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Please cite this article THE USE OF REPERFUSION THERAPY IN A TRANSITION COUNTRY WITHOUT FULLY APPLICABLE PHARMACO-INVASIVE STRATEGY

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UDC:

DOI: https://doi.org/10.2298/VSP190118090K

When the final article is assigned to volumes/issues of the Journal, the Article in Press version will be removed and the final version appear in the associated published volumes/issues of the Journal. The date the article was made available online first will be carried over.
THE USE OF REPERFUSION THERAPY IN A TRANSITION COUNTRY WITHOUT FULLY APPLICABLE PHARMACO-INVASIVE STRATEGY

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Abstract

**Background/Aim:** The pharmaco-invasive (PI) therapy is recommended strategy in patients (pts) with ST elevation myocardial infarction (STEMI) unable to undergo timely primary percutaneous coronary intervention (pPCI). The primary endpoint was to find the cohorts of pts who are not treated by any reperfusion therapy (RT) and the second endpoint was to see the outcome of the pts treated with RT, in a transition country without fully applicable PI therapy.

**Methods:** The data used are those of the Hospital National Registry for Acute Coronary Syndrome of Serbia (HORACS).

**Results:** The significant predictors of the withdrawing of the application of any RT in the model (c 75.6%, SE 0.004, 95% CI 0.748-0.761) were age (≥65 yr), heart failure (Killip II-IV), diabetes, and the time to first medical contact (FMC) (>360 min). In patients without RT, mortality was 15.7%, in pts treated with fibrinolysis (FT) was 10.5% and in pts treated with pPCI was 6.2% (p<0.000). Within 3 hours to FMC, higher in-hospital mortality was in FT pts (FT 8.7% vs. pPCI 4.3%). FT treated patients were older, had more comorbidities and heart failure (HF). However, after propensity score matching, in order to adjust the differences among the pts, the mortality rate remained higher, but not statistically significant (FT 8.8%. vs. pPCI 6.4%).

**Conclusions:** The balance of the best cost-benefit strategies for better use of RT is difficult to achieve in transition countries. The possibility for timely pPCI and PI therapy is not applicable, in high risk patients, older, pts with HF and diabetes, especially.

**Key words:** acute myocardial infarction with ST elevation, reperfusion therapy, transition countries, high-risk patients
Apstrakt

Uvod/Cilj: U skladu sa preporukama za lečenje bolesnika sa akutnim infarktom miokarda sa elevacijom ST segmenta (STEMI), ukoliko bolesnici ne mogu blagovremeno da odu na primarnu perkutanu intervenciju (pPCI) treba da se primeni farmako-invazivna (FI) strategija lečenja. Primarni cilj ove studije je da odredi koja grupa bolesnika se uopšte ne leči reperfuzionom terapijom (RT), dok je sekundarni cilj da analizira ishod bolesnika lečenih RT, u zemlji u tranziciji gde mreža za primenu FI terapije nije u potpunosti razvijena.

Metode: Podaci koji su korišćeni su Hospitalni Nacionalni Registar za Akutni Koronarni Sindrom Srbije (HORACS).

Rezultati: Značajni prediktori za izostanak primene RT su prikazani u modelu (c 75.6%, SE 0.004, 95% CI 0.748-0.761) u koji su uključene godine starosti (≥65), srčana insuficijencija (Killip klasa II-IV), dijabetes, i vreme do prvog medicinskog kontakta (PMK) (>360 min). Kod bolesnika koji nisu lečeni RT, mortalitet je bio 15.7%, kod bolesnika lečenih fibrinolitičkom terapijom (FT) 10.5%, a kod bolesnika lečenih pPCI 6.2% (p<0.000). U grupi bolesnika koji su do PMK stizali za 3 sata, mortalitet lečenih FT je bio veći (FT 8.7% vs. pPCI 4.3%). Bolesnici lečeni FT su bili stariji, sa više komorbiditeta i sa učestalijim znacima srčane insuficijencije (SI). Ipak, posle primenjenog “propensity skora”, sa ciljem da se izbegnu razlike izmedju dve grupe bolesnika, mortalitet u FT grupi je ostao veći, ali nije bilo statističke značajnosti (FT 8.8%. vs. pPCI 6.4%).

