Novel insights in reperfusion therapy and stent thrombosis in the drug eluting stent era

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Chapter 4

Aborted myocardial infarction in patients undergoing primary PCI: long term outcomes

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ABSTRACT

Aims: To assess the prognosis of patients with aborted myocardial infarction (MI) after primary percutaneous coronary intervention (PPCI).

Methods and results: 179 consecutive patients with ST-segment elevation MI (STEMI) were enrolled within a fixed protocol for PPCI (Leiden MISSION! project), 90 patients received abciximab bolus in the hospital (in-hospital group) and 89 patients received abciximab bolus in the ambulance (pre-hospital group). 32 patients (18%) fulfilled the criteria for an aborted MI. Left ventricular ejection fraction at 3 months measured with myocardial scintigraphy was higher in the aborted MI group compared to the established MI group (62.3 vs. 55.3, p = 0.001). The cumulative incidence of mortality, recurrent MI, revascularization procedures and heart failure was lower in the aborted MI group than in the established MI group (16% vs. 36%, p = 0.02).

Conclusion: In patients with STEMI treated with PPCI, the incidence of aborted MI was 18%. Patients with aborted MI had better left ventricular function at 3 months and superior prognosis than those with established MI.

INTRODUCTION

Effective and rapid reperfusion is the most important goal in the treatment of patients with acute ST-segment elevation myocardial infarction (STEMI).[1,2] Primary percutaneous coronary intervention (PPCI) with adjunctive abciximab therapy is the preferred strategy for reperfusion in the treatment of STEMI, because it has been shown to produce superior clinical outcomes as compared with fibrinolytic therapy.[3-6]

The ultimate objective of reperfusion therapy is early and complete recanalization of the infarct-related artery (IRA) in order to limits or even prevents clinically detectable myocardial necrosis, resulting in aborted myocardial infarction (MI).[7]

The term aborted infarction has been used to describe patients submitted to fibrinolysis who had minimal increase in cardiac enzymes together with a favourable evolution of the electrocardiographic modifications typical for acute STEMI.[7-13] The PPCI associated rate of aborted MI is still unknown; even a standardized definition of aborted MI after PPCI is lacking.

In an earlier study using prehospital abciximab facilitated PPCI, we found a threefold higher incidence of aborted myocardial infarction in the prehospital group. Our database of the prehospital treated patients has been extended with 1 year clinical follow-up.

In the present report we present the 3 month left ventricular function and the one year clinical follow up for patients with aborted MI.

METHODS

This is a single center prospective study. All patients were treated according to the institutional STEMI protocol (MISSION!) implemented at Leiden University Medical Center (LUMC),[14] which included standardized pre-hospital, in-hospital and outpatient clinical framework for decision making and treatment. Our hospital provides a round-the-clock service of PPCI with 6 trained PCI physicians and dedicated nurses.

Main results of MISSION! Study are published elsewhere.[14] For this sub-study patients were eligible if STEMI symptoms started < 9 hours before the procedure, the electrocardiogram (ECG) demonstrated STEMI (ST-segment elevation ≥ 0.2 mV in ≥ 2 contiguous leads in V1 through V3 or ≥ 0.1 mV in other leads), and received abciximab prior to PPCI. Exclusion criteria were left bundle branch block, recent surgery, recent stroke, recent spinal trauma, hemorrhagic diatheses, severe liver or kidney failure and known contraindications for therapy with abciximab, aspirin, clopidogrel or heparin.

Halfway during the study (December 2006), a new strategy for early abciximab administration starting in the ambulance was adopted within the MISSION! protocol (Figure 1). 179 consecutive patients, who fulfilled the inclusion and exclusion criteria for this sub-study, were enrolled: 90 patients (**the late group**), in whom abciximab was initiated in the coronary care unit or catheterization laboratory before the intervention; Then 89 patients (**the early group**), in whom abciximab bolus was given in the ambulance before transport to the catheterization laboratory. No informed consent is required, since the MISSION! protocol is the standard STEMI care regimen in the region Hollands-Midden, The Netherlands.

All patients had a high quality 12-lead ECG recorded at presentation as well as within 90 min after PPCI. ECGs were recorded at the patient's home by trained paramedics with Lifepak-12 Defibrillator/Monitor Series (Medtronic, Redmond, WA,USA), If the ECG fulfills the positive identification criteria of the prehospital MISSION! standard order form, the ECG was transmitted directly as a fax to the computer network of our hospital (Lifenet RS system; Medtronic) and assessed by the attending cardiologist who determined the patient's eligibility for PPCI, based on predefined criteria.

