ORIGINAL ARTICLE

An observational, prospective study of the pharmaco-invasive strategy approach to ST-segment myocardial infarction (STEMI) in the era of primary percutaneous coronary intervention based on Elias Heart Centre Interventional Registry (EIRE Study). The Southern Romanian experience

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Abstract: **Aims –** The objective of our study is to compare pharmaco-invasive strategy (PhIS) in terms of safety and efficacy, with primary percutaneous coronary intervention (pPCI) strategy as standard therapy for STEMI patients from remote areas. **Background –** At present, primary percutaneous coronary intervention (pPCI) is the preferred reperfusion strategy for STEMI patients. However, despite pPCI being the gold standard, it is not always achievable due to variables such as lack of cardiac catheterization services and delays in the first medical contact-to-balloon time. **Methods –** This observational study is based on a prospective analysis of a cohort of 157 patients with ST-elevation myocardial infarction, over nine months, at Elias University Hospital (EUH). The study assessed the safety and efficacy of a sequence of fibrinolytic therapy in the first contact hospital before being referred to our center for PCI (PhIS, 35 patients, 22.29%) versus angioplasty alone (pPCI, 122 patients, 77.70%) during hospitalization. The primary outcomes studied were in-hospital death, and major adverse cardiac events (MACE), while secondary outcomes were the length of in-hospital stay, and the safety of the procedure. **Results –** The median reperfusion time was lower for the PhIS group compared to the primary PCI group (4 hours, IQR:6.25 vs 7 hours, IQR:12.38, p<0.05). The left ventricular systolic function (%) on arrival at EUH was higher in the PhIS group compared with the PCI alone group (46.55; 95%CI 42.42-49.15 vs 41.73; 95%CI 39.91-43.34; p=0.04). The mean number of diseased vessels, including the culprit-lesion, were similar in the two groups (2.84 vs 2.82, p=0.09). The in-hospital mortality rate was lower in the PhIS group than in the primary PCI group (1 patient; 2.9% vs 18 patients; 14.80%; p=0.05), while the number of in-hospital major adverse cardiac events (MACE) was not significantly different (17.10% vs 26.20%; p=0.27). There was no difference of the median length of hospitalization (6 days, IQR:2 vs 5 days, IQR:3; p=0.67) for the PhIS, and primary PCI groups, respectively. The safety endpoints of the procedures were similar in the two groups. **Conclusions –** Pharmaco-invasive strategy (PhIS) had clinical and procedural outcomes (in-hospital MACE, length of in-hospital stay) similar to primary percutaneous coronary intervention (pPCI), in case of long distances to catheterization laboratories. Efficient thrombolysis makes PhIS a viable alternative in saving lives with a lower rate of in-hospital death than pPCI. Performed thrombolysis in a local non-PCI center and referral of the STEMI patients to a 24/7 catheterization laboratory may be a good option for areas where the infrastructure of such facilities is weak.

Keywords: ST-segment elevated myocardial infarction (STEMI); Pharmaco-invasive strategy (PhIS); Primary percutaneous coronary intervention (pPCI).

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Rezumat: Obiective – Obiectivul studiului nostru a fost să compare eficacitatea și siguranța strategiei farmaco-invazive (PhIS) cu cea a angioplastiei primare (pPCI), la pacienții cu infarct miocardic cu supradenivelare de segment ST (STEMI). **Introducere –** În prezent, angioplastia primară percutanată (pPCI) este strategia preferată de reperfuzie pentru pacienții cu STEMI. Deși angioplastia primară este considerată strategia standard, aceasta nu este posibilă întotdeauna, datorită unor cauze legate de lipsa de servicii permanente de angiografie și de întârzieri dintre diagnosticul STEMI până la repermeabilizarea arterei coronare responsabile de infarctul miocardic acut. **Metode –** Acest studiu observațional se bazează pe o analiză prospectivă a unei cohorte de 157 pacienți cu infarct miocardic cu supradenivelare de segment ST, pentru o perioadă de 9 luni, la Spitalul Universitar Elias (EUH). Studiul a evaluat eficacitatea și siguranța procedurilor la pacienții cu STEMI care au fost supuși terapiei fibrinolitice la primul spital de contact, înainte de a fi transferați către spitalul nostru pentru angioplastie coronariană (PhIS, 35 pacienți, 22.29%) față de cei supuși doar angioplastiei primare (pPCI, 122 pacienți, 77.70%), pe durata spitalizării. Efectele studiate au fost decesul intraspitalicesc și evenimentele adverse cardiovasculare majore (MACE), precum și durata spitalizării sau siguranța procedurilor. **Rezultate –** Mediana timpului de reperfuzie a fost mai scăzută în grupul strategiei farmaco-invazive comparativ cu grupul angioplastiei primare (4 ore, IQR:6.25 vs 7 ore, IQR:12.38, p<0,05). Funcția sistolică a ventriculului stâng (%) la sosirea la EUH a fost mai mare în grupul PhIS comparativ cu grupul pPCI (46.55%; 95%CI 42.42-49.15 vs 41.73; 95%CI 39.91-43.34; p=0.04). Numărul mediu de vase cu boală aterosclerotică, inclusiv vasul responsabil de infarctul miocardic, a fost similar în cele două grupuri (2.84 vs 2.82, p=0.09). Rata mortalității intraspitalicești a fost mai scăzută în grupul PhIS decât în grupul pPCI (1 pacient; 2.9% vs 18 pacienți; p=0.05), în timp ce numărul evenimentelor adverse cardiovasculare majore (MACE) nu a fost semnificativ diferit (17.10% vs 26.20%; p=0.27). Nu am observant nici o diferență pentru durata mediană a spitalizării (6 zile, IQR:2 vs 5 zile, IQR:3; p=0.67) între grupurile strategiei farmaco-invazive și angioplastiei primare. Siguranța procedurilor a fost similară în cele două grupuri. **Concluzii –** Strategia farmaco-invazivă (PhIS) are rezultate clinice și procedurale (evenimente adverse cardiovasculare majore intraspitalicești, durata spitalizării) similare cu angioplastia primară (pPCI), pentru zonele situate la distanțe mari până la laboratoarele de cateteterism cardiac. Tromboliza eficientă face ca strategia farmaco-invazivă sa fie o alternativă eficientă, cu o mortalitate intraspitalicească mai scăzută decât angioplastia primară singură. Tromboliza eficientă în primul spital de contact a pacienților cu STEMI, urmată de transferul într-un centru cu activitate permanentă de cateterism cardiac, poate fi o bună opțiune pentru zonele unde infrastructura cu asemenea facilități nu este încă dezvoltată.

Cuvinte cheie: Infarct miocardic acut cu supradenivelare de segment ST (STEMI); Strategia farmaco-invazivă (PhIS); Angioplastie primară percutanată (pPCI).

I. BACKGROUND

ST-segment Elevation Myocardial infarction (STEMI) is one of the leading causes of death worldwide with a significant impact on healthcare resources and expenditure[1]. All major international guidelines (ESC 2017, ACC/AHA 2013, NICE 2013) clearly state that primary Percutaneous Coronary Intervention (pPCI) is the preferred reperfusion strategy for STEMI patients[2-4]. Furthermore, its superiority over fibrinolysis alone has been repeatedly demonstrated in numerous clinical trials[5]. However, despite pPCI being the gold standard, it is not always achievable due to the lack of cardiac catheterisation services and delays in the first medical contact-to-needle time[5]. Consequently, pharmaco-invasive strategy (PhIS), which consists of a sequence of fibrinolytic therapy performed in the local hospital followed by patient transfer to a PCI-capable centre for coronary angioplasty, is common practice in many countries[6].

Should the maximum expected delay from STEMI diagnosis to PCI be greater than 120 minutes for patients presenting within 12 hours of symptoms onset, fibrinolytic therapy has to be performed as an intermediate step before referring the patient to a 24/7 PCI-capable facility[2]. Nevertheless, many patients do not meet these treatment criteria due to multiple logistical, geographical and resource-related issues. As a result, many patients from remote areas are transferred for PCI outside the recommended 120 minutes of transportation time without having received thrombolytic therapy (delayed PCI). Furthermore, the effectiveness of pPCI performed outside the recommended transfer time from diagnosis is not apparent, and recent studies suggest that early intervention with PhIS may be superior to delayed PCI[7].

Moreover, many clinical studies have investigated delays in the door-to-balloon time and current guidelines state that a 30 minutes door-to-balloon time is optimal for effective reperfusion[2]. However, it is unclear how pre-hospital delays such, as the time from chest pain (CP) onset to contacting emergency services influences the outcome of reperfusion therapy.

Due to the lack of interventional facilities and skilled interventionists, many patients with STEMI cannot immediately benefit from mechanical reperfusion via angioplasty with stents. Similar situations in other European countries led to the reassessment and reintroduction of fibrin-specific thrombolytic agents in STEMI management protocols, when the transfer time from the FMC (local hospital) to the catherization laboratory facility exceeds two hours[2].

II. OBJECTIVES

Our prospective, observational study sought to investigate the efficacy and safety of pharmaco-invasive strategy (PhIS) versus primary PCI (pPCI) in the context of the Romanian Ministry of Health's Acute Myocardial Infarction-Priority Action (AMI-PA) Programme for STEMI. We also considered whether PhIS should be a model of care for STEMI patients who are outside the 120 minutes transfer time from diagnosis to PCI in the context of a real-world system.

III. METHODS

Study **design.** We prospectively recruited 157 consecutive patients with STEMI, over nine months, from January 1st to October 1st, 2018, as our institution provides 24/7 catheterization laboratory services on rotation, for patients coming from within an 58,584 km^2 area of Bucharest with the longest distance of 340 km.

The protocol was designed by a team of clinical and interventional cardiologists at Elias University hospital (EUH) and approved by the hospital's research and ethics committee. Data collection and data analysis were carried out by the authors at the Heart Department. The study was not sponsored by any third parties; no other party had any involvement in the study design, data analysis, or manuscript preparation. The authors confirm the accuracy of the data and analysis.

Patient inclusion criteria. Patients were eligible for inclusion in the study if they had evidence of ongoing CP and dynamic ECG changes consistent with STEMI[2].