Zaključak: Primena reperfuzione terapije, uz postignuti idealan balans potrošnje i koristi je teško izvodljiva u zemljama u tranziciji. Mogućnosti za blagovremenu primenu pPCI, kao i FI terapije, posebno su ograničene kod visoko rizičnih, starijih bolesnika, kod bolesnika sa znacima SI, komorbiditetima i dijabetesom. Ključne reči: akutni infarkt miokarda sa ST elevacijom, reperfuzionata terapija, zemlje u tranziciji, visoko rizični bolesnici
Introduction

The better outcome of patients (pts) with acute myocardial infarction with ST elevation (STEMI) is directly dependent on reperfusion therapy (RT). A timely primary percutaneous coronary intervention (pPCI) is the preferred therapy for ST-segment elevation myocardial infarction (STEMI). The prompt coronary reperfusion as early as from the symptom onset, pPCI within two hours and fibrinolysis (FT) within ten minutes from the first medical contact (FMC) are difficult to achieve, especially in economically undeveloped countries. However, in the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) STEMI guidelines it is clearly recommended that the optimal organization of the STEMI systems of care at a community level is needed. Offering pPCI to the maximum proportion of pts within the recommended time spans provides optimal care in the pre-hospital setting, including a rapid and accurate diagnosis, the pre-activation of the cardiac catheterization laboratory, and the initiation of pharmacological reperfusion therapy by fibrinolysis (FT) if pPCI cannot be offered in a timely fashion. However, in the last few years, the use of pharmaco-invasive (PI) strategy of the FT therapy and pPCI, respectively, within 2-24 hours seems to be as good as pPCI, especially in the areas where pPCI is not available within the recommended time. The latest results have showed that the pts treated with the PI strategy of therapy, compared with pPCI, presented within 3 hours after the symptom onset, but who were unable to undergo pPCI within 1 hour, had the similar percentage of the composite primary endpoint consisting of death, shock, congestive heart failure, and re-infarction in 30 days. The rates of 1 year overall mortality were similar between the two groups of PI vs. pPCI. However, the conclusion of this study may be controversial, since there was a similar risk of the primary end point in the two study groups and a significantly higher risk of intracranial bleeding with early fibrinolysis. Thus pPCI remains the treatment of choice in such patients who have close access to cath lab centers.

The strategy of STEMI treatments at the community, regional and national levels has been supported and recommended in order to increase the proportion of the patients receiving timely pPCI by bypassing closer hospitals without interventional facilities.

In Serbia, however, the overall proportion of untimely reperfused eligible STEMI patients remains high. It might be the caused the insufficient PCI network or unused PI
The cardiovascular outcome is different between Eastern and Western European countries and the performance measures for reperfusion in STEMI has significantly improved with a greater use of pPCI. However, it is not clear that PI strategy is the same important as pPCI in developing and transition countries. It has not been applicable on time in remote regions of developing country. Moreover, transportation of high risk patients is particularly difficult. On the other hand, FT is very expensive therapy. Consequently, the best cost-benefit strategies for the high risk patients and for the patients who treated by FT and need transportation in PCI centre are not clear in these countries.

The primary endpoint was to find the cohorts of patients who are not threatened by any reperfusion therapy (RT). The second endpoint was to see the outcome of the patients treated by RT (pPCI or FT) in a transition country without fully applicable pharmaco-invasive strategy.

**Materials and Methods**

**Data Collection and the Study Population**

We used the data of the Hospital National Registry for Acute Coronary Syndrome of Serbia (HORACS). The registry was filled-in by the attending physicians in the 54 Coronary Care Units (CCU) in Serbia for all the pts with an acute coronary syndrome (ACS). There were 7 primary PCI centres and 2 were open round-the-clock (24h/7days). In Serbia, there were 9 University Centres at that time. All pts’ data, clinical diagnoses, treatments, and the hospital outcome were collected, and all the definitions were in accordance with the guidelines. The HORAKS registry was designed so as to reflect an unbiased, representative population of pts with ACS. It was an observational study. We included consecutive pts with the diagnosis of an acute myocardial infarction with an ST elevation (STEMI), according to the European guidelines, hospitalized during 3 years (2007-2009). To further narrow our study population, we excluded: the pts <18 years of age, the pts who presented to the FMC with the unknown or invalid date/time of reference for the hospital arrival or the application of RT (pPCI or FT) and then only observed the pts who arrived within 18 hours from the symptom onset to the FMC. The patients who arrived within 3h from the symptom onset to the FMC and who were treated with reperfusion therapy were additionally analysed.
Statistical Analysis

