

# ***Thrombolysis failure with Streptokinase in ST-elevation myocardial infarction***

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## **Abstract**

In patients with acute ST elevation myocardial infarction (STEMI), coronary reperfusion with primary percutaneous coronary intervention (PCI) or fibrinolysis improve the prognosis. The main reason to prefer PCI, if it can be performed timely within 120 minutes, is his high incidence of reperfusion compared to thrombolysis. About 25-50% of patients treated with streptokinase fail to achieve successful reperfusion and these patients have poor prognosis.

The aim of this study was to determine independent factors related to thrombolysis failure with Streptokinase in STEMI patients using clinical and electrocardiogram criteria.

**Methods:** A prospective observational study conducted over 9 years including patients treated with Streptokinase for STEMI. Thrombolysis failure was defined using electrocardiogram criteria. Multivariate analysis was used to identify factors related to thrombolysis failure.

**Results:** From a total of 510 patients included, 198 (37%) failed fibrinolysis. The mean age of those patients was  $60 \pm 11$  years, 83% of the population were male. The average delay chest pain to first medical contact (FMC) was  $224 \pm 170$  minutes. Door to needle time was less than 30 minutes. The failure was associated with four variables including Female gender (aOR: 2.05, 95% CI 1.27-3.30;  $P < 0.001$ ), the delay from chest pain to FMC  $> 180$  min (aOR: 2.413, 95% CI 1.67-3.47;  $p < 0.001$ ), Extended anterior infarct (OR: 2.01, 95% CI 1.05-3.84;  $p = 0.033$ ) and cardiogenic Shock (OR: 7.12, 95% CI 1.66-30.48;  $p = 0.008$ ).

**Conclusion:** Streptokinase had a failure rate of 37%. Female gender, a longer delay from pain to first medical contact, extended anterior infarction, and cardiogenic shock were highly predictive of thrombolysis failure.

**Keywords:** Streptokinase, Thrombolysis, Failure, STEMI, Predictors

## Introduction

Primary percutaneous coronary intervention (PCI) is the recommended reperfusion strategy in patients presenting with a ST-segment elevation myocardial infarction (STEMI) (1). Intravenous thrombolysis is the most widely used reperfusion strategy if timely primary PCI cannot be performed. Streptokinase, a non-specific fibrinolytic still recommended. This strategy prevents approximately 20–30 deaths per 1000 patients treated, with a proportional reduction in mortality of up to 25% in certain subgroups (2). However, it's not always successful. In the angiographic sub-study of the GUSTO-I trial, the 90-minute arterial patency rate (defined by the presence of TIMI grade 2 or 3 flow) was 54% in patients who received Streptokinase, with only 29% of patients having TIMI grade 3 flow (3). The most well-known factor of thrombolysis failure was the delay from the pain onset. De Balder demonstrated in 2001 that the direct effect on tissue perfusion depends on mechanical, rheological, metabolic, and hematological factors(4).

This study aimed to identify predictive factors of thrombolysis failure in patients treated with Streptokinase for STEMI.

## Methods

### Study design and setting:

We conducted a prospective observational study for 9 years (January 2009 to December 2016).

### Study population:

**Inclusion criteria:** Patients who were admitted to the emergency department for STEMI and treated with Streptokinase as a reperfusion strategy.

**Exclusion criteria:** Presence of contraindications to streptokinase therapy, patients presenting with evolved myocardial infarction, or dying within 90 minutes of streptokinase therapy.

**Data collection:** Data were recorded in real time on a specific form.

## Definitions

STEMI was identified by the onset of typical chest pain lasting more than 20 minutes, unrelieved by nitrate, and associated with typical ST-segment elevation on the standard 12-lead ECG.

Thrombolysis strategy: Streptokinase was administered at the standard dose of  $1.5 \times 10^6$  units over 60 minutes. All patients received aspirin, clopidogrel, and heparin as recommended in the European Society of Cardiology (1). An ECG was recorded just before starting the Streptokinase infusion, and a second ECG was recorded 90 minutes later.

The criteria for thrombolysis failure were:

- Persistent pain
- Less than 50% resolution of the ST-segment elevation in the worst lead and no accelerated idioventricular rhythm 90 minutes after the initiation of thrombolytic treatment.

**Data analysis:** Statistical analysis was carried out with SPSS (version 18.0) statistical software package.

Data were presented as frequency and percent for categorical variables and as mean with standard deviation for quantitative variables.

A univariate analysis comparing the two groups was performed, with the chi-square test with Yates' correction or Fisher's exact test when appropriate, odds ratio (OR) with 95% confidence intervals (CI), and the unpaired t-test.

The logistic regression analysis with thrombolysis failure as the dependent variable was run. The analysis was performed with a binary logistic regression and “enters” method, with an entry criterion of 0.05 and removal criteria of 0.10. Differences were statistically significant with  $p<0.05$  or when the 95% confidence interval (CI) of the odds ratio (OR) excluded the value of 1.

