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Features of the Reperfusion Therapy for ST-Segment Elevation Myocardial Infarction According to the Russian Registry of Acute Myocardial Infarction – REGION-IM

Aim Based on data from the Russian REGION-IM registry, to study the features of reperfusion therapy in patients with ST-segment elevation myocardial infarction (STEMI) in real-life clinical practice.

Material and methods REGION-IM is a multicenter prospective observational study. The observational period is divided into 3 stages: during the stay in the hospital and at 6 and 12 months after inclusion in the registry. The patient's records contain demographic and history data; information about the present case of MI, including the time of the first symptom onset, first contact with medical personnel, and admission to the hospital; coronary angiography (CAG) data, percutaneous coronary intervention (PCI) data, and information about the thrombolytic therapy (TLT).

Results Reperfusion therapy was performed in 88.9% of patients with STEMI. Primary PCI (pPCI) was performed in 60.6% of patients. The median time from the onset of symptoms to pPCI was 315 minutes [195; 720]. The median time from ECG to pPCI was 110 minutes [84;150]. Isolated TLT was performed in 7.4%, pharmaco-invasive treatment tactics were used only in 20.9% of cases. The median time from ECG to TLT (prehospital and in-hospital) was 30 minutes [10; 59], whereas the median time from ECG to prehospital TLT was 18 minutes [10; 39], and in 63% of patients, TLT was performed more than 10 minutes after diagnosis. PCI followed TLT in 73% of patients.

Conclusion The frequency of reperfusion therapy for STEMI in the Russian Federation has increased considerably in recent years. The high frequency of pPCI is noteworthy, but the timing of pPCI does not always comply with clinical guidelines. The results of this registry confirm the high demand for pharmaco-invasive strategies in real-life clinical practice. Taking into account geographical and logistical features, implementing timely myocardial reperfusion requires prehospital TLT. However, the TLT frequency in the Russian Federation is still insufficient despite its proven maximum effectiveness in the shortest possible time from the detection of acute MI.

Keywords Cardiovascular diseases; ischemic heart disease; acute coronary syndrome; myocardial infarction; acute myocardial infarction registry; PCI; thrombolysis

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Introduction

Cardiovascular disease (CVD) hold the lead among the causes of morbidity and mortality in the Russian Federation (RF), including in the working age population. In 2020, coronary artery disease (CAD) accounted for 54.2% of all cardiovascular mortality, with myocardial infarction (MI) deaths reaching 58,079 [1].

The main cause of ST-segment elevation myocardial infarction (STEMI) is the compromised integrity of the atherosclerotic plaque cap with thrombus formation on its surface, which completely occludes the lumen of the infarct-related coronary artery [2] resulting in acute ischemia and myocardial necrosis. Reperfusion therapy aimed at reversing the thrombotic occlusion of the coronary artery is the mainstay of STEMI treatment. Three reperfusion strategies are currently available: mechanical reperfusion (primary percutaneous coronary intervention (pPCI)), pharmacological reperfusion (thrombolytic therapy (TLT)), and pharmaco-invasive therapy (thrombolysis followed by early angiography and mechanical intervention if indicated).

PCI is the gold standard for the treatment of STEMI. Several studies have demonstrated its superiority in terms of efficacy and safety over other reperfusion strategies [3]. However, time to reperfusion of the infarct-related artery is of paramount importance in managing STEMI patients. The earliest possible restoration of myocardial perfusion in acute myocardial infarction limits the area of damage, reduces the risk of complications, and improves prognosis [4].

Current guidelines suggest that TLT should be conducted if pPCI is impossible within 120 minutes of diagnosis [5–8]. Given that thrombolysis is ineffective in about 30% of patients with STEMI and that coronary artery re-occlusion often occurs after successful TLT, pharmaco-invasive therapy is the preferred approach to treating STEMI when timely pPCI is not possible [9].

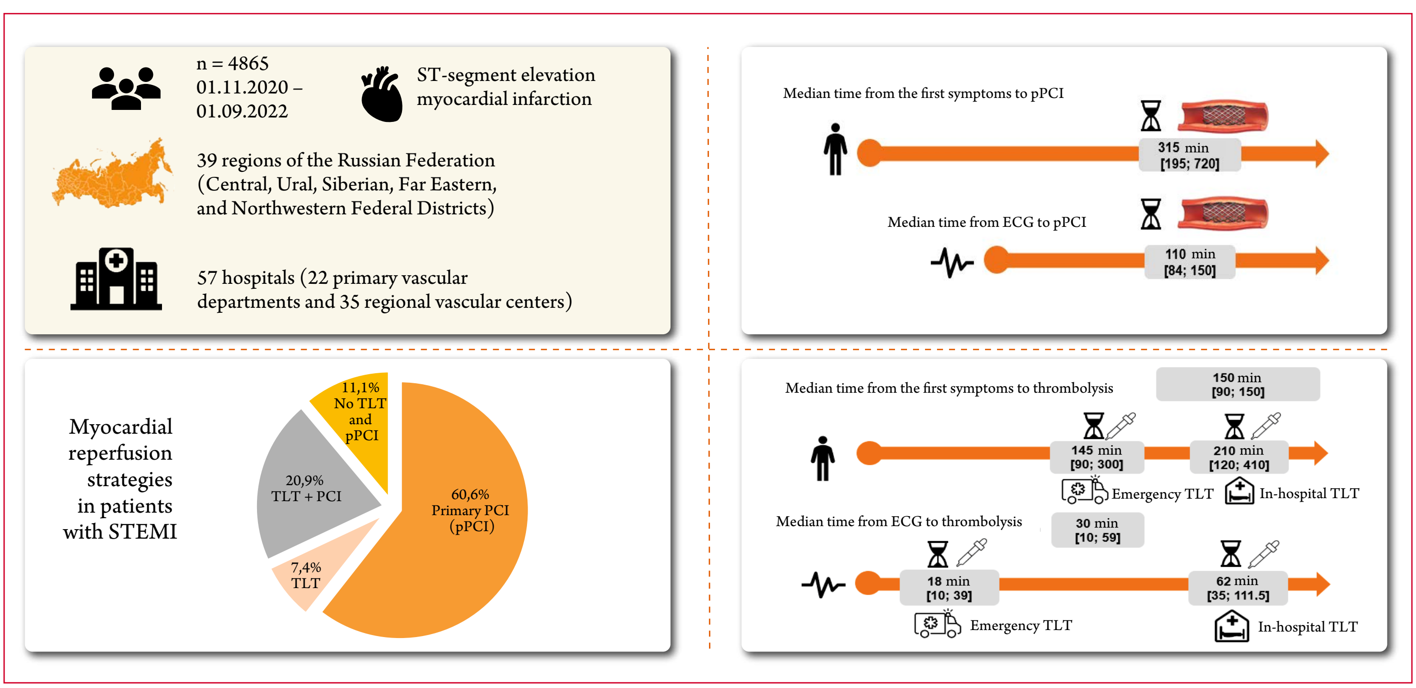
In recent years, the number of vascular centers with equipped angiographic departments has increased significantly in the Russian Federation. However, due to the vast territories, including remote and inaccessible areas, it is impossible to always deliver patients to invasive hospitals on time. In this regard, the pharmaco-invasive strategy for the treatment of STEMI remains a relevant and reasonable approach to reperfusion therapy.

The objective of this study was to investigate the peculiarities of reperfusion therapy in STEMI patients in real-world clinical practice based on the data from the Russian REGION-MI registry. As well as to determine the compliance of the therapy with clinical guidelines, to estimate the time to reperfusion in each of the treatment strategies, to study the peculiarities of TLT, to determine the number of patients who may benefit from pharmaco-invasive therapy instead of untimely PCI.

