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New insights in management and prognosis in acute myocardial infarction

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1

Introduction

Background on acute myocardial infarction

Coronary heart disease, including acute myocardial infarction, remains a major cause of morbidity and mortality in Western society.¹⁻³ In the Netherlands, the mortality rate of coronary heart disease is approximately 10.000 patients per year.³ Improved prevention and treatment in the last decades has led to decreased incidence and mortality of acute myocardial infarction.⁴ As a consequence, a large number of patients that survived and were successfully treated for their acute myocardial infarction remain with or gain further morbidity requiring rehospitalizations due to recurrent myocardial infarctions, revascularization procedures, and heart failure. Therefore, coronary heart disease is also a substantial economic burden costing more than 2% of all healthcare costs in The Netherlands.³

Acute myocardial infarction is a severe clinical event characterized by myocardial necrosis caused by insufficient coronary flow due to a rupture or erosion of an atherosclerotic plaque and subsequent platelet aggregation.⁵ Criteria for the diagnosis are symptoms of ischemic pain, specific electrocardiographic changes and rise of cardiac biomarker values. ST-segment elevation myocardial infarction (STEMI) is defined by typical elevation of the ST-segment on the electrocardiogram as a result of the acute and mainly total occlusion of the infarct related coronary artery by the atherosclerotic plaque with thrombus. The insufficient epicardial blood flow limits the distal myocardial perfusion with consequently myocardial ischemia and eventually necrosis as a result. The myocardial necrosis and the adaptive changes in surviving myocytes surrounding the necrosis lead to dilatation and impaired contractility of the ventricle. This ventricular dysfunction may lead to symptomatic heart failure.⁶ Furthermore, it is likely that atherosclerotic plaques in other parts of the coronary arteries will cause coronary events.

10

General aim

In this thesis, we aimed to evaluate adjunctive treatment during primary percutaneous coronary intervention (PCI) to improve myocardial perfusion and to study prognosis to reduce the morbidity and mortality in patients with STEMI.

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

The treatment of STEMI includes primary PCI and pharmacological therapy. Urgent restoration of epicardial blood flow to provide reperfusion into the affected part of the myocardium is the goal of primary PCI. During PCI, the plaque and thrombus are compressed

towards the vessel wall by balloon angioplasty and/or stenting. However, this intervention may also induce embolization of atherothrombotic particles that lead to obstruction of the microcirculation.⁷⁻⁹ This is thought to be the main cause of impaired myocardial perfusion despite restoration of epicardial blood flow and occurs in up to 50% of patients.⁸ Impaired myocardial perfusion is associated with larger infarct size and increased long-term mortality.¹⁰⁻¹² Therefore, adjunctive mechanical and pharmacological therapies are being developed to improve the myocardial reperfusion and clinical outcome. Recently, manual thrombus aspiration and glycoprotein (GP) IIb/IIIa inhibitors are implemented during primary PCI. They are both associated with improved myocardial perfusion and clinical outcome in patients with STEMI in several trials and meta-analyses.¹³⁻¹⁷ In **part 1** of this thesis, we focus on manual thrombus aspiration as an adjunctive mechanical therapy and on GP IIb/IIIa inhibitors as an adjunctive pharmacological therapy, both during primary PCI.

Thrombus burden

Large thrombus burden is associated with increased occurrence of distal embolization of atherothrombotic particles.¹⁸⁻²⁰ Although distal embolization is not frequently observed during the coronary angiogram, undetectable microembolization is suspected to occur.^{9,18,20,21} Meanwhile, limited data are available regarding the impact of angiographically observed thrombus burden on myocardial perfusion and outcome. Currently, manual thrombus aspiration is frequently the first intervention during primary PCI in patients with STEMI. With the catheter the atherothrombotic material is retrieved by manual suction in the infarct-related lesion. This adjunctive step is thought to improve the myocardial perfusion by reducing the amount of embolized atherothrombotic particles that lead to obstruction of the distal microcirculation.⁷⁻⁹ However, it is not known whether there is a difference in benefit of thrombus aspiration between patients with large and with small thrombus burden. Still, atherothrombotic material is retrieved in a considerable proportion of patients without angiographic evidence of thrombus.^{16,22} In **chapter 2**, we evaluated whether angiographically observed thrombus burden is associated with outcome and secondly whether the use of thrombus aspiration is beneficial irrespective of the amount of thrombus burden.