ST segment elevation was measured manually 20 ms after the end of the QRS complex (the J point) using a hand-held caliper. The sum of ST-segment elevation in leads V1 to V6, I, and aVL was added to the sum of ST-segment depression in leads II, III, and aVF for anterior MI. For inferior MI, the sum of ST-segment elevation in leads II, III, and aVF (and I, aVL, V5, and V6, if present) were added to the sum of ST-segment depression in leads V1 to V4.[13] All ECGs were collected and analyzed by an investigator blinded to the assigned treatment. Total ST-segment deviation at inclusion was compared to that taken within 90 minutes after PPCI. ST-segment resolution ≥ 50% of the initial ST-segment deviation was calculated.

All patients received abciximab (Centocor, Leiden, The Netherlands) as a bolus injection of 0.25 mg/kg bodyweight, followed by 0.125 µg/kg/min with a maximum of 10 µg/min as a continuous infusion for 12 hours. All patients received an equivalent of 300 mg of acetylsalicylic acid, 600 mg clopidogrel as a loading dose, and heparin given as a bolus of 5000 IU at the start of the PCI procedure. After the procedure, all patients received aspirin (75 mg/day) indefinitely and clopidogrel (75 mg/day) for one year. Other medications were systematically prescribed according to MISSION! protocol.[14]

Creatine kinase (CK) activity (Roche Hitachi Modular P800, Roche Diagnostics; upper limit of normal (ULN) = 200 U/L) and cardiac troponin-T (TnT) concentration (3rd generation Elecsys 2010 analyzer, Roche Diagnostics; The detection limit of the assay is 0.01 µg/l. The decision limit used for diagnosis of MI is 0.03 µg/l, with an imprecision of < 10%) in plasma were determined at admission and every 6 h in the first 48 h after PPCI. Subsequently these levels were determined every day up to discharge, unless clinical events suggested repeat measurements. The cumulative release of CK in the first 48h was calculated as a measure of infarct size in each patient by an investigator blinded to the assigned treatment.[15]

Coronary angiography was performed by the femoral approach. All patients underwent PPCI and stenting of the IRA according to standard techniques. Stent implantation was successfully completed in all patients. Procedural success was defined as residual stenosis < 20% and TIMI flow grade 3. Initial and post procedural TIMI flow grade of the IRA[16] were assessed off-line by two experienced interventionalists blinded to the assigned treatment.

In our earlier study we used the following definition of aborted MI: In a well equipped center for PPCI, aborted MI can be defined as a combination of the following: 1) typical chest pain > 30 min with initial ST-segment elevation (indicative of transmural myocardial ischaemia), 2) ST-segment deviation resolution of ≥ 50% within 90 min post-PPCI, 3) peak CK release less than 3 times ULN within the first 48 hours post-PPCI, and 4) presence of a significant coronary artery stenosis (defined as > 70% reduction in lumen diameter) at the territory of suspected ischemia.

According to the MISSION! protocol all included patients underwent a myocardial perfusion study at 90 days post PPCI. An ECG gated SPECT acquisition at rest using intravenous Technetium 99m Tetrofosmin (MYOVIEW, Amersham, Buckinghamshire, UK) was used to

measure the LV ejection fraction (LVEF) 90 days after PPCI. LVEF was calculated using an automated and validated method (QGS software, version 2.0, Cedars-Sinai Medical Center, Los Angeles, CA, USA). Detailed methods are described elsewhere.[17] Patients with a history of previous infarction were excluded from MYOVIEW analysis (1 patient (3%) of aborted MI group and 10 patients (7%) of established MI group), 6 patients (6%) had incomplete analysis due to technical difficulties. LVEF assessment was done by an investigator blinded to the assigned treatment.

According to the MISSION! protocol patients were scheduled at a dedicated out-patient clinic after 1, 3, 6 and 12 months. Clinical outcome was evaluated through the monitoring of major adverse cardiac events (MACE) occurring at any time during the follow up. Only the most serious event of MACE was used to calculate the cumulative MACE per patient according to the following sequence: death > MI > revascularization > heart failure. Death was defined as "all-cause" death at follow-up. MI during follow-up was defined as recurrent chest pain with a new elevation in CK (by > 50% of the last measured value or ≥ 2 x normal upper limit) and/or new changes in the ECG (ST-segment elevation, new Q waves). Target vessel (TVR) and target lesion revascularization (TLR) were defined as any revascularization procedure of the target vessel or target lesion (from 5 mm distally to the stent up to 5 mm proximally to the stent), respectively. Heart failure (HF) during follow-up is defined as either the presence of rales in more than one third of the lung fields that did not clear with coughing or evidence of pulmonary oedema on chest radiograph. Major hemorrhagic events during hospitalization are defined as intracranial bleeding or bleeding associated with a decrease in hemoglobin level of ≤ 3mmol/L (5 g/dL). Other bleeding complications not fulfilling these criteria were considered minor.

