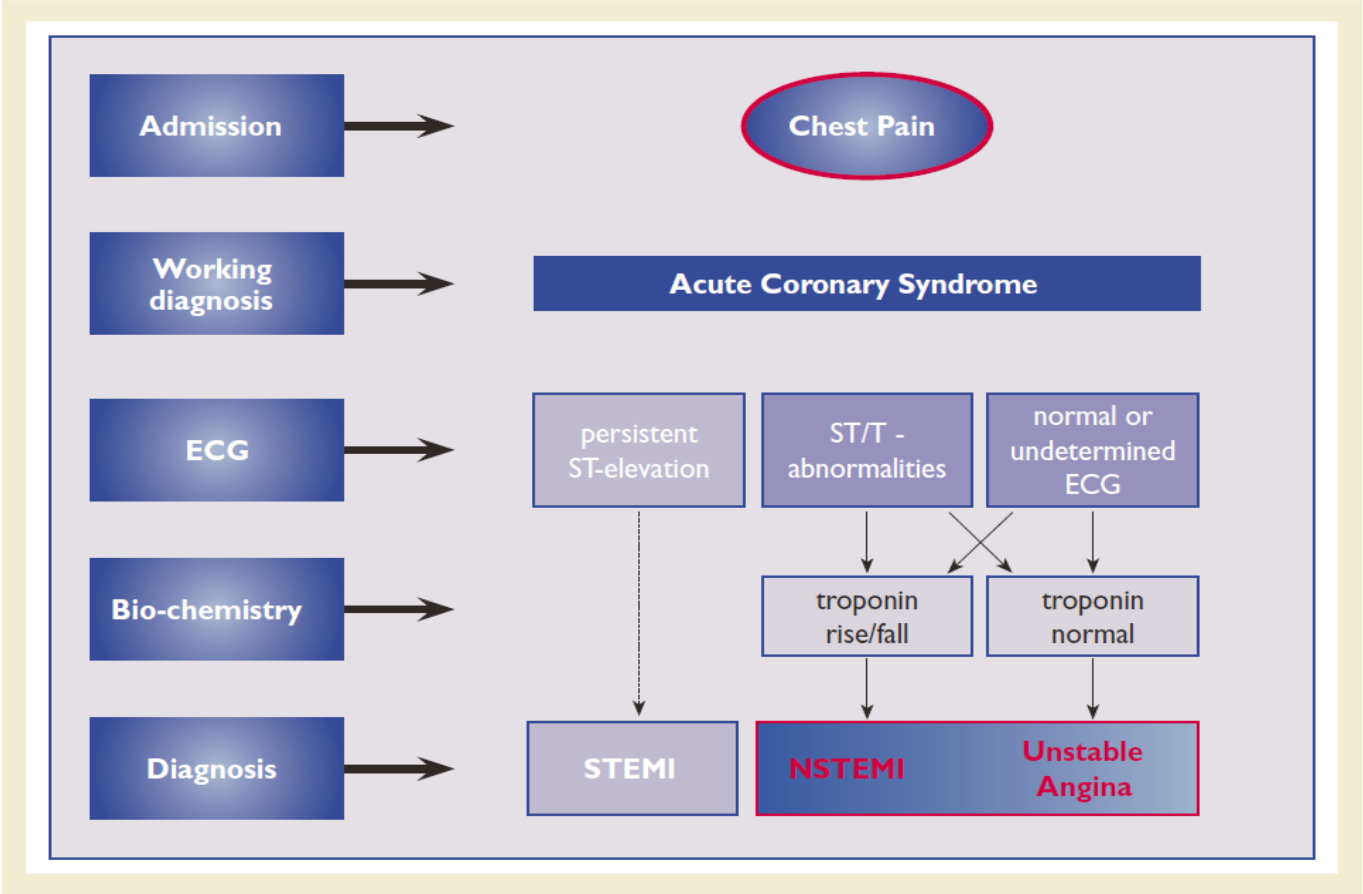



**Figure 1: The spectrum of ACS. ECG=electrocardiogram; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction. From Hamm et al. (2011) Fig. 1**

diagnostic and therapeutic cascade is chest pain, but the classification of patients is based on ECG findings according to the *European society of cardiology*:[2]

1. **Patients with acute chest pain and persistent (>20 min) ST-segment elevation.**

Patients with ST-elevation ACS (STE-ACS) generally reflect acute total coronary occlusion. Most of these patients will ultimately develop an ST-elevation myocardial infarction (STEMI). Therapy of these patients is aimed at rapid, complete and sustained reperfusion by primary angioplasty or fibrinolytic therapy.

2. **Patients with acute chest pain but without persistent ST-segment elevation.**

These patients have ECG changes other than ST-segment elevation or no ECG changes at presentation. The initial strategy is to alleviate ischemia and other symptoms, monitoring with serial ECGs, and to repeat measurements of markers of myocardial necrosis. At presentation in the hospital, the working diagnosis of non-ST-elevation ACS (NSTE-ACS), based on blood tests will be further specified as non-ST-elevation myocardial infarction (NSTEMI) or unstable angina. In a certain number of patients, CHD will subsequently be excluded as the cause of symptoms.

Figure 1 shows the evolution from working diagnosis to final diagnosis for patients presenting with chest pain.

## 1.3 Cardiac markers

Blood tests play a central role in establishing a diagnosis and risk stratification for patients suggestive of ACS. Troponin blood tests make it possible to distinguish between NSTEMI and unstable angina pectoris.[2] Troponins are more specific and sensitive than the traditional cardiac enzymes such as creatine kinase (CK), its isoenzyme MB (CK-MB), and myoglobin.[2] Elevation of cardiac troponins reflects myocardial cellular damage.[2] When an AMI occurs either with ST-elevation or not, a rise in troponin occurs within ±4 hours after symptom onset.[2]

Troponin assays are available as cardiac troponin-T (cTnT) and cardiac troponin-I (cTnI). There is no fundamental difference between these two assays.[2] The diagnostic cut-off for myocardial infarction is defined in the *universal definition of myocardial infarction* as a cardiac troponin measurement exceeding the 99$^{th}$ percentile of a normal reference population using an assay with an imprecision of ≤10% at the upper reference limit.[3]

### 1.3.1 Diagnostic performance characteristics

Diagnostic performance characteristics indicate how well a certain diagnostic tool is capable of identifying the sick and healthy patients. This can be visualized in a two-by-two table:

**Table 1: Two-by-two table diagnostic performance characteristics**

| | **Disease status** | |
|---|---|---|
| **Test result** | **Diseased** | **Non-diseased** |
| **Positive** | True Positive (TP) | False-Positive (FP) |
| **Negative** | False-Negative (FN) | True-Negative (TN) |

The proportion of patients with the disease who have a positive test result can be calculated as TP/(TP+FN). This probability is called the sensitivity or true-positive ratio (TPR).[4] Similarly, the proportion of patients without the disease who have a negative test result is TN/(FP+TN). This probability is called the specificity or true-negative ratio (TNR).[4] Sensitivity and specificity describe how often the test is correct in the diseased and non-diseased groups respectively.[4]

For an individual selected randomly from the study population upon which the estimates of sensitivity and specificity were based, the probability of disease given a positive test result may be obtained from the two-by-two table. This probability is calculated as TP/(TP+FP) and is called the positive predictive value (PPV).[4] Similarly the probability of non-diseased given a negative test result can be calculated as TN/(TN+FN) and is called the negative predictive value (NPV).[4] The PPV and NPV are both examples of post-test probabilities.[4] These post-test probabilities are not test characteristics and are not generalizable because they depend on the pre-test probability of disease.[4] The pre-test probability for disease is reflected by the prevalence for that disease in the population.

## 1.4 Treatment strategies

The Dutch Foundation Of Cardiology (Nederlandse Vereniging Voor Cardiologie, NVVC) employs the ESC guidelines on revascularisation in case of AMI. STE-ACS and NSTE-ACS have different treatment strategies. The myocardial ischemia in these patients is however life threatening in both groups.[5] The culprit coronary stenoses are easily identified by angiography in the majority of cases.[5] Angiography is an imaging technique used to visualize the blood flow through veins or arteries using a contrast agent and X-ray, CT or MRI.

**NSTE-ACS**

The invasive treatment strategy always starts with angiography to find the culprit lesion.[5] After the identification of the culprit stenosis and possible other non-culprit stenoses possible treatments are percutaneous coronary intervention (PCI), also known as stenting, or coronary artery bypass grafting (CABG), also known as bypass surgery. The mode of revascularization should be based on the severity and distribution of the coronary artery disease.[5]

**STE-ACS**

For STE-ACS treatments options are primary PCI and fibrinolysis. Primary PCI is defined as percutaneous intervention in the setting of STEMI without previous or concomitant fibrinolytic treatment.[5] Primary PCI is associated with improved outcomes compared with fibrinolytic therapy.[6] In primary PCI it is essential to try to minimize any time delays to improve patient outcomes.[5] Currently in the Netherlands there are 30 PCI-capable centres resulting in a broad coverage.[7] If the expected delay is more than 2 hours, patients should immediately receive fibrinolysis and then be transferred to a PCI-capable centre where angiography and PCI should be performed in a time window of 3-24 hours.[5] The incremental benefit of primary PCI over timely fibrinolysis is jeopardised when primary PCI delay exceeds 60-120 minutes.[8,9]

## 1.5 Symptoms suggestive of ACS in primary care

Chest pain or other symptoms suggestive of ACS are a common complaint in primary care. The prevalence of chest pain in primary care ranges from 0.68% to 2.7%, with differences occurring between countries and because of different inclusion criteria.[10–12] In the Netherlands, yearly incidence rates for pain attributed to the heart and pressure, tightness and heaviness attributed to the heart in primary care are 5.2 and 4.1 per 1000 patient years respectively based on 2012 figures obtained by ICPC (international classification of primary care) codes.[13] Currently the Netherlands have around 16.8 million inhabitants. This would mean that per year around 156.000 patients contact their general practitioner (GP) for pain attributed to the heart or pressure, tightness and heaviness attributed to the heart.

Past studies showed that a majority of patients presenting with chest pain have aetiologies other than of cardiac origin. *The task force on the management of chest pain* reported in 2002 that cardiac origins of chest pain make up around 20% of consultations for chest pain at the GP.[14] Chest wall and musculoskeletal aetiologies make up the largest proportion of consultations for chest pain as can be seen in Table 2.

More recent studies show that a cardiac origin for chest pain in primary care is present in 14.7%, 15% and 16% of patients.[15–17]

The same *task force on the management of chest pain* reported significant differences in aetiology of chest pain between various different clinical settings as can be seen in Table 3. Because of these differences, prevalence figures of underlying conditions for chest pain cannot be extrapolated between these clinical settings.

### 1.5.1 General practitioner's clinical assessment

Several signs and symptoms show associations with CHD as can be seen in Table 4. However in a meta-analysis by Bruyninckx et al. (2008) on signs and symptoms in diagnosing AMI and ACS, conclusions were that no important role for signs and symptoms can be defined in the clinical assessment.[18] A systematic review by Mant et al. (2004) shared this conclusion.[19]

Bruins Slot et al. (2011) state in their study that the GP's assessment accompanied with a clinical decision rule (CDR) on signs and symptoms would add to ruling in cases that, based on the judgement by the GP, would have been missed.[20] This might be contradictory with the studies by Bruyninckx et al. (2008) and Mant et al. (2004) but can be explained because GPs tend to overestimate the risk on ACS but also missed a small number of ACS cases, that would have been included using the CDR on signs and symptoms.

An interesting observation by Bösner et al. (2010) on the GP's management decision after diagnosing or excluding CHD is that of those patients, whom are not diagnosed as having CHD by the GP, 55% is referred for an electrocardiogram (ECG) and 6.7% is referred to a cardiologist. This might be due to the GP not being confident about his assessment or his knowledge about the limitations of clinical assessment on signs and symptoms alone.

## 1.6 Point-of-care-testing

Point-of-care-testing (POCT), also known as near patient testing (NPT) entails the ability of performing blood tests near patients. Its advantage is reduced time to decision-making, because transportation of the specimen and preparation are no longer needed and thus the results are known earlier.[21] Point of care testing for ACS is available for cardiac troponin I and T (cTnI, cTnT), creatinine kinase MB (CK-MB), myoglobin and heart-type fatty acid-binding protein (H-FABP). Several studies towards the effectiveness of POCT for ACS have already been conducted. The results of these studies, however, are conflicting with each other. Tomonaga et al. (2011) conclude that POCT for ACS, heart failure and thromboembolic events leads to a substantial benefit and more correct diagnoses within primary care.[25] On the other hand Junker et al. (2010) state that troponin POCT for cardiovascular conditions such as AMI are not capable of reliably excluding an AMI because troponin levels may still be under the detection threshold at the beginning of symptoms.[21]

**Table 2: Diagnoses of patients with chest pain, in general practice (percentages). From Erhardt et al. (2002) Fig.2**[14]

| Disorder/disease | Klinkman et al. (1994)[22] n=396 | Lamberts et al. (1991)[23] n=1875 | Svavarsdóttir et al. (1996)[10] n=190 |
|---|---|---|---|
| Psychiatric | 8 | 11 | 5 |
| Cardiac | 16* | 22† | 18 |
| Chest wall/musculoskeletal | 36 | 45 | 49 |
| Gastrointestinal | 19 | 2 | 4 |
| Respiratory/pulmonary | 5 | 3 | 6 |
| Pulmonary embolism | | | 2 |
| Other/no diagnosis | 16 | 17 | 16 |

*Final diagnosis (episode). Of all cardiovascular diagnoses 13% was (possible) acute myocardial infarction and 87% was angina pectoris.
†Final diagnosis: of all cardiovascular diagnoses 29% was myocardial infarction, 37% was angina pectoris.

**Table 3: Aetiology of chest pain in various clinical settings. From Erhardt et al. (2002) Fig.1**[14]

| Aetiology | General practitioner % | Dispatch centre % | Ambulance crew % | Emergency department % |
|---|---|---|---|---|
| Cardiac | 20 | 60 | 69 | 45 |
| Musculoskeletal | 43 | 6 | 5 | 14 |
| Pulmonary | 4 | 4 | 4 | 5 |
| Gastro-intestinal | 5 | 6 | 3 | 6 |
| Psychiatric | 11 | 5 | 5 | 8 |
| Other | 16 | 19 | 18 | 26 |

**Table 4: Associations between signs and symptoms and CHD. From Bösner et al. (2010) Table 2**[24]

| Sign or symptom | OR (95% CI) |
|---|---|
| Patient assumes cardiac origin of pain | 3.20 (1.53 - 6.60) |
| Age (female ≥65 years, male ≥55 years) | 2.81 (1.43 - 5.53) |
| Stinging pain | 0.44 (0.24 - 0.87) |
| Cough | 0.08 (0.01 - 0.77) |
| Pain worse with exercise | 4.27 (2.31 - 7.88) |
| Known clinical vascular disease | 5.13 (2.83 - 9.30) |
| Known heart failure | 2.93 (1.30 - 6.59) |
| Known diabetes mellitus | 2.21 (1.10 - 4.45) |
| Localised muscle tension | 0.46 (0.24 - 0.89) |
| Pain reproducible by palpation | 0.27 (0.13 - 0.56) |

OR: Odds ratio. CI: Confidence interval

Further, Bruins Slot et al. (2013) state in their systematic review that there is no ideal POCT for diagnosing AMI within six hours after the onset of symptoms.[26] Too many false negatives were reported which led to an unsafe assessment of patients. This also led the Dutch general practitioners foundation (Nederlands Huisarts Genootschap, NHG) to discourage the use of POCT for cardiac markers within primary care.[27]

However, given the magnitude of the number consultations for symptoms suggestive of ACS and the rather low prevalence of ACS within this group, reducing the amount of unnecessary referrals for ACS could have a big impact on resources saved at Dutch EDs. If this is the case the use of POCT in primary for patients with symptoms suggestive of ACS might be a cost-effective alternative.

## 1.7 Research questions

Current cost-effectiveness evidence concerning the use of POCT for ACS is scarce. Within the emergency department it is found that a POCT panel assay of cardiac markers has a 0.004 probability of being

dominant (i.e. cheaper and more effective) over standard care for patients with suspected myocardial infarction.[28] This study showed that the cost-effectiveness was sensitive to changes in the diagnostic performance characteristics of the used POCT.

Therefore, the current exploratory study aims to estimate the cost-effectiveness of the GP's clinical assessment combined with one POCT for diagnosing patients with symptoms suggestive of ACS compared with GPs relying on their clinical assessment only. Additionally, the minimum required sensitivity and specificity for the GP's clinical assessment combined with POCT to be cost-effective will be approximated in a threshold analysis.

It is expected that inadequate diagnostics in terms of missed diagnoses are associated with increased mortality and new heart failure cases. Therefore, secondary outcomes comprise out of differences in mortality and new heart failure cases between the two strategies.

# 2 Methods

## 2.1 Health economic evaluation

This study assesses the potential cost-effectiveness of POCT for patients with symptoms suggestive of ACS presenting at primary care through a health economic evaluation. Economic evaluation is defined by Drummond et al. (2005) as: '*the comparative analysis of alternative courses of action in terms of both their costs and consequences.*'[29] A decision model is constructed to assess the potential cost-effectiveness of the GP's clinical assessment combined with one POCT for diagnosing patients with symptoms suggestive of ACS compared with GPs relying on their clinical assessment only. The model is constructed from a societal point of view and a lifelong time horizon.

### 2.1.1 Model structure and nature

The model is made in the form of a decision tree. The decision tree models two different strategies for diagnosing patients with symptoms suggestive of ACS in primary care. See Figure 2 for the decision tree. This model is populated with individual patients following the decision tree, making the model a patient level simulation model (also known as a micro simulation or individual sampling model).[30] Patient level simulations allow for a precise allocation of costs, consequences and other model parameters based on individual patient characteristics such as age and gender.[30] The result is an integral hypothetical cohort of patients that tries to represent society by each individual having their own set of parameters. A cohort model does not allow for this.

The two strategies under investigation are: clinical assessment with one POCT for cardiac markers; the *POCT strategy*, and clinical assessment without POCT for cardiac markers; the *non-POCT strategy*. Clinical assessment by the GP is defined as anamnesis, including family anamnesis, and physical examination as described in the NHG directive for ACS.[27]

After the strategy distinction the model distinguishes patients on their true disease state, whether they have an ACS or not and if they do, which classification of ACS according to the ESC (Figure 1): UAP, NSTEMI or STE-ACS/STEMI (Figure 2). Depending on the diagnostic performance of the two strategies, the true ACS patients are either referred to the emergency department (ED) by ambulance when either strategy suggests ACS is present or send home when this is not the case. An ED referral in this case is a true-positive (TP) referral. When the ACS is missed, the patients is false-negatively (FN) send home. For patients with TP test results, the decision tree ends at the ED either when the patient's condition is fatal, before or after treatment or when the patient recovers and survives due to this treatment. Patients with FN test results are send home by the GP while a life threatening condition is present. These patients at some point are assumed to experience more severe complaints and/or die. It is assumed that patients in this situation who survive will refer themselves directly to the ED or call for an ambulance. The tree ends when the patient dies at home because of the ACS or when the patient is admitted at the ED at which he dies or survives because of treatment.

Because early mortality associated with acute myocardial infarction has fallen in the past decades, many patients with ischemic heart disease survive longer and eventually develop chronic congestive heart failure.[1] This probability of new heart failure is included in the model for surviving ACS patients. When ACS is not present, it is possible in either strategy to suggest ACS is present at which the GP will refer the patient to the ED. This referral however, is a false-positive (FP) one. At the ED no ACS causing the symptoms will be found and the patient is send home ending the tree. When the patient is true-negatively assessed by either strategy, the GP might further investigate the origin of the chest complaints after which the patient will be send home and the tree ends.

### 2.1.2 Model parameters

The model described in the previous paragraph is populated with different parameters representing probabilities, costs and effects. Probabilities reflect which path patients will take when moving through the decision tree. Which costs have to be taken into

account depends on the perspective of the economic evaluation. Since this economic evaluation is performed from a societal perspective, not only direct health care costs, but also indirect costs, which may represent a burden for society, have been taken into account. Costs of loss of production due to illness or consultation are part of these indirect costs. Finally, parameters for effectiveness are inserted into the model. The effectiveness of the two strategies is measured in patient's life expectancy, adjusted for the health-related quality of life i.e. quality adjusted life years (QALYs). Lifetime QALYs are allocated to each individual patient when its final health state is determined. Estimates for the probability and effectiveness parameters will be obtained by a systematic search and review of literature using electronic databases. A systematic review allows for a more objective appraisal of the evidence.[31] A search protocol with appraisal and substantiation of the results is included in appendix II. All parameters identified and their estimates are shown in Table 5-10.

### 2.1.3 Probabilities

**Model population**

Since the nature of the model is at the patient level, each individual patient at the start of the simulation is allocated an: age, gender, probability of ACS, and true disease. Age is allocated with 10-year increments. The age groups are: 35-44, 45-54, 55-64, 65-74, and ≥75. These allocations together with gender are based on probabilities derived from a German cohort of consecutive chest pain patients presenting in primary care (Table 5).[15] This cohort did not stratify ACS patients according to the ESC guidelines described previously.[2] Therefore stratification of ACS patients in UAP, NSTEMI and STE-ACS/STEMI is based on a Dutch study of primary care chest pain patients who were referred on suspicion of ACS.[32]

**Diagnostic performance characteristics**

Estimates of the probabilities for TP, FN, TN, FP test results are based on the sensitivity and specificity of the GP's clinical assessment.

The systematic search of medical literature for the performance of the clinical assessment by the GP for ACS yielded only one study. This study by Bösner et al. (2010) was deemed not useable in the model since the reported sensitivity and specificity were not based on whether or not the patient got referred by the GP but on a preliminary diagnosis by the GPs, independent of their referral decisions. This led to an overestimation of specificity (98%) and underestimation of sensitivity (50%).[16] When used in the model this would result in biased referral rates of ACS and healthy patients for the non-POCT strategy. Instead, results from a study by Nilsson et al. (2008) are used in the model. Nilsson et al. explicitly state the sensitivity and specificity for the '*GP's action in daily practice'* including referral to secondary care. However Nilsson et al. (2008) studied not only the GPs diagnostic performance for ACS, but for all IHD, including stable conditions like angina pectoris. The reported sensitivity and specificity were 88.3% and 72.2% respectively.[33]

**Mortality and chronic heart failure**

Mortality and chronic heart failure rates for the different conditions are derived by consulting large multinational registries for ACS. Mortality and heart failure rates reported by Goldberg et al. (2004) based on the GRACE registry were appraised to represent the best approximation of these probabilities, and provided stratified figures for UAP, NSTEMI and STEMI (Table 5).[34,35] The GRACE project tries to reflect a generalizable sample of patients hospitalized with acute coronary syndrome. 90 community and teaching hospitals located in 14 countries across four continents are participating in this observational study. Details of the methodology of GRACE have been previously described.[34,36] In another identified GRACE study by Granger et al. (2003) an odds ratio of 1.7 per 10 years increase in age for mortality was found by a multivariable regression model (Table 6).[37] The mortality rates reported by Goldberg et al. (2004) are allocated to the model age groups according to the median age of the cohort in the study. The odds ratio of 1.7 per 10 years increase in age is then used to calculate the mortality rates for the remaining age groups.

