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Is delayed facilitated percutaneous coronary intervention better than immediate in reperfused myocardial infarction? Six months follow up findings

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***Abstract. Background*: There are several new strategies proposed to improve the outcome of patients with ST-elevation myocardial infarction (STEMI). One approach is the resurgent use of facilitated percutaneous coronary interventions (PCI). Until recently, deciding whether immediate PCI after combined treatment (facilitated PCI) is more appropriate than delayed PCI (short time) has not been investigated. The aim of this study, therefore, was to investigate the outcomes in patients initially successfully treated pharmacologically and immediate PCI < 2 hr, and in patients initially successfully treated with pharmacological therapy and with delayed PCI (12–72 h).**

***Methods*: 451 reperfused STEMI patients, aged 18 to 75 years, class I–II Killip, with an acceptable echocardiographic window and admitted within 12 hs of the onset of symptoms were randomized into two groups. All patients had to have successful reperfusion, to receive the combination of a standard tirofiban infusion or abciximab plus half dose rtPA. Thereafter, patients were sub-grouped as follows:group 1 (immediate PCI) patients had PCI within 2 h; and group 2 (delayed PCI) patients in which PCI was performed after 12 hs and within 72 hs.**

***Results*: The 225 reperfused (immediate-PCI) and 226 reperfused (delayed-PCI) patients (time from randomization to PCI 165 ± 37 min in immediate PCI versus 45.1 ± 20.2 h in delayed PCI group) showed similar results in ejection fraction, CK release and patency of the IRA. In addition, the delayed PCI group showed a significant reduction in ischemic events, restenosis and bleedings ($P = 0.005$, 0.01, 0.01 respectively) and significant reduced angiographic evidence of thrombus formation in the infarction-related artery (IRA) ($p = 0.001$).**

***Conclusion*: Our data suggest the safety and possible use of delayed facilitated PCI in patients with STEMI, and that delayed PCI in patients treated with combined lytic and IIb/IIIa inhibitors appears to be as effective and possibly superior (reduced ischemic events and repeat PCI) as immediate PCI. The patients in this study were successfully reperfused, with TIMI-3 flow and our data may not apply to patients with TIMI 0–2 flow. This strategy could allow transferring the reperfused patients and performing PCI after hours <72 hours and not immediately, thereby reducing the number of urgent PCI and costs, obtaining similar results, but mostly causing less discomfort to the patient. Our results had to be interpreted with caution, because current guidelines do not recommend the combined therapy, but suggest further studies.**

***Abbreviated abstract.* The study was aimed to investigate the outcomes in patients initially successfully treated pharmacologically and immediate PCI <2 h, and in patients initially successfully treated with pharmacological therapy and delayed PCI (12–72 h). All patients had to have successful reperfusion, to receive the combination of a standard abciximab or tirofiban infusion plus half dose rtPA. Similar results were observed in both groups. Delayed PCI group showed a significant lower incidence in restenosis (0.01), minor bleedings (0.005), ischemic events (0.01) and a reduced angiographic evidence of thrombus formation in IRA (0.001). Our data suggest the safety and possible use of delayed facilitated PCI in patients with STEMI. Our results had to be interpreted with caution, because current guidelines do not recommend the combined therapy, but suggest further studies.**

***Key Words.* Acute myocardial Infarction, Facilitated Percutaneous Coronary Interventions, Combined therapy, GIIb/IIIa inhibitors, Delayed Percutaneous Coronary Interventions.**

Introduction

An ongoing challenge for the clinical cardiologist remains the choice of optimal reperfusion treatment for patients with ST-segment elevation acute myocardial infarction STEMI [1]. Several studies showed a clear superiority of primary PCI over pharmacological thrombolysis for the treatment of STEMI, with

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higher initial reperfusion rates, improved event-free survival, and lower incidence of intracranial bleeds. However, the capability of hospitals of performing primary percutaneous coronary interventions (PCI) is low, <25% in the USA e about 10% in the Europe [2,3]. Recent studies have continued to demonstrate improved clinical outcomes with primary PCI compared with pharmacological reperfusion, even for patients who need to be transferred to a tertiary centre [4–8]. Given the need to minimize the reperfusion time and the paramount importance of TIMI flow grade 3, there are several new strategies proposed to improve outcomes for STEMI patients. One approach has been the resurgent use of facilitated PCI [9–13]. Until recently, deciding whether immediate PCI after combined treatment (facilitated PCI) is more appropriate than delayed PCI (short time), in obtaining complete clinical stabilization and performing elective PCI, has not been investigated. In our previous pilot study we observed the safety of delayed facilitated PCI in selected low risk reperfused STEMI and we also showed that patients with delayed PCI had similar results in EF and CK release, and a favourable not significant trend in ischemic events, restenosis and bleedings, and a significant reduction in thrombotic residues in IRA [14]. Because the differences were small and not reaching significant values, we planned to enrol a larger number of unselected patients to investigate in patients initially successfully treated pharmacologically and immediate PCI <2 h, versus patients initially successfully treated with pharmacological therapy and delayed PCI (12–72 h) the incidence of ischemic events and clinical restenosis urging to reangiography and repeat PCI during 6 months of follow up.

