Early risk stratification in patients with chest pain

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Chapter 1

Introduction

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INTRODUCTION

Patients presenting with chest pain suggestive of myocardial ischemia are a heterogeneous group with widely varying risks. Early triage in these patients is important and may be challenging(1). In patients with a conclusive electrocardiogram, management is straightforward(2). However, the majority of patients with chest pain has a normal or non-diagnostic electrocardiogram on presentation at the emergency room. Early risk stratification in such patients, i.e. identification of those at low risk that can be safely discharged home and those at high risk that need hospitalization, is difficult. It has been demonstrated that patients discharged home with missed diagnosis of myocardial infarction or unstable angina have a substantial risk of adverse cardiac events(3;4). To reduce the number of patients inappropriately discharged home, accurate yet simple methods for risk assessment are needed. At this moment the recommended strategy is based on the American College of Cardiology/American Heart Association guidelines for the management of patients with unstable angina and non-ST-elevation myocardial infarction.

Biochemical markers
Several biochemical markers may be used for the evaluation of patients with chest pain, such as markers of myocardial damage, markers of inflammation, markers of coagulation, and markers of left ventricular dysfunction. Markers of myocardial damage are most widely used in rule out protocols. In addition, the ACC/AHA guidelines recommend only markers of myocardial damage: “serial cardiac specific troponin is the preferred marker, but serial creatine kinase-MBmass is also acceptable. In patients presenting within 6 hours of presentation early markers of myocardial damage, such as CK-MB subforms, should be considered in addition to cardiac troponins”(5).

Negative serial troponin identifies patients at low risk(6). However, a negative troponin does not by itself exclude significant disease, and such patients may experience adverse clinical events(8-11). Therefore, additional tests are needed to identify the troponin negative chest pain patients at low risk that can be discharged home safely and, on the other hand, to identify patients at high risk that should be admitted for further evaluation and management.

Several studies have shown that C-reactive protein, a non-specific inflammatory marker, has additional predictive value in patients with negative serial troponin (or in patients with
the lowest levels of cardiac troponin)(12-14).(15) The lowest risk is observed in patients with both a normal troponin and a normal C-reactive protein. However, these studies have been performed in patients with unstable coronary syndrome. Markers of inflammation, such as C-reactive protein in combination with serial negative troponin may be important in early triage of rule-out populations, but has not been evaluated before.

**Dobutamine stress echocardiogram**
The exercise electrocardiogram as a pre-discharge stress test has been recommended by the American College of Cardiology/American Heart Association guidelines(5). However, it has limited value in patients with uninterpretable electrocardiogram and in patients unable to exercise(16;17). An alternative approach in such patients is pharmacological stress imaging, e.g. dobutamine stress echocardiography or nuclear stress imaging(5;16;18). Dobutamine stress echocardiography, compared to exercise electrocardiography, does not depend on exercise performance or on electrocardiographic changes for the detection of ischemia, it has better sensitivity and specificity(19), earlier detection of ischemia is possible according to the ischemic cascade(20), and it provides information on cardiac anatomy and left ventricular function(21). Dobutamine stress echocardiography, compared to nuclear imaging, has comparable high sensitivity and specificity, but is less costly, may be used as a bedside test and may be more available(19).

The prognostic value of dobutamine stress echocardiography has been demonstrated in different patient populations(22;23). However, only a few small studies(24-27) have evaluated (dobutamine) stress echocardiography in patients presenting with chest pain at the emergency room. The value of dobutamine stress echocardiography in troponin negative chest pain patients after ruling out acute coronary syndrome has not been investigated before.

**OUTLINE OF THE THESIS**
The general aim of this thesis was to investigate diagnostic tests (biochemical markers and dobutamine stress echocardiogram) for early risk stratification in patients presenting with chest pain and a normal or non-diagnostic electrocardiogram (part I). In addition, early
risk stratification in patients with acute coronary syndrome by means of troponin and C-reactive protein is evaluated (part II).

The specific objectives of the different studies are given in the respective chapters of this thesis.

**Part I. Patients with a normal or non-diagnostic electrocardiogram**

Early triage may be difficult in patients presenting with chest pain to the emergency room. Protocols have been designed to rule out acute coronary syndrome ("rule out protocols"). Patients in whom acute coronary syndrome have been ruled out may be discharged home safely. Chapter 2 describes selected studies that evaluated different diagnostic tests used as part of rule-out protocols in the emergency department.

Rule out protocols have most often relied on creatine kinase-MB activity measurements. In 1995 a new, rapid and sensitive creatine kinase-MB mass assay was introduced into the rule-out protocol of our emergency department. Chapter 3 evaluates whether ruling out myocardial infarction with the new protocol (compared to the "old protocol"), resulted in the reduction of length of stay in the emergency department without compromising safety. In chapter 4 it is evaluated whether myocardial infarction can be ruled out with high sensitivity by means of serial creatine kinase-MB mass, measured at admission and at 7 hours after the onset of symptoms, in patients presenting to the emergency department early after the onset of chest pain. The evaluation includes the presence or absence of a significant increase between serial creatine kinase-MB mass values, i.e. an increase within the reference limits which cannot be explained by analytical or biological variation.

Several components of the inflammatory response are associated with the initiation and progression of atherosclerosis. Markers of inflammation are not used in rule-out protocols so far, but may have important value for clinical decision making in patients with chest pain. Chapter 5 investigates the prognostic value of markers of inflammation (C-reactive protein and erythrocyte sedimentation rate) in troponin T-negative chest pain patients with a normal or non-diagnostic electrocardiogram discharged home from the emergency department.

Atherosclerotic plaque disruption with superimposed thrombus formation and tissue factor induced thrombin generation play an important role in acute coronary syndromes. Therefore, systemic markers of coagulation and fibrinolytic pathway, such as tissue factor
and tissue factor pathway inhibitor, may be useful in the triage of patients with chest pain. These markers of hemostasis are evaluated in chapter 6.

Stress testing has been recommended as part of a rule out protocol before discharge or within 72 hours after discharge in low-risk chest pain patients, i.e. in patients with an uneventful observation period and normal serial markers. Chapter 7 evaluates the prognostic value of a predischarge dobutamine stress echocardiogram in low-risk chest pain patients, identified by a standard rule-out protocol and a negative serial troponin T.

**Part II. Patients with acute coronary syndrome**

Elevated concentrations of C-reactive protein, a non-specific acute phase reactant, and troponin I, a cardiac-specific marker of myocardial damage, have been found to be associated with a higher risk for cardiac events in patients with an acute coronary syndrome. In chapter 8 the prognostic value of C-reactive protein alone and in combination with troponin I is assessed in patients with unstable angina or non-Q-wave myocardial infarction.

Increased C-reactive protein is an important prognostic indicator for early risk stratification in patients with an acute coronary syndrome, independent of, and in combination with an increased cardiac troponin. However, increases in both troponin and C-reactive protein also occur secondary to myocardial damage. In the chapters 9 and 10 the early release kinetics of C-reactive protein and troponin T as a consequence of myocardial damage are analyzed. In addition, the time interval after onset of symptoms during which baseline C-reactive protein can still be regarded as an independent prognostic parameter is evaluated. From these data, the optimal timing for troponin T and C-reactive protein sampling for prognostic purposes is proposed.

Chapter 11 summarizes and briefly discusses the main findings derived from the studies described in the previous chapters.