**Missed ACS**

In case of false-negatively send home patients, the ACS is missed by the GP. Patients with a missed

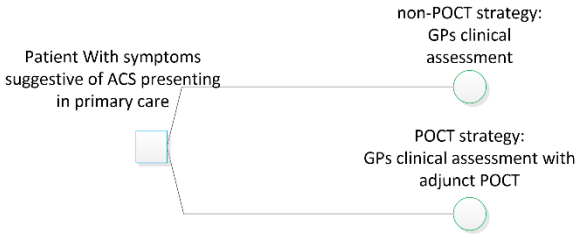



**Figure 2A: Decision tree: strategy outlining**

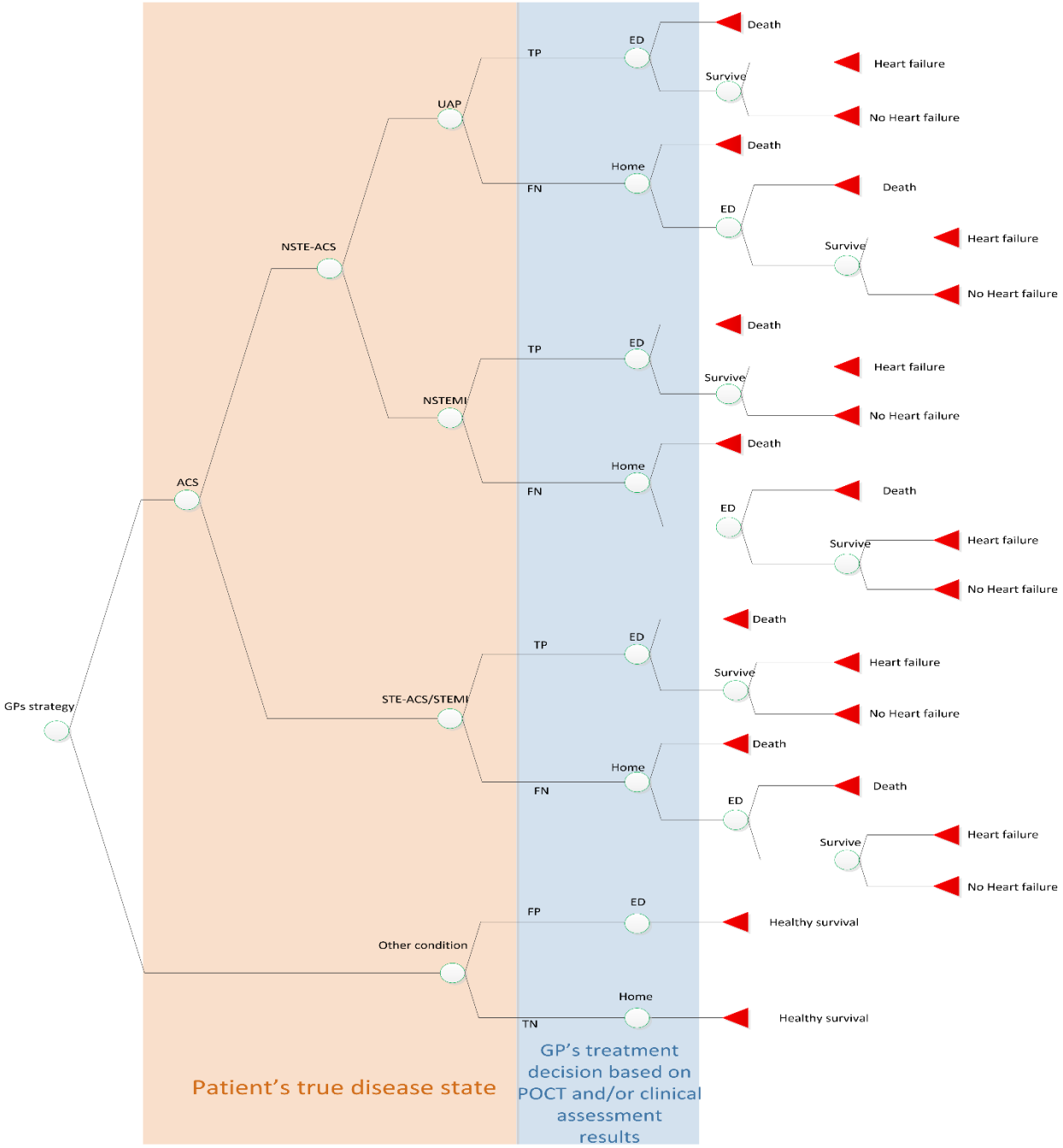



**Figure 2B: Decision tree: continuation for both strategies**

diagnosis of ACS are at higher risk of experiencing negative outcomes such as mortality and heart failure.[38,39] The systematic literature search resulted in two studies for use in the model. Pope et al. (2000) reported mortality hazard ratios for missed UAP and AMI of 1.7 and 1.9 respectively (Table 6).[38] Sequist et al. (2005) reported a heart failure rate among missed AMIs of 0.44.[39] This rate is also applied for missed UAP patients in the present study.

**POCT delay**

For myocardial infarctions early provision of therapy, particularly reperfusion therapy, is critical to the patients' benefit and is associated with improved outcomes.[40] By carrying out POCT at the GP's office it is likely this will increase the time of the patient being at the GP's office. Compared with patients attending GPs without POCT facilities these patients will experience a delay in receiving the specialised care provided by emergency departments in case of present ACS. For STEMI patients the effects of delay are modelled as a delay to receiving primary PCI. Given that there are 30 PCI capable centres in the Netherlands is seems reasonable to think that the majority of the STEMI patients will receive primary PCI instead of fibrinolytic therapy.[7] The systematic literature search yielded an increase in mortality probability for STEMI patients of 0.0018 per 10 minutes of delay (Table 6).[9] For UAP and NSTEMI patients no evidence was found that the amount of delay that can be caused by POCT at the GP causes significant changes in health outcomes. Identified studies investigated treatment delays of at least 12 hours for NSTE-ACS.[41,42] The amount of delay because of POCT is set at 30 minutes.

### 2.1.4 Quality of life

Quality of life is modelled in QALYs. Depending on the patient's final health stage, age and gender, remaining lifetime QALYs are allocated. Lifetime QALYs are a multiplication of expected remaining lifetime and the health related quality of life of this lifetime.[29] Health related quality of life is influenced by the patient's health state. Utility scores indicate the health related quality of life for different health states. The life time QALY estimates for the different conditions in the model are derived using the cost-effectiveness analyses (CEA) registry and consultation with previous health economic studies published in the Health Technology Assessment (Winchester, England) (HTA) journal.[43,44]

**NSTEMI, STEMI**

Consulting with the registry and the HTA journal did not result in separate utility weights or QALY estimates for STEMI and NSTEMI patients. Consequently, these patients are grouped together as AMI for which various utility weights and QALY estimates are available. No studies were identified who presented Dutch utility weights. The HTA journal yielded a systematic review and economic model for diagnostic strategies for ACS by Goodacre et al. (2013).[45] This study provided lifetime QALY estimates for AMI, discounted at 3% and based on remaining life expectancy reported by Polanczyk et al. (1999) and utility weights for AMI of 0.78 reported by Ward et al. (2007) (Table 8).[46,47]

**UAP**

For UAP patients, no HTA publication provided already calculated lifetime QALYs or utility weights. The CEA registry did reveal several studies who reported utility weights for UAP patients. However no long term mortality rates were identified for UAP alone so no lifetime QALY estimates could be calculated. A study by Chang et al. (2003) reports the 5-year mortality of AMI to be 10.19% higher than UAP, therefore the lifetime AMI QALYs reported by Goodacre et al. (2013) were increased by this 10.19% (Table 8).[45,48]

**Heart failure**

For heart failure the life time QALYs are calculated using long term mortality data from a Dutch study on heart failure: the Groningen longitudinal study by van Jaarsveld et al. (2006).[49] The Groningen longitudinal study provides Dutch estimates on mean survival time of heart failure patients since time of diagnosis. These survival times are multiplied with a utility score of 0.636 reported by Sullivan et al. (2009) identified through the CEA registry.[50] A discount rate of 3% per year is applied for the lifetime QALY calculation. The resulting lifetime QALYs for heart

**Table 5: Model probabilities, their deterministic value, range, distribution and source**

| Population Age distribution | Deterministic value | Range | Distribution | Source |
|---|---|---|---|---|
| ≥75 | 0.1642 | n/a | | Bösner, 2009[15] |
| 65-74 | 0.2450 | n/a | | Bösner, 2009[15] |
| 55-64 | 0.1939 | n/a | Dirichlet(199, 297, 235, 253, 228) | Bösner, 2009[15] |
| 45-54 | 0.2087 | n/a | | Bösner, 2009[15] |
| 35-44 | 0.1881 | n/a | | Bösner, 2009[15] |
| **ACS Probability** | | | | |
| ≥75 | 0.0815 | 0.0435-0.1195 | Beta(16.22, 182.78) | Bösner, 2009[15] |
| 65-74 | 0.0519 | 0.0267-0.0771 | Beta(15.41, 281.59) | Bösner, 2009[15] |
| 55-64 | 0.0333 | 0.0104-0.0562 | Beta(7.83, 227.17) | Bösner, 2009[15] |
| 45-54 | 0.0111 | 0-0.0240 | Beta(2.81, 250.19) | Bösner, 2009[15] |
| 35-44 | 0.0148 | 0-0.0305 | Beta(3.37, 224.63) | Bösner, 2009[15] |
| **Gender among ACS population** | | | | |
| Male | 0.5455 | 0.3984-0.6926 | Beta(24, 20) | Bösner, 2009[15] |
| **Gender among non-ACS population** | | | | |
| Male | 0.4366 | 0.4082-0.4650 | Beta(510, 658) | Bösner, 2009[15] |
| **ACS type** | | | | |
| NSTE-ACS | 0.727 | 0.620-0.834 | Beta(48, 18) | Bruins Slot, 2013[32] |
| UAP when NSTE-ACS | 0.292 | 0.163-0.421 | Beta(14, 34) | Bruins Slot, 2013[32] |
| **Mortality probability** | | | | |
| UAP at ED after TP test result (median age: 66.6) | 0.027 | 0.024-0.030 | Beta(223.97, 8071.03) | Goldberg, 2004[35] |
| NSTEMI at ED after TP test result (median age: 68.1) | 0.059 | 0.054-0.064 | Beta(442.5, 7057.5) | Goldberg, 2004[35] |
| STE-ACS/STEMI at ED after TP test result (median age: 63.4) | 0.078 | 0.072-0.084 | Beta(644.28, 7615.72) | Goldberg, 2004[35] |
| **Heart failure probability** | | | | |
| UAP at ED after TP test result | 0.092 | 0.085-0.099 | Beta(565.71, 5583.29) | Goldberg, 2004[35] |
| NSTEMI at ED after TP test result | 0.179 | 0.169-0.189 | Beta(932.41, 4276.59) | Goldberg, 2004[35] |
| STE-ACS/STEMI at ED after TP test result | 0.184 | 0.174-0.194 | Beta(1007.58, 4468.42) | Goldberg, 2004[35] |
| All ACS after FN test result | 0.444* | 0.214-0.674 | Beta(8, 10) | Sequist, 2005[39] |

ACS: acute coronary syndrome, NSTE-ACS: non st-elevation acute coronary syndrome, UAP: unstable angina pectoris, ED: emergency department, STE-ACS: st-elevation acute coronary syndrome, STEMI: st-elevation myocardial infarction, TP: true-positive, FN: false-negative, n/a: not available

*Formally this rate is based only on AMI patients.

**Table 6: Model probability modifiers, their deterministic value, range, distribution and source**

| Probability modifier | Deterministic value | Range | Distribution | Source |
|---|---|---|---|---|
| Mortality odds ratio per 10 years increase in age | 1.7 | 1.52-1.82 | LogNormal(0.53, 0.05) | Granger, 2003[37] |
| Mortality risk ratio missed UAP | 1.7 | 0.2-17.0 | LogNormal(0.53, 1.13) | Pope, 2000[38] |
| Mortality risk ratio missed NSTEMI | 1.9 | 0.7-5.2 | LogNormal(0.64, 0.51) | Pope, 2000[38] |
| Mortality risk ratio missed STE-ACS/STEMI | 1.9 | 0.7-5.2 | LogNormal(0.64, 0.51) | Pope, 2000[38] |
| Increase in mortality per 10 min delay for STE-ACS/STEMI | 0.0018 per 10 minutes delay | n/a | | Nallamothu, 2007[9] |

UAP: unstable angina pectoris, NSTEMI: non st-elevation myocardial infarction, STE-ACS: st-elevation acute coronary syndrome, STEMI: st-elevation myocardial infarction, n/a: not available

**Table 7: Diagnostic performance of clinical assessment by GP for ACS, their deterministic value, range, distribution and source**

| Performance characteristic | Deterministic value, % | Range, % | Distribution | Source |
|---|---|---|---|---|
| Sensitivity | 88.3 | 80.2-96.5 | Beta(53, 7) | Nilsson, 2008[33] |
| Specificity | 72.2 | 68.1-76.4 | Beta(320, 123) | Nilsson, 2008[33] |

**Table 8: Model discounted life time QALYs, their deterministic value, range, distribution and source**

| Health State | Age | Deterministic value | Range | Distribution | Source |
|---|---|---|---|---|---|
| UAP | ≥75 | 2.678 | 2.153-3.202 | Gamma(100, 0.027) | Goodacre, 2013[45] Chang, 2003[48] |
| | 65-74 | 5.124 | 4.120-6.128 | Gamma(100, 0.051) | |
| | 55-64 | 7.416 | 5.962-8.869 | Gamma(100, 0.074) | |
| | 45-54 | 10.435 | 8.390-12.480 | Gamma(100, 0.104) | |
| | 35-44 | 13.443 | 10.808-16.078 | Gamma(100, 0.134) | |
| NSTEMI/STEMI | ≥75 | 2.430 | 1.954-2.906 | Gamma(100, 0.024 | Goodacre, 2013[45] |
| | 65-74 | 4.650 | 3.739-5.561 | Gamma(100, 0.047) | |
| | 55-64 | 6.730 | 5.411-8.049 | Gamma(100, 0.067) | |
| | 45-54 | 9.470 | 7.614-11.326 | Gamma(100, 0.095) | |
| | 35-44 | 12.200 | 9.809-14.591 | Gamma(100, 0.122) | |
| Male healthy patients | ≥75 | 3.087 | 2.482-3.692 | Gamma(100, 0.031) | Goodacre, 2013[45] |
| | 65-74 | 7.560 | 6.078-9.042 | Gamma(100, 0.076) | |
| | 55-64 | 11.499 | 9.245-13.753 | Gamma(100, 0.115) | |
| | 45-54 | 15.817 | 12.717-18.917 | Gamma(100, 0.158) | |
| | 35-44 | 19.450 | 15.638-23.262 | Gamma(100, 0.195) | |

| Health State | Age | Deterministic value | Range | Distribution | Source |
|---|---|---|---|---|---|
| Female healthy patients | ≥75 | 2.990 | 2.404-3.576 | Gamma(100, 0.03) | Goodacre, 2013[45] |
| | 65-74 | 7.352 | 5.911-8.793 | Gamma(100, 0.074) | |
| | 55-64 | 11.194 | 9.000-13.388 | Gamma(100, 0.112) | |
| | 45-54 | 15.411 | 12.390-18.432 | Gamma(100, 0.154) | |
| | 35-44 | 18.968 | 15.250-22.686 | Gamma(100, 0.190) | |
| Male heart failure patients | ≥75 | 2.047 | 1.646-2.448 | Gamma(100, 0.02) | Van Jaarsveld, 2006[49] Sullivan, 2009[50] |
| | <75 | 2.718 | 2.185-3.250 | Gamma(100, 0.027) | |
| Female heart failure patients | ≥75 | 2.144 | 1.724-2.564 | Gamma(100, 0.021) | Van Jaarsveld, 2006[49] Sullivan, 2009[50] |
| | <75 | 3.505 | 2.818-4.192 | Gamma(100, 0.035) | |

UAP: unstable angina pectoris, NSTEMI: non st-elevation myocardial infarction, STEMI: st-elevation myocardial infarction

**Table 9: Model costs, their deterministic value, range, distribution and source**

| Description | Age | Deterministic value, € | Range, € | Distribution | Source |
|---|---|---|---|---|---|
| GP consultation per 10 minutes | All | 29.74 | 20.99-38.48 | Gamma(44.444, 0.669) | Hakkaart-van Roijen, 2010[51] |
| POCT at GP | All | 30 | 1-200 | Gamma(1, 30) | Assumption |
| Ambulance to ED | All | 535.25 | 377.89-692.61 | Gamma(44.444, 12.043) | Hakkaart-van Roijen, 2010[51] |
| Treatment UAP | All | 3216.40 | 2270.78-4162.03 | Gamma(44.444, 72.369) | DBC tariffs[52,53] |
| Treatment NSTEMI | All | 4255.99 | 3004.73-5507.25 | Gamma(44.444, 95.760) | DBC tariffs[52,53] |
| Treatment STEMI | All | 4414.56 | 3336.68-5712.44 | Gamma(44.444, 99.328) | DBC tariffs[52,53] |
| Diagnostics for healthy patients at ED | All | 674.58 | 476.26-872.91 | Gamma(44.444, 15.178) | DBC tariffs[52,53] |
| Discounted lifetime healthcare costs UAP patients | ≥75 | 1080.16 | 762.59-1397.73 | Gamma(44.444, 24.304) | Goodacre, 2013[45] Chang, 2003[48] |
| | 65-74 | 2065.81 | 1458.46-2673.16 | Gamma(44.444, 46.481) | Goodacre, 2013[45] Chang, 2003[48] |
| | 55-64 | 2990.70 | 2111.43-3869.96 | Gamma(44.444, 67.291) | Goodacre, 2013[45] Chang, 2003[48] |
| | 45-54 | 4205.88 | 2969.35-5442.41 | Gamma(44.444, 94.632) | Goodacre, 2013[45] Chang, 2003[48] |
| | 35-44 | 5417.69 | 3824.89-7010.49 | Gamma(44.444, 121.898) | Goodacre, 2013[45] Chang, 2003[48] |
| Discounted lifetime healthcare costs NSTEMI, STEMI patients | ≥75 | 980.27 | 692.07-1268.47 | Gamma(44.444, 22.056) | Goodacre, 2013[45] |
| | 65-74 | 1874.77 | 1323.59-2425.95 | Gamma(44.444, 42.182) | Goodacre, 2013[45] |
| | 55-64 | 2714.13 | 1916.17-3512.08 | Gamma(44.444, 61.068) | Goodacre, 2013[45] |
| | 45-54 | 3816.93 | 2694.76-4939.11 | Gamma(44.444, 85.881) | Goodacre, 2013[45] |

| Description | Age | Deterministic value, € | Range, € | Distribution | Source |
|---|---|---|---|---|---|
| Discounted lifetime healthcare costs NSTEMI, STEMI patients | 35-44 | 4916.68 | 3471.17-6362.18 | Gamma(44.444, 110.625) | Goodacre, 2013[45] |
| Discounted lifetime healthcare costs male heart failure patients | ≥75 | 13423.12 | 9476.73-17369.52 | Gamma(44.444, 302.020) | RIVM cost of illness tool[54] Gommer, 2011[55] Van Jaarsveld, 2006[49] |
| | <75 | 17820.34 | 12581.16-23059.52 | Gamma(44.444, 400.958) | |
| Discounted lifetime healthcare costs female heart failure patients | ≥75 | 14059.24 | 9925.82-18192.66 | Gamma(44.444, 316.333) | RIVM cost of illness tool[54] Gommer, 2011[55] Van Jaarsveld, 2006[49] |
| | <75 | 22982.88 | 16225.91-29739.85 | Gamma(44.444, 517.115) | |
| Production loss per hour per male patient | 55-64 | 40.77 | 28.78-52.75 | Gamma(44.444, 0.917) | Hakkaart-van Roijen, 2010[51] |
| | 45-54 | 40.18 | 28.37-51.99 | Gamma(44.44, 0.904) | Hakkaart-van Roijen, 2010[51] |
| | 35-44 | 36.71 | 25.92-47.50 | Gamma(44.44, 0.826) | Hakkaart-van Roijen, 2010[51] |
| Production loss per hour per female patient | 55-64 | 30.20 | 21.32-39.08 | Gamma(44.44, 0.680) | Hakkaart-van Roijen, 2010[51] |
| | 45-54 | 30.20 | 21.32-39.08 | Gamma(44.44, 0.679) | Hakkaart-van Roijen, 2010[51] |
| | 35-44 | 30.28 | 21.38-39.18 | Gamma(44.44, 0.681) | Hakkaart-van Roijen, 2010[51] |

GP: general practitioner, POCT: point of care testing, ED: emergency department, UAP: unstable angina pectoris, NSTEMI: non st-elevation myocardial infarction, STEMI: st-elevation myocardial infarction

**Table 10: Production time lost per health state, their deterministic value, range, distribution and source**

| Health state | Deterministic value | Range | Distribution | Source |
|---|---|---|---|---|
| ACS | 4,8570 weeks | 1.498-8.216 | Gamma(409.56, 0.01) | Mourad, 2013[56] |
| Heart failure | 18,8930 weeks | 11.487-26.299 | Gamma(44.44, 0.43) | Spannheimer, 1998[57] |
| Healthy patient referred to ED | 6,5000 hours | 3.952-9.048 | Gamma(44.44, 0.15) | Assumption |
| Healthy patient not referred to ED with POCT | 0,8333 hours | 0.507-1.160 | Gamma(44.44, 0.02) | Assumption |
| Healthy patient not referred to ED without POCT | 0,3333 hours | 0.203-0.464 | Gamma(44.44, 0.01) | Assumption |

ACS: acute coronary syndrome, ED: emergency department, POCT: point of care testing

**Healthy patients**

Goodacre et al. (2013) also reported the remaining lifetime QALYs for healthy patients. These were reported with one year increments in age. For use in the health economic model, averages were calculated for the age-groups corresponding with the age-groups used in the health economic model (Table 8).[45]

### 2.1.5 Costs

The estimates for cost parameters are obtained by consulting with the Dutch healthcare authority (Nederlandse Zorgautoriteit, NZA), the Dutch college of health insurances (College voor Zorgverzekeringen, CVZ) and the Dutch National Institute for Public Health and Environment (Rijksinstituut voor Volksgezondheid en Milieu, RIVM). All costs are in 2012 Euros (€).

**General Practitioner and ambulance**

The CVZ reports reference prices for a 10 minute GP consultation and ambulance transportation to be €28 and €504 respectively. Using the consumer price index from 2009 to 2012 provided by the Dutch central bureau for statistics (Centraal Bureau voor de Statistiek, CBS), these prices are converted to 2012 prices (Table 9).[51,58]

**POCT**

To estimate costs for POCT for ACS in primary care the Dutch healthcare authority is consulted for tariffs for available cardiac biomarkers: Tariffs for troponin, CK-MB, and myoglobin lab tests in 2012 are € 9,14; € 9,43 and € 9,00 respectively.[52] The order fee for lab tests is € 13,73. A single cardiac biomarker would then approximate a tariff of € 23. Since the POCT device is situated in a GP practice and not in a laboratory processing orders for large amounts of patients, the capital costs, such as investment and depreciation of the POCT device is shared between fewer patients, increasing the per patient costs. To incorporate this in the model, the costs for a single cardiac POCT marker is increased to € 30. Also a deliberately higher estimate for uncertain costs is a safe approach when drawing conclusions on cost-effectiveness.

**Treatment UAP, NSTEMI, STEMI and diagnostics for healthy patients**

Treatment costs for ACS and the costs of diagnostics for healthy patients at the ED are derived from the NZA and by consulting with the diagnosis treatment combination (DTC) information system (DIS). DTCs are allocated to patients in Dutch secondary care and are based on diagnosis and treatment received. DTCs are divided in two segments A and B. Tariffs for A-segment DTCs are determined annually by the NZA and are maximum tariffs. Tariffs for B-segment DTCs are freely negotiable between healthcare providers and insurers. A-segment DTCs of interest for this study are all PCI related DTCs with or without additional nursing days. These tariffs are derived by consulting with the NZA's tariff application.[52] B-segment DTCs of interest comprise mainly out of nursing days and general diagnostics. The average selling prices of these DTCs were derived from the DIS.[53] The DIS also provides volume estimates for the different DTCs declared for UAP, NSTEMI, STEMI and healthy patients so weighted average costs could be calculated per health state modelled. All tariffs are in 2012 euro's since not all data from 2013 and 2014 is processed in DIS yet. Only less than 1% and 45% of the DTCs are processed for these years respectively. For 2012 this is 85%. See appendix III for an elaboration on costs calculations of UAP, NSTEMI, STEMI and healthy patients.