Materials and Methods

Population

The study included 451 STEMI patients consecutively admitted to hospital during the period December 1999 to October 2004.

Eligibility criteria

Patients had to have criteria for STEMI, Killip class I–II, an acceptable echocardiograph window, and had to receive combined pharmacological reperfusion treatment within 12 h of pain onset. All patients admitted into the study had to have successful reperfusion during thrombolysis. On ECG there had to be an ST elevation of >1 mm in the peripheral leads and/or 2 mm in precordial leads, involving more than one lead, with concomitant alterations of the segmentary kinetics in the echocardiogram performed at entry. The age limit was >18 years and <75 years. Local ethical committee approved the study and informed consent was obtained from all the patients.

Exclusion criteria

Patients not suitable for thrombolysis, with a left bundle branch block, a history of cardiomyopathy or heart failure, class >2 Killip, and who showed unsuccessful reperfusion, and receiving full thrombolysis, were excluded.

Reperfusion criteria

There had to be evidence of typical behaviour of the ST segment with rapid reduction (50 to 70% within 1 hour) in 12 leads ECG continuous monitoring, rapid pain regression, and early ventricular arrhythmias within 1 hour of the start of thrombolysis. The rapid ST segment reduction (50–70% within 1 hour) in 12 leads ECG continuous monitoring was considered mandatory and associated with one of the other reperfusion criteria. ST-segment measurements were done at J + 60 ms in the single lead with maximal ST-segment elevation. All data were analyzed by an experienced cardiologist who was blinded to assignment. The rapid ST-segment reduction was considered the most important sign of successful reperfusion [15–17].

STEMI classification

STEMI were classified according to the localisation of the alteration in segmental contractility in the echocardiogram performed at entry and according to the localisation of the alterations of the ST segment in the standard 12 lead ECG + V3R–V4R lead taken at entry before reperfusion treatment. All patients received on admission also our standard treatment of nitrates (5–100γ/ml), aspirin (160 mg/die) and, where possible, three 5-mg intravenous doses of metoprolol. The thrombolytic drug used was recombinant tissue plasminogen activator ((50 mg rtPA), 15 mg as bolus and then 35 mg over 30 minutes of infusion. In addition., at entry all patients also received ticlopidine (500 mg) or clopidogrel (300 mg) (continued at least for six months, ticlopidine 500 mg/day and clopidogrel 75 mg/day), statins and the usual post-STEMI treatment (beta-blockers, ACE-inhibitors, etc) and continued after discharge.

Study protocol

All the patients suitable for combined pharmacologic reperfusion treatment received the combination of half dose rtPA (50 mg) plus a standard abciximab infusion of 0.25 mg/Kg as bolus and subsequent infusion of 0.125 mcg/kg min for 12 hs or tirofiban 0.4 mcg/kg/min for 30 min followed by an infusion of 0.1 mcg/kg/min for 72 hs, as well as aspirin. All patients received heparin therapy according to TIMI-14 trial (low dose heparin schedule), and the heparin infusion was adjusted to TIMI-14 levels (a bolus of 60 U/Kg, maximum 4,000 U and infusion of 7 U/Kg/min, maximum 800 U/h. For both groups, the infusion was adjusted according to a monogram to a target activated partial thromboplastin time of 50 to 70 s [12]. Patients receiving combined treatment and showing signs of successful reperfusion within one hour from starting combined reperfusive treatment were randomized into two groups immediate-PCI <2 h versus delayed PCI (12–72 h). Randomization was

performed using a preliminary computer algorithm prepared by external coordinating centre; the assignment of patients was decided by an independent external team of physicians. The patients were randomly and externally assigned to the immediate or delayed PCI by a central telephone system. The events were communicated by treating physicians to randomization centre and this centre provides elaboration of data to the end of the study. The treating physicians were blinded of the results up to final analysis.

Group Immediate PCI group
after combined pharmacologic treatment and successful reperfusion, performed immediate angiography and PCI <2 h. These patients also completed treatment with GP IIb/IIIa inhibitors after PCI according to the combination used. GP IIb/IIIa inhibitors and/or heparin were discontinued only in case of side effects (bleedings and platelet reduction).

Group Delayed PCI group
after combined pharmacologic treatment and successful reperfusion, performed delayed angiography and PCI (12–72 h). These patients also completed treatment with GP IIb/IIIa inhibitors after PCI according to the combination used. GP IIb/IIIa inhibitors and/or heparin were discontinued in case of side effects (bleedings and platelet reduction).

Patients (both groups) without reperfusion signs, within one hour from starting treatment were considered failed thrombolysis and were immediately referred for rescue PCI/CABG. Because randomization was performed after having observed successful reperfusion within 1 hour from combined pharmacological treatment these patients were not included into the study.

