Alma Mater Studiorum – Università di Bologna

DOTTORATO DI RICERCA IN

SCIENZE CHIRURGICHE

Ciclo XXXII

Settore Concorsuale: 06/D1

Settore Scientifico Disciplinare: MED/11

FIBRINOLYSIS VERSUS PRIMARY PCI IN STEMI PATIENTS ENROLLED IN THE INTERNATIONAL SURVEY OF ACUTE CORONARY SYNDROMES IN TRANSITIONAL COUNTRIES

Presentata da: Dott**.** Peter Louis Amaduzzi

Coordinatore Dottorato:

Prof. Annalisa Patrizi

Supervisore:

Prof. Raffaele Bugiardini

Esame finale anno 2020

ABSTRACT

Primary angioplasty has been shown to be more effective than fibrinolysis in terms of mortality and adverse outcomes. More recent data, however, suggests that timely reperfusion with fibrinolysis is comparable to primary angioplasty. The current study gathered data from the International Survey of Acute Coronary Syndromes in Transitional Countries registry. Among 7406 ST-elevation myocardial infarction patients presenting within 12 hours from symptom onset, 6315 underwent primary percutaneous coronary intervention and 1091 were treated with fibrinolysis. The primary outcome was 30-day mortality, while the secondary outcome was a composite of 30-day incidence of death, severe left ventricular dysfunction, stroke or reinfarction. Patients who underwent primary angioplasty tended to have a greater cardiovascular risk profile and were slightly older. On the other hand, patients treated with fibrinolysis received less anti-platelet medications yet were more often prescribed beta blockers in the acute phase. Among those who received fibrinolysis, 43% underwent coronary angiography while 32.3% were treated with a subsequent angioplasty. Total ischemic time was lower in patients undergoing fibrinolysis (185 minutes) than in those treated with primary angioplasty (258 minutes). Rates of primary and secondary combined endpoints were higher in patients receiving fibrinolysis compared to those receiving primary angioplasty (7.8% vs. 4.1%; $p<0.0001$; OR 1.97, 95% CI, 1.38-2.81; and 14.8% vs. 10.1%, $p<0.0001$; OR 1.43, 95% CI, 1.12-1.81). When considering only patients receiving reperfusion within 3 hours, regardless of reperfusion strategy, differences in mortality (6.3% vs. 4%, $p=0.094$, for fibrinolysis or primary angioplasty, respectively; OR 0.87, 95% CI, 0.35-2.16) and in the combined secondary endpoint were no longer observed (12.9% vs 10.8%, $p=0.33$; OR 0.98, 95% CI, 0.58-1.64), and female sex was no longer a significant predictor of adverse outcomes. When performed 3 hours from symptom onset, fibrinolysis is safe and feasible, in terms of mortality and adverse outcomes, compared to primary angioplasty.

INTRODUCTION

The advent of angioplasty, as an alternative reperfusion strategy to thrombolysis for ST-elevation myocardial infarction (STEMI), brought forth significant reductions in the rates of death, re-infarction, and stroke. The therapeutic benefits of primary percutaneous coronary intervention (pPCI) are confirmed by an abundance of data deriving from clinical trials comparing thrombolysis with primary angioplasty [1-5]. Besides the choice of reperfusion strategy, another determining factor associated with the outcomes of patients with STEMI is total ischemic time, an association reinforced by the notion of "time is muscle" [6]. In fact, European Society of Cardiology (ESC) Guidelines for the management and treatment of patients with STEMI recommend adopting a reperfusion strategy based on delays associated with these treatments. Current ESC guidelines recommend primary PCI over thrombolysis if PCI can be performed within 120 minutes from symptom onset; conversely, thrombolysis is recommended when PCI cannot be performed within 120 minutes [6]. Total ischemic time is related to both patient delay and system delay and, while the former is dependent on educating patients, the latter is determined by many logistic factors, including on-site emergency health care, transfer delays, and in-hospital delays [6].

Unfortunately, real world clinical practice often differs in terms of system delay, which are dependent on a lack of or underdevelopment of pPCI networks and emergency services. For this reason, many low-middle income countries (LMIC) are characterized by lower reperfusion rates and subsequently higher rates of mortality [7-9]. Data from Eastern European countries has shown that, among other factors, a time to admission exceeding 12 hours is associated with a lack of reperfusion [8]. Therefore, both patient and system delay are paramount to receiving the ideal reperfusion strategy and ameliorating outcomes in patients with STEMI.

Current guideline recommendations for choice of reperfusion strategy are largely dependent upon data from randomized clinical trials. Observational data has suggested comparable outcomes of

the two reperfusion strategies when these are applied within a limited time frame. The current study was aimed at the evaluation and comparison of thrombolysis and pPCI in the real-world context of a large registry.

METHODS

Data was derived from 41 centers, in 12 countries, belonging to the International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-TC; ClinicalTrials.gov Identifier: NCT01218776) registry between 2010 and 2018 [10-20]. Among participating centers, 22 are tertiary health care institutions able to perform PCI and/or cardiac surgery, while the remaining 19 are secondary centers with an intensive cardiac care unit. The University of Bologna Alma Mater Studiorum is the coordinating center for the registry. Patients were eligible for inclusion if they were older than 18 years of age, had symptoms consistent with an acute coronary syndrome, evidence of new or presumed new significant ST-segment changes, T-wave changes, or new left bundle branch block on serial electrocardiograms and/or elevated cardiac biomarkers of necrosis.

Study population

Among 17,513 patients with an acute coronary syndrome (ACS), 6794 were excluded because they were admitted for a Non-ST-elevation acute coronary syndrome (NSTEACS). Of the 10,719 STEMI patients, 2441 (22%) did not receive any reperfusion treatment and were therefore excluded. Of the remaining 8278 reperfused STEMI patients, 872 were excluded because the time from symptom onset to admission was greater than 12 hours. Of the remaining 7406, 6315 underwent pPCI while 1091 received fibrinolysis.