A univariate and multivariate analysis were performed in order to determine the predictors of the patients profiled for receiving the RT. The variables were included and analysed in a categorical manner. A multiple backward regression analysis was performed, with a significance of p=0.05 for the removal of the variables from the model. The Hosmer-Lemeshow statistics for the goodness of fit were calculated. A stepwise logistic regression analysis was performed so as to assess the significance of the factors generally thought to be related to the clinical decision of RT.

Additionally, because the study was observational and the pts were not randomly assigned to either type of treatment, the events in both treatment groups were matched using the propensity score matching. A propensity score analysis was performed by using a logistic regression model, with the 1-to-1 matching without a replacement for pPCI versus the FT group in order to adjust the differences among the pts. All statistical analyses were performed by the SPSS statistical package for Windows.

Results

A total of 15354 consecutive STEMI pts, mean age 63.58±11.97 years, med. 64 (55-73) from the HORAKS registry, were included in our analysis. There were 8502 (55.4%) pts treated with reperfusion therapy (Table 1). In patients without RT, mortality was 15.7%, in pts treated with fibrinolysis (FT) was 10.5% and in pts treated with pPCI was 6.2% (p<0.000). There were 84.3% of the pts who arrived within 12h, and 15.7% of those who arrived 12-18 h from the symptom onset to the first medical contact. The main reasons why the pts did not receive RT are shown in Figure 1. In Figure 2, the model is presented, with the prediction value c statistic 75.6%, 95% CI 0.748-0.761, for a decision on whether to or not to apply RT (the Hosmer-Lemeshow test, $\chi^2=8.899$, p=0.351, SE 0.004). The significant predictors for making a decision not to apply RT were age (≥65 yrs), heart failure (Killip II-IV), diabetes, and the time from the symptom onset (>360 min.).

A total 4986 pts (58.6%) arrived within three hours from the symptom onset to the first medical contact. Their mean age being 59.6±11.4, and med 59 (IQR 52-69). There
were more pts who received FT 3277 (65.7%). On the other side, 1709 (34.3%) received pPCI.

The baseline characteristics, comorbidities, and previous coronary diseases are shown in Table 1. The pts in the FT group were older (60.1±11.3 vs. 58.7±11.5, p<0.000), with a higher prevalence of diabetes (20.1% vs. 17.6%, p=0.004), and renal failure (4.3% vs. 3.1%, p=0.035). There was a significant difference between the two reperfusion groups regarding the span time from the symptom onset to the FMC (p<0.001).

The significant predictors which determinate the type of reperfusion therapy (p-PCI or FT) were the arrival at the non-PCI capable centre, the previous pPCI, the time from the symptom onset, heart failure (p<0.001), diabetes (p=0.019), and renal failure (p=0.035), the localization of myocardial infarction (p=0.024), previous angina pectoris (p=0.010). The high-risk patients, with heart failure, diabetes and renal failure were treated more with FT. The significant predictors for applying pPCI were the treatment at the PCI centre, the university centre, the centre with an on-site cardiologist and the previous PCI in the past medical history (Figure 3).

The mortality rate (8.7% vs. 4.3%) and the worse in-hospital outcome: heart failure (27.9% vs. 18.5%), the composite of the mortality events and/or re-infarction (11.4% vs. 7.2%), cardiac arrest (12.2% vs. 7.2%), a mechanical post-myocardial complication (4.4% vs. 1.7%), post-infarction angina (12.1% vs. 5.5%) and arrhythmia (41.6% vs. 23.9%) were significantly more often found in the FT group if compared with the pPCI group, p<0.001 (Table 2).