After starting treatment and successful reperfusion, BP, HR, and ECG were monitored continuously. Blood CK and TNI levels were measured every 3 h during the 1st 24 h and then every 6 h until normalisation (CK), in order also to determine the enzymatic CK peak (12 h) in delayed group. and just after randomisation (at entry), they had an echocardiogram. The biochemical criteria were also used as a post-thrombolysis criterion of reperfusion (for patients from immediate PCI group). In addition, biochemical criteria were also used to check a rise after PCI. Major and minor bleeding was defined according to the criteria of the TIMI II trial [18].

Catheterization procedure and angiographic analysis

All the patients underwent angiography (<2 and 12–72 hours according to randomisation) and it was carried out through the right or left femoral artery. Additional heparin was given in the cathlab depending on the activating clotting time, with a target of 250 s. Interventional success was defined as stent implanted, residual stenosis <15%, and TIMI grade 3 flow after stent implantation. The decision to perform PTCA/CABG was based on angiographic findings (>70% stenosis) and left ventricular function. Restenosis was defined as >50% diameter stenosis by quantitative angiography. In-stent restenosis was classified, in 4 patterns: proliferative (>10 mm in length and extend beyond the proximal or distal margins of the stent, and total occlusion). ECG and angiographic data were analysed by an independent core laboratory, in order to reduce bias in the assessment of reperfusion. Coronary flow was assessed according to Thrombolysis in Myocardial Infarction (TIMI) grading score [19].

Follow up

Patients enrolled in the study were regularly followed up as outpatients for six months to check the incidence of ischemic events (the recurrence of chest pain and ST change, a positive stress test). Patients carried out echocardiographic examination before discharge and 1 month after treatment when, as part of the PCI protocol, they were also submitted to exercise testing, as well as 3 and 6 months after. Patients showing ischemic events or a positive stress test underwent further angiography to evaluate the presence of restenosis.

All the components of the endpoints and all clinical events were reviewed and adjudicated by an independent events committee who were unaware of treatment assignment. The angiography was not repeated in the patients who were asymptomatic and showed negative stress test during follow up.

Echocardiography was carried
Out according to a standard procedure and the LVEF was determined by the area-length method. Two observers blinded to the clinicaland ECG data, evaluated the 2-dimensional echocardiographic images. In the case of any discrepancies, the 2-dimensional echocardiographic images were again reviewed, and a decision was taken by consensus. The mean of 3 measurements was used and the interobserver and intraobserver coefficients of variation were 4% and 3%, respectively. Echocardiographic images were used according to our previous study [20], to obtain detailed informations about extension and localization (culprit IRA) and confirmation of STEMI. The echocardiogram allowed us to evaluate also the evolution of left ventricular size during the follow up.

Statistical analysis

We performed a multiple regression sample size calculating basing on a β value of 0.10 (90% power) and α value of 0.05. We calculated the simple size taking into account the results of our previous pilot study [14] and our findings for restenosis and ischemic events. Therefore the sample size obtained was 182 for group and this number was assumed as minimum one for this study patients. To overcome the incidence of 20–25% of failed thrombolysis, the sample size was estimated at 500 patients, 250 in each arm. Statistical analysis was performed according to the intention-to-treat principle. We calculated event distributions with the

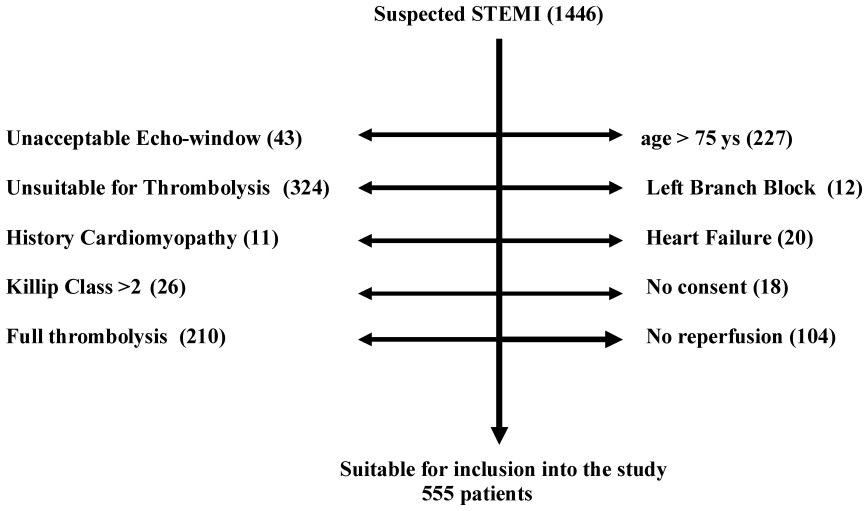


Fig. 1. *All hospitalized patients.*

Kaplan-Meyer method and compared them by log-rank analysis. Data were analysed using the two-tailed t-test to identify differences between groups. Nominal data were analysed by the Chi-square test and $p < 0.05$ was assumed as statistically significant. All calculations were done with SPSS statistical software and the results are expressed as mean ± SD.

