Introduction
The management of patients with ST-segment elevation myocardial infarction (STEMI) has considerably improved over the past decades, with many factors involved in the reduction of mortality, including earlier diagnosis and treatment of the acute event, improved management of complications such as recurrent ischemia and heart failure, and general availability of pharmacologic therapies such as aspirin, beta-blockers, ACE-inhibitors and IIb-IIIa inhibitors (1). Most attention, however, has been focused on early restoration of antegrade flow in the infarct-related artery. The two methods to achieve this goal are thrombolytic therapy and immediate coronary angiography followed by primary angioplasty if appropriate (1).

Angioplasty for STEMI was first described as a rescue therapy in case of failed intracoronary thrombolysis, and was studied extensively as adjunctive therapy, performed immediately (within hours), early (within 1-2 days), late (after 2 days), or electively for residual ischemia and/or post-infarction angina, after intravenous thrombolytic therapy. Primary angioplasty, without the use of thrombolytic therapy, was described in 1983 (2). It can be applied as an alternative reperfusion therapy in candidates for thrombolytic therapy, and is the only reperfusion option in many patients with STEMI ineligible for thrombolytic therapy.

Advantages of acute coronary angiography

The safety and diagnostic potential of coronary angiography during the early hours of acute myocardial infarction has been reported more than twenty years ago (3). In addition to being a prelude to angioplasty, acute coronary angiography offers several advantages. Patient management after the acute event is facilitated by the knowledge of the coronary anatomy. It allows identification of a large subgroup of patients who can be discharged early (2-3 days) after the acute event (4), as well
as 5-10% of patients who have an indication for elective coronary artery bypass grafting on anatomical grounds, such as left main disease and/or severe triple vessel disease (5). Some patients presenting with symptoms and signs of acute myocardial infarction should not undergo reperfusion therapy and this can only be ascertained by angiography. For instance, some patients with spontaneous reperfusion of a small infarct-related coronary artery, or patients with a cardiac event without thrombotic occlusion of a coronary artery or non-cardiac condition, that may mimic acute myocardial infarction. Finally, patients with aortic dissection extending into the aortic root or with a coronary anatomy unsuitable for angioplasty can be considered for acute surgical intervention. In other words, the major advantage of primary angioplasty strategy for STEMI, is the fact that early therapeutic strategy could be made according to coronary anatomy and clinical situation, just within a few hours after STEMI, as all of these patients will undergo immediate angiography.

**Primary angioplasty in patients eligible for thrombolytic therapy.**

Primary coronary angioplasty, when performed by experienced operators, restores TIMI 3 flow in over 90% of patients, and the reocclusion rate is very low. This compares favourably with 50-70% of patients who achieve normal flow after thrombolysis (Figure 1) (6). These effects on myocardial flow explain the better outcome of patients with STEMI treated by primary angioplasty when compared with thrombolysis.
Figure 1. Graphic display of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow immediately after randomization: comparison between the angiographic results from the Zwolle and the GUSTO trials (6). The data on TIMI flow in the GUSTO trial were gathered from different patients, who were randomly assigned to angiography at different time intervals after start of therapy. GUSTO indicates the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary artery study; tPA indicates tissue plasminogen activator; SK indicates streptokinase. Reprinted with permission from the Elsevier Science Ltd (de Boer MJ. et al. Eur Heart J 1995; 16: 1347-55).

