Catheterization and Cardiovascular Interventions 65:484–491 (2005)

Facilitated Primary Coronary Intervention With Abciximab and Very Low Dose of Alteplase During Off-Hours Compared With Direct Primary Intervention During Regular Hours

Mauro Maioli,* MD, Michela Gallopin, MD, Mario Leoncini, MD, Francesco Bellandi, MD, Anna Toso, MD, and Roberto Piero Dabizzi, MD

In patients with acute myocardial infarction (AMI), the off-hour presentation is one of the major determinants of door-to-balloon delay. Moreover, the nighttime presentation is associated with increased mortality after primary coronary intervention (PCI). The prompt starting of a therapy able to start recanalization of the infarct-related artery before intervention might improve the results of off-hour primary PCI. We compared the outcome of 212 consecutive patients with AMI undergoing either direct or facilitated PCI according to the hour of presentation. Patients arriving off-hours were pretreated with alteplase (20 mg) and abciximab and underwent facilitated PCI. Patients presenting on-hours underwent direct PCI. A basal Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 was observed in 1.0% of patients undergoing direct PCI and in 44% of patients undergoing facilitated PCI ($P = 0.001$). More patients starting PCI with a TIMI 3 flow achieved a postinterventional fast TIMI frame count (72.0% vs. 38.8% direct PCI group vs. 34.9% facilitated PCI group with basal TIMI 0–2; $P = 0.001$) and a TIMI perfusion grade 3 (66.0% vs. 38.8% direct PCI group vs. 39.7% facilitated PCI group with basal TIMI 0–2; $P = 0.004$). Preinterventional TIMI flow grade 3 was associated with a higher gain in left ventricular ejection fraction at 1 month (10.9% ± 6.4% vs. 7.0% ± 9.6% direct PCI group vs. 6.1% ± 6.0% facilitated PCI group with basal TIMI 0–2; $P = 0.005$). No significant difference was observed in major bleedings, although there was a trend toward a higher risk in the facilitated PCI group. Patients in the facilitated PCI group achieving a basal TIMI 3 flow showed improved myocardial reperfusion and better left ventricular function recovery. Bleeding complications associated with combination therapy remained an important concern. © 2005 Wiley-Liss, Inc.

Key words: acute myocardial infarction; facilitated percutaneous coronary intervention

INTRODUCTION

Several studies have shown that primary coronary percutaneous intervention (PCI) in acute myocardial infarction (AMI) is superior to thrombolysis even when angioplasty entails a time delay up to 3 hr [1,2]. However, it is known that, also in the setting of primary PCI, time-to-treatment is a critical determinant of myocardial salvage and mortality [3–5]. For patients directly referred to centers with catheterization facilities, one of the most important predictors of door-to-balloon delay is the off-hour presentation [6]. Moreover, the nighttime presentation is associated with increased mortality after primary PCI due to the higher rate of failed procedures [7]. We hypothesized that a strategy of facilitated PCI during off-hours could improve the results of PCI during off-hours by starting recanalization of the infarct-related artery pharmacologically while waiting for intervention. Combination therapy with very low dose of alteplase (20 mg bolus) and full-dose abciximab can potentially achieve this goal, maintaining a good safety profile [8]. Accordingly, the results obtained with such a protocol of facilitated PCI performed at nighttime and during weekends and holidays were compared with those of direct PCI performed during regular hours.

Division of Cardiology, Misericordia e Dolce Hospital, Prato, Italy

*Correspondence to: Dr. Mauro Maioli, Via degli Arcipressi 3, 50143, Florence, Italy. E-mail: mauromaioli@tiscali.it

Received 19 May 2004; Revision accepted 17 March 2005

DOI 10.1002/ccd.20427
Published online 22 June 2005 in Wiley InterScience (www.interscience.wiley.com).

MATERIALS AND METHODS

Population and Study Protocol

Patients with AMI presenting with chest pain lasting more than 30 min associated with ST segment elevation greater than 0.2 mV in at least two contiguous leads and symptom onset within 6 hr were included in this prospective study. Patients with cardiogenic shock were included and no upper age limit was defined. The only exclusion criterion was inability to obtain informed consent.