Results

Of the 1,446 patients with STEMI, 324 were unsuitable for thrombolysis, 227 were >75 years, 43 had an unacceptable echocardiographic window, 11 had history of cardiomyopathy, 26 were in Class >2 Killip, 12 had left branch block (LBB), 20 suffered from heart failure (EF <40%), 18 refused the consent (figure 1), and 210 were referred to hospital after full thrombolysis and they were excluded from the study. Before randomization, 104 patients did not show reperfusion within 1 h from treatment and they were referred to rescue PCI. Only 451 (319 males, 132 females), consecutive reperfused patients (age ranged from 32 to 71 years) met the entry criteria and were randomized in two groups (figure 2): immediate-PCI (<2 h) versus delayed-PCI (12–72 h). Both groups had similar clinical data and risk factors. Table 1 shows the baseline clinical characteristics of the two groups, STEMI localization and treatment received. No difference in CK peak and EF was observed between the two groups at entry and during hospitalization.

The immediate PCI group (<2 h)

225 patients showed rapid reperfusion with subsequent stable clinical status, and underwent immediate angiography (<2 h) and PCI where indicated. The IRA showed TIMI 3 flow for the all the 225 patients (Table 2). 213 patients showed rapid reperfusion <30 min after starting combined treatment and they also presented with rapid regression of pain and a 50–70% reduction of the ST-segment. 12 patients showed signs of reperfusion after 30 min (40–45 min) after starting combined treatment and vessel patency was confirmed in the subsequent angiography, which was performed <2 h.

The delayed PCI group (12–72 h)

226 patients, showed rapid reperfusion by non-invasive criteria, total clinical stabilization and the angiography with subsequent delayed PCI (12–72 h) where indicated, showed IRA patency (TIMI 3 flow) in all the 226 patients (Table 2). Rapid reperfusion within 30 min after starting combined treatment was observed in 211 patients and they also presented with rapid regression of pain and reduction 50 to 70% of the ST-segment. Signs of reperfusion were observed in 15 patients 30 min (40–45 min) after starting combined treatment. IRA patency was confirmed by angiography 12–72 h thereafter.

A significant difference in thrombus formation. was observed between two groups, 90 (37.5%) patients from immediate-PCI group and 37 (15.9%) patients from the delayed-PCI group, ($p = 0.001$) (Table 3). No difference was observed between two groups in the stent length, diameter and number of implanted stents; both groups were also displayed similarly for diseased vessels. In both groups the percent of drug eluting stents was homogeneous (31 in immediate group and 29 in delayed group), and these devices were employed especially in small vessels and ostial lesions. All the remaining patients received bare metal stents. During the long period of enrolment homogenously both groups received the devices commercially available. The PTCA or CABG (3 vessel disease) incidence was similar in both groups (Table 3).

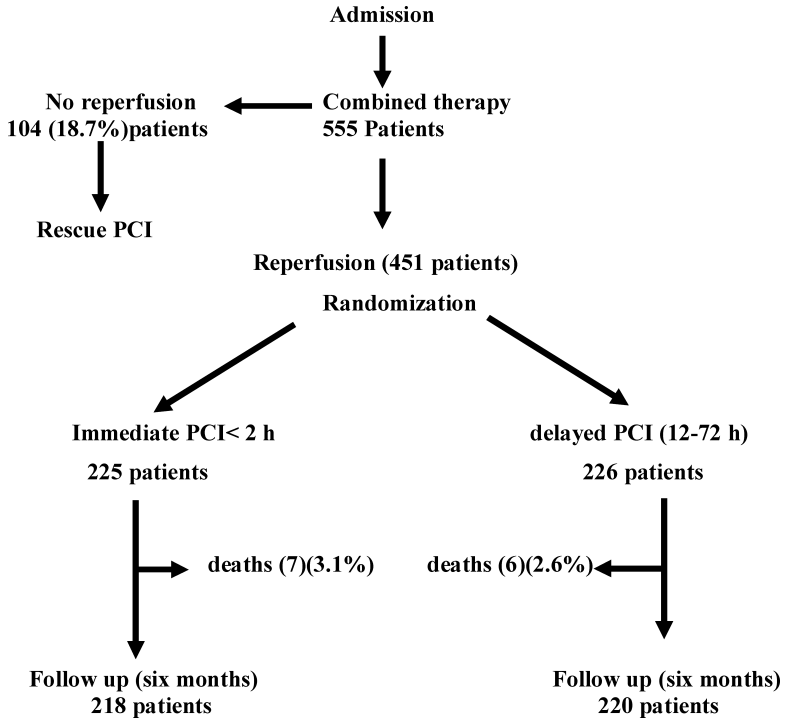


Fig. 2. *Protocol of the study.*

Side effects

The were 10 cases of major bleedings in the **immediate PCI group (<2 h),** 1 mild grade pericardial bleeding, six cases of severe haematuria which remitted after heparin withdrawal, one case of hematemesis, two case of intracranial haemorrhage (not disabiliting stroke) and 43 cases of minor bleedings (mostly access site), no blood transfusions were required. Seven patients showed platelet reduction <100.000, 6 hours after starting tirofiban treatment and only one patient required platelet transfusion. There were 8 major bleedings (2 patient had retroperitoneal bleeding, 5 patients severe haematuria, and 1 patient hematemesis) **in the delayed-PCI group (12–72 h**) and 23 cases of minor bleedings (access sites), no transfusion was required ($p = 0.01$). Eight patients showed platelet reduction <100.000 6 hours after starting tirofiban treatment, (table 2).No patients in both groups showed any significant increase in TNI, myoglobin, CK and CK-MB in the immediate post PCI phases and in the subsequent 48-h period. No death and ischemic events (acute or sub-acute stent thrombosis) was observed during hospitalization period.

