GENERAL INTRODUCTION
AND OUTLINE OF THE THESIS
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Acute coronary syndrome
Acute coronary syndrome (ACS) encompasses a clinical spectrum of signs and symptoms that are most commonly caused by intracoronary atherosclerotic plaque rupture or erosion with superimposed thrombus formation and distal embolization. This intracoronary thrombus may lead to (partial) occlusion of the artery and a reduction in blood flow leading to clinical symptoms such as chest pain. Despite the common pathophysiological substrate, the clinical presentation of ACS is diverse. It ranges from ST-segment elevation myocardial infarction (STEMI), where the coronary artery is totally occluded by thrombus, to non-ST-segment elevation acute coronary syndrome (NSTE-ACS) characterized by a partially or intermittently occlusive thrombus.

After distinguishing ACS patients within the population presenting with suspected cardiac chest pain or ischemic equivalent, patients can be classified by the electrocardiogram (ECG) as follows: STEMI and NSTE-ACS. Based on cardiac biochemical markers such as creatine kinase MB or troponin that indicate the presence of myocardial necrosis, NSTE-ACS can be subdivided into non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina. A flow-chart of ACS is presented in Figure 1.

Partly enclosed within the classification STEMI and NSTE-ACS, is the diagnosis of myocardial infarction, which is based on the presence and amount of myocardial cell necrosis in a clinical setting of myocardial ischemia. A global task force involving members of The European Society of Cardiology (ESC), the American College of Cardiology (ACC), the American Heart Association (AHA), and the World Heart Federation have proposed criteria for the diagnosis of MI. In addition to the above described spontaneous MI (Type 1), criteria are presented for Type 2 secondary MI (increased oxygen demand or decreased supply), Type 3 unexpected cardiac death, and Type 4 and 5 (revascularization) procedure-related MI.

Treatment strategies
ACS is a condition prone to ischemic and other complications that may lead to death or MI on short or long-term. The treatment of ACS is directed at improving outcomes by reducing the occurrence of these complications. Furthermore, its targets are the relief of symptoms and the progression of further disease. The treatment generally consists of two major components, pharmacotherapy and coronary revascularization. Besides patient-related characteristics, the chosen treatment strategies within these components depend on the (working) diagnosis. The major groups within the pharmacological treatment of ACS include anticoagulants, antiplatelet agents, anti-ischemic agents and other medication such as lipid-lowering medication.

Regarding coronary revascularization, patients with STEMI preferably undergo timely mechanical reperfusion by primary percutaneous coronary intervention (PCI) in order to restore coronary blood flow in the occluded artery. It has been shown that primary PCI reduces the incidence of adverse ischemic outcomes,
including mortality, when compared to intravenous thrombolysis. Primary PCI should be performed as early as possible, because delays in reperfusion are associated with an increase in mortality.

Comparable to STEMI, coronary revascularization improves prognosis in selected patients presenting with NSTE-ACS. However, in contrast to patients with STEMI, two treatment strategies are generally used in clinical practice with respect to coronary angiography and revascularization in patients with NSTE-ACS: the routine invasive and selective invasive strategy. The routine invasive strategy consists of early coronary angiography within 24 to 72 hours and subsequent revascularization, where appropriate. The selective invasive or conservative strategy consists of initial pharmacological stabilization and angiography (and subsequent revascularization) if the pharmacological therapy fails and/or (recurrent) ischemia is detected. Whether a routine invasive strategy is beneficial depends on early risk of complications associated with invasive procedures on one side versus the prevention of ischemic events during follow-up. One of these early complications is the occurrence of a procedure-related MI, of which the prognostic significance is a topic for discussion. The ACC/AHA and ESC guidelines recommend a routine invasive strategy for patients presenting with NSTE-ACS without life-threatening symptoms but with high-risk features using one of the validated risk scores. This recommendation is supported by meta-analyses showing evidence of an early hazard balanced by a late benefit, resulting in
a significant reduction in the combined outcome of death or MI. Regarding the late benefit, long-term (5-year) follow-up was present from two earlier major trials, the RITA-3 (Randomized Intervention Trial of unstable Angina 3) and FRISC II (Fast Revascularization in InStability in Coronary artery disease II). Both emphasized the importance of long-term outcomes, showing differences in short-term and long-term mortality. Furthermore, both showed a benefit of the routine invasive strategy that was more pronounced in high-risk patients.

