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The impact of diabetes on electrocardiographic ST resolution and clinical outcome of acute ST elevation myocardial infarction following fibrinolytic therapy

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SOUHRN

Cíl: Zjistit souvislost mezi diabetem na jedné straně a kvalitou rozlišení zobrazení segmentu ST a klinického výsledku na straně druhé, po fibrinolýze u pacientů po prvním infarktu myokardu s elevací segmentu ST (ST elevation myocardial infarction, STEMI).
Metody a výsledky: Prospektivně se shromažďovaly klinické údaje 275 po sobě následujících pacientů po prvním STEMI, jimž byla do šesti hodin po nástupu bolesti na hrudi podána streptokináza. Rozlišení segmentu ST ≥ 50 % v době 90 minut po fibrinolýze bylo považováno za známku úspěšné reperfuze. Souvislost diabetu s rizikem neúspěšné reperfuze, rozvojem srdečního selhání a nemocniční mortalitou byla hodnocena před adjustací na další rizikové faktory postižení koronárních tepen a po ní.
Rozlišení segmentu ST ≥ 50 % bylo přítomno u 45,1 % nediabetiků a 48,7 % diabetiků (p = 0,1). Srdeční selhání bylo častější a nemocniční mortalita vyšší u diabetiků (25,7 % vs. 14,8 %; p = 0,03, resp. 17,8 % vs. 8,4 %; p = 0,03). U diabetiků existovala vyšší pravděpodobnost koronarografického průkazu postižení tří cév (23 % vs. 8 %; p < 0,001). Po adjustaci na vstupní charakteristiky nebyl diabetes nezávisle spojen s neúspěšnou reperfuzí ani závažnými srdečními příhodami včetně srdečního selhání a nemocniční mortality.
Závěry: Kvalita rozlišení segmentu ST není případnou přítomností diabetu ovlivněna. I když u diabetiků byla popsána vyšší prevalence srdečního selhání a nemocniční mortality po léčbě STEMI streptokinázou, jejich nepříznivá prognóza je nejspíše důsledkem vyšší zátěže dalšími rizikovými faktory postižení koronárních tepen.

ABSTRACT

Objective: To investigate the association of diabetes with ST segment resolution and clinical outcomes after fibrinolysis in patients with first ST elevation myocardial infarction (STEMI).
Methods and results: Clinical information from 275 consecutive patients with first STEMI, who received streptokinase within six hours of chest pain initiation, was collected prospectively. ST resolution ≥ 50%, ninety minutes after fibrinolysis was considered as a sign of successful reperfusion. Association of diabetes with the risk of reperfusion failure, development of heart failure and in-hospital mortality was determined before and after controlling for other coronary risk factors.

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ST resolution ≥ 50% was present in 45.1% of non-diabetics and 48.7% of diabetics (p = 0.1). Heart failure and in-hospital mortality were more common in diabetics (25.7% vs. 14.8%, p = 0.03 and 17.8% vs. 8.4%, p = 0.03, respectively). Diabetics were more likely to have three-vessel disease in coronary angiography (23% vs. 8%, p < 0.001). After controlling for baseline characteristics, diabetes was not independently associated with reperfusion failure and major adverse cardiac events, including heart failure and in-hospital mortality. **Conclusions:** ST resolution is not affected by the presence of diabetes. Although diabetics have higher prevalence of heart failure and in-hospital mortality after treatment of STEMI with streptokinase, their poor outcome is most likely due to higher burden of simultaneous coronary risk factors.

Keywords:
Diabetes mellitus
Electrocardiography
Myocardial infarction
Thrombolysis

Introduction

ST elevation myocardial infarction (STEMI) is a major cause of morbidity and mortality worldwide. Timely management of STEMI, using reperfusion therapy, including fibrinolysis and primary percutaneous coronary intervention (PPCI), leads to a better outcome for these patients [1]. However, treatment success and later prognosis after reperfusion therapies vary among individuals [2,3]. Generally, primary-PCI is associated with an improved outcome in comparison to intravenous fibrinolysis [4,5]. Nevertheless, considering the fact that fast access to a center with PPCI facility is not feasible in every situation, even nowadays, intravenous fibrinolysis plays a great role in treatment of patients in many parts of the globe [6,7].