Table 1. *Clinical data of all the reperfused patients. Data are expressed as mean ± SD.*

	Immediate PCI	Delayed PCI	*P*
patients No	225	226	
Sex F/M	68/157	64/162	
Age	59.1 ± 12	58.9 ± 13	0.86
CK peak max (IU/l)	1878 ± 525	1910 ± 487	0.58
EF%	51.4 ± 12	51.6 ± 14	0.87
ESV(ml/m2)	40.5 ± 6	40.3 ± 7	0.94
Hypertension	62 (27.5%)	69 (30.5%)	0.67
Diabetes	39 (17.3%)	43 (19%)	0.69
Hypercholester (>200 mg/ml)	82 (36.4%)	86 (38%)	0.88
Smoking habit	78 (34.7%)	74 (32.7%)	0.83
Inferior STEMI	119 (52.9%)	122 (54%)	0.96
Anterior STEMI	77 (34.2%)	83 (36.7%)	0.77
Lateral STEMI	29 (12.9%)	21 (9.3%)	0.34
Ticlopidine	12 (5.3%)	15 (6.6%)	0.72
Clopidogrel	213 (94.7%)	211 (93.4%)	0.97
Previous STEMI	47 (20.9%)	51 (22.6%)	0.81
Previous CABG	10 (4.4%)	12 (5.3%)	0.85
Previous PCI	21 (9.3%)	19 (8.4%)	0.33

STEMI = ST-elevation Acute Myocardial Infarction; EF = Ejection fraction. CABG: Coronary artery by-pass grafting; PCI = Percutaneous coronary intervention.

Follow up (six months)

Immediate PCI group

In the follow up (180 days) 41 (18.2%) patients showed pain at rest and ECG alteration recurrence (9 (4%) of these showed ST elevation with troponin I positive, 32 (14.2%) were with ST depression and troponin I positive), and 24 (10.7%) patients showed pain and ECG alteration during exercise test, and angiography again performed showed restenosis in previously PTCA treated vessels in 51 (22.7%) patients. Seven

Table 2. *Results of the study. All patients with successful reperfusion.*

	Immediate-PCI	Delayed-PCI	*P*
Patients No	225	226	
CABG/PTCA	12/203 (5.3%/90.2%)	10/207 (4.4%/91.5%)	
Time from symptom onset to PCI	3.4 ± 1.6 h	49.5 ± 22 h	
Time from thrombolysis to PCI	151 ± 23 min	46.2 ± 20 h	
Time from randomization to PCI	135 ± 25 min	45.6 ± 21 h	
Major Bleeding (in hospital)	10 (4.4%)	8 (3.5%)	0.81
Minor Bleeding (in hospital)	43 (19.1%)	23 (10.1%)	0.01
Platelet reduction (<100.000 Ptl)	7 (3.1%)	8 (3.5%)	0.98

CABG: Coronary artery bypass graft; PTCA = coronary angioplasty; rtPA = recombinant tissue-type plasminogen activator. LAD = Left anterior descending; CX = Circumflex; RCA = right coronary artery.

Table 3. *Angiographic characteristics of Infarct Related Artery (IRA) in all reperfused patients. TIMI flow was acquired before PCI.*

	Immediate PCI	Delayed PCI	*P*
TIMI 3 flow	225	226	
LAD	80 (35.5%)	82 (36.3%)	0.98
CX	23 (10.2%)	20 (8.8 %)	0.77
RCA	122 (54.2%)	124 (54.9%)	0.99
Stent Diameter mm	3.4 ± 0.3	3.3 ± 0.6	0.82
Stent length mm	16.7 ± 6.2	16.5 ± 6.5	0.73
Drug eluting stents	31	29	0.98
Direct stenting	79	81	0.98
Evidence of thrombus formation	90 (40%)	37 (16.4%)	0.001
3 vessels	36 (16%)	31 (13.7%)	0.64
2 vessels	82 (36.4%)	81 (35.8%)	1.0
1 vessel	97 (43.1%)	105 (46.5%)	0.72
No Critical Stenosis	10 (4.4%)	9 (4%)	1.0

LAD = Left anterior descending artery; CX = Circumflex coronary artery; RCA = Right coronary artery.

