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The use of reperfusion therapy in transition countries without fully applicable pharmacoinvasive strategy

Upotreba reperfuzione terapije u zemljama tranzicije bez potpuno primenljive farmakoinvazivne strategije

Gordana Krljanac*†, Milika Ašanin*†, Nataša Mickovski Katalina‡, Sladjan D. Milanović§, Jovana Bjekić§, Lidija Savić*, Predrag Mitrović*, Marina Djurović†‖, Zorana Vasiljević†

University Clinical Center of Serbia, *Clinic of Cardiology, ‖Clinic of Endocrinology, Belgrade, Serbia; University of Belgrade, †Faculty of Medicine, §Institute for Medical Research, Belgrade, Serbia; ‡Institute of Public Health of Serbia "Dr. Milan Jovanović Batut", Center for Prevention and Control of Diseases, Department for Prevention and Control of Noncommunicable Diseases, Belgrade, Serbia

Abstract

Background/Aim. The pharmacoinvasive (PI) therapy is a recommended strategy in patients (pts) with ST elevation myocardial infarction (STEMI) unable to undergo timely primary percutaneous coronary intervention (p-PCI). The aim of the study was to find out the cohorts of pts who are not treated by any reperfusion therapy (RT) as well to determine the outcome of the pts treated with RT in a transition country without fully applicable PI therapy. **Methods.** The study analyzed data from 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 years), heart failure (Killip II-IV), diabetes mellitus, and the time to first medical contact (FMC) (> 360 min). In patients without RT, mortality was 15.7%, in pts treated with fibrinolytic therapy (FT) was 10.5%, and in pts treated with pPCI, it was 6.2% ($p <$ 0.000). Within 3 hours to FMC, higher in-hospital mortality was in FT pts (FT 8.7% *vs* p-PCI 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 in FT pts but not statistically significantly higher than in p-PCI pts (FT 8.8% *vs* p-PCI 6.4%). **Conclusion.** The balance of the best cost-benefit strategies for better use of RT is difficult to achieve in transition countries. The possibility for timely p-PCI and PI therapy is especially not applicable in high-risk patients, older pts, pts with HF, and those with diabetes mellitus.

Key words:
drug therapy; st elevation myocardial infarction; myocardial reperfusion; risk factors; serbia; treatment outcome.

Apstrakt

Uvod/Cilj. Preporuke za lečenje bolesnika sa akutnim infarktom miokarda sa elevacijom ST segmenta (STEMI), nalažu da se kod bolesnika koji ne mogu blagovremeno da odu na primarnu perkutanu intervenciju (p-PCI) primeni farmakoinvazivna (FI) strategija lečenja. Cilj rada bio je da se utvrde karakteristike bolesnika koji se uopšte ne leče reperfuzionom terapijom (RT), kao i da se analizira ishod lečenja pomoću RT, u zemlji u tranziciji u kojoj mreža za primenu FI terapije nije u potpunosti razvijena. **Metode.** Za istraživanje su korišćeni podaci bolničkog Nacionalnog registra 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 melitus, i vreme do prvog medicinskog kontakta (PMK) (> 360 min). Kod bolesnika koji nisu bili lečeni RT, mortalitet je bio 15,7%, kod bolesnika lečenih fibrinolitičkom terapijom (FT) iznosio je 10,5%, a kod bolesnika lečenih p-PCI 6,2% ($p <$ 0,000). U grupi bolesnika koji su do PMK stizali za 3 sata, mortalitet lečenih pomoću FT bio je veći od mortaliteta bolesnika lečenih p-PCI (FT 8,7% *vs* p-PCI 4,3%). Bolesnici lečeni pomoću FT bili su stariji, sa više komorbiditeta i sa učestalijim znacima srčane insuficijencije. Ipak, posle primenjenog *propensity* skora, sa ciljem da se izbegnu razlike između dve grupe bolesnika, mortalitet u FT grupi ostao je veći, ali bez statistički značajne razlike u odnosu na bolesnike lečene p-PCI (FT 8,8%. *vs* p-PCI 6,4%). **Zaključak.** Primena RT, uz postignuti idealan balans potrošnje i koristi, teško je izvodljiva u zemljama u tran

Correspondence to: Gordana Krljanac, University Clinical Center of Serbia, Clinic of Cardiology, Pasterova 2, 11 000 Belgrade, Serbia. E-mail: gkrljanac@yahoo.com; gkrljanac@gmail.com.

ziciji. Mogućnosti za blagovremenu primenu p-PCI, kao i FI terapije, posebno su ograničene kod visoko rizičnih, starijih bolesnika, kod bolesnika sa znacima srčane insuficijencije, komorbiditetima i dijabetesom melitusom.