Reperfusion success after fibrinolysis is commonly evaluated non-invasively by comparing electrocardiograms (ECG) of the patients, before and after the fibrinolytic administration [8,9]. Resolution of ST segment after ST elevation on the ECG is associated with reperfusion success [7,9]. Reperfusion failure is attributed to different factors, including diabetes [2,10–12]. However, angiographic findings in diabetics after fibrinolysis therapy may be similar to non-diabetics regarding infarct related artery patency after fibrinolysis [13,14]. Contrary to what is expected, establishment of a good flow in epicardial arteries of diabetic patients, detected by angiography, may not be accompanied by ST resolution on ECG [13]. Microvascular pathologies, which impair myocardial perfusion in diabetics, are probable cause of ST resolution failure and poor prognosis of the diabetics [11]. In addition, diabetic patients in most studies are older with higher prevalence of coronary risk factors [14,15], which may partly describe the differences. Other predictors of ST resolution are not also consistent in various studies [3,16,17]. On the other hand, including the patients of clinical trials [18] and using different fibrinolytic medications in some of these studies [14] which may have dissimilar therapeutic responses [9,19], complicates the interpretation and application of the results to a single agent in real-life clinical settings. In addition, there are studies that have reported diminishing adverse impact of diabetes on short-term outcomes after myocardial infarction at least in certain subsets of population, which is attributed partly to the better use of therapeutic methods in diabetics [20,21].

Regarding these facts, we designed a cohort study to investigate the impact of diabetes on response of patients with STEMI to Streptokinase as a fibrinolytic agent, using electrocardiography as a non invasive method. We also sought to find any relationship between the presence of diabetes and short term major adverse cardiac events (MACE) including heart failure and hospital mortality, after treatment of STEMI with streptokinase.

Methods

Study population

This prospective cohort study included patients with first presentation of STEMI, who received streptokinase (Streptase: Aventis Behringer GmbH) within six hours after the onset of index chest pain in the emergency room as an alternative management strategy in our hospital when catheterization laboratories were busy or unavailable to perform PPCI. The study was started in March 2012 in Madani Heart Center, Tabriz, Iran and completed in March 2014. The design of the study was reviewed and approved by the institutional review board committee at Tabriz University of medical sciences.

All patients with clinical and electrocardiographic signs of acute myocardial infarction with ST-segment elevation were screened and those with a history of coronary artery bypass graft surgery or PCI, history or electrocardiographic evidence of a previous MI, left bundle branch block or pacemaker implantation along with those patients received fibrinolytic therapy in a referring hospital, were excluded from the study.

Study design

All demographic, electrocardiographic, echocardiographic, angiographic and serum biochemical data as well as prescribed medications during hospitalization and subsequent clinical outcomes were recorded in prepared questionnaires.

Patients were allocated to two groups based on the presence or absence of diabetes. In our study, patients with a history of diabetes mellitus, who were under treatment with oral hypoglycemic agents and/or insulin as well as patients with hemoglobin $A_{1c} \geq 6.5\%$ were considered as diabetics. Non-diabetic patients were identified with hemoglobin A_{1c} levels of < 6.5% in the absence of such therapy. STEMI was defined as the presence of typical chest pain lasting more than 30 minutes and ST elevation of more than 0.2 mV from the J point at least in two consecutive precordial leads or more than 0.1 mV in two limb leads on the admission ECG, along with elevated myocardial enzymes, which was defined as an increase of one point above the 99th percentile cut off point for creatinine-kinase MB (CK--MB) and Cardiac-Troponin I (cTNI). Development of heart failure during the treatment course was defined as having pulmonary rales on auscultation and/or signs of congestion on Chest-x-Ray.

In candidates for fibrinolysis, Streptokinase was administered at a dose of 1.5 million units, over 30 minutes, diluted in 100 ml of normal saline along with standard therapy for STEMI including aspirin and heparin.

Electrocardiographic assessment

The baseline ECGs before administrating streptokinase and ECGs recorded 90 min after fibrinolysis were evaluated to determine the extent of ST segment resolution. The sum of ST segment elevation in all leads on primary ECG minus the sum of ST segment elevation in the second ECG was divided by the sum of ST segment elevation in the primary ECG and expressed as percentage. A resolution of 50 percent or more from the initial ST elevation was considered as a significant ST resolution and a sign of successful response to streptokinase.