**Ethical consideration:** The prospective study is approved by the Ethics Committee of Ben Arous Hospital. Patient consent was obtained for the collection of data and subsequent follow-up.

**Declaration of interests:** All authors declare no competing interests.

## Results

### *General characteristics of the study population:*

In the local registry, 1300 patients were included. Seventy percent were treated with fibrinolysis (Figure 1). We included 510 patients with a mean

Mean parameters at admission were: Systolic blood pressure:  $139\pm34$  mmHg; diastolic blood pressure:  $87\pm18$  mmHg; Heart rate:  $79\pm21$  bpm; Respiratory Rate:  $18\pm4$ ; SpO<sub>2</sub>:  $96\pm11\%$ .

The mean delay from chest pain to first medical contact was  $181\pm141$  minutes.

The initial ECG analysis resulted in the diagnosis of acute inferior myocardial infarction (52%), anterior myocardial infarction (38%), acute inferoposterior myocardial infarction (31%), acute anterolateral myocardial infarction (9%), and acute extended anterior myocardial infarction (28%).

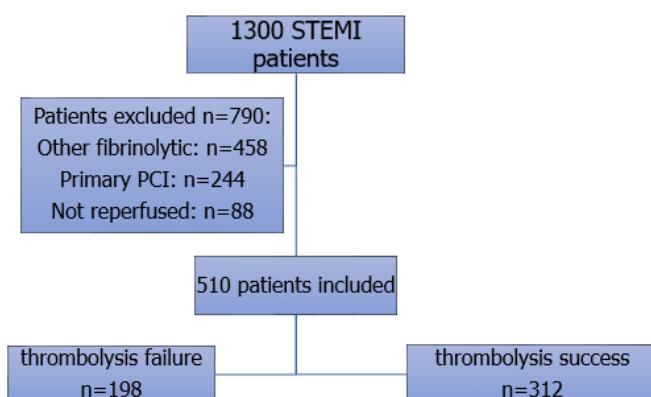
Initial hemodynamic complications were dominated by (%): hypotension (17), bradycardia (12), acute heart failure (11), cardiogenic shock (5), ventricular fibrillation (4.5). Failure was observed in 37% (n=198) of patients.

In-hospital mortality rate among patients treated with Streptokinase was 1%.

### Comparative study:

The comparative study between patients who failed thrombolysis and patients who succeeded thrombolysis identified Gender, smoking, delay of consultation, and extended anterior wall as related factors to fibrinolysis failure (Table 1).

Cardiogenic shock was more frequent in the group of failed thrombolysis (Table 1). Univariate analysis is represented in Table 2. In multivariate analysis, we identified four independent factors of thrombolysis failure: female gender, active smoking, delay pain to first medical contact  $>180$  minutes, extended anterior infarct, Killip $>III$ , and cardiogenic shock (Table 2).



**Figure 1: Flowchart of study population**

age of  $59\pm11$  years, and 83% of the population were male. Principal comorbidities were (%) smoking (76), hypertension (31), diabetes (28), dyslipidemia (12).

**Table 1: Comparative analysis of the groups**

	Failure N=198	Success N=312	p-value
<b>Sex ratio</b>	3.3	7.18	0.003
<b>Mean age (years) ±SD</b>	60±11	58±11	0.061
<b>Risk factors:</b>			
<b>Current smoking n (%)</b>	133(68)	252(81)	<0.001
<b>Hypertension n (%)</b>	69(35)	87(28)	0.095
<b>Diabetes n (%)</b>	65(33)	76(24)	0.036
<b>Dyslipidemia n (%)</b>	30(15)	31(10)	0.076
<b>Median delay pain to FMC (min) ±SD</b>	224±170	153±116	<0.001
<b>Extended anterior infarct n (%)</b>	65(33)	66(21)	0.003
<b>Clinical criteria</b>			
<b>Heart rate (bpm) ±SD</b>	80±24	78±40	0.179
<b>Systolic blood pressure (mmHg) ±SD</b>	136±37	140±33	0.278
<b>Killip class ≥3</b>	12(6)	2	<0.001
<b>Door to needle time (min) ±SD</b>	27±19	26±17	0.535
<b>Creatinine (μmol/l) ±SD</b>	86±39	81±21	0.037
<b>Glycemia (mmol/l) ±SD</b>	12±6	10±5	0.002
<b>Bradycardia n (%)</b>	17 (9)	45 (14.5)	0.05
<b>Acute heart failure n (%)</b>	12 (6)	14 (4.5)	0.415
<b>Cardiogenic shock n (%)</b>	21 (11)	5 (2)	<0.001
<b>Cardiac arrest n (%)</b>	10 (5)	17 (5.5)	0.858