Categorical variables were presented as counts and proportions (percentages) and compared by Pearson chi-square analysis or Fisher exact test. Normal distribution of continuous data was tested using a Kolmogorov-Smirnov test. Continuous and normally distributed data are presented as mean ± 1 SD and were compared by unpaired *t* test. Not-normally distributed data are expressed as median with interquartile range (IQR), and the Mann-Whitney *U* test was used to compare differences between two groups.

The LV function data was analyzed only in surviving patients with exclusion of patients with previous AMI. Clinical outcomes were presented as Kaplan-Meier survival estimates and were compared using the log-rank test.

All p-values are two-tailed, and statistical significance was defined if $p < 0.05$. All analyses were performed with SPSS version 14.0 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

Study population consists of 179 consecutive patients who underwent PPCI according to the MISSION! protocol. Thirty-two patients (18%) fulfilled the criteria of aborted MI.

Table 1 compares patients with aborted MI to those with established MI. The two groups show no significant differences in baseline characteristics, although there was a trend toward increased incidence of aborted MI in patients with anterior MI compared to those with inferior MI (62% vs. 38%, $p = 0.053$). Pre-hospital abciximab administration was more frequent in the aborted MI group compared to established MI group (72% vs. 45%, $p = 0.006$).

Table 1 Characteristics of patients with aborted myocardial infarction compared to patients with established myocardial infarction.

	Aborted MI (n= 32)	Established MI (n= 147)	P
Age (years)	59±12	60 ±12	NS
Age ≥ 75 yrs, n (%)	5 (16)	21 (14)	NS
Male gender, n (%)	27 (84)	113 (77)	NS
Risk factors, n (%)			
Previous MI	1 (3)	10 (7)	NS
Hypertension	14 (44)	49 (34)	NS
Diabetes mellitus	6 (19)	15 (10)	NS
Hypercholesterolemia	15 (47)	63 (43)	NS
Current Smoking	20 (63)	84 (58)	NS
Positive Family history	14 (44)	65 (45)	NS
Killip class ≥ 2, n (%)	0	6 (4)	NS
Pre-hospital abciximab, n (%)	23 (72)	66 (45)	0.006*
Anterior MI, n (%)	20 (62)	66 (45)	0.053
Symptom to balloon (min)	130 (100-165)	155 (114-240)	NS‡
Symptom to abciximab (min)	70 (54-117)	115 (67-195)	0.005‡
Infarction related artery, n (%)			
LM/ LAD	19 (59)	61 (41)	NS*
CX	2 (6)	21 (14)	
RCA	11 (35)	65 (45)	
Multivessel disease, n (%)			
2-vessel	7 (22)	42 (29)	NS*
3-vessel	6 (19)	24 (17)	
Initial TIMI flow grade, n (%)			
0-1	8 (26)	106 (73)	<0.001*
2-3	23 (74)	39 (27)	
∑ ST-segment deviation on admission (mm)	14 ± 8	19 ± 10	0.01†
Cumulative 48-h CK release (U/L)	965 ± 886	11515 ± 8179	<0.001‡

*Data are presented as number of patients (%), mean ± standard deviation or median (interquartile rang). *Compared using Chi-square or Fisher exact test, †compared using unpaired t test, ‡ compared using Mann-Whitney U test. **∑**= sum, TIMI = Thrombolysis In Myocardial Infarction, CK=creatine kinase, CX= Circumflex artery, MI=myocardial infarction, NS= not significant, LAD= Left anterior descending, LM= Left main, RCA= Right coronary artery, TnT= Troponin T.*

The median time between symptoms onset and abciximab bolus administration for the total study population was 105 min (IQR 60-165 min). However, it was significantly shorter in the aborted MI (70 min, IQR 54-117 min) compared to the established MI group (115 min, IQR 67-195 min). Time from onset of symptoms to balloon inflation did not differ significantly between patients with aborted MI and those with established MI (table 1).