Ključne reči:
lečenje lekovima; infarkt miokarda sa st elevacijom; miokard, reperfuzija; faktori rizika; srbija; lečenje, ishod.

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 (p-PCI) is the preferred therapy for STEMI [1]. The prompt coronary reperfusion as early as the symptom onset, p-PCI within two hours, and fibrinolytic therapy (FT) within ten minutes from the first medical contact (FMC) are difficult to achieve, especially in economically undeveloped countries [2]. However, in the European Society of Cardiology (ESC) [3] and the American College of Cardiology/American Heart Association (ACC/AHA) STEMI guidelines [4], the optimal organization of the STEMI systems of care at a community level is needed. Offering p-PCI to the maximum proportion of pts within the recommended time spans provides optimal care in the prehospital setting, including a rapid and accurate diagnosis, the preactivation of the cardiac catheterization laboratory, and the initiation of pharmacological RT by FT if p-PCI cannot be offered in a timely fashion. However, in the last few years, the use of pharmacoinvasive (PI) strategy of the FT and p-PCI, respectively, within 2–24 hours seems to be as good as p-PCI, especially in the areas where p-PCI is not available within the recommended time [3, 5]. The latest results have shown that the pts treated with the PI strategy of therapy, compared with p-PCI, presented within 3 hours after the symptom onset, but who were unable to undergo p-PCI within 1 hour, had a similar percentage of the composite primary endpoint consisting of death, shock, congestive heart failure, and re-infarction in 30 days [5]. The rates of 1-year overall mortality were similar between the two groups of PI *vs* p-PCI [6]. 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 FT [6]. Thus, p-PCI remains the treatment of choice in such patients who have close access to catheterization laboratory centers.

The strategy of STEMI treatments at the community, regional, and national levels has been supported [7] and recommended in order to increase the proportion of the pts receiving timely p-PCI by bypassing closer hospitals without interventional facilities [8].

In Serbia, however, the overall proportion of untimely reperfused eligible STEMI patients remains high [9]. It might be caused by the insufficient PCI network or unused PI therapy [9–11]. The cardiovascular outcome is different between Eastern and Western European countries [12–16], and the performance measures for reperfusion in STEMI have significantly improved with greater use of p-PCI [17]. However, it is unclear that PI strategy is as important as p-PCI in developing and transition countries [16, 18, 19]. It has not been applied on time in remote regions of developing countries. Moreover, transportation of high-risk patients is particularly difficult. On the other hand, FT is a very expensive therapy. Consequently, the best cost-benefit strategies for the high-risk patients and the patients treated by FT and who need transportation in PCI centers are unclear in these countries.

The primary aim of this study was to find out the cohorts of patients who were not treated by any RT. The second aim was to determine the outcome of the pts treated by RT (p-PCI or FT) in a transition country without a fully applicable PI strategy.

Methods

Data collection and the study population

We used the data of the Hospital National Registry for Acute Coronary Syndrome of Serbia (HORACS) [9, 11]. The registry was filled in by the attending physicians in the 54 Coronary Care Units (CCU) in Serbia for all the pts with the acute coronary syndrome (ACS). There were 7 primary PCI centers and 2 were open round-the-clock (24 h/7 days). In Serbia, there were 9 University Centers at that time. All pts' data, clinical diagnoses, treatments, and the hospital outcome were collected, and all the definitions were in accordance with guidelines [1]. The HORACS registry was designed to reflect an unbiased, representative population of pts with ACS. This observational study included consecutive pts with the diagnosis of a STEMI, according to the European guidelines, hospitalized for 3 years (2007–2009). To further narrow our study population, we excluded the following: pts < 18 years of age; pts who presented the FMC with unknown or invalid date/time of reference for the hospital arrival or the application of RT (p-PCI or FT). Then, only observed the pts were those who arrived within 18 hrs from the symptom onset to the FMC. The patients who arrived within 3 h from the symptom onset to the FMC and who were treated with RT were additionally analyzed.