A total number of 157 patients with ST-segment elevation myocardial infarction (STEMI) were admitted to EUH for PCI via ambulance as follows: 96 patients (61.14%) directly from the scene of CP to EUH for primary PCI; 26 patients (16.56%) from the first medical hospital (FMH) without fibrinolytic therapy (delayed PCI subgroup); 35 patients (22.29%) from community hospitals (FMH) after fibrinolytic therapy (PhIS group). The patients referred from the FMH (26 plus 35 patients) were screened for eligibility by local doctors and communicated via mobile to the Cardiologist on-duty at EUH (Figure 1).

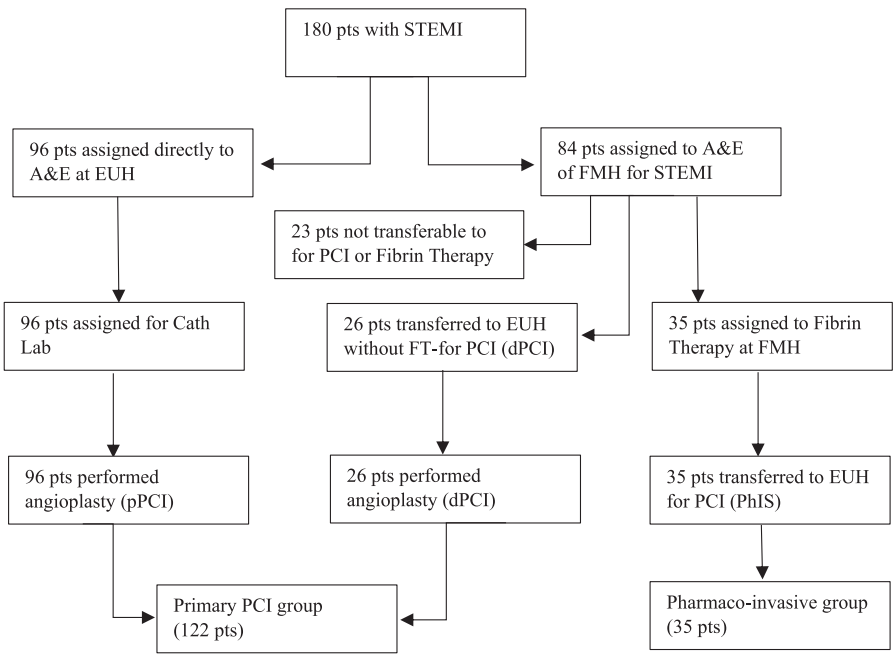

Figure 1. Flow chart with the randomization of patients with STEMI.
FT – fibrin therapy; A&E – accident and emergency department; dPCI – delayed PCI; FMH – first medical hospital.

Patients in remote areas, outside the transport time of 120 minutes (61 patients, 38.86%), were initially assessed at the FMH where they received a loading doses of Aspirin and Clopidogrel (or Ticagrelor). Some of these STEMI patients (35 patients) received fibrinolytic therapy and unfractionated heparin, before being transferred to EUH for percutaneous coronary intervention (PCI) of the infarct-related coronary artery (IRCA). The choice of fibrinolytic and the dose administered were at the discretion of the FMH cardiologist/acute medical unit (AMU) physician. The patients from an area within a two hours reach of an interventional center (96 patients, 61.14%) were transferred directly by ambulance to our hospital and assessed in the emergency department (ED) before undergoing angiography. The patients were consented accordingly.

Intervention. We performed diagnostic angiography on all patients diagnosed with STEMI and implanted stents when technically possible. The stents implanted were drug-eluting, covered under the Romanian Ministry of Health's national programme (AP-IMA). The protocol allowed for the use of unfractionated heparin, glycoprotein IIb/IIIa (Gp IIb/IIIa) antagonists at the discretion of the interventional Cardiologist on-duty. A TIMI 3 flow, grade III myocardial blush and less than 10% residual coronary stenosis were the aims of PCI.

Endpoints and definitions. The primary endpoints of the study were in-hospital major adverse cardiac events (MACE), in-hospital death of any cause, and a combination of in-hospital MACE, death and recurrent chest pain. Secondary endpoints included the length of hospitalization and the safety of interventional procedures: the amount of contrast agent used (ml), time of X-ray exposure (minutes), radiation dose air kerma (AK), dose-area product (DAP). In-hospital major adverse cardiac events (MACE) were a combination of cardiogenic shock, recurrent ischemia/MI, clinically driven target revascularization, stroke, ventricular tachycardia /fibrillation (VT/VF), pulmonary oedema and heart failure.

Statistical analysis. Categorical data are reported as numbers (percentages %) for its variables such as gender, in-hospital deaths, MACE, risk factors, recurrent chest pain, Killip class on admission and infarct-related coronary artery (IRCA). We used the Pearson's chi-square test and Fischer's exact test for group comparisons. Data for continuous variables are presented as mean±SE (%) when the distribution is uniform for age, hs-cTnI on admission (ng/l) and as medians and interquartile range (IQR) when the distribution is not uniform for treatment times.

We performed comparisons of the central tendency of the baseline characteristics and endpoints of the two treatment groups using the *t*-test for normally distributed continuous variables, and nonparametric tests (Wilcoxon rank-sum test or Mann-Whitney rank sum test) to compare the numerical variables and the abnormally distributed continuous variables.

We used the Kaplan-Meier method to assess the time to primary endpoints and to create survival estimates. Chi-square test was also used to compare the rates of death or recurrent chest pain between the treatment groups. All p-values were two-sided, and a *p*-value <0.05 was considered statistically significant. We assessed the odds ratio for in-hospital MACE and death. The statistical analysis was performed with an SPSS program, version 21 (Statistical Package for the Social Sciences) software (IBM SPSS Statistics, USA).

IV. RESULTS

Baseline characteristics. Baseline characteristics of the patients were well balanced across the two groups, with no differences among age, gender and risk factors, except for a higher non-significant prevalence of diabetes mellitus (p=0.08) and active smoking (p=0.08) in the PhIS group compared with the standard treatment (pPCI) group (Table 1). Of the 61 patients from rural areas, outside a 2 hours reach of Cath lab facilities, only 35 patients of them (57.37%) received fibrinolytic therapy in the local hospital, before being transferred to our hospital (EUH) (Table 1).

The median chest pain duration time (hours) from chest pain onset (CP) to local hospital (FMH) (CP-to-FMH time) assessment is similar in the PhIS group and in the primary PCI group (4h, IQR:6.25 vs 5h, IQR:11.50, p=0.43), but the median time from CP onset (hours) to EUH is non-significantly longer in the PhIS group compared with the pPCI group (9h, IQR:7.25 vs 7h, IQR:12.38, p=0.07). This may be explained by the time necessary for fibrinolytic therapy at the local hospital, for the PhIS group. We have to mention that from 35 patients of the PhIS group, only 23 patients (65.71%) arrived within 12 hours, while from the 122 patients of the pPCI group only 82 patients (67.21%) arrived within 12 hours to EUH (Figure 2).

The median revascularization time, from CP onset to fibrinolytic therapy at the FMH for the PhIS group was significantly lower compared with the time from CP to primary PCI at EUH (CP-to-EUH time) for

Table 1. Key baseline characteristics of the patients with STEMI according to strategy of diagnosis and referral in STEMI-EIRE.

Characteristics	PhIS	pPCI	p-value
Number (%)	35 (22.30%)	122 (70.70%)	
Age, yo, mean±SD (95% CI)	61.06±13.34 (56.48-65.64)	63.13±13.99 (60.62-65.64)	0.43[b,d]
Male gender, number (%)	26 (74.28%)	85 (69.67%)	0.60[*,d]
Diabetes mellitus, number (%)	7 (20%)	44 (35.06%)	0.080[*,d]
Hypertension, number (%)	22 (62.85%)	79 (64.75%)	0.90[*,d]
Active smoker, number (%)	19 (54.28%)	52 (42.62%)	0.08[*,d]
Hypercholesterolemia, number (%)	18 (51.42%)	59 (48.36%)	0.67[*,d]
Family history of CAD, number (%)	2 (5.71%)	14 (11.47%)	0.33[*,d]
Previous CAD, number (%)	4 (11.42%)	12 (9.83%)	0.84[*,d]
Shortness of breath, number (%)	6 (17.42%)	23 (18.85%)	0.82[*,d]
Distance to EUH, km, mean±SD, (95%CI)	207.82	154.29	0.05[*]
CP onset to revascularization, hours (median, IQR)	4 (6.25)	7 (12.38)	0.05[*]
CP onset to EUH, hours, median (IQR)	9 (7.25)	7 (12.38)	0.07[*]
CP onset to EUH less than 12 hours, number (%)	(65.71%)	(67.21%)	0.91[d]
Resuscitation before admission at EUH, number (%)	1 (2.85%)	14 (11.47%)	0.12[*,c,d]
hs-cTn on admission (ng/ml), mean±SD (95%CI)	112.62±73.27 (86.20-139.04)	76.03±73.15 (61.66-90.40)	0.02[b,d]
Killip class on admission, n (%) I II III IV	35 (100%) 32 (91.42%) 1 (2.85%) 0 (0%) 2 (5.71%)	122 (100%) 95 (77.86%) 5 (4.09%) 6 (4.91%) 16 (13.11%)	0.07[*], 0.08[d] 0.07[*] 0.73[*] 0.18[*] 0.22[*]
Left ventricle ejection fraction on admission (%), trimmed mean5%±SD (95%CI)	46.55±9.79 (42.42-49.15)	41.74±12.27 (38.91-43.34)	0.04[b,d]
Time from door-to-needle (min), median (IQR)	59(49)	60 (49)	0.93[d]

[a] STEMI-EIRE: STEMI Elias Interventional Registry; [b] *p*-value calculated with *t*-test; [c] p-value calculated with Pearson chi-square/Fischer test; dp-value calculated with ANOVA; [*] The *p* value was assessed using Mann-Whitney U test, as an alternative for the distribution where skewness and kurtosis were outside the range (-1, +1) and (-2,+2), respectively; Data are presented as mean±SD (%) for age, hs-cTnI, LVEF, time from door-to-needle, as medians for the treatment times, and as numbers (percentages) for risk factors, time from chest pain onset to FMH/EUH, resuscitation, Killip class.

primary PCI group (4h, IQR:6.25 vs 7h, IQR:12.38; p<0.05).