**Lifetime healthcare costs**

Lifetime healthcare costs represent the accumulation of healthcare costs due to the patient's health state during the remainder of the patient's life. The use of POCT in primary care is expected to influence the patient's outcome by correctly diagnosing ACS in more cases. Consequently, a difference in lifetime healthcare costs is expected. Lifetime healthcare costs for NSTEMI and STEMI were taken from the same study by Goodacre et al. (2013) as were the QALY estimates for NSTEMI and STEMI (Table 8).[45] As these costs were reported in GBP(£), they were converted to Euros by using the 01-01-2013 exchange rate of 1.225.[59] To estimate the lifetime healthcare costs for UAP, lifetime healthcare costs for NSTEMI and STEMI were taken and increased by the same 10.19% used to estimate the lifetime UAP QALYs (Table 8).[48] The lifetime healthcare costs for heart failure were estimated by dividing the total healthcare costs for heart failure in 2007 in the Netherlands by the absolute point prevalence of heart failure in 2007 in

the Netherlands.[54,55] The resulting cost per patient estimate was converted to the 2012 price levels by using the consumer price index provided by the CBS.[58] Combining this estimate with the already found mean survival times in the Groningen longitudinal study, while discounting with a rate of 3%, resulted in lifetime healthcare costs for heart failure stratified in age and gender (Table 8).[49]

**Costs of production loss**

Production losses occur when labour time is lost due to patients receiving healthcare.[29] In this health economic evaluation, production losses occur for all patients. Important differences are expected within the GP practice between those with and without POCT, since drawing, analysing and interpreting the sample takes extra time. As mentioned before, the use of POCT in primary care is also expected to influence the patients' outcome. This is also expected to influence the production losses. The costs of production losses comprise out of the volume of the labour time lost due to receiving healthcare and the valuation of this lost labour time.[51] The volume of labour time lost due to ACS is based on a study by Mourad et al. (2013).[56] The average reported duration of sick leave for AMI is 34 days.[56] For UAP patients the same amount of sick leave is used in de model. For heart failure, Spannheimer et al. (1998) reports an average sick leave of 132.25 days. [57] These sick leave durations are converted to sick leave in weeks. Using the friction costs method, as recommended by the CVZ, the amount of labour hours lost due to sick leave is calculated assuming 1540 possible work hours per year.[51] The friction period in the Netherlands is determined to be 23 weeks, meaning that additional labour time lost after 23 weeks is assumed to be resolved by the employer and is not accounted for when calculating production losses.[51] The volume of labour time lost for patients dying in the model is set at the maximum friction time of 23 weeks. The volume of labour time lost for patients without ACS due to visiting the GP and the ED are assumptions (Table 10).

The valuation of production losses per hour is corrected for Dutch elasticity of labour time relative to production with 0.8. This means that production is lowered with 8% when the labour time is lowered by 10%.[51] These valuations per hour are given in Table 9 stratified in age and gender. In de model the final costs of production loss are calculated by multiplying the volume with the valuation per hour of labour time lost, corresponding with the patient's age, gender and health state.

## 2.2 Running the model

Individual patient flow through the model is determined by random number generation provided by Microsoft Excel 2010 (Microsoft Corporation, Redmond/WA) and the model probabilities described above. A random number equal or smaller than the probability used in the model resulted in the corresponding event to occur or a condition being present. In both the strategies the same cohort of patients is modelled with identical random numbers. Between strategy differences found in costs and QALYs are thus only attributable to the differences between the strategies. After the patient's final health state is determined, QALYs and costs are allocated corresponding with the patient's health state, demographics and path through the model.

### 2.2.1 Stochastic uncertainty

The patient level nature of the model introduces stochastic uncertainty, meaning that variation in output between model runs occurs due to different random numbers being sampled.[60] This stochastic uncertainty is assessed in a similar way as described by Karnon et al. (2003) by running the model 50 times with sample sizes of 1000, 10.000 and 20.000 patients while keeping the model parameters constant at their deterministic values.[61] The resulting estimates of incremental costs and QALYs are depicted on a cost-effectiveness plane (Figure 3). The dispersion of estimates shrinks as the sample size is increased. With 20.000 patients the incremental costs are varying between €50 and €75 while the incremental QALYs vary between 0 and 0,006. With 20.000 patients the spread is sufficiently reduced while the computational burden for the following analyses will still be acceptable.

### 2.2.2 Analyses

**Threshold analysis**

A threshold analysis by means of a two-way sensitivity analysis is performed for the combined sensitivity and specificity of the GP's clinical assessment and POCT. The sensitivity and specificity are varied on an interval ranging from 67%-100%. The model is run 60 times per combination of sensitivity and specificity. Whether or not the POCT strategy is cost-effective compared with the non-POCT strategy depends on the incremental cost-utility ratio (ICUR) i.e. the extra costs for one extra QALY gained. When the ICUR is lower or equal to the willingness to pay (WTP) threshold per QALY, the POCT strategy can be considered cost-effective. In the Netherlands there is no strict WTP threshold. A common used threshold is €30.000/QALY which approximates the WTP threshold utilized in the UK of £30.000/QALY.[62] While applying this threshold, for each combined sensitivity the minimum required combined specificity to be cost-effective is estimated. The result is a cost-effectiveness threshold between the POCT and non-POCT strategy.

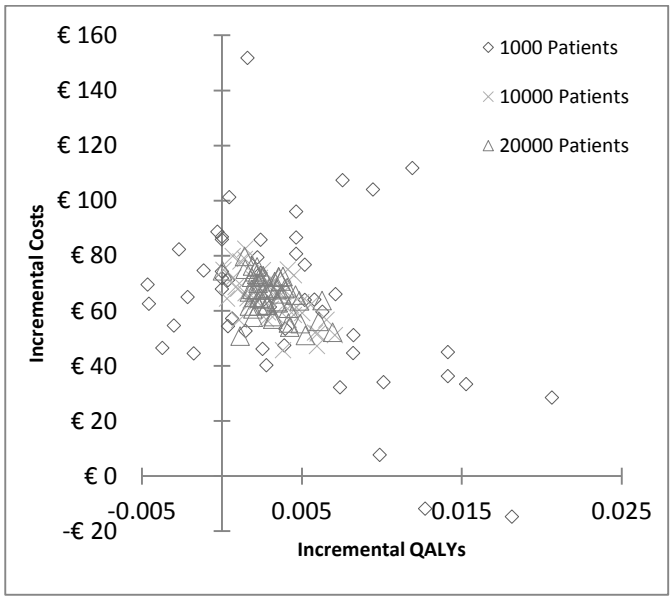



**Figure 3: Stochastic uncertainty for various sample sizes, depicted on a cost effectiveness plane**

**One-way sensitivity analysis**

One-way sensitivity analyses are performed on all parameters to investigate the individual impact of changes in input parameters on the cost-effectiveness.[29] The ranges of the different parameters reported in Table 5-10 act as the lower and upper limit for the one-way sensitivity analysis. For the model probabilities these ranges consist out of 95% confidence intervals reported in the identified literature. For QALY and cost estimates these ranges consist of 95% confidence intervals constructed with standard errors of 10% and 15% of their mean value respectively. An exception to this rule are the costs of POCT, this range is manually set at € 1-200. The probability of ACS as well as the lifetime QALYs, lifetime costs and production loss costs are varied simultaneously for all age groups. Per varied parameter the model is run 60 times with 20.000 patients and the mean ICUR is calculated. A tornado diagram ranks the parameters on their impact magnitude.

**Deterministic analysis**

Six combinations of combined sensitivity and combined specificity of the POCT strategy positioned on the cost-effectiveness threshold are further analysed deterministically to estimate the accompanying ICURs, number of false-positives and false-negatives avoided and risk ratios for mortality and new heart failure cases. The model is run 60 times per combination and results are given in boxplots.

**Probabilistic sensitivity analysis**

The model is also analysed probabilistically by means of Monte Carlo simulations with 5000 iterations. Distributions are assigned to all the parameters under investigation. All probability and diagnostic performance parameters have beta distributions assigned to them with the exception of the multinomial age group parameter which is assigned a dirichlet distribution (Table 5,7).[30] Alpha and beta parameters for the beta distributions are all obtained from the same published literature as were the deterministic values. The parameters modifying the probabilities are assigned a LogNormal distribution (Table 6).[30] The required log mean value and log standard error are calculated with the reported means and confidence intervals of the original publications. Utility values are commonly assigned a beta distribution when they are far away from zero.[30] The utility parameter for heart failure is therefor assigned a beta distribution with the alpha and beta parameters calculated with an assumed standard error of 10% of

the deterministic values. The other health states in the model do not work with utility values to estimate QALYs but rather get lifetime QALYs assigned based on existing medical literature. A gamma distribution, which is constrained to the interval 0 to positive infinity, is used instead to fit the lifetime QALY distributions (Table 8).[30] The alpha and beta parameters are calculated utilizing the method of moments approach with an assumed standard error of 10% of the deterministic lifetime QALY values.[30] In a similar way cost and production loss parameters are assigned a gamma distribution utilizing an assumed standard error of 15% of the deterministic value. To reflect the uncertainty around the costs of POCT, its standard error was set at 100% of the mean. The 5000 iterations are run whilst drawing random values from the assigned distributions. The results are depicted on a cost-effectiveness plane.

Multiple Monte Carlo simulations are run while keeping the same six combinations of combined sensitivity and specificity for the POCT strategy as were analysed deterministically constant. This way the uncertainty around all other parameters is assessed. Cost-effectiveness acceptability curves (CEACs) with WTP thresholds ranging from €0 until €200.000 are generated for each Monte Carlo simulation to show the probability of the POCT strategy being cost-effective compared with the non-POCT strategy, while applying different WTP thresholds. In generating the CEACs, QALY loss for a reduction in costs was not accepted as a cost-effective alternative. This prevents simulations from being classified as cost-effective while they actually reduce the quality of care for a monetary benefit.

# 3 Results

## 3.1 Threshold analysis

Simultaneously varying the sensitivity and specificity of the POCT strategy resulted in the cost-effectiveness threshold shown in Figure 4. Any combination of sensitivity and specificity of the POCT strategy positioned in the red area is not cost-effective because the ICUR is larger than the WTP of € 30.000. Additionally there might be QALYs lost compared with the non-POCT strategy. Any combination of sensitivity and specificity positioned in the green areas of the threshold analysis are cost-effective approaches and result in QALYs gained. In the lighter green area, the ICUR is positive, meaning an increase in costs, but remains under the WTP threshold. In de darker green area the ICUR is negative meaning costs are saved and the POCT strategy dominates the non-POCT strategy i.e. less costs and more QALYs generated. Further, the threshold analysis shows that the required sensitivity is able to decline as long as the specificity increases and still be cost-effective. This decline continues until a sensitivity of 91% is reached at which an increase in specificity does not allow a further decline in sensitivity while still be cost-effective.

## 3.2 One-way sensitivity analysis

To judge each parameters individual influence on the cost-effectiveness of the POCT strategy compared with the non-POCT strategy a one-way sensitivity analysis is performed. 49 parameters or parameter sets in case of age specific parameters were analysed. The spread between ICURs generated with lower and upper bound parameter values (tables 5-10) are plotted on a tornado diagram centered around the mean ICUR of € -4.317,69 per QALY resulting from a sensitivity of 91% and specificity of 82% for the POCT strategy. The eight most influencing parameters are shown in Figure 5. The tornado diagram shows that the costs of POCT and the specificity of the GP's assessment are able to increase the ICUR until above the WTP threshold of € 30.000/QALY making the non-POCT strategy more cost-effective. All other parameters are not able to cross the WTP threshold.

## 3.3 Deterministic analysis

The six numbered points in threshold analysis (Figure 4) represent the combinations of sensitivity and specificity for the POCT strategy that are further analysed deterministically. The ICURs for these six

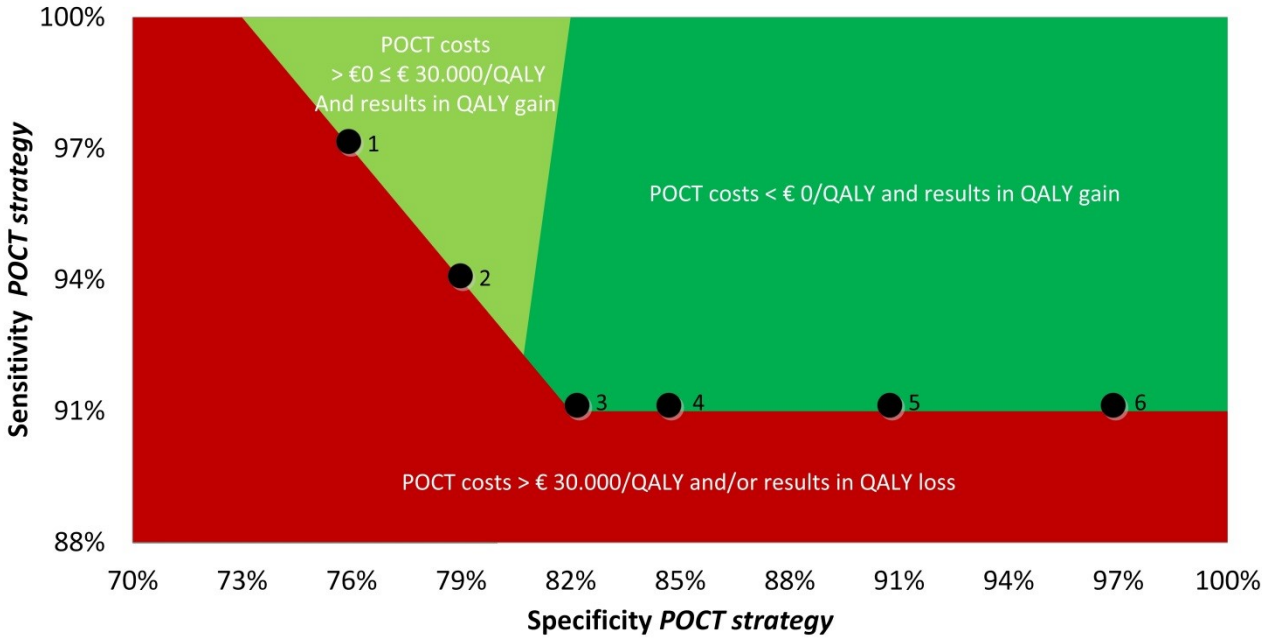



**Figure 4: Results of threshold analysis at WTP: € 30.000. The numbered points are combinations of sensitivity and specificity that are further analysed deterministically and probabilistically.**

**Table 11: ICUR results of deterministic analyses of six combinations of sensitivity and specificity for the POCT strategy. Results from 60 model runs with 20.000 patients**

| Combination | Sensitivity/specificity POCT strategy | ICUR, median (IQR) |
|---|---|---|
| 1 | 97%/76% | € 19.691 (€ 14.532 - € 26.846) |
| 2 | 94%/79% | € 13.773 (€ 8.437 - € 19.155) |
| 3 | 91%/82% | € -3.834 (€ -7.269 - € 957) |
| 4 | 91%/85% | € -52.704 (€ -91.236 - € -82.251) |
| 5 | 91%/91% | € -162.359 (€ -261.406 - € -97.561) |
| 6 | 91%/97% | € -225.874 (€ -397.479 - € -137.473) |

ICUR: incremental cost-utility analysis, POCT: point of care testing, IQR: inter quartile range

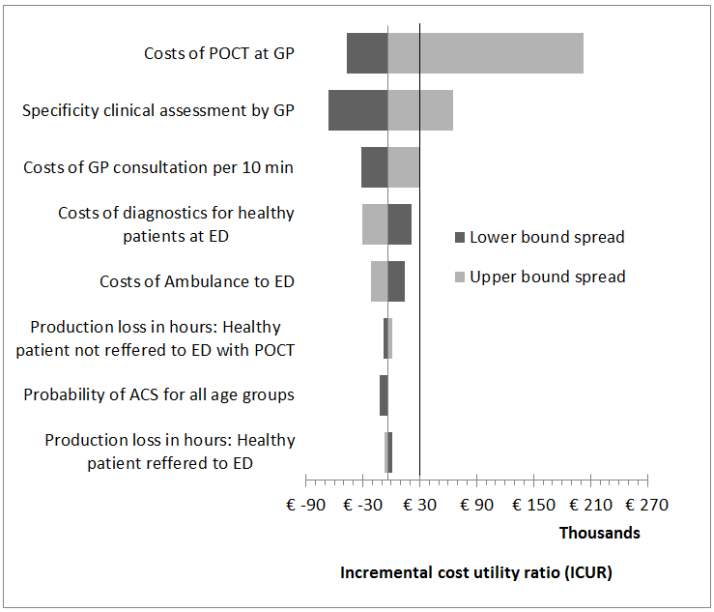



**Figure 5: Tornado diagram showing the 8 most influencing model parameters on the cost-effectiveness of the POCT strategy compared with the non-POCT strategy.**

combinations are reported in Table 11. The first combination representing a sensitivity and specificity of 97% and 76% respectively for the POCT strategy results in the highest ICUR. Combinations 3-6 result in negative median ICURs meaning that costs are saved per QALY gained for the POCT strategy compared with the non-POCT strategy.

Differences in the occurrences of mortality and new heart failure cases between the two strategies are expressed as risk ratios for the POCT strategy versus the non-POCT strategy. The lowest risk ratios (meaning the largest difference) for both mortality and new heart failure are found for 97% sensitivity and 76% specificity (Figure 6-7). The risk ratios increase as long as the sensitivity declines. For combinations 3-6 the sensitivity remains stable at 91%, resulting in similar risk ratios for mortality and heart failure between these combinations. The differences that

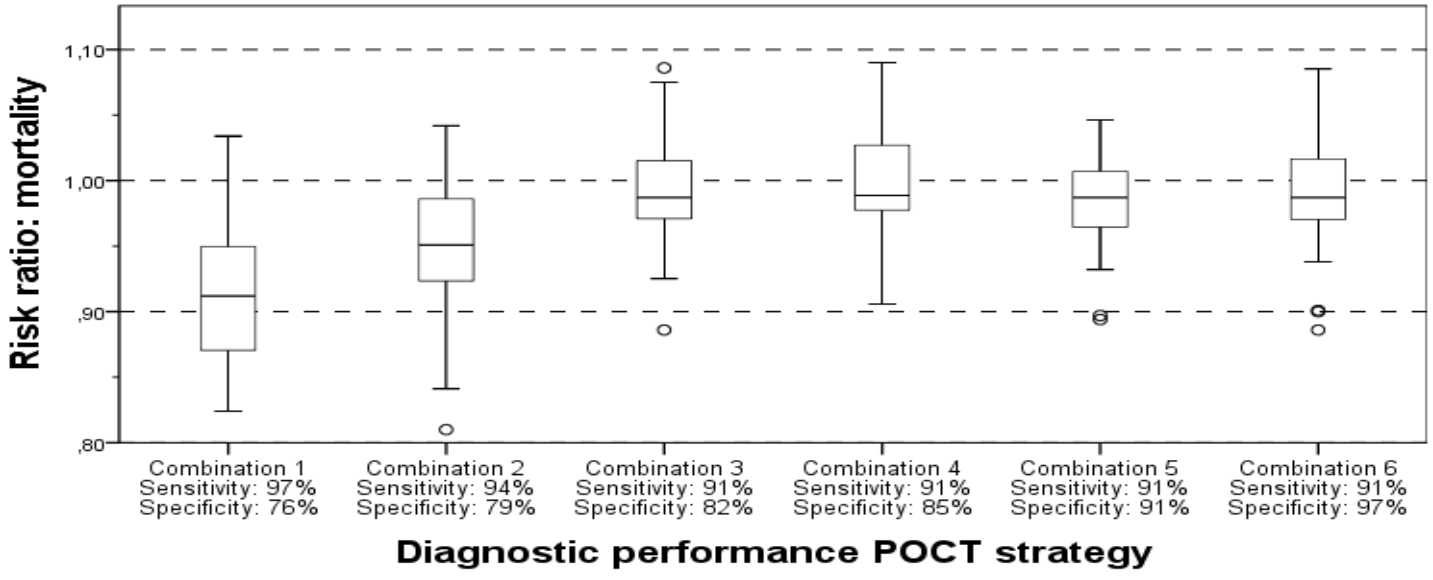



**Figure 6: Boxplots showing risk ratios for mortality of six combinations of sensitivity and specificity for the POCT strategy. Results from 60 model runs with 20.000 patients**

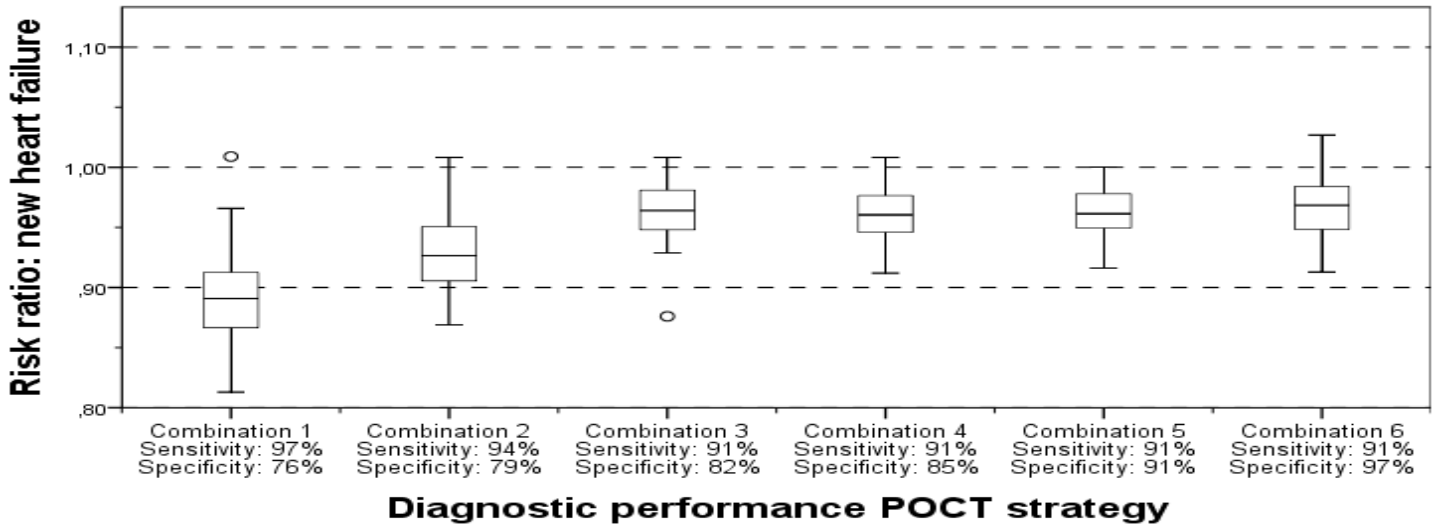



**Figure 7: Boxplots showing risk ratios for new heart failure of six combinations of sensitivity and specificity for the POCT strategy. Results from 60 model runs with 20.000 patients.**

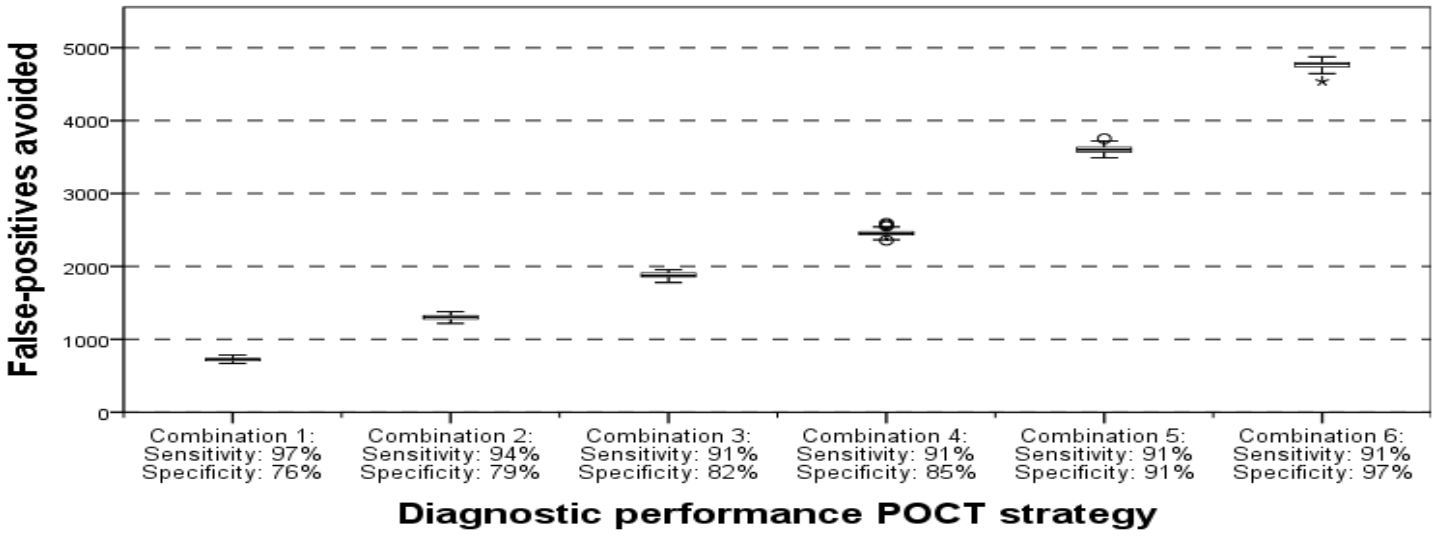



**Figure 8: Boxplots showing the number of false-positives avoided in diagnosing ACS of six combinations of sensitivity and specificity for the POCT strategy. Results from 60 model runs with 20.000 patients.**

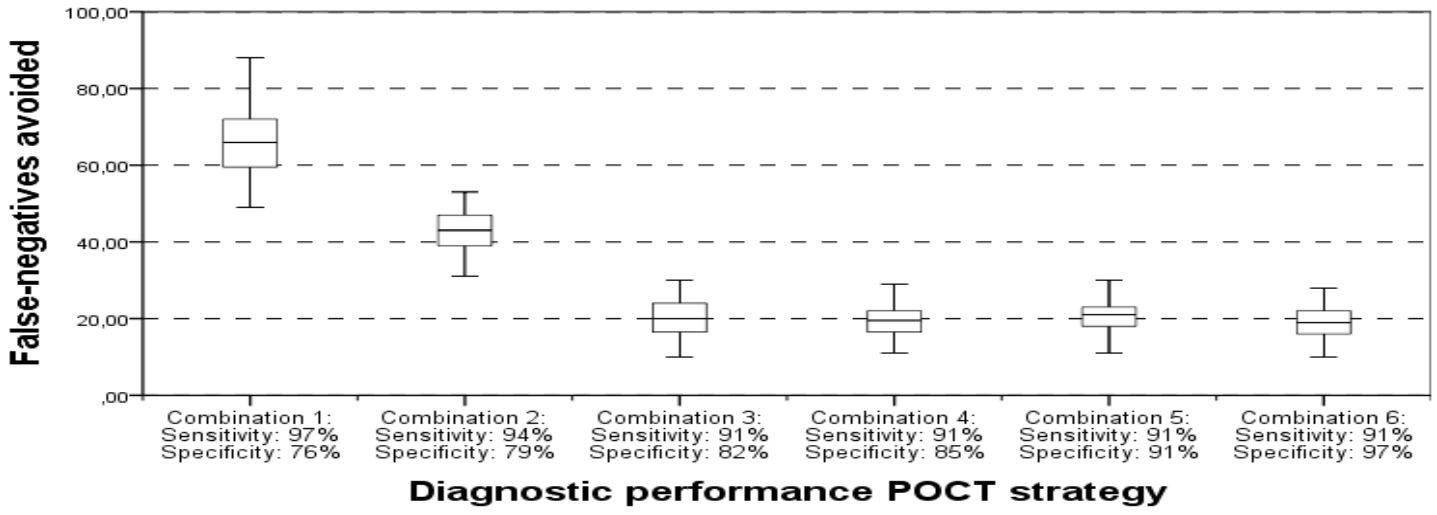



**Figure 9: Boxplots showing the number of false-negatives avoided in diagnosing ACS of six combinations of sensitivity and specificity for the POCT strategy. Results from 60 model runs with 20.000 patients.**

do occur are explained by the stochastic uncertainty in the model, introduced due to the patient level nature of the model.