From March 2001 to August 2003, 212 consecutive patients with AMI were directly referred to our hospital, which provides a round-the-clock service of primary PCI, with four trained physicians and dedicated nurses. At night and during weekends and holidays, the staff on call comes in from home. Among the 212 patients, 117 arrived at the emergency department after hours (from 6:00 p.m. to 8:00 a.m., 95 patients, 81%; or at daytime during weekends and holidays, 22 patients, 19%); 4 of these patients had contraindications to lytic therapy and underwent direct PCI. The remaining 113 patients were treated with alteplase (20 mg single bolus) and started abciximab at standard dose (bolus 0.25 mg/kg followed by 0.125 μg/kg/min 12-hr infusion), while the catheterization laboratory was getting ready (facilitated PCI group). Thereafter, primary PCI was performed, leaving stent implantation at the discretion of the physician. Ninety-five out of 212 patients arrived at the emergency room during regular hours (from 8:00 a.m. to 6:00 p.m., from Mondays to Fridays) and underwent immediate primary PCI according to standard technique. Stent implantation and abciximab adjunctive therapy were left at the discretion of the treating physician. Therefore, the direct PCI group included 99 patients (95 + 4 with contraindications to lytic therapy). On admission, all patients were also treated with aspirin (325 mg), heparin, and clopidogrel (loading dose 300 mg). The dose of heparin was adjusted according to the presence or absence of concomitant abciximab therapy. Left ventricular function was evaluated by two-dimensional echocardiography within 24 hr from admission and at 1 month. After discharge, patients entered a clinical follow-up.

Angiographic Analysis

In all patients, basal and post-PCI coronary angiographies were analyzed offline, in the best projection to visualize the infarct-related artery. The degree of the stenosis was evaluated by quantitative coronary angiography performed with a digital system (Acom QuantCor, Siemens, Germany) using the guiding catheter as a scaling device. TIMI flow grades [9], corrected TIMI frame count [10], and TIMI perfusion grades [11] were assessed according to previously described definitions. Fast TIMI 3 flow was defined as a corrected TIMI frame count < 23 frames [12].

Endpoints

The primary endpoint of the study was the postinterventional angiographic result, evaluated in terms of corrected TIMI frame count. PCI was considered successful if a TIMI flow grade 3 was restored in the absence of a residual stenosis $> 50\%$. Secondary endpoints were left ventricular functional recovery at 1 month, bleeding complications, in-hospital and 6-month clinical outcome. Left ventricular function was evaluated by echocardiography before PCI and at 1 month. Major bleedings were considered those requiring transfusion or life-threatening because of location (intracranial, retroperitoneal). Major adverse cardiac events included death, recurrent myocardial infarction, re-PCI, coronary artery bypass surgery, and stroke.

Statistical Analysis

Categorical variables were compared by Pearson's chi-square analysis or Fisher's exact test. Continuous variables are presented as mean ± one standard deviation or median with interquartile ranges and were compared by Student's *t*-test or one-way ANOVA as appropriate. For posthoc comparisons, the Bonferroni correction was applied. All *P* values are two-tailed. Differences in late cardiac events were examined with Kaplan-Meier survival curves and their associated log-rank test statistics. All analyses were performed with SPSS version 8.0 (SPSS, Chicago, IL) statistical software. Statistical significance was defined as $P < 0.05$.

RESULTS

Baseline clinical characteristics of the 212 patients enrolled are summarized in Table I. No significant difference was observed in the major demographic or clinical features between the two groups. Preprocedural times are detailed in Table I. No significant difference was observed in chest pain-to-hospital time, while, as expected, door-to-angiography and door-to-balloon times were significantly longer in the facilitated PCI group.

Basal Coronary Angiography

At basal angiography, the two groups were comparable in terms of major coronary anatomical findings. In particular, the incidence of one-, two-, or three-vessel

TABLE I. Baseline Clinical Characteristics and Preprocedural Times*

	Direct PCI group (n = 99)	Facilitated PCI group (n = 113)	*P*
Age (years)	66 ± 13	65 ± 13	0.264
Age ≥ 75 years (%)	27 (27.3)	28 (24.8)	0.679
Female sex (%)	29 (29.3)	24 (21.2)	0.177
Risk factor			
Hypertension (%)	41 (41.4)	39 (34.8)	0.325
Diabetes mellitus (%)	24 (24.2)	18 (15.9)	0.130
History of smoking (%)	41 (41.4)	54 (47.8)	0.352
Hypercholesterolemia (%)	31 (31.3)	43 (38.1)	0.304
Prior myocardial infarction (%)	15 (15.2)	14 (12.4)	0.559
Preinfartual angina (%)	26 (26.3)	25 (22.3)	0.505
Prior CABG (%)	2 (2.0)	1 (0.9)	0.485
Prior PCI (%)	7 (7.1)	12 (10.6)	0.367
Anterior AMI (%)	43 (43.4)	49 (43.4)	0.992
Killip class ≥ 2 (%)	37 (38.9)	35 (31.0)	0.229
TIMI risk score	5.3 ± 2.8	4.9 ± 2.5	0.199
Left ventricular EF (%)	40 ± 9	40 ± 7	0.507
Chest pain to hospital (min)	101 (69–188)	109 (67–154)	0.606
Needle-to-angiography time (min)		37 (27–50)	
Door-to-angiography time (min)	44 (37–61)	60 (48–76)	0.001
Door-to-balloon time (min)	54 (47–75)	72 (59–90)	0.001

*Data are presented as mean value ± SD or number (%) of patients; procedural times are presented as median with interquartile ranges. PCI, percutaneous coronary intervention; CABG, coronary artery by-pass graft; AMI, acute myocardial infarction; EF, ejection fraction.