The third treatment time of our research, the median door-to-needle time was similar in the two groups: (59 minutes, IQR: 49 vs 60 minutes, IQR: 49; p=0.93) for the PhIS group and the pPCI group, respectively.

The need for cardio-pulmonary resuscitation (CPR) was slightly less frequent in the pharmaco-invasive strategy group compared to primary PCI (1 patient, 2.90% vs 14 patients, 11.50%; p=0.12).

We assessed the patients on admission and noted the Killip class. Overall, the pharmaco-invasive strategy (PhIS) group had a better Killip class on admission than the pPCI group, but it was not statistically significant (p=0.07).

We found a significantly higher level of the high-sensitivity cardiac troponin I mean (hs-cTnI) on admission (expressed in ng/l) in the PhIS group compared with the pPCI group (112.62±73.27, 95%CI=86.20-139.04 vs 76.03±73.15, 95%CI=61.66-90.40; p=0.01) (Figure 3).

The trimmed mean LVEF (%) on admission was significantly higher for patients who underwent fibrinolytic therapy before PCI (PhIS group) compared with patients in the primary PCI group (46.55±9.79; 95%CI: 42.42-49.15 vs 41.74%±12.27; 95%CI: 38.91-43.34; p=0.04) (Figure 3).

Procedural and safety outcomes. There were five leading operators, who performed interventional procedures for both groups, according to the catheterization laboratory on-duty Rota. The number of vessels affected was similar in the PhIS group compared with the primary PCI group (2.82 vs 2.84; p=0.09). The median total length of stents (mm) implanted is similar in the two groups, PhIS and primary PCI (25, IQR=18 vs 28, IQR=23, p=0.09). The post-interven-

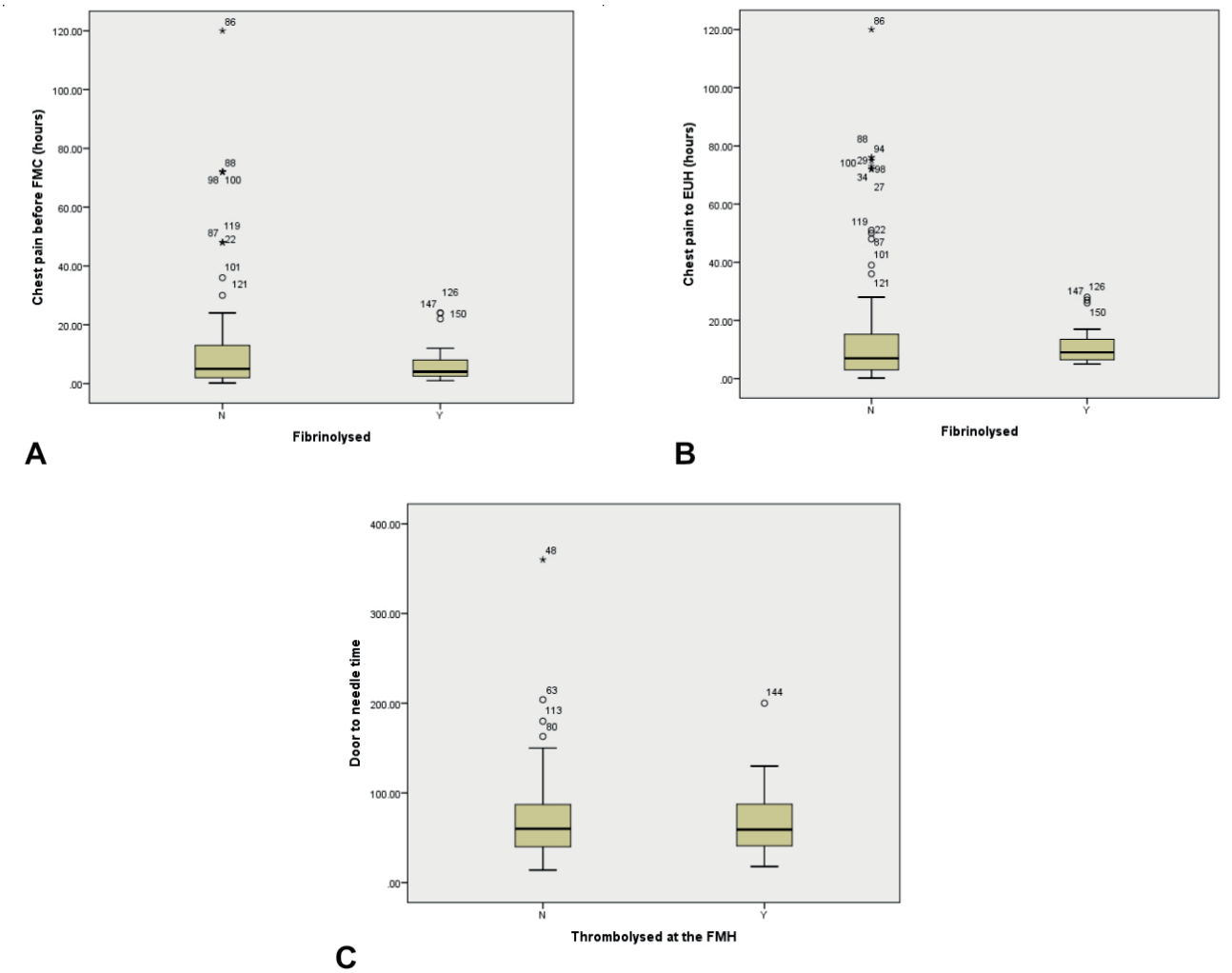

Figure 2. Therapeutical times for the two groups, pPCI (no fibrin therapy) and PhIS (thrombolysed before PCI).
a) Time from chest pain onset to FMH (hours);
b) Chest pain to EUH time (hours);
c) Door-to-needle time (hours).

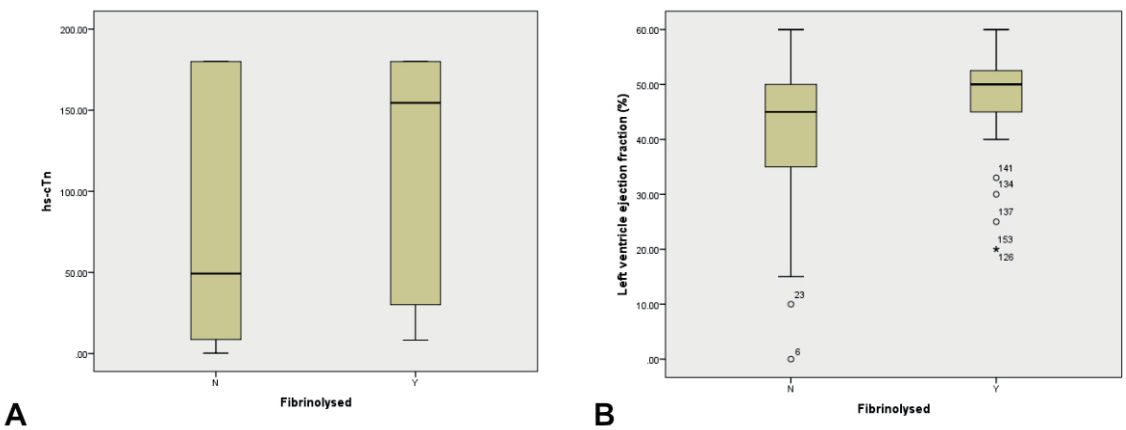

Figure 3. Clinical characteristics boxplots for the 2 groups, pPCI (no fibrin therapy) and PhIS (thrombolysed before PCI).
a) Level of high-sensitivity cardiac troponin on admission (ng/l);
b) Left ventricle ejection fraction on admission (%).
N – pPCI group, Y – PhIS group.

tional need for Gp IIb/IIIa is significantly lower in the PhIS strategy group than in the primary PCI group (8.60% vs 25.40%, p=0.03).

Safety. We assessed the safety of procedures by assessing time of exposure to X-Ray, kinetic energy released per unit mass (radiation dose air kerma), dose-area product (DAP), and the amount of contrast used during Cath lab interventions for both groups. All the measured safety outcomes were similar for the two groups, (PhIS vs pPCI) (Figure 4).

Efficacy outcome. The procedural and clinical outcomes results are displayed below (Table 2, Figures 5-7). The median length of hospital stay was similar in the two groups (6 days, IQR: 3 vs 5 days, IQR: 3, p=0.67), in the PhIS group and the pPCI group, respectively.

In-hospital major adverse cardiac events (MACE). The primary endpoint, in-hospital major adverse cardiac events (MACE) is similar in the PhIS group compared with the pPCI group (17.10% vs 26.20%, p=0.27). The odds ratio (OR) for developing MACE is with no statistical significance lower in the PhIS group (OR: 0.582, 95%CI: 0.221-1.531; p=0.27). The relative risk (RR) for developing MACE is with 34.6% less in the PhIS group than the primary PCI group (RR:0.654; 95% CI:0.298-14.35, p=0.37), but was found to not be statistically significant (Table 2, Figures 5-6). The risk estimate for the presence of MACE was 18.9% higher in pPCI group (OR:1.189, 95%CI=0.570-2.478).