Table 4. *Results after six mounts of follow-up.*

	Immediate PCI	Delayed PCI	*P*<
Patients No	225	226	
Ischemic events	41 (18.2%)	22 (9.7%)	0.005
Troponin I positive (STEMI)	9 (4%)	6 (2.6%)	0.61
Troponin I positive (NSTEMI)	32 (14.2%)	16 (7.0%)	0.039
Positive Stress test	24 (10.6%)	25 (11%)	0.99
Positive stress test + Ischemic events	65 (28.9%)	47 (20.8%)	0.005
Restenosis	51 (22.6%)	34 (15%)	0.01
EF%	55.2 ± 11	54.7 ± 12	0.64
ESV (ml/m2)	37.2 ± 4	37.8 ± 5	0.16
No. critical stenosis	14 (6.2%)	13 (5.7%)	0.99
New PCI (IRA)	51 (22.6%)	34 (15%)	0.01
Mortality	7 (3.1%)	6 (2.6%)	0.99

PCI = percutaneous coronary intervention. IRA = infarct related artery. EF = ejection fraction. STEMI = ST-Elevation Myocardial infarction; NSTEMI = No-ST-Elevation Myocardial Infarction.

(3.1%) patients died in the first 180 days after discharge.

Delayed PCI group

In the follow up 22 patients (9.7%) showed pain and ECG changes recurrence at rest, 6 patients (2.6%) showed ST elevation and troponin I positive, 16 (7.0%) showed ST depression and troponin I positive), and 25 patients (11%) showed pain with ECG changes during exercise test ($p = 0.005$). The subsequent angiography showed restenosis in PTCA treated vessel in 34 (15%) patients ($p = 0.013$) (Table 4). None ischemic events (recurrent chest pain and ECG changes) occurred in this group from thrombolysis to angiography. Six (2.6%) patients died during the follow-up. None difference was observed between patients receiving tirofiban (301(54.2%) patients) or abciximab (254 (45.7%) patients) regarding incidence of reperfusion, side effects during hospitalization period, and ischemic events and restenosis during follow up (Table 5). Kaplan-Meyer curves performed to compare the incidence of primary (ischemic events) and or combined end-points (ischemic events and restenosis) show that the beneficial effects of delayed PCI are early evident and they continued during the follow up period. Long-Rank test showed significant differences between two groups (figure 3). Ejection fraction (EF) and end systolic volume ESV) were similar in both groups either at baseline (51.4% + 12 vs 51.6% + 14 and 40.5 + 6 vs 40.3 + 7 ml/m2) or after 6 months of follow up (55.2% + 11 vs 54.7% + 12 and 37.2 + 4 vs 39.8 + 5,respectively), $p =$ ns.

Discussion

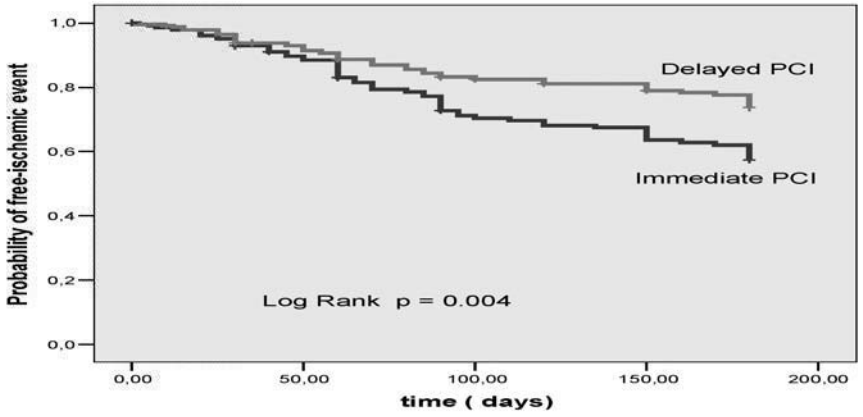
Despite the continued superiority of mechanical intervention even in the setting of inter-hospital transfer, it is clear that a prolonged delay in achieving reperfusion has deleterious effects. A recent analysis of PCI patients in NRMI registry demonstrated that a door-to balloon time >2 h was associated with a 41% to 62% increase in mortality, compared with patients with shorter intervention times [21]. Another important concept concerning the efficacy of PCI for STEMI