TABLE II. Basal Angiographic Findings and Postinterventional Angiographic Results*

	Direct PCI group (n = 99)	Facilitated PCI group (n = 113)	*P*
Multivessel coronary disease (%)	59 (59.6)	54 (47.8)	0.086
Two vessels (%)	42 (42.4)	39 (34.5)	0.237
Three vessels (%)	16 (16.2)	13 (11.5)	0.325
Infarct coronary artery (%)			0.387
Left anterior descending (%)	40 (40.4)	52 (46.0)	
Left circumflex (%)	21 (21.2)	14 (12.4)	
Right coronary (%)	37 (37.4)	46 (40.7)	
Bypass graft (%)	1 (1.0)	1 (0.9)	
Infarct artery stenting (%)	95 (96.0)	105 (92.9)	0.339
Stent length (mm)	17.1 ± 7.1	16.7 ± 6.0	0.287
Final minimal lumen diameter (mm)	2.88 ± 0.69	3.01 ± 0.55	0.151
Final TIMI flow grade 3 (%)	91 (91.9)	109 (96.5)	0.129
Final cTFC	30 ± 19	26 ± 13	0.045
Final cTFC < 23 (fast TIMI 3 %)	39 (39.4)	58 (51.3)	0.054
Final TIMI perfusion grade 3 (%)	39 (39.4)	58 (51.3)	0.054

*Data are presented as mean value ± SD or number (%) of patients. cTFC, corrected TIMI frame count.

disease and the infarct-related artery were evenly distributed between the direct PCI and the facilitated PCI groups (Table II).

Basal coronary flow in the infarct-related artery as assessed by TIMI grades was better in the facilitated PCI group vs. direct PCI group (1.76 ± 1.30 vs. 0.32 ± 0.73; $P = 0.001$). Of notice, only one patient in the direct PCI group showed a basal TIMI flow grade 3, while this was observed in almost half of the patients in the facilitated PCI arm (1% vs. 44.2%; $P = 0.001$). Figure 1 details the distribution of preinterventional TIMI flow grades between the two study groups.

Procedural Results and Impact on Left Ventricular Function

Primary coronary angioplasty was successful in 91/99 patients (92%) in the direct PCI group and in 109/113 patients (96%) in the facilitated PCI group ($P = 0.129$). The procedure included stenting in most patients of both groups, with a similar mean total stent length and final luminal diameter (Table II). At the time of PCI, 68.0% of patients in the direct PCI group were treated with abciximab.

A significant difference was observed between the two groups in final coronary perfusion of the infarct-related

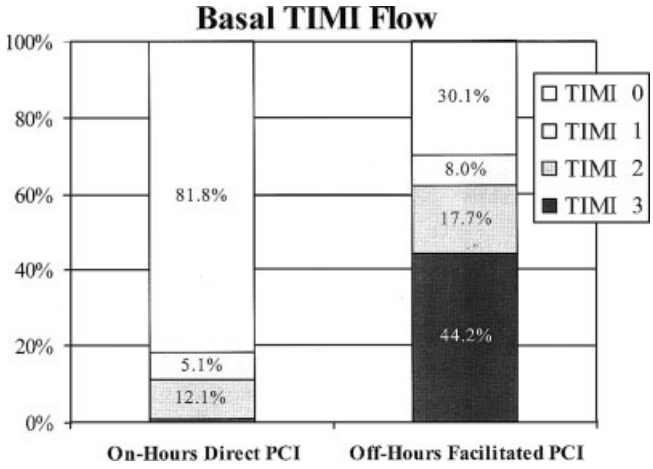

Fig. 1. TIMI flow at basal angiography.

artery as assessed by corrected TIMI frame count (Table II). The mean gain in left ventricular ejection fraction at 1 month was not significantly different between the direct and the facilitated PCI groups (7.0% ± 9.2% vs. 8.3% ± 6.6%, respectively; NS; $P = 0.259$).

When analyzing the results according to the preinterventional TIMI flow grade, more patients starting PCI with a TIMI flow grade 3 achieved a postinterventional fast TIMI flow grade 3 as well as a TIMI perfusion grade 3 (Table III). A preinterventional TIMI flow grade 3 was also associated with a better recovery in left ventricular function at 1 month, as evaluated by the mean gain in left ventricular ejection fraction (10.9% ± 6.4% vs. 7.0% ± 9.3% direct PCI group vs. 6.1% ± 6.0% facilitated PCI group with basal TIMI 0–2; $P = 0.004$; Fig. 2).

