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Features of Parenteral Anticoagulant Therapy in Patients With Myocardial Infarction According to the Russian Register of Acute Myocardial Infarction – REGION-IM

Aim	To study specific features of the parenteral anticoagulant therapy for acute myocardial infarction (MI) in the Russian Federation and to evaluate the consistency of the prescribed parenteral anticoagulant therapy with the effective clinical guidelines.
Material and Methods	REGION-MI, the Russian rEGIstry for acute myOcardial iNfarction, is a multicenter observational study. This registry includes all patients admitted to hospitals with a documented diagnosis of ST-elevation acute MI (STEMI) and non-ST-elevation acute MI (NSTEMI) based on the criteria of the Forth Universal Definition of MI of the European Society of Cardiology. Risk of bleeding was assessed with the Academic Research Consortium for High Bleeding Risk (ARC-HBR) scale, and risk of major bleeding in patients with NSTEMI was additionally assessed with the CRUSADE scale.
Results	From November 01, 2020 through April 03, 2022, 5025 patients were included into the REGION-MI registry. At primary vascular departments, 70.5% of patients were administered unfractionated heparin (NFH); at regional vascular centers, 37.1% of patients were administered NFH, 29.6% enoxaparin, 20,2% NFH in combination with enoxaparin, 6.8% fondaparinux, 4.2% NFH in combination with fondaparinux, and 1.9% nadroparin. At the prehospital stage, NFH was used as an anticoagulant support for the thrombolytic therapy (TLT) in 84% of patients, and low-molecular heparins (LMH) were used in 16%. At the hospital stage, UFH was administered to 64.4% of patients, and enoxaparin was administered to 23.9% of patients. Among the patients who had undergone primary percutaneous coronary intervention (PCI), 40% received NFH, 25% enoxaparin, 22% NFH in combination with enoxaparin, 7% fondaparinux, and 4% NFH in combination with fondaparinux. In conservative and invasive tactics of therapy for NSTEMI, NFH was also administered more frequently (43 and 43%, respectively), followed by (according to frequency of administration) enoxaparin (36 and 34%, respectively), NFH in combination with enoxaparin (10 and 16%, respectively), fondaparinux (7 and 6%, respectively), and NFH in combination with fondaparinux (3 and 1%, respectively).
Conclusion	According to the Russian registry of acute MI, REGION-MI, with all strategies for the treatment of MI, parenteral anticoagulants are not prescribed in full consistency with clinical guidelines. The most frequently used parenteral anticoagulant is NFH. Despite the high efficacy and safety of fondaparinux, the frequency of its administration remains unjustifiably low not only in the Russian Federation but also in other countries. The same can be said about the administration of enoxaparin to patients who had received TLT. Attention should be paid to physicians' awareness of recent clinical guidelines, to minimize the prehospital treatment with parenteral anticoagulants, to limit this treatment to the TLT support, and to provide continuity between all stages of medical care.

Keywords	Cardiovascular diseases; ischemic heart disease; acute coronary syndrome; myocardial infarction; registry of acute myocardial infarction; parenteral anticoagulant therapy
For citations	Boytsov S.A., Shakhnovich R.M., Tereschenko S.N., Erlikh A.D., Pevsner D.V., Gulyan R.G. Features of Parenteral Anticoagulant Therapy in Patients With Myocardial Infarction According to the Russian Register of Acute Myocardial Infarction – REGION-IM. Kardiologiia. 2022;62(10):3–15. [Russian: Бойцов С.А., Шахнович Р.М., Терещенко С.Н., Эрлих А.Д., Певзнер Д.В., Гулян Р.Г. Особенности парентеральной антикоагулянтной терапии у больных инфарктом миокарда по данным Российского рЕГИстра Острого иНфаркта миокарда – РЕГИОН–ИМ. Кардиология. 2022;62(10):3–15].

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Cardiovascular diseases are the uncontested leading cause of disability and death in the Russian Federation. Coronary artery disease (CAD) is a leading cause of death among circulatory diseases. According to the Russian Statistics Agency (Rosstat), 508,657 people died of CAD in Russia in 2020, of whom 58,079 patients died of myocardial infarction (MI). Short-term and long-term prognosis after MI is still unfavorable despite the fact that the possibilities of treating patients with MI have increased significantly over the past decade the due to the common administration of drugs with proven efficacy, and the use of invasive treatments [1, 2].

Intracoronary thrombosis caused by rupture and erosion of an unstable atherosclerotic plaque is the main pathogenetic element of acute MI. Parenteral anticoagulants are of the main components of pathogenetic therapy of MI with proven effect on the prognosis. They suppress the formation and activity of the key coagulation factor, thrombin, and reduce the risk of thrombotic complications.

The Russian registry of acute MI (REGION-MI) is a multicenter observational cohort study that excludes any interference in clinical practice. The inclusion of patients began in 2020 and will continue for 24 months. The registry was created to collect data on the diagnosis and treatment of patients with acute MI in Russian hospitals, treatment results, short-term and long-term outcomes.

Objective

Analyze data on parenteral anticoagulant therapy of patients with acute MI in the Russian Federation depending on the treatment strategy, assess the compliance of the administered parenteral anticoagulant therapy with current clinical guidelines, and compare the results obtained with similar findings of international studies [3].

Material and Methods

The Russian rEGIstry Of acute myocardial iNfarction (REGION-MI) is a multicenter observational study. The registry includes all patients admitted to hospitals with acute ST-segment elevation MI (STEMI) and non-ST-segment elevation MI (NSTEMI) diagnosed according to 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 participate in the study and the personal data processing consent. The study design is exclusively observational. The study protocol and the informed consent form were approved by the ethics committee of the Academician Chazov National Medical Research Center.

The study is conducted in the Quinta CRM platform. The follow-up period is divided into 3 stages: observation during hospital stay, 6 and 12 months after inclusion in the registry. The design of the registry has been previously described in detail [3].

The risk of bleeding was assessed using the Academic Research Consortium for High Bleeding Risk (ARC-HBR) score, the risk of major bleeding in patients with NSTEMI was additionally assessed by the CRUSADE score.

The following statistical methods of data processing were applied. Descriptive statistics (expected value, standard deviation (SD), median, quartiles, minimum/maximum) to summarize the primary results obtained from case report forms. Confidence assessment (expected value, SD) that allows assessing the parameters of interest with the specified reliability. Statistical processing of data was carried out using IBM SPSS Statistics v.24. All anamnestic, clinical, and laboratory data obtained were processed using analysis of variance. The quantitative parameters were expressed as means (M), mean square deviation, errors of mean (m), standard deviations (SD), medians (Me), 95% confidence intervals (CI). The frequency of a sign or an event was determined for qualitative variables.

Results

Clinical and demographic characteristics of patients

The registry involves 56 facilities (34 regional vascular centers (RVCs) and 22 primary vascular departments (PVDs)) that are part of the "MI Network" in the Central, Ural, Siberian, and Far Eastern Federal Districts (a total 41 regions of the Russian Federation). From 01.11.2020 to 03.04.2022, a total of 5,025 patients were included in the REGION-MI registry (Table 1).

High risk of bleeding was determined in 30.3% of patients with MI according to the ARC-HBR score (Figure 1). And 32.5% of patients with NSTEMI had high or very high risk of bleeding according to the CRUSADE score.

Treatment strategy for patients with MI

Eighty nine percent of patients with STEMI underwent reperfusion therapy. Primary PCI was the most common reperfusion treatment (72%), a pharmacoinvasive approach (thrombolytic therapy (TLT) + PCI) was applied in 21% of patients, 7% of patients received TLT, and 11% of patients were treated conservatively.

PCI and conservative treatment were used in 63% and 37% of patients with NSTEMI, respectively.

Parenteral anticoagulant therapy for STEMI

Unfractionated heparin (UFH) was the most commonly used anticoagulant whatever treatment strategy was

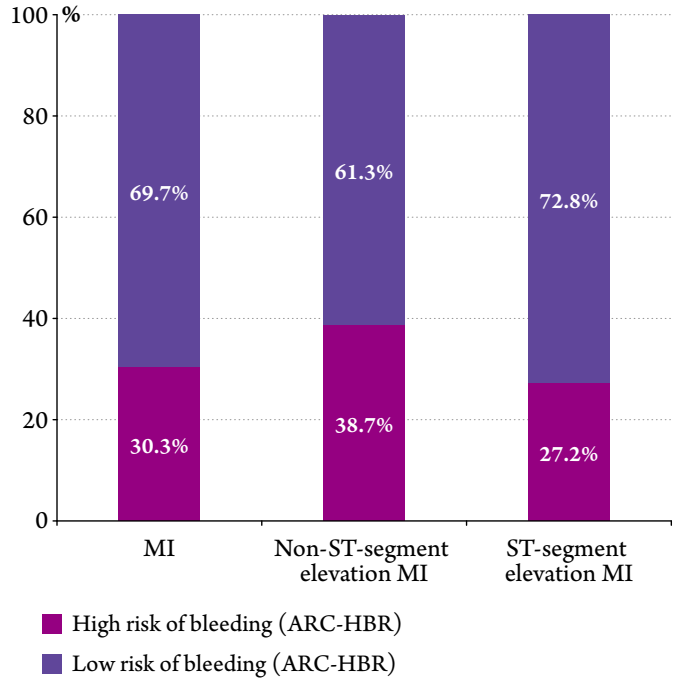
ISSN 0022-9040. Kardiologiia. 2022;62(10). DOI: 10.18087/cardio.2022.10.n2238

