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## Primary PCI for acute myocardial infarction

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# 1

## General Introduction



## General Introduction

Acute myocardial infarction is generally due to the sudden obstruction of a coronary artery by the formation of a thrombus at the site of a fissured or ruptured atherosclerotic plaque (1,2). Reperfusion therapy aims at restoration of antegrade flow in the occluded infarct-related artery (3). This reduces infarct size and improves clinical outcome (4-6).

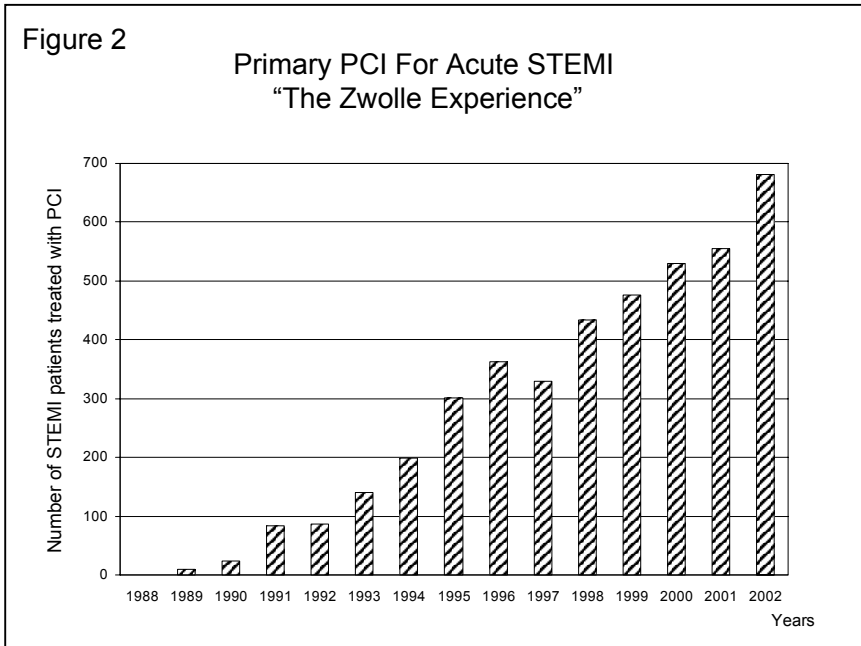
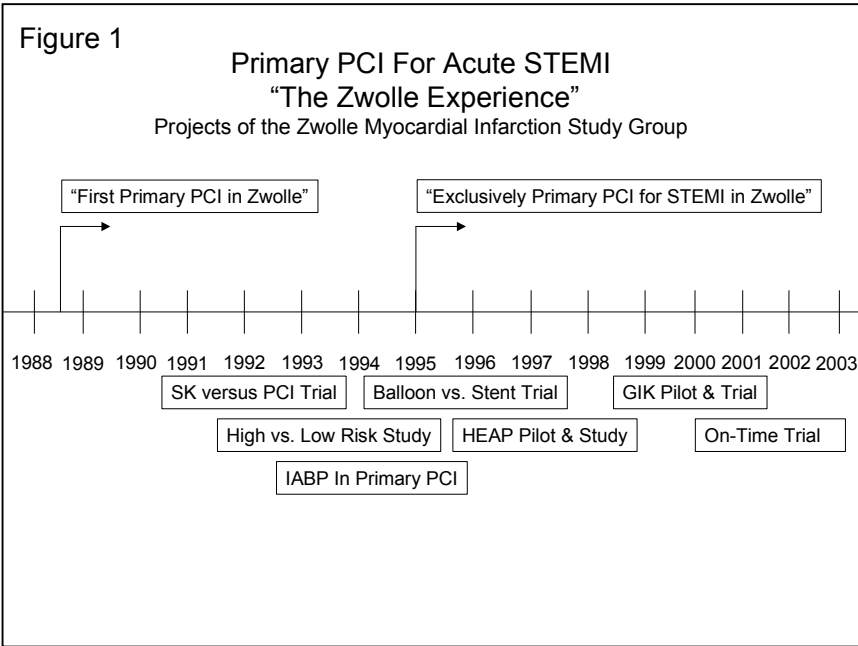
In the late seventies of the past century, Andreas Gruntzig and Peter Rentrop first described new therapies were developed that can be used to achieve reperfusion in patients with acute myocardial infarction: thrombolytic treatment and percutaneous coronary intervention (7-9). Reperfusion therapy was first introduced using thrombolytic agents, initially administered intracoronary and later intravenously. These agents were able to reduce in hospital mortality of acute myocardial infarction from approximately 15-20% to 10% (10). Furthermore, this treatment can be administered in all hospitals and even in a pre-hospital setting. 60 to 90 minutes after administration, it leads to a reopening of the infarct related artery in approximately 50-60% of all cases. Even the most modern thrombolytic regimen leads to a sustained patency of <70% and 30% of these patients will have reocclusion during the months after the index myocardial infarction (11). PCI for acute myocardial infarction was first reported by Hartzler (12) and later by O'Neill (13) comparing intracoronary thrombolysis and balloon angioplasty. However, in the early nineties, with percutaneous coronary intervention (PCI), higher rates of successful reperfusion were possible. PCI achieved a sustained patency of the infarct related artery of >90% with a significantly lower incidence of reinfarctions. This led to two sides in the world of cardiology at the end of the past century; protagonists and antagonists of mechanical reperfusion by PCI versus pharmacological reperfusion in the treatment of acute ST segment elevation myocardial infarction. Protagonists of primary PCI were supposed not to live in the "real world" (14-19). Growing evidence has revealed primary PCI as the most effective treatment for acute myocardial infarction, even if a patient has to be transported to another hospital to undergo this treatment (20-23).