After the propensity score, there were 3256 matched pairs of pts in the two groups treated with RT, who were so matched according to the categories of age, gender, the time to FMC (≤180 minutes), diabetes and heart failure (Killip II-IV) (Table 3). When the two therapy condition groups were compared, the mortality rate was higher in the FT group, but it was not significantly different: FT 8.8% vs. pPCI 6.4% (Figure 4).

**Discussion**

The pPCI remains the treatment of choice in such patients who have close access to PCI centres. The one third STEMI patients have ischemic time from FMC to pPCI more than 120 minutes.\(^\text{18}\) Consider to results of less shock and heart failure in PI threated pts, it
could be greater clinical benefit in situations where PCI related delays such as occur in real-world situations. 

The unsolved problem is the strategy of improving RT in the remote regions in developing and transition countries particularly. The balance of cost-benefit therapy is difficult achieved. The advantage with the fibrinolytic agent in situation where an urgent invasive procedure and transportation of high risk patients is not possible may be very important, however it include the extra cost of the FT. The dilemma is the PI strategy as reasonable and useful option for every patient who cannot undergo timely pPCI and is it possible in every regions and countries. The best cost-benefit strategies for the successfully reperfused patients by FT and the high risk patients are unclear.

Moreover, according to the studies published in the last ten years, the choice of reperfusion therapy (pPCI or FT) should not only be based on the time that has elapsed from symptoms onset to FMC. Reperfusion therapy in Serbia was less applied in high-risk pts. The problems of the treatment of high-risk pts and the gaps seem to persist in a large number of the studies and registries in not only low-income countries, but in developed countries as well. In STREAM study, 3/5 of pharmaco-invasive successfully reperfused patients who underwent scheduled angiography approximately 18 hours after FT, excellent angiographic, 12-lead ECG metrics, and clinical outcomes were achieved. On the other hand, the patients requiring rescue PCI after contemporary fibrinolysis, aspirin, clopidogrel, and enoxaparin in combination, with completed PCI within 140 minutes after FT had the high 30-day composite event rates of death, shock, chronic heart failure, and reinfarction (18.7%). These data support that although PI treated, patients requiring rescue angiography had greater baseline risk with more co-morbidities and worse 30-day outcomes compared with successful fibrinolytic-treated patients. The patients requiring rescue PCI should be immediately transported in to the capable centre of completing rescue intervention after the administration of fibrinolysis.

The Factors that Influenced the Withdrawing of Reperfusion Therapy

In Serbia, there were 37.3% STEMI pts presenting within 12 hours from the symptom onset to the FMC and ECG who did not receive any type of reperfusion therapy. The other 62.7% were treated with RT, of which 24.4% were treated with pPCI and 38.3% were treated with FT. In the other countries registries the results were similar. 

In
Serbia, patients without reperfusion therapy were older (≥65 yrs), came later after the symptom onset (>360 min), had heart failure (Killip II-IV), comorbidities such as diabetes, a previous stroke, renal failure, anaemia, previous coronary diseases, except previous PCI and the arrival at a non-PCI capable and non-University centre without a cardiologist on site. The situation was similar in other registries: in the SNAPSHOT ACS registry\textsuperscript{27} patients without RT were older, there were more those of the female gender, with comorbidities, and atrial fibrillation. In the GRACE Registry\textsuperscript{10}, they were older and of the female gender; a history of heart failure, prior MI, or diabetes were found to be independently associated with a lack of reperfusion therapy.\textsuperscript{10} In the CRUSADE\textsuperscript{29} and TETAMI registries\textsuperscript{30}, the results were similar, too.

In our study, the average time span from the symptom onset to the FMC was significantly shorter in the FT group, 80.9±37.4 vs. 92.4±36.4 minutes. If pts arrived within 2 hours, FT was applied in 45.3% and pPCI in 22.8%. However, if they arrived later, more than 2 hours, the percentage of the applied RT became similar: FT 23.7% and pPCI 21.3%.

The important predictors that influenced on strategy of treatment with RT were the time span from the symptom onset, the anterior localization of myocardial infarction, the previous PCI, the arrival at the PCI centre, the arrival at the university centre, where cardiologists were on site. If pts had heart failure, previous coronary diseases, diabetes and renal failure, the patients were treated more by FT. Further, if pts arrived 2h after the symptom onset, with the anterior localization of MI, and the previous PCI, the doctors decided to a greater extent to apply pPCI.