Table 5. *Analysis of sub-groups receiving tirofiban or Abciximab.*

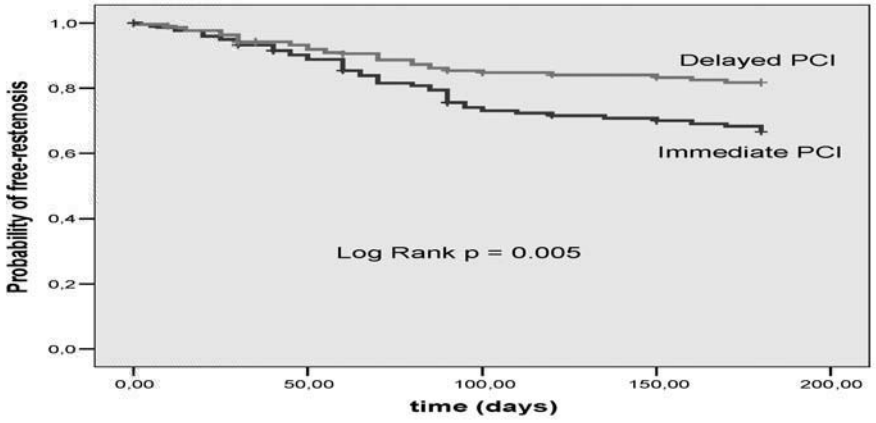
	Tirofiban (301 patients) 54.2%			Abciximab (254 patients) 45.7%		
	Immediate 152 (50.4%)	delayed 149 (49.5%)	$p<$	immediate 127 (50%)	delayed 127(50%)	$p<$
Unreperfused	55 (18.2%)			49 (19.2%)		0.88
Minor bleeding	19 (12.3%)	7 (4.7%)	0.045	24 (18.9%)	16 (12.6%)	0.31
Mayor bleedings	3 (2%)	2 (1.3%)	0.99	7 (5.5%)	6 (4.7%)	0.99
Platelet reduction	3 (2%)	3 (2%)	1.0	4 (3.1%)	5 (3.9%)	0.99
Thrombus formation	52 (34.2%)	22 (14.8%)	0.05	38 (29.9%)	15 (11.8%)	0.05
Ischemic events	26 (17.1%)	13 (8.7%)	0.08	15 (11.8%)	9 (7%)	0.33
Positive stress test	12 (7.9%)	14 (9.4%)	0.82	12 (9.4%)	11 (8.7%)	0.99
New PCI (IRA)	29 (19%)	19 (12.7%)	0.26	22 (17.3%)	15 (11.8%)	0.36
No critical stenosis	9 (5.9%)	8 (5.4%)	0.99	5 (3.9%)	5 (3.9%)	1.0

is the observed clinical benefit of achieving TIMI flow 3 before mechanical intervention [22–24]. The mortality benefit associated with primary PCI in ST-segment elevation myocardial infarction may be lost if door-to–balloon time is delayed by >1 h as compared with fibrinolysis door-to-needle time [25]. Unfortunately, the transfer strategy of these studies cannot be replicated in general practice. Randomized clinical trials defining invasive care for the stable post-thrombolytic patient reported conflicting results [26–31]. The recent ASSENT-4 PCI study showed that mechanical reperfusion was not improved when patients were given full dose fibrinolysis before primary PCI. In fact, clinical outcomes were worse for patients who received combined pharmaco-mechanical reperfusion, compared to those who received PCI alone. One possible explanation for differences between the two groups was insufficient platelet inhibition, especially in the fibrinolysis group, which. did not receive GP IIb/IIIa inhibitors. This might offer an explanation for the lower than expected TIMI 3 flow rates prior to PCI, as well as the increased rate of peri-procedural ischemic complications in the PCI plus thrombolysis group. [32]. Studies using the combination of thrombolysis with GPIIb/IIIa inhibitors have theorized that this combination can engender more stable reperfusion by potentiating fibrinolysis with platelet desegregation [12–13,29,33]. Although primary PCI, in comparison with thrombolysis, may guarantee a higher rate of reperfusion in patients presenting late, it cannot prevent myocardial necrosis, which is related to the duration of occlusion, particularly in high risk patients. Therefore, all efforts should be made to shorten total ischemic time, not only for thrombolysis but also for primary PCI [34–36]. In fact, every minute of delay in treatment of patients with STEMI does affect 1-year mortality, not only in thrombolysis but also in primary PCI. The risk of 1-year mortality is increased by 7.5% for each 30-minute delay [37]. A combined pharmacoinvasive approach capitalizing on the rapidity of initiation and widespread feasibility of pharmacologic reperfusion to promptly restore at least some myocardial blood flow, coupled with the more complete restoration achievable with subsequent PCI, merits consideration as an optimal approach [38]. The temporal window for efficacy of PCI can be broadened by employing pharmacologic components as part of the pharmacoinvasive recanalization strategies [39,40]. Previous and larger studies [29,33], showed a significant reduction in recurrence of ischemic events and urgent PCI in comparison with full thrombolysis., but mostly that more rapid and complete ST resolution occurs with half-dose TNK/abiciximab [32] whereas less reinfarction occurs amongst those patients with > or 70% ST resolution [40–43]. The choice of combined treatment was determined because during STEMI the dynamic interplay between factors promoting thrombosis versus those promoting thrombolysis is shifted in favour thrombosis. Although thrombolytic agents target the fibrin mesh component of thrombus, their use is associated with both heightened thrombin activity and platelet activation. In this scenario we planned our study to verify if it was possible to delay PCI after combined treatment. Both groups received the same combined pharmacological treatment, and all patients underwent PCI, immediate <2 h or delayed 12–72 h. Our data suggest the possibility to perform facilitated PCI 12–72 hours after combined treatment (half dose of thrombolytic drug plus GP IIb/IIIa inhibitors) in patients with STEMI. The bleeding risk was acceptable and the delayed PCI group showed a significant reduction in minor bleedings. In fact, one only patient (from immediate PCI group) had not fatal intracranial bleeding. The most important result was the safety of this combination. We used also the combination of tirofiban with half dose of thrombolytic agent, in agreement with our and other reports which showed the efficacy of this combination [42–45] The high dose bolus was not used because this protocol was reported only recently [46]. Our study was not addressed to compare different GP IIb/IIIa inhibitors, but it was performed to evaluate if a delayed interventional strategy after combined treatment in this setting of patients was possible independently of thrombolytic drug and GP IIb/IIIA inhibitor combination. This is the first time that two different strategies (immediate and delayed facilitated PCI) were used in the setting of STEMI

GRAF:1 Kaplan-Meyer cumulative event curves for primary end point (ischemic events)



GRAF:2 Kaplan-Meyer cumulative event curves for secondary end-point (restenosis).