**Table 2: Predictors of thrombolysis failure**

Characteristics	univariate analysis		Multivariate analysis	
	HR (95%) CI	p-value	HR (95%) CI	p-value
<b>Female Gender</b>	2.13 (1.35-3.37)	<0.001	2.054(1.27-3.30)	<0.001
<b>Current smoking</b>	2.14 (1.46-3.16)	<0.001	1.89 (1.14-3.11)	0.012
<b>Diabetes</b>	(0.463-1.006)	0.005		
<b>Pain to FMC &gt;180 min</b>	1.602 (1.32-1.93)	<0.001	2.413(1.67-3.47)	<0.001
<b>Extended anterior infarct</b>	2.68 (1.59-3.56)	0.02	2.015(1.05-3.84)	0.033
<b>Killip class ≥3</b>	2.02 (1.59-2.57)	<0.001	5.19 (1.06-25.2)	0.009
<b>Creatinine &gt;80μmol/l</b>	1.18 (0.90-1.55)	0.245		
<b>Glycemia &gt;8mmol/l</b>	1.05 (0.79-1.39)	0.71		
<b>Cardiogenic shock</b>	1.837 (1.47-2.29)	<0.001	7.12(1.66-30.48)	0.008

CI: confidence interval, FMC: first medical contact, Min: minutes.

**Discussion**

In this study, we have studied the extent of failed thrombolysis in 510 patients admitted to the emergency department for STEMI and treated with Streptokinase. We have also studied the association of failed fibrinolysis with demographic, clinical, and prognostic variables, and we identified predictive factors of fibrinolysis failure.

The extent of thrombolysis failure was 37%. In several studies, it varies from 15 to 50%. It depends on the criteria used for failed thrombolysis, the drug used, and the inclusion and exclusion criteria used. In Sudhindra Rao et al study (5) failed thrombolysis was observed in 40% of patients using the same criteria as the present study. Purcell IF et al (6), who used 120min ECG post thrombolysis with Streptokinase, and Katyal VK et al (7), who used < 30% at 90min as criteria, observed 34% failed thrombolysis.

Failed fibrinolysis had a higher percentage of females in the present study, and it represents an independent predictive factor of failure with an odds ratio = 2.054. Similar observation was made in GISSI-2(8), Gabriel IB et al (9), and M Sezer et al (10) studies. It can be explained by the high rate of atypical presentation and late consultation among women (11).

Diabetes is one of the important cardiovascular factors, and diabetics have a poor prognosis after STEMI, which can be partly due to abnormal microvascular flow. In the present study, diabetics had a higher trend of failed fibrinolysis. The same results were found by Keshav Singh et al (12).

Smoking was seen in a higher percentage of patients with successful thrombolysis in this study. Similar observation was made by GISSI (8) and Sezer et al. (10), Zahger et al (13) showed that smoking was significantly associated with successful thrombolysis and lower mortality, which can be attributed to the incidence of acute MI in younger age and a lesser atherosclerotic burden, and more thrombus at the site in smokers.

Time from onset of symptoms to first medical contact in this study was significantly higher in the failed group ( $224 \pm 170$  min) when compared to the successful group ( $153 \pm 116$  min). GISSI-2 (9) showed a significantly higher proportion of successful thrombolysis in patients presenting within 3 hours. We found that presentation after 180 minutes was an independent predictive factor of fibrinolysis failure. In this context, Bonnefoy et al. (14) demonstrated the non-inferiority of thrombolysis compared to primary PCI when performed in the first three hours.

An extended anterior wall myocardial infarction was seen in 33% and 21% of patients with failed and successful thrombolysis, respectively. There was a trend towards a higher occurrence of failed thrombolysis in anterior wall MI. Gabriel IB et al (9) and GISSI 2(10) showed this observation in significant proportions.

The pathophysiology of those findings was explained by the fact that the length of the culprit artery distal to left-system lesions was longer, and a greater percentage of the vessel lay distal to the culprit stenosis in left-system lesions. It could be speculated that slower flow in the left system may

be related to more extensive necrosis and increased myocardial edema as a result of the large myocardial mass subtended by the longer arteries(15).

In the present study, cardiogenic shock was identified as an important predictive factor of thrombolysis with an odds ratio of 7.12. In the SHOCK registry trial (16), Successful thrombolysis was obtained only for 26% of patients in cardiogenic shock. One mechanism for the thrombolysis failure associated with cardiogenic shock may be a greater impairment of coronary blood flow, and thus a lower effect of fibrinolytic agents, compared with patients with better hemodynamics (17).

## Conclusion

In STEMI patients seen in Tunisia, Streptokinase had a failure rate of 37%. Female gender, a longer delay from pain onset to first medical contact (more than 3 hours), extended anterior infarction, and cardiogenic shock were highly predictive of thrombolysis failure. Patients with those criteria may benefit from an invasive reperfusion strategy earlier to improve morbidity and mortality or fibrinolysis with specific agents as a part of the pharmaco-invasive strategy.

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