Table 1. Clinical and demographic characteristics of the included patients (n=5,025)

Parameter	Value
Male, %	69.1
Age, years, M ± m (min–max)	62.8 ± 12.0 (18–97)
Patients ≥ 75 years old, %	15.2
Age of male patients, years (M ± m)	59.7 ± 11.0
Age of female patients, years (M ± m)	69.9 ± 11.1
Patients without a history of MI, %	81.8
Patients with recurrent MI, %	17.4
Smokers, %	38.1
Patients with arterial hypertension, %	83.4
Patients with angina pectoris, %	32.7
Patients with CHF, %	24.6
Patients with a history of AF, %	9.7
Patients with a history of stroke/transient ischemic attack, %	7.6
Patients with a history of PCI/CABG, %	10.1
Mean body weight, kg, M ± m (min–max)	83.0 ± 16.0 (30–200)
Patients with body weight < 60 kg, %	4.2
Patients with hemoglobin <10 g/dL, %	3.0
Patients with CKD (eGFR <60 mL/min/1.73 m^2), %	28.1
eGFR, %	
• ≥ 60 mL/min/1,73 m^2	71.9
• 30–59 mL/min/1,73 m^2	24.4
• 15–29 mL/min/1,73 m^2	2.8
• < 15 mL/min/1,73 m^2	0.9
STEMI, %	72.8

eGFR, estimated glomerular filtration rate;
STEMI, ST-segment elevation myocardial infarction;

Figure 1. Distribution of all patients with MI according to the risk of bleeding (ARC-HBR)



chosen. Figure 2 shows the frequency of the administration of all anticoagulants and their combinations approved for STEMI. Bivalirudin was not administered in any patients.

The analysis of the frequency of the prescription of parenteral anticoagulants in different treatment strategy groups according to international non-proprietary names (INN) considered the prescription of a drug as a monotherapy and in combination with other drug: UFH was also the most frequently prescribed drug irrespective of the treatment strategy (Figure 3). Fondaparinux was prescribed to only 3% of patients from the STEMI conservative treatment group.

Figure 4 shows the frequency of the administration of parenteral anticoagulants in different treatment strategy groups, where 100% is all parenteral anticoagulants in a specific treatment strategy.

At the prehospital stage, UFH was administered more frequently as anticoagulant support for TLT (84%), and low-molecular-weight heparin (LMWH) was used in 16% of patients. Despite the fact that LMWH was administered more frequently during hospital treatment than at the prehospital stage, UFH remained the most commonly used anticoagulant (64.4%), enoxaparin was prescribed in 23.9% of cases (Figure 5).

Parenteral anticoagulant therapy for NSTEMI

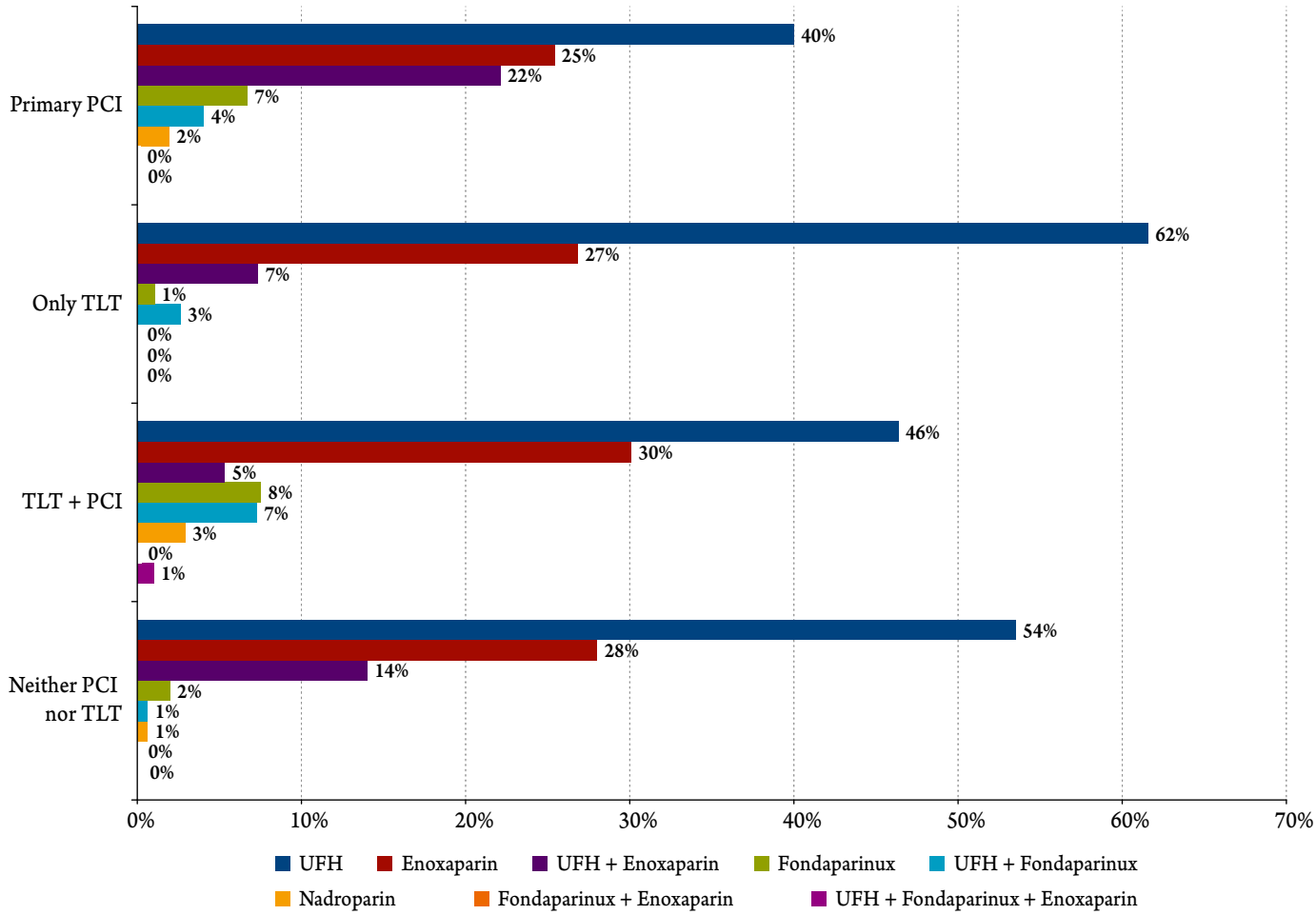
The use of parenteral anticoagulant therapy for patients with NSTEMI was nearly the same in the conservative and invasive treatment groups: UFH was the most frequently used anticoagulant (43% and 43%, respectively), followed by enoxaparin (36% and 34%, respectively), a combination of UFH and enoxaparin (10% and 16%, respectively), fondaparinux (7% and 6%, respectively), and a combination of UFH and fondaparinux (3% and 1%, respectively; Figure 6). Bivalirudin was not administered in any patients. Figure 7 shows the frequency of the prescription of each anticoagulant, where 100% is all patients in a specific treatment strategy group. Figure 8 shows the frequency of the administration of each anticoagulant, where 100% is all anticoagulant drugs prescribed in a specific treatment strategy group.

Parenteral anticoagulant therapy depending on the risk of bleeding

Parenteral anticoagulant therapy for STEMI (Figure 9) and NSTEMI (Figure 10, Figure 11) did not significantly differ in patients at high and low risk of bleeding (ARC-HBR).