A recent overview of 23 randomized comparisons, involving a total of 7739 patients (7), has shown that compared to thrombolysis, primary angioplasty results in a significantly lower short-term mortality (7% vs 9%), non-fatal reinfarction (3% versus 7%) and stroke (1% vs 2%). Long-term follow-up data of the Zwolle trial on 395 patients randomly assigned to angioplasty or intravenous streptokinase (8), showed at 5±2 years follow-up that primary angioplasty was associated with a significant reduction in mortality (13% vs 24%) (Figure 2), and nonfatal reinfarction (6% and 22%). Total medical charges per patient were similar in the angioplasty group (U.S. $ 16.090) and in the streptokinase group (U.S. $ 16.813). That costs are not higher, and in fact even may be lower for primary angioplasty than for thrombolysis, has been shown in several
settings (9). Given the superior safety and efficacy of primary angioplasty, this treatment is now preferred when logistics allow this approach. The results of primary angioplasty are in part dependent on the setting in which it is performed, and therefore the results from various hospitals may differ considerably. This is a consequence of the fundamental difference between a procedure and pharmacotherapy (10), and has been shown for angioplasty for stable and unstable angina. Quality control, outcome monitoring and adherence to guidelines and recommendations of task forces of the American College of Cardiology/American Heart Association are therefore of crucial importance (1).

**Primary PTCA vs Streptokinase for Acute MI**

**Zwolle Randomized Trial**

*Figure 2.* This figure shows the Kaplan-Meier survival curves in the Zwolle trial (15), comparing primary angioplasty with streptokinase, during a follow-up period of 7 years. In patients allocated to angioplasty, the significant reduction in mortality rate, observed before hospital discharge, is even more pronounced at 7 years follow-up, when compared to Streptokinase. Reprinted with permission from the Massachusetts Medical Society (Zijlstra F. et al. NEJM 1999; 341: 1413-9).
Role of time-to-treatment in primary angioplasty

The aim of a successful therapeutic strategy in STEMI is to restore myocardial flow as soon as possible from symptom onset. As demonstrated in animal models (11-13), the duration of coronary occlusion is a main determinant of infarct size. Therefore, late reperfusion is expected to result in less myocardial salvage and, conceivably, in a higher mortality rate, in comparison with early reperfusion, even when optimal mechanical reperfusion would be applied. Although the prognostic role of time to therapy has clearly been demonstrated in patients with STEMI treated by thrombolysis (14-16), there is still doubt with regard to its role in patients treated with primary angioplasty (16-19).

Brodie et al (17) observed a better outcome among patients undergoing primary angioplasty within 2 hours from symptom onset, whereas a relatively stable mortality rate was observed between 2 to 12 hours. These data were confirmed by Cannon et al. (12) who, in a cohort of 27080 patients undergoing primary angioplasty, found only door-to-balloon time but not symptom-onset-to-balloon time to be associated with mortality. In consistence with these data, Zijlstra et al (16), in a recent pooled-analysis of several randomized trials comparing primary angioplasty and thrombolysis, found a direct relationship between time from symptom onset to treatment only in patients treated by thrombolysis, but not by primary angioplasty. In a recent report, Antoniucci et al (20) found, in a population of 1332 patients undergoing primary angioplasty, a relationship between time-delay and mortality only in high-risk patients.
Risk stratification in primary angioplasty

The prognosis of patients with STEMI has considerably improved over the past decades. However, the outcome remains poor in subsets of patients, mainly in those with cardiogenic shock and acute left main occlusion. Although several factors have have been identified as determinants of outcome in patients with STEMI treated with primary angioplasty, so far no score has been set up for prognostic stratification of these patients. Since several angiographic parameters have been identified as main and independent predictors of mortality in patients treated with mechanical reperfusion, prognostic scores obtained by patients treated with thrombolysis may be inaccurate when applied to these patients. The availability of risk scores would be useful to identify low-risk patients, who could be managed with early discharge with potential implications in terms of cost reduction in the treatment of STEMI.

Strategies in primary angioplasty:

A) Coronary Stenting

For several years, stenting has been avoided in the setting of STEMI, because the implantation of a metallic device, within a thrombotic environment, such as that of a plaque disruption resulting in myocardial infarction, would be likely to precipitate stent thrombosis with resultant vessel occlusion. Vigorous anti-coagulation, necessary to avoid stent thrombosis, exposed the patient to the risk of major bleeding and vascular complications (21). All these considerations had led most investigators to restrict stenting in STEMI to bail-out situations. However, improvement of stent deployment techniques and advances in antiplatelet therapy (22-25) have shown that stenting in the setting of STEMI is safe and effective (26-29). Our randomized trial on long-term
follow-up (2 years) has shown that stenting is a safe and cost-effective strategy for STEMI (28). These findings have been confirmed by other randomized trials (26-36).

