Treatment strategies and risk stratification in acute coronary syndromes

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SUMMARY OF THE THESIS

This thesis concerns treatment strategies and risk stratification in acute coronary syndromes (ACS). 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.

The first part (Chapters 2 to 8) describes routine invasive and selective invasive or conservative treatment strategies for patients presenting with NSTE-ACS. Because NSTE-ACS is characterized by a subtotal epicardial coronary occlusion, there is no transmural ischemia, and a proportion of patients respond to initial medical treatment. The second part (Chapters 9 to 13) describes the prognostic value of baseline electrocardiography and serum biomarkers in patients with ACS.

Part A Treatment strategies for acute coronary syndromes

For patients presenting with NSTE-ACS, two treatment strategies have been compared extensively in the past decade: a routine invasive strategy and a selective invasive or conservative strategy. With the routine invasive strategy, all patients undergo coronary angiography (CAG) with subsequent percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) if suitable. With the selective invasive strategy, patients undergo CAG if optimal medical treatment fails and the patient develops recurrent symptoms. Many randomized controlled trials and meta-analyses have assessed the effects of both strategies on adverse outcomes. The benefit of revascularization is difficult to compare and tends to be underestimated in these trials due to different proportions of patients crossing over from the selective arm to revascularization. In general, the benefit is more pronounced when the difference in revascularization rates between invasive and conservative arms is large.

Chapter 2 describes the long-term outcomes of the ‘Invasive versus Conservative Treatment in Unstable coronary Syndromes’ (ICTUS) trial in which these two strategies were compared. We showed that at 5-year follow-up, we could not demonstrate a long-term benefit of a routine invasive strategy in reducing death or MI in patients presenting with NSTE-ACS and elevated troponin T. This was irrespective of the patients baseline risk profile.

Two other large clinical trials have been performed in which these two strategies were compared which have long-term follow-up available: FRISC-II (Fragmin and Fast Revascularization during Instability in Coronary Artery Disease) and RITA-3 (Randomized Trial of a Conservative Treatment Strategy Versus an Interventional Treatment Strategy in Patients with Unstable Angina). These trials showed
inconsistent long-term results regarding the benefit of either treatment strategy. After pooling patient-level data of these trials (the FRISC II – ICTUS – RITA-3: FIR collaboration), we described in Chapter 3 that a routine invasive strategy reduces long-term rates of cardiovascular death or MI and the largest absolute effect was seen in higher-risk patients. Chapter 4 shows that the long-term benefit of the routine invasive over the selective invasive strategy is attenuated in younger patients less than 65 years of age and in females by the raised risk of early procedure-related events which seem to have no consequences for long-term cardiovascular mortality.

We believe that the most important explanation for the differences between the ICTUS trial and the FRISC II and RITA-3 trials is the intensity of revascularization in the treatment arms. Compared to the other trials, a high intensity of revascularization was observed in the selective treatment arm in ICTUS. As we have shown previously, NSTE-ACS patients benefit from revascularization, but this is independent of the intended treatment strategy as long as the threshold for CAG in an initial medically treated patient is low. After the publication of the long-term results of the ICTUS trial and the FIR collaboration, the routine invasive strategy was endorsed the highest level of recommendation for high risk patients in the European guidelines for clinical practice. In the American guidelines, a class I recommendation (should be performed) is made for the routine invasive strategy and a IIb (may be performed) is made for the selective invasive strategy.

In patients in which a routine invasive strategy is chosen, the optimal timing of CAG is unknown. In a retrospective analysis of the FIR database in patients presenting with NSTE-ACS, described in Chapter 5, the timing of angiography was not related to long-term cardiovascular mortality or MI. Based on a few recently performed trials, current European and American guidelines recommend that timing of CAG and revascularization should be based on patient risk profile. Excluding patients who are hemodynamically or electrically unstable and should undergo urgent CAG, whereas patients at high risk are recommended to undergo CAG within 24 hours.

Because few data is available on the implementation of treatment strategies in clinical practice over a longer time period, we used the Swedish national SWEDHEART database to assess trends in the implementation of these treatment strategies. In Chapter 6 we show that there has been an increase in the use of a routine invasive strategy in NSTE-ACS patients over the course of 12 years in Sweden. An absolute increase was mainly observed in low-risk patients, while a similar relative increase was observed in all risk groups.

An important point in the discussion of treatment strategies is the “early hazard” of the routine invasive strategy. The use of the routine invasive treatment strategy is associated with an “early hazard”, composed of procedure-related MIs. Procedure-related myonecrosis frequently occurs after PCI or CABG. It can result from side-branch occlusion, disruption of collateral flow, distal embolization, coronary dissection, microvascular plugging, and myocardial trauma during CABG. In Chapters 7 and 8 we describe that these procedure-related MIs probably do not have large clinical consequences, in contrast to spontaneously occurring MI.
Part B Risk stratification in acute coronary syndromes

Over the last decades, 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.

The first two chapters of part B concern risk stratification in patients with NSTE-ACS. In Chapter 9, we show that the baseline electrocardiogram provides long-term prognostic value for cardiovascular death or MI. These were mainly qualitative characteristics such as the presence of ST-segment depression or a left bundle branch block. Quantitative ECG characteristics provided no incremental discrimination compared with qualitative data.

Besides the established baseline electrocardiogram, multiple serum biomarkers have been identified that are associated with adverse outcomes. A novel biomarker, growth-differentiation factor 15 (GDF-15), is produced in response to oxidative stress, inflammation and tissue injury. As shown in Chapter 10, GDF-15 provides prognostic information for mortality and spontaneous MI and can be used to identify patients at high risk during long-term follow-up.

In the last three chapters of part B, we describe that the combination of different biomarkers improves prognostication in STEMI patients. Based on data from our local PCI database, Chapter 11 shows that addition of a multimarker, consisting of glucose, estimated glomerular filtration rate and N-terminal pro-brain natriuretic peptide, to a model including established risk factors improves the prediction of mortality in STEMI patients undergoing primary PCI. Because these biomarkers partly reflect different pathophysiological processes (glucose indicates accelerated atherosclerosis, renal function assessed by the creatinin clearance indicates vascular damage, and N-terminal pro-brain natriuretic peptide indicates hemodynamic stress) the combination of these biomarkers provides additional prognostic value. Furthermore, the use of a simple risk score based on these biomarkers identifies a high-risk subgroup for mortality. The simple risk score was validated in an independent database from Groningen, The Netherlands, as described in Chapter 12. In order to further explore the association between our multimarker risk score and higher mortality risk, we assessed the association between this score and several cardiovascular mechanistic markers of outcomes in Chapter 13. Mechanistic markers are measurements or physical signs used as surrogates for clinical outcomes, and effects on these markers should associate with clinical outcomes. The multimarker risk score is associated with angiographic, electrocardiographic and cardiac magnetic resonance mechanistic markers of outcomes. These data support the ability of the multimarker risk score to identify patients at high-risk of sub-optimal reperfusion and cardiac magnetic resonance outcomes and may aid in the early triage of patients who stand to benefit most of adjuvant treatments in STEMI.