Parenteral anticoagulant therapy depending on treatment facility: primary vascular department (PVD) and regional vascular center (RVC)

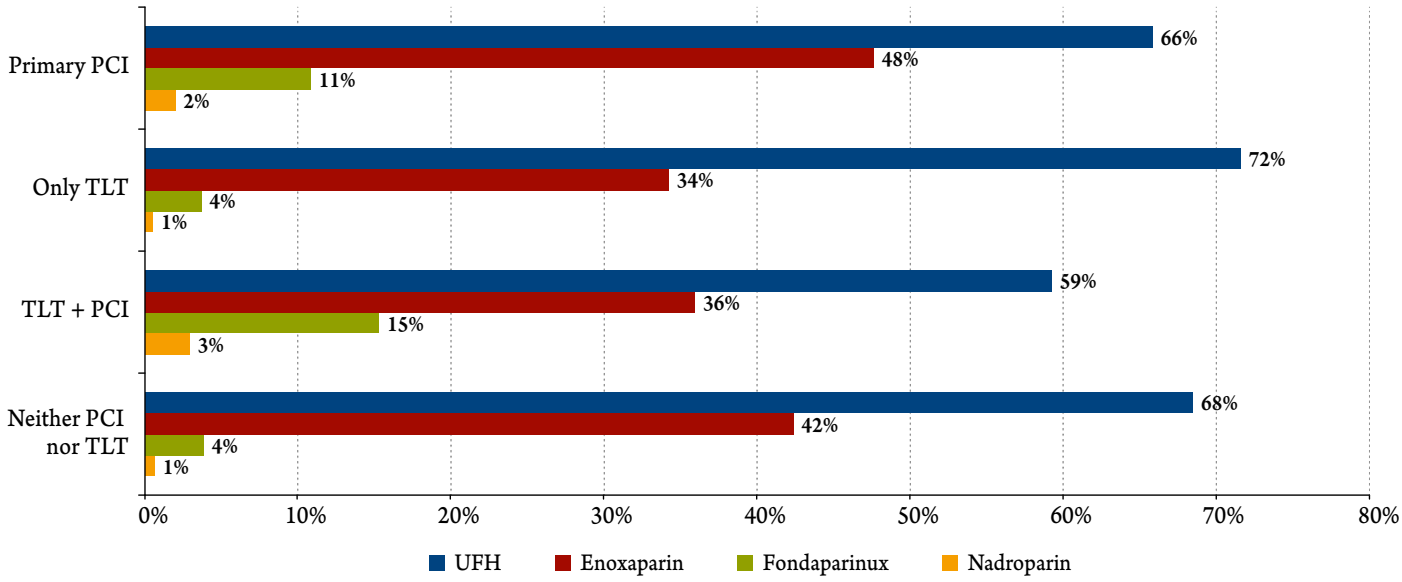
Figure 2. Distribution of patients with STEMI according to the administered anticoagulation regimens in different management groups



Hereafter in figures:

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

Figure 3. Frequency of the prescription of anticoagulant drugs according to INNs in patients with STEMI in different management groups (primary PCI, TLT without PCI, TLT followed by PCI, conservative treatment)



Several drugs could be administered at the same time to one patient, which is why a total of prescriptions in a group can be more than 100%.

ISSN 0022-9040. Kardiologiia. 2022;62(10). DOI: 10.18087/cardio.2022.10.n2238

Figure 4. Frequency of the prescription of anticoagulant drugs in each group of patients with STEMI (group total of100 %)

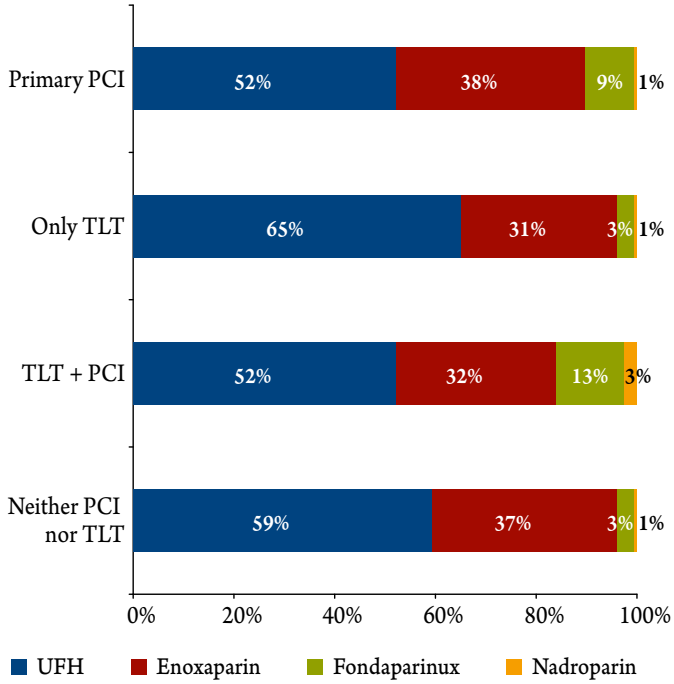
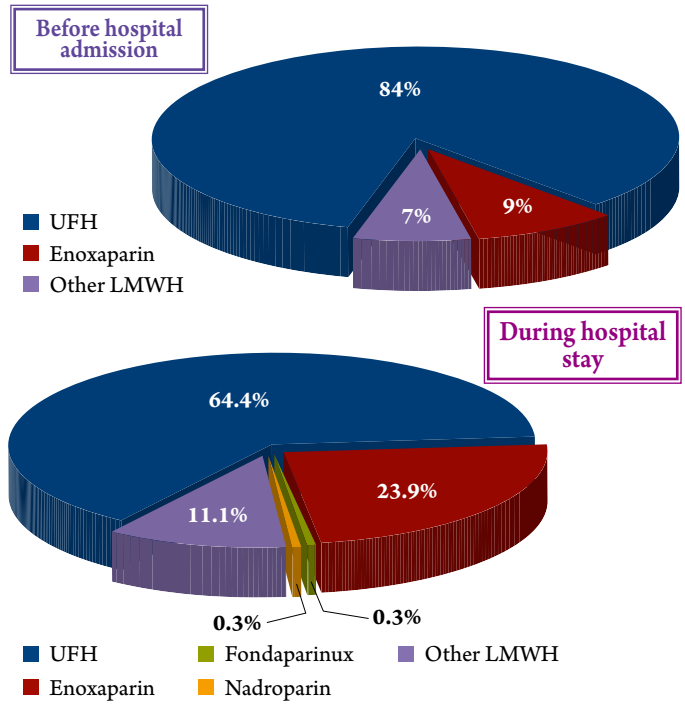


Figure 5. Frequency of the prescription of various anticoagulants in TLT before hospitalization and during hospital stay

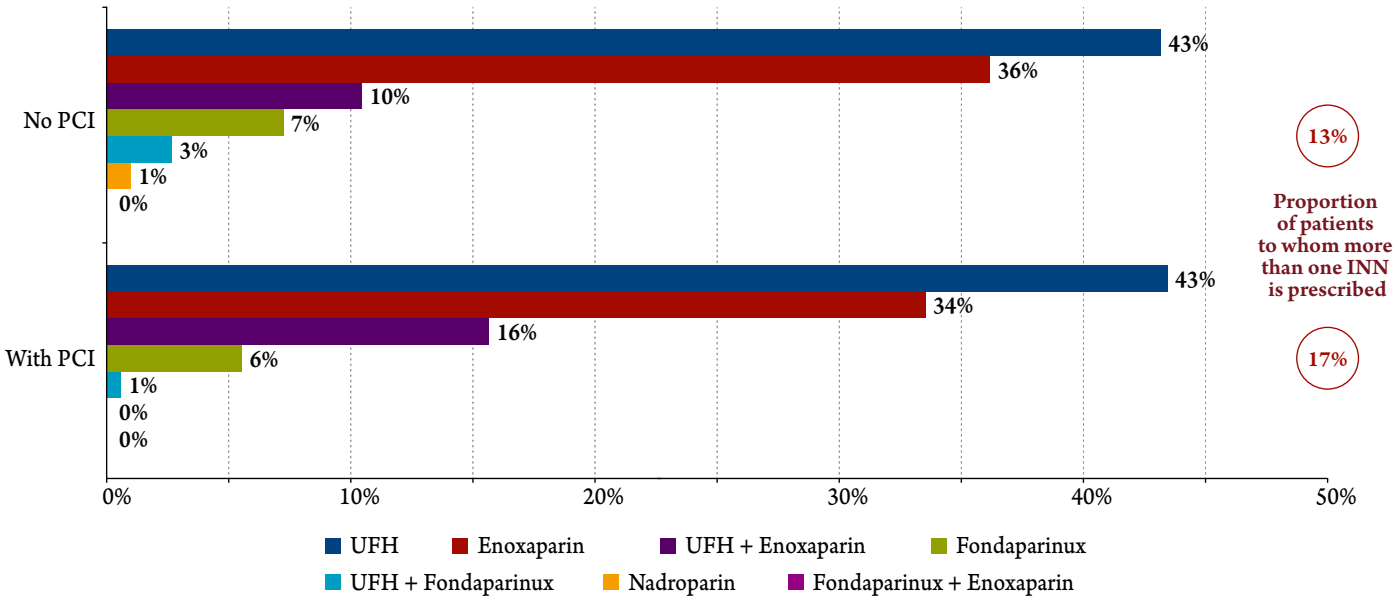


Hereafter in figures:

STEMI, ST-segment elevation myocardial infarction.

LMWH, low-molecular-weight heparin.