In the STREAM study\textsuperscript{5}, the median time from the symptom onset to the FMC was similar in both groups: FT 62 (40–100) vs. pPCI 61 (35–100) minutes, and the patients treated with FT went to the PCI within 3-24 hours. In Serbia, the network system for PI therapy is not fully applicable. Until it is becomes completely implemented, it is very important that the treatment strategy should be individual.\textsuperscript{30} The new guidelines\textsuperscript{3} are clear, although the waiting time depends on a few important factors, such as transportation and the hospital equipment. If a patient is younger, <65 years of age, with the anterior localization of MI, it is better to use pPCI than FT, and wait for the inflation of a balloon maximum 40-45 minutes. After that time, FT could be a better choice. It is not the same situation if a doctor has patients older than 65 years of age, with a low, inferior MI, in which case it might not be a big mistake if pts wait ≥3 hours for RT.\textsuperscript{30} The possibilities of
postponing RT in the older could be explained by collaterals and the preconditioning of myocardium in these patients.\textsuperscript{31}

Throughout the history of the application of RT from pre-hospital fibrinolysis to PI therapy, it seems that fibrinolysis has a very important position in STEMI patients, especially in the regions where PCI centres are farther.\textsuperscript{31-35} From 1995 to 2015 there was decrease in application of FT (from 40\% to 6\%) and increase in pPCI (from 12\% to 77\%) in France\textsuperscript{34} and decrease in FT (from 66\% to 7\%) and increase in PCI (from 12\% to 61\%) in SWEDHEART/RISK-HIA registry\textsuperscript{36}, also. In Serbia, it seems that patients with a higher risk, who needed sooner, more efficient therapy, were not treated well enough, and they rather received FT irrespective of the undeveloped PI strategy. The financial reason may be explanation because network of PI therapy has not been fully applied, yet.

The Outcome of Patients Treated with Reperfusion Therapy

After analysed patients treated with FT in STREAM study it was determined that PI treated patients with greater baseline risk with more co-morbidities requiring rescue angiography. These pts had worse 30-day outcomes compared with successful fibrinolytic-treated patients and scheduled PCI.\textsuperscript{37}

In Serbia, the mortality of the pts who arrived within 3 hours was different between the groups of the pts treated with FT (8.7\%) and the pts treated with pPCI (4.3\%). However, after using the propensity score in the two similar groups of patients, FT vs. pPCI, with respect to age $\geq 65$ (35.1\% vs. 37.1\%), gender (male 30.1\% vs. 30.6\%), the time from the symptom onset $< 180$ min (47.6\% vs. 47.5\%), diabetes (20.6\% vs. 19.9\%) and Killip-class heart failure $> 1$ (25.9\% vs. 21.8\%), the mortality rate was higher, but not significantly different in the FT group (FT 8.8\% vs. pPCI 6.4\%).

In the last years the situation in Serbia is better after full opening 7 pPCI 24h/7days centres. However, the percentage of patients who did not treated with RT is the same, percentage of patients treated by FT is lower and patients who go to pPCI is higher. In the last years, mortality of reperfused and non-reperfused patients is not significantly improved.\textsuperscript{38}

Limitation of the study
Not fully applicable network of PI therapy in Serbia is a possible limitation of the present study. Furthermore, the differences between the two reperfusion groups were observed. There were more high-risk patients in the fibrinolysis group, which was solved by using the propensity score.

**Conclusion**

The possibility for timely pPCI and PI therapy is not applicable, in high risk patients, older, pts with HF and diabetes, especially. The unsolved problems were reperfused patients by FT who should go to the PCI centre after that and especially high risk patients. It is necessary that strategy of STEMI patients be modified and precise in developing and transition countries without possibility for timely pPCI and without network fully applicable pharmaco-invasive therapy. The improvement of treating these pts has two pathways: the opening more pPCI centers and as well as important, using more PI therapy. The balance of the best cost-benefit strategies is difficult to achieve in remote regions and developing countries.