Definitions and Outcomes

Delays to reperfusion, expressed as a median with interquartile range (IQR), were reported as total ischemic time, defined as time from symptom onset to time of reperfusion. The primary outcome was 30-day mortality, while the secondary outcome was a composite of 30-day incidence of death, severe left ventricular dysfunction [defined as the presence of a left ventricular ejection fraction (LVEF) of less than 35%], stroke or reinfarction. In-hospital outcomes were recorded during hospital stay, while 30-day events were recorded during the corresponding follow-up visit.

Safety end points were major and minor non-CABG bleeding events as established by the TIMI study group. Major bleeding was defined as any episode of intracranial bleeding or clinical signs of hemorrhage in association with a decrease in hemoglobin >5 mg/dL. TIMI minor bleeding events were defined as any observable signs of hemorrhage resulting in a reduction of hemoglobin between 3-5 mg/dL.

Statistical analysis

Demographic, clinical, and therapeutic variables were compared using Pearson's χ^2 for categorical variables and Kruskal Wallis rank-sum test for continuous variables. Results are presented as means ± standard deviations or median (with interquartile range) for continuous variables and numbers and percentages for categorical variables.

Multivariate logistic regression analysis, adjusting for relevant demographic, clinical, and therapeutic variables, was used to evaluate independent predictors of primary and secondary outcomes in STEMI patients arriving within 12 hours from symptom onset receiving either fibrinolysis or pPCI. Fixed covariates included in the analysis were sex, age, cardiovascular risk factors (hypercholesterolemia, hypertension, diabetes mellitus, smoking, and family history of CAD), history of any cardiovascular disease (CVD) [including prior angina, prior MI, prior revascularization, prior heart failure, prior stroke, and prior peripheral vascular disease], systolic blood pressure (SBP) at admission, and heart rate (HR) at admission. Covariates applied as dummy variables were relevant in-hospital medications administered during the acute phase, including aspirin, clopidogrel, betablockers, and heparins.

A second multivariate logistic regression analysis was performed, using the same fixed model, to identify predictors of adverse outcomes in STEMI patients arriving within 12 hours form symptom onset but receiving reperfusion within 3 hours from symptom onset. Results are presented as odds rations (OR) with 95% confidence intervals (95% CI). Statistical analyses were performed in STATA 14 (StataCorp. College Stations, TX, USA)

RESULTS

Baseline characteristics

Demographic and baseline characteristic of 7046 STEMI patients with time from symptom onset to admission less than 12 hours are shown in Table 1. Patients administered fibrinolysis were slightly younger than those who underwent pPCI (59.1±11.6 vs 60.5±11.6, p=0.0001). On the other hand, a similar rate of women underwent either reperfusion strategy (26.6% for fibrinolysis vs. 28.5%, p=0.2).

Tab. 1 – Demographic and clinical characteristics of STEMI patients undergoing reperfusion within 12 hours from symptom onset with either primary PCI or fibrinolysis

Characteristics	Total population (N=7406)	Fibrinolysis (N=1091)	pPCI (N=6315)	p-value
Demographic characteristics				
Age	60.3±11.6	59.1±11.6	60.5±11.6	0.0001
Women	2088 (28.2)	290 (26.6)	1798 (28.5)	0.2
BMI	27.3±4.2	27.3±4.2	27.3±4.1	0.98
Cardiovascular risk factors				
Hypercholesterolemia	2690 (41.1)	292 (35.3)	2398 (42)	<0.0001
Diabetes mellitus	1483 (20.6)	231 (22.5)	1252 (20.3)	0.1
Hypertension	4656 (64.3)	595 (57.1)	4061 (65.5)	<0.0001
Current smoker	3354 (50.5)	512 (53.7)	2842 (50)	0.03
Family history of CAD	2051 (30.1)	231 (23.4)	1820 (31.3)	<0.0001
Clinical history of ischemic heart disease				
Prior angina pectoris	906 (12.2)	115 (10.5)	791 (12.5)	0.07
Prior myocardial infarction	781 (10.6)	106 (9.7)	675 (10.7)	0.33
Prior PCI	793 (10.7)	52 (4.8)	741 (11.7)	<0.0001
Prior CABG	45 (0.6)	9 (0.8)	36 (0.6)	0.32
Clinical history of cardiovascular diseases				
Prior heart failure	44 (0.6)	16 (1.5)	28 (0.4)	<0.0001
Prior stroke	195 (2.6)	24 (2.2)	171 (2.7)	0.3
Prior PVD	93 (1.3)	32 (2.9)	61 (1)	<0.0001
Clinical presentation				
SBP at admission (mmHg)	139.7±25	137.2±28.4	140.2±24.3	<0.0001
Heart rate at admission (bpm)	80.2±22.4	79.6±31.2	80.3±20.5	<0.0001
Killip Class ≥ 2	913 (22.8)	234 (27.6)	679 (21.5)	<0.0001

Values are shown as either mean ± SD for continuous variables or number and percent for categorical variables.

With regards to cardiovascular risk factors, patients treated with primary angioplasty, when compared to those who were administered fibrinolysis, had a higher rate of hypercholesterolemia (42% vs 35.3%, respectively; p<0.0001) and hypertension (65.5% vs. 57.1%, respectively; p<0.0001). Smoking, however, was more prevalent in fibrinolysis patients (50% vs. 53.7%, p=0.03).

In terms of clinical history of ischemic heart disease and cardiovascular disorders, significant differences were observed in the history of prior PCI, history of heart failure and of peripheral vascular disease (PVD). The history of prior angioplasty was more prevalent among those who underwent pPCI than those reperfused with fibrinolysis (11.7% vs. 4.8%, respectively; p <0.0001). On the contrary, prior heart failure and history of PVD were less prevalent among pPCI patients than fibrinolysis patients (0.4% vs. 1.5%, p<0.0001 and 1% vs. 2.9%, p<0.0001, respectively).