Outcomes of the study

Significant response to streptokinase on ECG as well as clinical outcomes, including development of heart failure, in-hospital mortality and major adverse cardiac events (MACE), defined as a composite of both heart failure and hospital mortality, were compared in patients with and those without diabetes.

Statistical analysis

Statistical software SPSS (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0.Chicago, United States) was used for data analysis. Continuous variables were presented as mean ± standard deviation or median (25–75% interquartile), and categorical variables were reported as frequencies and percentages. Fisher's exact test or Chi-square analysis was done as appropriate to compare the frequencies of categorical variables. Either independent t-test or equivalent non-parametrical Mann-Whitney U-Test was used to compare the continuous variables between two study groups. Multivariate logistic regression analysis was performed to determine the independent effect of diabetes on study endpoints. A P value less than 0.05 was considered statistically significant.

Results

A total number of 275 patients were eligible to enter the study. The mean age of patients was 60.3±10.9 years. Among the study sample, 201 out of 275 patients (73.1%) were male and 74 out of 275 (26.9%) were female. Diabetes was present in 113 patients (41.1%) and 162 patients (58.9%) were non-diabetics. Table 1 compares demographic variables, medications, and serum laboratory data in diabetic and non-diabetic patients.

The mean age of diabetics was significantly higher than non-diabetics (61.6±12.2 vs. 58.4±12.9, $p = 0.03$). Among study sample, 63.7% of diabetics and 79.6% of non-diabetics were male ($p = 0.03$). Diabetic patients had significantly higher prevalence of hyperlipidemia (42.5% vs. 14.8%, $p < 0.001$). Prevalence of hypertension was higher in diabetics (68.1% vs. 30.9%, $p < 0.001$). Family history of premature cardiovascular diseases was also more common in diabetic patients (10.6% vs. 2.5%, $p = 0.005$).

Diabetics had higher creatinine levels than non-diabetics ($p = 0.01$). Admission blood glucose was higher in diabetics ($p < 0.001$). Pain to needle time was available only in 146 patients. A Mann-Whitney U Test revealed a significant difference in the pain to needle time of diabetics (median = 4 h, 25–75% interquartile: 2–5, n = 79) and non-diabetics (median = 4 h, 25–75% interquartile: 3–6, n = 66), U = 2 074, z = –2.14, $p = 0.03$, r = .17. Comparing the mean ranks showed a longer pain to needle time in non-diabetics than in diabetics. (mean rank: 81.07 for non-diabetics vs. 66.26 for diabetics).

Cardiac biomarker levels were compared using Mann-Whitney U test. There were no significant differences between two groups regarding peak cardiac enzyme levels. Aspirin use was similar in diabetics and non-diabetics. Beta-blockers were used in 77% of diabetics and 82.1% of non-diabetics with no significant difference between two groups ($p = 0.2$). The use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) was significantly higher in diabetics and calcium-channel blockers were more frequently used in non-diabetics (table 1).

During hospitalization period, diabetic patients were more likely to develop left bundle branch block after fibrinolysis (7.1% vs. 1.9%, $p = 0.03$). Development of atrioventricular block and atrial fibrillation were not significantly different in diabetics and non-diabetics (table 2). Ventricular tachycardia or fibrillation after the first day of hospitalization was more common in diabetics; however, the difference was not statistically significant (6.2% vs. 1.9%, $p = 0.05$). Left ventricular ejection fraction less than 40% was present in 49.6% of diabetics and 45.7% of non-diabetics with no significant difference. Regarding the findings of coronary angiography, performed during hospitalization, prevalence of three-vessel coronary disease was significantly higher in diabetics (23% vs. 8%, $p < 0.001$).

Based on electrocardiographic evaluations, ST resolution ≥50%, 90 minutes after receiving the standard dose of streptokinase, was present in 128 out of 275 patients (46.5%) and the remaining 147 patients (53.5%) had response failure. There was no significant difference between diabetics and non-diabetics in their response to streptokinase. ST resolution ≥50% was present in 55 out of 113 diabetics (48.5%), and it was present in 73 out of 162 non-diabetics (45.5%), $p = 0.8$. Mean ST segment resolution was 42.88 ± 29.05 percent in diabetics and it was 38.67±27.76 percent in non-diabetics (p = 0.1).