Figure 6. Distribution of patients with NSTEMI according to the prescribed anticoagulant regimens (group total of 100 %) in the conservative and invasive (PCI) treatment groups



Hereafter in figures:

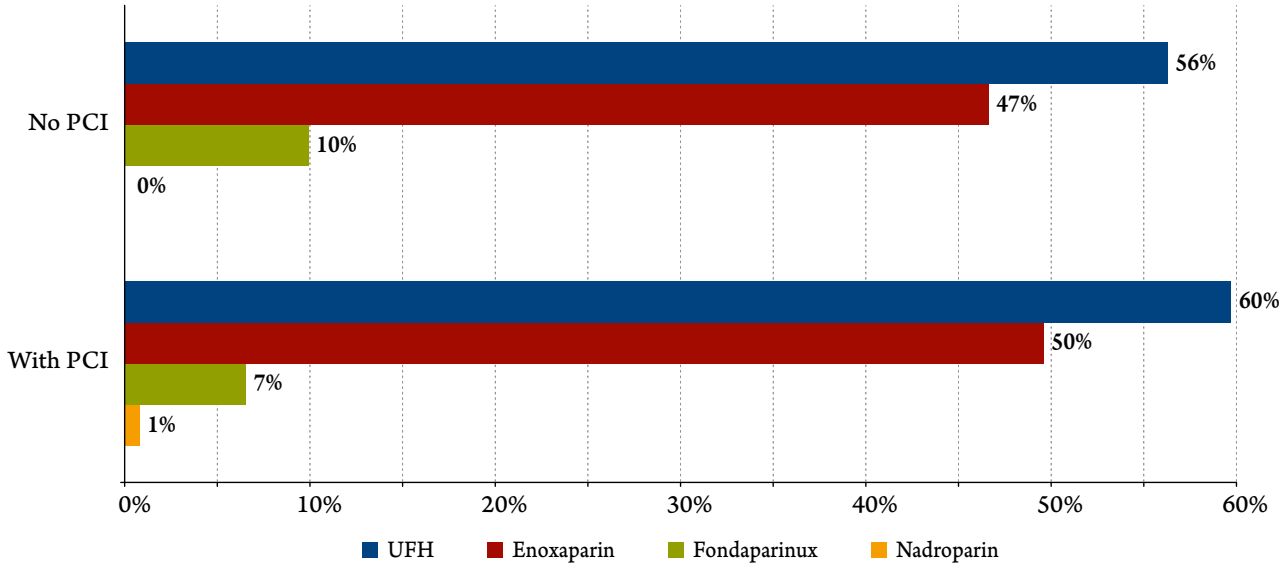
NSTEMI, non-ST-segment elevation myocardial infarction.

UFH, enoxaparin, and fondaparinux were prescribed to 70.5%, 25.3%, and 2.8% of patients in PVDs, respectively. The analysis of the prescriptions in RVCs showed that there was a tendency to prescribe combinations of anticoagulants: UFH (37.1%), enoxaparin (29.6%), UFH in combination with enoxaparin (20.2%), fondaparinux (6.8%), UFH in combination with fondaparinux (4.2%), nadroparin (1.9%) (Figure 12).

Peculiarities of administering fondaparinux

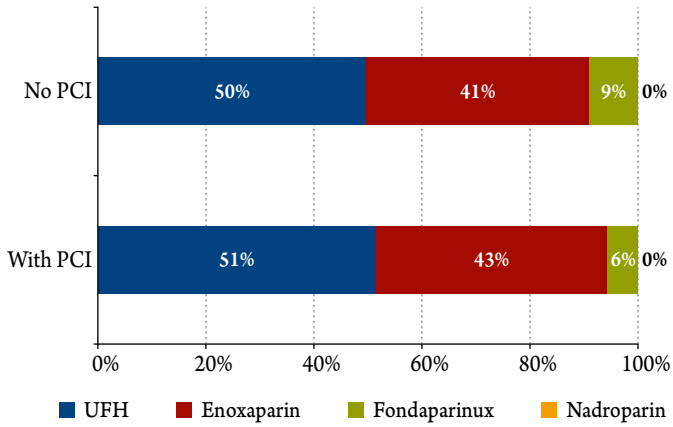
Fondaparinux was prescribed more frequently to patients without CHF (87.2% versus 12.8% of patients

Figure 7. Frequency of prescriptions of anticoagulants by Inn in patients with NSTEMI in the conservative and invasive treatment strategies groups



Several drugs could be administered at the same time to one patient, which is why a total of prescriptions in a group can be more than 100%.

Figure 8. Frequency of the prescription of anticoagulant drugs in each group of patients with NSTEMI (group total of 100 %)



with CHF), without a history of MI (82.2% versus 17.8% of patients with a history of MI), younger than 75 years (84.2% versus 15.8% ≥75 years old), at a lower risk of bleeding according to ARC-HBR (75.9% versus 24.1% of patients at high risk of bleeding).

Route of UFH administration

Subcutaneous UFH was administered in 19.3% of patients with MI, which contradicts clinical guidelines. The frequency of suboptimal use of UFH was 25.2% in patients with NSTEMI and 17.5% in STEMI (Figure 13).

Discussion

According to the current clinical guidelines of the European Society of Cardiology (ESC) and the Russian Society of Cardiology (RSC) for the management of STEMI and STEMI, all patients should receive parenteral anticoagulant therapy in addition to antiplatelet therapy from the moment of diagnosis of MI. Anticoagulant therapy should be discontinued after PCI (if procedure is successful and there are no other indications), and if PCI is not performed, it should be continued until discharge from the hospital or day 8 of hospital treatment if a patient is not discharged earlier [4–7].

Parenteral anticoagulant therapy is chosen primarily based on the MI treatment strategy. For example, the key factors influencing the choice of parenteral anticoagulant drug are the fact of performing reperfusion therapy and its method.

According to foreign and Russian data, the frequency of reperfusion therapy is high in STEMI, and primary PCI is the most common and preferred method of myocardial reperfusion. In the REGION-MI registry, the frequency of reperfusion therapy is comparable to the European data: 89% of patients with STEMI underwent myocardial reperfusion: 64% of patients were subjected to primary PCI, 8% underwent TLT followed by PCI, and 7% received TLT.

Invasive treatment was implemented in the majority of patients with NSTEMI. PCI was performed in 63% of patients with NSTEMI included in the REGION-MI registry.

Parenteral anticoagulant therapy in invasive treatment of patients with MI

Parenteral anticoagulant therapy is recommended for all patients with ACS undergoing PCI. UFH, enoxaparin, and bivalirudin can be used as anticoagulant support for

ISSN 0022-9040. Kardiologiia. 2022;62(10). DOI: 10.18087/cardio.2022.10.n2238

Figure 9. Frequency of the prescription of various parenteral anticoagulant drugs for STEMI in high risk and low risk of bleeding (ARC-HBR)