Analysing the amount of false-positives and false-negatives avoided shows that the amount of false-positive referrals avoided increases as the specificity of the POCT strategy increases (Figure 8). False-positive referrals avoided results in cost savings due to patients without ACS being prevented from being sent to the ED for further diagnostics. The amount of false-negatives avoided is highest at a sensitivity of 97% and shrinks with a declining sensitivity of the POCT strategy (Figure 9). False-positives avoided lead to more health benefit (QALYs) because fewer patients with ACS are missed by the GP.

## 3.4 Probabilistic sensitivity analysis

The same six combinations of sensitivity and specificity further analysed deterministically are also analysed probabilistically for their cost-effectiveness. While keeping the sensitivity and specificity combinations constant, all other model parameters were sampled probabilistically as described in the methods section. The incremental costs and QALYs were plotted in cost-effectiveness planes. These scatterplots can be found in appendix IV. At a sensitivity of 97% and a specificity of 76% the majority (91%) of simulations are positioned the top-right quadrant of the cost-effectiveness plane, representing an increase in QALYs and increased costs for the POCT strategy compared with the non-POCT strategy. As the POCT strategy's sensitivity decreases and the specificity increases, the concentration of the simulations move closer to the origin of the cost-effectiveness plane and at a specificity of 97% almost all (99.9%) simulations are situated in the bottom half of the cost-effectiveness plane, representing a decrease in costs for the POCT

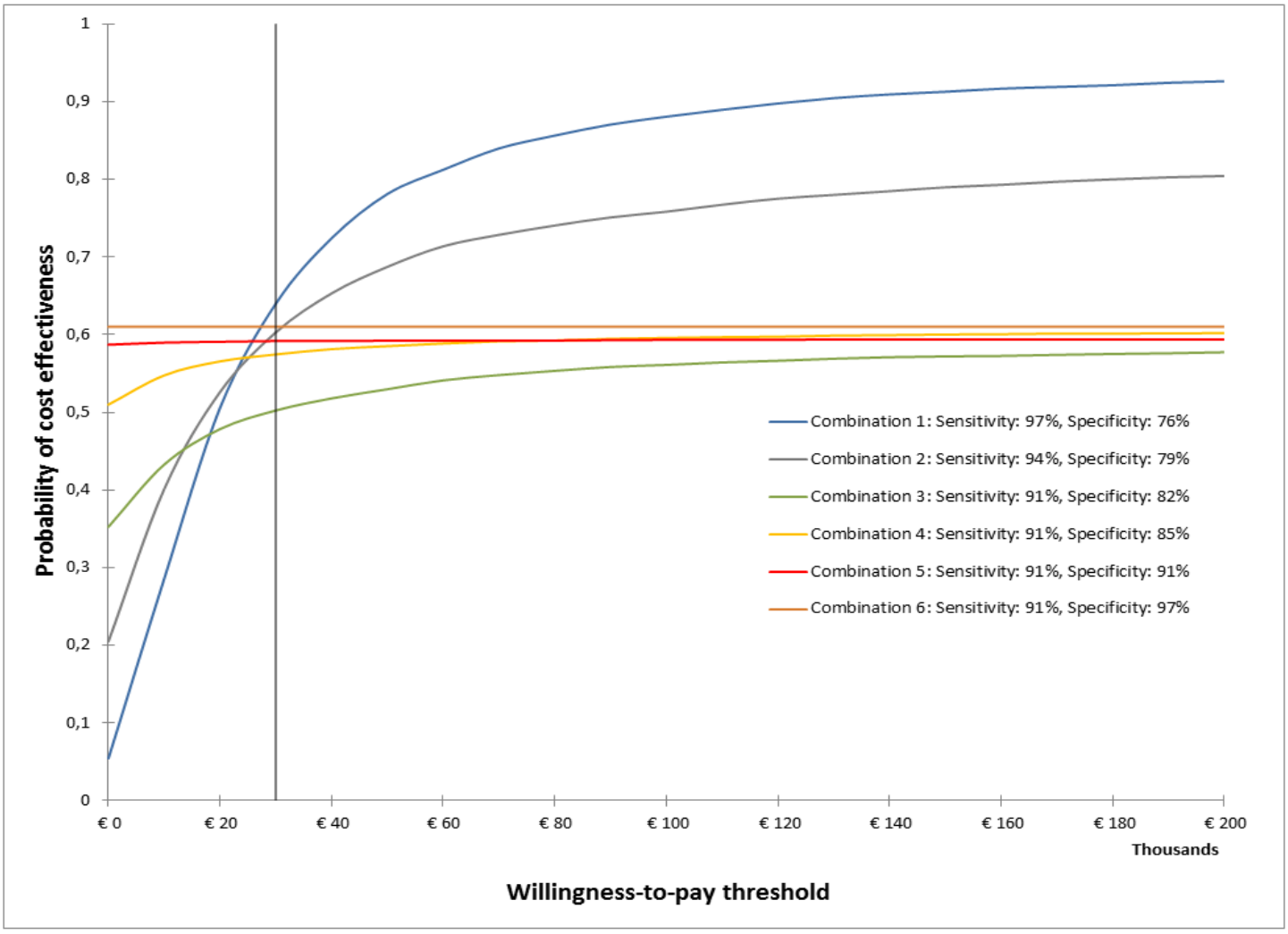



**Figure 10: Cost-effectiveness acceptability curves of six combinations of sensitivity and specificity for the POCT strategy.**

strategy. However 37.9% of these simulations also result in a decrease in QALYs.

Cost-effectiveness acceptability curves (CEACs) for the six combinations of sensitivity and specificity are shown in Figure 10. At a WTP of € 30.000 all combinations are at least 50% probable of being cost-effective. Combination 1 with a sensitivity of 97% and a specificity of 76% for the POCT strategy has the highest probability for cost-effectiveness at € 30.000 WTP. Also for higher WTPs, combination 1 has the highest chance of being cost-effective. For lower WTPs, combination 6 with a sensitivity of 91% and specificity of 97% has the highest probability of being cost-effective.

# 4 Discussion

## 4.1 Interpretation of results

This exploratory economic evaluation analysed the cost-effectiveness of the GP's clinical assessment combined with one POCT for diagnosing patients with symptoms suggestive of ACS compared with GPs relying on their clinical assessment only. The threshold analysis shows that cost-effectiveness can be achieved if the POCT can increase the GP's sensitivity for referring ACS patients to the ED from 88.3% to 91% and the GPs specificity from 72.2% to 82%. To remain cost-effective with a lower sensitivity would require a higher specificity and vice versa, which indicates a trade-off between required sensitivity and specificity of the POCT strategy.

The probabilistic sensitivity analyses showed how changes in the required sensitivity and specificity for the POCT strategy influenced the POCT strategy's location on the cost-effectiveness plane. Changing the required sensitivity shifts the strategy along the horizontal axis in the cost-effectiveness plane, representing incremental QALYs gained. This is explained by the sensitivity influencing the amount of false-negative test results (Figure 9), which is associated with QALY loss due to an increase in adverse events such as mortality and development of heart failure. On the other hand, changes in required specificity shift the POCT strategy along the vertical axis representing incremental costs. This is explained by the specificity influencing the amount of false-positive test results (Figure 8), who are associated with healthcare costs due to avoidable ambulance and ED costs.

The probabilistic sensitivity analysis also shows that an increasing proportion of the simulations result in negative incremental QALYs while the sensitivity decreases. Since all simulations resulting QALY loss are deemed not cost-effective the progressively more horizontally shaped CEACs for the lower sensitivities are explained.

Hence, cost-effectiveness for use of an adjunct POCT in primary care can be achieved by either resulting in increased health benefit expressed in QALYs gained and/or by saving costs through a reduction in the number of false-positive ED referrals. Additionally, if the costs per patient for POCT and the additional time required to perform POCT (reduction in costs of GP consultation) can be lowered, cost-effectiveness is likely to be achieved at lower sensitivity and/or specificity levels, judging from the one-way sensitivity analysis (Figure 5).

In the background it was stated that the yearly incidence for symptoms suggestive of ACS for the complete Dutch populations would be around 156.000 per year. If all GPs in the Netherlands would dispose of POCT devices with a sensitivity of 91% and specificity of 82%, around 14.602 false positive ED referrals can be avoided saving € 17.665.462 ED and ambulance costs. On the other hand, an average of only 21,85 consultations per year are for chest complaints in an average sized GP practice of 2350 patients.[63] So the incentive for single GP practices to invest in a POCT device for such a small population might be low and also be financially unattractive, especially without reimbursement by healthcare insurers. For larger primary care practices consisting of multiple collaborating GPs, serving a larger patient population the investment in a POCT device for ACS is seems more attractive. Costs are shared between more GPs and more patients will benefit from it.

## 4.2 Strengths

To our knowledge this is the first study investigating the cost-effectiveness of POCT in primary care for patients with symptoms suggestive of ACS. The threshold analysis provides the POCT industry with clear performance goals which their products need to achieve in order to be cost-effective in the Netherlands, when applying a WTP of € 30.000/QALY. The patient-level structure of the model allowed for a specific allocation of probabilities, costs and QALYs to match with certain patient characteristics. In combination with the age and gender distribution based on a primary care chest pain cohort, the resulting model population is a good reflection of a true chest pain population in primary care. The

extensive search and appraisal of recent medical literature to estimate the model parameters adds to this study's strength in informing about the cost-effectiveness of POCT for primary care patients with symptoms suggestive of ACS.
Another strength of the health economic model is that no specific POCT device or test is analysed. The model can easily be adapted to process different estimates for costs and delay times to match with specific POCT devices and calculate their cost-effectiveness.

## 4.3 Limitations

This study's limitations are primarily caused by the vast amount of input parameters used in the model. The model is developed for the Netherlands however, parameter estimates are mostly derived from different studies performed in different countries other than the Netherlands, simply because Dutch data was unavailable or lacking. By only including studies performed in western countries, population heterogeneity is tried to keep to a minimum. Additionally the sensitivity analyses were used to monitor and capture the parameter's impact on the cost-effectiveness.
Limitations in cost estimation occurred when patient-level costs for ACS patients were unavailable. Tariffs were used for estimation of in-hospital and ED costs. However it is known that these tariffs may not reflect the true opportunity costs of the services provided to these patients.[29] Furthermore, in estimating the lifetime costs for ACS patients in the Netherlands no Dutch data informing about these costs could be found. The English costs used instead might not reflect the Dutch healthcare costs for these patients. However, it is not expected that the uncertainty around these cost parameters are able to bias the study results significantly, because the costs are incremental between the two strategies. Only when an individual patient dies in one strategy and not in the other, a difference in costs occurs.
Another limitation involves differences in the performance of POCT between UAP, NSTEMI and STEMI. The model does not distinguish between the POCT's performance in diagnosing these conditions. So the performance of POCT is modelled to be equal between different ACS patients. Troponin for example, is hardly elevated in UAP patients because myocardial damage in UAP patients is not present and troponins will not enter the bloodstream.[2] Since this is an explorative and early cost-effectiveness analysis, focussing on one particular cardiac marker and its specific performance like troponin was found too limiting. Therefor different performances for diagnosing UAP, NSTEMI and STEMI were not incorporated in the model and one should be aware of that when interpreting the results.
Finally, some assumptions had to be made for several input parameters. Assumptions were made for costs of POCT, production time lost and the extra amount of delay because of POCT. The costs of POCT were based on costs of available cardiac markers in central laboratories and increased to € 30 to cover the extra overhead costs. The one-way sensitivity analysis shows that there is some space for increasing costs before exceeding the WTP threshold of € 30.000/QALY but this space is small. Assumptions for loss of production time were only made for the time lost at the GP and ED when ACS is not present. The one-way sensitivity analysis shows that they are in the top 8 of most influencing parameters, however the variation in the ICUR is still small and the WTP threshold is not exceeded. The amount of extra delay because of POCT is an important parameters because time is of the essence for STEMI patients and the extra delay might influence the outcome for these patients.[40] Additionally, higher consultation costs occur when performing POCT takes more time. Some POCT devices require a venous blood sample for their analysis and/or their analysis takes several minutes to complete, increasing the delay. Given this and to prevent underestimation of the effect of delay on STEMI patients' outcomes the delay was (over)estimated at 30 minutes. Lower delay times will likely reduce the ICUR.

## 4.4 Implications for the Dutch healthcare

In Dutch primary care POCT is frequently performed. Most primary care practices dispose over POCT devices for screening urine, measuring blood glucose

and haemoglobin.[64,65] Recently also a POCT for C-reactive protein (CRP) is in demand by GPs in the Netherlands.[64,65] This CRP POCT got included in the NHG's directive for acute cough after studies by Cals et al. (2009, 2010) investigating the GP's antibiotic prescription behaviour with and without the use of a POCT CRP test for lower respiratory tract infections.[66–68] This sequence of events shows that POCT in primary care is adopted when its effectiveness proves to be sufficient.

For ACS this is currently not the case, as mentioned before, the NHG discourages the use of POCT for ACS. However, Howick et al. (2014) studied which conditions GPs would actually want to use a POCT in their practice. 62.7% of respondent GPs indicated they would want to use a POCT for acute cardiac diseases, and 65% of the respondents would use a troponin POCT if it were available.[65] So the desire for an increased certainty at which ACS is diagnosed in primary care is present. Yet, evidence for the effective and safe use of POCT for patients with symptoms suggestive of ACS in primary care, as there is for CRP POCT, is scarce or lacking, especially in a Dutch setting. Only one study was found to be performed in the Netherlands and studied the use of a heart-type fatty acid-binding protein (H-FABP) POCT in primary care for patients suspected of ACS.[32] They concluded that the H-FABP POCT cannot be used to safely exclude ACS but can only be used safely on patients otherwise not referred to hospital by the GP.[32]

The H-FABP POCT for primary care use is currently also under study in a clinical trial.[69] The H-FABP POCT is added to the GP's clinical assessment for ACS and the diagnostic performance of the POCT and usual care group will be compared.[69] If this study provides evidence in favour of the use of POCT for ACS, its implementation is one step closer to reality.

When the results of this clinical trial become available, the present study's health economic model can be used to estimate the possible cost-effectiveness of this H-FABP POCT on a societal level. Therefore, the health economic model can fairly easily be adapted to simulate this trial's specific population and improve this model's external validity to match with a Dutch population.

A Swiss study by Tomonaga et al. (2011) found a sensitivity and specificity of 90% and 92% respectively for the GP's working diagnosis for ACS supplemented with a cTnT POCT test.[25] According to the present study's deterministic analysis, the performance reported by Tomonaga et al. (2011) would not result in a cost-effective outcome for the POCT strategy. However, the sensitivity is only lacking 1% for it to become cost-effective and, due to parameter uncertainty in the present model the actual required sensitivity for the POCT strategy could be lower resulting in a cost-effective approach.

The potential to save ED costs, makes the use of POCT for ACS an interesting development for healthcare insurers as well. It is likely that they would rather pay for POCT in primary care and have ACS excluded than paying for extensive diagnostics at the ED after which ACS is excluded. When sufficient effectiveness and cost-effectiveness evidence is available, the healthcare insurers are more likely to reimburse POCT for ACS in primary care. When they do, the incentive for GPs to implement POCT for ACS in their practice is enlarged and more GPs will implement POCT.

This chain of events would be an ideal scenario, however it is of utmost importance that the quality of care is not compromised by more missed ACS patients resulting in a reduced quality of care which indirectly increases the healthcare costs due to more adverse events occurring. To prevent this, also after implementation of POCT for ACS the number of false-negative and false-positive test results should be monitored and when performance is lacking, the cause should be identified or the use of POCT should be reconsidered.

## 4.5 Recommendations for future research

In secondary care troponin is the most used marker to indicate myocardial damage. A major drawback for troponin however, is that a rise in troponin blood levels occurs at approximately 4 hours after onset of symptoms.[2] Patients presenting within these 4 hours might thus still be under the detection threshold. Consequently, in the ED, patients are serial tested for troponin to detect a rise or fall in troponin while

constantly being monitored by the ED's facilities.[2] Troponin alone might therefor not be the ideal POCT for detecting ACS in primary care. Serial testing for early presenters in primary care is undesirable and unethical because of lacking monitoring facilities in primary care practices. Therefore, a POCT troponin supplemented with one or more other markers for myocardial damage might prove to be a better and safer approach in diagnosing early presenters with symptoms suggestive of ACS in primary care. Possible additional candidates for this early multi-marker approach could be myoglobin, H-FABP or high sensitive troponin. Kurz et al. (2011) studied the diagnostic performance of these tests at presentation of patients suggestive of ACS at the ED. The sensitivities reported were 76.0%, 88.89% and 82.14% for myoglobin, H-FABP, and high sensitive troponin respectively.[70] The myoglobin and H-FABP tests are available as POCT, the high sensitive troponin is not but it is likely it will become available in the future. The use of an early multi-marker approach in a primary care setting should be subject of future research when an individual POCT proves to be unsufficient. However, progressing towards an early multi-marker POCT approach for ACS in primary care increases the costs of the POCT strategy and cost-effectiveness compared with the non-POCT strategy will be more difficult to attain.

To improve the future use of POCT for patients presenting with symptoms suggestive of ACS in primary care it is recommended that an accompanying clinical decision rule (CDR) is developed. Clinical decision rules combine patient characteristics together with possible test results to give an overall score related to a probability of disease and guide the diagnostic work-up.[20] Several attempts have already been undertaken but were moderately successful.[20,71] Neither of these attempts included POCT results in the CDR. When a, sufficiently performing POCT strategy is identified through research, consecutive research by a multidisciplinary team of clinicians and clinical chemists should focus on developing a CDR to further optimize the POCT use and ACS diagnostics in primary care. It will be a challenge to find a good balance in the sensitivity and specificity trade-off that occurs when applying different cut-off values for distinguishing between diseased or non-diseased patients. The present study helps to understand how this trade-off between sensitivity and specificity influences the cost-effectiveness and could therefore be taken into consideration when developing the new CDR.

Another recommendation for future research is to study the use of POCT for ACS in GP practices already disposing over and using an ECG in their clinical assessment of patients suggestive of ACS. Braspenning et al. (2004) reported that 45% of GPs in the Netherlands dispose of an ECG.[72] It is expected that the benefit POCT offers in diagnosing STEMI patients is influenced when also an ECG can be made. Depending on the time it takes POCT to generate a result, an ECG might be quicker in detecting patients with an ST-elevation, making a POCT obsolete in the diagnostic process. The benefit of POCT remains only for NSTEMI and UAP patients, possibly reducing the cost-effectiveness of POCT for ACS as well.

As a final recommendation, the presented health economic model can be expanded to incorporate and simulate more patient-level characteristics. These should consist out of characteristics known to influence the risk of cardiovascular events such as: *diabetes mellitus, rheumatoid arthritis, previous cardiovascular disease, smoker status, family history of cardiovascular disease, nutritional habits, alcohol intake, physical activity, blood pressure, body-mass index, hyperlipidaemia and blood glucose levels*. These characteristics are already used by Dutch GPs in assessing the 10-year risk on disease or mortality by cardiovascular diseases.[73] When incorporated in to the model, different pre-test probabilities of disease are allocated based on the above patient characteristics. The model already proved to be sensitive to this pre-test probability of disease represented by the 'probability of ACS' in the one-way sensitivity analysis (Figure 5). Consecutive subgroup analyses will show if POCT for ACS can more cost-effectively be applied for patients with certain characteristics.

# 5 Acknowledgements

First of all I would like to thank my supervisors, Ron Kusters, Lotte Steuten and Michelle Kip for supervising me in this last phase of my Health Sciences study. Our conversations were always interesting and provided me with relevant information and insight to work on my master assignment. Ron Kusters' widespread experience as clinical chemist, also with point-of-care-testing in collaboration with GPs was very helpful in tackling my assignment. Lotte Steuten helped me in the economic approach of my assignment and provided me with useful tools and methodology concerning economic evaluation. Michelle Kip, I would like to thank you helping me understand economic modelling in Excel and reviewing my Excel model. I would also like to thank Maarten IJzerman for his time and effort, substituting Lotte Steuten as member of my examination committee. Then, I want to thank Maarten van den Burg and Erwin Oeben from Radiometer for the interesting and fruitful meetings we had discussing the use of POCT in primary care, technical aspects and ongoing developments regarding POCT. Next, my thanks go out to Ester Boelen and Anais Dufour from the Jeroen Bosch hospital in 's Hertogenbosch, the Netherlands, for providing me with the necessary insight in the complex structure of DTCs (DBC's) for declaring hospital costs relevant for my assignment. Finally I would like to thank my fellow health sciences students for their support, discussions and the good times we had together finishing our studies.

# 6 References


1. Rubin R, Strayer DS. *Rubin's pathology : clinicopathologic foundations of medicine*. 5th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2008.