“Time is muscle”. However, the value of primary PCI for acute myocardial infarction extends beyond the therapeutic window for thrombolysis. Thrombolysis has the most benefit when administered within the first 2 hours after symptoms onset, but may still be beneficial when administered within 12-18 hours after symptoms onset (24). Primary PCI has benefit over the first 6 hours after symptoms onset and in daily clinical practice 12-24 hours between onset of chest pain and PCI is accepted (25-28). While primary PCI in the late eighties only comprised balloon angioplasty, resulting in better survival when compared to thrombolytic therapy, the introduction of intracoronary stents has improved clinical outcome compared to balloon angioplasty only (29-35). Although mechanical reperfusion therapy appears to be superior to pharmacological treatment, we must bear in mind that the occlusion is almost always due to a thrombus (superimposed on a fissured plaque). Therefore, it may be of interest to develop additional therapies to reduce the thrombus load and/or embolization of the thrombus and/or debris of the plaque. Additional pharmacological treatment has been proposed and especially the introduction of glycoprotein IIb-IIIa receptor antagonists may improve myocardial reperfusion at the cellular level, since the glycoprotein IIb-IIIa receptor is the final common pathway for platelet aggregation. However, until now only abciximab has proven to be effective and offer benefit in primary PCI; when administered, higher rates of TIMI 3 before and after PCI are achieved and with a lower incidence of subacute thrombosis. Subsequently, this leads to improved left ventricular function and better clinical outcome (35-48). Although intracoronary stenting has benefit over balloon angioplasty only, early stent thrombosis was a major issue at the beginning of the introduction of intracoronary stents. Nowadays, additional (pre and post) treatment with thienopyridines (ticlopidine and clopidogrel) is recommended when intracoronary stents are used (48-55) and the incidence of stent thrombosis, although still of clinical importance, has declined considerably and has become rare. Glycoprotein IIb-IIIa receptor antagonists and thienopyridines are available with their more specific platelet inhibitory effects but the coagulation cascade also needs to be addressed in acute ST segment myocardial infarction. Patients undergoing primary PCI are generally be pretreated with unfractionated

heparin and substitution with low molecular weight heparin appears to be promising as are new direct thrombin inhibitors (56-68). With the use of pharmacological agents both thrombus formation and embolization are reduced. However, it is conceivable that additional mechanical invasive strategies may also offer benefit in protecting from distal embolization from thrombus and/or atherosclerotic debris during primary PCI. Although thrombectomy and distal protection devices theoretically may lead to less distal embolization, the efficacy needs to be investigated in patients treated with primary PCI for acute myocardial infarction (69-74), as in the currently ongoing Emerald trial (PercuSurge). Distal embolization is considered to play, at least partly, a role in the occurrence of the no-reflow phenomenon (this thesis). Several pharmacological interventions (nitroglycerine, nitroprusside, papavarine, verapamil and adenosine) have been proposed when there is angiographic evidence of reduced myocardial reperfusion (no-reflow), but evidence from randomized trial is lacking to administer these agents to prevent or treat no-reflow (75-83). Nevertheless, although there is limited evidence that pharmacological treatment may affect the no-reflow phenomenon, there is some evidence that direct stenting (when feasible) may reduce the occurrence of no-reflow (84). This introduction emphasizes the benefit and describes some issues and progresses made in the field of primary PCI for acute ST segment myocardial infarction. However, all evidence that reveals superiority of primary PCI over pharmacological treatment only has come from invasive cardiology centers with a large experience in PCI procedures for many years. Therefore, it must be remembered that primary PCI should be performed in high volume (>400 cases per year) centers with fully equipped interventional laboratories and experienced staff and nurses, all available 24 hours a day, 7 days a week (85-88).