Material and Methods

The Russian registry of acute myocardial infarction (REGION-MI) is a multicenter prospective observational study [10]. The register includes all patients admitted to

Central illustration. Features of the Reperfusion Therapy for ST-Segment Elevation Myocardial Infarction According to the Russian Registry of Acute Myocardial Infarction – REGION-IM



TLT, thrombolytic therapy; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

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hospitals with the diagnosis of acute MI established using the criteria of the ESC Guidelines on Fourth Universal Definition of Myocardial Infarction (2018). Patients are included in the study after they or their representatives have signed the informed consent to take part in the study and the personal data processing consent. The study protocol and the informed consent form were approved by the Ethics Committee of the Academician Chazov National Medical Research Center. This project has been developed and is carried out following the ethical principles of the Declaration of Helsinki, the ICH harmonized tripartite guideline, and the Russian GOST standard on Good Clinical Practice. The study is conducted on the Quinta platform (certificate of state registration of computer program No. 2016615129 «Universal software complex for collection, processing, and management of geographically distributed clinical and epidemiological data in remote access mode, copyright Aston Consulting JSC»). The case report form contains the following data: demographic characteristics; clinical characteristics and medical history; information on the current case of MI (time of the onset of the first symptoms, time of the first medical care encounter, time of hospitalization); findings of laboratory tests and clinical examinations, coronary angiography and PCI; information on the thrombolytic therapy; drug therapy (drugs administered at the time of admission, before hospitalization, and during the hospital stay); clinical outcomes during the hospital stay. The follow-up period is divided into 3 stages: observation during the hospital stay, 6 and 12 months after enrollment in the registry.

IBM SPSS Statistic version 24 was used for statistical processing of data. All anamnestic, clinical, and laboratory data obtained were processed using analysis of variance. The means (M), the standard deviations (σ), the errors of the mean (m), the medians (Me), and the interquartile ranges (IQR) were determined for the quantitative parameters. The non-parametric Kruskal-Wallis multiple comparison (Holm method) was used to compare several independent samples. The non-parametric statistical Mann-Whitney U-test was used to compare two independent samples by any quantitative attribute. The frequency of a sign or an event was determined for qualitative variables. The chi-squared test was used to compare the frequency of an attribute. Pairwise comparisons were made using a pairwise proportion test with the Holm correction.

Results

The REGION-MI registry involves hospitals included in the MI Network in the Central, Ural, Siberian, and Far Eastern Federal Districts (a total of 39 Russian regions). A total of 57 hospitals (22 hospitals with primary vascular departments (PVDs) and 35 regional vascular centers (RVCs)) were included in the study. Of the 22 PVDs, 12 departments are equipped with angiographic systems; 8 PVDs with angiographic systems are located in regional centers and 4 PVDs with angiographic systems are located in district centers.

Of the patients included in the study, 81.6% were hospitalized immediately in RVCs. 18.4% were hospitalized in PVDs, and 18.9% of them were subsequently transferred to RVCs for coronary angiography (CAG) and PCI.

Clinical and demographic characteristics of patients

Over the period from 01.11.2020 to 01.09.2022, 4,865 patients were included in the registry. The clinical and demographic characteristics of patients are provided in Table 1.

Frequency and features of different reperfusion strategies for the treatment of STEMI

Reperfusion therapy was conducted in 88.9% of STEMI patients included in the study (Figure 1), pPCI was performed in 60.6% of patients, isolated TLT was carried out in 7.4%, and pharmaco-invasive approaches were used in 20.9% of cases (Figure 1). Overall, 28.3% of patients received TLT. Among the patients who underwent PCI, 74.3% received pPCI.

The median age, the percentage of patients who were > 75 years old, patients with ischemic stroke/transient ischemic attack (IS/TIA), chronic heart failure (CHF), and a history of chronic kidney disease (CKD) (GFR < 60 mL/min/1.73 m^2) were statistically significantly higher in the group of patients who did not receive reperfusion therapy compared to those who received reperfusion therapy (Table 2).

Patients who did not receive reperfusion treatment, compared to patients for whom pPCI or pharmaco-invasive strategy (PCI after TLT) were chosen, were statistically significantly more likely to have a history of atrial fibrillation (AF), decreased hemoglobin <10 g/dL, and angina pectoris before the index event (Table 2).

Reperfusion therapy time intervals

The time of the first electrocardiogram (ECG) is used hereinafter as the time of the first medical encounter in order to standardize the data.

Time from the onset of symptoms to initial medical encounter

Initial medical encounter (predominantly ambulance) occurred in 38% of patients within 6 hours of symptom onset and in 20% of patients within the first hour of symptom onset (Figure 2). The median time from the onset of the first symptoms to the first ECG was 150 [69; 519] minutes.

Time from ECG to hospitalization

Figure 3 shows the distribution of patients by time intervals from the moment of ECG (diagnosis) to hospitalization (within the first hour, within two hours, and later than two hours) for different reperfusion treatment strategies.

Time to pPCI

The median time from the onset of symptoms to pPCI was 315 [195; 720] minutes. The median time from ECG to pPCI was 110 [84;150] minutes (Figure 4).

pPCI was performed within 120 minutes from ECG in 58% of patients and within 90 minutes in 41% of patients (Figure 5).

Time to TLT

The median time from the onset of first symptoms and the first ECG to TLT is presented in Figure 6. The median time from the first symptoms to (pre-hospital and in-hospital TLT) was 150 [90;150] minutes. The median time from the onset of symptoms to pre-hospital TLT performed before hospitalization was 145 [90; 300] minutes. The median time from the onset of symptoms to in-hospital TLT was 210 [120; 410] minutes. The median time from ECG to (pre-hospital and in-hospital) TLT was 30 [10; 59] minutes. Meanwhile, the median time from ECG to pre-hospital TLT was 18 [10; 39] minutes. The median time from ECG to in-hospital TLT was 62 [35; 111.5] minutes.

Table 1. Clinical and demographic characteristics of the included patients (n = 4865)

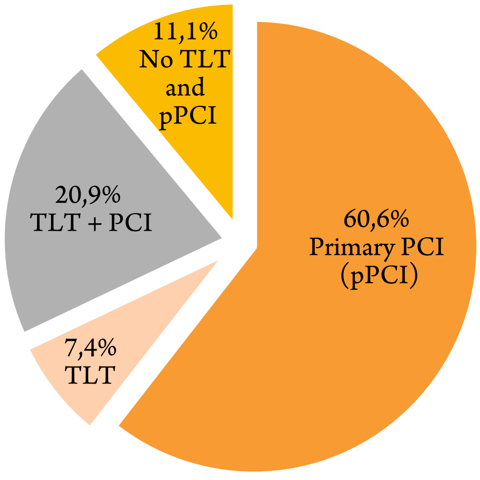
Parameter	Value
Mean age, years, M ± m (min – max)	62 ± 11 (18–96)
Age > 75 years, %	13.7
Male, %	70.5
Mean age of males, years, M ± m (min – max)	59 ± 11 (18–97)
Mean age of females, years, M ± m (min – max)	69 ± 11 (26–97)
Weight ≤ 60 kg, %	6.7
Smokers, %	50.4
History of IS/TIA, %	7.4
Patients with arterial hypertension, %	83.2
Patients with CHF, %	23.0
History of AF, %	8.0
GFR < 60 mL/min/1.73 m², %	28.1
Patients with angina pectoris, %	30.6
History of PCI/CABG, %	8.6
Patients without history of MI, %	85.5
Patients with recurrent MI, %	14.5

MI, myocardial infarction; CHF, chronic heart failure; IS, ischemic stroke; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; PCI, percutaneous coronary intervention; GFR, glomerular filtration rate; AF, atrial fibrillation.