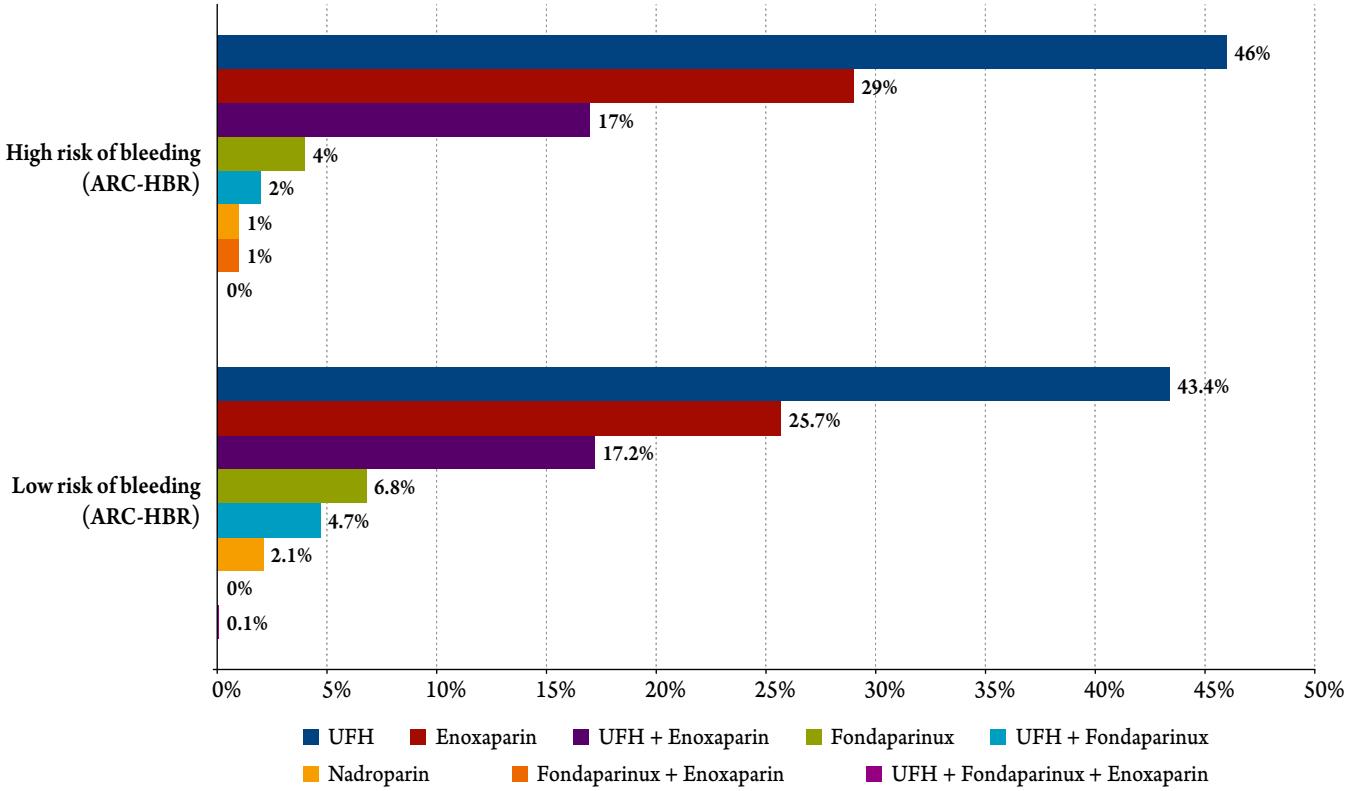
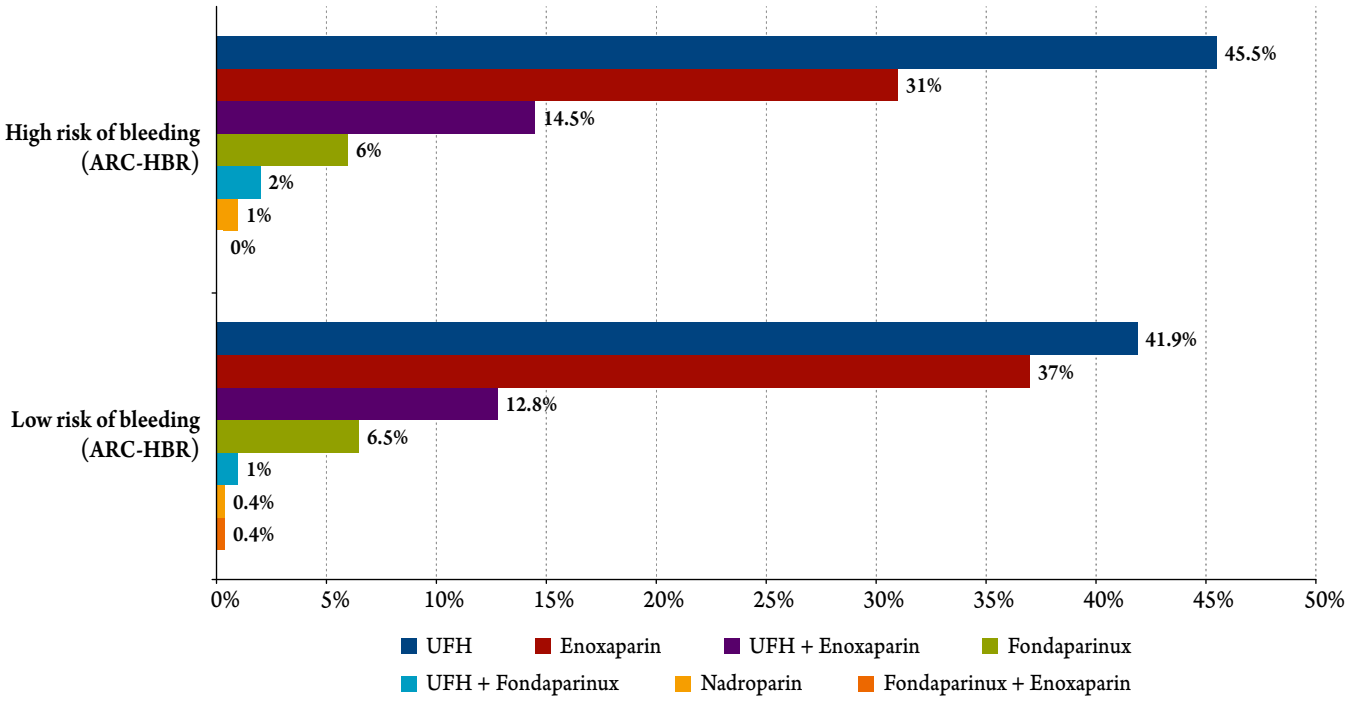
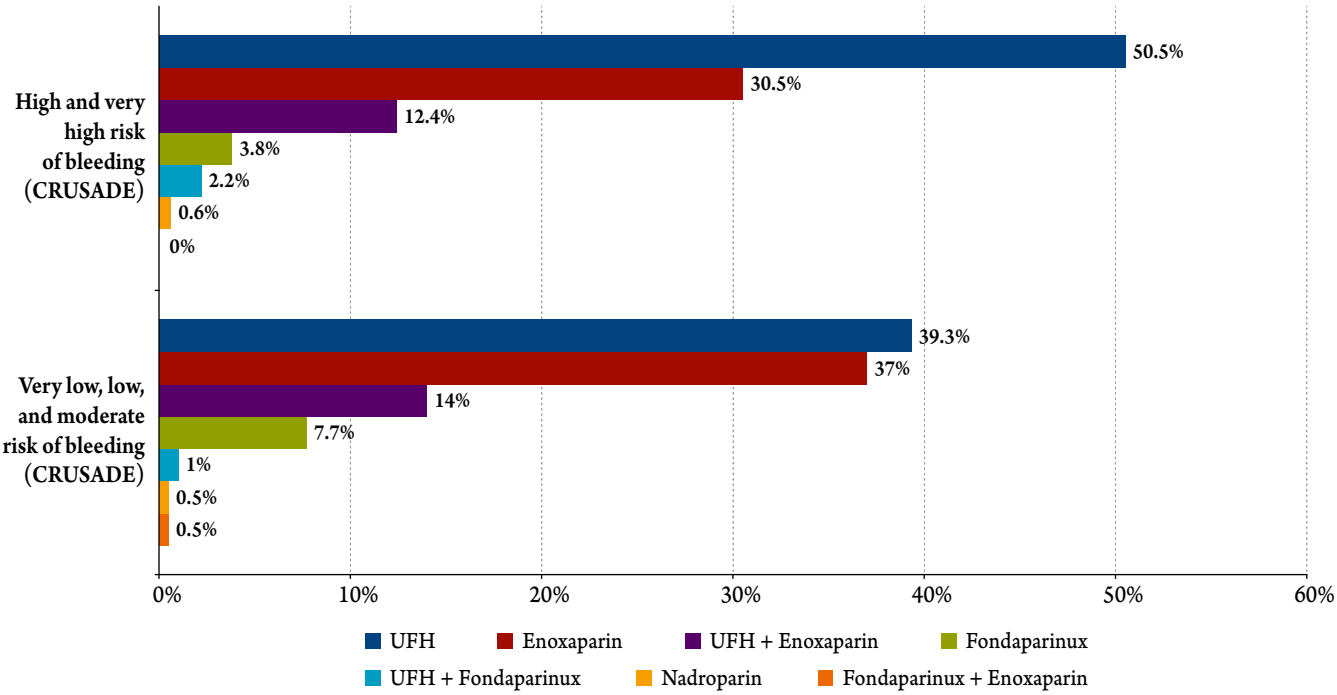


Figure 10. Frequency of the administration of various parenteral anticoagulant drugs for STEMI depending on the risk of bleeding (ARC-HBR)



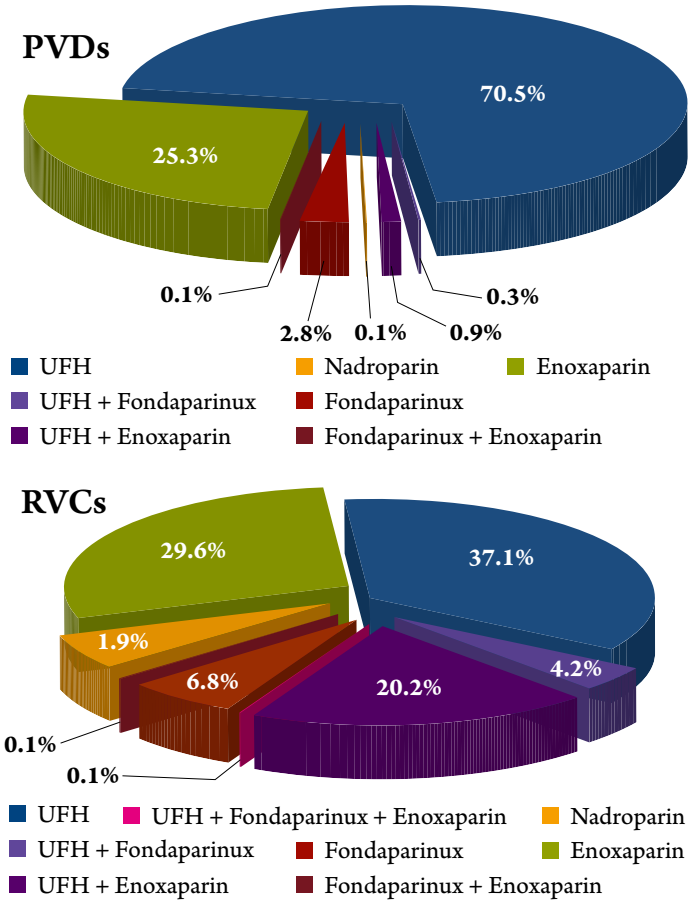
PCI [4–7]. Intravenous bolus administration of UFH is traditionally used as anticoagulant support for PCI in most cases in real-world clinical practice. However, LMWH enoxaparin has some benefits over UFH: a predictable and safe anticoagulant effect without the need for monitoring, a lower risk of developing heparin-induced thrombocytopenia (HIT), and lower mortality rates and a lower risk of bleeding in primary PCI compared