GRAF:3 Kaplan-Meyer cumulative events curves for Combined end points (restenosis plus ischemic events)

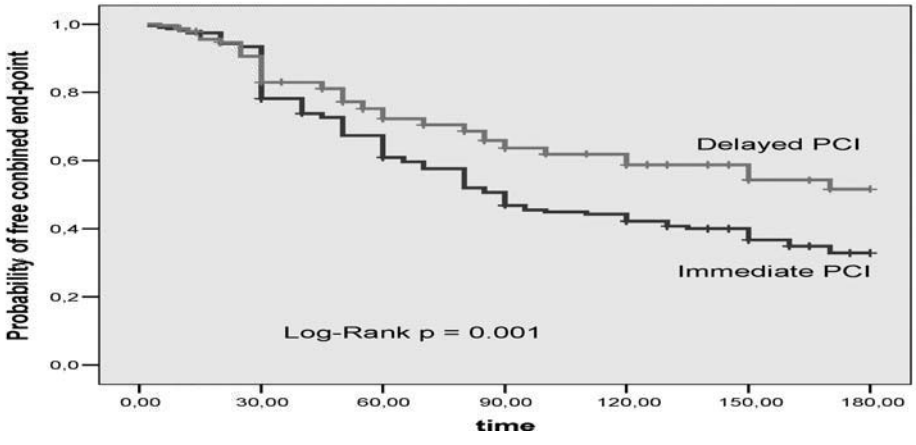


Fig. 3.

treated with combined therapy and with a short window between the pharmacologic reperfusion therapy and PCI. We thought that the delayed strategy could allow us to perform PCI after full pharmacologic preparation (GP IIb/IIIa inhibitors, clopidogrel/ticlopidine, aspirin, heparin, statin etc.). It is possible, that the significant reduction in angiographic thrombus formation in culprit plaque and restenosis in the follow up in delayed-PCI group were due to complete pharmacologic treatments. In this way, when the patients performed PCI the culprit plaque was more stable than in group performing immediate-PCI. A recent report from

the ASSENT PLUS ST-monitoring sub-study showed that patients, with early ST events, were found to have a residual thrombus in 22% of cases, as compared with 7.5% in patients without early ST events, and patients with late ST events had residual thrombi in 46% of cases, as compared with 15% in patients without such late events. These data suggest that recurrent ST events during the first days of a STEMI are associated with persistence of thrombi in the IRA, whereas an absence of ST events identifies a group with low risk for residual thrombi [47]. The observations of a significant reduction in thrombus formation in the IRA of the delayed PCI group, add new and important suggestions for delayed PCI. In fact, it is possible that reduced incidence of thrombi may determine a lower incidence of early or late ischemic events. We hypothesized that the combination of statin, anti-platelet agents (aspirin, ticlopidine/clopidogrel), and heparin can determine a more complete stabilization and a reduction of activity of culprit lesions and the subsequent reduction of restenosis process in delayed PCI group. In addition, circadian variations may have a profound effect on the practice of primary PCI. A majority of patients are treated during routine duty hours. Patients treated during off-hours have a higher incidence of failed PCI and consequently a worse clinical outcome than patients treated during routine duty hours [48]. In this way we can reduce the risk of PCI during off-hours. In conclusion, our data suggest that delayed PCI in patients treated with combined lytic and IIb/IIIa inhibitors appears as effective and possibly superior (reduced ischemic events and repeat PCI) to immediate PCI. This treatment could be useful, not only in patients admitted in hospitals without interventional laboratory, because it allows performing PCI in stable patients (as elective PCI) and in this way avoid the important problems determined by urgent PCI. This strategy could also allow to transfer the patients with successful reperfusion to tertiary centre after hours (12–72 h) and not immediately and reduce the number of urgent PCIs with subsequent reduction of costs, obtaining similar results, but mostly obtaining a minor discomfort for the patients. Our results had to be interpreted with caution, because the combined therapy in other and larger clinical trials [29,33] showed different results and important problems, and actually the current guidelines do not recommend this strategy. We think that our data could suggest further larger clinical trials of combination therapy.

Limitations of the study

The high dose of clopidogrel administered could have determined a better patency rate of the infarct-related artery and reduced ischemic complications, but both groups were homogeneously given clopidogrel. The addition of the clopidogrel could justify the high rate of TIMI 3 flow observed in our study [49]. In addition, in the current investigation drug eluting stents (DES) were implanted only in the selected patients. It is possible that a higher use of DES might further minimize the impact of our study. Another important limitation is the combined therapy that is not recommend up to now.

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