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

Introduction
The thesis covers the diagnostics, risk stratification and the treatment strategies in those patients with a non ST-segment elevation acute coronary syndrome (NSTE-ACS). This condition is quite prevalent and it is responsible for a high morbidity and mortality. The thesis consists out of three parts. The first part of the thesis involves the evaluation of different treatment strategies in patients with a NSTE-ACS. The second part of the thesis is dedicated to the use of biomarkers in the evaluation of patients with a NSTE-ACS. It evaluates the behaviour of the cardiac neurohumoral system in patients with acute chest pain. The third part of the thesis provides several exemplary case studies regarding the often challenging differential diagnostics in patients suffering from acute chest pain.

General introduction and outline of the thesis
Chapter 1 contains the general introduction. This introductory chapter provides background information on the acute coronary syndrome, its differential diagnostics and the diverse treatment protocols. The chapter also contains information on the pharmacological treatment of the NSTE-ACS. It serves as background information and thereby helps further knowledge and understanding.

Part 1: Timing of PCI in the acute coronary syndromes without ST-segment elevation
Chapter 2 reports the results of the OPTIMA trial. This multicentre strategy trial evaluated high risk patients with a suspected non acute ACS by means of an acute coronary angiogram. Wherever the diagnosis could be confirmed and the so called culprit lesion was thought to be eligible for PCI, the patients would be randomised to an immediate or deferred PCI by 24 hours. All patients received extensive medical therapy including the triple antiplatelet inhibition. Although the trial was ended prematurely due to a slow patient recruitment rate, the results were clear.
Compared to the 24 hour deferred strategy, the immediate PCI was associated with the occurrence of greater (presumed periprocedural) myocardial damage. Pharmacological pre-treatment showed a preventative benefit. In addition, this chapter included the correspondence which resulted from the publication of the OPTIMA trial.

Chapter 3 contains a review article regarding the evaluation and invasive treatment in patients with a suspected ACS. The article reviewed the several diagnostic strategies and includes the criteria for an invasive approach. In principle, it suggests that the likelihood of an ACS should determine the diagnostic method of choice. For example, CT angiography appears to be a reliable diagnostic tool in ruling out coronary disease and determining other causes of chest pain in patients with a low likelihood of an ACS. On the other hand, with a high likelihood of an ACS, one also needs a diagnostic test with a high specificity, which means a low chance of a false negative test result. Therefore, the golden standard remains an invasive coronary angiography. Whenever the diagnosis of an NSTE-ACS is made, risk assessment should be performed. For this purpose, several validated tools such as the TIMI and GRACE risk scores have been developed. An invasive strategy is advised in those patients who score with an intermediate to high risk. However, in the current literature the results are diverse. The trials are difficult to compare due to differences in the intensity of pharmacological regimes. The following issue regards the timing of revascularisation, namely PCI, in this group of patients. The trial results were once again diverse. Although mortality differences were not noted, acute revascularisation seems to be associated with a higher incidence of periprocedural myocardial damage. Qualitative interpretation of the trials and their subjects suggest a biphasic response. Intervention applied too hastily is associated with an increased periprocedural risk while the prolonged delay of intervention increases the risk of a new spontaneous ischemic episode. The turning point seems to be after a few hours and depends most likely on the speed of initiation and the intensity of the pharmacological therapy.

Part 2: Biochemical determinants of the non ST-elevation acute coronary syndrome.
Part 2 approaches the evaluation of NT-proBNP as a biomarker for the NSTE-ACS. In a response to an increase in myocardial wall tension, the myocytes produce the brain
natriuretic peptide (BNP). During this process the precursor protein pre-proBNP is split into the active neurohormone BNP and the alleged inactive peptide chain NT-proBNP. These peptides are used in the diagnostics of patients with heart failure in the past years. However, recent studies have shown that ischemia can also result in BNP and NT-proBNP production.

**Chapter 4** concerns an observational study which evaluates the dynamics of NT-proBNP concentration in patients with an ACS. The research showed that the plasma NT-proBNP concentration increases steadily with maximum values around 24 hours after the onset of chest pain. However, the degree in the rise of the maximum concentration varied quite a lot between patients. This observation has been further studied in **Chapter 5**. In this study, the maximum plasma concentration was related to the severity of the ACS. Accordingly, the culprit lesion was identified during the diagnostic catheterisation. The evaluation suggested a relation between the maximum concentration and the localisation of the culprit lesion. Also, the degree of myocardial damage, measured as a maximum troponin rise, was related to the degree of NT-proBNP elevation. These results suggest that NT-proBNP elevation in patients with acute chest pain can be considered as an integral of the severity of the underlying event.

**Chapter 6** concerns the diagnostic properties of NT-proBNP in patients with a NSTE-ACS. The study evaluated the relationship between baseline NT-proBNP concentration and the presence of an evolving MI. Because ischemia often proceeds necrosis, it was hypothesized that an early elevated NT-proBNP could predict the occurrence of a hard ischemic event such as a myocardial infarction. There appeared to be a clear relationship between NT-proBNP elevation and the presence of an evolving MI. This relationship was also present in patients with negative biomarkers of necrosis at baseline. The optimum cut off value was determined to be 40 pmol/L. However, it was also assessed that the absence of NT-proBNP elevation at baseline would not reliably rule out the presence of an evolving MI.

**Chapter 7** is a clinical review which elaborated on biochemical changes in the circulation as a result of myocardial ischemia. These biomarkers play an increasingly important role in diagnostics, risk stratification and they thereby guide treatment choices. Diverse pathophysiological biomarkers are described in a structured fashion.
They include the markers of necrosis, biochemical strain and inflammation. Troponin appears to be the most useful biomarker in identifying those patients at a high risk for recurrent MI and the natriuretic peptides are the most useful for identifying those at risk for heart failure and death. It concludes with the prospects on the multi-marker approach. Assessing combinations of pathobiologically diverse biomarkers may provide a better risk evaluation method and further channel subsequent therapy. This is a novel concept however and needs to be validated for its incremental value by using clinical trials.

**Part 3: Case studies in presumed acute coronary syndromes**

This part was added to the thesis in order to emphasise that there is no such thing as a “routine chest pain patient”. It illustrates the challenging differential diagnostics regarding acute chest pain by using four different case studies. The physician has a wide arsenal of diagnostic tools in his approach and these can be used in specific circumstances. It is important to look for certain clues in the evaluation of a patient which may point to such an alternative diagnosis.

**Chapter 8** describes a case study of a young man who was presented with a presumed NSTE-ACS. There were eminent ECG changes and there appeared to be a typical troponin rise. However, because of the remarkably low risk of coronary artery disease and the presence of aspecific symptomatology, carbon monoxide poisoning was suspected and later proven by blood gas analysis.

**Chapter 9** contains a case study which refers to the proper use of the ECG in patients with a suspected ACS. After an extensive diagnostic evaluation a patient was diagnosed with the Brugada syndrome.

**Chapter 10** discusses the value of a rather new diagnostic modality namely, coronary CT angiography. It illustrates the early evaluation of patients with a low to intermediate likelihood for having an ACS. A presumed low risk patient would swiftly be diagnosed with a NSTE-ACS and could thereby undergo full pharmacological treatment.

**Chapter 11** describes the fourth and last case report. It illustrates that with the use of a coronary CT angiography in patients with a low to intermediate likelihood of an ACS curious results can occur. In this particular case a rare congenital anomaly was detected. It is most likely that this finding was unrelated to the symptoms.