Choice of thrombolytic agent

The frequency of prescribing thrombolytic drugs is presented in Figure 7. Fortelyzin was the most frequently

Figure 1. Frequency of different reperfusion strategies in STEMI patients



STEMI, ST-segment elevation myocardial infarction; pPCI, primary percutaneous coronary intervention; TLT, thrombolytic therapy.

Figure 2. Distribution of patients depending on time from the onset of the first symptoms to the first ECG

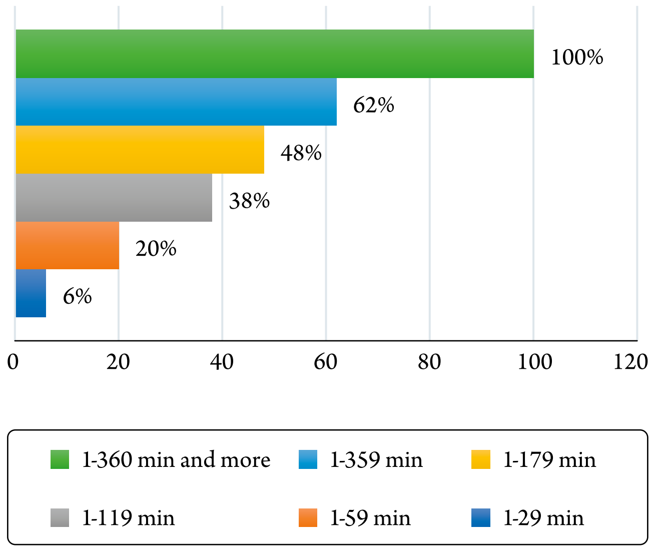


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Table 2. Clinical and demographic characteristics of patients included in the study depending on the treatment strategy

Parameter	No reperfusion (A) n = 539	pPCI (B) n = 2947	TLT (C) n = 358	Pharmacoinvasive treatment (D) n = 1021	p-value*
Median age, years (Me [IQR], min – max)	66 [58; 75] (21 – 97)	62 [54; 70] (18 – 95)	63 [55; 70] (29 – 91)	61 [54; 68] (25 – 95)	**A>B (0.000)** **A>C (0.000)** B=C (0.700) **A>D (0.000)** **B>D (0.040)** C=D (0.140)
Age > 75 years, %	25.4	13.5	12.6	8.6	**A>B (0.000)** **A>C (0.000)** B=C (0.696) **A>D (0.000)** **B>D (0.000)** C=D (0.076)
Male, %	59.4	70.8	74.0	74.2	**A<B (0.000)** **A<C (0.000)** B=C (0.449) **A>D (0.000)** B=D (0.115) C=D (0.991)
Weight ≤ 60 kg, %	9.8	6.4	5.1	6.5	**A>B (0.032)** A=C (0.083) B=C (1.000) A=D (0.100) B=D (1.000) C=D (1.000)
History of IS/TIA, %	12.0	7.6	5.7	5.3	**A>B (0.005)** **A>C (0.010)** B=C (0.455) **A>D (0.000)** **B>D (0.043)** C=D (0.873)
Patients with arterial hypertension, %	87.2	82.6	79.4	84.1	A=B (0.056) **A>C (0.016)** B=C (0.365) A=D (0.365) B=D (0.365) C=D (0.214)
Patients with CHF, %	35.4	21.8	24.6	19.3	**A>B (0.000)** **A>C (0.003)** B=C (0.246) **A>D (0.000)** B=D (0.227) C=D (0.125)
History of AF, %	13.5	7.4	8.5	6.7	**A>B (0.000)** A=C (0.123) B=C (0.950) **A>D (0.000)** B=D (0.950) C=D (0.859)
GFR < 60 mL/min/1.73 m², %	41.2	25.7	27.1	28.6	**A>B (0.000)** **A>C (0.000)** B=C (1.000) **A>D (0.000)** B=D (0.256) C=D (1.000)
Patients with angina pectoris, %	37.8	28.8	35.4	30.2	**A>B (0.000)** A=C (0.877) **B<C (0.049)** **A>D (0.017)** B=D (0.877) C=D (0.237)
History of PCI/CABG, %	8.5	9.7	8.5	5.6	A=B (1.000) A=C (1.000) B=C (1.000) A=D (0.192) **B>D (0.000)** C=D (0.304)
Patients without history of MI, %	78.2	85.7	84.2	89.1	**A<B (0.000)** A=C (0.065) B=C (0.522) **A<D (0.000)** **B<D (0.026)** C=D (0.060)
Hemoglobin <100 g/dL, %	5.4	2.5	2.6	1.6	**A>B (0.002)** A=C (0.237) B=C (1.000) **A>D (0.000)** B=D (0.388) C=D (0.715)

IM, myocardial infarction; CHF, chronic heart failure; IS, ischemic stroke; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; PCI, percutaneous coronary intervention; GFR, glomerular filtration rate; AF, atrial fibrillation; * nonparametric Kruskal-Wallace test (Holm method) for multiple comparisons was used; statistically significant p-values are printed in bold.

prescribed thrombolytic drug (36.2%). Streptokinase was administered in very rare cases (0.9%).

Pre-hospital TLT was performed in 63% of patients. Fortelyzin (42.3% and 25.8%) and tenecteplase (23.5% and 18.5%) were statistically significantly more frequently prescribed at the pre-hospital stage compared to the in-hospital stage ($p < 0.001$ and $p = 0.002$, respectively, Figure 7). At the in-hospital stage, alteplase was prescribed significantly more frequently (in 38.1% and 14% of patients; $p < 0.001$), the second most frequently prescribed thrombolytic agent was fortelyzin (25.8%, Figure 7).

Pharmaco-invasive strategy

PCI was performed after TLT in 73% of patients. There were more patients of < 75 years of age among patients who underwent PCI after TLT than among those after isolated TLT (91.4% and 87.4%, respectively, $p = 0.029$), patients without history of MI (89.1% and 84.2%, respectively, $p = 0.016$), and without CHF (80.7% and 75.4%, respectively, $p = 0.034$). TLT was successful in 63% of cases. Among patients who received PCI after TLT, life-saving PCI was conducted after unsuccessful TLT in 44% early PCI was performed after successful TLT in 56% of cases.