The Dutch ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) multicenter randomized trial compared the treatment strategies in NSTE-ACS patients with an elevated troponin T value. In contrast to the aforementioned studies, the ICTUS trial showed no benefit of the early invasive strategy for the composite of death, MI, or rehospitalization for anginal symptoms at 1- and 3-year follow-up. In order to investigate the occurrence of late clinical events, we reported the 5-year outcomes of the ICTUS trial. The first part of the thesis concerns the long-term outcomes of ICTUS, and results from the FRISC II, ICTUS and RITA-3 (FIR) collaboration in which individual patient data from the three trials was pooled.

**Prognostication and risk stratification**

Over the last decade, mortality and morbidity have substantially deceased among patients with ACS, including those with a MI, due to improvements in revascularization strategies and optimal pharmacotherapy. However, patients at high risk of complications and adverse clinical events remain. The ability to differentiate between patients at high- and low-risk may be a valuable tool to optimize the use of different treatment strategies, which may improve patient outcomes. After the diagnosis of ACS, it is recommended to stratify the patients according to risk for adverse outcomes. The assessment of the patients' risk subsequently aids in therapeutic decision making. As mentioned above, guidelines recommend a routine invasive strategy for patients presenting with NSTE-ACS with high-risk features. An example of a high-risk feature of patients with ACS is the presence of diabetes. Besides the clinical history and evaluation, tools used for the identification of high-risk features include electrocardiography, biomarkers, and imaging modalities.

Although individual characteristics can indicate a patients’ risk, the combination of several characteristics might improve prognostication and risk stratification of patients, especially if they are indicative of different underlying pathophysiologic mechanisms.

For clinical practice, several integer risk scores have been developed and validated which can assist treating physicians in easy and fast risk assessment. The TIMI (Thrombolysis In Myocardial Infarction) and GRACE (Global Registry of Acute Coronary Events) integer risk score are commonly used for clinical risk assessment in ACS. These risk scores are mainly based on readily available clinical symptoms and signs.

With regards to blood biomarkers, there have been multiple reports on associations with outcomes. As mentioned above, combining these markers
might improve prognostication, especially because of the differing processes reflected by these frequently described biomarkers (troponin indicates myocardial cell necrosis, c-reactive protein indicates inflammation, glucose indicates accelerated atherosclerosis, renal function assessed by the creatinin clearance indicates vascular damage, and N-terminal pro-brain natriuretic peptide indicates hemodynamic stress) \(^{23}\). Indeed, it has been demonstrated that combining several of these biomarkers improves the prognostication for short-term and 1-year outcomes in patients with NSTE-ACS \(^{24-26}\). The multiple biomarkers were identified as independent predictors for outcomes, even if established clinical signs and symptoms were taken into account. The combination of several biomarkers to improve risk stratification in patients with STEMI has been sparsely addressed \(^{27}\). The second part of the thesis concerns risk stratification in ACS, including a multiple biomarker strategy for prognostication in STEMI. For the latter, we used data of consecutive STEMI patients who underwent primary PCI in our institution. Data was captured in our institutional PCI database and biomarker database.

**OUTLINE OF THE THESIS**

**Part 1: Treatment strategies for acute coronary syndromes**

The first part of the thesis focuses on treatment strategies in ACS. First, the long-term outcomes of the Dutch multicenter ICTUS trial are described, which compared a routine invasive with a selective invasive strategy in patients with NSTE-ACS. Furthermore, a meta-analysis of long-term outcomes of the FRISC II, ICTUS and RITA-3 data are described. Pooling of the data provided us more power to investigate the effect of treatment strategies on the outcome mortality. The pooled dataset provided us with an opportunity to investigate the effects of timing of angiography within a routine invasive strategy, and whether the effects of treatment strategies differ among subgroups such as elderly patients. Because routine early procedures are associated with an increased hazard for the development of procedure-related MIs, we investigated the prognostic significance of these events. Finally, the use of invasive procedures in ACS patients over more than a decade from a large Swedish database is described.

**Part 2: Risk stratification in acute coronary syndromes**

The second part of the thesis comprises risk stratification in ACS. In NSTE-ACS we describe the association between growth-differentiation factor 15, a novel biomarker that has been detected in infarcted myocardium and in atherosclerotic plaques, and long-term outcomes. Furthermore, the association between admission electrocardiographic characteristics and long-term outcomes are described. In STEMI patients, the (additional) prognostic value of multiple biomarkers for mortality are described. Second, we validate the prognostic value of these biomarkers in an external cohort of STEMI patients and describe the association with short-term mechanistic markers of outcomes.
INTRODUCTION AND OUTLINE

REFERENCE LIST