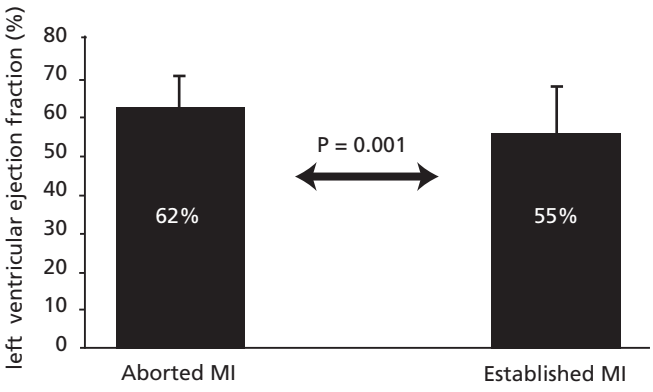
Initial angiographic evaluations showed no significant differences between aborted and established MI groups regarding the infarction related artery and number of diseased vessels prior to PPCI (table 1). At initial angiography the aborted MI group showed higher early reperfusion rate of the IRA (TIMI 2-3 flow) compared to the group with established MI (74% vs. 27%; $p < 0.001$).

Aborted MI patients had a significantly lower sum of ST-segment deviation on their ECG at time of admission compared to patients with established MI ($p = 0.01$) (table 1).

The cumulative 48-h CK release was significantly lower in the aborted MI group (965 ± 886 U/L) than in the established MI group (11515 ± 8179 U/L; $p < 0.001$) (table 1).

After 3 months, 160 LV function studies from 28 (88%) patients in the aborted MI group (1 patients excluded because of previous MI, and 1 patients died and 2 patients had incomplete analysis) and from 132 (89%) patients in the established MI group (10 patients excluded because of previous MI, 1 patient died and 4 patients had incomplete analysis) were analyzed. LVEF was significantly higher in the aborted MI group (62.3 ± 8.1%) compared to the established MI group (55.3 ± 11.3%, $p = 0.001$) (Figure 1).

Figure 1 Left ventricular function by myocardial scintigraphy 90 days after infarction in patients with aborted infarction compared to those with established infarction.



All patients were followed for one year. Cumulative MACE occurred in 39 patients; the incidence of cumulative MACE was significantly lower in the aborted MI group than in the established MI group (9% vs. 25%, $p = 0.03$) (Table 2).

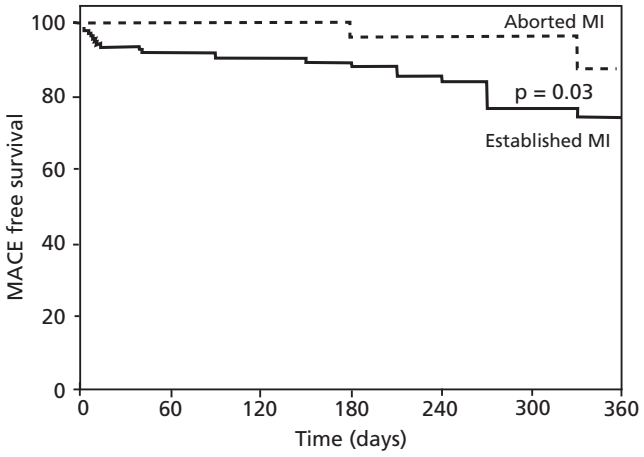
Table 2 Incidence of major adverse cardiac events in patients with aborted MI compared to established MI.

	Aborted MI (n= 32)	Established MI (n= 147)	P
Cumulative MACE*, n (%)	3 (9%)	37 (25%)	0.03
Death, n (%)			
Cardiac	0	3 (2%)	NS
Non-cardiac	1 (3%)	2 (1%)	
Recurrent MI, n (%)	1 (3%)	7 (5%)	NS
Revascularization, n (%)			
TVR	0	8 (5%)	0.08
TLR	0	4 (3%)	
Non- TVR	1 (3%)	10 (7%)	
Heart failure, n (%)	0	13 (9%)	0.07
Major bleeding, n (%)	2 (6%)	10 (7%)	NS

*Data are presented as number (%) of patients. MACE= major adverse cardiac events including death, recurrent infarction, revascularization and heart failure; MI= myocardial infarction; TLR= target lesion revascularization; TVR= target vessel revascularization. * only the most serious event was used per patient*

Figure 2 Kaplan-Meier estimates for survival free from major adverse cardiac events (MACE) among patients with aborted and established myocardial infarction.

Higher MACE-free survival at 1 year in the aborted MI group in comparison to the established MI group (log-rank p=0.03). MACE = major adverse cardiac events; MI = myocardial infarction.



Mortality, recurrent MI, revascularization procedures and heart failure were less likely in the aborted MI group compared to established MI (Table 2). No differences were noted between the two groups with regard to the occurrence of major bleeding complications (2 patients (6%) of the aborted MI group and 10 patients (7%) of the late group).

