Towards optimisation of mechanical reperfusion therapy for acute myocardial
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Summary and clinical implications

This thesis addresses diverse aspects of daily clinical practice in a setting where all patients presenting with acute myocardial infarction are treated with primary angioplasty. The importance of pre-hospital infarction-diagnosis and triage, the influence of pharmacological pre-treatment before primary angioplasty, the extent of platelet aggregation inhibition with different antiplatelet treatment regimens, the importance of initial patency of the infarct-related artery and outcome after failure of mechanical reperfusion therapy are analysed.

Chapter 1 starts with an introduction and overview of this thesis.

In chapter 2 we evaluate, in the PHIAT (Pre-Hospital Infarction Angioplasty Triage) project, safety and feasibility of in-ambulance electrocardiography facilities for pre-hospital triage and direct transfer to an interventional centre to undergo immediate coronary angiography and angiography-guided therapy. The ambulances were equipped with a defibrillator and electrocardiography unit with computerised electrocardiographic analysis. Patients with acute myocardial infarction symptoms and fulfilling certain criteria compatible with a large myocardial infarction were included. During the study period, 284 patients met the PHIAT criteria. Eleven percent of the identified patients did not have an acute myocardial infarction. Primary angioplasty was successful in 94%. Pre-hospital triage reduced time to treatment; in 32% of the patients triage resulted in direct transportation to the interventional centre instead of transportation via the nearest community hospital. Pre-hospital triage in the ambulance is a safe and feasible way to identify patients with acute myocardial infarction in order to transport them directly to an interventional centre. All efforts should be made to implement pre-hospital infarction diagnosis and triage in the ambulance service structure. So far, many regions in the Netherlands have adopted this “Zwolle” concept.

In chapter 3 we give an overview of different possibilities of pre-procedural pharmacological therapy for patients with acute myocardial infarction treated with primary angioplasty. With the increasing use of primary angioplasty, more patients will be transferred to an interventional centre. As the importance of an open infarct-related artery at acute angiography becomes clear, pharmacological pre-treatment with a glycoprotein IIb/IIIa receptor blocker, on top of administration of aspirin and heparin, with the aim to open the infarct-related vessel during transportation seems to be the treatment of choice, especially because of its relative safety.

In chapter 4 we describe the influence of pre-hospital administration of aspirin and heparin on initial patency of the infarct-related artery in patients with acute myocardial infarction treated with primary angioplasty. Angiographic data and 30-day clinical outcome of 1702 acute myocardial infarction patients treated with primary angioplasty were studied: 860 patients received aspirin and heparin before transportation to our hospital and 842 patients received these agents in our hospital. The Thrombolysis In Myocardial Infarction (TIMI) 2 or 3 flow in the infarct-related artery was higher in the group treated with aspirin and heparin in the pre-
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Hospital phase (31% versus 20%, RR 0.65 [95%CI 0.55-0.78], p<0.001). Patients with TIMI 2 or 3 flow on the initial angiogram had a higher angioplasty success rate (94% versus 89%, p<0.001), a smaller enzymatic infarct size, a higher left ventricular ejection fraction and a lower 30-day mortality (1.6% versus 3.4%, p=0.04). All patients with acute myocardial infarction, transported to an interventional centre to undergo primary angioplasty, should be treated with aspirin and heparin in the pre-hospital phase, before admission to the interventional centre.

In chapter 5 we discuss the results of the Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) trial. In this trial, 507 patients with acute myocardial infarction, who were transferred to undergo primary angioplasty, were randomised to early, pre-hospital initiation of Tirofiban (Early) or to initiation of Tirofiban in the catheterisation laboratory (Late). A large proportion of patients (41%) was diagnosed and randomised in the ambulance, without intervention of a physician. In the Early group, Tirofiban was administered a median of 59 minutes (range 11-178) earlier than in the Late group. At initial angiography, TIMI 3 flow was present in 19% in the Early group and in 15% in the Late group (p=0.22). Thrombus or fresh occlusion was present in 60% in the Early and 73% in the Late group (p=0.002). A pre-procedural myocardial blush grade 2 or 3 was more often present in the Early group (30% versus 22%, p=0.04). No difference in TIMI 3 flow or myocardial blush grade was found between the groups after primary angioplasty. At one-year follow-up, the combined incidence of death or recurrent myocardial infarction was not different between the groups (7.0% versus 7.0%, p=0.99). As this study excluded very high-risk patients, future studies on facilitation of primary angioplasty should focus on the high-risk population, which may specifically benefit from an open infarct-related vessel before primary angioplasty.