Table 3. Comparison of key time intervals depending on treatment strategies and transfer to different types of hospitals

Time intervals	Patients admitted to PVDs without angiographic systems who were not transferred to RVCs or PVDs equipped with angiographic systems (A)	Patients admitted to PVDs without angiographic systems who were transferred to RVCs or PVDs equipped with angiographic systems (B)	Patients admitted immediately to RVCs (C)	Patients admitted to PVDs equipped with angiographic systems (D)	p value*
Median time from the first symptoms to the first ECG, minutes	300 [90; 840]	224.5 [90; 930]	137.5 [60; 390]	144.5 [68.8; 472.5]	A=B (0.806) **A>C (0.030)** **B>C (0.001)** A=D (0.107) **B>D (0.039)** D=C (0.326)
Median time from the first ECG to hospitalization, minutes	60 [30; 195]	60 [30; 120]	60 [43; 102]	60 [40; 110]	A=B (0.721) A=C (0.995) B=C (0.961) A=D (0.689) B=D (1.000) C=B (0.953)
Median time from the first ECG to primary PCI, minutes	–	875 [437.5; 2010.0]	108.5 [81.3; 150]	113 [88; 150]	**B>C (0.000)** **B>D (0.000)** D=C (0.461)
Median time from the first symptoms to primary PCI, minutes	–	2220 [936; 4788]	280 [180; 618.8]	270 [180; 600]	**B>C (0.000)** **B>D (0.000)** D=C (0.711)
Median time from the first symptoms to TLT at any stage, minutes	240 [120; 410]	240 [130; 578.8]	150 [90; 300]	145 [87.5; 337.5]	A=B (1.000) A=C (0.105) **B>C (0.000)** A=D (0.219) **B>D (0.003)** **C>D (0.956)**
Median time from the first symptoms to pre-hospital TLT, minutes	330 [120; 457.5]	207.5 [119; 465]	145 [80; 275]	145 [87.5; 360]	A=B (0.331) **A>C (0.005)** **B>C (0.035)** A=D (0.052) B=D (0.437) C=D (0.481)
Median time from the first symptoms to in-hospital TLT, minutes	135 [90; 210]	245 [157.5; 757.5]	205 [120; 337.5]	165 [105; 232.5]	A=B (0.091) A=C (0.464) B=C (0.271) A=D (0.940) B=D (0.221) C=D (0.590)
Median time from ECG to TLT at any stage, minutes	30 [30; 59]	30 [30; 85]	28 [10; 50]	15 [10; 35]	A=B (0.642) **A>C (0.009)** **B>C (0.001)** **A>D (0.001)** **B>D (0.000)** C=D (0.086)
Median time from ECG to pre-hospital TLT, minutes	30 [30; 35]	30 [10; 30]	18 [10; 30]	12 [98; 30]	A=B (0.093) **A>C (0.004)** B=C (0.330) **A>D (0.001)** B=D (0.200) C=D (0.255)
Median time from ECG to in-hospital TLT, minutes	48.5 [30; 63.8]	80 [36; 120]	65 [45; 105]	70 [45; 105]	A=B (0.484) A=C (0.755) B=C (1.000) A=D (1.000) B=D (0.909) C=D (1.000)
Median time from TLT conducted at any stage to PCI, minutes	–	–	234 [150; 578]	154 [115; 240]	**C>D (0.000)**

PVD, primary vascular department; RVC, regional vascular center; TLT, thrombolytic therapy;
PCI, percutaneous coronary intervention; ECG, electrocardiogram; * nonparametric Kruskal-Wallace test (Holm method) for multiple comparisons was used; statistically significant p values are printed in bold.

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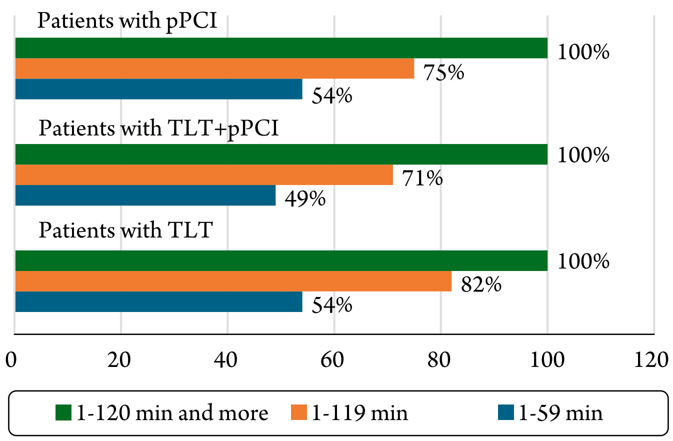
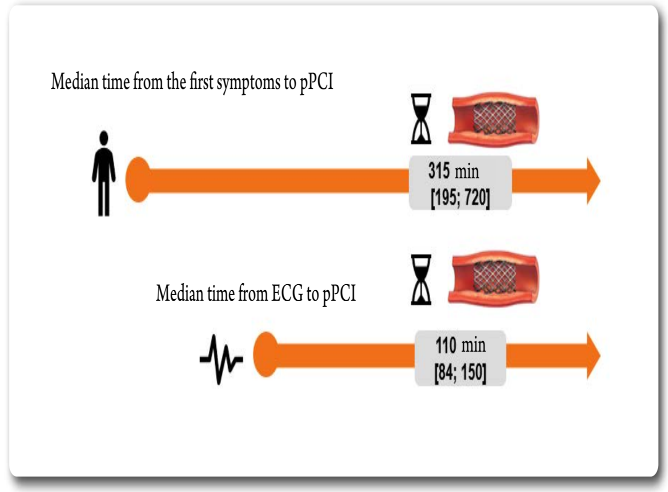
Figure 3. Distribution of patients by time from ECG to hospitalization depending on treatment strategy (primary PCI, pharmaco-invasive strategy, or TLT alone, respectively)



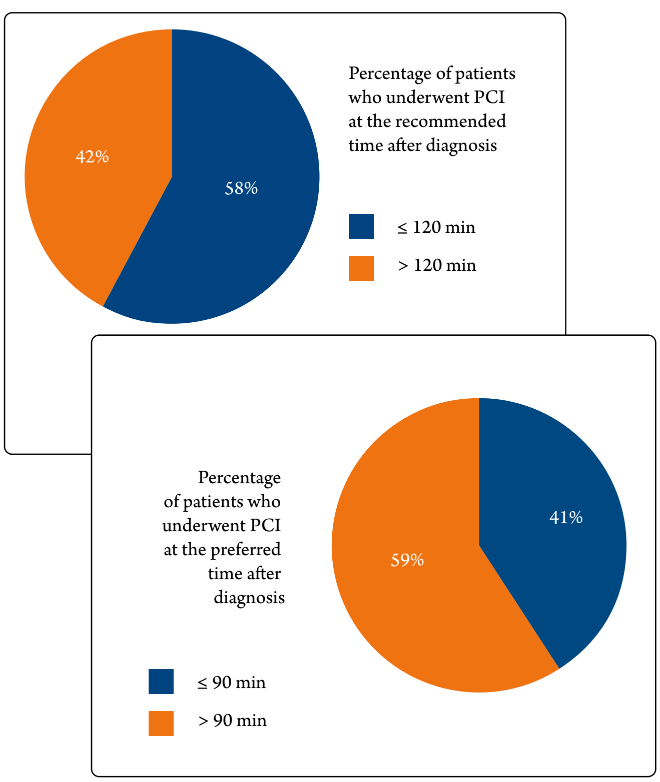
pPCI, primary percutaneous coronary intervention; TLT, thrombolytic therapy.

Figure 4. Median time from the first symptoms and ECG to pPCI



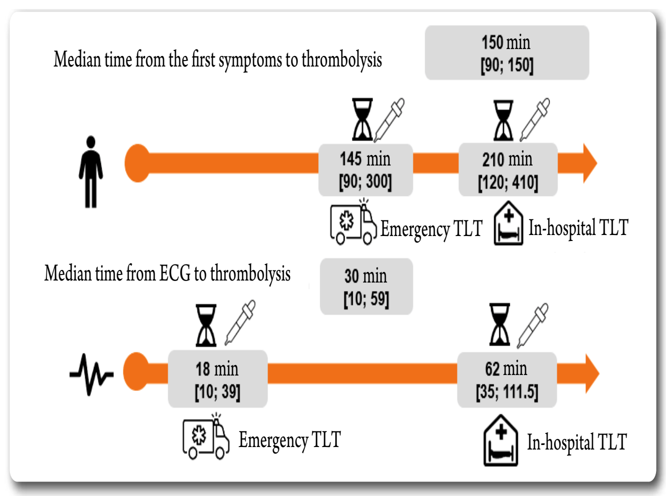
pPCI, primary percutaneous coronary intervention; ECG, electrocardiogram.