In-hospital death. The other primary endpoint, in-hospital mortality, was more frequent in the primary angioplasty (pPCI) group compared to patients from remote areas who underwent fibrinolytic therapy at the FMH initially (PhIS), approaching the statistical significance (18 patients, 14.80%, vs 1 patient, 2.90%, p=0.05). The major causes for in-hospital death are reported in table 6. The relative risk (RR) of death for patients with pPCI is 5.12 times higher than the PhIS

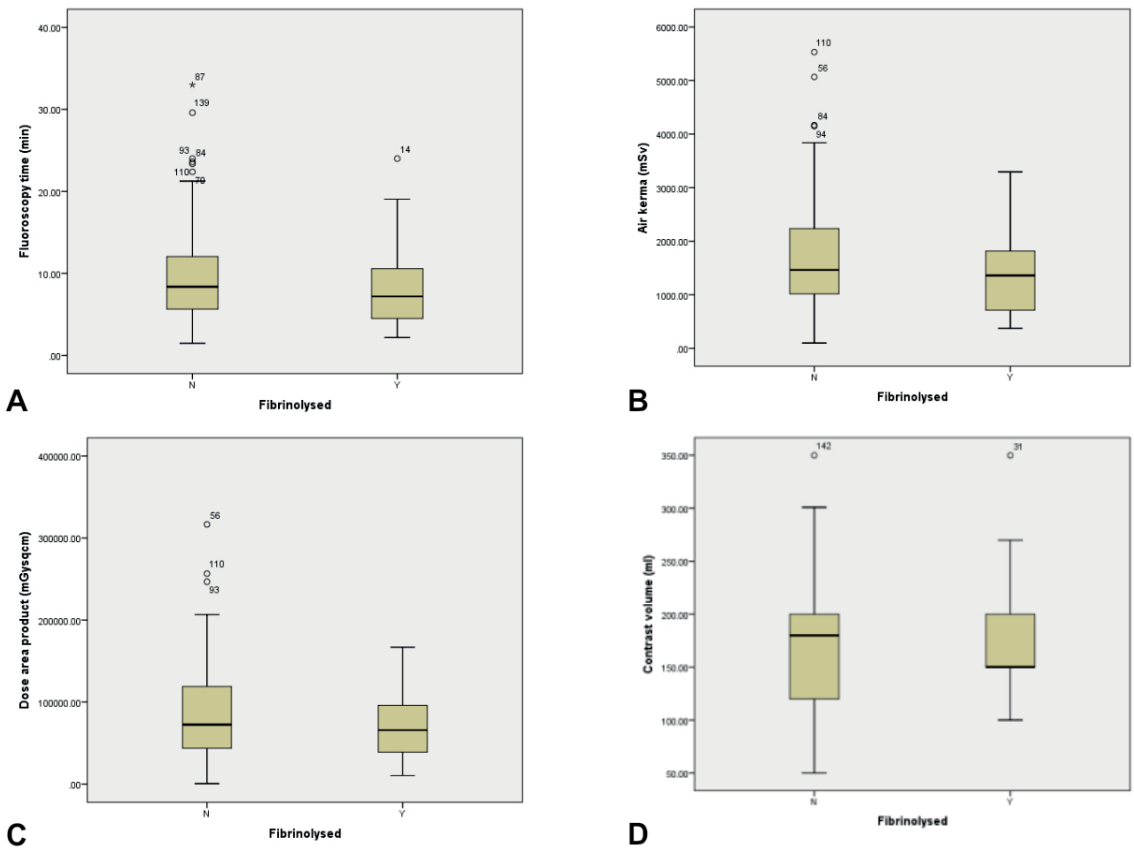

Figure 4. The angiographic outcomes for the 2 group: pPCI (no fibrin therapy), and PhIS (thrombolysed before PCI). All the measured safety outcomes were similar for the 2 groups, PhIS vs pPCI.
a) The median fluoroscopy time (min);
b) The median air kerma (AK) (mSv);
c) The median dose area product (DAP) (mGycm2);
d) The median contrast volume (ml).

Table 2. Clinical and procedural outcomes in patients with STEMI according to the strategy management in STEMI-EIRE.

Characteristics	PhIS	pPCI	p-value
Number (%)	35 (22.30%)	122 (77.70%)	
Diagnostic angiography (%)	35 (22.30%)	122 (77.70%)	
Number of vessels diseased, including the IRCA (%)	34 (97.14%)	119 (97.54%)	0.09[d]
No vessel	1 (2.85%)	3 (2.45%)	
One vessel	24 (68.60%)	63 (51.60%)	
Two vessels	6 (17.10%)	31 (25.40%)	
More than 3 vessels	4 (11.40%)	25 (20.50%)	
Infarct-related coronary artery, number (%)			
LMCA	1 (2.85%)	6 (4.91%)	0.60[*]
LAD	17 (48.57%)	54 (44.26%)	0.65[*]
LCx	3 (8.57%)	13 (10.65%)	0.54[*]
RCA	14 (40.00%)	47 (38.52%)	0.77[*]
Localization of culprit lesion, number (%)			0.14[d]
Proximal	18 (51.40%)	45 (36.90%)	
Medial	8 (22.90%)	40 (32.80%)	
Distal	3 (8.60%)	15 (12.30%)	
Number of stents implanted, number (%)			0.45[*]
No stents	5 (14,30%)	22 (18%)	
1 stent	23 (65.70%)	66 (54.10%)	
2 stents	16 (17.10%)	23 (18.90%)	
More than 3 stents	0 (0%)	11 (9%)	
Diameter (μm), median (IQR)	3 (0.88)	3 (0.75)	0.88[b,d], 0.92[*]
Length of total stents implanted (μm), median (IQR)	25 (18)	28 (23)	0.20[*]
In-hospital MACE, number (%)	6 (17.10%)	32 (26.20%)	0.27[d,*]
Recurrent chest pain (%)	2 (6.3%)	4 (3.3%)	0.48
In-hospital death (%)	1 (2.90%)	18 (14.80%)	0.05[d,c,*]
Combined primary endpoint, number (%)	9 (25.71%)	54 (44.26%)	0.15[*], 0.10[d]
Length of in-hospital stay, days, median(IQR),	6 (2)	5 (3)	0.67[*]
Operators, number (%)			0.38[*]
A	13 (37.10%)	36 (29.50%)	0.56[*]
B	6 (17.10%)	19 (15.57%)	0.73[*]
C	5 (14.30%)	33 (27.04%)	0.12[*]
D	11 (31.40%)	29 (23.77%)	054[*]
E	0 (0%)	5 (4.10%)	0.54[*]
Fluoroscopy time (min), median (IQR)	7.19 (6.29)	8.38 (6.48)	0.17[*]
Air Kerma (kinetic energy released per unit mass) AK (mSv), median (IQR)	1360 (1129)	1462.35 (1259)	0.24[*]
Dose Area Product (DAP), mGycm2, median (IQR)	65777.50 (60071.25)	72393 (76325.50)	0.31[*]
Contrast volume (ml), median (IQR)	150 (55)	180 (80)	0.85[d,b], 0.70[*]
Need for GP IIb/IIIa (%)	3 (8.60%)	31 (25.40%)	0.03[*c,d]

[a] STEMI-EIRE: STEMI Elias Interventional Registry; [b] *p*-value calculated with *t*-test; [c] *p*-value calculated with Pearson chi-square/Fischer test; dp-value calculated with ANOVA; [*] The *p* value was assessed using Mann-Whitney U test, as an alternative for the distribution where skewness and kurtosis were outside the range (-1, +1), and (-2, +2) respectively; Data are presented as mean±SD for length of total stents implanted, and as numbers (percentages) for number of vessels diseased, infarct-related artery, number of stent implanted, maximum diameter of stent, MACE, recurrent chest pain, length of in-hospital stay, in-hospital death, fluoroscopy time, air kerma, dose-area product, contrast volume. IRCA – infarct related coronary artery.

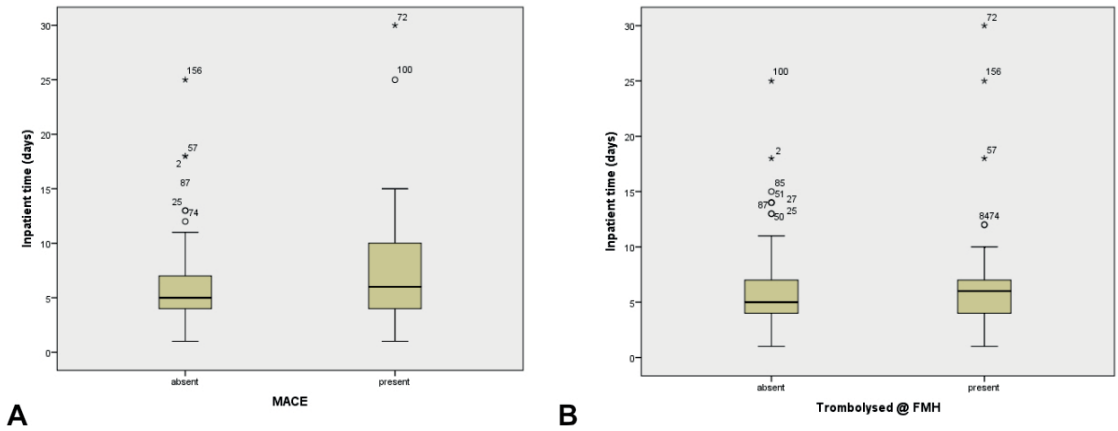

Figure 5. The in-patient hospitalization (days) for MACE and fibrin therapy.
a) For the patients with MACE (right) and without MACE (left);
b) In-patient time duration (days) for patients of the pPCI group (left) and for PhIS group (right).