In-Hospital and Late Clinical Outcome

Overall in-hospital mortality was 4.7% (10 patients), without significant difference between the facilitated and the direct PCI group (3.5% vs. 6.1%, respectively; NS; $P = 0.294$). Patients with baseline TIMI flow grade 3 showed a particularly favorable clinical outcome, with no major cardiac events during index hospitalization and very few events at follow-up (median time to last follow-up or major cardiac events = 230 days; interquartile range = 95–324 days; Table IV, Fig. 3).

As far as safety is concerned, no significant difference was observed in the incidence of major bleedings between the direct PCI and the facilitated PCI groups (3.0% vs. 6.2%, respectively; NS; $P = 0.226$), although there was a trend toward more bleedings associated with combination therapy.

DISCUSSION

The present study shows that off-hour patients showing a preinterventional normal epicardial flow after combination therapy with very-low-dose alteplase and full-dose abciximab achieved a better myocardial reperfusion despite a longer door-to-balloon time when compared to direct PCI performed during regular business hours. Moreover, early angiographic benefit translated into a better recovery in left ventricular ejection fraction at 1 month and an overall favorable clinical outcome. Bleeding complications related to combination therapy remained a major concern despite the very low dose of thrombolytic drug.

Relevance of Time to Reperfusion in Primary Coronary Angioplasty

It is well known that the efficacy of thrombolytic therapy is inversely related to time to treatment. Although such a relationship is not so clear-cut in primary PCI, several studies have shown that time to reperfusion remains an important determinant of infarct size, mortality, and overall clinical outcome also in this setting. In particular, Cannon et al. [3] showed that patients undergoing primary PCI within 60 min from arrival had an in-hospital mortality rate 15% lower than patients treated between 61 and 120 min; death rate increased up to 40–60% in patients with a door-to-balloon time greater than 120 min. Similarly, a recent study by the Zwolle study group points out the relation between ischemic time and primary PCI, in particular in the absence of preprocedural antegrade flow [13]. According to Liem et al. [14], the median additional delay of 43 min due to transferring patients for primary PCI was associated with a more extensive myocardial damage and lower ejection fraction at 6 months. For patients directly referred to centers with catheterization facilities, the nighttime presentation is recognized as the most important predictor of door-to-balloon delay [6]. In the present study, the delay due to the off-hour presentation was comparable to that observed by Liem et al. [14] for transferring patients and therefore can be expected to affect infarct size adversely.

Primary PCI and Off-Hour Presentation

Previous studies reporting the results of primary PCI during the off-hours showed conflicting results. Some reported no significant differences in clinical outcome [15–17]. However, the populations were relatively small and therefore the studies were underpowered to test differences in mortality; in one study the off-hour presentation did not cause a longer ischemic and door-to-balloon times [17], and in another work a possible selection bias could have affected the results since only 23% of the patients were treated during the night [15]. A much larger study of 1,702 patients documented a twofold increase in mortality in patients with nighttime presentation linked to the higher rate of

TABLE III. Postinterventional Angiographic Results According to Basal TIMI Grade Flow*

	Direct PCI group basal TIMI flow 0–2 (n = 98)	Facilitated PCI group		
		Basal TIMI flow 0–2 (n = 63)	Basal TIMI flow 3 (n = 50)	*P*
Final TIMI flow grade 3 (%)	90 (91.8)	60 (95.2)	49 (98.0)	0.288
Final cTFC	30 ± 19[a]	28 ± 12	22 ± 13[a]	0.012
Final cTFC < 23 (fast TIMI 3) (%)	38 (38.8)[a]	22 (34.9)[b]	36 (72.0)[a,b]	0.001
Final TIMI perfusion grade 3 (%)	38 (38.8)[a]	25 (39.7)[b]	33 (66.0)[a,b]	0.004

*Data are presented as mean value ± SD or number (%) of patients.
[a]$P < 0.05$ for direct PCI group vs. TIMI 3 facilitated PCI group.
[b]$P < 0.05$ for TIMI 0–2 facilitated PCI group vs. TIMI 3 facilitated PCI group.