Figure 5. Percentage of patients who underwent PCI within the recommended time frame



pPCI, primary PCI.

Figure 6. Median time from the first symptoms and ECG to thrombolysis



TLT, thrombolytic therapy; ECG, electrocardiogram.

The median time from pre-hospital TLT to PCI was 190 [125; 393] minutes (Figure 8). The median time from in-hospital TLT to PCI was 645 [229; 1414] minutes. Among patients who underwent TLT, a thrombolytic agent was administered within the recommended time frame, i.e., within 10 minutes of diagnosis, in only 37% of cases. The median time from successful TLT to PCI was 295 [150; 943] minutes. The median time from TLT failure to PCI was 167 [127; 276] minutes.

Specifics of reperfusion strategy depending on the type of hospital (PVD and RVC)

It is noteworthy that since the start of the REGION-MI registry, 12 out of 22 PVDs have been equipped with angiographic systems, and therefore the percentage of pPCI procedures performed in PVDs is quite high. The frequency of pPCI was 53% among patients hospitalized in PVDs and 73% among patients hospitalized in PVDs with angiographic systems (Figure 9). Compared to patients hospitalized in RVCs, patients hospitalized in PVDs

Figure 7. Frequency of the administration of different thrombolytic agents

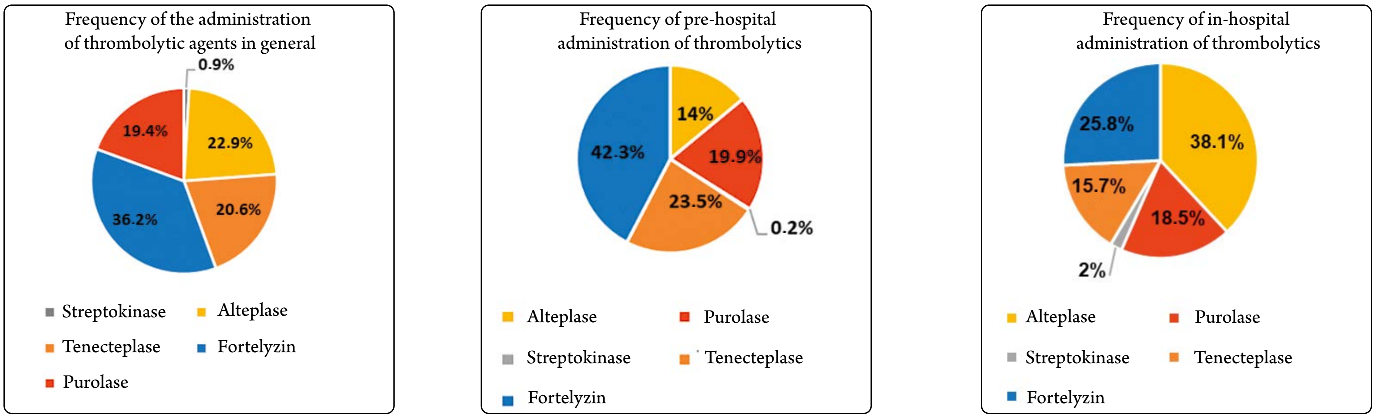
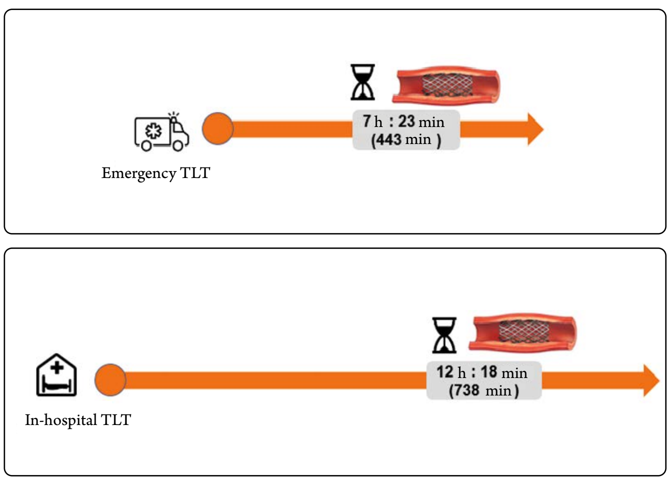


Figure 8. Median time from TLT to PCI



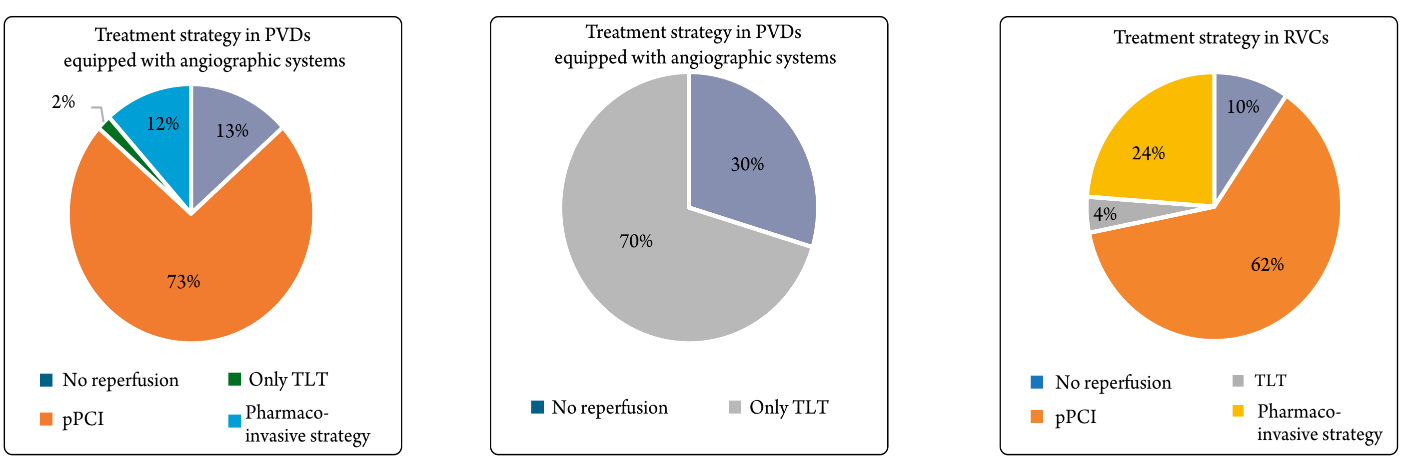
TLT, thrombolytic therapy.

were more likely to receive only TLT (predominantly in PVDs without angiographic systems) or no reperfusion treatment. Patients were expectedly more likely to undergo pPCI and pharmaco-invasive treatment in RVCs (Figure 9).

Fortelyzin was used as a thrombolytic drug in 51% of patients in PVDs. In RVCs, fortelyzin was also ordered more often than other drugs (in 33% of patients), 23% of patients were treated with tenecteplase, and 25% received alteplase (Figure 10). Table 3 shows the time intervals of reperfusion strategies in patients hospitalized in different types of hospitals in terms of transfer.