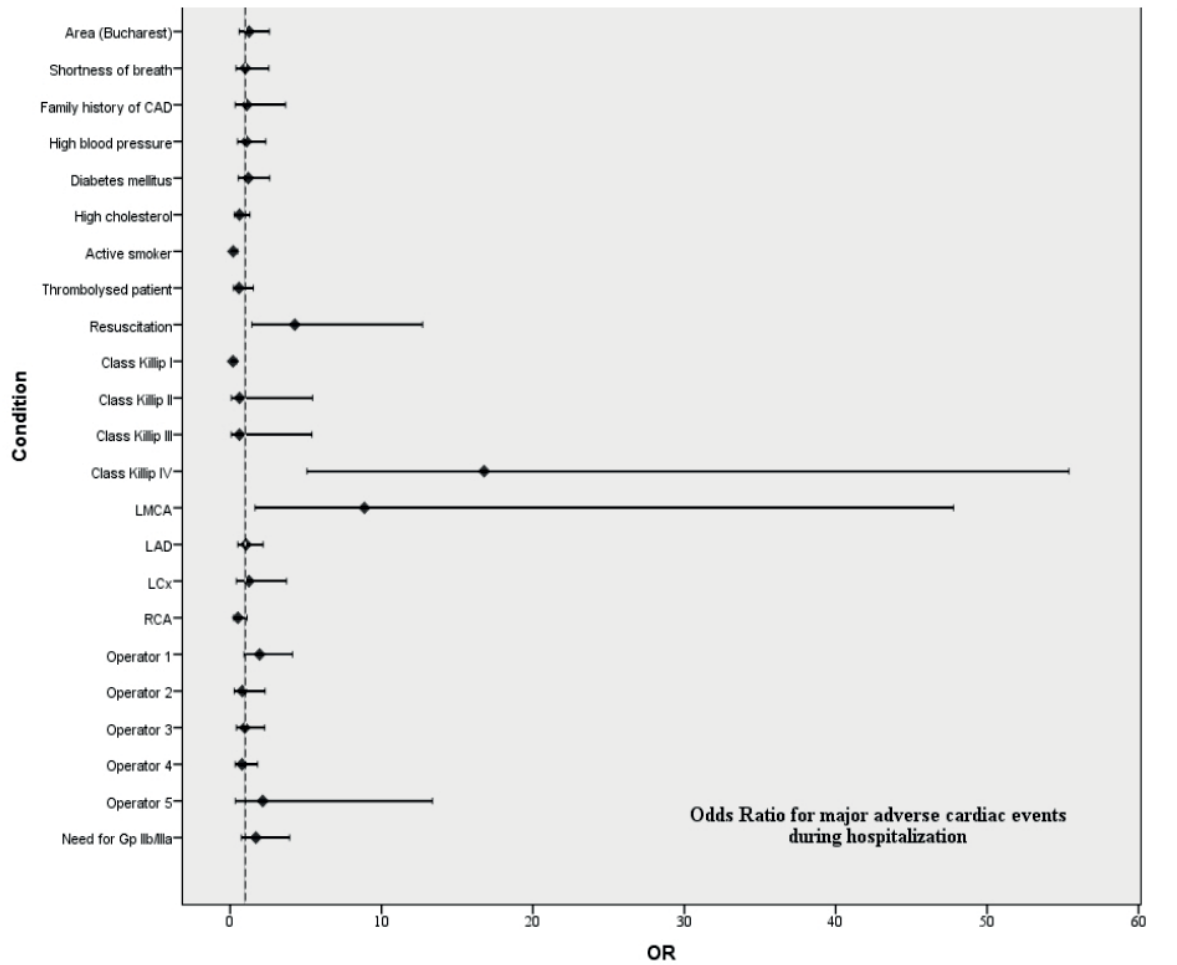

Figure 6. The predictors of the major adverse cardiac events during hospitalization.
Patients with age over 70 yo, resuscitated before/on admission, with Killip class IV, with LVEF less than 40%, with troponin over 80 ng/ml on admission, with LMCA involved as IRCA, have higher risk of developing MACE during in-hospital stay. Other predictors like active smoking, Killip class I, and length of stents less than 30mm have protective action, decreasing the risk of in-hospital MACE. The male gender, high cholesterol, diabetes mellitus, high blood pressure, family history of CAD, previous CAD, dyspnoea, fibrin therapy before PCI, class Killip II and III, coronary artery except LMCA, operators, need for Gp IIb/IIIa, AK, DAT, amount of contrast, diameter of stents, troponin over 80 ng/ml, total number of vessel disease, in-hospital stay, chest pain to EUH time, irrespective of the cut off (8, 12, 16 or 24 hours), culprit lesion, number of stents over 2, have similar odds for developing MACE.

group, but not statistically significant (95% CI: 0.71-36.94; p=0.07). The odds ratio for developing in-hospital death was lower for the PhIS group compared with the pPCI group but was not statistically significant (OR:0.17; 95%CI: 0.022-1.321; p=0.09) (Table 2, Figure 7).

Recurrent chest pain. There is no significant difference in the prevalence of recurrent chest pain between the two groups, PhIS vs pPCI (6.3% vs 3.3%, p=0.61).

In-hospital MACE distribution, according to the infarct-related coronary artery (IRCA). Since the primary endpoint (in-hospital MACE) proved similar among the two groups (PhIS, pPCI), we queried if the in-hospital MACE is dependent upon the infarct-related coronary artery. When we tested the null hypothesis with Independent-Samples Kruskal-Wallis test, we found that the distribution of major adverse cardiac events (MACE) is not similar across the four vessels (LMCA, LAD, LCx, RCA; p=0.02).

In-hospital mortality distribution, according to the IRCA. When we compared the rate of in-hospital death according to the culprit lesion, irrespective to the treatment strategy group, we found significant differences between the LMCA and each of the other culprit vessels: LAD (p=0.02), RCA (p=0.005), LCx (p=0.03), There is no significant difference of the in-

Table 3. Correlations between characteristics.

	Correlation	Characteristic	Correlation coefficient	p
In-hospital death	Strong	in-hospital MACE	rS=0.565	0.0001
		composite primary endpoint	rS = 0.729	0.0001
		the Killip class on admission	rP = 0.530, rS = 0.459	0.0001
	Medium	LVEF	rP = -0.339,	0.0001
	Weak	high cholesterol	rS = -0.293	0.0001
		active smoking	rS = -0.265	0.001
		remote areas	r = 0.168	0.035
		age	rP = 0.166	0.038
		fibrinolytic therapy before referral to EUH	rS = -0.152	0.058
	No correlation	time from CP onset to FMH	rS = 0.023	0.777
		time from CP onset to EUH	r = 0.012	0.885
In-hospital MACE	Strong	Killip class on admission	rP = 0.552	0.0001
	Medium	active smoking	rS = -0.302	0.0001
	Weak	LVEF	rP = 0.287	0.001
		age	rP = 0.167	0.037
		infarct-related artery	rP = -0.151	0.061
		level of fluoroscopy	rP = 0.148	0.087
		level of high cholesterol	rS = -0.102	0.205
	No correlation	time from CP onset to FMH	rS = 0.007	0.929
		time from CP onset to EUH	rS = -0.045	0.585
		fibrinolytic therapy at FMH	rS = 0.088	0.271
		hypertension	rS = 0.013	0.877
		family history of CAD	rS = 0.013	0.872
		location of thrombus within the artery	rP= 0.015	0.863
		number of vessels diseased	rP = 0.053	0.515
		diabetes mellitus	rS = -0.053	0.512
		countryside area	rS= -0.047	0.559
Length of hospitalization	Moderate	LVEF on admission	rS = 0.320	0.0001
	Weak	hs-cTnI	rS = 0.231	0.009
		fluoroscopy time	rS = 0.122	0.174
	No correlation	time from CP onset to FMH	rS = 0.108	0.204
		time from CP onset to EUH	rS = 0.096	0.257
		Killip class on admission	rS = 0.051	0.542
Number of stents	Strong	contrast volume	r = 0.502	0.0001
	Moderate	air kerma	r = 0.353	0.0001
		fluoroscopy time	r = 0.304	0.0001

rP – Pearson's coefficient of correlation; rS – Spearman's coefficient of correlation; p-value significantly statistic when p<0.05.

hospital mortality between the 2 groups (PhIS and pPCI) when the cause of STEMI is one of the other three vessels: LAD, RCA or LCx.

Composite endpoint of in-hospital MACE, recurrent CP, and in-hospital death, according to the IRCA. When we analyzed the primary composite endpoint (MACE, recurrent CP, death) we found significant differences in respect to the location of the culprit lesion. The number of composite endpoint events was significantly higher when LMCA was the IRCA compared with LAD (p=0.002) and with RCA (p=0.01), irrespective of the treatment time or fibrinolytic therapy at FMH.

Correlations. We assessed the correlations among the variables of the two groups, to find any relationship, before using regression tests to identify the quantitative relationship between the dependent variables (in-hospital MACE, deaths, duration of hospitalization) and independent variables (age, gender, risk factors, treatment times, hs-cTnI, out-of-the hospital resuscitation, cardiac arrest), and Killip class or LVEF on admission (Table 3).

There is a strong correlation of the number of in-hospital death, with in-hospital MACE (p=0.0001), with the Killip class on admission (p=0.0001), and a medium correlation with LVEF on admission (p=0.0001). Interestingly, there is no correlation between the number of in-hospital deaths and time from CP onset to FMH (p=0.77) or to EUH (p=0.88).

There is a moderate correlation of in-hospital MACE with the Killip class on admission (p=0.0001), with active smoking (r= -0.302, p=0.0001). There is no correlation between in-hospital MACE and the time from CP onset to FMH (r= 0.007, p=0.92) or to EUH (r= -0.045, p=0.58), and no correlation with fibrinolytic therapy at FMH (r= 0.088, p=0.27).

There is a moderate correlation of the length of hospitalization with LVEF on admission (r= 0.320, p=0.0001), and a weak correlation with hs-cTnI (r= 0.231, p=0.009), fluoroscopy time (r= 0.122, p=0.17). We remark that there is no correlation between duration of hospitalization and time from CP onset to FMH (r = 0.108, p = 0.20) or EUH (r= 0.096, p = 0.25), or with Killip class on admission (r = 0.051, p = 0.54).

There is a weak correlation of fibrinolytic therapy at local hospital with the in-hospital death (r= -0.152, p=0.05), and with in-hospital MACE (r= 0.088, p=0.27). There is a strong correlation between the number of stents and the contrast volume (r= 0.502, p=0.0001), and a moderate correlation with air kerma (r= 0.353, p=0.0001), or fluoroscopy time (r= 0.304, p=0.0001).

Interestingly, there is no correlation between resuscitation and any of the following characteristics: in-hospital death, length of in-hospital stay, recurrent chest pain, number of additional diseased vessels, hs-cTnI on admission, or age.

Odds ratio. We used a multivariable regression model for predictors of the primary efficacy outcome. In the multivariate analysis for the STEMI patients, the following factors were associated with major cardiovascular events and in-hospital death, irrespective of fibrinolytic therapy before PCI (Tables 4-5, Figures 6-8).

The odds of developing in-hospital major adverse cardiac adverse (MACE) are mentioned in table 4 and displayed in figure 6. Patients aged over 60 yo (OR: 2.414; p=0.02), resuscitated before EUH, with Killip class IV on admission (OR:4.267; p=0.009), with LVEF less than 40% (OR:2.663; p=0.01), or with LMCA involvement (OR:8.864; p=0.001) have higher odds risk for developing in-hospital MACE. Interestingly, active smoking patients (OR 0.197, p=0.0001) have the lowest risk of developing in-hospital MACE, after PCI for an ST-elevation myocardial infarction.