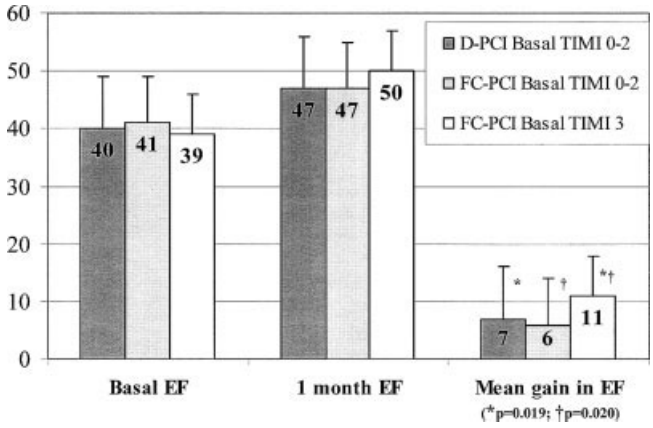

Fig. 2. Left ventricular function according to basal TIMI grade flow. EF, ejection fraction; D-PCI, direct PCI group; F-PCI, facilitated PCI group.

failed PCI [7]. A circadian variation in the occurrence of MI was also observed, suggesting that time of treatment can be independent of time to treatment and linked to both pathophysiologic daily periodicity and different performance of the healthcare team [18].

A strategy of facilitated PCI during the off-hours could potentially act on both delay, heightened thrombogenicity and medical performance, by starting early recanalization of the infarct-related artery. In fact, performing PCI on an open artery reduces the probability of a failed procedure [19] and generally makes PCI less troublesome. It is possible to speculate that this advantage could balance the lower performance of the medical team at night.

Previous Studies on Facilitated PCI

To date, published information on facilitated PCI is mainly derived from trials aimed at testing the effectiveness of combination therapy as a reperfusion strategy per se. In these trials, PCI was performed only in a subgroup of the patients enrolled according to the angiographic result after pharmacological therapy. In the TIMI 14 trial [8], combination therapy was effective in improving both basal flow at 60 and 90 min as well as the results of PCI. Similar results were obtained by the SPEED [20] and the INTEGRITI [21] trials. A recent meta-analysis [22] of 4,924 patients comparing facilitated PCI with standard treatment showed a significantly better outcome in the facilitated PCI group (OR = 0.67; 95% CI = 0.46–0.96; $P = 0.00001$ for death, nonfatal MI, and target vessel revascularization) with a nonsignificant trend toward more bleedings (OR = 1.12; 95% CI = 0.86–1.47).

Results of the Present Study

The main result of the present study was that combination therapy with very-low-dose alteplase and abciximab improved the results of off-hour primary PCI when effective in restoring early epicardial reperfusion. The off-hour presentation was not associated with an increased rate of failed procedures as reported by previous studies [7], possibly related to the advantage of starting the procedure with a TIMI flow 2–3 in most patients. Early and more complete myocardial revascularization translated into an improvement in left ventricular function at 1 month. These results are consistent with previous observations that pointed out the relevance of basal TIMI flow grade 3 on left ventricular function recovery [23] and mortality [19]. Of notice, in the present study, the failure in achieving a basal TIMI 3 flow with combination therapy does not seem to have affected adversely the postinterventional angiographic result when compared to direct PCI.

In the present study, we found a relevant difference in basal TIMI flow between the two groups because of a low rate of TIMI 2–3 grade flow in the direct PCI group (13%). It should be noticed that this patient group was treated before PCI with heparin and ASA only. Our data are comparable with the rate of TIMI 2–3 flow found in the placebo arm (ASA and heparin) of the ADMIRAL trial (10.8%) [24].

The pharmacological regimen for combination therapy was chosen on the basis of the results of the TIMI 14 trial [8], which showed that adding a very low dose of lytic to standard-dose abciximab could improve the

TABLE IV. In-Hospital and Late Clinical Outcome According to Basal TIMI Grade Flow*

	Direct PCI group basal TIMI flow 0–2 (n = 98)	Facilitated PCI group		
		Basal TIMI flow 0–2 (n = 63)	Basal TIMI flow 3 (n = 50)	*P*
In-hospital outcome				
Death (%)	6 (6.1)	4 (6.3)	0	0.195
Recurrent ischemia (%)	3 (3.1)	2 (3.2)	0	0.458
Repeat PCI (%)	1 (1.0)	0	0	0.560
CABG (%)	2 (2.0)	1 (1.6)	0	0.606
Stroke (%)	0	0	0	
MACE (%)	10 (10.2)	5 (7.9)	0	0.070
Heart failure	17 (17.3)[a]	7 (11.1)	1 (2.0)[a]	0.023
MACE + heart failure (%)	21 (21.4)[b]	9 (14.3)	1 (2.0)[b]	0.007
Late outcome				
Death (%)	10 (10.2)	5 (7.9)	0	0.082
Recurrent AMI	4 (4.4)	1 (1.7)	1 (2.0)	0.780
Repeat PCI (%)	6 (6.7)	0	2 (4.0)	0.220
CABG (%)	3 (3.4)	1 (1.7)	1 (2.0)	0.801
MACE (%)	20 (20.4)[c]	6 (9.5)	3 (6.0)[c]	0.048
Heart failure (Rehospitalization)	15 (16.7)	6 (10.2)	3 (6.0)	0.188
MACE + heart failure (%)	32 (32.7)[d]	12 (19.0)	6 (12.0)[d]	0.033