Upon hospital arrival, patient who underwent pPCI had a slightly higher heart rate (80.3±20.5 bpm vs. 79.6±31.2 bmp, p<0.0001) and systolic blood pressure (140.2±24.3 mmHg vs 137.2±28.4 mmHg, p<0.0001) than those treated with fibrinolysis. Accordingly, more patients treated with fibrinolysis arrived with a Killip Class of 2 or greater (27.6 vs 21.5, p<0.0001).

In-hospital treatment

Although the rates of pharmacological therapy were high in all STEMI patients, regardless of reperfusion strategy, some differences were present between the two cohorts (Tab. 2). Medications given less frequently to fibrinolysis patients than to pPCI patients were aspirin (97.4% vs 99.5%, respectively; p<0.0001), clopidogrel (86.4% vs. 95.1%, p<0.0001), and statins (97.3% vs. 93.8%, p<0.0001). Conversely, beta blockers and heparins were given more frequently to fibrinolysis patients than to pPCI patients (85% vs 76%, p<0.0001, and 95.7% vs 87.3%, p<0.0001; respectively). Regarding in-hospital procedures, 43% of patients treated with fibrinolysis underwent coronary

angiography (CAG), while 32.3% were subsequently treated with PCI. Among these patients for which indication for angioplasty was recorded, 22.5% underwent rescue PCI.

Lastly, when comparing total ischemic time (time from symptom onset to reperfusion), patients treated with fibrinolysis had a shorter median delay to reperfusion compared to pPCI patients (185 minutes compared to 258 minutes, respectively).

Tab. 2 – In-hospital medications, interventions, and delays of STEMI patients undergoing reperfusion within 12 hours from symptom onset with either primary PCI or fibrinolysis

Characteristics	Total population (N=7406)	Fibrinolysis (N=1091)	pPCI (N=6315)	p-value
In-hospital acute medications				
Aspirin	7295 (99.2)	1058 (97.4)	6237 (99.5)	<0.0001
Clopidogrel	6876 (93.8)	938 (86.4)	5938 (95.1)	<0.0001
Heparins	6472 (88.5)	1040 (95.7)	5432 (87.3)	<0.0001
Beta blockers	5655 (77.3)	924 (85)	4731 (76)	<0.0001
ACE-I	5314 (79.5)	881 (81.1)	4433 (79.2)	0.151
Statins	6468 (96.7)	1020 (93.8)	5448 (97.3)	<0.0001
In-hospital procedures				
Coronary angiography		460 (43)	6315 (100)	<0.0001
PCI		343 (32.3)	6315 (100)	<0.0001
Rescue PCI	--	41/182 (22.5)	--	--
Postprocedural TIMI grade III	--	--	2068/2192 (94.3)	--
Reperfusion delays				
Total ischemic time to fibrinolysis (min) [median (IQR)]	--	185 (120-285)	--	
Total ischemic time to pPCI (min) [median (IQR)]	--	--	258 (150-366)	

Outcomes

Primary and secondary combined endpoints, as defined in the methods, can be seen in Tab. 3. Rates of death at 30 days were higher in patients treated with fibrinolysis compared to pPCI patients (7.8% vs. 4.1%, p<0.0001). In addition, the 30-day rates of the combined endpoint of death, reinfarction, severe LV dysfunction, and stroke were higher after reperfusion with fibrinolysis than pPCI (14.8% vs. 10.1%, p<0.0001). This was determined not only by the greater 30-day mortality but by the

incidence of severe LV dysfunction as well a(7.5% vs. 4.5%, p<0.0001). The safety endpoint of TIMI non-CABG major and minor bleeding events occurred more often in fibrinolysis patients than in those treated with pPCI (1.8% vs 1.0%, p=0.0.015).

Tab. 3 – 30-day outcomes of STEMI patients undergoing reperfusion within 12 hours from symptom onset with either primary PCI or fibrinolysis

Characteristic	Total population (N=7406)	Fibrinolysis (N=1091)	pPCI (N=6315)	p-value
Combined endpoint	796 (10.8)	161 (14.8)	635 (10.1)	<0.0001
Mortality	345 (4.7)	85 (7.8)	260 (4.1)	<0.0001
Severe LV dysfunction	369 (5)	82 (7.5)	287 (4.5)	<0.0001
Stroke	16 (0.2)	1 (0.1)	15 (0.2)	0.3
Reinfarction	125 (1.7)	2 (0.2)	123 (2)	<0.0001
Bleeding	83 (1.12)	20 (1.8)	63 (1.0)	0.015

A multivariable analysis was performed adjusting for relevant characteristics, including demographic and risk factor variables, along with those describing CVD medical history and clinical presentation (Tab. 4). In the overall STEMI population of patients arriving at a hospital within 12 hours of symptom presentation reperfused with either fibrinolysis or pPCI, thrombolytic therapy was associated with an increased risk of death (OR 1.97, 95% CI, 1.38-2.81). Other than reperfusion strategy, female sex (OR 1.34. 95% CI, 1.01-1.79) and older age (OR 1.05, 95% CI, 1.04-1.06) increased the risk of death at 30 days. Additional clinical factors associated with an increased risk of death at 30 days were diabetes mellitus (1.57, 95% CI, 1.16-

Tab. 4 – Multivariable analysis showing factors associated with death in the overall population

Variable	OR	95% CI	p-value
Fibrinolytic therapy	1.97	1.38-2.81	<0.0001
Female sex	1.34	1.01-1.79	0.041
Age	1.05	1.04-1.06	<0.0001
Hypercholesterolemia	0.55	0.41-0.74	<0.0001
Diabetes Mellitus	1.57	1.16-2.12	0.003
Hypertension	0.64	0.48-0.86	0.002
Smoking status	0.71	0.52-0.97	0.032
Family history of CAD	1.00	0.71-1.40	0.9
Prior angina pectoris	1.14	0.76-1.72	0.5
Prior MI	1.07	0.69-1.67	0.8
Prior revascularization	1.51	0.95-2.40	0.082
History of prior CVD	1.90	1.18-3.07	0.008
SBP at admission§	1.26	1.14-1.39	<0.0001
HR at admission§§	1.22	1.13-1.33	<0.0001

§categorized by decreasing intervals of 10 mmHg
§§categorized by increments of 10 bpm
*including history of prior stroke, PVD, and heart failure

2.12), a positive clinical history of CVD (1.90, 95% CI, 1.18-3.07), low systolic blood pressure at admission (1.26, 95% CI, 1.14-1.39), and high heart rate at admission (1.22, 95% CI, 1.13-1.33).