2. Hamm CW, Bassand J-P, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevatio. *Eur Heart J*. 2011;32(23):2999-3054. doi:10.1093/eurheartj/ehr236.

3. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. *Circulation*. 2007;116(22):2634-53. doi:10.1161/CIRCULATIONAHA.107.187397.

4. Hunink M, Glasziou P, Siegel J, et al. *Decision making in health and medicine*. 12th ed. New York: Cambridge University Press; 2012.

5. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. *Eur Heart J*. 2010;31(20):2501-55. doi:10.1093/eurheartj/ehq277.

6. Keeley EC, Boura J a, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*. 2003;361(9351):13-20. doi:10.1016/S0140-6736(03)12113-7.

7. Dutch Association Of Cardiology(Nederlandse Vereniging Voor Cardiologie). White lists PCI and ICD(Witte lijsten PCI en ICD). 2014. Available at: https://www.nvvc.nl/richtlijnen/witte-lijsten.

8. Boersma E. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J*. 2006;27(7):779-88. doi:10.1093/eurheartj/ehi810.

9. Nallamothu B, Fox K a a, Kennelly BM, et al. Relationship of treatment delays and mortality in patients undergoing fibrinolysis and primary percutaneous coronary intervention. The Global Registry of Acute Coronary Events. *Heart*. 2007;93(12):1552-5. doi:10.1136/hrt.2006.112847.

10. Svavarsdóttir AE, Jónasson MR, Gudmundsson GH, Fjeldsted K. Chest pain in family practice. Diagnosis and long-term outcome in a community setting. *Can Fam Physician*. 1996;42:1122-8. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2146490&tool=pmcentrez&rendertype=abstract. Accessed November 7, 2014.

11. Nilsson S, Scheike M, Engblom D, et al. Chest pain and ischaemic heart disease in primary care. *Br J Gen Pract*. 2003;53(490):378-82. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1314597&tool=pmcentrez&rendertype=abstract.

12. Verdon F, Burnand B, Herzig L, Junod M, Pécoud A, Favrat B. Chest wall syndrome among primary care patients: a cohort study. *BMC Fam Pract*. 2007;8:51. doi:10.1186/1471-2296-8-51.

13. Nielen M, Spronk I, Davids R, Zwaanswijk M, Verheij R, Korevaar J. Dutch institute for healthcare research: Incidence and prevalence of healthproblems in the Dutch general practice in 2012 (Nederlands instituut voor onderzoek van de gezondheidszorg: Incidentie en prevalentie van gezondheidsproblemen in de Nederlandse hui. 2013. Available at: www.nivel.nl/node/3094 .

14. Erhardt L, Herlitz J, Bossaert L, et al. Task force on the management of chest pain. *Eur Heart J*. 2002;23(15):1153-1176. doi:10.1053/euhj.2002.3194.

15. Bösner S, Becker A, Haasenritter J, et al. Chest pain in primary care: epidemiology and pre-work-up probabilities. *Eur J Gen Pract*. 2009;15(3):141-6. doi:10.3109/13814780903329528.

16. Bösner S, Haasenritter J, Hani MA. Accuracy of general practitioners' assessment of chest pain patients for coronary heart disease in primary care: cross-sectional study with follow-up. *Croat Med J*. 2010:243-249. doi:10.3325/cmj.2010.51.243.

17. Verdon F, Herzig L, Burnand B, et al. Chest pain in daily practice: occurrence, causes and management. *Swiss Med Wkly*. 2008;138(23-24):340-7. doi:2008/23/smw-12123.

18. Bruyninckx R, Aertgeerts B, Bruyninckx P, Buntinx F. Signs and symptoms in diagnosing acute myocardial infarction and acute coronary syndrome: a diagnostic meta-analysis. *Br J Gen Pract*. 2008;58(547):105-11. doi:10.3399/bjgp08X277014.

19. Mant J, McManus R, Oakes R. Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care. *Health Technol Assess (Rockv)*. 2004;8(2). Available at: http://www.hta.nhs.uk/pdfexecs/summ802.pdf. Accessed April 4, 2014.

20. Bruins Slot MHE, Rutten FH, van der Heijden GJMG, Geersing GJ, Glatz JFC, Hoes AW. Diagnosing acute coronary syndrome in primary care: comparison of the physicians' risk estimation and a clinical decision rule. *Fam Pract*. 2011;28(3):323-8. doi:10.1093/fampra/cmq116.

21. Junker R, Schlebusch H, Luppa P. Point-of-care testing in hospitals and primary care. *Dtsch Arztebl Int*. 2010;107(33):561-567. doi:10.3238/arztebl.2010.0561.

22. Klinkman MS, Stevens D, Gorenflo DW. Episodes of care for chest pain: a preliminary report from MIRNET. Michigan Research Network. *J Fam Pract*. 1994;38(4):345-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8163958. Accessed March 27, 2014.

23. Lamberts H, Brouwer H, Mohrs J. Reason for encounter- & episode- & process oriented standard output from the Transition Project. Parts I and II. 1991.

24. Bösner S, Becker A, Abu Hani M, et al. Accuracy of symptoms and signs for coronary heart disease assessed in primary care. *Br J Gen Pract*. 2010;60(575):e246-57. doi:10.3399/bjgp10X502137.

25. Tomonaga Y, Gutzwiller F, Lüscher TF, et al. Diagnostic accuracy of point-of-care testing for acute coronary syndromes, heart failure and thromboembolic events in primary care: a cluster-randomised controlled trial. *BMC Fam Pract*. 2011;12(1):12. doi:10.1186/1471-2296-12-12.

26. Bruins Slot MHE, van der Heijden GJMG, Stelpstra SD, Hoes AW, Rutten FH. Point-of-care tests in suspected acute myocardial infarction: a systematic review. *Int J Cardiol*. 2013;168(6):5355-62. doi:10.1016/j.ijcard.2013.08.002.

27. Rutten FH, Grundmeijer H, Grijseels EWM, et al. Dutch General Practitioners Association directive: acute coronary syndrome (NHG standaard: acuut coronair syndroom). 2009. Available at: https://www.nhg.org/standaarden/volledig/nhg-standaard-acuut-coronair-syndroom-eerste-herziening.

28. Fitzgerald P, Goodacre SW, Cross E, Dixon S. Cost-effectiveness of point-of-care biomarker assessment for suspected myocardial infarction: the randomized assessment of treatment using panel Assay of cardiac markers (RATPAC) trial. *Acad Emerg Med*. 2011;18(5):488-95. doi:10.1111/j.1553-2712.2011.01068.x.

29. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programmes*. 3rd ed. New York: Oxford University Press; 2005.

30. Briggs AH, Claxton K, Sculpher M. *Decision modelling for health economic evaluation*. 1st ed. New York: Oxford University Press; 2006.

31. Egger M, Davey Smith G, Altman D. *Systematic reviews in health care*. 6th ed. London: BMJ Publishing Group; 2007.

32. Bruins Slot MHE, Rutten FH, van der Heijden GJMG, et al. Diagnostic value of a heart-type fatty acid-binding protein (H-FABP) bedside test in suspected acute coronary syndrome in primary care. *Int J Cardiol*. 2013;168(2):1485-9. doi:10.1016/j.ijcard.2012.12.050.

33. Nilsson S, Ortoft K, Mölstad S. The accuracy of general practitioners' clinical assessment of chest pain patients. *Eur J Gen Pract*. 2008;14(2):50-5. doi:10.1080/13814780802342622.

34. The GRACE investigators. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) Project: a multinational registry of patients hospitalized with acute coronary syndromes. *Am Heart J*. 2001;141(2):190-9. doi:10.1067/mhj.2001.112404.

35. Goldberg RJ, Currie K, White K, et al. Six-month outcomes in a multinational registry of patients hospitalized with an acute coronary syndrome (the Global Registry of Acute Coronary Events [GRACE]). *Am J Cardiol*. 2004;93(3):288-93. doi:10.1016/j.amjcard.2003.10.006.

36. Steg PG, Goldberg RJ, Gore JM, et al. Baseline characteristics, management practices, and in-hospital outcomes of patients hospitalized with acute coronary syndromes in the Global Registry of Acute Coronary Events (GRACE). *Am J Cardiol*. 2002;90(4):358-63. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12161222.

37. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med*. 2003;163(19):2345-53. doi:10.1001/archinte.163.19.2345.

38. Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med*. 2000;342(16):1163-70. doi:10.1056/NEJM200004203421603.

39. Sequist TD, Bates DW, Cook EF, et al. Prediction of missed myocardial infarction among symptomatic outpatients without coronary heart disease. *Am Heart J*. 2005;149(1):74-81. doi:10.1016/j.ahj.2004.06.014.

40. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33(20):2569-619. doi:10.1093/eurheartj/ehs215.

41. Damman P, van Geloven N, Wallentin L, et al. Timing of angiography with a routine invasive strategy and long-term outcomes in non-ST-segment elevation acute coronary syndrome: a collaborative analysis of individual patient data from the FRISC II (Fragmin and Fast Revascularization During Instability. *JACC Cardiovasc Interv*. 2012;5(2):191-9. doi:10.1016/j.jcin.2011.10.016.

42. Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med*. 2009;360(21):2165-75. doi:10.1056/NEJMoa0807986.

43. Center for the Evaluation of Value and Risk in Health. The cost-effectiveness analysis registry. *Inst Clin Res Heal Policy Stud Tufts Med Cent*. 2007. Available at: www.cearegistry.org. Accessed July 3, 2014.

44. Health Technology Assessment. Health Technology Assessment. 2014. Available at: http://www.journalslibrary.nihr.ac.uk/hta.

45. Goodacre S, Thokala P, Carroll C, et al. Systematic review, meta-analysis and economic modelling of diagnostic strategies for suspected acute coronary syndrome. *Health Technol Assess*. 2013;17(1):v-vi, 1-188. doi:10.3310/hta17010.

46. Polanczyk CA, Kuntz KM, Sacks DB, Johnson PA, Lee TH. Emergency department triage strategies for acute chest pain using creatine kinase-MB and troponin I assays: a cost-effectiveness analysis. *Ann Intern Med*. 1999;131(12):909-18. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10610641. Accessed July 18, 2014.

47. Ward S, Lloyd Jones M, Pandor a, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess*. 2007;11(14):1-160, iii-iv. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17408535.

48. Chang W-C, Kaul P, Westerhout CM, et al. Impact of sex on long-term mortality from acute myocardial infarction vs unstable angina. *Arch Intern Med*. 2003;163(20):2476-84. doi:10.1001/archinte.163.20.2476.

49. Van Jaarsveld CHM, Ranchor A V, Kempen GIJM, Coyne JC, van Veldhuisen DJ, Sanderman R. Epidemiology of heart failure in a community-based study of subjects aged ≥ 57 years: incidence and long-term survival. *Eur J Heart Fail*. 2006;8(1):23-30. doi:10.1016/j.ejheart.2005.04.012.

50. Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making*. 2009;26(4):410-20. doi:10.1177/0272989X06290495.

51. Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. *Manual for costs research: methods and standard prices for economic evaluations in healthcare (Handleiding voor kostenonderzoek: methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg)*.; 2010. Available at: https://cvz.nl/binaries/content/documents/zinl-www/documenten/publicaties/overige-publicaties/1007-handleiding-voor-kostenonderzoek/Handleiding+voor+kostenonderzoek.pdf. Accessed April 4, 2014.

52. Dutch Healthcare Authority (Nederlandse zorgautoriteit). Diagnosis treatment combination: healthcare products tariff application (DBC zorgproducten tarief applicatie). 2014. Available at: http://dbc-zorgproducten-tarieven.nza.nl/nzaZpTarief/Welkom.aspx. Accessed July 6, 2014.

53. Diagnostic treatment combination maintenance (DBC onderhoud). Open diagnostic treatment combination information system data (Open DBC informatie systeem data). 2014. Available at: http://www.opendisdata.nl/. Accessed July 6, 2014.

54. National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu RIVM). Cost-of-illness tool (Kosten-van-ziekten tool). 2011. Available at: http://www.kostenvanziekten.nl/. Accessed July 5, 2014.

55. Gommer A., Poos MJJ. Heart failure: prevalence, incidence en mortality for age and gender (Hartfalen: prevalentie, incidentie en sterfte naar leeftijd en geslacht). *Public Heal Futur Reconnaiss (Volksgezondheid Toekomst en Verkenning)*. 2011. Available at: http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/hartvaatstelsel/hartfalen/cijfers-hartfalen-prevalentie-incidentie-en-sterfte-uit-de-vtv-2010/. Accessed July 5, 2014.

56. Mourad G, Alwin J, Strömberg A, Jaarsma T. Societal costs of non-cardiac chest pain compared with ischemic heart disease--a longitudinal study. *BMC Health Serv Res*. 2013;13:403. doi:10.1186/1472-6963-13-403.

57. Spannheimer a, Goertz a. PCV7 Economic Evaluation of Torasimide in Congestive Heart Failure in Germany. *Value Heal*. 1998;1(1):51-51. doi:10.1046/j.1524-4733.1998.1100497.x.

58. Central Bureau for Statistics (Centraal bureau voor statistiek CBS). Consumersprices; price index 2006 = 100 (Consumentenprijzen; prijsindex 2006=100). 2014. Available at: http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=71311NED&D1=0&D2=0&D3=64,77,90,103,116,129,142,155,168,181,194,219,232,245&VW=T. Accessed July 28, 2014.

59. Tax administration: Customs(Belastingdienst: Douane). Stocklist january 2013(Koerslijst januari 2013). 2013. Available at: http://www.belastingdienst.nl/wps/wcm/connect/bldcontentnl/belastingdienst/douane_voor_bedrijven/nasl agwerken_en_overige_informatie/koerslijsten/koertslijsten_2013/koerslijst_jan_2013. Accessed July 28, 2014.

60. Stevenson MD, Brazier JE, Calvert NW, Lloyd-Jones M, Oakley JE, Kanis J a. Description of an individual patient methodology for calculating the cost-effectiveness of treatments for osteoporosis in women. *J Oper Res Soc*. 2004;56(2):214-221. doi:10.1057/palgrave.jors.2601903.

61. Karnon J. Alternative decision modelling techniques for the evaluation of health care technologies: Markov processes versus discrete event simulation. *Health Econ*. 2003;12(10):837-48. doi:10.1002/hec.770.

62. National Institute for Health and Care Excellence (NICE). *Guide to the methods of technology appraisal 2013*.; 2013.

63. Braspenning J, Doorn-Klomberg A Van. Time expenditure in general practice (Tijdsbesteding in de huisartsenpraktijk). *Huisarts Wet*. 2012;55(december):542-547. Available at: http://link.springer.com/article/10.1007/s12445-012-0276-3. Accessed April 4, 2014.

64. Kleinveld H, Raijmakers M, Vermeer H, Oosterhuis W. *Vision statement Dutch association of clinical chemists: point-of-care tests in primary care (Visiedocument NVKC: Point-of-care testen in de eerste lijn).*; 1-8.

65. Howick J, Cals JWL, Jones C, et al. Current and future use of point-of-care tests in primary care: an international survey in Australia, Belgium, The Netherlands, the UK and the USA. *BMJ Open*. 2014;4(8):e005611. doi:10.1136/bmjopen-2014-005611.

66. Cals JWL, Butler CC, Hopstaken RM, Hood K, Dinant G-J. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. *BMJ*. 2009;338:b1374. doi:10.1136/bmj.b1374.

67. Cals JWL, Schot MJC, de Jong SAM, Dinant G-J, Hopstaken RM. Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. *Ann Fam Med*. 2010;8(2):124-33. doi:10.1370/afm.1090.

68. Verheij T, Hopstaken R, Prins J, et al. Dutch General Practitioners Assosciation directive: acute cough (NHG standaard: acuut hoesten). 2011. Available at: https://www.nhg.org/standaarden/volledig/nhg-standaard-acuut-hoesten.

69. Clinicaltrials.gov. Incremental Value of Point of Care H-FABP Testing in Primary Care Patients Suspected of Acute Coronary Syndrome (RAPIDA). 2013. Available at: http://clinicaltrials.gov/show/NCT01826994.

70. Kurz K, Giannitsis E, Becker M, Hess G, Zdunek D, Katus H a. Comparison of the new high sensitive cardiac troponin T with myoglobin, h-FABP and cTnT for early identification of myocardial necrosis in the acute coronary syndrome. *Clin Res Cardiol*. 2011;100(3):209-15. doi:10.1007/s00392-010-0230-y.

71. Gencer B, Vaucher P, Herzig L, et al. Ruling out coronary heart disease in primary care patients with chest pain: a clinical prediction score. *BMC Med*. 2010;8:9. doi:10.1186/1741-7015-8-9.

72. Braspenning JCC, Schellevis FG, Grol R. *Second national study into diseases and operations in general practice. (Tweede nationale studie naar ziekten en verrichtingen in de huisartspraktijk).* Utrecht/Nijmegen: NIVEL/WOK; 2004.

73. Dutch General Practitioners Association (Nederlands Huisarts Genootschap). Dutch General Practitioners Association directive: cardiovascular risk management (NHG standaard: cardiovasculair risicomanagement). *Huisarts Wet*. 2012;55(1):14-28. Available at: https://www.nhg.org/standaarden/volledig/cardiovasculair-risicomanagement.

# Appendix I: Abbreviations

| | |
|---|---|
| **ACS** | **Acute coronary syndrome** |
| **AMI** | **Acute myocardial infarction** |
| **CABG** | **Coronary artery bypass grafting** |
| **CAD** | **Coronary artery disease** |
| **CBS** | **Centraal Bureau voor de Statistiek** |
| **CDR** | **Clinical decision rule** |
| **CEA** | **Cost-effectiveness analyses** |
| **CEAC** | **Cost-effectiveness acceptability curve** |
| **CHD** | **Coronary heart disease** |
| **CK-MB** | **Creatine kinase-MB** |
| **CRP** | **C-reactive protein** |
| **cTnI** | **Cardiac troponin I** |
| **cTnT** | **Cardiac troponin T** |
| **CVZ** | **College voor Zorgverzekeringen** |
| **DIS** | **DTC information system** |
| **DTC** | **Diagnosis treatment combination** |
| **ECG** | **Electrocardiogram** |
| **ED** | **Emergency department** |
| **ESC** | **European Society of Cardiology** |
| **FN** | **False-negative** |
| **FP** | **False-positive** |
| **GBP** | **Great Britain Pound** |
| **GP** | **General practitioner** |
| **GRACE** | **Global Registry of Acute Coronary Events** |
| **H-FABP** | **Heart-type fatty binding protein** |
| **HTA** | **Health technology assessment** |
| **ICPC** | **International classification of primary care** |
| **ICUR** | **Incremental cost-utility ratio** |
| **IHD** | **Ischaemic heart disease** |
| **IQR** | **Inter quartile range** |
| **NHG** | **Nederlands Huisarts Genootschap** |
| **NPT** | **Near-patient testing** |
| **NPV** | **Negative predictive value** |
| **NSTE-ACS** | **Non ST-elevation acute coronary syndrome** |
| **NSTEMI** | **Non ST-elevation myocardial infarction** |
| **NVVC** | **Nederlandse Vereniging Voor Cardiologie** |
| **NZA** | **Nederlandse Zorgautoriteit** |
| **PCI** | **Percutaneous coronary intervention** |
| **POCT** | **Point-of-care-test(ing)** |
| **PPV** | **Positive predictive value** |
| **QALY** | **Quality adjusted life year** |
| **RIVM** | **Rijksinstituut voor Volksgezondheid en Milieu** |
| **STE-ACS** | **ST-elevation acute coronary syndrome** |
| **STEMI** | **ST-elevation myocardial infarction** |
| **TN** | **True-negative** |
| **TNR** | **True negative ratio** |
| **TP** | **True-positive** |
| **TPR** | **True positive ratio** |
| **UAP** | **Unstable angina pectoris** |
| **WTP** | **Willingness-to-pay threshold** |

# Appendix II: Search protocol

This search protocol describes the systematic search and appraisal of medical literature to be used in the health economic model. Both medical databases and registries have been consulted. The appendix is divided in three sections, one describing the database search, one describing the registry search and one describing the search for QALY and utility estimates.

## In- and exclusion criteria

Inclusion criteria comprise mainly of a specification of the population from which the parameter data will be derived. The prevalence rates will need to be derived from a GP population that has presented with chest complaints. The diagnostic performance characteristics for clinical assessment also need to be derived from a GP population presenting with chest complaints. Mortality rates for the different conditions need to be derived from both an ED population and a home population in the case of a false negative. Heart failure rates also need to be derived from an ED population. For the utility values no inclusion criteria are formulated only exclusion criteria. The specific inclusion criteria per parameter are given in the results section. The exclusion criteria are the same for all parameters: non-western population, non-English language, before 2003, insufficient methodological quality.

## Study quality

Study quality is assessed by several available tools designed for this purpose. Which tool to use depends on the study design. Observational studies identified for prevalence and mortality figures are assessed using the checklists developed by the STROBE-Statement.[1] The STROBE statement is a checklist of items that should be addressed in articles reporting on the three main study design of analytical epidemiology: cohort, case-control, and cross-sectional studies.[1] Although the checklist is a useful tool for assessing the reporting of observational studies, it is not an instrument to evaluate the quality of the observational research.[1] Therefore the STROBE checklist is used alongside with several items from the Newcastle-Ottawa quality assessment scale (NOS). The NOS is a risk of bias assessment tool for observational studies and is recommended by the Cochrane Collaboration for use in systematic reviews.[2,3] In case of randomized controlled trials, the Jadad score[4] is used for assessing study quality.

## Database search results

The databases searched will be Scopus and the Cochrane database for systematic reviews. Scopus is used because it is the largest abstract and citation database of peer-reviewed literature covering, besides others, the field of medicine by providing access to the MEDLINE database.