In multivariate analysis after adjustment for age, sex, hyperlipidemia, hypertension, smoking and family history of premature cardiovascular diseases, diabetes was not an independent predictor of response to streptokinase therapy (odds ratio [OR] for ST resolution <50% in diabetics: [0.62; 95% confidence interval, CI]: [0.35–1.09]), $p = 0.1$).

Heart failure and in-hospital mortality were more prevalent in diabetics (25.7% vs. 14.8%, OR: 1.98; 95% CI [1.08–3.63], $p = 0.03$ and 17.8% vs. 8.4%, OR: 2.36; 95% CI [1.1–5.08], $p = 0.03$, respectively) (table.3). Major cardiac adverse events were significantly more common in diabetics (32.7% vs. 18.1%, OR: 2.2; 95% CI [1.22–3.94], $p = 0.008$). In multivariate analysis after adjustment for age, sex, hyperlipidemia, hypertension, smoking and family history, diabetes was not independently associated with heart failure, in-hospital mortality and major adverse cardiac events. After exclusion of patients with hospital mortality, mean hospital stay length was similar in diabetics and non-diabetics in both univariate and multivariate analysis (table 3).

Table 1 – Comparison of demographic variables, medications, and serum laboratory data in diabetic and non-diabetic patients.

	Non-diabetics N = 162	Diabetics N = 113	*p* value
Age	58.44 ± 12.9	61.68 ± 12.2	0.03
Sex (male)	129 (79.6%)	72 (63.7%)	0.03
Family history	4 (2.5%)	12 (10.6%)	0.005
Hyperlipidemia	24 (14.8%)	48 (42.5%)	<0.001
Hypertension	50 (30.9%)	77 (68.1%)	<0.001
Smoker	57 (35%)	18 (15.9%)	0.2
Hematocrit (%)	43.01 ± 6.37	42.25 ± 6.73	0.3
Creatinine[a] (mg/dL)	1 (0.8–1.1)	1.1 (0.9–1.3)	0.01
Admission serum glucose (mg/dL)	121.85 ± 44.23	269.12 ± 128	<0.001
CPK[a] (u/l)	508 (238–1 293)	668 (224–1 522)	0.5
CPKMB[a] (ng/mL)	66 (36–108)	63.5 (35–172)	0.3
CTNI[a] (ng/mL)	1.9 (0.5–9)	2.7 (0.6–10.7)	0.3
Anterior myocardial infarction	81 (51.6%)	67 (59.3%)	0.2
Presentation delay (hours)[a]	4 (3–6)	4 (2–5)	0.04
Coronary angioplasty	23 (14.2%)	30 (26.5%)	0.01
Unfractionated heparin	94 (58.0%)	82 (72.6%)	0.01
Low molecular weight heparin	51 (31.5%)	31 (27.4%)	0.4
Aspirin	155 (95.7%)	110 (97.3%)	0.4
Beta-blockers	133 (82.1%)	87 (77.0%)	0.2
Calcium-channel blockers	141 (87.0%)	38 (33.6%)	<0.001
Intravenous nitrate	99 (61.1%)	75 (66.4%)	0.3
Oral nitrate	90 (55.6%)	51 (45.1%)	0.08
ACE-inhibitors/ARB	107 (66.1%)	88 (77.9%)	<0.04
Diuretics	42 (25.9%)	44 (38.9%)	0.02

ACE inhibitors – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blockers, CK-MB – creatine kinase-MB; CPK – creatine phosphokinase, cTNI – cardiac troponin I.
[a] Values are stated as median (25–75% interquartile).

Discussion

According to the results of this study, ST segment resolution on ECG after fibrinolysis with streptokinase does not differ between diabetic and non-diabetic patients suffering from STEMI. Despite similar therapeutic response to fibrinolysis, diabetic patients have higher rates of heart failure and in-hospital mortality. However, diabetes is not an independent predictor of short-term adverse cardiac events after STEMI.