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Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
Data sharing is not applicable to this manuscript.

Consent for publication
Consent to publish was obtained from all relevant parties.

Ethics approval and consent to participate
This study was approved by the local Ethics Committee of the Faculty of Medicine; University of Belgrade (No 29/V-18).

Authors’ contributions:
GK, MA, NMK, ZV, JB and SDM wrote the manuscript, GK, ZV, SDM, JB, LS, MD, PM and MA design the study, analyse the data and review the manuscript.

Supporting:
This work was supported by Ministry of Education, Science and Technological Development of the Republic of Serbia. Title of the project: “Acute coronary syndrome-acute myocardial infarction and unstable angina pectoris: contemporary diagnostic methods
and therapeutic options in purpose better survival the patients, and place, and opportunities of Serbia as transition country”. Number: 175084 and partly 451-03-68/2020-14/200015

**Abbreviations:**

FMC: first medical contact

FT: fibrinolysis therapy

PI: pharmaco-invasive

pPCI: primary percutaneous coronary intervention

RT: reperfusion therapy

STEMI: ST elevation myocardial infarction

| Table 1. The baseline characteristics, comorbidities and previous coronary diseases |
| Baseline characteristics | Without RT N=6852 | FT (18h) N=5132 | p-PCI (18h) N=3370 | p | FT(3h) N=3277 | p-PCI(3h) N=1709 | P |
|--------------------------|-------------------|-----------------|-------------------|---|----------------|----------------|---|
| Age (mean±SD, med, IQR)  | 67.1±11.6 59 (59-76) | 61.2±11.3 61 (53-70) | 60.0±11.7 59 (52-69) | <0.001 | 60.1±11.3 59 (52-69) | 58.7±11.5 58 (51-67) | <0.001 |
| Gender (male/female) (%) | 60.6/39.4 | 68.0/32.0 | 70.5/29.5 | <0.000 | 70.6/29.4 | 72.1/27.9 | 0.277 |
| Anterior myocardial infarction (%) | 44.1 | 42.4 | 44.1 | 0.137 | 41.1 | 44.4 | 0.025 |
| Atypical symptoms (%) | 12.2 | 4.5 | 3.6 | <0.001 | 4.1 | 3.1 | 0.068 |
| Time from symptom onset (minute) (mean±SD, med, IQR) | 290±270 180 (90-420) | 160±152 120 (60-180) | 206±184 150 (90-240) | <0.001 | 80.9±37.4 | 92.4±36.4 | <0.001 |
| Transport to hospital Independently (%) | 16.1 | 16.4 | 18.5 | <0.001 | 16.0 | 18.7 | <0.001 |
| Emergency (%) | 52.8 | 61.5 | 60.0 | <0.001 | 64.0 | 63.5 | 1 |
| Other medical ambulance or hospital (%) | 31.1 | 22.1 | 21.5 | <0.001 | 20.0 | 17.8 | <0.001 |
| Comorbidities | | | | | | | |
| Hypertension (%) | 68.7 | 63.5 | 65.8 | <0.001 | 61.3 | 63.0 | <0.001 |
| Hyperlipidemia (%) | 41.9 | 63.5 | 65.8 | <0.001 | 43.9 | 51.4 | <0.001 |
| Diabetes (%) | 29.9 | 22.2 | 20.2 | <0.001 | 20.1 | 17.6 | 0.004 |
| Previous stroke (%) | 8.2 | 4.5 | 5.1 | <0.001 | 3.9 | 4.3 | 0.489 |
| Renal failure (%) | 6.8 | 4.3 | 2.9 | <0.001 | 4.3 | 3.1 | 0.035 |
| Anemia (%) | 5.9 | 3.3 | 2.3 | <0.001 | 3.0 | 2.6 | 0.416 |
| Peripheral vascular diseases (%) | 8.4 | 4.8 | 3.3 | <0.001 | 4.0 | 3.2 | 0.203 |
| Previous coronary diseases | | | | | | | |
| Angina pectoris (%) | 31.6 | 22.8 | 20.9 | <0.001 | 21.8 | 18.7 | 0.010 |
| MI (%) | 24.8 | 15.8 | 14.5 | <0.001 | 15.9 | 14.2 | 0.122 |
| CABG (%) | 3.0 | 2.0 | 1.8 | <0.001 | 2.0 | 1.7 | 0.442 |
| PCI (%) | 5.2 | 3.1 | 19.7 | <0.001 | 3.0 | 16.0 | <0.001 |
**Legend**: CABG: coronary artery bypass grafting; IQR: interquartile range; MI: myocardial infarction; PCI: percutaneous coronary interventions; RF: renal failure; SD: standard deviation

