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# The state of platelet and plasma hemostasis as a predictor of coronary blood flow in patients with acute myocardial infarction

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| *Aim* | To study the relationship of the platelet function and plasma homeostasis with the blood flow in the infarct-related artery (IRA) and with the course of acute myocardial infarction (AMI). |
| *Material and methods* | This study included 93 patients with AMI (75 patients with ST-elevation AMI and 18 patients without ST segment elevation). 63 patients had TIMI 0–1 blood flow in the IRA and 30 patients had TIMI 2–3. Rotational thromboelastometry, impedance aggregometry, the endothelium-dependent vasodilation (EDVD) test, and the thrombodynamics test were performed for all patients. The primary clinical endpoint included the totality of in-hospital complications of AMI, and the secondary endpoint included the totality of out-of-hospital complications of AMI. Major bleedings (BARC 3–5) and minor bleedings (BARC 1–2) were evaluated separately. |
| *Results* | Patients with IRA TIMI 0–1 flow were characterized by a shorter blood clotting time (BCT), larger thrombus size and density, more intense platelet aggregation induced by arachidonic acid and ADP, and lower values of the EDVD test. It was found that the parameters of platelet aggregation induced by arachidonic acid (AUC Asa) in combination with BCT allowed assessment of the severity of IRA blood flow disorder (sensitivity 76%, specificity 71%) in patients with AMI, regardless of the presence of ST segment elevation on the ECG. In addition, the incidence of the primary endpoint was greater in patients with IRA TIMI 0–1 flow (41.3% and 16.7%, respectively; p=0.015). In patients with TIMI 2–3 flow in the long-term period of the disease, the incidence of minor bleedings was significantly higher (8.5% and 30.4%, respectively; p=0.045). |
| *Conclusion* | Compared to patients with preserved blood flow, patients with AMI and IRA TIMI 0–1 flow are characterized by endothelial dysfunction and more intense processes of thrombogenesis and platelet aggregation. It has been shown for the first time that the combination of two simple criteria for assessing hemostasis (AUC Asa; BCT) allows assessment of the degree of IRA blood flow disorder in patients with AMI. |

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In-hospital mortality in patients with acute myocardial infarction (AMI) remains within 6–9% despite the introduction of primary percutaneous coronary intervention (PCI) into routine clinical practice and a wide range of pharmacological drugs that significantly affect the course of the disease and the long-term prognosis [1, 2].

The resolution of ST-segment elevation is observed on repeated electrocardiograms (ECG) in 15–25% of acute ST-segment elevation MI (STEMI) patients, and blood flow is detected in the infarct-related artery (IRA) by coronary angiography (CAG) [3]. This phenomenon is associated with a lower incidence of hospital-acquired complications and more favorable long-term course of the disease [4, 5]. Moreover, some patients with acute non-ST-segment elevation MI (NSTEMI) have IRA occlusion, and the absence of ST-segment elevation is associated with a well-developed collateral network [6].

The severity of intracoronary thrombosis depends on platelet reactivity, activity of plasma hemostasis and endogenous fibrinolysis (EF), and the intensity of local inflammatory reaction. The endothelium actively participates in the regulation of these processes. The resulting blood flow in IRA is a product of the combination of these physiological processes.

## Objective

Investigate the relationship between the functional state of platelets and plasma hemostasis and the IRA blood flow, and the course of the disease in patients with AMI.

## Material and methods

This single-center prospective study included 93 patients. Patients were enrolled in of the Department of Cardiac Resuscitation of City Clinical Hospital n.a. I. V. Davydovsky from September 2019 to April 2022. At admission, 75 patients had STEMI upon admission and 18 patients had NSTEMI. AMI was established in accordance with the Fourth Universal Definition of Myocardial Infarction [7]. Every patient had CAG, then had his/her IRA revascularized. The study was conducted following the Declaration of Helsinki and was approval by the local ethics committee.

Inclusion criteria: STEMI or STEMI; onset of symptoms less than 24 hours before hospitalization; signed informed consent to participate in the study. Exclusion criteria: age above 80 years or below 18 years; onset of symptoms more than 24 hours before hospitalization; pre-hospital thrombolytic therapy; cardiogenic shock at admission; acute or chronic infectious processes; severe anemia or persistent bleeding; cancer; ongoing anticoagulant treatment.

Blood samples were collected from all patients before CAG for rotation thromboelastometry, impedance aggregometry, and thrombodynamics tests. Endothelium-dependent vasodilation (EDV) test was also performed.

IRA blood flow was classified using the TIMI flow grade scoring system [8]. CAG showed that 63 patients had of TIMI 0–1 blood flow in IRA, and 30 patients had TIMI 2–3 blood flow. Further comparisons were made between the two groups.