Diabetes is a contributor to a poor prognosis in patients with STEMI, regardless of the type of therapeutic management [4,11,22]. Older age and higher prevalence of simultaneous coronary risk factors in diabetic patients, as also seen in our study population, may contribute to the poor prognosis of the patients [1]. Moreover, the prothrombotic and proinflammatory states in diabetic patients as well as altered fibrin clot structure, which is more resistant to fibrinolysis by hemostatic system, appear to play a role in unfavorable outcome of diabetic patients in the course of acute coronary syndrome [23]. However, it should be noted that acute stress-induced hyperglycemia in non-diabetic patients experiencing myocardial infarction is also associated with modifications in hemostatic system [24] and an adverse effect on the outcome [25]. In this study, we compared patients with regard to their diabetes status; however, acute hyperglycemia in non-diabetics may also affect the therapeutic outcome after fibrinolysis.

Fibrinolysis, which is the commonly utilized therapy in non-PCI capable hospitals, lowers the short-term and long-term mortality in patients with STEMI [4,26]. The clinical benefit of fibrinolysis applies to the patients with diabetes, with even greater absolute benefit, due to higher rate of complications in this group of patients [26]. Although diabetic patients had a higher mortality rate in our study sample, ST resolution on ECG as a marker of myocardial reperfusion after treatment with streptokinase was not different between patients with and those without diabetes. With regard to the fact that patients with diabetes constitute a high-risk group [11], our results highlight the importance of administrating fibrino-

Table 2 – Comparison of electrocardiographic, clinical and coronary angiography findings between diabetic and non-diabetic patients

	Non-diabetics N = 162	Diabetics N = 113	*p* value
Electrocardiographic findings:			
ST segment resolution ≥ 50 %	73 (45.1%)	55 (48.7%)	0.8
ST segment resolution % (mean ± standard deviation)	38.67 ± 27.76	42.88 ± 29.05	0.1
Ventricular tachycardia/fibrillation on first day	8 (4.9 %)	5 (4.4 %)	0.8
Ventricular tachycardia/fibrillation after first day	3 (1.9 %)	7 (6.2 %)	0.05
Left-bundle-branch block	3 (1.9 %)	8 (7.1 %)	0.03
Right-bundle-branch block	6 (3.7 %)	9 (8.0 %)	0.1
Atrial fibrillation	5 (3.1 %)	5 (4.4 %)	0.5
Third degree block	5 (3.1 %)	4 (3.5 %)	0.8
Clinical findings:			
Ventricular septal rupture	2 (1.2%)	0 (0.0%)	–
Post myocardial infarction mitral regurgitation	44 (27.2%)	21 (18.6%)	0.1
Re-infraction	23 (14.2%)	9 (8%)	0.1
Heart failure	24 (14.8%)	29 (25.7%)	0.03
In-hospital mortality	13 (8.4%)	18 (17.8%)	0.03
Heart failure/In-hospital mortality	28 (18.1%)	33 (32.7%)	0.008
Hospital stay length (days) (mean ± standard deviation)	6.6 ± 5	6.6 ± 3.8	0.7
Coronary angiography:			
One-vessel disease	22 (13.6%)	11 (9.7%)	0.1
Two-vessel disease	26 (16.0%)	11 (9.7%)	0.3
Three-vessel disease	13 (8.0%)	26 (23.0%)	<0.001

Table 3 – Univariate and multivariate odds ratios for primary end points in diabetics

	Univariate odds ratio (95% confidence interval)	*p* value	Multivariate odds ratio[a] (95% confidence interval)	*p* value
ST segment resolution<50%	0.86 (0.53–1.4)	0.8	0.62 (0.35–1.09)	0.1
Heart failure	1.98 (1.08–3.63)	0.03	1.56 (0.78–3.1)	0.2
In-hospital mortality	2.36 (1.1–5.08)	0.03	1.61 (0.67-3.85)	0.2
Heart failure/hospital mortality	2.2 (1.22–3.94)	0.008	1.62 (0.83–3.15)	0.1
Hospital stay length	0.98 (0.91–1.03)	0.7	0.99 (0.89–1.11)	0.9

[a] Adjusted for age, sex, hypertension, hyperlipidemia, smoking and family history of cardiovascular diseases.

lytic agents in eligible patients regardless of their diabetic status [27].

