

# Triage-Now

**T**riage in **A**cute **G**eneral Chest Pain Patients **E**valuation

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## Investigators

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## **1.0 INTRODUCTION**

Chest pain is one of the most frequent reasons for admittance to the emergency department. The symptoms the patients present with are unspecific and a variety of cardiac, pulmonary, and skeletal reasons have to be considered. This has led to the implementation of chest pain units where these patients with unspecific symptoms and a multitude of differential diagnoses are evaluated by expert physicians. The rapid and accurate differentiation of acute coronary syndromes (ACS) from other causes of chest discomfort is of vital importance and in many cases it remains a clinical challenge. After evaluating a patient's symptoms, conducting a physical examination, and performance of an ECG the clinician is often left with considerable diagnostic uncertainty, which delays the initiation of appropriate therapy. During the last years beside creatin kinase MB and myoglobin the very specific troponins have evolved as cardiac enzymes which facilitate decision-making and have been introduced into the guidelines for acute coronary syndromes. Their well-known disadvantage is the lack of harmonisation in the determination method and the duration till relevant elevation of about four hours after the onset of the ischemic event. Myoglobin increases at an earlier time point, however, it is not specific. The limited power of these markers to detect myocardial necrosis early after chest pain onset has stimulated further efforts to search for new biological markers that either detect myocardial micronecrosis, which is not detected by current routine tests, or reflect pathophysiological processes that may precede myocardial cell injury. Further markers like hs-CRP and BNP among others have been examined in cardiovascular risk prediction in the emergency setting. But additional tools are needed that can predict the vulnerability of the patients' state if presenting with suspected acute coronary syndrome.

Given that we already have many established markers of CAD activity and future coronary heart disease risk, it will be imperative in the future to demonstrate the precise additive value of any newly discovered or proposed biomarkers over and above established practice.

Most importantly, it will be crucial to identify marker combinations that will offer a synergistic joint use. These markers should not be highly correlated and should improve diagnosis and risk prediction over and above troponin measures.

## **2.0 RESEARCH DESIGN AND METHODS**

### **2.1 Hypotheses**

Novel biomarkers are potent to enhance diagnosis of acute coronary syndromes in the general chest pain population. Decision-making can be facilitated and short-term as well as long-term outcome may be improved. In addition, in-hospital mortality and time to discharge might be significantly reduced.

### **2.2 Rationale**

Literature evidence suggests that triaging in the emergency department will be improved by the application of multiple different markers to assess ACS.(1)

Into an optimum combination easily available markers have to be introduced which represent complementary pathophysiological pathways and different states of ACS. Rapid and reliable test systems developed during the last years allow a point of care marker determination.

B-type natriuretic peptide (BNP) reflecting the degree of cardiac neurohormonal activation has been extensively investigated in cardiac disease. As a hormone indicator of myocardial stress (2) it has evolved as an excellent marker of heart failure in differential diagnosis, in the emergency setting and for therapy monitoring where it has already entered international guidelines. Its reliable characteristics as a bio-marker have spurred further investigations in other cardiovascular disease entities. Indeed, there is an increasing body of evidence for the concept that BNP might be an indicator of hypoxia and ischemia itself rather than a mere measure of myocyte stretch.(3-5) For patients with acute coronary syndromes impressive data have been generated for BNP in the prediction of short-term as well as long-term outcome. Under these conditions it provides information on survival and incident heart failure incremental to that of anthropometric data, clinical variables and even left ventricular ejection fraction.(6,7) For long-term mortality assessment it proved to be superior to necrosis markers.(8) BNP elevation does obviously not depend on acute necrosis, but may also indicate unstable states of CAD characterized by reversible ischemia under stress without significant rise of creatinine kinase or troponins.(9) In this context it might support the differential diagnosis of patients with cardiovascular disease in comparison with non-cardiac chest pain individuals apart from diagnosis of heart failure. First data have proposed a role for BNP in a multiple marker approach for ACS.(10) Currently an index pattern of necrosis markers and BNP is under investigation in the emergency setting which needs prospective confirmation in the general chest discomfort patient population.

In addition, inflammatory processes play a pivotal role in the pathogenesis of atherosclerosis and mediate the development of atheroma ranging from leukocyte recruitment to plaque rupture.(11) Evidence has emerged, that recruitment and activation of polymorphonuclear neutrophils forego myocardial cell injury and undergo substantial degranulation within the coronary circulation in settings of acute coronary syndrome. Leukocyte activation is intimately related to fissured, thrombosed plaques in patients with acute coronary syndrome.(12,13) Experimental studies have supported the proatherogenic role of myeloperoxidase (MPO) as it promotes the oxidation of LDL cholesterol and thus facilitates foam cell formation(14) and mediates atherosclerotic plaque rupture.(15) In addition, MPO leads to nitric oxide consumption resulting in endothelial dysfunction.(16-18) Clinically, levels of MPO are associated with the presence of coronary artery disease(19) and predict short term outcome in patients with acute coronary syndrome.(20,21) First epidemiological data in the AtheroGene cohort suggest a potential role of MPO in early detection of ACS and render it a promising complementary partner for a point of care management.