The median time from the first symptoms to time to the first ECG (initial medical encounter) was statistically significantly greater in patients initially admitted to the PVDs without angiographic systems (both those who were subsequently transferred and those who were not transferred) than in patients initially admitted to RVCs. The median time from ECG to hospitalization was

Figure 9. Frequency of different reperfusion strategies in PVDs and RVCs



PVD, primary vascular department; RVC, regional vascular center; pPCI, primary percutaneous coronary intervention; TLT – thrombolytic therapy

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Table 4. Comparison of key time intervals of medical care in PVDs equipped with angiographic systems depending on location (regional and district centers)

Time intervals	All patients admitted to PVDs equipped with angiographic systems, n = 416	Patients admitted to PVDs equipped with angiographic systems in regional centers, n = 302 (A)	Patients admitted to PVDs equipped with angiographic systems in district centers, n = 114 (B)	p value, comparison of A and B
Median time from the first symptoms to the first ECG, minutes	144.5 [68.8; 472.5]	150 [70; 497.5]	137 [65; 420]	0.697
Median time from the first ECG to hospitalization, minutes	60 [40; 110]	60.5 [36.5; 110]	60.00 [40; 115.5]	0.551
Median time from ECG to primary PCI, minutes	113 [88; 150]	110 [81; 150]	115 [90; 158]	0.242
Median time from the first symptoms to primary PCI, minutes	270 [180; 600]	270 [180; 633]	264 [172; 520]	0.502
Median time from the first symptoms to any TLT, minutes	145 [87.5; 337.5]	159 [87.4; 301]	139 [102; 360]	1.0
Median time from the first symptoms to pre-hospital TLT, minutes	145 [87.5; 360]	160 [87.5; 319.8]	140 [102.5; 360]	0.927
Median time from the first symptoms to in-hospital TLT, minutes	165 [105; 232.5]	165 [105; 232.5]	–*	–
Median time from ECG to any TLT, minutes	15 [10; 35]	14 [10; 30]	15 [10; 41]	0.763
Median time from ECG to pre-hospital TLT, minutes	12 [98; 30]	10.2 [9.3; 15]	15 [10.2; 41.1]	0.133
Median time from ECG to in-hospital TLT, minutes	70 [45; 105]	70 [45.0; 105.0]	–*	–
Median time from TLT to PCI conducted after any TLT, minutes	154 [115; 240]	140 [100; 272.5]	145 [107.5; 186.2]	0.829

PVD, primary vascular department; RVC, regional vascular center; TLT, thrombolytic therapy; PCI, percutaneous coronary intervention; ECG, electrocardiogram. * In-hospital TLT was not conducted in district centers.

similar in all groups. Transferred patients had statistically significantly longer median time from ECG to pPCI and longer total time of myocardial ischemia (median time from the first symptoms to pPCI or to any TLT) compared to the other groups (Table 3).

Patients admitted to PVDs without angiographic systems and who were not transferred, compared to those initially admitted to RVCs, were characterized by longer median time from symptom onset to ECG and pre-hospital TLT, and longer time from ECG to any TLT in general and pre-hospital TLT in particular, compared to both the RVC group and the group of patients admitted to PVDs with angiographic systems (Table 3).

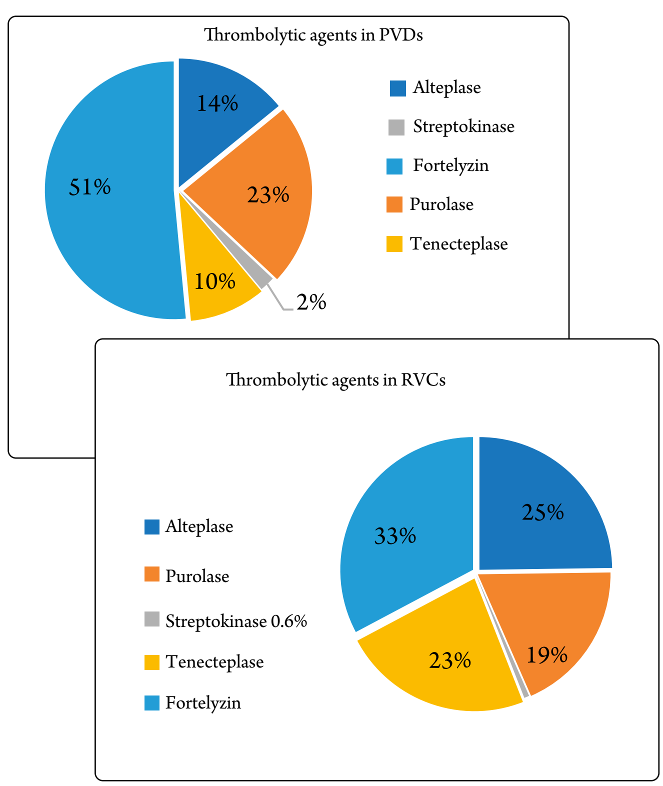
Table 4 reflects a separate comparison of key time intervals in PVDs with angiographic systems depending on their administrative affiliation (regional or district centers). Time indicators shown in PVDs with angiographic do not differ significantly between regional and district centers. In-hospital TLT was not conducted in district centers.

Discussion

Frequency of reperfusion therapy for STEMI in the Russian Federation and abroad

Before beginning a discussion of the findings, it should be noted that the material presented in this article does not reflect all of the study objectives. This article reviews the peculiarities of reperfusion therapy in the Russian

Figure 10. Frequency of the administration of different thrombolytic agents in PVDs and RVCs



PVD, primary vascular department; RVC, regional vascular center.

Federation. The impact of reperfusion strategy specifics on hospital outcomes, long-term prognosis of patients in 6 and 12 months is the task for future studies, when follow-up data of all patients included in the study will be available.

The frequency of reperfusion therapy in the Russian Federation and in developed countries is high. Over the past 6–7 years, the frequency of reperfusion therapy in general and the frequency of the preferred method of reperfusion PCI has increased in the Russian Federation. According to monitoring data from the Russian Ministry of Health, the percentage of patients with STEMI who received a particular type of reperfusion treatment increased from 51% to 73.3% from 2016 to 2021, and the frequency of PCI increased from 25% to 50.2% over the 5 years (http://asmms.mednet.ru). There was no significant change in the percentage of patients who received TLT (isolated and as part of a pharmaco-invasive strategy): 26% in 2016 and 23.1% in 2021. In our registry, reperfusion treatment was administered to a larger percentage of patients – 88.9% of cases. Among those who received reperfusion therapy, PCI was performed in 60.6%, TLT in 7.4%, and pharmaco-invasive treatment in 20.9%. According to the 2015 RECORD-3 registry, 32% of patients did not receive reperfusion treatment, and the frequency of PCI was significantly lower than in our study – at only 39%; the pharmaco-invasive approach was used more frequently – in 52% of cases [11].

According to the latest data from the large-scale STEMI registry ACVC-EAPCI EORP (Association for Acute CardioVascular Care and European Association of Percutaneous Cardiovascular Interventions under the umbrella of the ESC EURObservational Research Program STEMI Registry), conducted in 2015–2018 under the auspices of the European Society of Cardiology (ESC), which included data for 11,462 patients from ESC member countries, and several countries in the Middle East, Asia and Africa. The percentage of patients who did not have myocardial reperfusion was slightly lower than in the REGION-MI registry and was 9%. PCI was conducted more frequently than in our study (72.2% of patients), and the frequency of TLT (isolated and as part of a pharmaco-invasive strategy) was lower (18.8% of patients). In the European-only study, PCI was performed in an even higher percentage of patients – 85.4%, and TLT was performed in 7.6% of cases. Only 7% of patients did not receive reperfusion in European countries [12].