The results of this study are similar to the findings of a study published by Brattier et al. in which prognostic value of ST resolution more than 50% using a single lead after intravenous fibrinolysis was studied. In their population sample, pain to needle time was the only predictor of ST resolution failure in multivariate analysis [7]. Another study using the data from GUSTO-I trial (Global Utilization of Streptokinase and Tissue Plasminogen Activator [Alteplase] for occluded Coronary Arteries), evaluated only patient-related factors, which predict infarct-related artery patency after fibrinolysis and found no relationship between diabetes and the artery patency determined by subsequent angiography [28]. In another sub analysis of GUSTO-I trial, diabetic and non-diabetics treated with intravenous fibrinolytic, had similar frequency of reocclusion, left ventricular ejection fraction, regional and global ventricular function; however, a reduced compensatory hyperkinesia in the non-infarct zone was found in diabetics [29]. The same result regarding epicardial artery flow was noted in a study by Angela et al. In their study ST segment resolution after fibrinolysis was evaluated in addition to angiographic findings. Even though the similar artery patency was detected in diabetics and non-diabetics, the incidence of ST resolution after fibrinolysis was lower in diabetics, which is in contrast with our results [13]. They concluded that diabetes might play a role in microvascular level damage in patients receiving fibrinolytic therapy after STEMI [13,29]. Zarris et al. studied the incidence of ST resolution using a continuous ECG monitoring and reported lower incidence of ST resolution in diabetics. Mo-

reover, longer time was needed in diabetics to achieve ST resolution. Of note is that the majority of patients in their sample were treated by tissue plasminogen activator (t-PA) [14]. In a study by Masoomi et al., the response to streptokinase, defined as more than 70% resolution in ST segment, was lower in diabetics on the second ECG, taken 180 minutes after treatment [12]. In our study, 90 minutes ECG was considered as the second ECG and 50% or more resolution criteria was applied to interpretation of ECGs. The inconsistency of evidence regarding the role of diabetes in ST resolution after fibrinolytic therapy as a sign of reperfusion may partly originate from applying different criteria for assessing the response to fibrinolytic therapy. Another point to mention is the use of various fibrinolytic agents in studies [15,30] that may differ in therapeutic response or time to accomplish the full reperfusion [19].

Although in our patients, diabetes did not have a significant impact on reperfusion success by using electrocardiographic criteria 90 minutes after treatment with streptokinase, diabetics had higher prevalence of three--vessel coronary disease in subsequent angiographic studies, performed during hospital stay and not as a rescue procedure. Furthermore, coronary angioplasty during the hospital stay was significantly performed more commonly in diabetics. The greater burden of the disease in diabetics with myocardial infarction is illustrated by higher prevalence of multi vessel disease [29]. As described before, coronary risk factors are also more prevalent in diabetics [11,20,31]. The combined effects of these factors may be an underlying cause of the poor prognosis in diabetics [20,31]. However, the independent impact of diabetes on poor prognosis after myocardial infarction is a matter of controversy [4,11,20–22,31]. In our study, the incidence of heart failure, in-hospital mortality and major adverse cardiac events was significantly higher in diabetics in the univariate analysis. Though, the effect of diabetes diminished and lost its significance after adjustment for baseline characteristics of patients. Although several investigations demonstrated the adverse effects of diabetes on prognosis of patients after myocardial infarction [4,22], there are other studies in which diabetes was independently associated with adverse long--term outcomes but not with short-term adverse clinical outcomes [20,21]. On the other hand, the magnitude of adverse effect of diabetes on prognosis of patients after myocardial infarction is decreasing in recent years [32]. The appropriate management of diabetics and proper use of pharmacologic medications such as beta-blockers with established positive effects on prognosis, may also contribute to this finding [31–33].

Conclusion

We conclude that diabetics with STEMI have a similar response to streptokinase using the electrocardiographic assessment of ST segment resolution over time. The greater burden of atherosclerotic disease in diabetics with simultaneous higher prevalence of other coronary risk factors, prone this high-risk group to a poor outcome during hospitalization despite similar ECG findings after reperfusion.

Limitations of the study

This is a single-center study including relatively small number of patients. To avoid any bias related to efficacy of different fibrinolytic agents, only patients who received streptokinase were included in the study. In addition, duration of diabetes was not considered. Using continuous ECG monitoring as described recently may give further information about the predictors of fibrinolytic response [14], though this was not technically available in our center and only two snapshots, were evaluated.

Conflict of interests
No conflict of interest.

Funding body
None.

Ethical statement
I declare, on behalf of all authors, that the research was conducted according to Declaration of Helsinki.

Informed consent
I declare, on behalf of all authors, that informed consent was obtained from all patients participating in this study.

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