Statistical analysis

Univariate and multivariate analyses were performed in order to determine the predictors of the patients profiled for receiving the RT. The variables were included and analyzed categorically. 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 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 assigned randomly 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 on 1 matching without a replacement for p-PCI *vs* 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 15,354 consecutive STEMI pts, mean age 63.58 ± 11.97 years [median 64 (55–73) years], from the HORACS registry, were included in our analysis. There were 8,502 (55.4%) pts treated with RT (Table 1). In patients without RT, mortality was 15.7%, in pts treated with FT was 10.5%, and in pts treated with p-PCI was 6.2% ($p < 0.000$). There were 84.3% of pts who arrived within 12 h and 15.7% of those who arrived 12–18 h from the symptom onset to the FMC. 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% confidence interval (CI) 0.748–0.761, for a decision on whether 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 years), heart failure (Killip II-IV), diabetes mellitus, and the time from the symptom onset (> 360 min.).

A total of 4,986 (58.6%) pts arrived within three hours from the symptom onset to the FMC. Their mean age was 59.6 ± 11.4 yrs, and the median was 59 (IQR 52–69) yrs. More pts received FT [3,277 (65.7%)]. On the other hand, 1,709 (34.3%) patients received p-PCI.

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 years *vs* 58.7 ± 11.5 yrs, $p < 0.000$), with a higher prevalence of diabetes mellitus (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 that determinate the type of RT (p-PCI or FT) were the arrival at the non-PCI capable center, the previous p-PCI, the time from the symptom onset, heart failure ($p < 0.001$), diabetes mellitus ($p = 0.019$), and renal failure ($p = 0.035$), the localization of myocardial infarction ($p = 0.024$), previous angina pectoris ($p = 0.010$). High-risk patients with heart failure, diabetes mellitus, and renal failure were treated more with FT. Significant predic-

Table 1

The baseline characteristics, comorbidities and previous coronary diseases

Baseline characteristics	Without RT n = 6,852	FT (18 h) n = 5,132	p-PCI (18 h) n = 3,370	*p*	FT (3 h) n = 3,277	p-PCI (3 h) n = 1,709	*p*
Age (years), mean±SD, median (IQR)	67.1 ± 11.6 69 (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 (min), mean ± SD, median (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		64.0	63.5	
other medical ambulance or hospital	31.1	22.1	21.5		20.0	17.8	
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 or their treatment, %							
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

CABG − coronary artery bypass grafting; MI − myocardial infarction; PCI − percutaneous coronary intervention; p-PCI − primary PCI; FT − fibrinolytic therapy; RF − renal failure; SD − standard deviation; IQR − interquartile range.

