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In this thesis several aspects of the treatment of ST-segment elevation myocardial infarction (STEMI) by primary angioplasty have been analyzed. An overview of the literature concerning the role of primary angioplasty in the management of STEMI is given in Chapter 1.

In Chapter 2.1 we demonstrated the prognostic implication of time-to-treatment in patients with STEMI treated with primary angioplasty. A total of 103 patients (5.8%) had died at 1 year. Symptom-onset-to-balloon time was significantly associated with the rate of postprocedural TIMI 3 flow ($p = 0.012$), myocardial blush grade ($p = 0.033$) and 1-year mortality ($p = 0.02$). A stronger linear association between symptom-onset-to-balloon time and 1-year mortality was observed in non low-risk patients ($p = 0.006$) and those with preprocedural TIMI flow 0-1 ($p = 0.013$). No relationship was found between door-to-balloon time and mortality. At multivariate analysis, a symptom-onset-to-balloon time > 4 hours was identified as an independent predictor of 1-year mortality ($p < 0.05$).

In Chapter 2.2 the relationship between ischemic time and 1-year mortality was assessed as continuous function, and plotted using a quadratic regression model. The Cox proportional-hazards regression model was used to calculate relative risks (for each 30-minute), adjusted for baseline characteristics related to ischemic time. Variables related to time-to-treatment were age > 70 ($p < 0.0001$), female gender ($p = 0.004$), diabetes ($p = 0.002$) and previous revascularization ($p = 0.035$). Patients with successful reperfusion had a significantly shorter ischemic time ($p = 0.006$). A total of 103 patients (5.8%) had died at 1-year follow-up. Time-
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to-treatment was significantly related to 1-year mortality (p < 0.001). After adjustment for age, gender, diabetes and previous revascularization, each 30-minute delay was associated with a relative risk [95% CI] for 1-year mortality of 1.075 [1.008-1.15] (p = 0.041).

In Chapter 2.3 we analyzed the relationship between time-to-treatment, the extent of myocardial perfusion and myocardial damage. We found a significant relationship between increasing time-to-treatment, reduced myocardial blush and ST-segment resolution, and larger infarct size. These data were confirmed in the analysis restricted to patients with postprocedural TIMI 3 flow.

In Chapter 3.1 we assessed the outcome of patients treated with primary angioplasty for acute left main occlusion. Our study confirmed the high in-hospital mortality (56%) in these patients. However, in-hospital survivors showed a good long-term outcome. At multivariate analysis, poor or absent angiographic collateral circulation, postprocedural TIMI flow 0-2 and cardiogenic shock at presentation were independent predictors of in-hospital mortality.

In Chapter 3.2 we reported on the prognostic role of preprocedural TIMI flow on 1-year mortality. Poor preprocedural epicardial flow was associated with less procedural success, impaired myocardial perfusion and larger enzymatic infarct size, with a significant impact on mortality. However, when patients were stratified according to their risk profile, preprocedural TIMI 3 flow emerged as an independent predictor of 1-year mortality only in high-risk patients.
In Chapter 3.3 we found that the higher the Killip class at presentation, the more the myocardial perfusion was impaired. In fact the rate of myocardial blush grade 2-3 changed from 81.1% in patients in Killip 1 to 47.6% in patients in Killip class IV (p < 0.0001). This was partially explained by a higher rate of distal embolization observed in patients with advanced Killip class. The observed impaired perfusion may explain the poor outcome observed in patients with advanced Killip class. At multivariate analysis restricted to patients with heart failure at presentation, MBG 0-1 was found to be an independent predictor of 1-year mortality (RR [95% CI] = 2.92 [1.37-6.23], p = 0.005).