A recent meta-analysis reported data involving a total of 4120 patients randomized to stent (n = 2050) or balloon angioplasty (n = 2070) in 9 trials (37). Primary stenting significantly reduced the composite incidence of adverse cardiac events, mainly due to a reduction in the need for TVR (9.2% vs 18.7%, p < 0.001), without statistically significant difference in mortality (3.7 vs 3.6%, p = NS), and reinfarction (2.1% vs 2.9%, p = NS) (Figure 3).

**Pooled data: PTCA vs STENT in acute MI**

![Bar graphs show a pooled data analysis of the 6-12 months clinical outcome of patients with acute myocardial infarction (MI) randomized to balloon angioplasty or stenting. Primary stenting has been shown to be superior to balloon angioplasty, and this is mainly due to a significant reduction in restenosis after stenting, when compared to angioplasty.](image)

**Figure 3.**
Thus, despite the demonstrated superiority of stenting in comparison with balloon angioplasty in patients with STEMI, stenting does not result in a reduction in reinfarction and death. However, caution should be taken in extending these data to the “real world”, as currently available data have been obtained from selected patients, who are in relatively stable hemodynamic condition, and in whom the infarct-related artery is technically and anatomically considered suitable for stenting, performed by operators experienced with acute infarct intervention.

B) Glycoprotein IIb/IIIa inhibitors

The aim of a reperfusion therapy is to restore both epicardial (macrocirculation) and myocardial (microcirculation) flow. The strategy of incorporating IIb-IIIa inhibitors in primary angioplasty, aiming at a more effective initial reperfusion and a better sustained antithrombotic milieu, seems very attractive, particularly in association with stenting. In fact, the PAMI trial reported a paradoxical higher mortality in stented patients, attributed to an observed impaired flow, in comparison with balloon angioplasty (38). Furthermore, since the feasibility of long-distance transportation to PTCA centers showed by the PRAGUE (39) and DANAMI trials (40), pretreatment with IIb-IIIa inhibitors may determine early restoration of antegrade flow, with potential benefits in terms of infarct size and outcome, mainly in high-risk patients. Although the benefits of glycoprotein IIb-IIIa inhibitors have been shown in the setting of acute coronary syndromes (41), it is less well established in the setting of STEMI.
THIS THESIS

This thesis addresses multiple and diverse aspects of daily clinical practice in a setting where all patients presenting with acute myocardial infarction are treated with primary angioplasty. **Part 2** is focused on the prognostic role of time-delay in primary angioplasty. **Chapter 2** addresses the prognostic role of symptom-onset-to-balloon time and door-to-balloon time, whereas **Chapter 3** is focused on the relationship between time-to-treatment and mortality as continuous function. **Chapter 4** addresses the impact of time-to-treatment on myocardial perfusion.

**Part 3** addresses prognostic determinants in primary angioplasty. In **Chapter 5** the Zwolle experience and the determinants of long-term outcome in primary angioplasty for acute left main coronary occlusion are described. **Chapter 6** addresses the prognostic role of preprocedural TIMI flow, and **Chapter 7** the prognostic role of myocardial perfusion in patients with advanced Killip class at presentation. **Chapter 8** is focused on prognostic stratification after primary angioplasty.

**Part 4** describes the role of stenting and abciximab as adjunctive to primary angioplasty. **Chapter 9** addresses the role of routine stenting in primary angioplasty, with all patients randomized before angiography, thus without any exclusion criteria. In fact, all randomized trials so far conducted on stenting have included selected patients, after initial angiography. **Chapter 10** reports a comprehensive meta-analysis of all randomized trials on abciximab administration as adjunct to thrombolysis or primary angioplasty in patients with STEMI.
REFERENCES