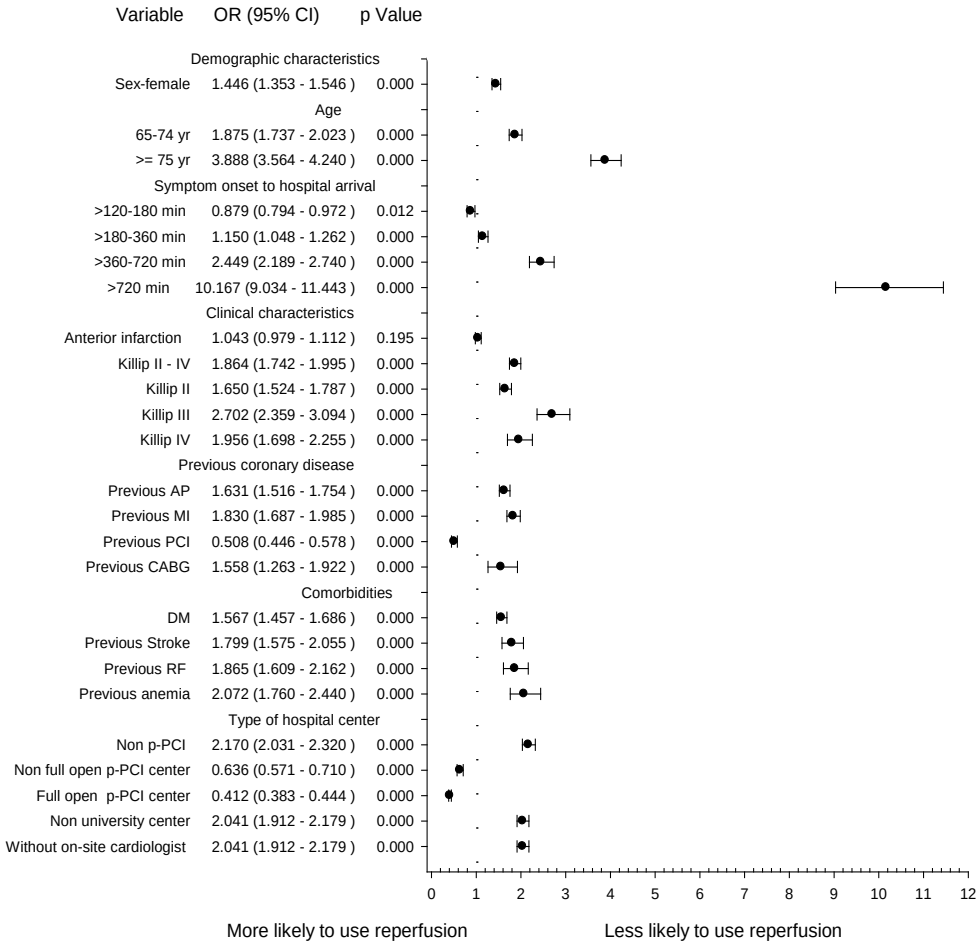

Fig. 1 – The predictors that indicate the absence of the application of reperfusion therapy (univariate analysis). OR − odds ratio; CI − confidence interval; AP − arterial pressure; MI − myocardial infarction; PCI − percutaneous coronary interventions; CABG − coronary artery bypass grafting; DM − diabetes mellitus; RF − reperfusion therapy; p-PCI − primary PCI.

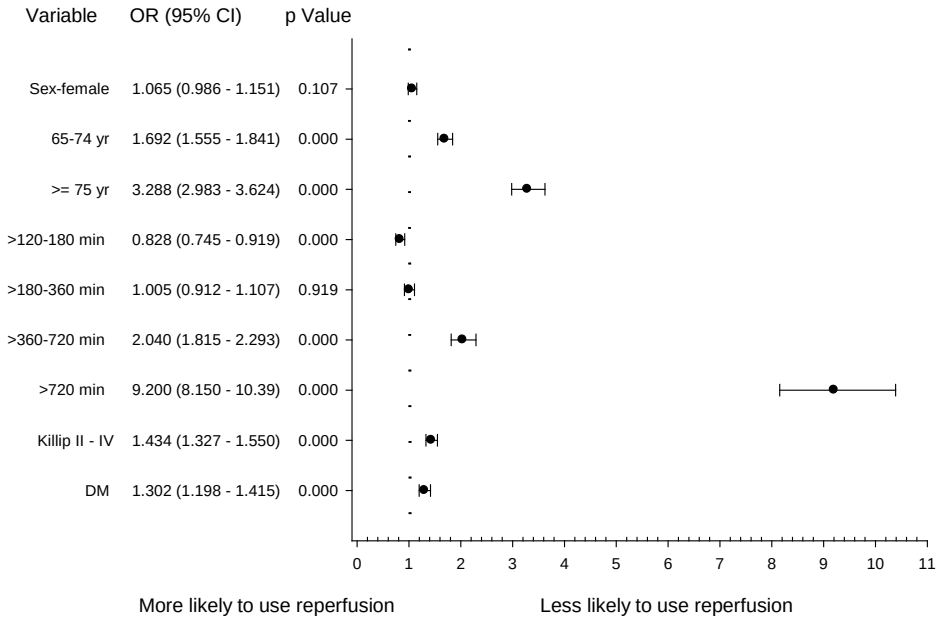

Fig. 2 – The model for predicting the absence of the application of reperfusion therapy. OR − odds ratio; CI − confidence interval; DM − diabetes mellitus.