*MACE, major adverse cardiac events.
[a]$P = 0.016$ for direct PCI group vs. TIMI 3 facilitated PCI group.
[b]$P = 0.003$ for direct PCI group vs. TIMI 3 facilitated PCI group.
[c]Log-rank 4.79, $P = 0.028$ for TIMI 0–2 direct PCI group vs. TIMI 3 facilitated PCI group.
[d]Log rank 5.85, $P = 0.015$ for TIMI 0–2 direct PCI group vs. TIMI 3 facilitated PCI group.

rate of TIMI flow grade 3 without a significant increase in bleeding complications (reported rate = 3%). The relatively small rate of expected TIMI flow grade 3 was still considered an acceptable target since our strategy included mechanical reperfusion anyway.

In the present study, 44% of the patients presenting off-hours and pretreated with alteplase and abciximab showed a basal TIMI flow grade 3. This finding is consistent with the results of the TIMI 14 trial [8], although in that trial angiography was performed later. The relatively small increments in the rates of TIMI flow grade 3 with time according to the present study (44%) and to the TIMI 14 trial at 60 min (47%) and at 90 min (53%) suggest that the large part of the effect of combination therapy occurs early after administration, which makes it suitable for facilitated primary PCI. As far as safety is concerned, the 6.2% incidence in major bleedings was disappointing and, although no significant difference was found with the direct PCI group, the observed trend reinforces the concern about bleeding risk associated with combination therapy despite the very low dose of lytic drug.

In the present study, the rate of TIMI 3 flow in the direct PCI group was lower than that reported by previous works [19,25,26]. A possible explanation could be the shorter door-to-balloon time and consequently the shorter time between aspirin and heparin administration and first angiography.

Lastly, in this study PCI was performed in all patients, even if a TIMI flow grade 3 was observed at baseline. This strategy is supported by de Lemos et al. [27], who showed a better ST segment resolution if PCI was added to combination therapy even in the presence of a normal basal flow.

Study Limitations

Our study has several limitations. First, the study was not randomized and therefore cannot assess whether facilitated PCI is actually superior to direct PCI in patients presenting off-hours. However, the group of patients presenting off-hours was well matched with the group of patients presenting during regular hours, making the differences observed in basal and post-PCI angiography unlikely due to chance.

A second limitation is related to the small sample size, which affects in particular the clinical results. For this reason, the primary endpoints of the study were angiographic markers of myocardial reperfusion, which were shown to predict clinical outcome and can therefore be used as surrogate for the hard clinical endpoints. Still, the positive trend observed is consistent with the angiographic results of this study as well as with previously published papers, supporting the rationale for further investigation on this therapeutic strategy.

Finally, the dosing regimen chosen for the facilitated PCI protocol is arbitrary, although based on the results of the