There is no difference between the risks of developing in-hospital MACE for the patients who received thrombolytic therapy before PCI (PhIS) compared with patients in the pPCI group (OR:0.582, 95%CI: 0.221-1.531; p=0.27).

Similarly, the odds of developing in-hospital death are displayed in table 5 and fig. 8. Patients older than 70 years of age, the need for resuscitation before EUH, LMCA involvement, Killip class IV on admission, a total length of stents over 33 mm, troponin level over 80 ng/l, more than two diseased vessels (including the IRCA) have statistically significant higher odds of death during hospitalization.

Interestingly and intriguing, active smoking (OR: 0.114, 95%CI 0.025-0.514, p=0.005) and high cholesterol patients (OR: 0.096, 95%CI 0.021-0.43, p=0.002) have the lowest risk of in-hospital death with a better prognostic irrespective of the therapy group they belong. The correlations described earlier in our research are in line, though, with these findings.

Killip class I have the lowest OR to develop in-hospital MACE (OR: 0.183, p=0.001) or death (OR: 0.088, 95%CI 0.03-0.251; p=0.0001). When we compared the Killip classes on admission, for the two groups, the in-hospital survival time (days) to a patient's death is better for PhIS group compared with the pPCI group (Killip I: 30 vs 9.96; Killip II: 14.50 vs 4; Killip III: 11 vs 7; Killip IV: 14 vs 7).

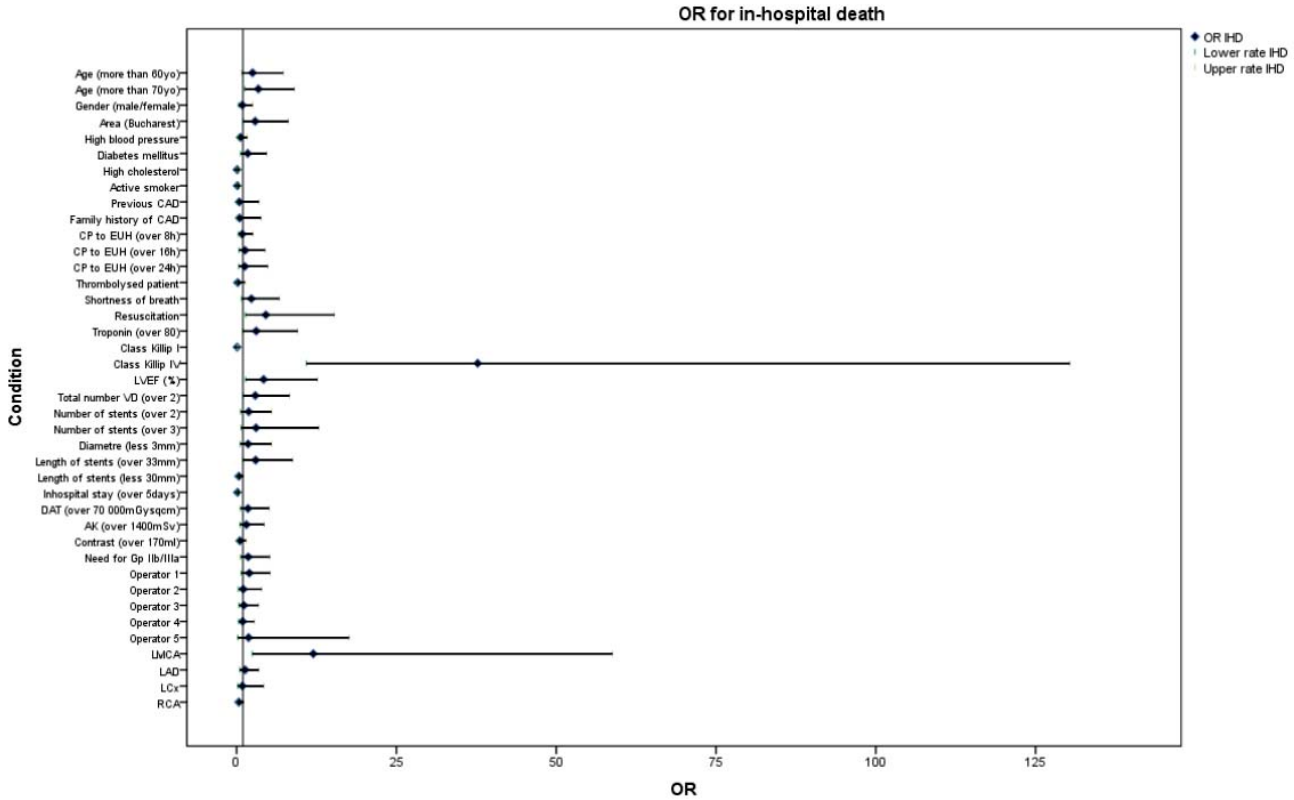

Figure 7. The predictors of the in-hospital death.
The age over 70 yo, Bucharest area, resuscitation, Killip class IV, troponin over 80 ng/ml, LVEF less than 40% on admission, the total number of vessel disease over 2, LMCA as IRA, length of stents over 33 mm, have higher odds of developing in-hospital death. Other predictors like active smoking, high cholesterol, Killip class I have protective action, decreasing the risk of in-hospital death.

Also, although the odds of in-hospital death are lower for the PhIS group compared with the pPCI group (OR: 0.17, 95% CI 0.22-1.321; p=0.09) it is not statistically significant.

Survival. The Kaplan-Meier survival curve during hospital stay shows a better result for the PhIS group compared to the pPCI group (Figures 8-9). When we compared the length of hospital stay, there are no significant differences among the groups with different IRCA (p=0.54).

V. DISCUSSION

To the best of our knowledge, this is the first prospective study in Romania assessing both pharmaco-invasive strategies and primary PCI in acute STEMI. Based on the STEMI Elias Hospital Interventional Registry (STEMI-EIRE), this pilot study compared the strategy of PCI after fibrinolytic therapy at the first local hospital, called pharmaco-invasive strategy (PhIS) with the standard therapy of primary PCI.

The following characteristics: age over 70 yo, resuscitation before admission to EUH, Killip class IV on admission, LVEF (%) less than 40% on admission, troponin over 80 ng/l on admission, total number of vessels disease, LMCA as IRCA, length of stents implanted over 33mm, are independent risk factors for developing in-hospital death. Similarly, age over 60 yo, resuscitation before EUH, Killip class IV on admission, LVEF less than 40% on admission, LMCA involvement are independent factors for developing in-hospital MACE.

The median treatment times from CP onset to the FMH in our study are in line with the RO-STEMI data (4 hours, IQR: 6, 25 vs 5 hours, IQR: 11.50) for PhIS and pPCI respectively. However, the median time from CP onset to a PCI capable center is higher, especially for patients referred from community hospitals without fibrinolytic therapy (7 hours, IQR: 12.38). In the RO-STEMI report, the median time for the CP onset to hospitalization was 6 hours across the all groups[8].

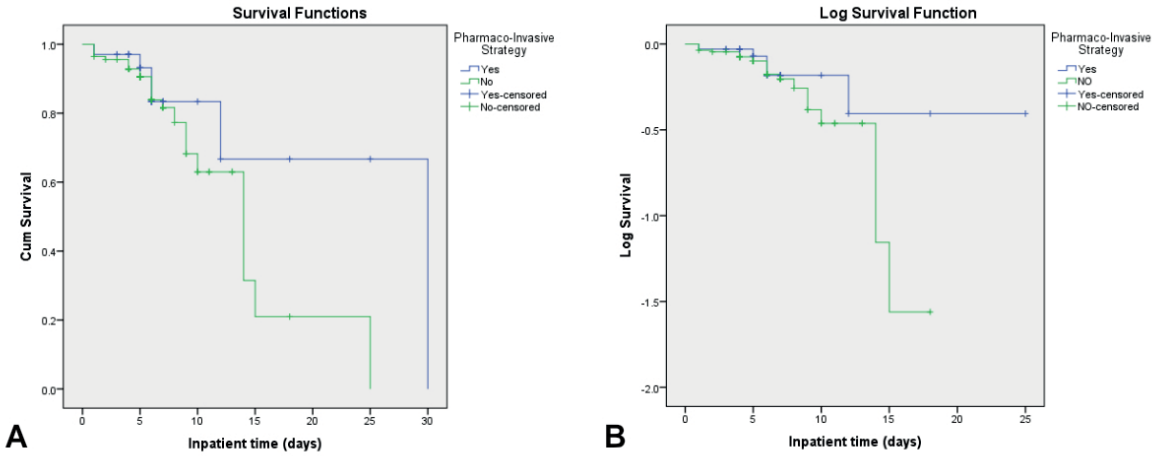

Figure 8. Kaplan-Meier survival curves, with the cumulative incidence of the primary endpoint (in-hospital death) during hospitalization in both treatment arms.
a) Kaplan-Meier curve for in-hospital death shows better in-hospital survival curves in favor of PhIS group. The estimate mean of death in the PhIS group compared with the pPCI group (29.147 days, 95%CI 27.50-30.78 vs 19.776 days, 95%CI 15.907-23.644; p=0.104).
b) The log survival function shows better results for the PhIS group compared with pPCI group.