Effects of delay on outcomes

A secondary analysis was performed on patients receiving reperfusion within 3 hours (180 minutes) from symptom onset. Baseline demographic, clinical and treatments variables are reported in Tables 5 and 6. In brief, compared to the total study population, patients reperfused within 3 hours from symptom onset were slightly younger (58.5±11.3 vs. 60.3±11.6). Furthermore, there were also less women receiving timely reperfusion (< 3 hours) (22% vs 28%).

Tab. 5 – Demographic and clinical characteristics of STEMI patients undergoing reperfusion within 3 hours from symptom onset with either primary PCI or fibrinolysis

Characteristics	Total population (N=1149)	Fibrinolysis (N=318)	pPCI (N=831)	p-value
Demographic characteristics				
Age	58.5±11.3	58.2±11.4	58.6±11.3	0.5
Women	253 (22)	69 (21.7)	184 (22.1)	0.9
BMI	27.5±4.1	27.4±4.2	27.6±4	0.4
Cardiovascular risk factors				
Hypercholesterolemia	397 (39.3)	85 (33.5)	312 (41.3)	0.03
Diabetes mellitus	228 (20.3)	66 (22.1)	162 (19.6)	0.4
Hypertension	673 (59.2)	169 (54.3)	504 (61)	0.04
Current smoker	565 (54.6)	156 (56.5)	409 (53.9)	0.5
Family history of CAD	254 (23.2)	61 (20.5)	193 (24.2)	0.2
Clinical history of ischemic heart disease				
Prior angina pectoris	114 (9.9)	28 (8.8)	86 (10.4)	0.4
Prior myocardial infarction	132 (11.5)	33 (10.4)	99 (11.9)	0.5
Prior PCI	80 (7)	12 (3.8)	68 (8.2)	0.009
Prior CABG	7 (0.6)	5 (1.6)	2 (0.2)	0.009
Clinical history of cardiovascular diseases				
Prior heart failure	13 (1.1)	8 (2.5)	5 (0.6)	0.006
Prior stroke	39 (3.4)	9 (2.8)	30 (3.6)	0.5
Prior PVD	20 (1.7)	13 (4.1)	7 (0.8)	<0.0001
Clinical presentation				
SBP at admission (mmHg)	141.2±27.7	136.3±29.1	143.1±26.9	<0.0001

Heart rate at admission (bpm)	79.5±27.9	76.2±19.1	80.8±30.5	0.0008
Killip Class ≥ 2	152 (24.6)	72 (30.3)	80 (21.1)	0.01
Values are shown as either mean ± SD for continuous variables or number and percent for categorical variables.				

Rates of in-hospital acute medications were similarly distributed in both the early reperfusion group and in the entire study population, as were rates of coronary angiography and PCI. Interestingly, rates of rescue PCI were lower in the early reperfusion group than in the total population (17.7% vs 22.5%, respectively). Lastly, the difference in delay between thrombolysis and primary angioplasty was inferior in patients receiving reperfusion within 3 hours from symptom onset (110 min vs 115 min and 185 min vs 285 min).

Tab. 6 – In-hospital medications, interventions, and delays of STEMI patients undergoing reperfusion within 3 hours from symptom onset with either primary PCI or fibrinolysis

Characteristics	**Total population (N=1149)**	**Fibrinolysis (N=318)**	**pPCI (N=831)**	**p-value**
In-hospital acute medications				
Aspirin	1137 (99.1)	309 (97.5)	828 (99.8)	<0.0001
Clopidogrel	1067 (93)	268 (84.5)	799 (96.3)	<0.0001
Heparins	1112 (97)	308 (96.9)	804 (97.1)	0.8
Beta blockers	857 (74.9)	273 (86.4)	584 (70.5)	<0.0001
ACE-I	925 (82.4)	262 (82.9)	663 (82.3)	0.8
Statins	1088 (94.9)	291 (92.1)	797 (96)	0.007
In-hospital procedures				
Coronary angiography	973 (84.9)	142 (45.1)	831 (100)	<0.0001
PCI	930 (81.3)	99 (31.6)	831 (100)	<0.0001
Rescue PCI	--	9/51 (17.7)	--	--
Postprocedural TIMI grade III	--	--	281/225 (96.9)	--
Reperfusion delays				
Total ischemic time to fibrinolysis (min) [median (IQR)]	--	110 (70-140)	--	--
Total ischemic time to pPCI (min) [median (IQR)]	--	--	115 (95-145)	--

The same multivariate adjusted model was applied only to those patients receiving either fibrinolysis or pPCI within 3 hours from symptom onset to evaluate the effect of total ischemic time and

reperfusion delay on mortality (Tab. 7). After adjustment for relevant demographic and clinical characteristics, risk factors, and acute medications, fibrinolytic therapy no longer differed from pPCI both in terms of risk of mortality (6.3% vs. 4%, respectively, p=0.94; OR 0.87, 95% CI, 0.35-2.16) and the combined endpoint (12.9% vs. 10.8%, respectively, p=0.33; OR 0.98, 95% CI, 0.58-1.64).

