Biochemical risk assessment and invasive strategies for acute coronary syndromes without ST-segment elevation

Riezebos, R.K.

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Chapter 1

General introduction and outline of the thesis

The non ST-elevation acute coronary syndrome and its treatment modalities
GENERAL INTRODUCTION

Acute coronary syndromes
Acute chest pain remains one of the most difficult challenges for clinicians. Nowadays, chest pain and related complaints account for 5-10% of the adult emergency and around 25% of all hospital admissions.\(^1\) In addition, the number of patients presented with complaints of chest pain tend to increase.\(^2\) In a typical population of patients presented for the evaluation of acute chest pain in emergency departments, about 20% of these patients have an acute coronary syndrome.\(^3,4\) The principal pathophysiological mechanism of an acute coronary syndrome (ACS) is myocardial underperfusion resulting from atherosclerotic plaque rupture or from erosion with different degrees of superimposed thrombus.\(^5,6\)

Differential diagnostics in patients with chest pain
A minority of patients, estimated to be around 10% of those presented with chest pain, do not have an acute coronary syndrome but other life-threatening problems such as pulmonary embolism or an acute aortic dissection.\(^1\) However, most patients are discharged either without a diagnosis or with the diagnosis of a non-cardiac condition. These non-cardiac conditions include musculoskeletal syndromes, gastrointestinal- and psychological disorders.

When evaluating cardiac chest pain, the ECG provides the initial classification. Patients are subdivided into those with a persistent ST-segment elevation (STEMI) and those without a persistent ST-segment elevation. The latter is called a non ST-elevation acute coronary syndrome (NSTE-ACS). The level of the biomarkers of necrosis above a certain prespecified threshold differentiates NSTE-ACS patients into those with a non ST-elevation myocardial infarction (NSTEMI) as opposed to those with an unstable angina. (Figure 1)
Cardiac Biomarkers

Cardiac biomarkers are a key element in diagnostics and in the management of the NSTE-ACS. During an acute coronary event dynamic changes can occur involving numerous biomarkers. The relative timing and the dynamics of each protein release provides information with respect to the onset of ischemia, size of infarction, risk of in-hospital complications, and long-term prognosis. These biomarkers represent diverse mechanisms which characterise the pathophysiology of an acute coronary syndrome. Markers of myocardial necrosis are of great importance. They relate to the amount of myocardial damage and are closely linked to a patients’ prognosis. Recent interest in myocardial neurohumoral mechanisms has identified the natriuretic peptides as strong prognostic markers following upon an ischemic event. Finally, markers of inflammation such as the C-reactive protein (CRP) are...
closely related to both the development of atherosclerosis and the risk of an acute ischemic event.9

**Treatment modalities in non ST-segment elevation acute coronary syndromes**

**Therapeutic strategies**

Patients with a NSTE-ACS have a diverse prognostic outcome. In short, the expected risk determines the extent of the pharmacologic and revascularization therapy. In order to estimate this risk, several (scoring) models have been developed.10,11 The patients who seem to benefit most from revascularization are those with an intermediate to high risk of future cardiac events.5,6

**FIGURE 2**

**Dynamics in cardiac biomarkers after myocardial infarction.**

![Dynamics in cardiac biomarkers after myocardial infarction](image)

CK-MB: creatinine kinase MB, cTn: cardiac troponin, HS-CRP: high sensitivity C-reactive protein, LDH: lactate dehydrogenase, MI: myocardial infarction, NT-proBNP: N-terminal proB-type natriuretic peptide
Pharmacological therapy

The treatment objective in NSTE-ACS is to stabilize the acute coronary lesion and to improve the balance of oxygen supply and demand. In addition, one should treat residual ischemia and commence secondary prevention. Anticoagulant and antiplatelet therapy is used to prevent further thrombosis and allow endogenous fibrinolysis to dissolve the thrombus and thereby reduce the degree of coronary stenosis.

Among the anticoagulants used are unfractionated heparin, several low molecular weight heparins and the factor Xa inhibitor fondaparinux. The latter is a selective factor-Xa inhibitor. Fondaparinux has proven to be effective and has a low bleeding risk. It is therefore the commonly preferred coagulant.\textsuperscript{4,12} The addition of platelet inhibitors to anticoagulant therapy provides a synergistic effect. The evidence for the dual antiplatelet therapy using aspirin in combination with a direct adenosine diphosphate (ADP) inhibitor, such as clopidogrel or prasugrel, is well established.\textsuperscript{13,14} In patients scheduled for percutaneous coronary intervention (PCI), prasugrel is currently advocated. It reduces future ischemic events, including stent thrombosis, at the cost of a moderately higher bleeding risk.\textsuperscript{15} Ticagrelor, a new reversible ADP inhibitor, was recently compared to clopidogrel in an ACS population. Ticagrelor proved superior in the prevention of ischemic events, without causing an increase in major bleeding. This resulted in a reduction in mortality.\textsuperscript{16} More evidence is eagerly awaited.