**Table 2. The complications and the outcome**

|                          | FT  | p-PCI | p       |
|--------------------------|-----|-------|---------|
|                          | N=3277 | N=1709 |         |
| Heart failure (%)        | 27.9 | 18.5  | <0.001  |
| Killip II (%)            | 19.5 | 13.2  | <0.001  |
| Killip III (%)           | 4.5  | 2.4   |         |
| Killip IV (%)            | 3.9  | 3.0   |         |
| Mortality (%)            | 8.7  | 4.3   | <0.001  |
| Reinfarction (%)         | 3.2  | 3.0   | 0.795   |
| Composite events         | 11.4 | 7.2   | <0.001  |
| (mortality and re-       |      |       |         |
| infarction) (%)          |      |       |         |
| Cardiac arrest (%)       | 12.2 | 7.2   | <0.001  |
| Mechanical               | 4.4  | 1.7   | <0.001  |
| complication (%)         |      |       |         |
| Postinfarction angina    | 12.1 | 5.5   | <0.001  |
| (%)                     |      |       |         |
| Arrhythmia (%)           | 41.6 | 23.9  | <0.001  |
Table 3. The characteristics of matching 3256 patients treated with FT and pPCI

| Baseline characteristics | FT (N=1538) | p-PCI (N=1758) |
|--------------------------|-------------|----------------|
| Age (mean±SD)            | 61.1±11.0   | 61.5±11.6      |
| Gender (male/female) (%) | 69.1/30.9   | 62.9/37.1      |
| Time from symptom onset (minute) (mean±SD, med, IQR) | 81.54±32.12 | 86.44±40.03 |
| Diabetes (%)             | 28.6        | 29.6           |
| Heart Failure (HF) (%)   | 29.5        | 18.7           |
| Killip II-IV             |             |                |
| Variable               | OR (95% CI)  | p Value |
|------------------------|--------------|---------|
| **Demographic characteristics** |              |         |
| Sex-female             | 1.446 (1.353-1.546) | 0.000   |
| Age                    |              |         |
| 65-74 yr               | 1.875 (1.737-2.023) | 0.000   |
| >= 75 yr               | 3.888 (3.564-4.240) | 0.000   |
| **Symptom onset to hospital arrival** |              |         |
| >120-180 min           | 0.879 (0.784-0.972) | 0.012   |
| >180-360 min           | 1.150 (1.048-1.262) | 0.000   |
| >360-720 min           | 2.449 (2.189-2.740) | 0.000   |
| >720 min               | 10.167 (9.034-11.443) | 0.000   |
| **Clinical characteristics** |              |         |
| Without on-site cardiologist | 2.041 (1.912-2.179) | 0.000   |
| Non university center  | 2.041 (1.912-2.179) | 0.000   |
| Full open p-PCI center | 0.412 (0.383-0.444) | 0.000   |
| Non full open p-PCI center | 2.041 (1.912-2.179) | 0.000   |
| Non p-PCI              | 2.170 (2.031-2.320) | 0.000   |
| Type of hospital center |              |         |
| Previous anemia        | 1.043 (0.979-1.112) | 0.195   |
| Previous RF            | 1.865 (1.609-2.162) | 0.000   |
| Previous Stroke        | 1.799 (1.575-2.055) | 0.000   |
| DM                     | 1.567 (1.457-1.686) | 0.000   |
| Comorbidities          |              |         |
| Previous AP            | 1.631 (1.516-1.754) | 0.000   |
| Previous MI            | 1.830 (1.687-1.985) | 0.000   |
| Previous PCI           | 0.508 (0.446-0.578) | 0.000   |
| Previous CABI          | 1.558 (1.263-1.922) | 0.000   |
| Previous coronary disease |              |         |
| Killip II - IV         | 1.864 (1.742-1.995) | 0.000   |