Tab. 7 – Primary and secondary outcomes in the overall population compared with patients receiving reperfusion within 3 hours.

Outcome	Fibrinolysis	pPCI	p-value	OR§	95% CI	p-value
Overall population						
Death at 30 days	85 (7.8)	260 (4.1)	<0.0001	1.97	1.38-2.81	<0.0001
Combined endpoint	161 (14.8)	635 (10.1)	<0.0001	1.43	1.12-1.81	0.004
Patients receiving reperfusion within 3 hours of symptom onset						
Death at 30 days	20 (6.3)	33 (4)	0.09	0.87	0.35-2.16	0.8
Combined endpoint	41 (12.9)	90 (10.8)	0.3	0.98	0.58-1.64	0.9

OR=odd ratio; CI=confidence interval.

§ Adjusted for sex, age, hypercholesterolemia, diabetes mellitus, hypertension, smoking status, family of history CAD, history of prior angina pectoris, history of prior MI, history of prior revascularization, history of cardiovascular disease*, systolic blood pressure at admission, and heart rate at admission, aspirin, clopidogrel, betablockers, heparins.

*including history of prior stroke, PVD, and heart failure

Furthermore, some factors associated with mortality in those patients receiving reperfusion within 3 hours differed from those not reperfused within that timeframe (Tab. 8). Notably, female sex no longer correlated with 30-day mortality when total ischemic time was reduced, regardless of reperfusion strategy (OR 1.41, 95% CI, 0.67-3.0). Older age, on the other hand, remained a predictive factor for mortality (OR 1.05, 95% CI, 1.02-1.09). Lower systolic blood pressures at admission, indicative of a worse ventricular function, were associated with an increased risk of death (OR 1.49, 95% CI, 1.17-1.89).

Tab. 8 – Multivariable analysis showing factors associated with death in patients receiving reperfusion within 3 hours from symptom onset.

Variable	**OR**	**95% CI**	**p-value**
Fibrinolytic therapy	0.87	0.35-2.16	0.8
Female sex	1.41	0.67-3.0	0.4
Age	1.05	1.02-1.09	0.002
Hypercholesterolemia	0.66	0.31-1.40	0.3
Diabetes Mellitus	2.1	0.96-4.43	0.07
Hypertension	0.50	0.25-1.03	0.06
Smoking status	0.62	0.28-1.39	0.3
Family history of CAD	0.83	0.32-2.16	0.7
Prior angina pectoris	1.34	0.39-4.6	0.6
Prior MI	0.73	0.22-2.47	0.6
Prior revascularization	3.39	1.00-11.5	0.049
History of prior CVD	1.73	0.55-5.39	0.3
SBP at admission§	1.40	1.11-1.76	0.005
HR at admission§§	1.13	0.92-1.38	0.2
§ categorized by decreasing intervals of 10 mmHg §§categorized by increments of 10 bpm			
*including history of prior stroke, PVD, and heart failure			

DISCUSSION

Clinical profile

Patients treated with fibrinolysis were slightly younger and had lower rates of hypercholesterolemia, hypertension, and family history of CAD. On the other hand, they tended to have a more frequent history of smoking, heart failure, and PVD. Upon admission, these patients tended to have a lower heart rate and systolic blood pressure, and subsequently presented more frequently with a Killip Class of 2 or greater. The observation that more patients with a higher prevalence of cardiovascular risk factors received pPCI may be explained by the greater benefits in terms of a reduction in the rates of mortality that these patients have been observed to possess [21].

Patients treated with fibrinolysis were less frequently given anti-platelet medications. Statins were also given less frequently to patients undergoing fibrinolysis. On the contrary, beta blockers were administered more frequently in patients receiving fibrinolysis when compared to those treated with pPCI.

Among those treated with fibrinolysis, 43% underwent coronary angiography, while 32% were treated with a subsequent PCI. Lastly, total ischemic time, defined as the time between symptom onset to the time of reperfusion, was significantly shorter in patients treated with fibrinolysis than in those receiving pPCI, which is likely due to greater in-hospital system delays and stopover delays.

Impact of delay to reperfusion

The greater therapeutic effect of pPCI over fibrinolysis has been observed in many randomized clinical trials (RCTs) [1-5] More recent RCT and observational data pertaining to reperfusion strategies in these patients have suggested a comparable therapeutic effect of thrombolysis and pPCI when delays are severely reduced [22-26]. The PRAGUE-2 investigators observed no difference in mortality, in patients receiving either fibrinolysis or transfer pPCI, when total ischemic time was less than 3 hours [22]. Results from the CAPTIM trial found no differences in mortality at 30 days between

prehospital fibrinolysis and transfer for pPCI [23]. The same investigators even found a reduced risk of 5-year mortality in patients receiving pre-hospital fibrinolysis within 2 hours compared to patients receiving pPCI within the same time frame [24].

Similar results were seen in observational data which found comparable outcomes in STEMI patients receiving either transfer pPCI or on-site thrombolysis within 2 hours [24, 25]. More observational data from the Vienna STEMI registry showed similar in-hospital mortality rates between pPCI and fibrinolysis when either were initiated within 2 to 3 hours from symptom onset [26]. Data from the FAST-MI registry found no differences between timely fibrinolysis and pPCI in terms the rates of in-hospital mortality or 1-year survival [27]. As expected, distance from the location of an acute coronary event and the point of care has been correlated with delay, which was found to be an independent predictor of mortality [28].

Much of this data is in line with what was observed in the current study. When considering all STEMI patients arriving within 12 hours from symptom onset, those treated with fibrinolysis have worse outcomes than those treated with pPCI. Among patients receiving timely reperfusion, in the case of the current study 3 hours, outcomes improve significantly in patients receiving fibrinolysis, to the point where these outcomes are comparable to pPCI.