Figure 11. Frequency of the prescription of various parenteral anticoagulant drugs and their combinations in patients with NSTEMI at a high and non-high risk of bleeding (CRUSADE)



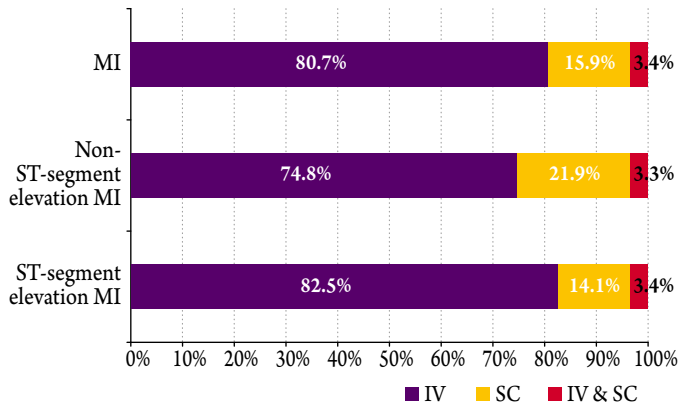
For the sake of clarity, patients are divided into two groups: group 1 includes patients with a high and very high risk of bleeding (CRUSADE), group 2 includes patients with a very low, low, and moderate risk of bleeding (CRUSADE).

Figure 12. Frequency of the prescription of various parenteral anticoagulant drugs in PVDs and RVCs



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

Figure 13. Frequency of various mode of UFH administration: intravenous (iv), subcutaneous (sc), iv + sc in patients with MI, NSTEMI, STEMI



to UFH [8]. Randomized controlled study ATOLL, which included 910 patients with STEMI subjected to primary PCI and compared the effect of intravenous bolus administration of enoxaparin 0.5 mg/kg with UFH, showed the benefits of enoxaparin in terms of overall clinical benefit (ischemic complications + bleeding) [9]. Thus, enoxaparin is a good alternative to UFH in patients with STEMI undergoing primary PCI [4, 6].

The administration of bivalirudin in primary PCI in patients with STEMI, compared with UFH, is associated with comparable mortality rates and higher incidence of recurrent MI (due to more frequent acute stent thrombosis) in the early post-reperfusion

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phase. It should be noted that the lower risk of bleeding reported in earlier studies is questioned now, because bivalirudin was compared with a combination of UFH and glycoprotein IIb/IIIa inhibitors [10, 11]. According to large observational study VALIDATE-SWEDEHEART (6,006 patients with STEMI and STEMI) based on the Swedish registry with the same name, bivalirudin did not show the benefits compared to UFH in preventing major bleeding [12]. In the current clinical guidelines for the management of ACS, both Russian and ESC, the class of recommendation decreased from I to IIa for bivalirudin in primary PCI for patients with STEMI to IIb in PCI for patients with NSTEMI. As shown by the recently published subanalysis of the VALIDATE-SWEDEHEART study, bivalirudin monotherapy had no benefits over UFH monotherapy in the group of elderly patients (≥75 years) [13]. Thus, the use of bivalirudin is only reasonable in patients with a history of HIT. Bivalirudin was not prescribed to any patient in the REGION-MI registry, which clearly indicates its low availability and low interest in its availability.

The use of selective factor Xa inhibitor fondaparinux compared with enoxaparin during PCI, in patients with NSTEMI according to randomized clinical trial (RCT) OASIS-5 and patients with STEMI according to OASIS-6, is associated with more frequent thrombosis of angiographic catheters (1.2% and 0.3%, respectively) [14, 15], thus, it is currently not recommended as the only anticoagulant support for PCI in patients with MI [4–7]. However, it should be noted that the frequency of catheter thrombosis can be significantly reduced without increasing the frequency of major bleeding by additional bolus administration of UFH at the standard PCI dose [16].

UFH is the absolute leader among parenteral anticoagulants in the clinical practice in terms of the frequency of the administration in patients with MI during PCI. The Portuguese Registry on Interventional Cardiology (PRIC), which includes data from 2,697 patients with STEMI (2016), UFH was used in 78% of patients to support primary PCI, and only 2% received LMWH (there were no data on the use of anticoagulants in the remaining 20% of patients) [17]. In the REGION-MI registry, patients who underwent primary PCI received UFH (40%), enoxaparin (25%), UFH in combination with enoxaparin (22%), fondaparinux (7%), and UFH in combination with fondaparinux (4%). During hospital treatment, patients with NSTEMI who underwent PCI received UFH (43%), enoxaparin (34%), UFH in combination with enoxaparin (16%), fondaparinux (6%), and UFH in combination with fondaparinux (1%). Interestingly, no patients received bivalirudin in the PRIC and REGION-MI registries. Some patients who underwent PCI received fondaparinux monotherapy (7% of patients with STEMI and 6% of patients with NSTEMI). This fact can be explained by inaccurate documentation (most of these patients obviously received additional bolus injection of UFH during PCI).

Special attention should be given to a switch from one anticoagulant to another. Switching from UFH to enoxaparin and from enoxaparin to UFH is not recommended due to significantly higher risk of bleeding. If a patient with NSTE-ACS received enoxaparin before PCI, it should be continued during the procedure to exclude the change of an anticoagulant drug during the intervention. In the REGION-MI registry, UFH and enoxaparin were administered in combination in 10% of patients in the NSTEMI conservative treatment group and 16% of patients in the NSTEMI invasive treatment group, which contradicts the current guidelines. This is most probably because of the frequent prehospital administration of UFH followed by the prescription of LMWH during hospital treatment.

Parenteral anticoagulant therapy in thrombolytic therapy of patients with STEMI

Enoxaparin (class IA) is recommended as the first-choice anticoagulant for patients with STEMI who received TLT [4]. These guidelines are based on the results of the ExTRACT–TIMI 25 study that included 20,479 patients with STEMI. The use of enoxaparin at a dose calculated based on body weight and adjusted for age and creatinine clearance demonstrated benefits over standard 48 hour infusion of UFH in reducing the risk of death and non-fatal MI by 17% in the next 30 days (9.9% and 12%, respectively; $p<0.0001$) whatever thrombolytic drug is used [18].

The superiority of fondaparinux over UFH in patients who underwent thrombolysis (streptokinase was used 73% of cases) was shown in the OASIS-6 RCT: the incidence of death and recurrent MI was 10.9% and 13.6%, respectively (OR 0.79; 95% CI 0.68–0.92; $p = 0.003$) [15]. It turned out that fondaparinux has benefits mainly in patients who received streptokinase. The results of that study were implemented in the ECS clinical guidelines, according to which intravenous bolus injection of fondaparinux followed by subcutaneous administration every 24 hours can be considered in TLT with exactly streptokinase (class of recommendations IIa, level of evidence B) [4]. The position regarding the administration of fondaparinux in TLT is universal in the American Heart Association (AHA) clinical guidelines

for the management of patients with STE-ACS: its use is allowed with any (including fibrin-specific) thrombolytic drug [19]. The 2020 RSC guidelines for the management of patients with STEMI recommend fondaparinux for patients who received TLT to reduce the overall risk of death or recurrent MI whatever thrombolytic drug is used (recommendation class IIa, level of evidence B). It is specifically emphasized that "…in patients who received other thrombolytics, including fibrin-specific drugs, it was at least as beneficial as UFH. It should not be kept in mind that fondaparinux sodium is a treatment of choice in mild to moderate thrombocytopenia or at the risk of heparin-induced thrombocytopenia."

According to a multicenter prospective study based on Spanish registry RESPIRE, which included 417 patients who underwent life-saving PCI (after TLT failure) in 2012–2013, 22.3% of patients did not receive additional therapy, UFH was administered in 36.6% of patients, abciximab 15.5%, abciximab in combination with UFH 10.5%, bivalirudin 5.7%, and enoxaparin 4.3% [20].

According to the REGION-MI registry, UFH was most commonly prescribed before hospitalization as adjuvant anticoagulant therapy with TLT (84%), enoxaparin was prescribed to 9% of patients, and 7% of patients received other LMWH. LMWH was prescribed more often during hospital treatment (35.3%) than at the prehospital stage, but less often than UFH (64.4%). Noteworthy, fondaparinux was prescribed to patients who received TLT relatively rarely (4%), which is likely to be due to a lack of awareness of the possibility of administering fondaparinux in patients of this category and its absence in the list of rescue medication.

Parenteral anticoagulant therapy in conservative treatment strategy for patients with STEMI

Fondaparinux is the anticoagulant drug of choice in conservative treatment strategy for patients with STEMI and NSTEMI due to the best safety and efficacy profile [5–7].