| Killip II              | 1.650 (1.524-1.787) | 0.000   |
| Killip III             | 2.702 (2.359-3.094) | 0.000   |
| Killip IV              | 1.956 (1.698-2.255) | 0.000   |
| Previous MI            | 1.830 (1.687-1.985) | 0.000   |
| Previous PCI           | 0.508 (0.446-0.578) | 0.000   |
| Previous CABI          | 1.558 (1.263-1.922) | 0.000   |
| Previous coronary disease |              |         |
| Killip II - IV         | 1.864 (1.742-1.995) | 0.000   |
| Killip II              | 1.650 (1.524-1.787) | 0.000   |
| Killip III             | 2.702 (2.359-3.094) | 0.000   |
| Killip IV              | 1.956 (1.698-2.255) | 0.000   |
| Clinical characteristics |              |         |
| Anterior infarction    | 1.043 (0.979-1.112) | 0.195   |
| >720 min               | 10.167 (9.034-11.443) | 0.000   |
| >360-720 min           | 2.449 (2.189-2.740) | 0.000   |
| >180-360 min           | 1.150 (1.048-1.262) | 0.000   |
| >120-180 min           | 0.879 (0.784-0.972) | 0.012   |
| >720 min               | 10.167 (9.034-11.443) | 0.000   |
| **Symptom onset to hospital arrival** |              |         |
| Without on-site cardiologist | 2.041 (1.912-2.179) | 0.000   |
| Non university center  | 2.041 (1.912-2.179) | 0.000   |
| Full open p-PCI center | 0.412 (0.383-0.444) | 0.000   |
| Non full open p-PCI center | 2.041 (1.912-2.179) | 0.000   |
| Non p-PCI              | 2.170 (2.031-2.320) | 0.000   |
| Type of hospital center |              |         |
| Previous anemia        | 1.043 (0.979-1.112) | 0.195   |
| Previous RF            | 1.865 (1.609-2.162) | 0.000   |
| Previous Stroke        | 1.799 (1.575-2.055) | 0.000   |
| DM                     | 1.567 (1.457-1.686) | 0.000   |
| Comorbidities          |              |         |
| Previous AP            | 1.631 (1.516-1.754) | 0.000   |
| Previous MI            | 1.830 (1.687-1.985) | 0.000   |
| Previous PCI           | 0.508 (0.446-0.578) | 0.000   |
| Previous CABI          | 1.558 (1.263-1.922) | 0.000   |
| Previous coronary disease |              |         |
| Killip II - IV         | 1.864 (1.742-1.995) | 0.000   |
| Killip II              | 1.650 (1.524-1.787) | 0.000   |
| Killip III             | 2.702 (2.359-3.094) | 0.000   |
| Killip IV              | 1.956 (1.698-2.255) | 0.000   |

**Figure 1.** The predictors that indicate the absence of the application of reperfusion therapy-univariate analyse
**Figure 2.** The model for the prediction of the absence of the application of reperfusion therapy

| Variable          | OR (95% CI)         | p Value |
|-------------------|---------------------|---------|
| More likely to use reperfusion | Less likely to use reperfusion |
| Sex-female       | 1.065 (0.986 - 1.151) | 0.107   |
| 65-74 yr          | 1.692 (1.555 - 1.841) | 0.000   |
| >= 75 yr          | 3.288 (2.983 - 3.624) | 0.000   |
| >720 min          | 0.828 (0.745 - 0.919) | 0.000   |
| >360-720 min      | 1.005 (0.912 - 1.107) | 0.919   |
| >180-360 min      | 2.040 (1.815 - 2.293) | 0.000   |
| >120-180 min      | 9.200 (8.150 - 10.39) | 0.000   |
| Killip II - IV    | 1.434 (1.327 - 1.550) | 0.000   |
| DM                | 1.302 (1.198 - 1.415) | 0.000   |
Figure 3. The predictors of the doctor’s decision on reperfusion therapy - univariate analysis
Figure 4. Matching 3256 patients treated with FT and pPCI by using the propensity score