Additional anticoagulation and antiplatelet therapies have been developed regarding a planned invasive strategy. Concomitant glycoprotein (GP) 2b3a inhibitors have been known to reduce ischemic events in high risk NSTE-ACS patients undergoing PCI.\textsuperscript{17} Alternatively, bivalirudin, a direct thrombin inhibitor, has been tried. This drug showed a better safety profile compared to GP 2b3a inhibitors and with a similar efficacy.\textsuperscript{18}

Pharmacological anti-ischemic therapies using nitrates and beta blockers are primarily implemented to reduce the myocardial oxygen consumption. Prospective data on beta blockers in NSTE-ACS are scarce and the recommendations are largely based on extrapolations from STEMI populations.\textsuperscript{5,6} Similarly, the use of nitroglycerin is mainly based on pathophysiological considerations and clinical experience.
Dihydropyridines should be avoided, especially in the absence of a beta-blocker in order to avoid reflex tachycardia’s. Adjunctive therapies with high dose statins and ACE inhibitors play a central role in plaque stabilisation and secondary prevention.

**Revascularization strategies**

A revascularization procedure will be considered when NSTE-ACS patients are thought to have a high risk for recurrent events. In theory, there exist two revascularization methods: PCI and coronary artery bypass grafting. Both methods have their particular benefits and their shortcomings. Choosing a revascularization method therefore depends mainly on the clinical characteristics, coronary anatomy and the patients’ preference. When both options are considered as equal, in general, PCI seems to relate to more repeat revascularization procedures whereas CABG relates to a higher rate of perioperative cerebral vascular accidents.

**Percutaneous coronary intervention**

The use of PCI in treating ischemic coronary artery disease has expanded considerably over the past three decades. This mildly invasive technique was first developed by Gruentzig in 1978. Despite a progressive increase in its clinical and anatomical applications, the success rate of coronary angioplasty has risen considerably and with a limited risk. Much of this improvement has resulted from the application of adjunctive technologies such as (drug eluting) stent implantation, refinements in anticoagulant and antiplatelet pharmacology. Nowadays, PCI has become the standard- and often preferred coronary revascularization method in the invasive treatment strategy of NSTE-ACS.

**When to perform percutaneous coronary intervention**

Over the past decade the question when to perform PCI in patients with NSTE-ACS has been a subject of much discussion. Among the initially stabilized patients whereby an early invasive strategy of coronary angiography is proposed, the optimal timing of an angiography remains questionable. Early or immediate catheterization with revascularization of unstable coronary lesions may prevent ischemic events that would otherwise occur during the medical therapy. Conversely, pre-treatment with
intensive antithrombotic therapy may diminish the thrombus burden and “passivate” the unstable plaques, improving the safety of percutaneous revascularization by reducing the risk of periprocedural ischemic complications.\textsuperscript{22}

**Aim and outline of the thesis**

This thesis consists of three parts. The first part involves the evaluation of treatment strategies in patients with NSTE-ACS. The second part of the thesis is dedicated to the use of biomarkers in the evaluation of patients with NSTE-ACS. The third part provides several exemplary case studies regarding the often challenging differential diagnostics in patients with acute chest pain.

**Part 1** of the thesis is dedicated to the timing of the invasive treatment of the NSTE-ACS.

**Chapter 2** describes the influence of the timing of intervention in patients with a NSTE-ACS. It includes a randomized clinical trial, called the OPTIMA trial. This trial evaluated two different treatment segments regarding the timing of PCI in patients admitted with NSTE-ACS and eligible for PCI. For this purpose, patients with a suspected intermediate to high risk ACS underwent acute coronary angiography to confirm the diagnosis of an ACS. In addition, information was provided on the eligibility for PCI. Those patients with a confirmed NSTE-ACS and suitable for treatment with PCI were randomized to immediate PCI or deferred PCI after 24 hours of pharmacological therapy. The published correspondence which resulted from this publication is included. **Chapter 3** provides the clinical perspective on the different strategies which are used in the treatment of NSTE-ACS. It includes a clinical review on the diagnostics, the risk assessment and the differing treatment strategies.

**Part 2** of the thesis involves the evaluation of the cardiac neuroendocrine response during a NSTE-ACS.

Serial sampling of NT-proBNP was performed in order to gain more insight into the dynamics of the cardiac neuroendocrine system following ischemia in patients with a NSTE-ACS. **Chapter 4** describes a prospective, observational study that evaluated the dynamic response of NT-proBNP using multiple serum samples in patients admitted
with NSTE-ACS. Consequently, an optimal timeframe of sampling was attempted in order to enhance its clinical value. In chapter 5 we portrayed the strong negative correlation between NT-proBNP elevation and the prognosis. The relationship between peak NT-proBNP concentrations with clinical, biochemical and angiographic characteristics of the ACS was then evaluated. Chapter 6 assesses the diagnostic properties of NT-proBNP. In a prospective fashion, the diagnostic properties of NT-proBNP regarding the presence of an evolving NSTEMI were determined. The definition of a practical diagnostic cut-off value was attempted on our part. Chapter 7 provides a clinical review on the strategic use of several pathobiologically diverse biomarkers which are used in the evaluation of patients with NSTE-ACS.

Part 3 of the thesis consists of exemplary case studies regarding the differential diagnostics in a presumed NSTE-ACS. Using four case reports, several diagnostic strategies were evaluated. Chapter 8 illustrates the value of using additional biochemical tests such as CO measurements. Chapter 9 involves the diagnostic use of an ECG. Chapter 10 and chapter 11 illustrate the early evaluation of patients with acute chest pain by using coronary computed tomography angiography.

Chapter 12 contains the summary and conclusion of the results of this thesis.
REFERENCES

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