In Chapter 3.4 we set up the Zwolle risk score for prognostic stratification of patients with STEMI treated with primary angioplasty. Variables included in our score were age, infarct location, Killip class at presentation, number of diseased vessels, time-to-treatment and postprocedural TIMI flow, all independent predictors of 30-day mortality in our population. Our score was able to identify a large category of unselected patients (score ≤ 3) at a very low risk for mortality (0.1% at 2 days, and 0.2% between 3 and 10 days), who could potentially be discharged early from the hospital (at 48 hours after the procedure). Since the eligibility for early discharge was identified in 83.4% of these patients (61.2% of the total population), this would have resulted in a significant reduction of in-hospital costs. The incremental cost-effectiveness ratio for late discharge was estimated at € 1,949.33. This means that a conventional discharge policy (prolonged 24 hours of hospitalization) in low-risk patients would save one life per 1097 patients, with additional costs estimated at € 194,933.33, in comparison with an early discharge policy.
In Chapter 4.1 we investigated the role of routine stenting in the real world of primary angioplasty. We randomized before angiography a total of 1683 consecutive patients to stent or balloon angioplasty. At 1-year follow-up, no benefits were observed with stenting in terms of death, reinfarction and target-vessel revascularization. Thus, until more information becomes available on the safety and advantages of drug-eluting stent in this high-risk subset of patients, our study strongly suggests that a policy of bail-out stenting is still the best option in primary angioplasty.

In Chapter 4.2 we performed a comprehensive meta-analysis of all randomized trials conducted on abciximab administration as adjunct to reperfusion therapies for STEMI. Fifteen studies were identified, involving 13,140 patients randomized to abciximab, and 14,910 to control. When compared to the control group, abciximab was associated with a significant reduction in long-term mortality in patients undergoing primary angioplasty (4.4% vs 6.1%, p=0.015), but not in those treated with thrombolysis (8.6% vs 8.3%, p=NS). Furthermore, abciximab was associated with a significant reduction in 30-day reinfarction, both in primary angioplasty (1.1% vs 1.9%, p=0.026) and in thrombolysis trials (2.3% vs 3.6%, p<0.0001), and in all trials combined (2.1% vs 3.3%, p<0.0001). Abciximab did not result in an increased risk of intracranial bleeding (0.65% vs 0.64%, p=NS), but was associated with an increased risk of other major bleeding complications when combined with thrombolysis (5.4% vs 3.1%, p<0.0001).
Future research and directions in the treatment of STEMI

Even though the reduction in mortality obtained by primary angioplasty in comparison with thrombolysis is significant, several aspects have still to be improved.

1) Primary angioplasty can guarantee restoration of antegrade flow, but can not avoid myocardial necrosis. Thus the aim in the treatment of myocardial infarction would be to improve the rate of abortion of MI and to reduce the extension of myocardial necrosis, by early drug administration at the time of diagnosis or during transportation to tertiary centers for primary angioplasty.

2) Despite the high rate of TIMI 3 flow that can be achieved with mechanical reperfusion, myocardial perfusion is suboptimal in a substantial percent of patients. Thus, all efforts should be aimed at reducing ischemia-reperfusion damage and protecting microcirculation from distal embolization. This can potentially be achieved by the additional use of strong antiplatelet therapy (glycoprotein IIb-IIIa inhibitors) (1-8). New mechanical devices have been introduced in the last years (transcatheter extraction atherectomy -TEC-, the Posis Angioget®, the PercuSurge Guardwire System®, Rescue Catheter®, distal protection devices), but so far only few and mainly non-randomized data are available in patients with acute myocardial infarction. Kaplan et al. (9) reported their experience in 100 patients with AMI treated with TEC. No reflow was observed in 6% of patients, with an in-hospital mortality of 5% and total six-month mortality of 10%. The safety and feasibility of TEC in acute myocardial infarction have yet to be proven in the TOPIT (TEC or PTCA in Thrombus) multicenter trial (10), in which 550 patients with acute coronary syndromes (including STEMI) will be randomised to balloon...
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angioplasty or TEC. Recently published data from two small randomized trials, showed that thrombus aspiration is associated with a significantly improved postprocedural myocardial perfusion (11-12). However, the skills and costs required for these techniques, the loss of time to achieve adequate flow through the infarct-related artery due to technical preparations and the risk of not reaching the culprit lesion are major limitations.

3) Experimental models have shown that hypothermia improves myocardial perfusion in the setting of myocardial infarction (13). It can easily be achieved by devices that can rapidly be inserted in central veins via percutaneous techniques and achieve core hypothermia. A small randomized trial has shown the feasibility of this technique in humans. Hypothermia (32-34°C) was associated with a smaller infarct size and better outcome, even though the differences were not statistically significant (14). Future larger randomized trials must be conducted in order to evaluate its benefits, particularly in high-risk conditions like cardiogenic shock.

