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TIMI 3 flow after primary angioplasty is an important predictor for outcome in patients with acute myocardial infarction

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■ **Abstract** *Background* Growing evidence suggests that poor coronary blood flow after primary percutaneous coronary intervention (PCI) is associated with unfavorable clinical out-come. We retrospectively evaluated data from our single center "real world patients" database of patients undergoing primary PCI to determine differences in clinical and angiographic patterns in patients with or without restoring thrombolysis in myocardial infarction (TIMI) flow 3. *Methods and results* Between 2001 and 2006, 500 patients underwent primary PCI for STEMI. In 430 patients, post-interventional TIMI flow 3 could be established. In this group, in-hospital mortality was significant lower (6.4% Vs. 32.9%; $P < 0.0001$), left ventricular ejection fraction was better (51.3 Vs. 44.2%; $P < 0.0001$), and prehospital fibrinolytic therapy (6.3% Vs. 14.3%; $P = 0.015$), cardiogenic shock (10.9% Vs. 24.3%; $P = 0.002$) and use of intra-aortic balloon pump were all more unlikely (5.8% Vs. 11.4%; $P = 0.045$) compared to patients with TIMI flow ≤ 2. In patients with post-interventional TIMI flow ≤ 2 the left anterior descending coronary artery (LAD) was significantly more often seen as the target vessel (54.3% Vs. 44.6%; $P = 0.039$). A regressions analysis showed that predictors leading to such flow patterns are diabetes ($P = 0.013$), pre-hospital fibrinolytic therapy ($P = 0.017$), cardiogenic shock ($P = 0.002$) and a 3-vessel disease ($P = 0.003$). After 6 months, patients without restored normal TIMI flow had worse New York Heart Association functional class (NYHA), and had to undergo repeat coronary angiography more often. *Conclusion* Post-interventional TIMI flow ≤ 2 is strongly associated with adverse out-come during hospitalization and after 6 months following hospitalization.

■ **Key words** TIMI flow – primary percutaneous coronary intervention – acute myocardial infarction – follow up – no reflow phenomenon

Introduction

Reperfusion therapy is the cornerstone of treatment for patients with acute ST-elevation myocardial infarction (STEMI). Timely reperfusion of the infarct-related coronary artery using fibrinolysis or PCI is central to optimal STEMI treatment [1–3, 10, 15, 18]. As our treatment center has a skilled PCI laboratory with an experienced interventional cardiologist on duty 24 h a day, patients admitted to our hospital undergo primary PCI if coronary arteries are suitable, as recommend in current standard guidelines [1] within <90 min door-to-balloon time.

The benefits of reperfusion therapy have been attributed to the prompt reestablishment of normal blood flow in the infarct-related artery, defined as thrombolysis in myocardial infarction (TIMI) 3 flow.

We investigated the clinical outcome at index hospitalisation and after 6 months in groups of patients with or without re-established TIMI three flow, using data from our acute PCI database of a "real world" outdoor patient cohort of 500 patients treated between February 2001 and October 2006.

Methods

■ Patient population

Results from 500 consecutive patients treated with acute PCI in acute STEMI were retrospectively acquired. STEMI was defined as typical ischemic chest pain within the previous 12 h and ST-segment elevations of >2 mm in at least two contiguous leads.

All patients underwent acute coronary angiography and, if eligible, direct or rescue angioplasty. All interventions were performed according to current standard guidelines [19–21].

As a pharmacological regimen, all patients received 500 mg Aspirin orally, 300 mg Clopidogrel and a weight adapted bolus of intravenous heparin (100 IE/kg) upon admission prior to entering the cathlab. A weight-adapted bolus (0.25 mg/kg) of abciximab (Reopro®, Lilly Corp) was also administered in all patients, with the exception of those who received prehospital fibrinolytic therapy. Administration of abciximab was established in our center as good clinical practice after data of positive impact in patients undergoing primary PCI came up [7, 9, 11]. Other medications, including betablockers, nitrates, and morphine were administered at the discretion of the physician on duty.

The antegrade radiocontrast flow of the infarct-related artery was determined on the final coronary angiogram by the operator with the use of TIMI criteria. The TIMI flow grades have been defined previously [22]. In brief, grade 0 perfusion is no antegrade flow beyond the point of occlusion; grade 1 is minimal incomplete perfusion of contrast medium around the clot; grade 2 (partial perfusion) is complete but delayed perfusion of the distal coronary bed with contrast material; and grade 3 (complete perfusion) is antegrade flow to the entire distal bed at a normal rate.