The conflicting result between older RCTs and newer data derived from RCTs and observational studies is likely due to numerous factors, amongst which improvements in reperfusion times and in pharmacotherapy, be they thrombolytics, anti-platelet medications, or cardioprotective therapy. Another determining factor seems to be the availability of pre-hospital fibrinolysis with transfer to a PCI capable center, which drastically shortens total ischemic time. Interestingly, the relationship between therapeutic effects of pPCI and reperfusion delay seem to be dependent upon risk profile [21].

Thrombolysis in specific subgroups

Women treated with fibrinolysis have been shown to have worse outcomes compared to men, in part due to the greater incidence of bleeding events. Data has shown that among women, pPCI, as opposed to fibrinolysis, is predictive of survival [29]. However, in the current study, when considering patients receiving a timely reperfusion, female sex is no longer predictive of 30-day mortality.

Representation of patients 75 years or older is sparse in large trials, often comprising around 10% of study populations [23, 30]. Older age has been shown to be predictive of adverse outcomes in patients receiving thrombolysis [31]. Similarly, in the current study, older age remains a significant predictor of 30-day mortality, even when accounting for delay to reperfusion. More recently, the STREAM investigative Team compared the efficacy and safety of primary angioplasty versus fibrinolysis combined with an early invasive strategy and found no difference in the primary composite endpoint (which consisted in 30-day death, shock, congestive heart failure, or reinfarction) among patients aged over 75 years of age (29.2% vs. 26.9%, respectively; OR 0.92, 95% CI 0.62-1.37) [30]. Worthy of note, the study protocol was amended by halving the dose of tenecteplase in patients older than 75 after observing high rates of intracranial hemorrhages [30]. Therefore, early fibrinolysis with a reduced dose of thrombolytic followed by an early invasive strategy in elderly patients in which delay to primary angiography is excessive may be safer while maintaining comparable efficacy.

Data from the current study show that diabetes, while predictive of mortality in the total study population, is not predictive in the subset of patients receiving reperfusion within 3 hours. Previous observations regarding 5-year outcomes in patients receiving reperfusion by either pPCI or thrombolysis showed that a thrombolytic approach was equivalent to primary angioplasty in diabetic patients, regardless of delay [24]. This difference is likely due to the higher overall cardiac risk profile in ISACS-TC registry patients, compared to the CAPTIM trial population.

The combined strategy

The combination of thrombolysis and early angiography with subsequent PCI has been established as standard of care. The pharmaco-invasive strategy consists in thrombolysis combined with an early routine angiography, between 2-24 hours from symptom onset, with the possibility to perform PCI if required. The safety and efficacy of this approach has been observed in both randomized controlled trials and meta-analyses [32-39]. Therefore, current guidelines recommend transferring patients to a PCI center after the administration of thrombolysis for an early angiography and PCI if necessary [6].

CONCLUSION

The current study has shown that timely reperfusion, in this case within 3 hours, with fibrinolysis, rather than pPCI, is feasible and safe in STEMI patients arriving within 12 hours of symptom onset, regardless of sex. This study shows that timely fibrinolysis is associated with similar rates of mortality and adverse events when compared to pPCI. This reperfusion strategy should be preferential in remote areas and in regions with underdeveloped angioplasty networks. Furthermore, tertiary centers should study associations between travel distance from the event locations to points of care and, subsequently, categorize zones based on these associations in order to facilitate caregivers in the selection of a reperfusion strategy.

References

1. Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JH, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med. 1993;328:680-4.
2. Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, Overlie P, Donohue B, Chelliah N, Timmis GC, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. N Engl J Med. 1993;328:673-9.
3. Boersma E; Primary Coronary Angioplasty vs. Thrombolysis Group. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. Eur Heart J. 2006;27:779-88.
4. Widimský P, Groch L, Zelízko M, Aschermann M, Bednár F, Suryapranata H. Multicentre randomized trial comparing transport to primary angioplasty vs immediate thrombolysis vs combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory. The PRAGUE study. Eur Heart J. 2000;21:823-31.
5. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. N Engl J Med. 1997;336:1621-8.
6. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients

presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39:119-77.

7. Widimsky P, Wijns W, Fajadet J, de Belder M, Knot J, Aaberge L, Andrikopoulos G, Baz JA, Betriu A, Claeys M, Danchin N, Djambazov S, Erne P, Hartikainen J, Huber K, Kala P, Klinceva M, Kristensen SD, Ludman P, Ferre JM, Merkely B, Milicic D, Morais J, Noc M, Opolski G, Ostojic M, Radovanovic D, De Servi S, Stenestrand U, Studencan M, Tubaro M, Vasiljevic Z, Weidinger F, Witkowski A, Zeymer U; European Association for Percutaneous Cardiovascular Interventions. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. Eur Heart J. 2010;31:943-57.
8. Cenko E, Ricci B, Kedev S, Vasiljevic Z, Dorobantu M, Gustiene O, Kneževic B, Milicic D8, Dilic M, Trninic D, Smith F, Manfrini O, Badimon L, Bugiardini R. Reperfusion therapy for ST-elevation acute myocardial infarction in Eastern Europe: the ISACS-TC registry. Eur Heart J Qual Care Clin Outcomes. 2016;2:45-51.
9. Rosselló X, Huo Y, Pocock S, Van de Werf F, Chin CT, Danchin N, Lee SW, Medina J, Vega A, Bueno H. Global geographical variations in ST-segment elevation myocardial infarction management and post-discharge mortality. Int J Cardiol. 2017;245:27-34.
10. Bugiardini R, Badimon L, Manfrini O. Rationale and design of the ISACS-TC (International Survey of Acute Coronary Syndromes in Transitional Countries) project. Eur Heart J Suppl 2014;16:A1-A6.
11. Bugiardini R, Cenko E, Ricci B, Vasiljevic Z, Dorobantu M, Kedev S, Vavlukis M, Kalpak O, Puddu PE, Gustiene O, Trninic D, Knežević B, Miličić D, Gale CP, Manfrini O, Koller A, Badimon L. Comparison of Early Versus Delayed Oral β Blockers in Acute Coronary Syndromes and Effect on Outcomes. Am J Cardiol 2016;117:760–767.