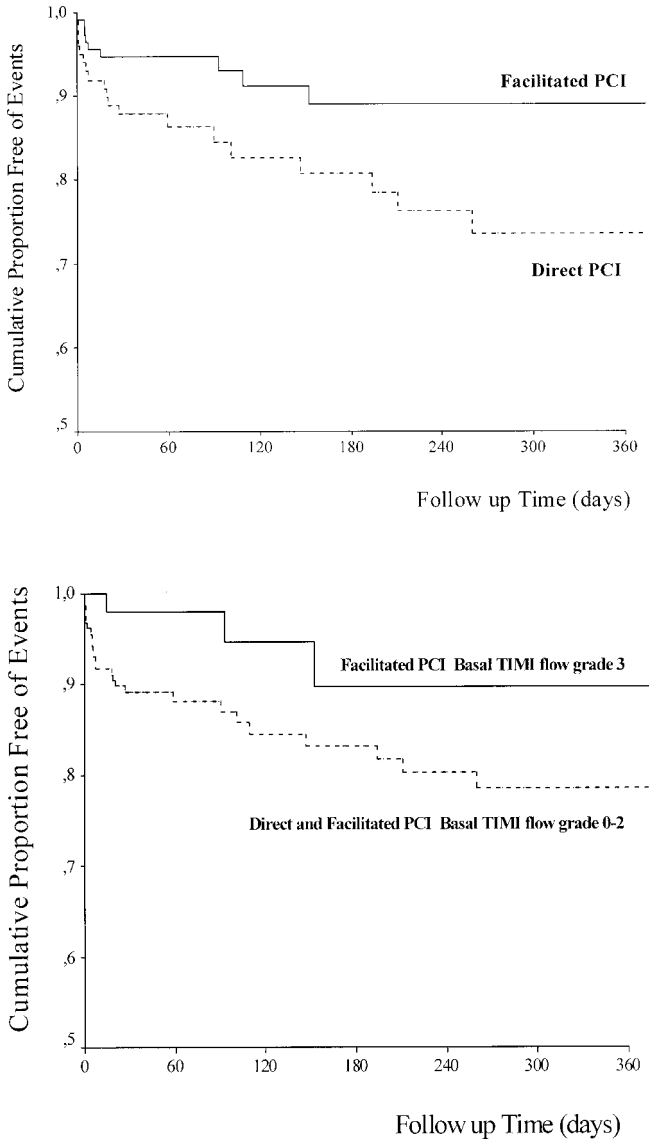

Fig. 3. One-year event-free survival for major adverse cardiac events according to facilitated PCI group and direct PCI group (log-rank 5.20; *P* = 0.022; top) and according to basal TIMI grade flow (*P* = 0.047 for basal TIMI flow 0–2 of direct and facilitated PCI groups vs. basal TIMI flow 3 of facilitated PCI group; bottom).

TIMI 14 trial. We cannot exclude that different pharmacological approaches could be superior in efficacy and safety.

In our series, combination of abciximab and very low dose of alteplase improved the results of primary PCI when effective in achieving a basal TIMI 3 flow. Bleeding risk remains a major drawback.

REFERENCES

1. Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaeck H, Thayssen P, Abilgaard U, Pedersen F, Madsen JK, Grande P, Villadsen AB, Krusell LR, Haghfelt T, Lomholt P, Husted SE, Vigholt E, Kjaergard HK, Mortensen LS, for theDANAMI-2 investigators. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. N Engl J Med 2003;349: 733–742.
2. Bonnefoy E, Lapostolle F, Leizorovicz A, Steg G, McFadden EP, Dubien PY, Cattan S, Boullenger E, Machecourt J, Lacroute JM, Cassagnes J, Dissait F, Touboul P. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomized study. Lancet 2002;360:825–829.
3. Cannon CP, Gibson M, Lambrew CT, Shoultz DA, Lewy D, Frenc WJ, Gore JM, Weaver WD, Rogers WJ, Tiefenbrunn AJ. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. JAMA 2000;283:2941–2947.
4. Brodie BR, Stuckey TD, Wall TC, Kissling G, Hansen CJ, Muncy DB, Weintraub RA, Kelly TA. Importance of time to reperfusion for 30-day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 1998;32:1312–1319.
5. Sheiban I, Fragasso G, Rosano GM, Dharmadhikari A, Tzifos V, Pagnotta P, Chierchia SL, Trevi G. Time course and determinants of left ventricular function recovery after primary angioplasty in patients with acute myocardial infarction. J Am Coll Cardiol 2001;38:464–471.
6. Angeja BG, Gibson CM, Chin R, Frederick PD, Every NR, Ross AM, Stone GW, Barron HV. Predictors of door-to-ballon delay in primary angioplasty. Am J Cardiol 2002;89:1156–1161.
7. Henriques JPS, Haasdijk AP, Zjilstra F. Outcome of primary angioplasty for acute myocardial infarction during routine duty hours versus during off-hours. J Am Coll Cardiol 2003;41:2138–2142.
8. Antman EM, Giugliano RP, Gibson CM, McCabe C, Coussement P, Kleiman NS, Vahanian A, Adgey AAJ, Menown I, Rupprecht HJ, Van der Wieken R, Ducas J, Scherer J, Anderson K, Van der Werf F, Braunwald E. Abciximab facilities the rate and extent of thrombolysis: results of the thrombolysis in myocardial infarction (TIMI) 14 trial. Circulation 1999;99:2720–2732.
9. TIMI study group. The thrombolysis in myocardial infarction (TIMI) trial. N Engl J Med 1985;31:932–936.
10. Gibson CM, Cannon CP, Daley WL, Dodge JT, Alexander B, Marble SJ, McCabe CH, Raymond L, Fortin T, Poole WK, Braunwald E. The TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996;93:879–888.
11. Van't Hof AWJ, Liem A, Suryapranata H, Hoorntje JCA, de Boer M, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction. Circulation 1998;97:2302–2306.
12. Hamada S, Nishiue T, Nakamura S, Sugiura T, Kamihata H, Miyoshi H, Imuo Y, Iwasaka T. TIMI frame count immediately after primary coronary angioplasty as a predictor of functional recovery in patients with TIMI 3 reperfused acute myocardial infarction. J Am Coll Cardiol 2001;38:666–671.
13. De Luca G, Suryapranata H, Zijlstra F, van't Hof AW, Hoorntje JC, Gosselink AT, Dambrink JH, de Boer MJ. Symptom-onset-to-ballon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. J Am Coll Cardiol 2003; 42:991–997.
14. Liem AL, Van't Hof AWJ, Hoorntje JCA, de Boer M, Suryapranata H, Zijlstra F. Influence of treatment delay on inferct size and clinical outcome in patients with acute myocardial infarction treated with primary angioplasty. J Am Coll Cardiol 1998;32: 629–633.