**Population prevalence**

The search for prevalence figures for STEMI, NSTEMI and UAP in a GP population are combined in one syntax.

| *Inclusion criteria* | *Exclusion criteria* |
|---|---|
| -In GP population | -Non-western population |
| -After presenting with chest complaints at GP office | -Non-English language |
| | -Before 2003 |
| | -Insufficient methodological quality |

| Parameter | Scopus Search syntax | Cochrane review library syntax |
|---|---|---|
| Population prevalence of ACS | **(30-04-2014) 84 Hits**<br>(TITLE-ABS-KEY(({**acute coronary syndrome**} W/10 (**primary** W/2 **care**)) OR (**"chest pain"** W/10 (**primary** W/2 **care**)) OR (**"chest complaint"** W/10 (**primary** W/2 **care**)) OR (**"st segment elevation myocardial infarction"** W/10 (**primary** W/2 **care**)) OR (**"st elevation myocardial infarction"** W/10 (**primary** W/2 **care**)) OR (**"st segment elevation myocardial infarct"** W/10 (**primary** W/2 **care**)) OR (**"st elevation myocardial infarct"** W/10 (**primary** W/2 **care**)) OR (**stemi** W/10 (**primary** W/2 **care**)) OR (**"non st segment elevation myocardial infarction"** W/10 (**primary** W/2 **care**)) OR (**"non st elevation myocardial infarction"** W/10 (**primary** W/2 **care**)) OR (**"non st segment elevation myocardial infarct"** W/10 (**primary** W/2 **care**)) OR (**"non st elevation myocardial infarct"** W/10 (**primary** W/2 **care**)) OR (**nstemi** W/10 (**primary** W/2 **care**)) OR (**"non stemi"** W/10 (**primary** W/2 **care**)) OR ({**unstable angina pectoris**} W/10 (**primary** W/2 **care**)) OR ({**unstable angina**} W/10 (**primary** W/2 **care**)) OR (**uap** W/10 (**primary** W/2 **care**)) OR ({**acute coronary syndrome**} W/10 {**family practice**}) OR (**"chest pain"** W/10 {**family practice**}) OR (**"chest complaint"** W/10 {**family practice**}) OR (**"st segment elevation myocardial infarction"** W/10 {**family practice**}) OR (**"st segment elevation myocardial infarction"** W/10 {**family practice**}) OR (**"st segment elevation myocardial infarct"** W/10 {**family practice**}) OR (**"st elevation myocardial infarct"** W/10 {**family practice**}) OR (**stemi** W/10 {**family practice**}) OR (**"non st segment elevation myocardial infarction"** W/10 {**family practice**}) OR (**"non st elevation myocardial infarction"** W/10 {**family practice**}) OR (**"non st segment elevation myocardial infarct"** W/10 {**family practice**}) OR (**"non st elevation myocardial infarct"** W/10 {**family practice**}) OR (**nstemi** W/10 | **(3-6-2014) 4 Hits**<br>#1 "acute coronary syndrome":ti,ab,kw or "chest pain":ti,ab,kw or chest complaint:ti,ab,kw or "st segment elevation myocardial infarction":ti,ab,kw or "st elevation myocardial infarction":ti,ab,kw (Word variations have been searched)<br>#2 "st segment elevation myocardial infarct":ti,ab,kw or "st elevation myocardial infarct":ti,ab,kw or "non st segment elevation myocardial infarction":ti,ab,kw or "non st elevation myocardial infarction":ti,ab,kw or "non st segment elevation myocardial infarct":ti,ab,kw (Word variations have been searched)<br>#3 "non st elevation myocardial infarct":ti,ab,kw or "NSTEMI":ti,ab,kw or "STEMI":ti,ab,kw or "non stemi":ti,ab,kw or "unstable angina pectoris":ti,ab,kw (Word variations have been searched)<br>#4 "unstable angina":ti,ab,kw or "UAP":ti,ab,kw (Word variations have been searched)<br>#5 primary near/2 care:ti,ab,kw or "family practice":ti,ab,kw or general near/2 prac*:ti,ab,kw or "gp":ti,ab,kw (Word variations have been searched)<br>#6 "glycoprotein":ti,ab,kw or emergency near/2 department:ti or "ED":ti or "hospital":ti or "emergency department":kw (Word variations have been searched) |

| | | |
|---|---|---|
| | **{family practice}**) OR (**"non stemi"** W/10 **{family practice}**) OR (**{unstable angina pectoris}** W/10 **{family practice}**) OR (**{unstable angina}** W/10 **{family practice}**) OR (**uap** W/10 **{family practice}**) OR (**{acute coronary syndrome}** W/10 (**general** W/2 **prac***)) OR (**"chest pain"** W/10 (**general** W/2 **prac***)) OR (**"chest complaint"** W/10 (**general** W/2 **prac***)) OR (**"st segment elevation myocardial infarction"** W/10 (**general** W/2 **prac***)) OR (**"st segment elevation myocardial infarction"** W/10 (**general** W/2 **prac***)) OR (**"st segment elevation myocardial infarct"** W/10 (**general** W/2 **prac***)) OR (**"st elevation myocardial infarct"** W/10 (**general** W/2 **prac***)) OR (**stemi** W/10 (**general** W/2 **prac***)) OR (**"non st segment elevation myocardial infarction"** W/10 (**general** W/2 **prac***)) OR (**"non st elevation myocardial infarction"** W/10 (**general** W/2 **prac***)) OR (**"non st segment elevation myocardial infarct"** W/10 (**general** W/2 **prac***)) OR (**"non st elevation myocardial infarct"** W/10 (**general** W/2 **prac***)) OR (**nstemi** W/10 (**general** W/2 **prac***)) OR (**"non stemi"** W/10 (**general** W/2 **prac***)) OR (**{unstable angina pectoris}** W/10 (**general** W/2 **prac***)) OR (**{unstable angina}** W/10 (**general** W/2 **prac***)) OR (**uap** W/10 (**general** W/2 **prac***)) OR (**{acute coronary syndrome}** W/10 **{gp}**) OR (**"chest pain"** W/10 **{gp}**) OR (**"chest complaint"** W/10 **{gp}**) OR (**"st segment elevation myocardial infarction"** W/10 **{gp}**) OR (**"st segment elevation myocardial infarction"** W/10 **{gp}**) OR (**"st segment elevation myocardial infarct"** W/10 **{gp}**) OR (**"st elevation myocardial infarct"** W/10 **{gp}**) OR (**stemi** W/10 **{gp}**) OR (**"non st segment elevation myocardial infarction"** W/10 **{gp}**) OR (**"non st elevation myocardial infarction"** W/10 **{gp}**) OR (**"non st segment elevation myocardial infarct"** W/10 **{gp}**) OR (**"non st elevation myocardial infarct"** W/10 **{gp}**) OR (**nstemi** W/10 **{gp}**) OR (**"non stemi"** W/10 **{gp}**) OR (**{unstable angina pectoris}** W/10 **{gp}**) OR (**{unstable angina}** W/10 **{gp}**) OR (**uap** W/10 **{gp}**)) AND NOT TITLE-ABS-KEY(**glycoprotein**) AND NOT TITLE((**emergency** W/2 **department**) OR (**ed**) OR (**hospital**)) AND NOT KEY((**{emergency department}**) OR (**ed**) OR (**hospital**))) AND DOCTYPE(**ar** OR **re**) AND PUBYEAR > **2002** AND (LIMIT-TO(LANGUAGE, **"English"**)) AND (LIMIT-TO(SUBJAREA, **"MEDI"**)) | #7 "ED":kw or "hospital":kw (Word variations have been searched)<br>#8 (#1 or #2 or #3 or #4) and #5 not (#6 or #7) Online Publication Date from Jan 2003 to Jun 2014 (Word variations have been searched) |

The syntaxes yielded 88 unique publications. By reviewing the title and abstract 23 publications were excluded because of a hospital setting being used. 6 publications were excluded because they met the non-western exclusion criterion. 21 publications were excluded because the population under study did not meet the inclusion criteria. 1 study got excluded because no results were published. 8 were excluded because they focused on non-cardiac chest pain. Finally 4 got excluded because the chosen study design would not result in reliable, valid prevalence figures. The remaining 25 publications were identified as potential source for prevalence figures. By reviewing these publications, 18 publications got excluded because no prevalence figures were given or could not be calculated. The remaining 7 publications are given in Table 12.

**Table 12: Systematic search results for prevalence of ACS**

| | | | n, (%), 95% CI | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Study** | **Region** | **Population** | **Total** | **STEMI** | **NSTEMI** | **UAP** | **ACS** | **Remarks** |
| Bösner, 2009[5] * | Germany | >35 years with chest complaints at GP | 1212 | | | | 44 (3.6), 2.7-4.8 | |
| Bösner, Haasenritter, 2009[6] * | Germany | >35 years with chest complaints at GP | 1212 | | | | 44† | |
| Bruins Slot, 2013[7] ‡ | Netherlands | Patients suspected of ACS by GP | 298 | 18 (6.0) | 34 (11.4) | 14 (2.7) | 66 (22.1) | Included patients were already suspected of ACS by GP after presenting with chest complaints. Patients deemed by the GP to receive acute care in hospital are not included. |
| Bruins Slot, 2011[8] ‡ | Netherlands | Patients suspected of ACS by GP | 298 | | | 14 (2.7) | 66 (22.1) | Included patients were already suspected of ACS by GP after presenting with chest complaints. Patients deemed by the GP to receive acute care in hospital are not included. |
| Gencer, 2010[9] § | Switzerland | >16 years who reported any type of chest pain at GP visit | 661 | | | 6 | 10 (1.6)† | No distinction between STEMI and NSTEMI was made |
| Haasenritter, 2012[10] | Germany | ≥35 years with chest pain at GP | 844 | | | | 21 (2.5) | |
| Verdon, 2008[11] § | Switzerland | >16 years presenting with thoracic pain at GP | 672 | | | 6 | 10 (1.6)† | No distinction between STEMI and NSTEMI was made |

*Study quality*

When assessing the quality of the studies summarized in table 1, studies reporting on the same cohort of patients will be assessed as one.

The Marburg heart studies scored 4/4 stars for the applicable criteria from the NOS and complied with all but 4 applicable recommendations from the STROBE statement checklist. The studies by Bruins Slot scored 3/4 stars for the NOS and complied with 3/30 recommendations from the STROBE statement checklist. The TOPIC studies had the lowest scores of both the NOS and the STROBE statement checklist; 2/4 and 2/28 respectively. Finally the study by Haasenritter, 2012[10] scored best for both the tools; 4/4 for the NOS and 2/29 for the STROBE statement checklist. The study quality results are summarized in Table 13.

**Table 13: Study quality results for ACS prevalence studies**

| Study | # NOS Stars #/max | # Non-compliances with applicable STROBE statement recommendations #/max |
|---|---|---|
| Marburg heart study: Bösner, 2009[5] and Bösner, Haasenritter, 2009[6] | 4/4 | 4/30 |
| Bruins Slot, 2013[7] and Bruins Slot, 2011[8] | 3/4 | 3/30 |
| TOPIC study: Gencer, 2010[9] and Verdon, 2008[11] | 2/4 | 4/28 |
| Haasenritter, 2012[10] | 4/4 | 2/29 |

*Applicability and conclusion*

Although the study by Haasenritter et al. (2012) scored best, the prevalence of ACS in this study will not be used in de health economic model. The reason for this is that no confidence interval is given for the prevalence. The Marburg heart study only scored less on the STROBE statement recommendations and did provide confidence intervals. This makes the Marburg heart study more suitable for use in the health economic model. Unfortunately the Marburg heart study only reports the prevalence of ACS without further stratification in STEMI, NSTEMI and UAP. The only study that provides this data is the study by Bruins Slot et al. (2013). A mayor concern for this study is the population under study; only patients who were already expected to have an ACS by their GP were included in the study. Also, patients who needed immediate care as judged by the GP were not included in the study. These two flaws are likely to result in a biased prevalence of ACS in the GP population. The reported prevalence is 22.1% which is much higher than the prevalence found in the other studies. Therefor this prevalence will not be used in the model. However the proportion of STEMI, NSTEMI and UAP in the ACS population found by Bruins Slot et al. (2013) is the best evidence found to estimate the population prevalence on these conditions, so they will be used in the health economic model.

The patient level origin of the health economic model requires ACS prevalence rates stratified in age groups. Bösner et al. (2009) provide this data as well. Using the 1 proportion 95% confidence interval equation to calculate 95% confidence intervals (Equation 1), the following estimates are obtained:

$$\hat{p} \pm (1.96^{*} \cdot \sqrt{\frac{\hat{p}(1-\hat{p})}{n}})$$

**Equation 1: 1 proportion 95% confidence interval**

Probability ACS:

| | |
|---|---|
| Age ≥75 | 8.15% (4.35-11.95) |
| Age 65-74 | 5.19% (2.67-7.71) |
| Age 55-64 | 3.30% (1.04-5.62) |
| Age 45-54 | 1.11% (0-2.4) |
| Age 35-44 | 1.48% (0-3.05) |
| Probability NSTE-ACS\|ACS: | 48/0.66 = 72.7% (62.0 - 83.4) |
| Probability STE-ACS/STEMI\|ACS: | 18/0.66 = 27.3% (16.6 - 38.0) |
| Probability UAP\|NSTE-ACS: | 14/0.48 = 29.2% (16.3 - 42.1) |
| Probability NSTEMI\|NSTE-ACS: | 34/0.48 = 70.8% (57.9 - 83.7) |

**Diagnostic performance characteristics clinical assessment**

The search for DPC's for STEMI, NSTEMI and UAP by the GP is combined in one syntax.

| *Inclusion criteria* | *Exclusion criteria* |
|---|---|
| -In GP population | -Non-western population |
| -After presenting with chest complaints | -Non-English language |
| | -Before 2003 |
| | -Insufficient methodological quality |

| Parameter | Scopus search syntax | Cochrane review library syntax |
|---|---|---|
| DPC for Clinical Assessment by GP | **(30-4-2014) 64 Hits**<br>(TITLE-ABS-KEY(({**acute coronary syndrome**} W/10 (**primary** W/2 **care**)) OR (**"chest pain"** W/10 (**primary** W/2 **care**)) OR (**"chest complaint"** W/10 (**primary** W/2 **care**)) OR (**"st segment elevation myocardial infarction"** W/10 (**primary** W/2 **care**)) OR (**"st elevation myocardial infarction"** W/10 (**primary** W/2 **care**)) OR (**"st segment elevation myocardial infarct"** W/10 (**primary** W/2 **care**)) OR (**"st elevation myocardial infarct"** W/10 (**primary** W/2 **care**)) OR (**stemi** W/10 (**primary** W/2 **care**)) OR (**"non st segment elevation myocardial infarction"** W/10 (**primary** W/2 **care**)) OR (**"non st elevation myocardial infarction"** W/10 (**primary** W/2 **care**)) OR (**"non st segment elevation myocardial infarct"** W/10 (**primary** W/2 **care**)) OR (**"non st elevation myocardial infarct"** W/10 (**primary** W/2 **care**)) OR (**nstemi** W/10 (**primary** W/2 **care**)) OR (**"non stemi"** W/10 (**primary** W/2 **care**)) OR ({**unstable angina pectoris**} W/10 (**primary** W/2 **care**)) OR ({**unstable angina**} W/10 (**primary** W/2 **care**)) OR (**uap** W/10 (**primary** W/2 **care**)) OR ({**acute coronary syndrome**} W/10 {**family practice**}) OR (**"chest pain"** W/10 | **(3-6-2014) 4 Hits**<br>#1 "acute coronary syndrome":ti,ab,kw or "chest pain":ti,ab,kw or chest complaint:ti,ab,kw or "st segment elevation myocardial infarction":ti,ab,kw or "st elevation myocardial infarction":ti,ab,kw (Word variations have been searched)<br>#2 "st segment elevation myocardial infarct":ti,ab,kw or "st elevation myocardial infarct":ti,ab,kw or "non st segment elevation myocardial infarction":ti,ab,kw or "non st elevation myocardial infarction":ti,ab,kw or "non st segment elevation myocardial infarct":ti,ab,kw (Word variations have been searched)<br>#3 "non st elevation myocardial infarct":ti,ab,kw or "NSTEMI":ti,ab,kw or "STEMI":ti,ab,kw or "non stemi":ti,ab,kw or "unstable angina pectoris":ti,ab,kw (Word variations have |

| | | |
|---|---|---|
| | **{family practice}**) OR (**"chest complaint"** W/10 **{family practice}**) OR (**"st segment elevation myocardial infarction"** W/10 **{family practice}**) OR (**"st segment elevation myocardial infarction"** W/10 **{family practice}**) OR (**"st segment elevation myocardial infarct"** W/10 **{family practice}**) OR (**"st elevation myocardial infarct"** W/10 **{family practice}**) OR (**stemi** W/10 **{family practice}**) OR (**"non st segment elevation myocardial infarction"** W/10 **{family practice}**) OR (**"non st elevation myocardial infarction"** W/10 **{family practice}**) OR (**"non st segment elevation myocardial infarct"** W/10 **{family practice}**) OR (**"non st elevation myocardial infarct"** W/10 **{family practice}**) OR (**nstemi** W/10 **{family practice}**) OR (**"non stemi"** W/10 **{family practice}**) OR (**{unstable angina pectoris}** W/10 **{family practice}**) OR (**{unstable angina}** W/10 **{family practice}**) OR (**uap** W/10 **{family practice}**) OR (**{acute coronary syndrome}** W/10 (**general** W/2 **prac***)) OR (**"chest pain"** W/10 (**general** W/2 **prac***)) OR (**"chest complaint"** W/10 (**general** W/2 **prac***)) OR (**"st segment elevation myocardial infarction"** W/10 (**general** W/2 **prac***)) OR (**"st segment elevation myocardial infarction"** W/10 (**general** W/2 **prac***)) OR (**"st segment elevation myocardial infarct"** W/10 (**general** W/2 **prac***)) OR (**"st elevation myocardial infarct"** W/10 (**general** W/2 **prac***)) OR (**stemi** W/10 (**general** W/2 **prac***)) OR (**"non st segment elevation myocardial infarction"** W/10 (**general** W/2 **prac***)) OR (**"non st elevation myocardial infarction"** W/10 (**general** W/2 **prac***)) OR (**"non st segment elevation myocardial infarct"** W/10 (**general** W/2 **prac***)) OR (**"non st elevation myocardial infarct"** W/10 (**general** W/2 **prac***)) OR (**nstemi** W/10 (**general** W/2 **prac***)) OR (**"non stemi"** W/10 (**general** W/2 **prac***)) OR (**{unstable angina pectoris}** W/10 (**general** W/2 **prac***)) OR (**{unstable angina}** W/10 (**general** W/2 **prac***)) OR (**uap** W/10 (**general** W/2 **prac***)) OR (**{acute coronary syndrome}** W/10 **{gp}**) OR (**"chest pain"** W/10 **{gp}**) OR (**"chest complaint"** W/10 **{gp}**) OR (**"st segment elevation myocardial infarction"** W/10 **{gp}**) OR (**"st segment elevation myocardial infarction"** W/10 **{gp}**) OR (**"st segment elevation myocardial infarct"** W/10 **{gp}**) OR (**"st elevation myocardial infarct"** W/10 **{gp}**) OR (**stemi** W/10 **{gp}**) OR (**"non st segment elevation myocardial infarction"** W/10 **{gp}**) OR (**"non st elevation myocardial infarction"** W/10 **{gp}**) OR (**"non st segment elevation myocardial infarct"** W/10 **{gp}**) OR (**"non st elevation myocardial infarct"** W/10 **{gp}**) OR (**nstemi** W/10 **{gp}**) OR (**"non stemi"** W/10 **{gp}**) OR (**{unstable angina pectoris}** W/10 **{gp}**) OR (**{unstable angina}** W/10 **{gp}**) OR (**uap** W/10 **{gp}**) AND ((**sensitivit***) OR (**specificit***) OR (**assess***) OR (**accuracy**) OR (**diagnos***) OR (**performance**))) AND NOT TITLE-ABS-KEY(**glycoprotein**) AND NOT TITLE((**emergency** W/2 **department**) OR (**ed**) OR (**hospital**)) AND NOT KEY((**{emergency department}**) OR (**ed**) OR (**hospital**))) AND DOCTYPE(**ar** OR **re**) AND PUBYEAR > **2002** AND (LIMIT-TO(LANGUAGE, **"English"**)) AND (LIMIT-TO(SUBJAREA, **"MEDI"**)) | been searched)<br>#4 "unstable angina":ti,ab,kw or "UAP":ti,ab,kw (Word variations have been searched)<br>#5 primary near/2 care:ti,ab,kw or "family practice":ti,ab,kw or general near/2 prac*:ti,ab,kw or "gp":ti,ab,kw (Word variations have been searched)<br>#6 "glycoprotein":ti,ab,kw or emergency near/2 department:ti or "ED":ti or "hospital":ti or "emergency department":kw (Word variations have been searched)<br>#7 "ED":kw or "hospital":kw (Word variations have been searched)<br>#8 (#1 or #2 or #3 or #4) and #5 not (#6 or #7) Publication Date from 2003, in Cochrane Reviews (Reviews and Protocols) and Other Reviews (Word variations have been searched)<br>#9 sensitivit*:ti,ab,kw or specificit*:ti,ab,kw or assess*:ti,ab,kw or accuracy:ti,ab,kw or diagnos*:ti,ab,kw (Word variations have been searched)<br>#10 performance:ti,ab,kw (Word variations have been searched)<br>#11 #8 and (#9 or #10) Publication Date from 2003, in Cochrane Reviews (Reviews and Protocols) and Other Reviews (Word variations have been searched) |

The syntaxes yielded 68 unique publications. By reviewing the title and abstract 11 publications were excluded because of a hospital setting being used. 5 publications were excluded because they met the non-western exclusion criterion. 19 publications were excluded because the population under study did not meet the inclusion criteria. 1 study got excluded because no results were published. 6 were excluded because they focused on non-cardiac chest pain. 3 got excluded because the chosen study design would not result in reliable, valid diagnostic performance characteristics estimates. Finally, 1 article was not retrievable. The remaining 22 publications were identified as potential source for evidence of DPC for clinical assessment. By reviewing these publications, 20 publications got excluded because no diagnostic performance characteristics for clinical assessment were given or could not be calculated. The remaining two publications are given in Table 14.

**Table 14: Diagnostic performance characteristics clinical assessment by GP**

| | | | n | Diagnostic performance characteristic, % (95% CI) | | | |
|---|---|---|---|---|---|---|---|
| **Study** | **Region** | **Population** | **Total** | **Sensitivity ACS** | **Specificity ACS** | **Sensitivity IHD** | **Specificity IHD** |
| Bösner, 2010[12] | Germany | >35 years with chest complaints at GP | 1212 | 50 (36-64) | 98 (97-99) | 69 (62-76) | 89 (87-91) |
| Nilsson, 2008[13] | Sweden | 20-79 years with a new episode of chest pain | 503 | | | 88% (80.2-96.5) | 72% (68.1-76.4) |

*Applicability and conclusion*

The reported sensitivity and specificity by Bösner et al. (2010) were not based on whether or not the patient got referred by the GP but on a preliminary diagnosis by the GPs independent of referral behaviour. This leads to an overestimation of specificity and underestimation of sensitivity for ACS and, when used in the model would result in biased referral rates of ACS and healthy patients for the non-POCT strategy. Instead the results from Nilsson et al. (2008) will be used in the model. Nilsson et al. (2008) explicitly state the sensitivity and specificity for the GPs action in daily practice including referral to secondary care. However Nilsson et al. studied not only the GPs diagnostic performance for ACS, but for all IHD, including stable conditions.

**Effect of delay of treatment at ED**

| *Inclusion criteria* | *Exclusion criteria* |
|---|---|
| -ED ACS population | -Non-western population |
| -Primary PCI for STE-ACS patients | -Non-English language |
| -Coronary angiography for NSTE-ACS patients | -Before 2003 |
| | -Insufficient methodological quality |

| Parameter | Scopus search syntax | Cochrane review library syntax |
|---|---|---|
| Effect of delay on outcomes | **(13-5-2014) 60 Hits**<br>(TITLE-ABS-KEY(({**acute coronary syndrome**} OR **"st segment elevation myocardial infarct*"** OR **"st elevation myocardial infarct*"** OR **stemi** OR **"non st segment elevation myocardial infarct*"** OR **"non st elevation myocardial infarct*"** OR **nstemi** OR **"non stemi"** OR **"myocardial infarct*"** OR {**unstable angina pectoris**} OR {**unstable angina**} OR **uap**)) AND KEY((**delay*** OR **timing** OR **slow** OR **postpone***) AND (**outcome*** OR **effect** OR **effects** OR **consequence***))) AND ((ABS((**delay*** OR **timing** OR **slow** OR **postpone***) W/10 (**outcome*** OR **effect** OR **effects** OR **consequence***))) OR (TITLE((**delay*** OR **timing** OR **slow** OR **postpone***) W/10 (**outcome*** OR **effect** OR **effects** OR **consequence***)))) AND DOCTYPE(**ar** OR **re**) AND PUBYEAR > **2002** AND (LIMIT-TO(LANGUAGE, **"English"**)) AND (LIMIT-TO(SUBJAREA, **"MEDI"**)) | **(4-6-2014) 37 Hits**<br>#1 "acute coronary syndrome":ti,ab,kw or "chest pain":ti,ab,kw or chest complaint:ti,ab,kw or "st segment elevation myocardial infarction":ti,ab,kw or "st elevation myocardial infarction":ti,ab,kw (Word variations have been searched)<br>#2 "st segment elevation myocardial infarct":ti,ab,kw or "st elevation myocardial infarct":ti,ab,kw or "non st segment elevation myocardial infarction":ti,ab,kw or "non st elevation myocardial infarction":ti,ab,kw or "non st segment elevation myocardial infarct":ti,ab,kw (Word variations have been searched)<br>#3 "non st elevation myocardial infarct":ti,ab,kw or "NSTEMI":ti,ab,kw or "STEMI":ti,ab,kw or "non stemi":ti,ab,kw or "unstable angina pectoris":ti,ab,kw (Word variations have been searched)<br>#4 "unstable angina":ti,ab,kw or "UAP":ti,ab,kw (Word variations have been searched)<br>#5 delay:ti,ab,kw or timing:ti,ab,kw or slow:ti,ab,kw or postpone*:ti,ab,kw (Word variations have been searched)<br>#6 outcome*:ti,ab,kw or effect:ti,ab,kw or effects:ti,ab,kw or consequence*:ti,ab,kw (Word variations have been searched)<br>#7 (#1 or #2 or #3 or #4) and #5 and #6 Publication Date from 2003, in Cochrane Reviews (Reviews and Protocols) and Other Reviews (Word variations have been searched) |

The syntaxes yielded 96 unique publications. By reviewing the title and abstract 13 publications met the non-Western exclusion criteria. 33 publications did not meet the population inclusion criteria of ED patients with ACS. 10 publications did not study the effects of delay. 8 publications reported the effect of delay for other treatments than stated in the inclusion criteria. 3 publications reported on an experimental uncommon treatment. 1 publication met the non-English language exclusion criteria. 1 publication did not present any results. Finally 4 publications were not retrievable. The remaining 23 publications were identified as potential source for evidence on the effect of delay on outcomes for ACS. By reviewing these a further 15 publications got excluded because the wrong treatment was used or a comparison was made between different approaches in the same treatment. The remaining publications are given in Table 15.

