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New insights in management and prognosis in acute myocardial infarction

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Summary of this thesis

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In the last decades, primary percutaneous coronary intervention (PCI) and pharmacological therapies have reduced the morbidity and mortality in patients with ST-segment elevation myocardial infarction (STEMI). However, STEMI remains a frequent cause of left ventricular dysfunction due to impaired myocardial perfusion and/or recurrent cardiovascular events. Therefore, the search for and evaluation of new treatments is important and ongoing. In this thesis we aim to evaluate adjunctive treatment during primary PCI to improve myocardial reperfusion and to identify high-risk patients who can benefit from adjunctive treatment.

Part I Developments in primary percutaneous coronary intervention after acute myocardial infarction

Despite optimal restoration of blood flow of the infarct-related coronary artery after primary PCI, impaired myocardial perfusion is still present in a significant portion of patients. Impaired myocardial perfusion is associated with larger infarct size, left ventricular dysfunction, and mortality.^{1,2} Impaired perfusion is likely to result from embolization of atherothrombotic particles in the distal microvasculature either spontaneously or during PCI.^{3,4} **Part 1** of this thesis focuses on strategies aimed to reduce distal embolization by the implementation of adjunctive mechanical and pharmacological therapies during primary PCI.

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Thrombus burden

In **Chapter 2** we evaluated the impact of the amount of thrombus burden as observed on the coronary angiogram on different outcome variables in patients with STEMI in whom primary PCI was performed with or without manual thrombus aspiration in routine clinical practice. In this retrospective study, we included 2969 unselected patients with STEMI of which 68% had a large thrombus burden. A large thrombus burden was associated with impaired myocardial perfusion defined as low myocardial blush grade (MBG) scored angiographically. Even in patients with restored epicardial blood flow, impaired myocardial perfusion was significantly higher in patients with a large thrombus burden. In accordance, large thrombus burden was associated with higher 1-year all-cause mortality. The second part of the study suggested that the use of thrombus aspiration was associated with improved myocardial perfusion in patients with large as well as with small observed thrombus burden. We found that retrieval of a macroscopic visible aspirate is still high in patients with an angiographically observed small thrombus burden, which may explain the benefit in this group. In conclusion, our study suggests that large thrombus burden is associated with worse outcome and that manual thrombus aspiration might have beneficial effect on myocardial perfusion,

irrespective of the observed thrombus burden.

Glycoprotein IIb/IIIa inhibitor - CICERO trial

In **Chapter 3** we presented the study design of the randomized controlled trial named Comparison of intracoronary versus intravenous abciximab administration during emergency reperfusion of ST-segment elevation myocardial infarction (CICERO). In this trial we randomized patients with STEMI in our centre within 12 hours of symptom onset to intracoronary or intravenous administered glycoprotein (GP) IIb/IIIa inhibitor abciximab during primary PCI. Patients received aspirin, clopidogrel and heparin prior to PCI, and thrombus aspiration was performed in the majority of patients. The primary endpoint was restored myocardial reperfusion defined as ST-segment elevation resolution on the electrocardiogram. The results presented in **Chapter 4** demonstrated that in 534 patients intracoronary administration of abciximab did not improve myocardial reperfusion compared to intravenous administration. Secondary endpoints, MBG and enzymatic estimation of infarct size, did show a beneficial effect. The occurrence of the safety endpoint, defined as incidence of in-hospital bleeding was low and similar in both groups. In conclusion and in contrast to earlier findings, the CICERO-trial did not demonstrate superiority of intracoronary compared to intravenous administration of abciximab in improving myocardial perfusion.

Part II Prognosis after acute myocardial infarction in routine clinical practice

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To improve the overall outcome in patients with STEMI, we have to identify patients with high-risk for new cardiovascular events and/or left ventricular dysfunction due to impaired myocardial perfusion. Risk assessment gives the ability to further personalise treatment by initiating earlier and more aggressive treatment and improve adherence to pharmacotherapy as this is often suboptimal in these patients.^{5,6} Examples of treatment strategies are; prevention of reinfarction by early revascularization of significantly narrowed non-infarct-related coronary arteries, adjunctive antithrombotic medication, and/or attenuation of the remodelling process by inhibitors of the renin angiotensin system and mineralocorticoid receptor antagonists.⁷⁻⁹ Furthermore, the identification of low-risk patients gives the ability to safely minimalise treatment and follow-up. Additionally, this can improve more efficient use of resources and reduce healthcare costs in our aging-population. **Part 2** of this thesis discusses imaging and blood-based biomarkers available during primary PCI, hospitalization, and follow-up and their prognostic value in patients with STEMI treated with primary PCI.