Glycoprotein IIb/IIIa inhibitor - CICERO trial

Today, several antiplatelet and anticoagulant agents are administered during STEMI, including aspirin, a P2Y₁₂ inhibitors, heparin and a GP IIb/IIIa inhibitor.^{23,24} Abciximab is a monoclonal antibody which binds to the GP IIb/IIIa receptor that is expressed on the surface of activated human platelets, hereby inhibiting platelet aggregation and thrombus formation. The GP IIb/IIIa inhibitor therefore prevents not only thrombus formation, but also promotes (dose-dependent) lysis of fresh thrombus.²⁵ In large randomized trials, GP IIb/IIIa inhibitors administered intravenously improved myocardial perfusion and clinical outcome.^{14,15} The

dose-dependent properties of GP IIb/IIIa inhibitors suggest that higher local concentration of abciximab by intracoronary administration may reduce the occurrence and disperse embolization of thrombotic material.^{25,26} The first small clinical studies, also show beneficial effects when the GP IIb/IIIa inhibitor is administered intracoronary.^{27,28} In **chapter 3 and 4**, we studied the effect of intracoronary versus intravenous administered GP IIb/IIIa inhibitor during primary PCI on myocardial reperfusion in a randomized trial called Comparison of intracoronary versus intravenous abciximab administration during emergency reperfusion of ST-segment elevation myocardial infarction (CICERO).

Part II Prognosis after acute myocardial infarction in routine clinical practice

To further improve the outcome of patients with STEMI, we should evaluate which patients have high risk of adverse clinical events. To achieve clinically applicable risk stratification, the risk factors should be easily available or assessed during routine clinical practice. The risk factors may include clinical factors, procedural factors and/or biomarkers. Early identification of high-risk groups may optimize the use of different treatment strategies that may improve their prognosis. Also, low-risk patients may benefit from earlier discharge, which can reduce healthcare costs. In **part 2** of this thesis, we focus on the ability to classify the risk of patients with STEMI in routine clinical practice.

12

Myocardial blush grade scored by the operator

Depending on the duration of coronary occlusion, myocardial infarction leads to destruction of the microvascular bed and necrosis of myocytes.²⁹ A substantial percentage of patients have signs of impaired myocardial perfusion despite treatment. Myocardial blush grade (MBG) is a simple visual angiographic assessment of myocardial perfusion, and therefore a measure of the extent of damage of the microvascular bed in the infarct area.¹² In several studies, the MBG scored by corelab is associated with ST-segment elevation resolution, enzymatic infarct size, left ventricular function, and long-term mortality.^{10,12,30,31} However, no study has reported whether MBG scored by the operator has prognostic value. The objective in **chapter 5** was the prognostic value of MBG scored by the interventional cardiologist during primary PCI in routine clinical practice.

Risk stratification by biomarkers

Several clinical risk scores have been developed to provide risk assessment in patients with STEMI. The number of variables used in most risk-scores make them difficult to apply in clinical practice. The prognostic value of a combination of three biomarkers that

is frequently and early assessed during routine clinical practice has been demonstrated.³² This finding may be explained by the fact that the biomarkers glucose, N-terminal pro-brain natriuretic peptide (NT-proBNP), and estimated glomerular filtration rate all reflect a different pathophysiological mechanism associated with acute myocardial infarction.³³ To verify the prognostic value of the three biomarkers, we externally validated the study in our STEMI cohort in **chapter 6** and determined whether the prognostic value is only driven by short-term mortality in a patient-pooled cohort in **chapter 7**.

Repeated measurements of NT-proBNP

The impaired myocardial perfusion causes a larger infarct size and decreased left ventricular ejection fraction (LVEF). These parameters of left ventricular dysfunction are the strongest predictors of morbidity and mortality after STEMI. NT-proBNP is synthesized and released by the myocardium in response to cardiac stretch and overload due to ventricular dysfunction.³⁴⁻³⁷ In many studies this association is determined with only one NT-proBNP value assessed during hospitalization. However, during STEMI the NT-proBNP level is also increased due to the acute ischemia, which may influence the association with left ventricular function. In **chapter 8** we described which time point of NT-proBNP measurements after STEMI has the strongest association with infarct size and LVEF.