All patients were invited for a follow-up visit 6 months after index hospitalisation. Clinical status and 12 lead ECGs were performed routinely. An exercise test was also performed at the discretion of the physician.

■ Statistical analysis

A multivariate binary logistic regression analysis was performed to determine which clinical and angiographic variables would independently predict poor post-interventional coronary flow (TIMI flow ≤ 2). Variables with a P-value < 0.05 were considered statistically significant as independent predictors.

Values are expressed as mean ± standard deviation or frequencies. Differences in continuous variables were analyzed using the Student's t test. P-values < 0.05 were considered statistically significant.

Results

■ Baseline characteristics

The baseline characteristics are listed in Table 1. Five hundred patients underwent primary angioplasty for myocardial infarction. In all, 70 patients (14%), 21 (30%) female, did not show TIMI 3 flow after intervention. The number of patients with TIMI 0.1, and two flows were 32 patients (46%), 12 patients (17%) and 26 patients (37%) respectively. In 430 patients (86%), 111 female (25.8%), the procedure was considered complete after establishing TIMI 3 flow. In 419 out of the 430 patients with post procedural TIMI 3 flow, TIMI 3 flow was established by PCI. In 11 patients (2.6%) angioplasty was not performed for various reasons. In three patients, a pericarditis was diagnosed. Seven patients did not show angiographic stenosis ≥50%. These 10 patients (2%) were excluded from our analysis because no significant stenosis in

Table 1 Baseline characteristics of patients undergoing acute coronary angiography

	TIMI flow = 3 (n = 430) n (%)	TIMI flow ≤ 2 (n = 70) n (%)	P-value
Age (SD); years	61 (13)	64 (14)	0.049
Female	111 (25.8)	21 (30)	0.086
Onset of symptom to hospital (SD), min	292.6 (527.9)	341.9 (558.7)	0.231
History			
Hypertension	230 (53.5)	32 (45.7)	0.05
Diabetes	58 (13.5)	19 (27.1)	0.003
Hypercholesterolemia	216 (50.2)	38 (54.3)	0.084
Prior PCI or myocardial infarction	123 (28.6)	18 (25.7%)	0.103
Prior bypass surgery	13 (3.0)	5 (7.1)	0.064
Current tobacco smoker	135 (31.4)	20 (28.5)	0.101
Prehospital thrombolytic therapy	27 (6.3)	10 (14.3)	0.015
Clinical presentation			
Killip class > 1	203 (47.2)	40 (57.1)	0.032
Cardiogenic shock	47 (10.9)	17 (24.3)	0.002

SD standard deviation, *PCI* percutaneous coronary intervention

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the coronary arteries could be found. In one patient coronary morphology was not suitable for PCI and was therefore sent for acute coronary artery bypass grafting (CABG).

Of the 70 patients with post procedural TIMI flow ≤ 2, PCI was performed in 57 patients. 13 patients did not undergo angioplasty for various reasons. In 10 cases, PCI was not performed for technical reasons and patients were treated conservatively. One patient exhibited a closed Ramus obliquus as the target vessel, which was therefore not suitable for PCI. One patient was sent for acute coronary artery bypass grafting (CABG) as a result of a left main stem stenosis in a three vessels disease. In another patient, peripheral coronary embolism lead to ischemia and the vessel was not suitable for PCI. The interventional success rate was 82.6% in this cohort. The overall success rate was 97.6% (476 patients out of 488).

Compared with the cohort with TIMI 3 flow, those with TIMI flow ≤ 2 were significantly more likely to be older, diabetic, hypertensive, and had unsuccessful prehospital fibrinolytic therapy with an indication for a "rescue PCI". Similarly, presentation with cardiogenic shock, defined as adverse hemodynamics such as heart rate >100 beats/min and blood pressure <100 mmHg, despite adequate fluid administration, was more common in patients with TIMI flow ≤ 2.

There was also a trend towards a longer period of chest pain in patients with post-interventional TIMI flow ≤ 2. However, due to a large standard deviation, a statistically significant difference was not observed.

■ Angiographic results and clinical outcome

Angiographic characteristics differed between the two patient groups. In this analysis, only those patients with significant coronary artery stenosis (*n* = 490) were included. As mentioned previously, ten patients did not undergo revascularisation (Tables 2 and 3).