The 2021 data from the Swedish SWEDEHEART registry are similar to the ACVC-EAPCI EORP registry and superior to the REGION-MI data in terms of reperfusion rates: reperfusion therapy was performed in 90% of patients, PCI in 86% of patients, and TLT in 3% of patients. However, the incidence of TLT is high in some remote regions of Sweden.

According to a report from the US National Cardiovascular Data Registry, the frequency of PCI for patients with STEMI in 2019–2020 was higher than in our registry for both urban (85.1%) and rural (73.2%) patients. But we are approaching those numbers. TLT was conducted significantly less frequently than in the REGION-MI registry: rural patients received TLT in 19.7% of cases and urban patients in 2.7% of cases [13].

Relevance of pharmaco-invasive strategy in the treatment of STEMI

Certainly, the efficacy of reperfusion therapy for STEMI is determined not only by its implementation, but also by its promptness. Time to reperfusion is a critical factor in myocardial salvage and survival. If reperfusion is started within an hour of the first symptoms of MI, 65 lives can be saved per 1,000 patients treated [14].

According to current clinical guidelines, timely pPCI is the preferred treatment strategy for STEMI patients. The advantage of PCI over TLT is only maintained for the first 120 minutes from diagnosis to recanalization of the infarct-related artery [5, 6]. This was confirmed by results from one of the largest MI registries, the National Registry of Myocardial Infarction (NRMI), which included data from 192,509 patients from 645 hospitals: multivariate adjusted odds of death with pPCI and TLT were identical with a pPCI delay of 114 minutes (95% CI: 96–132 minutes; $p < 0.001$) [15].

Ignoring TLT and using late PCI beyond 120 minutes after the first ECG is associated with worse survival in patients with STEMI. According to the French registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction (FAST-MI), five-year survival was 10% higher with a pharmaco-invasive strategy (89.8%) compared to late PCI (79.5%; adjusted hazard ratio (HR) 1.51; CI: 1.13–2.02) and is similar to timely PCI (88.2%, adjusted HR 1.02; CI: 0.75–1.38) [16].

According to the STREAM analysis, when there was a PCI delay of more than 90 minutes, the pharmaco-invasive strategy had an advantage over PCI in achieving the composite endpoint of death, heart failure, cardiogenic shock, and MI (13.9% and 17.9%, respectively, for time interval of 55–97 minutes, $p = 0.148$; 13.5% and 16.2%, for > 97 minutes, $p = 0.470$) [17].

In addition to the implications for mortality, the use of a pharmaco-invasive strategy results in a lower incidence of cardiogenic shock compared to PCI. In a meta-analysis of the STREAM, CAPTIM, and WEST trials, patients randomized to the pharmaco-invasive strategy group had a significantly lower risk of cardiogenic shock than patients

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who underwent PCI (3.76% versus 5.67%; OR 0.65, CI: 0.46–0.92; p = 0.02). There was also a trend toward a lower incidence of CHF in the pharmaco-invasive strategy group (7.83% versus 9.70%; OR 0.79, CI 0.59–1.04; p = 0.10) [18]. These differences may be explained by earlier reperfusion and myocardial preservation.

These data formed the basis for the current Russian and European clinical guidelines, which recommend TLT to reduce the risk of death in patients with STEMI with a symptom duration of less than 12 hours when PCI cannot be performed within 120 minutes of diagnosis. Thrombolytic administration should be started within 10 minutes of diagnosis [5, 6]. Pre-hospital TLT is recommended to further reduce the risk of death [5, 6].

According to the 2019 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Guidelines, a pharmaco-invasive strategy may be considered as an alternative to pPCI in case of early recourse to medical care (less than 3 hours from the onset of symptoms) and low bleeding risk if prompt pPCI is unavailable (low class of recommendation, medium level of evidence) [19].

The findings of an Australian observational study published in 2023 also favor a pharmaco-invasive approach when timely pPCI is not possible. The study included 2091 patients with STEMI (80% male) who were admitted to Liverpool Hospital in Sydney within 12 hours of the onset of symptoms (between October 2003 and March 2014). Of these patients, 1077 patients (52%) underwent pPCI (68% timely PCI and 32% late PCI) and the others (48% of patients) received pharmaco-invasive treatment (33% of patients underwent emergency PCI after TLT failure and 67% of patients underwent PCI after effective TLT). The 3-year mortality was 11.1% in the pPCI group (6.7% timely pPCI and 20.2% late pPCI) and 6.2% in the pharmaco-invasive strategy group (9.4% in TLT failure followed by emergency PCI and 4.8% effective TLT and PCI performed within 24 hours) ($p < 0.01$). After assessing outcomes using the fit index selection method, the adjusted risk of death was higher for late PCI compared to a pharmacoinvasive approach with effective TLT (hazard ratio (HR) 2.2 (95% CI: 1.2–3.1). Patients who underwent late PCI were more likely to die than those who received pharmacoinvasive therapy. Although one-third of patients who receive TLT require life-saving PCI, a pharmacoinvasive approach is preferred when pPCI is expected to be late because it provides better outcomes than late pPCI [20].

Real-world clinical data confirm the need for pharmaco-invasive treatment of STEMI, as time to PCI, according to our and other registries, often does not meet the requirements of clinical guidelines. According to the REGION-MI registry, 60.6% of patients underwent pPCI, but 42% of them received late PCI. It is clear that a better strategy in these patients would be to perform pre-hospital TLT followed by early PCI. Time from ECG to pPCI was shorter in REGION-MI than in the ACVC-EAPCI EORP STEMI registry (110 minutes and 195 minutes, respectively). However, the percentage of patients who received late pPCI is comparable to the REGION-MI data (42% and 38.2%, respectively) [11]. We should pay attention to the heterogeneity of the data in the ACVC-EAPCI EORP STEMI registry due to the wide geographic coverage of the included hospitals, and to the absence (or inclusion of a small number of patients) from large European countries, such as France, Germany, and the United Kingdom, which may also constitute a limitation of the study. An almost twofold difference was found when comparing the REGION-MI data on ECG-pPCI time with the 2021 data from the SWEDEHEART registry (110 minutes in the REGION-MI registry and 62 minutes in the SWEDEHEART registry).

However, there were inconsistencies with clinical guidelines for TLT. In our group of patients receiving TLT, 37% underwent in-hospital TLT despite clinical guidelines, with a median ECG-to-in-hospital TLT time of an unacceptable 62 minutes.

Median time from ECG to emergency pre-hospital TLT also exceeded the recommended time frame (10 minutes) and was 18 minutes. Median ECG-to-TLT time in the SWEDEHEART registry was similar to REGION-MI with 25 minutes and 30 minutes, respectively. According to our data, the difference in time from symptom onset to TLT between pre-hospital and in-hospital administration was 65 minutes, which is extremely large for a dynamic disease like MI. This is another reason to use pre-hospital TLT as much as possible.

Time from the onset of symptoms to ECG was shorter in the REGION-MI registry than in the ACVC-EAPCI EORP registry (150 minutes versus 221.6 minutes, respectively) [11]. Such delays can be attributed to both late recourse to medical care by patients and logistical delays. Public education and optimization of MI networks are required to eliminate delays at this stage. Among other things, late initial medical encounters underscore the relevance of minimizing delays in subsequent stages of management.

Choice of thrombolytic agents

According to current clinical guidelines, fibrin-specific thrombolytics are preferred because they are less likely to cause allergic reactions and more likely to achieve successful reperfusion. For example, the incidence of the composite endpoint (death and stroke) in the GUSTO study was significantly lower with the fibrin-specific agent alteplase compared to streptokinase (6.9% and 7.8%, respectively, p = 0.006) [21].