The benefits of fondaparinux in patients with STEMI without reperfusion therapy over UFH and placebo was proved in the OASIS-6 RCT: the incidence of death and recurrent MI was 12.2% in the fondaparinux group and 15.1% in the control group by day 30 (OR 0.80; 95% CI 0.65–0.98; p=0.003) [15]. Despite the available evidence and the high class of recommendations of the ECS and RSC for fondaparinux in the conservative treatment of patients with STEMI, only 3% of patients without myocardial reperfusion received fondaparinux as anticoagulant therapy according to the REGION-MI registry. The most frequently prescribed drugs were UFH (54%), enoxaparin (28%), and their combination (14%).

Parenteral anticoagulant therapy for patients with NSTEMI

OASIS-5 is a key RCT that directly compared fondaparinux and enoxaparin in patients with NSTEMI and demonstrated lower 30-day mortality in the fondaparinux group with similar clinical efficacy compared to enoxaparin. The reduction in mortality was achieved in the fondaparinux group in the long-term, after 30 days of follow-up, by reducing mortality due to bleeding [14].

The results of several observational studies also indicate that fondaparinux was preferred over LMWH in NSTE-ACS, primarily due to a lower risk of hemorrhagic complications. A retrospective multicenter observational study based on the Brazilian ACS registry, which included 2,282 patients, also support the benefits of fondaparinux over enoxaparin, such as a significant decrease in the composite endpoint of cardiogenic shock, recurrent MI, death, stroke, and bleeding (13.8% and 22%, respectively; OR 2.93; p=0.007) and bleeding (2.3% and 5.2%, respectively; OR 4.55; p=0.037) [21]. According to one of the largest multicenter observational studies based on the Swedish SWEDEHEART registry (2006–2010), which included 40,616 patients with NSTEMI (median age 73 years,37% of female patients), fondaparinux was associated during hospital treatment with a lower risk of major bleeding (1.1% and 1.8%, respectively; OR 0.54; 95% CI 0.42–0.70) and death (2.7% and 4.0%, respectively; OR 0.75; 95% CI 0.63–0.89), and the benefits persisted for the following 180 days [22]. However, despite clear benefits, fondaparinux was prescribed less frequently than LMWH (36.4% and 63.6%, respectively) [22]. The results of the analysis of another prospective multicenter registry ARIAM-Andalucia (2015–2017), in which 2,094 patients with NSTEMI (median age 64 years, 27.7% of female patients) admitted in cardiac intensive care units, also show that fondaparinux is used less frequently than enoxaparin (18% and 82%, respectively), but the frequency of the administration of fondaparinux increased during the study period (trend p<0.0001) [23]. The frequency of the prescription of fondaparinux in NSTEMI is relatively lower in the Russian Federation than in Europe and the United States. In a series of independent Russian registries RECORD (2007–2008), RECORD-2 (2009–2011), and RECORD-3 (2015), the frequency of the administration of fondaparinux in patients with NSTE-ACS was 0.5%, 8.1%, and 11.6%, respectively [24]. According to the REGION-MI registry, the unreasonably rare use of fondaparinux, the efficacy and higher safety of which was shown in patients with NSTEMI, has remained almost unchanged in the Russian

ISSN 0022-9040. Kardiologiia. 2022;62(10). DOI: 10.18087/cardio.2022.10.n2238

clinical practice in the past 15 years: fondaparinux was prescribed in only 7% of patients with NSTEMI who received conservative treatment. This situation can be explained by a certain conservatism and the lack of awareness of physicians about the availability of an alternative to enoxaparin and UFH. It should be noted that some studies showed benefits of fondaparinux over enoxaparin, including in terms of cost-effectiveness [25–28]. In 2015, AHA a document regulating drug therapy of ACS in patients with chronic kidney disease (CKD), according to which fondaparinux is a drug of choice in patients with CKD stage III (creatinine clearance 30–60 mL/min) [29]. At the same time, in the REGION-MI registry, fondaparinux (monotherapy) was mainly prescribed to patients without CKD: the percentage of patients with CKD (eGFR <60 mL/min/1.73 m^2) was 18.2% of all fondaparinux cases.

The Russian REGION-MI registry demonstrate a paradox of administering fondaparinux in patients without positive history and at a low risk of bleeding: fondaparinux was more often prescribed to patients without CHF, without a history of MI, younger than 75 years, and at a low risk of bleeding (ARC-HBR). A similar trend was also observed in the Swedish SWEDEHEART registry: patients who received fondaparinux were on average 2 years younger, less likely to have CHF (14.5% and 18.7%, respectively) and a history of MI (28.2% and 32.2%, respectively) than patients who received enoxaparin, [22]. According to our data, patients at a high risk of bleeding (ARC-HBR, CRUSADE) did not generally receive safer anticoagulant therapy.

Another important deviation from the guidelines in the Russian clinical practice, which was detected during the analysis of the REGION-MI registry, was ineligible route of administration of UFH: 19.3% of patients with MI received UFH as subcutaneous injections, the frequency of subcutaneous administration of UFH among patients with NSTEMI and STEMI was 25.2% and 17.5%, respectively. Given the proven clinical efficacy of UFH in patients with ACS only in the form of continuous infusion with the monitoring of activated partial thromboplastin time [30, 31], approximately a quarter of patients received ineffective treatment (subcutaneous administration) that did not comply with the clinical guidelines. It's not a new problem, the results are similar to the previously published data of Russian registries RECORD-2 and RECORD-3: Subcutaneous UFH was administered in 31.5% of patients with NSTE-ACS [24].

Conclusion

According to the Russian Registry of Acute Myocardial Infarction REGION-MI, parenteral anticoagulant drugs are not prescribed in full compliance with the clinical guidelines in all treatment strategies for patients with myocardial infarction. Despite the available clinical guidelines, irrespective of the type of myocardial infarction, treatment strategy and patient's clinical characteristics, unfractionated heparin was the most commonly used parenteral anticoagulant, which is especially true for the primary vascular departments. Despite the high efficacy and safety of fondaparinux shown in a number of studies, the frequency of its prescription remains unreasonably low in the Russian Federation as well as in other countries. The same can be said about the administration of enoxaparin in patients who received thrombolytic therapy. Attention should be paid to the awareness of physicians about the latest clinical guidelines and the benefits of fondaparinux and enoxaparin in the relevant treatment strategies. It seems reasonable to minimize the prescription of parenteral anticoagulant therapy before hospitalization and limit it to accompanying thrombolytic therapy in order to avoid switches between anticoagulant drugs ordered by ambulance team and physicians during hospital treatment, which potentially increases risk of bleeding. The continuity between all levels of medical care is important in terms of prescribing parenteral anticoagulant therapy for myocardial infarction to achieve the best-possible treatment efficacy and safety.

Limitations

Only hospitals included in the "MI Network" participate in the registry, which excludes the analysis of cases of acute myocardial infarction in non-specialized hospitals; not all regions of the Russian Federation currently participate in the registry. It is not possible to include all patients with myocardial infarction hospitalized like in most such registries; there is a certain system for selection.

Acknowledgements

We thank Aston Consulting for technical organization and management of the REGION-MI registry and, particularly, Natalia Yurievna Dmitrieva for the statistical and analytical data processing. The authors thank Amgen, AstraZeneca, Boehringer Ingelheim, Novartis, Aspen, Sanofi, Abbott, Akrikhin, Evroservice, and P-PHARM for their support of the REGION-MI registry.

No conflict of interest is reported.