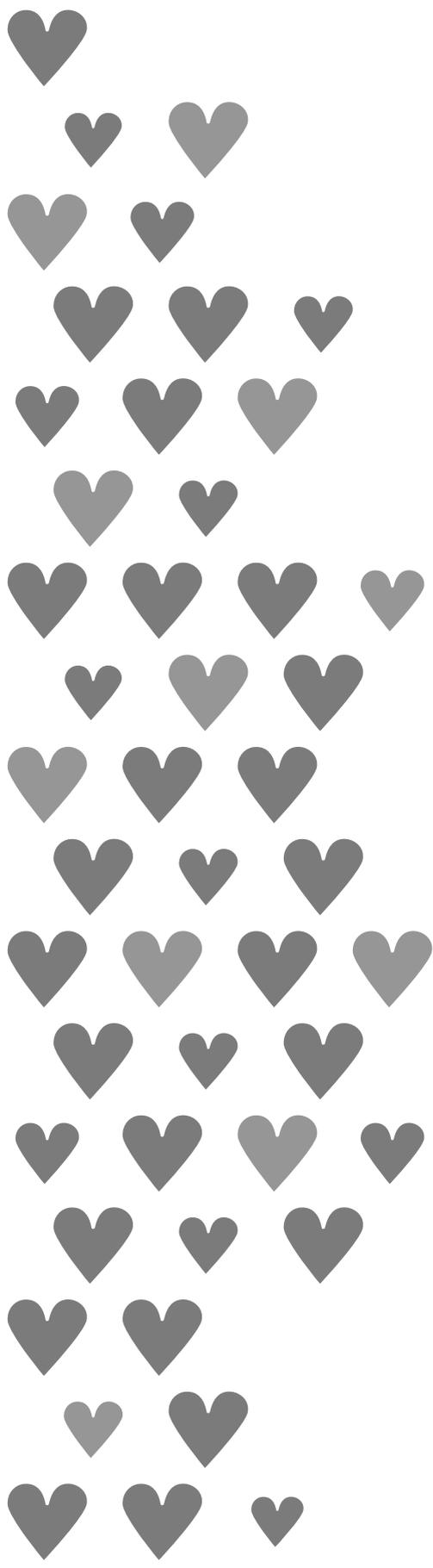
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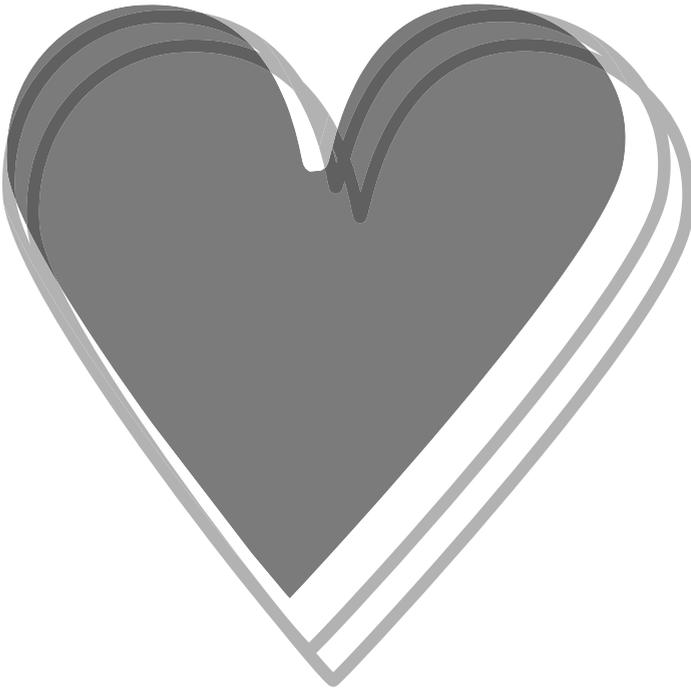
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PART I

Developments in primary percutaneous coronary intervention after acute myocardial infarction