tors for applying p-PCI were the treatment at the PCI center, the university center, the center 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%), mechanical postmyocardial complication (4.4% *vs* 1.7%), postinfarction angina (12.1% *vs* 5.5%), and arrhythmia (41.6% *vs* 23.9%) were significantly more often found in the FT group when compared with the p-PCI group, respectively ($p < 0.001$) (Table 2).

After the propensity score, there were 3,256 matched pairs of pts in the two groups treated with RT, who were so

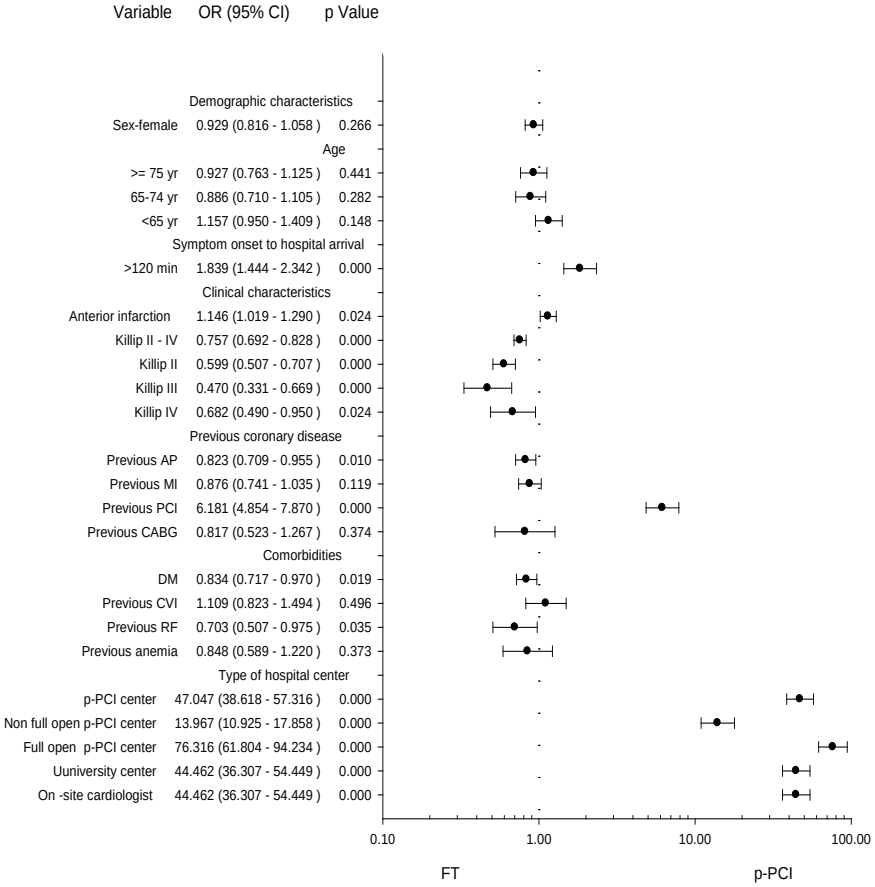

Fig. 3 – The predictors of the doctor's decision on reperfusion therapy (univariate analysis). OR − odds ratio; CI − confidence interval; AP − arterial pressure; MI − myocardial infarction; PCI − percutaneous coronary interventions; CABG − coronary artery bypass grafting; DM − diabetes mellitus; CVI − cerebrovascular insult; RF − reperfusion therapy; FT – fibrimolytic therapy; p-PCI − primary PCI.