Apart from these biomarkers favoured for a multiple marker approach in ACS certainly a whole range of additional inflammatory and tissue candidate markers with a potential use in the emergency setting could be focussed on.

## 2.3 Purpose

- The primary objective of the present study is to assess the applicability of novel blood markers in the early differential diagnosis of acute coronary syndromes. In a multiple marker approach recently described indicators are tested and new biomarkers are examined in context with rapid diagnosis finding.
- The secondary objective is to assess the predictive value of multiple markers according to 30 day and 6 months outcome.
- The third objective is to assess the effect of an enhanced early diagnosis of cardiac diseases on in-hospital mortality and, finally, on duration of hospital stay and cost effectiveness.

## 2.4 Overall Study Design

- Number of Centers: 1                      Location: chest pain unit
- Number of subjects: 1500 consecutive patients with acute chest pain
- Non-interventional surveillance study
- Patients presenting to the chest pain unit of the Department of Medicine II, Johannes Gutenberg-University, Mainz

## 2.5 Study Population

### *Inclusion criteria:*

- Only patients who are able to give consent. This has to be carefully verified in each case, by the doctors leading the study;
- Men or women  $\geq 18$  and  $\leq 85$  years of age;
- Patients with chest discomfort and suspected Acute Coronary Syndrome (STEMI, NSTEMI and unstable angina);
- Written informed consent.

### *Exclusion criteria:*

- Obvious traumatic disease
- Patients with hemoglobin  $\leq 10$  g%
- Patients with cardiogenic shock
- Other significant laboratory abnormalities that the investigator feels may compromise the patient's safety by participation in the study;
- Women who are pregnant or breast feeding;
- Refusal to provide written informed consent;
- Unavailability of a telephone number and insufficient contact information as well as permanent residence abroad;
- Unreliability as a study participant as based on the investigator's prior knowledge of the patient, such as the inability or willingness to participate in or complete the study or the presence of concurrent physical or psychological disorders that may make it impractical for the patient to participate in or complete the study.

## 2.6 Study schedule, Clinical assessments and Visit procedures

### 2.6.1 Enrolment

- i)* Subjects admitted to the chest pain unit who have been identified to meet the first two inclusion criteria (N=1500) will be invited to participate in the study.
- ii)* Written informed consent will be obtained.
- iii)* A pre-test probability whether the patient has MI and/or ACS will be assessed to perform a Bayesian analysis.
- iv)* Routine blood work is performed according to the chest pain unit admission scheme (Serum lipid profiles, glucose, electrolytes, renal function tests, blood cell count).
- v)* The physician on duty decides on the diagnostic and therapeutic proceedings independent of the participation in the study

In context with the study the following steps are undertaken:

- a) History:* A detailed history will be taken to obtain information about demographics, traditional risk factors, known cardiac disease, other pertinent medical history and medication use.
- b) Medication since chest pain onset:* Documentation of kind and doses of medication administered since beginning of chest discomfort.
- c) Physical examination:* A physical examination will document cardiovascular, respiratory, and gastrointestinal systems including blood pressure, heart rate, waist and hip circumference, height and weight.
- d) Chest discomfort:* A detailed description of the chest pain symptomatic will be documented: Time of onset, first occurrence/recurrence, intensity, persistence, influence of drug administration (nitroglycerine).
- e) ECG:* The ECG on admission is registered. Consecutive ECGs if available are documented, too. The ECG data are evaluated by an independent observer according to the following electrocardiographic signs: new/old ECG changes, sinus rhythm/atrial fibrillation/further rhythm abnormalities, ST-elevation/-depression, T-inversion, unspecific changes.
- f) Biochemistry:*

**At enrolment**

- markers of primary interest: troponin I, creatinkinase MB, myoglobin, B-type natriuretic peptide (Triage Test Biosite), and myeloperoxidase;
- potential further markers: GPx-1 and CRP, urinary isoprostane levels;
- in house routine ischemia tests: troponin T, CK-MB;
- storage:

10ml serum	1 tube a 7,5ml	9 aliquots
10ml Citrat-Plasma	2 tube a 5ml or 1 tube a 10ml	9 aliquots
23ml EDTA-Plasma	2 tube a 2,5ml and 2 tube a 9ml	22 aliquots
10ml EDTA-Plasma, DNA-Extraction		
10ml urine		

### **3 hours after enrolment**

- markers of primary interest: troponin I, creatinkinase MB, myoglobin, B-type natriuretic peptide (Triage Test Biosite), and myeloperoxidase;
- potential further markers: GPx-1 and CRP, urinary isoprostane levels;
- in house routine ischemia tests: troponin T, CK-MB;
- storage:

10ml serum	1 tube a 7,5ml	9 aliquots
10ml Citrat-Plasma	2 tube a 5ml or 1 tube a 10ml	9 aliquots
23ml EDTA-Plasma	2 tube a 2,5ml and 2 tube a 9ml	22 aliquots