Thus, patients with TIMI flow ≤ 2 were more likely to have initial TIMI flow ≤ 1 (*P* = 0.015), left anterior descending and saphenous vein grafts as infarct-related artery, a left ventricular ejection fraction <50%, and were more likely to undergo rescue PCI after prehospital intravenous thrombolytic therapy and treatment with an intra-aortic balloon pump (*P* = 0.045).

There was a significant difference observed in overall mortality during index hospitalization between patients who achieved TIMI flow ≤ 2 and TIMI flow 3 (32.9 Vs. 6.4%, *P* < 0.0001) after their primary PCI. Follow-up mortality after 6 months was not statistically different between the two groups.

However, presentation of New York heart association classification (NYHA-Class) at the 6-month

Table 2 Angiographic data of patients showing significant coronary artery stenosis

	TIMI flow = 3 (*n* = 420) *n* (%)	TIMI flow ≤ 2 (*n* = 70) *n* (%)	*P*-value
Infarct-related artery			
Left anterior descending	190 (45.2)	38 (54.3)	0.039
Left circumflex	67 (16)	10 (14.3)	0.137
Right coronary	152 (36.2)	17 (24.3)	0.016
Saphenous vein graft	6 (1.4)	4 (5.7)	0.033
Left main	5 (1.2)	1 (1.4)	0.399
Three vessels disease	76 (18.1)	19 (27.1)	0.027
Initial TIMI flow			
0	265 (63.1)	49 (70)	0.059
1	62 (14.8)	13 (18.6)	0.097
2	52 (12.4)	8 (11.4)	0.155
3	41 (9.7)	0 (0)	0.0013
Post-procedure TIMI flow			
0	0 (0)	32 (45.7)	
1	0 (0)	12 (17.1)	
2	0 (0)	26 (37.2)	
3	420 (100)	0 (0)	
Intra-aortic balloon pump	25 (5.9)	8 (11.4)	0.045
Stentthrombosis	34 (7.9)	6 (8.6)	0.179
Left ventricular ejection fraction (SD)	51.3 (11.8)	44.2 (13.1)	0.00001

SD standard deviation, *TIMI* thrombolysis in myocardial infarction

Table 3 Follow up data

	TIMI Flow = 3 (*n* = 420) *n* (%)	TIMI Flow ≤ 2 (*n* = 70) *n* (%)	*P*-value
In hospital mortality	27 (6.4)	23 (32.9)	<0.0001
6 month follow up	393	47	
Lost of follow up	18 (4.5)	3 (6.4)	
Death	17 (4.2)	2 (4.3)	0.293
NYHA I	183 (51.1)	16 (38.1)	0.037
NYHA II	122 (34.1)	21 (50.0)	0.018
NYHA III	42 (11.7)	3 (7.1)	0.155
NYHA IV	11 (3.1)	2 (4.8)	0.258
Cardiac catheterization	133 (37.2)	23 (54.7)	0.012
TVR	52 (39.1)	4 (17.4)	0.025
PCI of non target vessel	22 (16.6)	4 (17.4)	0.232
ad CABG	4 (3.0)	0	

NYHA New York Heart Association, *TVR* target vessel revascularization, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *TIMI* thrombolysis in myocardial infarction

follow-up visit was significantly different. Patients with TIMI flow ≤ 2 were more likely to present in NYHA class ≥1 and to undergo repeated coronary angiography. However, target vessel revascularisation in these catheterizations was performed more often in the patients with post-interventional TIMI flow 3 (*P* = 0.025).

Table 4 Logistic regression analysis for independent predictors of postinterventional TIMI flow ≤ 2

Variable	Beta coefficient	Standard error	P-value	Odds ratio	95% confidence intervall
Cardiogenic shock	0.993	0.326	0.002	2.700	1.425–5.116
Three vessel disease	0.877	0.294	0.003	2.404	1.351–4.277
Prehospital thrombolytic therapy	0.976	0.408	0.017	2.653	1.191–5.906
Diabetes mellitus	0.781	0.316	0.013	2.185	1.176–4.060
Constant	−2.482	0.201	<0.001	0.084	

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■ Predictors of TIMI flow ≤ 2

Resorting to stepwise logistic regression, four independent predictors of TIMI flow ≤ 2 were identified: prehospital thrombolytic therapy, cardiogenic shock, three vessel disease, and diabetes mellitus. The most powerful predictors were cardiogenic shock and three vessel disease. Prehospital thrombolytic therapy and diabetes mellitus were also associated with a higher probability of a TIMI flow ≤ 2. The overall predictability of the regression model was 85.8% (Table 4).