4) It has been shown, in fact, that myocardium can be regenerated from hematopoietic or mesenchymal (stromal) stem cells derived from the bone marrow (15-17). Early studies in humans with direct intracoronary infusion or injection of bone marrow-derived cells have been shown to be feasible and associated with improved function (18-19). The complementary action of myocardial reperfusion and myocardial regeneration seems very attractive and exciting. In fact, even though advanced and well-run regional project will hopefully contribute in the future to significantly shorten time-to-treatment in STEMI, we will be unable to find ways to get all patients early enough for maximal myocardial salvage (abortion of STEMI).
5) The results in patients with advanced Killip class at presentation, particularly in those with cardiogenic shock, remain unsatisfactory. Since the proven advantages of mechanical revascularization in this subset of patients (20), these patients should be pretreated medically (IIb-IIIa inhibitors or thrombolytics) in order to quickly achieve optimal recanalization, and categorically referred to angioplasty centers for mechanical revascularization. Surprisingly, data from the GRACE Registry have shown that in clinical practice these patients are less likely to receive any reperfusion therapy (21). Future randomized trials should focus on the additional use of left ventricular assist device in these patients (22).

6) Finally, it remains a question what should be the way to evaluate the efficacy of additional therapeutic strategies in mechanical reperfusion. In fact, since the very low-mortality achieved with mechanical reperfusion in the treatment of STEMI, particularly in high-volume, experienced centers, it is quite unlikely to further improve this endpoint. By the use of infarct size, smaller randomized trials can be conducted successfully, whereas regarding mortality, high-risk patients should be selected, instead of conducting mega-trials enrolling low and medium risk patients.
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Final comments and recommendations

The main goal in the treatment of STEMI is to open the infarct-related artery as good and as quick as possible. Still unclear is whether primary angioplasty should be the preferred therapeutic strategy in all patients or should be limited to higher-risk patients. Since the safety of transferring patients to tertiary centers with primary angioplasty facilities has been demonstrated, the number of patients treated with mechanical revascularization will hopefully increase. All efforts should be attempted in order to shorten ischemic time. If we define our goal for the future as effective myocardial reperfusion within 2 hours after symptoms onset in all patients with acute myocardial infarction, it is clear that we still have a long way to go.

Organized projects with regional referring specialized centers, earlier diagnosis by 12-lead electrocardiography at home, or in the ambulance, well-trained nurses involved in the transportation and additional adequate pharmacological pretreatment of patients directly from home to the cath-lab, are needed to achieve this goal. Prehospital diagnosis of STEMI allows preparations before patient’s arrival and will result in an important improvement in the delivery of reperfusion therapy. In patients treated with primary angioplasty, it results in a 30-40 minutes shorter time to first balloon inflation (23), and where angioplasty is not available, it allows the pre-hospital and more rapid administration of thrombolytic therapy.

Until more information becomes available, we would like to propose the following percutaneous coronary intervention (PCI) strategy for STEMI (Figure 1). Patients with STEMI, admitted to local hospitals, should be classified into low-risk and high-risk patients, according to the clinical and ECG findings at admission. Intravenous thrombolysis should
be given immediately to low-risk patients, followed by randomization to conservative or invasive strategy, as our previous trial (24) has shown that primary PCI in these low-risk patients has no additional benefits on mortality. However, to address whether the incidence of reinfarction could be reduced by adjunctive PCI procedure, patients allocated to invasive strategy should be transferred for PCI or stenting, on semi-elective basis, for instance on the following day or before hospital discharge, whereas, all high-risk patients should be transferred immediately for primary PCI or stenting, with or without pre-treatment with adjunctive pharmacologic agent.

**Figure 1**  
**PCI Strategy for Acute MI**

- **Acute MI**  
  - **Local Hospitals**
  - **Low risk**  
    - Thrombolysis
    - Randomization  
      - Conservative
      - Invasive  
      - PCI/Stent  
      - Semi-elective
  - **High risk**  
    - Randomization  
      - Adjunctive Therapy
      - Placebo  
      - Primary PCI/Stent
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References