12. Cenko E, Ricci B, Kedev S, Vasiljevic Z, Dorobantu M, Gustiene O, Knežević B, Miličić M, Dilic M, Trninic D, Smith F, Manfrini O, Badimon L, Bugiardini R. Reperfusion therapy for ST-elevation acute myocardial infarction in Eastern Europe: the ISACS-TC registry. Eur Heart J Qual Care Clin Outcomes 2016; 2:45–51.
13. Bugiardini R, Dorobantu M, Vasiljevic Z, Kedev S, Knežević B, Miličić D, Calmac L, Trninic D, Daullxhiu I, Cenko E, Ricci B, Puddu PE, Manfrini O, Koller A, Badimon L; ISACS-TC Investigators. Unfractionated heparin-clopidogrel combination in STelevation myocardial infarction not receiving reperfusion therapy. Atherosclerosis 2015; 241:151–156.
14. Cenko E, Ricci B, Vasiljevic Z, Kedev Z, Knežević B, Trninic D, Daullxhiu I, Gustienė O, Miličić D, Manfrini O, Dorobantu M, Bugiardini R. Relation between Systolic Blood Pressure and In-hospital Mortality in Acute Coronary Syndromes. J Hypertens Res 2015; 1:17–27.
15. Bugiardini R, Manfrini O, Majstorovic Stakic M, Cenko E, Boytsov S, Merkely B, Becker D, Dilić M, Vasiljević Z, Koller A, Badimon L. Exploring In-hospital Death from Myocardial Infarction in Eastern Europe; From the International Registry of Acute Coronary Syndromes in Transitional Countries (ISACS-TC); on the behalf of the Working Group on Coronary Pathophysiology & Microcirculation of the European Society of Cardiology. Curr Vasc Pharmacol 2014; 12:903–909.
16. Dorobantu M, Tautu O.-F, Fruntelata A, Calmac L, Tatu-Chitoiu G, Bataila V, Dimulescu D, Craiu E, Nanea T, Istvan A, Babes K, Macarie C, Militaru C, Cenko E, Manfrini O. Hypertension and acute coronary syndromes in Romania: Data from the ISACS-TC registry. Eur Heart J Suppl 2014; 16:A20–A27.
17. Vasiljevic Z, Krljanac G, Davidovic G, Panic G, Radovanovic S, Mickovski N, Srbljak N, Markovic-Nikolic N, Curic-Petkovic S, Panic M, Cenko E, Manfrini O, Martelli I, Koller A, Badimon L, Bugiardini R. Gender differences in case fatality rates of acute myocardial infarction in Serbia. Eur Heart J Suppl 2014; 16: A48–A55.

18. Trninic D, Dilic M, Vasiljevic Z, Kulic M, Srdić S, Dobrijević N, Sabanovic- Bajramovic N, Begic A, Kukavica N, Vukcevic V, Davidovic G, Panic G, Saric J, Zrnic M, Matic I, Trifunovic N, Martelli I, Cenko E, Manfrini O, Koller A, Badimon L, Bugiardini R. Clinical profile of patients with no-reperfusion therapy in Bosnia and Herzegovina and Serbia. Eur Heart J Suppl 2014; 16:A67–A73.
19. Manfrini O, Dorobantu M, Vasiljevic Z, Kedev S, Knežević B, Miličić D, Dilic M, Trninic D, Daullxhiu I, Gustiene O, Ricci B, Martelli I, Cenko E, Koller A, Badimon L, Bugiardini R. Acute coronary syndrome in octogenarian patients: Results from the international registry of acute coronary syndromes in transitional countries (ISACSTC) registry. Eur Heart J Suppl 2014; 16:A87–A9.
20. International Survey of Acute Coronary Syndromes in Transitional Countries (ISACSTC). Available at https://clinicaltrials.gov/ct2/show/NCT01218776
21. De Luca G, Cassetti E, Marino P. Percutaneous coronary intervention-related time delay, patient's risk profile, and survival benefits of primary angioplasty vs lytic therapy in ST-segment elevation myocardial infarction. Am J Emerg Med. 2009;27:712-9.
22. Widimský P, Budesínský T, Vorác D, Groch L, Zelízko M, Aschermann M, Branny M, St'ásek J, Formánek P; 'PRAGUE' Study Group Investigators. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial--PRAGUE-2. Eur Heart J. 2003 Jan;24(1):94-104.
23. 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; Comparison of Angioplasty and Prehospital Thromboysis in Acute Myocardial Infarction study group. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. Lancet. 2002;360:825-9.