The article was received on 30/06/2022

REFERENCES

1. Mandelzweig L, Battler A, Boyko V, Bueno H, Danchin N, Filippatos G et al. The second Euro Heart Survey on acute coronary syndromes: characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. European Heart Journal. 2006;27(19):2285–93. DOI: 10.1093/eurheartj/ehl196
2. Puymirat E, Battler A, Birkhead J, Bueno H, Clemmensen P, Cottin Y et al. Euro Heart Survey 2009 Snapshot: regional variations in presentation and management of patients with AMI in 47 countries. European Heart Journal: Acute Cardiovascular Care. 2013;2(4):359–70. DOI: 10.1177/2048872613497341
3. Boytsov S.A., Shakhnovich R.M., Erlikh A.D., Tereschenko S.N., Kukava N.G., Rytova Yu.K. et al. Registry of Acute Myocardial Infarction. REGION-MI – Russian Registry of Acute Myocardial Infarction. Kardiologiia. 2021;61(6):41–51. [Russian: Бойцов С.А., Шахнович Р.М., Эрлих А.Д., Терещенко С.Н., Кукава Н.Г., Рытова Ю.К. и др. Регистр острого инфаркта миокарда. РЕГИОН–ИМ – Российский рЕГИстр Острого иНфаркта миокарда. Кардиология. 2021;61(6):41-51]. DOI: 10.18087/cardio.2021.6.n1595
4. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal. 2018;39(2):119–77. DOI: 10.1093/eurheartj/ehx393
5. Collet J-P, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. European Heart Journal. 2021;42(14):1289–367. DOI: 10.1093/eurheartj/ehaa575
6. Averkov O.V., Duplyakov D.V., Gilyarov M.Yu., Novikova N.A., Shakhnovich R.M., Yakovlev A.N. et al. 2020 Clinical practice guidelines for Acute ST-segment elevation myocardial infarction. Russian Journal of Cardiology. 2020;25(11):251–310. [Russian: Аверков О.В., Дупляков Д.В., Гиляров М.Ю., Новикова Н.А., Шахнович Р.М., Яковлев А.Н. и др. Острый инфаркт миокарда с подъемом сегмента ST электрокардиограммы. Клинические рекомендации 2020. Российский кардиологический журнал. 2020;25(11):251-310]. DOI: 10.15829/29/1560-4071-2020-4103
7. Barbarash O.L., Duplyakov D.V., Zateischikov D.A., Panchenko E.P., Shakhnovich R.M., Yavelov I.S. et al. 2020 Clinical practice guidelines for Acute coronary syndrome without ST segment elevation. Russian Journal of Cardiology. 2021;26(4):149–202. [Russian: Барбараш О.Л., Дупляков Д.В., Затейщиков Д.А., Панченко Е.П., Шахнович Р.М., Явелов И.С. и др. Острый коронарный синдром без подъема сегмента ST электрокардиограммы. Клинические рекомендации 2020. Российский кардиологический журнал. 2021;26(4):149-202]. DOI: 10.15829/1560-4071-2021-4449
8. Silvain J, Beygui F, Barthelemy O, Pollack C, Cohen M, Zeymer U et al. Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. BMJ. 2012;344:e553. DOI: 10.1136/bmj.e553
9. Montalescot G, Zeymer U, Silvain J, Boulanger B, Cohen M, Goldstein P et al. Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: the international randomised open-label ATOLL trial. The Lancet. 2011;378(9792):693–703. DOI: 10.1016/S0140-6736(11)60876-3
10. Cassese S, Byrne RA, Laugwitz K-L, Schunkert H, Berger PB, Kastrati A. Bivalirudin versus heparin in patients treated with percutaneous coronary intervention: a meta-analysis of randomised trials. EuroIntervention. 2015;11(2):196–203. DOI: 10.4244/EIJY14M08_01
11. Capodanno D, Gargiulo G, Capranzano P, Mehran R, Tamburino C, Stone GW. Bivalirudin versus heparin with or without glycoprotein IIb/IIIa inhibitors in patients with STEMI undergoing primary PCI: An updated meta-analysis of 10,350 patients from five randomized clinical trials. European Heart Journal: Acute Cardiovascular Care. 2016;5(3):253–62. DOI: 10.1177/2048872615572599
12. Erlinge D, Koul S, Eriksson P, Scherstén F, Omerovic E, Linder R et al. Bivalirudin versus heparin in non-ST and ST-segment elevation myocardial infarction – a registry-based randomized clinical trial in the SWEDEHEART registry (the VALIDATE-SWEDEHEART trial). American Heart Journal. 2016;175:36–46. DOI: 10.1016/j.ahj.2016.02.007
13. Wester A, Attar R, Mohammad MA, Isma N, James S, Omerovic E et al. Bivalirudin Versus Heparin Monotherapy in Elderly Patients With Myocardial Infarction: A Prespecified Subgroup Analysis of the VALIDATE-SWEDEHEART Trial. Circulation: Cardiovascular Interventions. 2020;13(4):e008671. DOI: 10.1161/CIRCINTERVENTIONS.119.008671
14. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB et al. Comparison of Fondaparinux and Enoxaparin in Acute Coronary Syndromes. New England Journal of Medicine. 2006;354(14):1464–76. DOI: 10.1056/NEJMoa055443
15. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB et al. Effects of Fondaparinux on Mortality and Reinfarction in Patients With Acute ST-Segment Elevation Myocardial Infarction: The OASIS-6 Randomized Trial. JAMA: The Journal of the American Medical Association. 2006;295(13):1519–30. DOI: 10.1001/jama.295.13.joc60038
16. The FUTURA/OASIS-8 Trial Group, Steg PG, Jolly SS, Mehta SR, Afzal R, Xavier D et al. Low-Dose vs Standard-Dose Unfractionated Heparin for Percutaneous Coronary Intervention in Acute Coronary Syndromes Treated With Fondaparinux: The FUTURA/OASIS-8 Randomized Trial. JAMA: The Journal of the American Medical Association. 2010;304(12):1339–49. DOI: 10.1001/jama.2010.1320
17. Caldeira D, Pereira H, Marques A, Alegria S, Calisto J, Silva PC da et al. Adjuvant antithrombotic therapy in ST-elevation myocardial infarction: Contemporaneous Portuguese cross-sectional data. Revista Portuguesa de Cardiologia. 2019;38(11):809–14. DOI: 10.1016/j.repc.2019.02.015
18. Gabriel RS, White HD. ExTRACT-TIMI 25 trial: clarifying the role of enoxaparin in patients with ST-elevation myocardial infarction receiving fibrinolysis. Expert Review of Cardiovascular Therapy. 2007;5(5):851–7. DOI: 10.1586/14779072.5.5.851
19. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2013;61(4):e78–140. DOI: 10.1016/j.jacc.2012.11.019
20. De la Torre Hernández JM, Sadaba Sagredo M, Telleria Arrieta M, Gimeno de Carlos F, Sanchez Lacuesta E, Bullones Ramírez JA et al. Antithrombotic treatment during coronary angioplasty after failed thrombolysis: strategies and prognostic implications. Results of the RESPIRE registry. BMC Cardiovascular Disorders. 2017;17(1):212. DOI: 10.1186/s12872-017-0636-9
21. Soeiro A de M, Silva PGM de B e, Roque EA de C, Bossa AS, César MC, Simões SA et al. Fondaparinux versus Enoxaparin - Which is the Best Anticoagulant for Acute Coronary Syndrome? - Brazilian Registry Data. Arquivos Brasileiros de Cardiologia. 2016;107(3):239–44. DOI: 10.5935/abc.20160127
22. Szummer K, Oldgren J, Lindhagen L, Carrero JJ, Evans M, Spaak J et al. Association Between the Use of Fondaparinux vs Low-Molecular-Weight Heparin and Clinical Outcomes in Patients With Non–ST-Segment Elevation Myocardial Infarction. JAMA. 2015;313(7):707–16. DOI: 10.1001/jama.2015.517
23. Almendro-Delia M, Izquierdo-Bajo Á, Madrona-Jiménez L, Blanco-Ponce E, Seoane-García T, García-del Río M et al. Fondaparinux versus enoxaparin in the contemporary management of non-ST-elevation

ISSN 0022-9040. Kardiologiia. 2022;62(10). DOI: 10.18087/cardio.2022.10.n2238

acute coronary syndromes. Insights from a multicenter registry. International Journal of Cardiology. 2021;332:29–34. DOI: 10.1016/j.ijcard.2021.02.081
24. Erlikh A.D. Fondaparinux in acute coronary syndrome without ST segment elevation – justification for using and real clinical practice. Atherothrombosis. 2018;1:26–32. [Russian: Эрлих А.Д. Фондапаринукс при остром коронарном синдроме без подъемов сегмента ST – обоснование для использования и реальная клиническая практика. Атеротромбоз. 2018;1:26-32]. DOI: 10.21518/2307-1109-2018-1-26-32
25. Pepe C, Machado M, Olimpio A, Ramos R. Cost-effectiveness of fondaparinux in patients with acute coronary syndrome without ST-segment elevation. Arquivos Brasileiros de Cardiologia. 2012;99(1):613–22. DOI: 10.1590/S0066-782X2012005000060
26. Kossovsky M, Keller P, Mach F, Gaspoz J. Fondaparinux versus enoxaprin in the management of acute coronary syndromes in Switzerland: A cost comparison analysis. Swiss Medical Weekly. 2012;142:w13536. DOI: 10.4414/smw.2012.13536
27. Permsuwan U, Chaiyakunapruk N, Nathisuwan S, Sukonthasarn A. Cost-Effectiveness Analysis of Fondaparinux vs Enoxaparin in Non-ST Elevation Acute Coronary Syndrome in Thailand. Heart, Lung and Circulation. 2015;24(9):860–8. DOI: 10.1016/j.hlc.2015.02.018
28. Alfonso Ross Terres J, Lozano-Ortega G, Kendall R, Sculpher MJ. Cost-effectiveness of fondaparinux versus enoxaparin in non-ST-elevation acute coronary syndrome in Canada (OASIS-5). BMC Cardiovascular Disorders. 2015;15(1):180. DOI: 10.1186/s12872-015-0175-1
29. Washam JB, Herzog CA, Beitelshees AL, Cohen MG, Henry TD, Kapur NK et al. Pharmacotherapy in Chronic Kidney Disease Patients Presenting With Acute Coronary Syndrome: A Scientific Statement From the American Heart Association. Circulation. 2015;131(12):1123–49. DOI: 10.1161/CIR.0000000000000183
30. Telford AnneM, Wilson C. Trial of heparin versus atenolol in prevention of myocardial infarction in intermediate coronary syndrome. The Lancet. 1981;317(8232):1225–8. DOI: 10.1016/S0140-6736(81)92399-0
31. The RISC Group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. The Lancet. 1990;336(8719):827–30. DOI: 10.1016/0140-6736(90)92336-G