Myocardial blush grade scored by the operator

In **Chapter 5** we described that the operator-scored imaging biomarker, MBG measured at the end of the primary PCI, was an independent predictor of 1-year all-cause mortality in 2118 consecutive patients with STEMI. This predictive value remained significant when restoration of blood flow was achieved and after correction for other well-known predictive variables. Furthermore, our cohort was large enough to categorize MBG in 4 groups with decreasing prognosis per grade, with a markedly poor prognosis in patients with a MBG of 0; classified as no myocardial blush. Compared with other functional outcome parameters, such as obtained from magnetic resonance imaging (MRI) and echocardiography, the operator-scored MBG has the important practical advantage that it can be assessed easy and directly after the primary PCI. In conclusion, this study indicates that operator-scored MBG is a valuable and cheap tool in early risk stratification that can be easily used in routine clinical practice.

Risk stratification by biomarkers

Risk stratification by blood-based biomarkers was investigated in **Chapters 6 and 7**. First we validated a multimarker model and simplified risk score based on admission levels of three biomarkers to predict mortality in patients with STEMI that were developed in the original cohort.¹⁰ In our comparable, real world cohort existing of 1321 patients with STEMI, we showed that glucose, N-terminal pro-brain natriuretic peptide (NT-proBNP), and estimated glomerular filtration rate were all independent predictors of mortality. The addition of all three biomarkers provided incremental prognostic value on top of established risk factors. The simplified risk score accurately identified low-, intermediate-, and high-risk subgroups. Secondly, we pooled the original cohort with our validation cohort (resulting in a total of 2355 patients with STEMI) to determine whether the simplified risk score could not only predict short-term mortality, but also long-term mortality in 30-days survivors. The study showed that low-, intermediate-, and high-risk subgroups were associated with increasing mortality up to 30-days as well as for the period up to 4-years thereafter. In conclusion, this simplified risk score may be valuable in clinical practice, as it is easy to use and can provide early risk assessment per patient.

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Repeated measurements of NT-proBNP

In **Chapter 8** we distinguished the optimal timing of NT-proBNP measurements after STEMI for the prediction of left ventricular ejection function (LVEF) and infarct size determined by MRI at 4 months. Data of the GIPS-III trial were used.¹¹ In the GIPS-III trial, metformin was compared to placebo in patients with first STEMI and without known diabetes. Metformin did not improve LVEF at 4 months. NT-proBNP was measured during hospitalization and during follow-up. In the 271 patients included in this post-hoc analysis, most NT-proBNP

measurements were associated with LVEF and infarct size. However, the predictive value of NT-proBNP measured during hospitalization was limited. This observation was in contrast to the strong association of NT-proBNP measured during follow-up to LVEF and infarct size. These results may have implications for clinical practice as NT-proBNP measured during hospitalization as a prognostic marker can be omitted and patients with high NT-proBNP levels during follow-up can be treated earlier and more aggressive to improve outcome.

Discussion and future treatment strategies in acute myocardial infarction

In addition to our own studies, other studies have also focussed on manual thrombus aspiration and GP IIb/IIIa inhibitors in reducing distal embolization during primary PCI. We observed benefit of manual thrombus aspiration in our retrospective cohort study of patients with STEMI. However, after initial positive findings in randomised trials using surrogate endpoints and early meta-analyses,^{12,13} the more recent and larger trials were neutral.¹⁴⁻¹⁷ In the TASTE trial with 7244 patients, thrombus aspiration did not reduce 30-days or 1-year mortality.^{15,16} The results of the TOTAL trial, including 10,732 patients with STEMI, indicated that routine thrombus aspiration does not improve the combined endpoint consisting of cardiovascular death, recurrent myocardial infarction, cardiogenic shock or severe heart failure at 6 months.¹⁷ Although an improvement in periprocedural reperfusion markers were found in the TOTAL trial; i.e. ST-segment resolution and reduction in distal embolization. Interestingly, bailout thrombus aspiration was allowed after predilatation or after stent deployment. Furthermore, the rate of GP IIa/IIIb inhibitor administration was significantly lower in the thrombus aspiration group. Therefore, further studies to evaluate the benefit of thrombus aspiration in selected cases, like in patients with large thrombus burden and as bailout in case of no-reflow are still of interest. However, in both trials no difference in outcome was found in subgroup analysis based on the thrombus burden. The different results in our study compared to the more recent trials may be the result of continued improvements in other treatment strategies such as the more frequent use of newer stents, bivalirudin, and newer generation P2Y₁₂ inhibitors. Meanwhile, guidelines provide a Class IIa recommendation for routine manual thrombus aspiration,^{7,8} and the more recent guideline a Class IIb recommendation for selected use.¹⁸ In future guidelines, the recommendation of thrombus aspiration is likely to be downgraded based on the recent trials.