15. Zahn R, Schiele R, Seidl K, Schuster S, Hauptmann KE, Voigtlander T, Gottwik M, Berg G, Kunz T, Glunz HG, Limbourg P, Senges J. Daytime and nighttime differences in patterns of performance of primary angioplasty in the treatment of patients with acute myocardial infarction. Am Heart J 1999;138:1111–1117.
16. Beohar N, Chandwaney R, Lynne M, Goodreau LM, Davidson CJ. In-hospital and long-term outcomes of patients with acute myocardial infarction undergoing direct angioplasty during regular and after hours. J Invas Cardiol 2001;13:669–672.
17. Garot P, Juliard JM, Benamer H, Steg PG. Are the results of primary percutaneous transluminal coronary angioplasty for acute myocardial infarction different during the ''off'' hours? Am J Cardiol 1997;79:1527–1529.
18. Spencer FA, Becker RC. Circadian variations in acute myocardial infarction: patients or health care delivery? J Am Coll Cardiol 2003;41:2143–2146.
19. Stone GW, Cox D, Garcia E, Brodie BR, Morice MC, Griffin J, Mattos L, Lansky AJ, O'Neill WW, Grines C. Normal flow (TIMI 3) before mechanical reperfusion therapy is an independent determinant of survival in acute myocardial infarction: analysis from the PAMI trials. Circulation 2001;104:636–641.
20. Herrmann HC, Moliterno DJ, Ohman EM, Stebbins AL, Bode C, Betriu A, Forycki F, Miklin JS, Bachinsky WB, Lincoff AM, Califf RM, Topol EJ. Facilitation of early percutaneous coronary intervention after reteplase with or without abciximab in acute myocardial infarction: results fron the SPEED (GUSTO-4 pilot) Trial. J Am Coll Cardiol 2000;36:1489–1496.
21. Zeymer U, Van de Werf F, Giugliano RP, Roe MT, Kitt MM, Strony JT, Harrington RA, Braunwald E, the INTEGRITI investigators. Effects of facilitated percutaneous coronary intervention on myocardial perfusion and clinical outcome in patients treated with tenecteplase and eptifibatide for acute myocardial infarction. Eur Heart J 2002;4(Suppl):23.
22. Casella G, Capecchi A, Ottani F, Sangiorgio P, Pavesi PC, Bracchetti D. Facilitated PTCA in acute myocardial infarction: a meta-analysis of available studies. Eur Heart J 2002;4(Suppl):24.
23. Ross AM, Coyne KS, Reiner JS, Greenhouse SW, Fink C, Frey A, Moreyra E, Traboulsi M, Racine N, Riba AL, Thompson MA, Rohrbeck S, Lundergan CF. A randomized trial comparing primary angioplasty with a strategy of short-acting thrombolysis and immediate planned rescue angioplasty in acute myocardial infarction: the PACT trial. J Am Coll Cardiol 1999;34:1954–1962.
24. Montalescot G, Barragan P, Wittemberg O, Ecollan P, Elhadad S, Villain P, Boulenc JM, Morice MC, Maillard L, Pansieri M, Choussat R, Pinton P. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med 2001;344:1895–1903.
25. Stone GW, Grines CL, Browne KF, Marco J, Rothbaum D, O'Keefe J, Hartzler G, Overlie P, Donohue B, Chelliah N, Timmis GC, Vlietstra R, Strzelecki M, Puchrowicz-Ochocki S, O'Neill W, Marco J. Predictors of in-hospital and 6 month outcome after acute myocardial infarction in reperfusion era: the primary angioplasty in myocardial infarction (PAMI) trial. J Am Coll Cardiol 1995;25: 370–377.
26. Stone GW, Brodie BR, Griffin JJ, Costantini C, Morice MC, St Goar FG, Overlie P, Popma JJ, McDonnell J, Jones D, O'Neill WW, Grines C. Clinical and angiographic follow-up after primary stenting in acute myocardial infarction: the primary angioplasty in myocardial infarction (PAMI) stent pilot trial. Circulation 1999;99:1548–1554.
27. de Lemos JA, Gibson CM, Antman EM, Murphy EM, Morrow DA, Schuhwerk KC, Schweiger M, Coussement P, Van de Werf F, Braunwald E. Abciximab and early adjunctive percutaneous coronary intervention are associated with improved ST-segment resolution after thrombolysis: observations from the TIMI 14 trial. Am Heart J 2001;141:592–598.