In the specific setting of pre-hospital therapy, thrombolytics administered as a single bolus without the need for continuous infusion [tenecteplase, recombinant staphylokinase (Fortelyzin)] have a certain advantage from the point of view of convenience and ease of use. However, one should be guided primarily by clinical efficacy and the frequency of achieving reperfusion. In this respect, the thrombolytics available in the Russian Federation (prourokinase, fortelyzin, alteplase, tenecteplase) are considered comparable [22].

According to the REGION-MI registry, fortelyzin and alteplase are the most commonly used thrombolytics in the Russian Federation. Fortelyzin and tenecteplase were administered more frequently in the pre-hospital setting than in the in-hospital setting, most likely due to ease of use (single bolus administration).

Tenecteplase was also the most commonly used thrombolytic agent according to data from the international STEMI registries [23, 24].

Specifics of PCI within a pharmacoinvasive strategy

All patients who have received thrombolytics (before hospitalization or during hospital stay without the possibility of PCI) should be immediately transferred to a 24-hour PCI center, as all patients who have undergone TLT are candidates for CAG. This recommendation is based on the results of the NORwegian study on DIstrict treatment of ST-elevation myocardial infarction (NORDISTEMI), which compared two treatment strategies after TLT using tenecteplase in patients with long transport times (> 90 minutes) from remote communities in South East Norway: immediate transfer to a PCI center for CAG and PCI if indicated and a conservative approach with ischemia control and transfer to a PCI center if necessary. The overall incidence of death, MI, and stroke was higher in the conservative treatment group than in the early invasive strategy group (15.9% and 6.0%, respectively; hazard ratio 0.36 (95% CI: 0.16–0.81; p = 0,01) [25].

Time to PCI is determined by thrombolysis efficacy (life-saving or routine PCI within 2–24 hours). In case of TLT failure (failure to achieve a > 50% ST-segment reduction within 60–90 minutes), urgent life-saving PCI is recommended [5, 6]. After successful TLT (> 50% ST-segment reduction within 60–90 minutes after thrombolytic administration), early (2–24 hours after initiation of thrombolysis according to the ESC guidelines or 3–24 hours according to the ACC guidelines) CAG is recommended with the intention of performing PCI in the infarct-related artery [6]. If angiography and PCI (if indicated) cannot be performed within 2–24 hours after successful TLT for any reason, they should be performed later during the hospital stay [5].

According to the REGION-MI registry, PCI was not performed after TLT in 27% of patients, which is significantly less than in the ACVC-EAPCI EORP registry, where PCI was not performed after TLT in 58.7% of patients [10]. It should be noted that the median time to early PCI in the REGION-MI registry did not exceed acceptable values and was 3 hours 10 minutes for PCI after pre-hospital TLT and 10 hours 45 minutes after in-hospital TLT. The median time to life-saving PCI of 2 hours 47 minutes was unsatisfactory and may be explained by delays in transfer to an invasive hospital.

Notably, there were statistically significantly more patients aged >75 years with a history of MI and CHF in our study in the TLT group compared with the group of patients who underwent PCI after TLT. Moreover, patients aged >75 years with CKD, CHF, and a history of IS/TIA were generally less likely to receive reperfusion therapy. The paradox of lower compliance with clinical guidelines in the high-risk patient group (treatment-risk paradox) has long been known and has been repeatedly described in several studies and registries [26], including the lower frequency of PCI for the treatment of MI in elderly patients compared to patients younger than 75 years [27, 28]. According to a small Russian retrospective study conducted in 2016 [29], only 31% of patients with STEMI in the ≥75 year group were referred for routine delayed PCI after TLT. In our registry, 66.2% of patients aged over 75 underwent PCI after TLT. The management of MI in this age group continues to be a challenge for physicians due to comorbidity and the simultaneous presence of both high ischemic and hemorrhagic risk.

Specifics of reperfusion therapy for STEMI in the different types of hospitals

In our study, the median time from first symptoms to primary medical encounter (first ECG) was statistically significantly shorter in patients admitted RVCs than in patients admitted to PVDs. This is most likely due to the fact that PVDs are mainly located in remote small settlements, district centers, where time to seeking medical care (calling an ambulance) is traditionally longer than in larger population centers, which inevitably leads to higher mortality due to MI. This is probably due to the level of education, less awareness and caution about myocardial infarction in the population.

As expected, total myocardial ischemia time was significantly longer in the transferred patients. Thus, if the total time of myocardial ischemia is 4 hours 40 minutes in

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patients admitted directly to RVCs, and 4 hours 30 minutes in patients admitted to PVDs equipped with angiographic systems; and it is 37 hours in transferred patients, which automatically assigns such patients to the group of late myocardial infarction and complicates the performance of PCI within the recommended 48 hours from symptom onset. Thus, the transfer takes approximately 32 hours before pPCI is performed. This underscores the need to improve the process of transfer to the centers equipped with angiographic systems in the Russian regions. The time from initial medical encounter to pPCI was also, not unexpectedly, statistically significantly longer for patients transferred from hospitals without angiographic systems to hospitals with angiographic systems (14 hours 36 minutes for those transferred from PVDs without angiographic systems and 1 hour 49 minutes for those initially admitted to RVCs, 1 hour 53 minutes for those initially admitted to PVDs equipped with angiographic systems; $p < 0.0001$ for both comparisons). This reflects the continuing need for pre-hospital TLT to prevent delayed myocardial reperfusion and the importance of the availability of centers equipped with angiographic systems.

The statistically significantly longer time from first symptoms to pre-hospital TLT in patients who were subsequently transferred than in patients initially admitted to RVCs is most likely due to late primary medical encounter (longer time from first symptoms to first ECG).

The number of PVDs equipped with angiographic systems is increasing in the Russian regions, which is also reflected in our registry, where more than half of the PVDs had angiographic systems. No statistically significant differences in time indicators were found in a separate analysis of key time indicators for patients treated in PVDs equipped with angiographic systems according to the administrative affiliation (regional or district centers).

Conclusion

According to the REGION-MI registry and the monitoring data of the Ministry of Health, the frequency of reperfusion therapy for STEMI has increased significantly in the Russian Federation in recent years and is approaching European levels. The high frequency of pPCI and median ECG-to-pPCI time of 110 minutes, which consistent with recommended interval, are noteworthy. However, time to pPCI does not comply with clinical guidelines in 42% of patients, which may be due to delays caused by both late recourse to medical care and time to hospitalization.

The results of the Registry support the need for a pharmaco-invasive treatment strategy in real-world clinical practice. Considering the geographical and logistic peculiarities (vast territories and remote settlements), for realization of timely myocardial reperfusion there is a need for pre-hospital TLT, the frequency of which in the Russian Federation, despite the proven maximum efficacy when administered as soon as possible after the diagnosis of acute MI, remains insufficiently high.

To improve the quality of treatment of STEMI, special attention should be paid to reducing time from the onset of first symptoms to reperfusion therapy (total ischemia time): increase public awareness of the symptoms of MI and the need for early recourse to medical care, minimize delays in getting patients to a PCI center, if pPCI cannot be performed within 120 minutes after the diagnosis, provide timely pre-hospital TLT; if hospitalized in a PVD where PCI is unavailable to transfer a patient to an invasive hospital as soon as possible.

Limitations

Only hospitals included in the MI Network are enrolled in the registry, which excludes the analysis of cases of acute MI in non-specialized hospitals; not all regions of the Russian Federation currently participate in the registry.

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