**Table 15: Effect of treatment delay for STE-ACS and NSTE-ACS**

| **STE-ACS** | | | | **Study quality assessment** | | |
|---|---|---|---|---|---|---|
| **Study** | **Region** | **Treatment strategy** | **Effect of delay** | **# NOS Stars Max 8** | **# Non-compliances with applicable STROBE statement recommendations #/max** | **Jadad score Max 5** |
| Farshid, 2012[14] | Australia | Local PCI vs transferred PCI | 0% mortality difference during 3.98 median follow-up years* | 7 | 5/32 | N/A |
| Hudson, 2011[15] | Multinational | PCI | **Door to balloon time**<br>\| | <60 min | 60-90 min | 90-120 min | >120 min |<br>\| 90-day mortality (%) \| 3.18 \| 4.00 \| 4.56 \| 5.34 |<br>\| 95% CI \| 2.13 - 4.23 \| 2.96 - 5.05 \| 3.37 - 5.74 \| 4.29 - 6.39 |<br>\| 30-day mortality (%) \| 2.4 \| 3.5 \| 4.0 \| 4.4 | 6 | 4/33 | N/A |
| Nallamothu, 2007[16] | Global | PCI and fibrinolysis | 6-month mortality increased by 0.18% per 10-min delay in door-to balloon time between 90 and 150 min. (95% CI, 0.08 - 0.35% per 10 min delay) | 7 | 3/33 | N/A |
| Pedersen, 2009[17] | Denmark | Field triage PCI vs routine PCI | Adjusted Hazard ratio 1 year all-cause mortality Field triage vs routine: 0.73 (95% CI, 0.47 - 1.13)* | 7 | 6/33 | N/A |
| Terkelsen, 2010[18] | Denmark | PCI | Adjusted Hazard ratio long-term (median: 3.4 years) mortality system delay per 1 hour increase: 1.10 (95% CI, 1,04 - 1,16)<br>Adjusted Hazard ratio long-term (median: 3.4 years) mortality door-to-balloon time per 1 hour increase: 1.14 (95% CI, 1.05 – 1.24) | 7 | 2/33 | N/A |
| Wang, 2011[19] | US | PCI | **Door-in-door-out time, min** \| **In-hospital-mortality (%)** \| **Adjusted Odds Ratio (95% CI)**<br>\| ≤30 \| 2.7 \| 1.0 (Reference)<br>\| 31-60 \| 4.0 \| 1.34 (0.96 - 1.86)<br>\| 61-90 \| 4.9 \| 1.41 (0.96 - 2.06)<br>\| >90 \| 8.3 \| 1.86 (1.36 - 2.54) | 7 | 4/33 | N/A |
| **NSTE-ACS** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Damman, 2012[20] | Multinational | Early (≤2 days) vs delayed (3-5 days) angiography | Adjusted Hazard ratio 5-year cardiovascular death early vs delayed angiography: 1.05 (95% CI, 0.75 - 1.47)* | 7 | 6/33 | N/A |
| Mehta, 2009[21] | US | Early (<24 hours) vs delayed (>36 hours) angiography | Hazard ratio 30-day death early vs delayed angiography: 0.86 (95% CI:, 0.58 – 1.29)*<br>Hazard ratio 6-month death early vs delayed angiography: 0.81 (95% CI:, 0.60 – 1.11)* | N/A | N/A | 4 |

*Not significant

*Study quality*

The study quality assessment results are also given in Table 15. The study by Mehta et al. (2009) is a randomized controlled trial and is therefore assessed using the Jadad[4] scale for randomized controlled studies. The other publications are all observational and are assessed with the NOS and the STROBE-checklist.

*Applicability and conclusion*

The quality of the publications for STE-ACS treatment delay differs slightly. The least scoring publication is the one by Hudson et al. (2011). The publication by Terkelsen et al. (2010) scored best with both the tools, however, since this study reports results over a long period of time, its results are of less use for in-hospital mortality estimates with treatment delay. The study by Wang et al. (2011) only studied patients who were transferred from a non-PCI capable hospital to a PCI capable one, and therefor is not truly representative for the entire population receiving PCI. The study by Nallamothu et al. (2007) will be used in the health economic model, its results are significant, the quality is sufficient and the follow-up time is acceptable. Treatment delay for NSTE-ACS will not be modelled because the delay time under study is far greater than the delay POCT would result in.

**Mortality rates missed ACS**

*Inclusion criteria*

-Missed ACS population

-Mortality rate or risk ratio reported

*Exclusion criteria*

-Non-western population

-Non-English language

-Before 2003

-Insufficient methodological quality

| Parameter | Scopus search syntax | Cochrane review library syntax |
|---|---|---|
| Mortality rate at Home because of FN | **(2-6-2014) 88 Hits**<br>(TITLE-ABS-KEY(({**acute coronary syndrome**} OR **"st segment elevation myocardial infarct*"** OR **"st elevation myocardial infarct*"** OR **stemi** OR **"non st segment elevation myocardial infarct*"** OR **"non st elevation myocardial infarct*"** OR **nstemi** OR **"non stemi"** OR **"myocardial infarct*"** OR **{unstable angina pectoris}** OR **{unstable angina}** OR **uap**) AND (**mortality** OR **{death rate}** OR **{death ratio}**) AND (**undiagnosed** OR **undetected** OR **missed**))) AND DOCTYPE(**ar** OR **re**) AND PUBYEAR > **2002** AND (LIMIT-TO(LANGUAGE, **"English"**)) AND (LIMIT-TO(SUBJAREA, **"MEDI"**)) | **(4-6-2014) 1 Hit**<br>#1 "acute coronary syndrome":ti,ab,kw or "chest pain":ti,ab,kw or chest complaint:ti,ab,kw or "st segment elevation myocardial infarction":ti,ab,kw or "st elevation myocardial infarction":ti,ab,kw (Word variations have been searched)<br>#2 "st segment elevation myocardial infarct":ti,ab,kw or "st elevation myocardial infarct":ti,ab,kw or "non st segment elevation myocardial infarction":ti,ab,kw or "non st elevation myocardial infarction":ti,ab,kw or "non st segment elevation myocardial infarct":ti,ab,kw (Word variations have been searched)<br>#3 "non st elevation myocardial infarct":ti,ab,kw or "NSTEMI":ti,ab,kw or "STEMI":ti,ab,kw or "non stemi":ti,ab,kw or "unstable angina pectoris":ti,ab,kw (Word variations have been searched)<br>#4 "unstable angina":ti,ab,kw or "UAP":ti,ab,kw (Word variations have been searched)<br>#5 undiagnosed:ti,ab,kw or undetected:ti,ab,kw or missed:ti,ab,kw (Word variations have been searched)<br>#6 mortality:ti,ab,kw or "death rate":ti,ab,kw or "death ratio":ti,ab,kw (Word variations have been searched)<br>#7 (#1 or #2 or #3 or #4) and #5 and #6 Publication Date from 2003, in Cochrane Reviews (Reviews and Protocols) and Other Reviews (Word variations have been searched) |

The syntaxes yielded 89 unique publications. By reviewing the title and abstract, 80 publications were excluded because the population under study did not match the inclusion criterion or mortality rates or risk ratios were not investigated. The remaining 9 publications were identified as potential source for evidence of mortality rates for ACS at home after a missed diagnosis. By reviewing these publications, 8 publications got excluded because no mortality rates or risk ratios were given. Because only one study provided useful evidence, more publications were sought in the bibliographies of the 9 publications initially identified. This resulted in 2 more, older studies reporting useful evidence. The results of the 3 publications are given in Table 16.

**Table 16: Mortality rates missed ACS**

| *Study* | *Region* | *Population* | *n* | *Effect* | # NOS Stars Max 8 | # Non-compliances with applicable STROBE statement recommendations #/max |
|---|---|---|---|---|---|---|
| Sequist, 2005[22] | US | Missed diagnoses of MI during outpatient visit with a general internist for chest pain. Diagnosis of MI within 1 month. | 18 | 1-month overall mortality: 38.8%<br>1-month mortality not in hospital: 22.2%<br>1-month new HF: 44.4% | 5 | 6/32 |
| McCarthy, 1993[23] | US | Patients with missed AMI at ED | 20 | Mortality: 10% (95% CI, 1.2 - 30.9)* | 5 | 6/31 |
| Pope, 2000[24] | US | Missed patients with acute cardiac ischemia stratified by AMI and UAP | 39 | 30-day AMI mortality: 10.5%<br>30-day UAP mortality: 5.0%<br>Adjusted mortality Risk ratio vs hospitalized AMI: 1.9 (95% CI, 0.7 - 5.2)<br>Adjusted mortality Risk ratio vs hospitalized UAP: 1.7 (95% CI, 0.2 – 17.0) | 8 | 5/33 |

*Not significant

*Study quality*

Study quality assessment results are given in Table 16. The studies by Sequist et al. (2005) and McCarthy et al. (1993) were case-control studies and were therefor assessed with the NOS case-control checklist. The study by Pope et al. (2000) was a cohort study.

*Applicability and conclusion*

Both the case-control studies were of limited quality compared with the study by Pope et al. (2000). They will therefore not be used in the health economic model for mortality rates for missed ACS. However Sequist et al. (2005) also reports the rate of new heart failure in the missed AMI population. Since the other studies do not report this, this rate will be used in the health economic model. A 95% confidence interval is calculated using the central limit theorem (Equation 1). The study by Pope et al. (2000) is of sufficient quality to be used for mortality rates and presents with very useful relative figures stratified in AMI and UAP to be used in the health economic model.

## Registry search

By consulting with 3 large (global) registries on ACS in hospitals, in-hospital mortality rates and heart failure rates for STEMI, NSTEMI and UAP will be derived for use in the health economic model. The consulted registries are briefly elaborated below.

**Global Registry of Acute Coronary Events (GRACE)**

The GRACE project tries to reflect a generalizable sample of patients hospitalized with acute coronary syndrome. 90 community and teaching hospitals located in 14 countries across 4 continents are participating in this observational study. Details of the methodology of GRACE have been previously described.[25,26]

In short all acute-care hospitals in a well-defined geographic area were recruited to participate. Patients in the registry had to be 18 years or older, alive at the time of presentation and had to be admitted for presumptive ACS. This is a combination of symptoms consistent with acute ischemia and at least one of the following: electrocardiographic changes consistent with an ACS, serial increases in serum biochemical markers of cardiac necrosis, and/or documentation of coronary artery disease. The ACS could not be accompanied by a significant co-morbidity, trauma or surgery.

All hospital-related data were collected at each study site by a trained coordinator using a standardized case report form comprising of: demographic characteristics, medical history, presenting symptoms, duration of pre-hospital delay, biochemical and ECG findings, treatments and various hospital outcome data. After discharge patients were followed up by telephone, clinic visits or through calls to their general practitioner.

**ACTION Registry-GWTG**

The ACTION Registry-GWTG was created to serve as a national AMI surveillance system, to contribute to the scientific enquiry process of AMI care, and to facilitate local and national quality improvement efforts.[27] It is a merger between the American College of Cardiology's (ACC) Acute Coronary Treatment and Intervention Outcomes Network (ACTION) and the American Heart Association (AHA) Get With the Guidelines (GWTG) Coronary Artery Disease Programme.

Patients with a primary diagnosis of STEMI or NSTEMI are eligible for enrolment into the registry. Inclusion criteria are: ischaemic symptoms at rest, lasting 10 minutes or more, occurring within 24 hours before admission or up to 72 hours for STEMI; ECG changes associated with STEMI; or positive cardiac markers associated with NSTEMI within 24 hours after initial presentation.[27] Therefore, only confirmed AMIs are entered into the database.[27]

Data elements that are measured in the registry include the ACC/AHA performance measures and class I recommendations of the ACC/AHA clinical practice guidelines. [28,29] Other data elements include patient demographics, presenting features, pre, acute and discharge medications, timing of care delivery, laboratory tests, procedure use and in hospital-patient outcomes.[27] Data are limited to only the in-hospital admission.[27]

**Euro Heart Survey ACS**

The European Society of Cardiology (ESC) sponsored a large scale Euro Heart Survey ACS in order to better delineate the characteristics, treatments and outcomes of acute coronary syndrome patients treated in representative ESC-member countries, and particularly to examine the adherence to current practice guidelines.[30] The Euro Heart Survey ACS is a prospective survey of 10484 patients from 25 ESC member countries with a final diagnosis of ACS.[30]

All patients with suspected ACS screened in an emergency room, chest pain unit, catheterization laboratory, or otherwise by the data collection officer with tentative diagnosis of AMI, rule-out MI, or suspected unstable angina were registered on a screening log.[30] Initially patients were grouped based on their initial ECG pattern: ACS with ST elevation, ACS without ST elevation, and ACS with an undetermined ECG pattern.[30] After a confirmed diagnosis of ACS, the patient got enrolled in the survey. Discharge diagnoses were recorded as: unstable angina, non-Q wave myocardial infarction, and Q wave myocardial infarction. In-hospital and 30-day results were recorded.[30]

The first Euro Heart Survey was conducted in 2000-2001. A second survey in 2004.

## Results

Since direct access to the registries was unavailable for this thesis, results were derived by consulting with publications using data from the registries. Results for mortality rates are given in tables 6-8, results for heart failure rates are given in tables 9-11.

**Table 17: In-hospital Mortality rates from GRACE**

| Study | n | Enrolment period | Mortality STEMI | Mortality NSTEMI | Mortality UAP | Overall mortality |
|---|---|---|---|---|---|---|
| Fox, 2007[31]* | | July - December '99 | 8.4% | | | |
| Fox, 2007[31]* | | July - December '05 | 4.6% | | | |
| Goldberg, 2004[32] | 24055 | April '99 - September '02 | 7.8% | 5.9% | 2.7% | 5.45% |
| Granger, 2003[33] | 13708 | April '99 - March '01 | 7.1% | | | |
| Steg, 2002[26] | 11543 | April '99 - December '00 | 7% | 5% | 3% | |

*Same publication with different enrolment periods under study

**Table 18: In-hospital mortality rates from ACTION registry-GWTG**

| Study | n | Enrolment period | Mortality STEMI | Mortality NSTEMI | Mortality UAP | Overall mortality |
|---|---|---|---|---|---|---|
| Chin, 2011[34]* | 82004 | January '07 - September '08 | 5.8% | | | |
| Peterson, 2010[27] | 147165 | January '07 - September '09 | | | | 4.8% |

*Possible bias due to excluded patients and sites

**Table 19: In-hospital mortality rates from Euro heart survey ACS**

| Study | Database | n | Enrolment period | Mortality STE-ACS | Mortality NSTE-ACS | Mortality undetermined ECG | Overall mortality |
|---|---|---|---|---|---|---|---|
| Hasdai, 2002[30] | EHS ACS-I | 10484 | September '00 - May '01 | 7.0% | 2.4% | 11.8% | 4.9% |
| Mandelzweig, 2006[35] * | EHS ACS-II | 6385 | March - October '04 | 5.3% | 2.5% | 6.6% | 4.0% |

*Difference in mortality with EHS-ACS-I is attributed to better guideline adherence.

**Table 20: Chronic heart failure rates from GRACE**

| Study | n | Enrolment period | CHF STEMI | CHF NSTEMI | CHF UAP | Overall CHF |
|---|---|---|---|---|---|---|
| Fox, 2007[31]* | | July - December '99 | 19.5% | | | |
| Fox, 2007[31]* | | July - December '05 | 11% | | | |
| Goldberg, 2004[32†] | 24055 | April '99 - September '02 | 18.4% | 17.9% | 9.2% | |
| Steg, 2002[26] | 11543 | April '99 - December '00 | 18% | 18% | 10% | |

*Same publication with different enrolment periods under study
† Not clear if heart failure is chronic or not

**Table 21: Chronic heart failure rates from ACTION registry-GWTG**

| Study | n | Enrolment period | CHF STEMI | CHF NSTEMI | CHF UAP | Overall CHF |
|---|---|---|---|---|---|---|
| Peterson, 2010[27] | 147165 | January '07 - September '09 | | | | 6.9% |

**Table 22: Chronic heart failure rates from Euro heart survey ACS**

| Study | Database | n | Enrolment period | CHF STE-ACS | CHF NSTE-ACS | CHF undetermined ECG | Overall CHF |
|---|---|---|---|---|---|---|---|
| Hasdai, 2002[30] | EHS ACS-I | 10484 | September '00 - May '01 | 20.2% | 12.7% | 29.8% | 17.0% |
| Hasdai, 2003[36] | EHS ACS-I | 9589 | September '00 - May '01 | 19.7%* | 12.7% | | |
| Mandelzweig, 2006[35†] | EHS ACS-II | 6385 | March - October '04 | | | | 12.4% |

*Difference with Hasdai, 2002 is explained by exclusion of missing data on gender.
† Difference in CHF rates with EHS-ACS-I is attributed to better guideline adherence.

**Applicability and conclusion**

As can be seen in the tables above, the GRACE registry provides the most data on mortality and heart failure rates for ACS. The Action registry-GWTG provides limited information and the mortality rate reported by Chin et al. (2011) may be biased because of excluded patients and sites. Unfortunately the Euro heart survey ACS applies a different stratification of ACS patients than used in the health economic model. In the EHS ACS studies identified it was not possible to transform the data to fit the STEMI, NSTEMI and UAP stratification used in the health economic model. This leaves the data obtained by the GRACE. Both Goldberg et al. (2004) and Steg et al. (2002) report stratified mortality and heart failure rates for STEMI, NSTEMI and UAP. The data presented by Goldberg et al. (2004) will be used in the model, since this data is more recent than the data presented by Steg et al. (2002). 95% Confidence intervals are calculated using the given sample size and point estimates and the equation for 95% confidence interval for 1 proportion (Equation 1):

95% CI Mortality rates, %:
STEMI: 7.2 - 8.4
NSTEMI: 5.4 - 6.4
UAP: 2.4 - 3.0

95% CI chronic heart failure rates, %:
STEMI: 17.4 - 19.4
NSTEMI: 16.9 - 18.9
UAP: 8.5 - 9.9

The health economic model requires age dependent mortality rates due to its patient level simulations. In the study by Granger et al. (2003), already identified during the registry search, an odds ratio of 1.7 (95% CI:1.52-1.82) for mortality per 10 years increase in age is reported.[33] This odds ratio is derived from the same registry, GRACE, as are the mortality rates reported by Goldberg et al. (2004).[32] Therefor this odds ratio will be combined with the mortality rates to calculate age dependent mortality rates.

## QALY and utility search

Life time QALY estimates for the different conditions under study will be will be derived using the CEA registry and consultation with previous health economic studies published in the Health Technology Assessment (Winchester, England) (HTA) journal.[37] The CEA registry is provided by Tufts Medical Centre in Boston and is a database with 3772 Cost-utility analyses on a wide variety of diseases and treatments.[38] The registry contains information of study characteristics such as the perspective, intervention, discounting rates, cost-effectiveness ratios and utility weights. In this study the registry is searched for utility weights for the conditions under study. The registry did not result in separate utility weights for STEMI and NSTEMI patients. Therefor these patients are grouped together as acute myocardial infarction. Studies were selected on region and publication date of original utility weight. No Dutch studies

were identified who presented useful utility weights. By searching the HTA journal, a systematic review and economic model for diagnostic strategies for ACS by Goodacre et al. (2013) was identified. [39] This study provided lifetime QALY estimates for AMI and healthy patients, discounted at 3% and based on remaining life expectancy reported by Polanczyk et al. (1999) and utility weights for AMI of 0.78 reported by Ward et al. (2007).[40,41] Estimates were stratified in different age groups and gender. The remaining QALYs for healthy patients were reported with one year increments in age. For use in the health economic model, averages were calculated for age-groups corresponding with the age-groups used in the health economic model. Results are presented in Table 23 and Table 24.

**Table 23: Life time QALYs for AMI patients**

| Age | Remaining QALYs |
|---|---|
| 30-44 | 12.20 |
| 45-54 | 9.47 |
| 55-64 | 6.73 |
| 65-74 | 4.65 |
| >75 | 2.43 |

**Table 24: Life time QALYs for healthy patients**

| Age | Remaining QALYs Men | Remaining QALYs Women |
|---|---|---|
| 35-44 | 19.45 | 18.968 |
| 45-54 | 15.817 | 15.411 |
| 55-64 | 11.499 | 11.194 |
| 65-74 | 7.56 | 7.352 |
| >75 | 3.0872 | 2.994 |

For UAP patients, unfortunately no HTA publication provided already calculated lifetime QALYs or utility weights. The CEA registry did reveal several studies who reported utility weights for UAP patients. All these studies used a utility weight of 0.77 reported by Goodacre et al. (2004).[42] One additional reference used for the utility weight for UAP patients was the study by Kim et al. (2005).[43] This study reported a utility weight of 0.748 and 0.752 for UAP and NSTEMI patients at 4 months and 1 year respectively after interventional treatment (angiography followed by revascularization when necessary).

In order to calculate life time QALYs for the different age groups in the model, information on long-term mortality for UAP stratified by age is needed. By conducting a quick literature search on long-term mortality for UAP, no studies were found providing the age stratified data needed. A study by Chang et al. (2003) reported the 5-year mortality of AMI to be 10.19% more than UAP.[44] In order to estimate the life time QALYs for UAP the life time QALYs found for AMI will be increased by this 10.19%. The results are presented in Table 25.

**Table 25: Life time QALYs for UAP patients**

| Age | Remaining QALYs |
|---|---|
| 30-44 | 13.44 |
| 45-54 | 10.43 |
| 55-64 | 7.42 |
| 65-74 | 5.12 |
| >75 | 2.68 |

For HF the life time QALYs were calculated by using long term mortality data from a Dutch study on HF: the Groningen longitudinal study by van Jaarsveld et al. (2006).[45] The Groningen longitudinal Study provides Dutch estimates on mean survival time of heart failure patients since time of diagnosis. Results are given in Table 26. The utility weights were

identified using the CEA registry. Unfortunately not all references for the used utilities were stated in the studies identified. Also several studies stratified the utility weights in different severity classes of HF which makes them of less use for the present study. Eventually, two suitable studies were identified using the CEA registry. Sullivan et al. (2009) reported a weight of 0.636 and Spertus et al. (2005) reported a weight of 0.67.[46,47] They are both from the US. The weight by Sullivan et al. (2009) will be used for QALY calculations since this study is the most recent. The life time QALYs for HF are given in Table 27.[46]

**Table 26: Mean survival time in months since HF diagnosis. Results from the Groningen longitudinal aging study**[45]

| STRATA | MEAN SURVIVAL TIME IN YEARS(95% CI) |
|---|---|
| MALE AGED ≤75 YEARS | 4.5 (3.75-5.17) |
| FEMALE AGED ≤75 YEARS | 5.92 (5.17-6.67) |
| MALE AGED >75 YEARS | 3.33(2.58-4.08) |
| FEMALE >75 YEARS | 3.5(2.83-4.08) |

**Table 27: Life time QALYs for Heart Failure patients**

| STRATA | LIFE TIME QALYS (95% CI) |
|---|---|
| MALE AGED <= 75 YEARS | 2.72 (2.29-3.09) |
| FEMALE AGED <=75 YEARS | 3.50 (3.09-3.90) |
| MALE AGED >75 YEARS | 2.05 (1.60-2.48) |
| FEMALE >75 YEARS | 2.14 (1.75-2.48) |

## References appendix II


1. Elm E Von, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61(4):344-9. doi:10.1016/j.jclinepi.2007.11.008.

2. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2014. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

3. Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. 5.1.0 [upd. The Cochrane Collaboration; 2011. Available at: http://handbook.cochrane.org/.