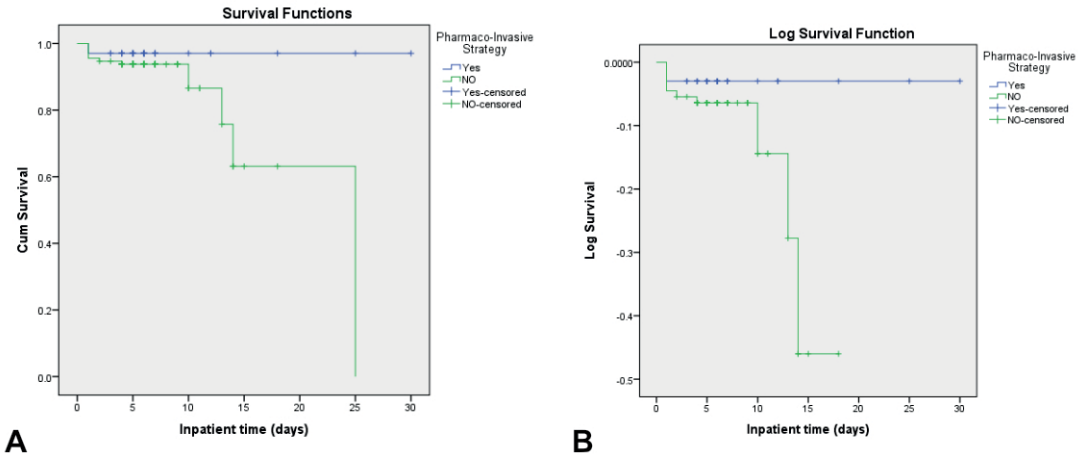

Figure 9. Kaplan-Mayer curves for in-hospital major cardiac events (MACE).
a) The estimate mean for in-hospital MACE is similar in the PhIS group compared with the pPCI group (22.821 days, 95%CI 16.046-29.597 vs 13.754 days, 95%CI 10.602-16.907; p=0.167). There are similar Kaplan-Meier MACE curves for the first 6 days only, but PhIS group has better in-hospital MACE results afterwards;
b) Kaplan–Meier MACE log survival curve showing disease-free survival by MACE during hospitalization, with similar in-hospital MACE curves for the first 6 days only, afterwards the PhIS curve has better outcome than pPCI curve.

Our primary outcomes (MACE and death during hospitalization) are in line with different studies carried out in countries with similar Cath lab networks: Canada[9], Egypt[10], India[11], USA[12], but also in countries like Denmark[13], where they compared pharmaco-invasive strategy with primary PCI.

In our study, the in-hospital MACE is similar in the two groups, but the other primary endpoint, in-hospital death, occurred less frequently in the pharmaco-invasive arm. This may be explained by the fact that we also considered patients who presented more than 12 hours from CP onset to EUH in the pPCI group, exceeding the time stated in guidelines. Nevertheless, a report of the ACC Foundation/AHA Task Force on practice guidelines states that the benefit from revascularization can extend up to 24 h, especially if there is ongoing evidence of coronary ischemia like our cases exceeding 12h[14].

Table 4. Multivariable regression model for predictors of in-hospital MACE.

Characteristics	Odds Ratio	LR-UR 95% CI	p-value
Age (more than 60yo)	2.414	1.098-5.307	0.028
Male gender (male)	0.631	0.291-1.367	0.243
Area (Bucharest)	1.245	0.599-2.588	0.557
Active smoking	0.197	0.08-0.484	0.001
High cholesterol	0.616	0.291-1.303	0.205
Diabetes mellitus	1.19	0.544-2.601	0.663
High blood pressure	1.065	0.483-2.346	0.876
Family history of CAD	1.104	0.333-3.661	0.871
Shortness of breath	0.996	0.388-2.553	0.993
Resuscitation before/on admission	4.267	1.432-12.709	0.009
Thrombolysed patient	0.582	0.221-1.531	0.273
LMCA	8.864	1.644-47.783	0.011
LAD	1.047	0.504-2.177	0.902
LCx	1.235	0.41-3.722	0.707
RCA	0.507	0.231-1.117	0.092
Killip class I	0.183	0.078-0.43	0.001
Killip class IV	16.771	5.076-55.408	0.001
Operator 1	1.943	0.917-4.118	0.083
Operator 2	0.797	0.276-2.304	0.676
Operator 3	0.963	0.409-2.269	0.932
Operator 4	0.776	0.333-1.81	0.557
Operator 5	2.148	0.345-13.363	0.412
Need for Gp IIb/IIIa	1.7	0.737-3.922	0.213
LVEF (%) on admission less than 40%	2.663	1.242-5.711	0.012
AK (over 1400mSv)	1.02	0.46-2.264	0.960
DAT (over 70 000mGysqcm)	1.433	0.641-3.204	0.380
Contrast (over 170ml)	0.568	0.249-1.3	0.181
Length of stents (less 30mm)	0.489	0.219-1.093	0.081
Diameter (less 3mm)	1.069	0.473-2.414	0.873
Troponin (over 80 ng/l)	1.346	0.589-3.073	0.481
Total number of VD (over 2)	1.128	0.535-2.376	0.752
In-hospital stay (over 5days)	0.805	0.332-1.948	0.630
CP to FMH (over 12h)	1.192	0.51-2.786	0.685
CP to EUH (over 8h)	0.941	0.434-2.04	0.878
CP to EUH (over 16h)	1.758	0.735-4.203	0.204
CP to EUH (over 24h)	1.864	0.722-4.809	0.198
Proximal culprit lesion	0.783	0.344-1.784	0.560
Number of stents (over 3)	1.837	0.501-6.737	0.359

Table 5. Multivariable regression model for predictors of the in-hospital death.

Characteristics	OR	LR-UR 95%CI	p-value
Age (more than 70yo)	3.399	1.275-9.058	0.014
Male gender	0.884	0.314-2.489	0.816
Area (Bucharest)	2.901	1.041-8.081	0.042
Active smoker	0.114	0.025-0.514	0.005
High cholesterol	0.096	0.021-0.43	0.002
Diabetes mellitus	1.73	0.638-4.691	0.281
High blood pressure	0.618	0.228-1.673	0.344
Family history of CAD	0.475	0.059-3.825	0.484
Previous CAD	0.437	0.054-3.513	0.424
Shortness of breath	2.308	0.795-6.7	0.124
Resuscitation before/on admission EUH	4.571	1.367-15.284	0.014
Fibrin therapy at FMH	0.17	0.022-1.321	0.090
LMCA	12	2.449-58.795	0.002
LAD	1.323	0.506-3.457	0.568
LCx	0.897	0.189-4.248	0.891
RCA	0.347	0.109-1.098	0.072
Killip class I	0.088	0.03-0.251	0.0001
Killip class IV	37.714	10.911-130.36	0.0001
Operator A	1.988	0.754-5.245	0.165
Operator B	1.045	0.28-3.902	0.948
Operator C	1.136	0.381-3.392	0.819
Operator D	0.94	0.317-2.788	0.911
Operator E	1.861	0.197-17.585	0.588
Need for Gp IIb/IIIa	1.813	0.633-5.195	0.268
LVEF (%) on admission less than 40%	4.224	1.407-12.683	0.010
AK (over 1400mSv)	1.532	0.545-4.307	0.418
DAT (over 70 000mGysqcm)	1.772	0.615-5.106	0.289
Contrast (over 170ml)	0.516	0.178-1.495	0.223
Length of stents (over 33mm)	2.976	1.01-8.767	0.048
Diameter (less 3mm)	1.788	0.584-5.471	0.309
Troponin (over 80 ng/l)	3.064	0.985-9.529	0.053
Total number VD (over 2)	2.926	1.035-8.272	0.043
In-hospital length (over 5days)	0.149	0.042-0.528	0.003
CP to FMH (over 12h)	0.953	0.286-3.182	0.938
CP to EUH (over 8h)	0.875	0.3-2.549	0.807
CP to EUH (over 16h)	1.317	0.39-4.442	0.658
CP to EUH (over 24h)	1.273	0.332-4.886	0.725
Culprit lesion (proximal)	1.016	0.336-3.071	0.977
Number of stents (over 3)	3.029	0.713-12.869	0.133

Table 6. Cases with in-hospital death.

Cases	STEMI	Cardiogenic shock before EUH	Diagnostic angiography	LV systolic function	Additional conditions
1	Anterior and lateral	Present	LAD disease	-	Aspiration pneumonia
2	Anterior	Present	3vd, including LMS	10%	-
3	Anterior	Present	LAD disease	10%	-
4	Inferior and RV	Present	LCx disease	-	CKD
5	LBBB	Present	No vessel disease	-	Right lobe pneumonia. Moderate AS. Moderate MR. Clostridium difficile enterocolitis
6	Anterior and lateral	Absent	2vd, LMS disease	30%	Large bowel malignant tumour
7	Anterior and lateral	Present	2vd, LMS-LAD-LCx disease	10%	Essential thrombocytosis
8	Anterior and inferior	Present	3vd with no revascularization option	30%	CKD. Hydronephrosis
9	Anterior	Present	Proximal LAD	40%	Aspiration bilateral pneumonia
10	Anterior	Absent	-	-	-
11	Posterior and lateral	Absent	3vd	40%	Cardiac tamponade. UTI
12	Anterior	Present	LMS disease	30%	-
13	Inferior and RV	Present	2vd, including RCA disease	25-30%	Complete AVB. Pneumonia (S. aureus septic shock)
14	Anterior and lateral	Absent	2vd	27%	Pneumonia
15	Anterior	Absent	2vd, including LAD disease	20%	-
16	Inferior and posterior	Dementia	Family declined diagnostic angiogram and PCI	50%	Bronho-pneumonia with Acinetobacter Baumanii, Klebsiella pneumoniae
17	NSTEMI	Present	3vd with LMS involvement		Aspiration pneumonia
18	Anterior and lateral	Absent	2vd	43%	-
19	Anterior and lateral	Absent	2vd	25-30%	Previous MI (2013)

LV-left ventricle; LMS-left main stem; CKD-chronic kidney disease; vd-vessel disease; RV-right ventricle; UTI-urinary tract infection.

Data from the Mayo Clinic STEMI database of patients treated with a pharmaco-invasive strategy or pPCI in a regional STEMI network from 2004 to 2012, using a multivariate analyses adjusting for age, gender, and other variables pointed out that there was no significant difference between the 2 strategies for 30-day MACE (RR: 0.66, 95% CI 0.36-1.21) or overall mortality (HR: 0.84, 95% CI 0.63-1.12)15.

Paradoxical findings, like lower OR of in-hospital MACE or death for the active smoking patients, have been observed. There is no doubt that diabetes and active smoking are risk factors for ACS/STEMI; it remains unclear whether active smoking is a risk factor for STEMI, but a factor with better prognosis for in-hospital MACE and death. High cholesterol seems to be "protective factor" for the in-hospital death.

In a 2016 editorial in the Romanian Journal of Cardiology, Frans van de Werf mentioned that the Strategic Reperfusion Early after Myocardial Infarction (STREAM) trial and the French Registry of Acute ST-elevation or Non-ST-elevation Myocardial Infarction (FAST-MI, 2015) study suggested that pharmaco-invasive strategy compares favourably with primary PCI16.