The Kaplan-Meier curves in figure 2 illustrate a significant trend toward a higher MACE-free survival at 1 year in the aborted MI group in comparison to the established MI group ($p = 0.03$).

DISCUSSION

This study demonstrates that aborted infarction is associated with improved LV function at 3 months and superior prognosis on long term follow-up.

Abortion of MI is thought to follow rapid early reperfusion of a thrombotic occlusion of an epicardial coronary artery such that myocardial necrosis cannot be detected by classical plasma biomarkers.[18] On the other hand, aborted MI may also occur in the absence of reperfusion therapy as a spontaneous variant of 'stuttering' infarction.[10,13,18] It has been postulated that in a subset of patients with suspected ST-segment elevation acute coronary syndromes, there is a subtle balance between coronary thrombosis and endogenous fibrinolysis, sometimes modulated by vasoconstriction, resulting in intermittent occlusion and spontaneous reperfusion.

Aborted infarction has been observed in 13-17% of patients after fibrinolysis.[10,11,13] This incidence rises to 25% of patients treated within 1 h after symptoms onset.[13] In our previous report, aborted MI is observed in 18% of patients after PPCI. Recently Sciagrà et al.[19] demonstrated an incidence of 15% aborted infarction in patients treated by primary PCI. Although Sciagrà and colleagues used another definition of aborted infarction, based on the finding of completely normal myocardial perfusion together with preserved regional and global function at 1 month follow up gated SPECT after PPCI, their findings support our results. aborted infarction is strongly related to shorter time to abciximab treatment in concordance with prior studies, in which aborted infarction was strongly related to a shorter time to fibrinolytic.[10,13]

In our prior study pre-hospital abciximab administration was the main predictor of aborted MI, and this effect could be related to the initiation of treatment within the first 2 hours after symptoms onset and to the higher IRA patency (TIMI 2-3) at presentation.

In this report, LVEF was significantly higher in patients with aborted MI compared to those with established MI. This result can be endorsed on the fact that aborted MI is the ultimate myocardial salvage which is the principal mechanism by which patients with STEMI benefit from reperfusion therapies especially in first 2-3 h after onset of symptoms (golden period) which is reflected by an improved LV systolic function.[20,21]

Myocardial salvage after primary angioplasty has been extensively evaluated in the STOPAMI studies[22-24] without reporting any aborted MI patients. However, they used myocardial perfusion scintigraphy before and after intervention, this method is distinctively different from myocardial enzyme release studies. Furthermore, a time interval from symptom onset to balloon inflation within 2 h, the golden period for myocardial salvage, was only achieved in very few patients in those studies. However in our study all patients receive abciximab within a median of 105 min pre PPCI, which may prevent distal embolization of atherothrombotic material associated with early PPCI.

The present study is the first prospective study evaluating the effect of aborted MI on LV

systolic function at 90 days with gated SPECT providing a long time window for recovery of LV function post-MI. Furthermore, the exclusion of patients with previous MI provided a possibility of evaluating more precisely the effect of infarction abortion on LV function.

The overall prognosis of aborted MI in our study was better compared to established MI group in accordance with Lamfers et al.[10,11]Also in the ASSENT-3 trial patients with aborted myocardial infarction, long-term mortality was 30% lower than that with established myocardial infarction after correction for baseline differences. In a subset of 300 patients (< 5%), who had aborted infarction and > 70% ST-segment resolution, 1-year mortality was very low.

It has been postulated that some of the patients with an initially altered natural history by "abortion" of their infarcts might subsequently be at higher risk for having reinfarction and thereby a "completion" of the initially aborted event.[9] In our study the incidence of recurrent MI tend to be lower in the aborted MI group in consistent with a subanalysis from the ASSENT-3 trial[13], which did not demonstrate a higher risk of recurrent infarction at 30 days in patients with an aborted infarction. Furthermore, The DANAMI 2[25] study showed a higher incidence of "reinfarction" after thrombolytic therapy (6.3%) than after primary coronary intervention (1.6%).

Our study support the concept of early and effective reperfusion strategy, provide best myocardial salvage and is associated with higher survival.

Study limitations

Our study is an interventional prospective, single-center study. Time of abciximab administration was not randomly assigned for the study groups. However, throughout the study period, a rigorously standardized protocol (MISSION!) concerning pre-, peri- and post-PPCI treatment was applied. So it seems unlikely that procedural changes over time other than the timing of abciximab administration have influenced the incidence of aborted MI.

CONCLUSION

In patients with STEMI treated with PPCI, the incidence of aborted MI was 18%. Aborted infarction is associated with improved LV function at 3 months and superior prognosis on long term follow-up.

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