4. Jadad a R, Moore R a, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8721797.

5. Bösner S, Becker A, Haasenritter J, et al. Chest pain in primary care: epidemiology and pre-work-up probabilities. *Eur J Gen Pract*. 2009;15(3):141-6. doi:10.3109/13814780903329528.

6. Bösner S, Haasenritter J, Hani M a, et al. Gender differences in presentation and diagnosis of chest pain in primary care. *BMC Fam Pract*. 2009;10:79. doi:10.1186/1471-2296-10-79.

7. Bruins Slot MHE, Rutten FH, van der Heijden GJMG, et al. Diagnostic value of a heart-type fatty acid-binding protein (H-FABP) bedside test in suspected acute coronary syndrome in primary care. *Int J Cardiol*. 2013;168(2):1485-9. doi:10.1016/j.ijcard.2012.12.050.

8. Bruins Slot MHE, Rutten FH, van der Heijden GJMG, Geersing GJ, Glatz JFC, Hoes AW. Diagnosing acute coronary syndrome in primary care: comparison of the physicians' risk estimation and a clinical decision rule. *Fam Pract*. 2011;28(3):323-8. doi:10.1093/fampra/cmq116.

9. Gencer B, Vaucher P, Herzig L, et al. Ruling out coronary heart disease in primary care patients with chest pain: a clinical prediction score. *BMC Med*. 2010;8:9. doi:10.1186/1741-7015-8-9.

10. Haasenritter J, Bösner S, Vaucher P, et al. Ruling out coronary heart disease in primary care: external validation of a clinical prediction rule. *Br J Gen Pract*. 2012;62(599):e415-21. doi:10.3399/bjgp12X649106.

11. Verdon F, Herzig L, Burnand B, et al. Chest pain in daily practice: occurrence, causes and management. *Swiss Med Wkly*. 2008;138(23-24):340-7. doi:2008/23/smw-12123.

12. Bösner S, Haasenritter J, Hani MA. Accuracy of general practitioners' assessment of chest pain patients for coronary heart disease in primary care: cross-sectional study with follow-up. *Croat Med J*. 2010:243-249. doi:10.3325/cmj.2010.51.243.

13. Nilsson S, Ortoft K, Mölstad S. The accuracy of general practitioners' clinical assessment of chest pain patients. *Eur J Gen Pract*. 2008;14(2):50-5. doi:10.1080/13814780802342622.

14. Farshid A, Arnolda L, Shadbolt B. Effect of transfer delay on left ventricular function after primary PCI for ST elevation myocardial infarction. *Heart Lung Circ*. 2012;21(11):689-94. doi:10.1016/j.hlc.2012.07.007.

15. Hudson MP, Armstrong PW, O'Neil WW, et al. Mortality implications of primary percutaneous coronary intervention treatment delays: insights from the Assessment of Pexelizumab in Acute Myocardial Infarction trial. *Circ Cardiovasc Qual Outcomes*. 2011;4(2):183-92. doi:10.1161/CIRCOUTCOMES.110.945311.

16. Nallamothu B, Fox K a a, Kennelly BM, et al. Relationship of treatment delays and mortality in patients undergoing fibrinolysis and primary percutaneous coronary intervention. The Global Registry of Acute Coronary Events. *Heart*. 2007;93(12):1552-5. doi:10.1136/hrt.2006.112847.

17. Pedersen SH, Galatius S, Hansen PR, et al. Field triage reduces treatment delay and improves long-term clinical outcome in patients with acute ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *J Am Coll Cardiol*. 2009;54(24):2296-302. doi:10.1016/j.jacc.2009.06.056.

18. Terkelsen CJ, Sørensen JT, Maeng M, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. *JAMA*. 2010;304(7):763-71. doi:10.1001/jama.2010.1139.

19. Wang TY, Nallamothu BK, Krumholz HM, et al. Association of door-in to door-out time with reperfusion delays and outcomes among patients transferred for primary percutaneous coronary intervention. *JAMA*. 2011;305(24):2540-7. doi:10.1001/jama.2011.862.

20. Damman P, van Geloven N, Wallentin L, et al. Timing of angiography with a routine invasive strategy and long-term outcomes in non-ST-segment elevation acute coronary syndrome: a collaborative analysis of individual patient data from the FRISC II (Fragmin and Fast Revascularization During Instability. *JACC Cardiovasc Interv*. 2012;5(2):191-9. doi:10.1016/j.jcin.2011.10.016.

21. Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med*. 2009;360(21):2165-75. doi:10.1056/NEJMoa0807986.

22. Sequist TD, Bates DW, Cook EF, et al. Prediction of missed myocardial infarction among symptomatic outpatients without coronary heart disease. *Am Heart J*. 2005;149(1):74-81. doi:10.1016/j.ahj.2004.06.014.

23. McCarthy BD, Beshansky JR, D'Agostino RB, Selker HP. Missed diagnoses of acute myocardial infarction in the emergency department: results from a multicenter study. *Ann Emerg Med*. 1993;22(3):579-82. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8442548.

24. Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med*. 2000;342(16):1163-70. doi:10.1056/NEJM200004203421603.

25. The GRACE investigators. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) Project: a multinational registry of patients hospitalized with acute coronary syndromes. *Am Heart J*. 2001;141(2):190-9. doi:10.1067/mhj.2001.112404.

26. Steg PG, Goldberg RJ, Gore JM, et al. Baseline characteristics, management practices, and in-hospital outcomes of patients hospitalized with acute coronary syndromes in the Global Registry of Acute Coronary Events (GRACE). *Am J Cardiol*. 2002;90(4):358-63. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12161222.

27. Peterson ED, Roe MT, Chen AY, et al. The NCDR ACTION Registry-GWTG: transforming contemporary acute myocardial infarction clinical care. *Heart*. 2010;96(22):1798-802. doi:10.1136/hrt.2010.200261.

28. Krumholz HM, Anderson JL, Brooks NH, et al. ACC/AHA clinical performance measures for adults with ST-elevation and non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Perfo. *J Am Coll Cardiol*. 2006;47(1):236-65. doi:10.1016/j.jacc.2005.10.020.

29. Cannon CP, Battler A, Brindis RG, et al. American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes. A report of the American College of Cardiology Task Force on Clinical Data Standards (Acute Coro. *J Am Coll Cardiol*. 2001;38(7):2114-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11738323. Accessed May 8, 2014.

30. Hasdai D, Behar S, Wallentin L, et al. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin; the Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). *Eur Heart J*. 2002;23(15):1190-201. doi:10.1053/euhj.2002.3193.

31. Fox K a a, Steg PG, Eagle K a, et al. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. *JAMA*. 2007;297(17):1892-900. doi:10.1001/jama.297.17.1892.

32. Goldberg RJ, Currie K, White K, et al. Six-month outcomes in a multinational registry of patients hospitalized with an acute coronary syndrome (the Global Registry of Acute Coronary Events [GRACE]). *Am J Cardiol*. 2004;93(3):288-93. doi:10.1016/j.amjcard.2003.10.006.

33. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med*. 2003;163(19):2345-53. doi:10.1001/archinte.163.19.2345.

34. Chin CT, Chen AY, Wang TY, et al. Risk adjustment for in-hospital mortality of contemporary patients with acute myocardial infarction: the acute coronary treatment and intervention outcomes network (ACTION) registry-get with the guidelines (GWTG) acute myocardial infarction mortality mode. *Am Heart J*. 2011;161(1):113-122.e2. doi:10.1016/j.ahj.2010.10.004.

35. Mandelzweig L, Battler A, Boyko V, et al. The second Euro Heart Survey on acute coronary syndromes: Characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. *Eur Heart J*. 2006;27(19):2285-93. doi:10.1093/eurheartj/ehl196.

36. Hasdai D, Porter A, Rosengren A, Behar S, Boyko V, Battler A. Effect of gender on outcomes of acute coronary syndromes. *Am J Cardiol*. 2003;91(12):1466-1469. doi:10.1016/S0002-9149(03)00400-4.

37. Health Technology Assessment. Health Technology Assessment. 2014. Available at: http://www.journalslibrary.nihr.ac.uk/hta.

38. Center for the Evaluation of Value and Risk in Health. The cost-effectiveness analysis registry. *Inst Clin Res Heal Policy Stud Tufts Med Cent*. 2007. Available at: www.cearegistry.org. Accessed July 3, 2014.

39. Goodacre S, Thokala P, Carroll C, et al. Systematic review, meta-analysis and economic modelling of diagnostic strategies for suspected acute coronary syndrome. *Health Technol Assess*. 2013;17(1):v-vi, 1-188. doi:10.3310/hta17010.

40. Polanczyk CA, Kuntz KM, Sacks DB, Johnson PA, Lee TH. Emergency department triage strategies for acute chest pain using creatine kinase-MB and troponin I assays: a cost-effectiveness analysis. *Ann Intern Med*. 1999;131(12):909-18. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10610641. Accessed July 18, 2014.

41. Ward S, Lloyd Jones M, Pandor a, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess*. 2007;11(14):1-160, iii-iv. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17408535.

42. Goodacre S, Nicholl J, Dixon S, et al. Randomised controlled trial and economic evaluation of a chest pain observation unit compared with routine care. *BMJ*. 2004;328(7434):254. doi:10.1136/bmj.37956.664236.EE.

43. Kim J, Henderson R a, Pocock SJ, Clayton T, Sculpher MJ, Fox K a a. Health-related quality of life after interventional or conservative strategy in patients with unstable angina or non-ST-segment elevation myocardial infarction: one-year results of the third Randomized Intervention Trial of unstable Angina (RITA-3). *J Am Coll Cardiol*. 2005;45(2):221-8. doi:10.1016/j.jacc.2004.10.034.

44. Chang W-C, Kaul P, Westerhout CM, et al. Impact of sex on long-term mortality from acute myocardial infarction vs unstable angina. *Arch Intern Med*. 2003;163(20):2476-84. doi:10.1001/archinte.163.20.2476.

45. Van Jaarsveld CHM, Ranchor A V, Kempen GIJM, Coyne JC, van Veldhuisen DJ, Sanderman R. Epidemiology of heart failure in a community-based study of subjects aged ≥ 57 years: incidence and long-term survival. *Eur J Heart Fail*. 2006;8(1):23-30. doi:10.1016/j.ejheart.2005.04.012.

46. Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making*. 2009;26(4):410-20. doi:10.1177/0272989X06290495.

47. Spertus J, Peterson E, Conard MW, et al. Monitoring clinical changes in patients with heart failure: a comparison of methods. *Am Heart J*. 2005;150(4):707-15. doi:10.1016/j.ahj.2004.12.010.

# Appendix III: Treatment costs specification

**Specification of UAP treatment costs per patient in 2012**

| Care product | Care product code | Segment | A-Segment tariff[1] | B-Segment average selling price[2] | Number of patients[2] |
|---|---|---|---|---|---|
| Ischemic heart disease without damage. Max 5 nursing or outpatient treatment days | 99499026 | B | | €1.950,00 | 13572 |
| Ischemic heart disease without damage. 6 to max 28 nursing or outpatient treatment days | 99499032 | B | | €6.220,00 | 3352 |
| Ischemic heart disease without damage. >28 nursing or outpatient treatment days | 99499031 | B | | NS | 36 |
| Medium diagnostics and treatment for ischemic heart conditions with or without damage. Without hospitalization | 99499015 | B | | €530,00 | 1222 |
| Light diagnostics and treatment for ischemic heart conditions with or without damage. Without hospitalization | 99499019 | B | | €200,00 | 503 |
| PCI class 1* | 979001103 | A | €3.490,52 | | 600 |
| PCI class 1 with nursing days | 979001104 | A | €4.867,51 | | 1797 |
| PCI class 2 | 979001096 | A | €5.350,92 | | 245 |
| PCI class 2 with nursing days | 979001097 | A | €6.799,66 | | 984 |
| PCI class 3 | 979001088 | A | €3.906,26 | | 178 |
| PCI class 3 with nursing days | 979001089 | A | €5.391,67 | | 328 |
| PCI class 4 | 979001083 | A | €4.788,81 | | 373 |
| PCI class 4 with nursing days | 979001084 | A | €6.448,38 | | 1055 |
| PCI class 5 | 979001081 | A | €7.905,36 | | 1 |
| PCI class 5 with nursing days | 979001082 | A | €12.122,58 | | 2 |

NS: Not specified

*Elaboration of PCI classes is provided at the end of this appendix

| | |
|---|---|
| Total number of patients | 24248 |
| Total cost | €77.991.367,90 |
| **Average treatment costs per UAP patient** | **€3.216,40** |

**Specification of NSTEMI treatment costs per patient in 2012**

| Care product | Care product code | Segment | A-Segment tariff[1] | B-Segment average selling price[2] | Number of patients[2] |
|---|---|---|---|---|---|
| Ischemic heart disease with damage. Max 5 nursing or outpatient treatment days | 99499020 | B | | €2.365,00 | 5002 |
| Ischemic heart disease with damage. 6 to max 28 nursing or outpatient treatment days | 99499028 | B | | €5.070,00 | 5070 |
| Ischemic heart disease with damage. >28 nursing or outpatient treatment days | 99499027 | B | | NS | 40 |
| PCI class 1* | 979001103 | A | €3.490,52 | | 180 |
| PCI class 1 with nursing days | 979001104 | A | €4.867,51 | | 942 |
| PCI class 2 | 979001096 | A | €5.350,92 | | 71 |
| PCI class 2 with nursing days | 979001097 | A | €6.799,66 | | 469 |
| PCI class 3 | 979001088 | A | €3.906,26 | | 21 |
| PCI class 3 with nursing days | 979001089 | A | €5.391,67 | | 135 |
| PCI class 4 | 979001083 | A | €4.788,81 | | 392 |
| PCI class 4 with nursing days | 979001084 | A | €6.448,38 | | 1561 |
| PCI class 5 | 979001081 | A | €7.905,36 | | 0 |
| PCI class 5 with nursing days | 979001082 | A | €12.122,58 | | 2 |

NS: Not specified

*Elaboration of PCI classes is provided at the end of this appendix

| | |
|---|---|
| Total number of patients | 13885 |
| Total cost | €59.094.360,65 |
| **Average treatment costs per NSTEMI patient** | **€4.255,99** |

**Specification of STEMI treatment costs per patient in 2012**

| Care product | Care product code | Segment | A-Segment tariff[1] | B-Segment average selling price[2] | Number of patients[2] |
|---|---|---|---|---|---|
| Ischemic heart disease with damage. Max 5 nursing or outpatient treatment days | 99499020 | B | | €2.365,00 | 7658 |
| Ischemic heart disease with damage. 6 to max 28 nursing or outpatient treatment days | 99499028 | B | | €5.070,00 | 5729 |
| Ischemic heart disease with damage. >28 nursing or outpatient treatment days | 99499027 | B | | NS | 59 |
| PCI class 1* | 979001103 | A | €3.490,52 | | 37 |
| PCI class 1 with nursing days | 979001104 | A | €4.867,51 | | 197 |
| PCI class 2 | 979001096 | A | €5.350,92 | | 10 |
| PCI class 2 with nursing days | 979001097 | A | €6.799,66 | | 95 |
| PCI class 3 | 979001088 | A | €3.906,26 | | 4 |
| PCI class 3 with nursing days | 979001089 | A | €5.391,67 | | 28 |
| PCI class 4 | 979001083 | A | €4.788,81 | | 1488 |
| PCI class 4 with nursing days | 979001084 | A | €6.448,38 | | 5527 |
| PCI class 5 | 979001081 | A | €7.905,36 | | 5 |
| PCI class 5 with nursing days | 979001082 | A | €12.122,58 | | 9 |

NS: Not specified

*Elaboration of PCI classes is provided at the end of this appendix

| | |
|---|---|
| Total number of patients | 20846 |
| Total cost | €92.025.892,97 |
| **Average treatment costs per STEMI patient** | **€4.414,56** |

**Specification of diagnostics costs per healthy patient in 2012**

| Care product | Care product code | Segment | B-Segment average selling price[2] | Number of patients[2] |
|---|---|---|---|---|
| Chest complaints with unknown cause. Max 5 nursing or outpatient treatment days | 99499017 | B | €1.215,00 | 43100 |
| Medium diagnostics and treatment for chest complaints with unknown cause. Without hospitalization | 99499016 | B | €435,00 | 52332 |
| Light diagnostics and treatment for chest complaints with unknown cause. Without hospitalization | 99499022 | B | €210,00 | 23148 |

NS: Not specified
*Elaboration of PCI classes is provided at the end of this appendix

| | |
|---|---|
| Total number of patients | 118580 |
| Total cost | €79.992.000,00 |
| **Average diagnostics cost per healthy patient** | **€674,58** |

## Elaboration of PCI classes

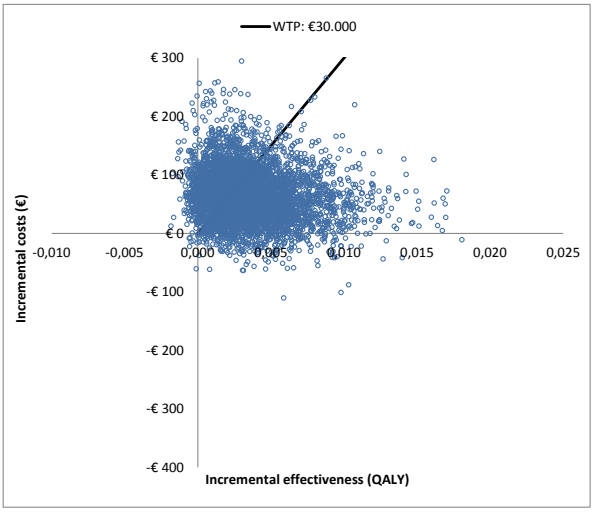
| | |
|---|---|
| PCI class 1 | PCI for removal of single coronary artery branch stenosis or intra coronary physiologic testing |
| PCI class 2 | PCI for removal of multiple coronary artery branch stenosis or passage coronary artery graft |
| PCI class 3 | PCI for removal of chronic occlusion of coronary arteries or closing coronary fistula or myocardial stem cell therapy or alcohol ablation for hypertrophic obstructive cardiomyopathy |
| PCI class 4 | Acute PCI |
| PCI class 5 | Percutaneous insertion of heart pump |

## References appendix III

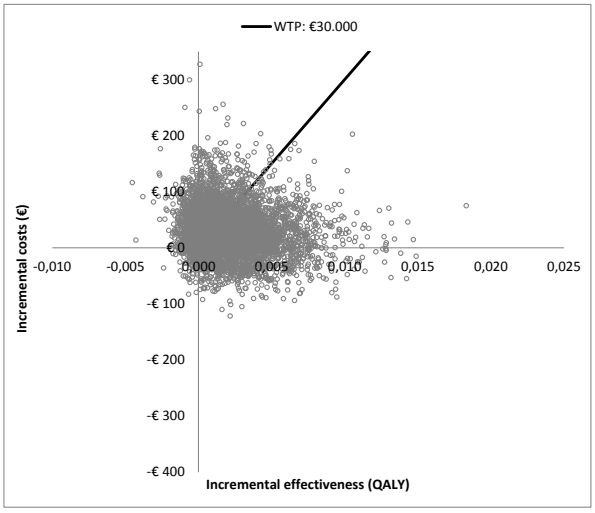

1. Dutch Healthcare Authority (Nederlandse zorgautoriteit). Diagnosis treatment combination: healthcare products tariff application (DBC zorgproducten tarief applicatie). 2014. Available at: http://dbc-zorgproducten-tarieven.nza.nl/nzaZpTarief/Welkom.aspx. Accessed July 6, 2014.

2. Diagnostic treatment combination maintenance (DBC onderhoud). Open diagnostic treatment combination information system data (Open DBC informatie systeem data). 2014. Available at: http://www.opendisdata.nl/. Accessed July 6, 2014.

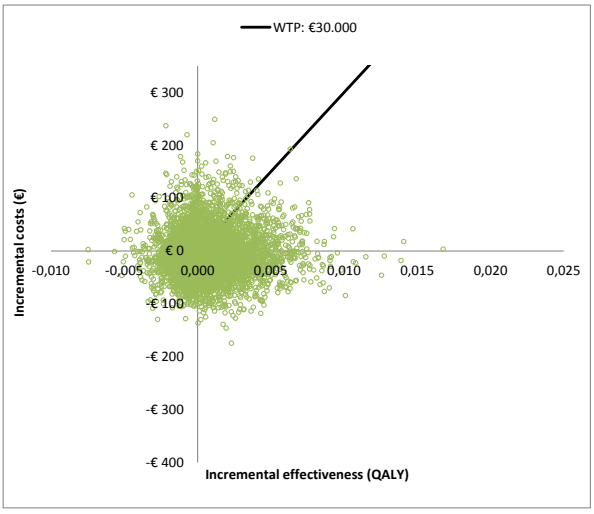
# Appendix IV: Scatterplots probabilistic sensitivity analysis



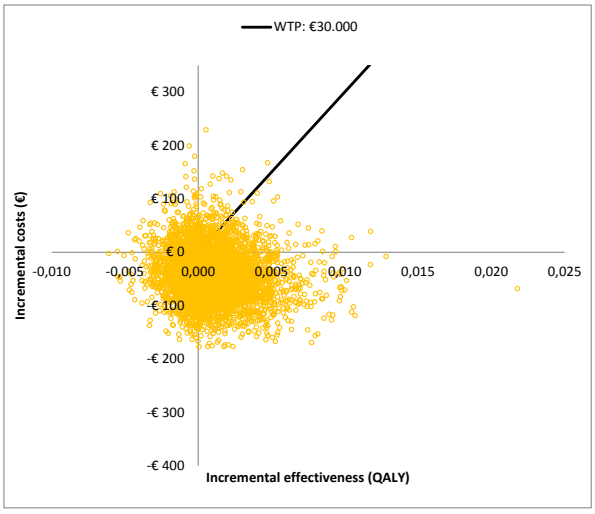

**Combination 1: sensitivity: 97% specificity: 76%**



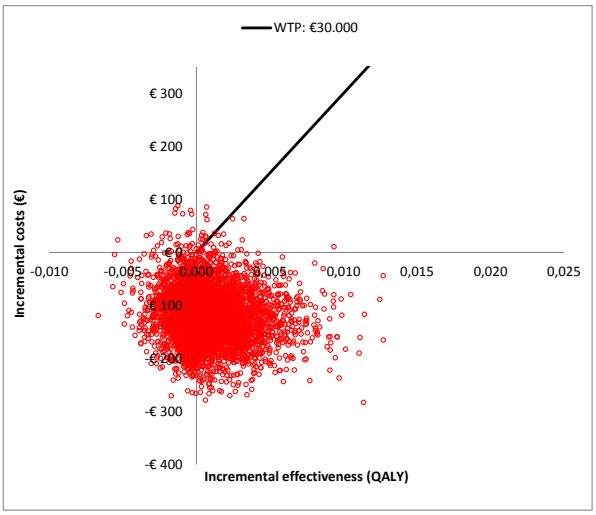

**Combination 2: sensitivity: 94% specificity: 79%**



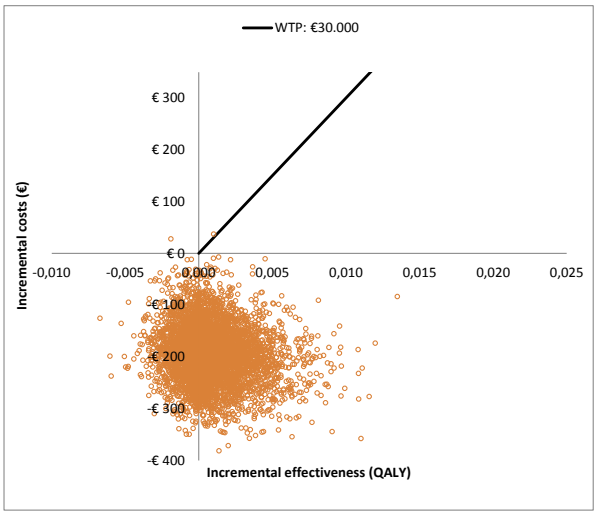

**Combination 3: sensitivity: 91% specificity: 82%**




**Combination 4: sensitivity: 91% specificity: 85%**




**Combination 5: sensitivity: 91% specificity: 91%**




**Combination 6: sensitivity: 91% specificity: 97%**