### **6 hours after enrolment**

- markers of primary interest: troponin I, creatinkinase MB, myoglobin, B-type natriuretic peptide (Triage Test Biosite), and myeloperoxidase;
- potential further markers: GPx-1 and CRP, urinary isoprostane levels;
- in house routine ischemia tests: troponin T, CK-MB;
- storage:

10ml serum	1 tube a 7,5ml	9 aliquots
10ml Citrat-Plasma	2 tube a 5ml or 1 tube a 10ml	9 aliquots
23ml EDTA-Plasma	2 tube a 2,5ml and 2 tube a 9ml	22 aliquots

All blood samples will be collected by venipuncture or through intravenous catheters. If hemoglobin concentration is between 10 and 11 g%, 50 ml of blood will be taken only once, at enrolment.

### **2.6.2 Diagnosis**

Diagnosis/exclusion of ACS will be obtained based on

- Patients with acute onset of prolonged chest pain or discomfort accompanied by ST-segment elevation or depression evolving into pathological Q-waves or T-wave inversion
- (Partially) occluded vessels demonstrated in coronary angiography
- Non cardiac chest pain group (documented by angiographic exclusion of coronary stenosis or stress test)

On the day of discharge the following parameters are documented:

- Final diagnosis after admission, based on coronary angiography or stress test
- Number of in-hospital days, number of days in the intensive care unit
- Documented non-fatal myocardial infarction
- Need for coronary artery bypass grafting
- Need for PCI

If available image data of

*Chest-X-ray*: signs of heart disease, signs of lung disease, abnormal heart dimensions, lung abnormalities.

*Echocardiography*: Transthoracic echocardiography will be performed, and the following variables will be recorded: M-Mode: LVDD, LVSD, LVDDI, LVSDI, FS, IVST, PWT, Wall-M (M-Mode); Two-dimensional echo: EDV, ESV, EDVI, ESVI, EF, LA, RA; Pulse Wave-Doppler: MV-VE, MV-VA, E/A, Dec-Time; Continuous Wave Doppler: transaortic valve flow, non-invasive pulmonary artery pressure).

### **2.6.3 Follow-up Information:**

30 days/6 months: The patients are sent a questionnaire and receive a personal phone call.

Information is obtained about the following events occurring after discharge: re-hospitalisation due to cardiac symptoms, heart catheterisation and diagnosis (number and degree of stenoses, need for PCI), documented non-fatal myocardial infarction (coronary angiogramme or pathological Q waves in at least two leads and/or symptoms and biochemical markers of infarction), coronary artery bypass grafting, death of cardiovascular causes between 30 days and 6 months after enrolment.

### **2.6.4 In-Hospital Stay, Cost-Effectiveness:**

The duration of an individual's in-hospital stay will be assessed as the number of days on the ICU and on the ward until discharge from the hospital. Costs will be cursorily calculated according to standard fees for interventions, days on the ICU, days on ward, total time of hospital stay.

### **2.7 Safety:**

As no interventions are planned for this study there should be no hazards for the patients enrolled in the study

### **2.8 Allowable Concurrent Medications**

Any medication can be taken during the study.

## **3.0 DATA ANALYSIS AND STATISTICS**

**3.1 Primary end-point:** The primary end-point of the study is the early/enhanced differential diagnosis of acute coronary syndromes due to CAD by use of combined analysis of five markers compared to single marker analyses (final diagnosis of ACS as reason for hospital admission).

**3.2 Secondary end-point:** The secondary end-point of the study is the strength of 30 days and 6 months risk prediction for diagnosis of CAD, revascularisation, non-fatal myocardial infarction, and cardiovascular death for single marker determination and combined analysis of five markers.

**3.3 Tertiary end-point:**

The tertiary end-point of the study is the impact of a multiple marker approach in acute risk stratification on in-hospital mortality, duration of hospital stay, and cost-effectiveness.

**3.4 Additional aim:** A further aim of the study is the detection and evaluation of promising markers (of myocardial necrosis, oxidative stress, inflammation) with potential use in differential diagnosis of acute coronary syndromes. A Bayesian analysis will be performed after assessing the pre-test probability that a MI and/or ACS are present.

#### **4.0 CONCLUSION AND RELEVANCE**

The present study will for the first time prospectively demonstrate the potential advantage of a novel multiple marker strategy in early diagnosis of ACS. Promising markers like myeloperoxidase and B-type natriuretic peptide are evaluated in addition to and in competition with routine necrosis markers. It has to be demonstrated whether

- 1) diagnosis can be enhanced by determination of these new markers
- 2) sufficient sensitivity and specificity are reached
- 3) early diagnosis can improve patient outcome
- 4) representation of acute CAD through biomarkers can be related to short-term and intermediate outcome
- 5) biomarkers can be related to imaging data
- 6) introduction of novel markers into routine determination is feasible
- 7) new laboratory tests are cost-effective in patient care.

In conclusion this study might help to further the current understanding of ACS and might achieve results to improve everyday emergency patient's care.

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