Discussion

Successful reperfusion therapy, achieved through mechanical or pharmacological intervention, is the goal in the treatment of patients with STEMI [3, 10, 18].

The objective of all interventions is restoration of normal TIMI 3 flow within the epicardial coronary vessels. Time to reperfusion is an important factor in this topic, as described previously [5, 23]. This could give an account for worse outcome in patients after unsuccessful prehospital fibrinolytic therapy with an indication for a "rescue PCI". Rescue patients evolve larger infarctions, likely explained by delay to reperfusion [4]. On the other hand we did not administer abciximab in these patients which might additionally have an impact on TIMI flow and clinical outcome. For this topic further investigation is needed in order to establish therapeutical regimen with GPIIb/IIIa antagonists on top of a failed thombolytic therapy.

The study populations in previously published data discussing the influence of TIMI flow on angiographic and clinical results are different from the study population evaluated here. Previous studies excluded patients after prehospital fibrinolysis, and patients with cardiogenic shock, renal insufficiancy, or those with child-bearing potential (unless the result of a recent pregnancy test was negative) [12], or compared different therapeutical regimens [6].

We present data of a single center "real world cohort" of 500 patients admitted to our hospital with STEMI. As PCI was attempted in many patients that would have been excluded in former randomized trials, restoration was not feasible in all patients despite high levels of technical experience amongst the operators, as an overall success rate of 97.6% indicates.

Putative mechanisms for suboptimal post-interventional epicardial coronary flow, known as "no reflow phenomenon", may be a multi-factor condition reflecting damage to microvascular integrity incurred both during ischemia and at the time of reperfusion. Possible related factors are microvascular damage or edema, neutrophil plugging of the microvessels, microvascular spasm, distal embolization of thrombus, and debris, or poor PCI result with a significant residual stenosis, dissection, or mural thrombosis [13, 14, 16, 17].

The post-interventional TIMI flow is an important prognostic value for in-hospital mortality and clinical outcome 6 months post-hospitalization [8].

This analysis of a "real world patient cohort" demonstrates that the success rate of primary PCI is lower in older patients than in younger patients, and this finding is associated with a higher mortality with primary PCI during STEMI in elderly patients. In addition, patients with STEMI showing the left anterior descending coronary artery or saphenous vein grafts as the culprit vessel are more likely to have poor final coronary blood flow.

Overall, age, clinical presentation, and infarct localization appear to be important factors impacting the outcome in patients with STEMI undergoing primary PCI. Predictors for poor post-interventional flow in the coronary arteries are three vessels disease, cardiogenic shock, diabetes mellitus, and inefficient prehospital thrombolytic therapy.

A finding that has not been previously described is that patients undergoing rescue PCI due to inefficient intravenous fibrinolytic therapy have a post-interventional TIMI flow ≤ 2 significantly more often. These findings warrant further evaluation. It is most plausible that the mechanisms described above result in impaired flow in the coronary arteries if pharmacological reperfusion is not successful.

Patients with TIMI flow ≤ 2 exhibited worse NYHA class at the 6 month follow-up visit, requiring coronary angiography more frequently at this timepoint in order to obtain invasive control. However, the rate of target vessel revascularisation following the decision to obtain invasive control at the 6 month follow-up visit was significantly lower in these patients. This may, on the one hand, be the result of the higher incidence of three vessel disease in these patients, without the need for another PCI (total chronic occlusion; no angiographic significant stenosis (<60%)). On the other hand, as is the case in this patient group, age is associated with higher levels of sclerosis in the small lumen diameter vessels, without the possibility of mechanical

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intervention resulting in stable angina upon long term follow up.

Conclusion

The inability to achieve successful coronary reperfusion is associated with a higher mortality in patients with acute myocardial infarction undergoing primary angioplasty. Prehospital fibrinolytic therapy, age, and infarct localisation increase the risk of poor final coronary blood flow. Post- interventional TIMI flow ≤ 2 is associated with a worse NYHA class at a 6 month follow-up visit, requiring a significantly higher number of repeated coronary angiograms to assess invasive coronary status.

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