In chapter 6 we report a quantitative analysis of the benefits of pre-hospital infarction angioplasty triage on outcome in patients undergoing primary angioplasty for acute myocardial infarction. In this study, pre-hospital infarction-diagnosis and triage in the ambulance (n=209) were compared with triage at a referral centre without facilities for primary angioplasty (n=258) in patients included in the On-TIME (Ongoing Tirofiban In Myocardial infarction Evaluation) trial. Baseline characteristics were not different, apart from a higher prevalence of male gender in patients recruited in the ambulance. The ambulance group had a significantly shorter time to treatment (177 versus 208 minutes, p<0.001), a higher initial patency rate (combined TIMI 2 or 3 flow 44% versus 35%, p=0.045), a better extent of myocardial reperfusion (Myocardial Blush Grade 3: 59% versus 47%, p=0.02; complete ST-segment resolution: 78% versus 67%, p=0.02), a trend towards a higher prevalence of aborted myocardial infarction (15% versus 10%, p=0.08) and a significantly lower rate of death or recurrent myocardial infarction at 1-year follow-up (3% versus 10%, p=0.004). The results of this study also confirm the importance of pre-hospital infarction diagnosis and triage in the ambulance, in order to transport patients with an acute myocardial infarction directly to an interventional centre.
In chapter 7 we evaluate the extent of achieved platelet aggregation inhibition in patients with acute myocardial infarction undergoing primary angioplasty and treated with different antiplatelet agents and dosages. Patients were treated with Clopidogrel before angiography and randomised to Abciximab, Tirofiban, high-dose Tirofiban, or no glycoprotein IIb/IIIa inhibitor. In case the patient was randomised to treatment with a glycoprotein IIb/IIIa inhibitor, the bolus, immediately followed by maintenance infusion, was administered after angiography, but before primary angioplasty in all patients. Platelet aggregation inhibition was assessed before angiography, immediately after primary angioplasty, and 1 and 6 hours afterwards. The total study population consisted of 112 patients. Platelet aggregation inhibition was variable for individuals and sub-optimal for all agents, particularly in the periprocedural period. Only with high-dose Tirofiban, mean periprocedural platelet aggregation inhibition exceeded 80%. Angiographic parameters after primary angioplasty were not different between the groups. No relationship was found between the level of platelet aggregation and parameters of primary angioplasty success (Thrombolysis In Myocardial Infarction frame count and myocardial blush grade), after combining the data from all four groups studied. Larger studies should be performed to assess whether dose adjustment or combination therapy of different antiplatelet agents can further improve platelet aggregation inhibition and clinical outcome.

In chapter 8 we focus on the impact of patency of the infarct-related artery on the coronary angiogram, both before and after primary angioplasty for acute myocardial infarction, on 30-day mortality. In a descriptive cohort study, data of 1702 consecutive patients treated with primary angioplasty for acute myocardial infarction were collected prospectively. Patients with a (partially) patent infarct-related artery (TIMI flow grade 2 or 3) before primary angioplasty had less damage to the myocardium and a lower 30-day mortality (1.6% versus 3.4%, p=0.04) compared with patients with an occluded artery. Patients with pre-hospital treatment with aspirin and heparin more often presented with a (partially) patent (TIMI flow grade 2 or 3) artery before angioplasty (31% versus 20%, p<0.001). After primary angioplasty, 95% of patients had a patent artery with a 30-day mortality of 2.2%. The 5% of patients with failed angioplasty had extensive myocardial damage and a 30-day mortality rate of 17%. All efforts should be made to obtain early and optimal restoration of antegrade flow of the infarct-related artery as early as possible, especially when transportation to interventional centres, with conceivably further time-delay, is required.

In chapter 9 we report the impact of any increase in initial patency of the infarct-related artery on outcome in patients with acute myocardial infarction treated with primary angioplasty. We studied clinical and angiographic data of 1702 patients with acute myocardial infarction treated with primary angioplasty. In 1683 patients (98.9%) initial patency could be assessed. TIMI 0 flow was present in 65%, TIMI 1 flow in 10%, TIMI 2 flow in 12% and TIMI 3 flow in 13%. Primary angioplasty was
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successful in 94.7%. All outcome measures showed improved outcome with increasing TIMI flow: increased success of primary angioplasty (p for trend < 0.001), increased incidence of myocardial blush grade 2/3 and 3 alone (p for trend < 0.001; p for trend < 0.001, respectively), decreased enzymatic infarct size (p for trend < 0.001), increased left ventricular ejection fraction (p for trend < 0.001), and decreased 30-day and 1-year mortality (p for trend = 0.019; p for trend = 0.008, respectively).

In chapter 10 we describe the impact of failed mechanical reperfusion in patients with acute myocardial infarction treated with primary angioplasty. In the study population of 1568 patients, reperfusion was successful in 93.1% and failed reperfusion occurred in 6.9%. Killip class > 1 at admission (OR 5.7, 95%CI: 3.1-10.4, p<0.001), a left anterior descending artery as the infarct-related artery (OR 2.0, 95%CI: 1.2-3.4, p=0.01) or a pre-procedural TIMI 0 or TIMI 1 flow (OR 4.7, 95%CI: 2.0-11.1, p<0.001), were independent predictors of failed reperfusion. Patients in whom reperfusion was not successful had a significantly lower left ventricular ejection fraction compared to patients with successful reperfusion (39.9 ± 11.9 versus 43.6 ± 11.2, p=0.007). In-hospital mortality was 16% versus 2% (p<0.001), 30-day mortality 21% versus 3% (p<0.001), and 1-year mortality 27% versus 5% (p<0.001) in patients with failed versus successful reperfusion. Within the group of patients with failed reperfusion, primary angioplasty was not successful in 52% and in 48% a late re-occlusion occurred during hospital stay. Left ventricular ejection fraction did not differ significantly between patients in whom primary angioplasty was not successful versus patients who suffered from late re-occlusion (39.0 ± 12.6 versus 40.5 ± 11.5, p=0.60). Patients in whom primary angioplasty was not successful had the highest initial (in-hospital) mortality rate and this trend remained stable during follow-up.