Table 2

The complications and the outcome

Complications	FT (n = 3,277)	p-PCI (n = 1,709)	*p*
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 (mortality and re-infarction) (%)	11.4	7.2	< 0.001
Cardiac arrest (%)	12.2	7.2	< 0.001
Mechanical complication (%)	4.4	1.7	< 0.001
Postinfarction angina (%)	12.1	5.5	< 0.001
Arrhythmia (%)	41.6	23.9	< 0.001

FT − fibrinolytic therapy; p-PCI − primary percutaneous coronary intervention.

matched according to the categories of age, gender, the time to FMC (≤ 180 min), diabetes mellitus, 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 compared to the p-PCI group: FT 8.8% *vs* pPCI 6.4% (Figure 4).

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 RT (p-PCI or FT) should not only be based on the time elapsed from symptoms onset to FMC. Reperfusion therapy in Serbia was less applied in high-risk

Table 3

The characteristics of matching 3,256 patients treated with FT and p-PCI

Baseline characteristics	FT n = 1,538	p-PCI n = 1,758
Age (years), 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,	81.54 ± 32.12	86.4 ± 40.03
Diabetes, %	28.6	29.6
Heart failure (Killip II-IV), %	29.5	18.7

FT − fibrinolytic therapy; p-PCI − primary percutaneous coronary intervention; SD − standard deviation.

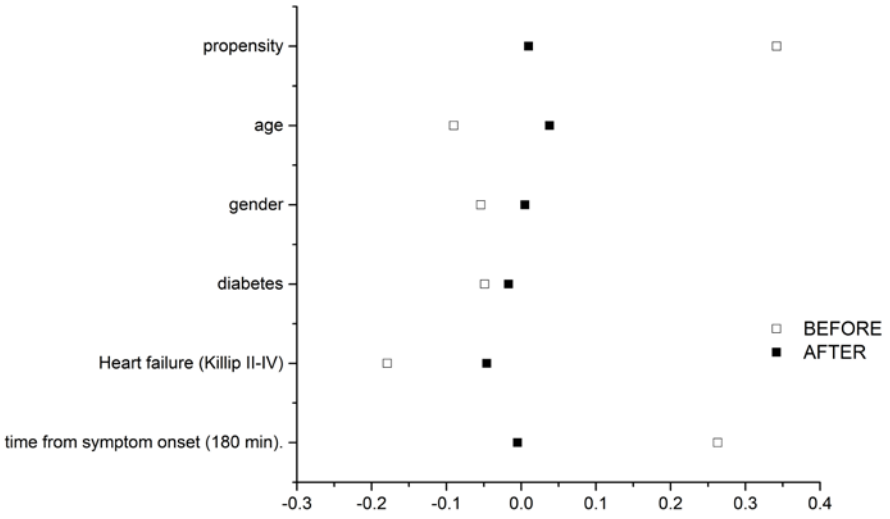

Fig. 4 – Matching 3,256 patients treated with fibrinolytic therapy and primary percutanous coronary intervention by using the propensity score.

Discussion

The p-PCI remains the treatment of choice in patients who have close access to PCI centers. One-third of STEMI patients have ischemic time from FMC to p-PCI of more than 120 minutes [18]. Considering the results of less shock and heart failure in PI-treated pts, it could be a greater clinical benefit in situations where PCI-related delays occur in real-world situations [6].

The unsolved problem is the strategy of improving RT in remote regions in developing and transition countries particularly. The balance of cost-benefit therapy is difficult to achieve. The advantage of the fibrinolytic agent in a situation where an urgent invasive procedure and transportation of high-risk patients is not possible may be very important. However, it includes the extra cost of the FT. The dilemma is whether the PI strategy is a reasonable and useful option for every patient who cannot undergo timely p-PCI and whether it is available in every region and country. The best cost-

pts. The problems of the treatment of high-risk pts and the gaps seem to persist in a large number of studies and registries in not only low-income countries [19–21] but in developed countries as well [22–26].

In the Strategic Reperfusion Early After Myocardial Infarction (STREAM) study [5] of 3/5 PI successfully reperfused patients who underwent scheduled angiography approximately 18 hours after FT, excellent angiographic, 12-lead electrocardiography (ECG) metrics, and clinical outcomes were achieved. On the other hand, the pts requiring rescue PCI after contemporary FT, aspirin, clopidogrel, and enoxaparin in combination, with completed PCI within 140 minutes after FT, had high 30-day composite event rates of death, shock, chronic heart failure, and reinfarction (18.7%) [27]. These data support findings that although PI-treated, pts requiring rescue angiography had greater baseline risk with more comorbidities and worse 30-day outcomes compared with pts successfully treated by FT. The patients requiring rescue PCI should be immediately transported to a

center capable of completing rescue intervention after the administration of FT [27].