GP IIb/IIIa inhibitors are available to combat the embolization of thrombotic material, partly caused by the mechanical revascularization procedure itself. Prior to the CICERO-trial, small

studies showed beneficial clinical effects of intracoronary abciximab administration.¹⁹ The meta-analysis, including the CICERO-trial, showed lower short-term mortality in patients receiving intracoronary compared to intravenous abciximab, without any increase of major bleeding episodes. However, beneficial effects could not be confirmed in the most recent and largest trial AIDA STEMI; no difference was observed on the primary composite endpoint of all-cause mortality, re-infarction, or new congestive heart failure within 90 days and at 12 months.^{20,21} The substudy with MRI performed within 1 week, demonstrated similar findings on infarct size, microvascular obstruction and ejection fraction.²² In recent years, the use of newer generation P2Y₁₂ inhibitors, prasugrel and ticagrelor, as adjuvant antiplatelet therapy has increased. This might influence the beneficial effects of GP IIb/IIIa inhibitors.²³ Furthermore, the HORIZONS-AMI trial, Euromax trial and BRIGHT trial showed a significant reduction of the combined clinical outcome when bivalirudin, a direct thrombin inhibitor, was administered compared to the administration of heparin plus abciximab or tirofiban.²⁴⁻²⁷ This outcome was dominated by the reduction in major bleeding episodes, but in some trials at the expense of stent thrombosis. However, the opposite was shown in the HEAT-PPCI trial, where heparin reduced the incidence of major adverse ischaemic events without increase in major bleeding complications compared to bivalirudin.²⁸ In the HEAT-PPCI trial, the use of GP IIb/IIIa inhibitors was around 14% in both groups. Current guidelines argue that the use of GP IIb/IIIa inhibitors should be considered in the event of thrombotic complications (large thrombus, total occlusion, no-reflow), as suggested by the authors of the AIDA-trial, although not supported by their subgroup analysis.^{18,21} Studies are ongoing to investigate novel combinations and timing of antiplatelet and anticoagulant therapy to combat the prothrombotic milieu during STEMI.

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Adjunctive mechanical and pharmacological therapies could be beneficial in selected patients, to achieve a more personalized treatment. Several risk scores have been developed in the past decade, of which only a few are used in routine clinical practice for patients with STEMI. The well-known Thrombolysis in Myocardial Infarction (TIMI) score includes established clinical risk factors to predict 30-days mortality derived before PCI; age, weight, diabetes, hypertension, systolic blood pressure, heart rate, anterior myocardial infarction, killip class, and time to treatment.²⁹ Factors that predicted death or myocardial infarction in-hospital and up to 6 months after discharge in the GRACE-study are: age, development (or history) of heart failure, peripheral vascular disease, systolic blood pressure, killip class, initial serum creatinine concentration, elevated initial cardiac markers, cardiac arrest on admission, and ST segment deviation.³⁰ The GRACE risk tool is already implemented in clinical practice to guide early interventional treatment in high-risk patients with non-ST-segment elevation myocardial infarction.³¹ The advantages of the TIMI risk score study and GRACE study are their prospective, multinational, and large myocardial infarction-populations, with a more

unselected population in the GRACE registry. The disadvantage of these risk scores is that therapy for patients with STEMI has evolved in the past decade, resulting in a substantial reduction in mortality. This effects the incidence and predictive value of several risk factors. Furthermore, the TIMI risk score is based on a trial in which patients were treated with fibrinolysis and the majority of the patients included in GRACE did not have a STEMI. Our risk score based on three biomarkers assessed at admission may be valuable in clinical practice to identify the risk per patient. However, our study was small and we did not study whether adjusting therapeutic interventions based on this risk stratification would result in a better outcome to warrant their use in routine clinical practice. An example of a risk score that is used in clinical practice with immediate consequence for prescribed therapy is the bleeding risk score CRUSADE, as patients with a high bleeding risk are prescribed clopidogrel instead of ticagrelor.³² Furthermore, risk scores can also be used in clinical trials, as the incidence of major adverse events is low in low-risk patients.³³ To improve the power of clinical trials with hard endpoints, only high-risk patients should be included based on a risk score. Secondly, imaging and blood-based biomarkers could be used as a surrogate endpoint once a high correlation has been proven with hard endpoints.

In the coming decades, patient-specific profiles, including genetic and genomic data as well as clinical and environmental factors, will play a major part in further individual risk stratification. As there exists large interindividual variability in the response to pharmacologic agents, the dose and type of medicine will be based on a patient-specific profile rather than solely based on study results of a patient population.³⁴ To date, genetic testing is already available to identify individuals with reduced function of CYP2C19 alleles who benefit less from clopidogrel.³⁵ And at least one common variant in the SLCO1B1 gene substantially alters the risk of simvastatin-induced myopathy, which may suggest that genotyping these variants may help to achieve the benefits of statin therapy more safely and effectively.³⁶ Furthermore, the human gastrointestinal microbiome also has effect on the pharmacokinetics.³⁷ Another area of interest will be the ability to review millions of patients' data registered in electronic medical records complemented with efforts to perform genome wide genotyping, so-called 'big data'.³⁸ With the enormous amount of clinical parameters, identification of specific risk groups will be easier and more precise than with the use of cohorts to date.

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