### **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 PCI for many years (Figure 1 and 2).



The second chapter addresses the extended data of long-term outcome in “The Zwolle Trial” (17). This randomized trial compared clinical outcome in patients with acute myocardial infarction treated with a thrombolytic agent or with PCI. The thrombolytic agent was streptokinase and PCI was performed in the pre-stent era and before the introduction of glycoprotein IIb-IIIa receptor antagonists. This second chapter is the background of treatment of acute myocardial infarction in the Isala Klinieken, De Weezenlanden Hospital; all patients presenting with acute ST segment elevation myocardial infarction are treated with primary PCI.

The third chapter addresses patients with ventricular fibrillation before arrival at the hospital. In-hospital mortality in acute myocardial patients over the years has been reduced from approximately 30% to 5-10%. However, out-of-hospital mortality in the early phase of acute myocardial infarction has remained the same and accounts for a large proportion of mortality in acute myocardial infarction (89). Sudden cardiac death is supposed to account for approximately 25-30% of total mortality in patients with acute myocardial infarction (90) This chapter is divided in 3 paragraphs. The first paragraph addresses clinical and angiographic features in patients with (at least early survival of) out-of-hospital ventricular fibrillation in a case control study. The second paragraph addresses the effect of the clinical surrogate of preconditioning on the occurrence of out-of-hospital ventricular fibrillation in the same case control study patient cohort of the first paragraph. In the last paragraph of this chapter, clinical features are studied in patients with ventricular fibrillation before primary PCI and during primary PCI, with the exclusion of patients with out-of-hospital ventricular fibrillation. This retrospective study in a large number of consecutive patients had two goals: firstly to confirm the conclusion of the case control studies (3.1, 3.2) and secondly to find new clinical features associated with early ventricular fibrillation before reperfusion therapy.

The fourth chapter contains 5 paragraphs, addressing angiographic features of patients treated with primary PCI. The objective of reperfusion therapy is not merely to restore flow in the epicardial artery, but to reperfuse the myocardium at risk (3). The “no-reflow” phenomenon, characterized by inadequate flow at tissue level despite a reopened epicardial coronary artery, was first described in



animals(91) and later in man, by contrast echocardiography (92), Doppler flow measurements (93), nuclear techniques (94), and magnetic resonance imaging (95). The “no-reflow” may occur due to, amongst others causes, plugging or embolization by thrombotic or atheromateous debris (96).

The incidence and relative clinical importance of these various mechanisms are unknown. Distal embolization may be in particular a complication of treatment with fibrinolytic agents or primary PCI during myocardial infarction (97,98). In the first paragraph, the relation between angiographic evidence of distal embolization and mortality is studied in the patients who were randomised to primary PCI in the “Zwolle Trial” with a 5 year clinical follow-up. Since distal embolization is associated with failed angioplasty, we studied the determinants and the effect of angiographic evidence of distal embolization in a large cohort of patients with successful PCI for acute ST segment elevation myocardial infarction in the following paragraph (3.2). In the third paragraph, the effect of angiographic evidence of distal embolization on the acute angiogram before PCI on short-term mortality and success of primary PCI was studied. In the fourth paragraph, the angiographic variables that were independently associated with reduced left ventricular function were used in an angiographic score model to assess short term mortality. In this score we also used the myocardial blush grade that was first described by van 't Hof et al. (99) in patients treated with PCI. In the last paragraph (3.5) we studied the importance of myocardial blush grade in a large consecutive group of patients with successful angiographic primary PCI, to study the hypothesis that angiographic success should not only include TIMI 3 flow after primary PCI but also comprise optimal myocardial blush grade.

In the fifth chapter, high-and low risk patients were stratified using only two parameters, available at presentation, in patients with acute myocardial infarction treated with primary PCI. These parameters were Killip class and age at presentation.

In the sixth and final chapter we studied the outcome in patients, treated during routine duty hours and off-hours. The conclusions of this study are important as primary PCI seems to be the treatment of choice for acute ST segment elevation

myocardial infarction and this therapy should be available twenty-four hours a day and seven days a week.

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