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 RT. The other 62.7% were treated with RT, of which 24.4% were treated with p-PCI, and 38.3% were treated with FT. In other countries' registries, the results were similar [16, 28, 29]. In Serbia, pts without RT were older (≥ 65 yrs), came later after the symptom onset (> 360 min), had heart failure (Killip II-IV), comorbidities such as diabetes mellitus, previous stroke, renal failure, anaemia, previous coronary diseases, except previous PCI and the arrival at a non-PCI capable and non-University center without a cardiologist on site. The situation was similar in other registries: in the SNAPSHOT ACS registry [28], patients without RT were older, there were more those of the female gender, with comorbidities, and atrial fibrillation. In the Global Registry of Acute Coronary Events (GRACE) Registry [10], they were older and of the female gender; a history of heart failure, prior myocardial infarction, or diabetes mellitus were found to be independently associated with a lack of RT [10]. In the CRUSADE [30] and TETAMI registries [31], the results were similar.

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

The important predictors that influenced the 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 center, the arrival at the university center, where cardiologists were on site. If pts had heart failure, previous coronary diseases, diabetes mellitus, and renal failure, pts were treated more by FT. Further, if pts arrived 2 h after the symptom onset, with the anterior localization of myocardial infarction, and the previous PCI, the doctors decided to a greater extent to apply p-PCI.

Throughout the history of applying RT from prehospital fibrinolysis to PI therapy, it seems that FT has a very important position in STEMI pts, especially in the regions where PCI centers are farther [32–36]. From 1995 to 2015, there was a decrease in applying FT (from 40% to 6%) and an increase in p-PCI (from 12% to 77%) in France [35], and also a decrease in FT (from 66% to 7%) and an increase in PCI (from 12% to 61%) in SWEDHEART/RISK-HIA registry [37]. In Serbia, it seems that pts with a higher risk, who needed a more efficient therapy sooner, were not treated well enough, and they received FT rather than the undeveloped PI strategy. Finances may be the reason why the network of PI therapy has not been fully applied yet.

After analyzing patients treated with FT in the STREAM study, it was determined that PI-treated pts with greater baseline risk and with more comorbidities required rescue angiography. These pts had worse 30-day outcomes compared with successful FT pts and scheduled PCI [27].

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* p-PCI, concerning age ≥ 65 (35.1% *vs* 37.1%), gender (male 30.1% *vs* female 30.6%), the time from the symptom onset < 180 min (47.6% *vs* 47.5%), diabetes mellitus (20.6% *vs* 19.9%) and Killip-class heart failure > 1 (25.9% *vs* 21.8%), the mortality rate was higher, but not significantly in the FT group compared to the p-PCI group (FT 8.8% *vs* p-PCI 6.4%).

In the last years, the situation in Serbia has been better after a full opening of 7 p-PCI 24/7 day-centers. However, the percentage of pts who were not treated with RT is the same, the percentage of pts treated by FT is lower, and the percentage of pts who go to p-PCI is higher. In the last years, mortality of reperfused and non-reperfused pts has not been significantly improved [27].

Limitation of the study

Not a 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 FT group, which was solved by using the propensity score.

Conclusion

The possibility for timely p-PCI and PI therapy is especially not applicable in high-risk patients, older patients, those with heart failure, and with diabetes. The unsolved problems were the reperfused pts by FT who should go to the PCI center after the therapy and especially high-risk patients. The strategy of STEMI pts must be modified and defined in the developing and transition countries without the possibility for timely p-PCI and without a network of fully applicable PI therapy. The improvement of treating these pts has two pathways: opening more p-PCI centers and, as important, using more PI therapies. Achieving the balance of the best cost-benefit strategies is difficult in remote regions and developing countries.

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