24. Bonnefoy E, Steg PG, Boutitie F, Dubien PY, Lapostolle F, Roncalli J, Dissait F, Vanzetto G, Leizorowicz A, Kirkorian G; CAPTIM Investigators, Mercier C, McFadden EP, Touboul P. Comparison of primary angioplasty and pre-hospital fibrinolysis in acute myocardial infarction (CAPTIM) trial: a 5-year follow-up. Eur Heart J. 2009;30:1598-606.
25. Pinto DS, Frederick PD, Chakrabarti AK, Kirtane AJ, Ullman E, Dejam A, Miller DP, Henry TD, Gibson CM; National Registry of Myocardial Infarction Investigators. Benefit of transferring ST-segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic declines as delays increase. Circulation. 2011;124:2512-21.
26. Kalla K, Christ G, Karnik R, Malzer R, Norman G, Prachar H, Schreiber W, Unger G, Glogar HD, Kaff A, Laggner AN, Maurer G, Mlczoch J, Slany J, Weber HS, Huber K; Vienna STEMI Registry Group. Implementation of guidelines improves the standard of care: the Viennese registry on reperfusion strategies in ST-elevation myocardial infarction (Vienna STEMI registry). Circulation. 2006;113:2398-405.
27. Danchin N, Coste P, Ferrières J, Steg PG, Cottin Y, Blanchard D, Belle L, Ritz B, Kirkorian G, Angioi M, Sans P, Charbonnier B, Eltchaninoff H, Guéret P, Khalife K, Asseman P, Puel J, Goldstein P, Cambou JP, Simon T; FAST-MI Investigators. Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment-elevation acute myocardial infarction: data from the french registry on acute ST-elevation myocardial infarction (FAST-MI). Circulation. 2008;118:268-76.
28. Schoos MM, Sejersten M, Hvelplund A, Madsen M, Lønborg J, Steinmetz J, Treschow PM, Pedersen F, Jørgensen E, Grande P, Kelbæk H, Clemmensen P. Reperfusion delay in patients treated with primary percutaneous coronary intervention: insight from a real world Danish ST-segment elevation myocardial infarction population in the era of telemedicine. Eur Heart J Acute Cardiovasc Care. 2012;1:200-9.

29. Stone GW, Grines CL, Browne KF, Marco J, Rothbaum D, O'Keefe J, Hartzler GO, Overlie P, Donohue B, Chelliah N, et al. Comparison of in-hospital outcome in men versus women treated by either thrombolytic therapy or primary coronary angioplasty for acute myocardial infarction. Am J Cardiol. 1995;75:987-92.
30. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, Sulimov V, Rosell Ortiz F, Ostojic M, Welsh RC, Carvalho AC, Nanas J, Arntz HR, Halvorsen S, Huber K, Grajek S, Fresco C, Bluhmki E, Regelin A, Vandenberghe K, Bogaerts K, Van de Werf F; STREAM Investigative Team. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. N Engl J Med. 2013;368:1379-87.
31. de Boer MJ, Ottervanger JP, van 't Hof AW, Hoorntje JC, Suryapranata H, Zijlstra F; Zwolle Myocardial Infarction Study Group. Reperfusion therapy in elderly patients with acute myocardial infarction: a randomized comparison of primary angioplasty and thrombolytic therapy. J Am Coll Cardiol. 2002;39:1723-8.
32. Larson DM, Duval S, Sharkey SW, Garberich RF, Madison JD, Stokman PJ, Dirks TG, Westin RK, Harris JL, Henry TD. Safety and efficacy of a pharmaco-invasive reperfusion strategy in rural ST-elevation myocardial infarction patients with expected delays due to long-distance transfers. Eur Heart J. 2012;33:1232-40.
33. Pu J, Ding S, Ge H, Han Y, Guo J, Lin R, Su X, Zhang H, Chen L, He B; EARLY-MYO Investigators. Efficacy and Safety of a Pharmaco-Invasive Strategy With Half-Dose Alteplase Versus Primary Angioplasty in ST-Segment-Elevation Myocardial Infarction: EARLY-MYO Trial (Early Routine Catheterization After Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Segment-Elevation Myocardial Infarction). Circulation 2017;136:1462-73.
34. Cantor WJ, Fitchett D, Borgundvaag B, Ducas J, Heffernan M, Cohen EA, Morrison LJ, Langer A, Dzavik V, Mehta SR, Lazzam C, Schwartz B, Casanova A, Goodman SG; TRANSFER-AMI Trial Investigators. Routine early angioplasty after fibrinolysis for acute myocardial infarction. N Engl J Med. 2009;360:2705-18.

35. Bøhmer E, Hoffmann P, Abdelnoor M, Arnesen H, Halvorsen S. Efficacy and safety of immediate angioplasty versus ischemia-guided management after thrombolysis in acute myocardial infarction in areas with very long transfer distances results of the NORDISTEMI (NORwegian study on DIstrict treatment of ST-elevation myocardial infarction). J Am Coll Cardiol. 2010;55:102-10.
36. Sinnaeve PR, Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Lambert Y, Danays T, Soulat L, Halvorsen S, Ortiz FR, Vandenberghe K, Regelin A, Bluhmki E, Bogaerts K, Van de Werf F; STREAM investigators. ST-segment-elevation myocardial infarction patients randomized to a pharmaco-invasive strategy or primary percutaneous coronary intervention: Strategic Reperfusion Early After Myocardial Infarction (STREAM) 1-year mortality follow-up. Circulation. 2014;130:1139-45.
37. Borgia F, Goodman SG, Halvorsen S, Cantor WJ, Piscione F, Le May MR, Fernández-Avilés F, Sánchez PL, Dimopoulos K, Scheller B, Armstrong PW, Di Mario C. Early routine percutaneous coronary intervention after fibrinolysis vs. standard therapy in ST-segment elevation myocardial infarction: a meta-analysis. Eur Heart J. 2010;31:2156-69.
38. D'Souza SP, Mamas MA, Fraser DG, Fath-Ordoubadi F. Routine early coronary angioplasty versus ischaemia-guided angioplasty after thrombolysis in acute ST-elevation myocardial infarction: a meta-analysis. Eur Heart J. 2011;32:972-82.
39. Sim DS, Jeong MH, Ahn Y, Kim YJ, Chae SC, Hong TJ, Seong IW, Chae JK, Kim CJ, Cho MC, Rha SW, Bae JH, Seung KB, Park SJ; Korea Acute Myocardial Infarction Registry (KAMIR) Investigators. Pharmacoinvasive Strategy Versus Primary Percutaneous Coronary Intervention in Patients With ST-Segment-Elevation Myocardial Infarction: A Propensity Score-Matched Analysis. Circ Cardiovasc Interv. 2016;9.pii:e003508. doi: 10.1161/CIRCINTERVENTIONS.115.003508.