The STREAM study showed that a strategy involving early fibrinolysis with bolus tenecteplase and contemporary antithrombotic therapy (aspirin, clopidogrel and enoxaparin) offers similar efficacy as the primary PCI in patients with STEMI admitted within 3 hours of symptom onset and who could not undergo primary PCI within 1 hour of first medical contact[7].

Regarding in-hospital mortality, our results are similar to the FAST-MI study for the PhIS group (2.9% in our study vs 4.3% in French Registry), while for the pPCI the in-hospital mortality is higher (14.80% in our study compared with 5% in FAST-MI)[17,18]. In our study, reperfusion was performed for the PhIS group by fibrinolytic therapy at FMH after a median time of 4 hours (IQR: 6.25h), while median CP onset-to-door

time at EUH for the pPCI group was 7 hours (IQR: 12.38), compared with time to reperfusion therapy in FAST-MI (median 130 minutes and 300 minutes, respectively).

There are two explanations for better results in the FAST-MI study: (1) the FAST-MI study took into consideration both STEMI and NSTEMI patients, and (2) by the longer median time to reperfusion in our trial[17,18].

It is interesting to discover that only over half (57.38%) of STEMI patients from remote areas outside of a 2 hours reach of a catheterization laboratory (Cath lab) received thrombolysis at the FMH before transfer to EUH, despite clear ESC guidelines for thrombolysis if the patients cannot reach a PCI-capable facility within 120 minutes[2]. Therefore, 42.62% of patients assessed at the FMH did not undergo thrombolysis before referral to a Cath lab for PCI. This may be explained by a lack of resources and skilled cardiologists/AMU physicians trained to administer thrombolytic agents in STEMI patients. The number of patients undergoing thrombolysis in our study (35 of 157 patients, 22.29%) is similar to number of patients receiving thrombolysis in the FAST-MI 2010 registry (291 of 1580 patients, 18.41%)[19].

The Canadian trial, at the University of Ottawa Heart Institute regional STEMI system (between April 2009 and May 2011, with 236 and 980 consecutive patients enrolled in pharmaco-invasive and primary PCI strategies, respectively) showed that there was no significant difference in the primary efficacy outcome (a composite of mortality, re-infarction, or stroke) (odds ratio: 1.54; p=0.21), but with a statistically non-significant tendency for increased bleeding in the PhIS group (odds ratio: 2.02; p=0.08)[10]. In our study, the OR for developing MACE is below one, with non-significant *p*-value, while the odds ratio for in-hospital death is 0.17 (p=0.090).

In a meta-analysis of randomized and controlled clinical trials of patients with STEMI, published in 2016, Roule et al. suggest that pharmaco-invasive strategy performed in the early prehospital setting was consistently associated with similar rates of short-term death and cardiovascular death and lower rates (decreased risk) of cardiogenic shock compared with pPCI[20].

It is debatable whether immediate fibrinolysis followed by timely coronary angiography provides a clinical outcome similar to that of pPCI performed early after acute STEMI. Regarding treatment times, there are conflicting views in literature whether PCI should be performed after a delay from fibrinolytic therapy (immediate stenting vs deferred stenting), in order to decrease the side effects, like distal embolization during stent implantation.

A study published in 2018, by Bendary et al (undertaken from December 2016 to June 2017) randomly assigned 60 patients to undergo either primary PCI (Group I) or immediate fibrinolysis with subsequent coronary angiography with PCI within 3 to 24 hours later (Group II). The results revealed no statistically significant difference in various components of in-hospital outcomes (including all-cause death and major bleeding up to 30 days) were found between groups[21].

In our trial, there was no correlation between in-hospital MACE and the time from CP onset to FMH (r=0.007, p=0.929) or to EUH (r=0.045, p=0.585). This is similar to a meta-analysis by Lee et al that indicated a significant relationship between prolonged total ischemic time and reduced risk of MACE after deferred stenting (OR:0.994, 95% CI: 0.990-0.998; p=0.027)[21]. Although deferred stenting carried a significantly lower risk of peri-procedural composite events and abnormal flow in patients undergoing primary PCI for STEMI, such benefits had no impact on MACE, which did not differ significantly by the timing of stent placement[22].

In our study, the door-to-needle time is close to one hour, similar for both groups. A trial published in the European Heart Journal in 2012, by Larson et al regarding safety and efficacy of a pharmaco-invasive reperfusion strategy in rural STEMI patients, less than 20% of STEMI patients transferred for PCI in the USA have a door to balloon time <2h. Moreover, despite a significantly longer door-to-balloon time, there were no significant differences in 30-day mortality (5.5 vs. 5.6%; p=0.94), or major bleeding (1.5 vs. 1.8%; p=0.65), or re-infarction/ischemia (1.2 vs. 2.5%; p=0.088) in patients undergoing PhIS strategy compared with patients presenting directly to the PCI center[12].

A meta-analysis from 2012, of seven eligible trials (2961 patients) published by Borgia, Di Mario et al, that compared early routine PCI after successful fibrinolysis vs standard therapy limiting PCI only to patients without evidence of reperfusion (rescue PCI), found no difference in the incidence of death at 30 days between the two strategies[23]. Early routine PCI after successful fibrinolysis in STEMI patients significantly reduced, the combined endpoint death/re-infarction (OR:0.65, 95% CI: 0.49-0.88; p=0.004) and recurrent ischemia at 30-day follow-up (OR:0.25, 95% CI: 0.13-

0.49; p<0.001), with no significant increase in adverse bleeding events or stroke. In regards to delay after STEMI diagnosis, these trials suggest that all patients receiving fibrinolysis should receive mechanical revascularization within 24 h from initial hospitalization[23].

Our study is very similar to another observational study, published in 2018, with 138 patients admitted with STEMI within 24 hours of symptom onset, in a single tertiary care center in India, over a 9-month period, that showed PhIS was as good as primary PCI in STEMI, where primary PCI may be delayed or not possible at all due to financial and logistical constraints. Incidence of composite primary endpoints (mortality within 30 days, cardiogenic shock and re-myocardial infarction) and secondary endpoints (arrhythmias, bleeding manifestations, ischemic stroke, ejection fraction, mechanical complications, and duration of hospital stay) in PhIS was non-inferior to primary PCI at one month after intervention11. In our study, in-hospital mortality was similar for the pPCI arm (14.80% in our study vs 18.90% in the Indian study). In terms of in-hospital mortality of the PhIS group, our study proves better results (2.90% vs 11.60%) than the Indian trial[11].

In regards to secondary outcomes (duration of in-hospital stay, safety of Cath lab procedure) no significant statistical differences was observed between the pharmaco-invasive strategy and primary PCI groups. There were similar amounts of contrast used, X-ray doses, AK and DAP in the two groups. The length of hospitalization was similar in both the PhIS and pPCI groups. We have to mention that we did not take into account local bleeding, as in our study the standard approach was via radial artery, as opposed to femoral approach previously used before 2010 as mentioned in some of the trials.

The conclusions of our research are similar to that of Di Mario and Wijns published in 2012, as it is very clear PhIS is an excellent strategy when STEMI patients face long distances to the Cath lab; although primary angioplasty is the preferred treatment if performed by an experienced team <120 minutes after first medical contact, the fibrinolytic therapy at the local hospital is "buying time" before patient transfer to a PCI capable facility[24].

Study limitations. We conducted the study at a tertiary care center equipped with an interventional Cath lab and not at the local hospital where the patients are first seen. Twenty three patients admitted from local hospitals were excluded from the total of 180 patients (12.77%), as they could not be transferred to our facility. We did not process the median time between fibrinolysis and PCI.

Our research did not take into consideration the time from the moment of CP onset to calling the ambulance or the time to reach the FMH. However, no clear data regarding the onset of chest pain were provided by the patients and patients often delayed calling the ambulance for CP. The long delay from symptom onset to seeking medical assistance may be due to a poor understanding of the relationship of their symptoms with a severe heart disease. This is one of the explanations of long delays from CP onset to Cath lab, and a possible explanation as to why some patients from local hospitals are not transferred to Cath labs facilities.

Of all the STEMI patients remote areas who could not reach our tertiary center within 120 minutes from the STEMI diagnosis, only 57.37% received fibrinolytic therapy.

Our study did not follow-up the patients after hospital discharge; we only took in-hospital endpoints into account. We also did not follow-up in-hospital bleeding, as we performed the procedures via radial approach.

CONCLUSIONS

Our study, based on a small observational cohort is one of the first local prospective studies, comparing PhIS with pPCI in Romania. The study shows that a strategy based on thrombolytic therapy before PCI for patients with STEMI appears to have similar procedural outcomes with slightly better results vs pPCI in terms of in-hospital death. The odds of developing in-hospital MACE are similar in the two groups (PhIS/pPCI). The treatment lags, for both PhIS and pPCI, are still high compared with other similar interventional studies. The treatment time from CP onset to reperfusion is longer in the primary PCI group to the PhIS group, and this may explain lower in-hospital death for the pharmaco-invasive group. In conclusion, our study did not show any significant differences between the two strategies, in terms of in-hospital MACE, but with better results for in-hospital death for pharmaco-invasive strategy. In-hospital death is considerably higher in patients with STEMI due to LMCA compared with LAD, RCA, or LCx, irrespective of the initial reperfusion therapy.

Pharmaco-invasive strategy is an option for patients with STEMI in areas where no facilities for primary PCI are available. It is not inferior to the gold standard

(pPCI), and we can consider it as a bailout solution with similar results in terms of efficacy and safety.

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Abbreviations and Acronyms

AMI-PA = Acute Myocardial Infarction-Priority Action
FMH = First medical hospital (local or community hospital)
EUH = Elias University Hospital
CPR = Cardio-Pulmonary Resuscitation
EIRE = Elias Interventional Registry of STEMI
PCI = percutaneous coronary intervention
pPCI = primary percutaneous coronary intervention
PhIS = pharmaco-invasive strategy
dPCI = delayed percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
hs-cTn = high-sensitivity cardiac troponin
IRCA = infarct-related coronary artery
LMCA = left main coronary artery
LAD = left anterior descending artery
LCx= left circumflex artery
RCA = right coronary artery
MACE = major adverse cardiac events

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