### *Blood collection method*

Blood samples for routine laboratory tests and tests were collected before CAG and the administration of unfractionated heparin by venipuncture with a Vacuette 21g needle. S-Monovette tubes (Sarstedt, Germany) with 3.2% sodium citrate 1:9 were used for the tests.

### *Rotation thromboelastometry*

The examination was carried out using a ROTEM device following a standard procedure [9]. The following parameters were analyzed: clotting time (CT), clot formation time (CFT), and lysis onset time (LOT), clot size at different time points of the test (A20, mm; A30, mm), maximum clot firmness (MCF) and maximum lysis (ML), and the percentage of remaining clot 30, 45 and 60 minutes after the onset of lysis (lysis index, Li 30, 45 and 60, respectively).

### *Impedance aggregometry*

The examination was performed using a Multiplate analyzer (Roche, Switzerland). Platelet aggregation was estimated by measuring the area under curve (AUC) and was expressed in aggregation units per minute. Platelet aggregation induced by arachidonic acid (AUC Asa), adenosine diphosphate (AUC ADP), and thrombin receptor activator peptide 6 (AUC TRAP-6) was evaluated.

### *Thrombodynamics*

The examination was carried out using a conventional technique [10]. The data obtained were used to calculate the following parameters: delay of the clot growth (Tlag), mean clot growth rate (V) and initial clot growth rate (Vi), clot size (CS) 30 minutes after the beginning of the test, clot density (D), spontaneous clotting time (Tsp); lysis onset time (LOT), lysis progression (LP, %/min), and clot lysis time (CLT).

### *EDV testing*

All patients underwent standard brachial EDV to assess endothelial function [11].

### *Assessment of clinical outcomes*

The following outcomes were assessed as hospital-acquired complications of AMI: death (including clinical); acute left ventricular failure (ALVF); stent thrombosis; major bleeding (BARC 3–5), and the need for platelet receptor blocker IIb/IIIa infusion, mechanical ventilation, mechanical support of blood circulation. The primary endpoint included all the above outcomes.

The following outcomes were evaluated in the long-term disease period (median follow-up of 7 months): death, cardiovascular death, recurrent AMI, late stent thrombosis, repeat emergency myocardial revascularization. These outcomes constituted the secondary endpoint. Major (BARC 3–5) and minor (BARC 1–2) bleeding was evaluated separately.

### *Statistical analysis*

Statistical analysis was performed using R v. 4.0.5 and IBM SPSS Statistics v. 26.0. The obtained values were distributed non-normally according to the Shapiro – Wilk test. The Mann-Whitney rank test was used to compare the groups. The two-tailed Fisher's exact test was used to analyze the categorical parameters. The sample size allowed detecting differences of the average strength (d=0.5) at the significance level of 0.05 and the power of 0.8. Logistic regression was used to predict IRA blood flow with the predictor significance level of $p<0.05$. The binary classification relationship was presented using a ROC curve and the AUC. The long-term disease prognosis was analyzed by plotting the Kaplan – Meier curves.


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## Results

### *Clinical and demographic characteristics of patients*

There were no significant differences in clinical and demographic characteristics between the two patient groups (Table 1).

### *Laboratory and clinical findings*

Patients with intact blood flow in IRA had higher left ventricular ejection fractions (LVEF) and lower levels of white blood cells (see Table 1).

**Table 1.** Clinical and demographic characteristics of patients

| Parameter | Patients with IRA blood flow TIMI 0–1 (n=63) | Patients with IRA blood flow TIMI 2–3 (n=30) | p |
|---|---|---|---|
| Age, years, Me [IQR] | 60.5 [53.0; 65.2] | 61.0 [51.0; 66.5] | 0.7 |
| Male, n (%) | 47 (74.6) | 25 (83.3) | 0.43 |
| Arterial hypertension, n (%) | 54 (85.7) | 26 (86.7) | 0.99 |
| Diabetes mellitus, n (%) | 10 (15.8) | 5 (16.7) | 0.98 |
| Dyslipidemia, n (%) | 19 (30.1) | 9 (30.0) | 0.99 |
| Smoking, n (%) | 24 (38.0) | 12 (40.0) | 0.98 |
| MI, n (%) | 3 (4.76) | 4 (13.3) | 0.2 |
| PCI, n (%) | 6 (9.7) | 2 (6.7) | 0.99 |
| Atrial fibrillation, n (%) | 4 (6.34) | — | 0.3 |
| Cerebrovascular accident, n (%) | 2 (3.2) | 2 (6.6) | 0.59 |
| **Outpatient treatment** | | | |
| Acetylsalicylic acid, n (%) | 10 (15.8) | 3 (10.0) | 0.54 |
| Clopidogrel, n (%) | — | 1 (3.4) | – |
| Ticagrelor, n (%) | 1 (1.6) | — | – |
| Beta blockers, n (%) | 12 (19.0) | 4 (13.3) | 0.57 |
| Statins, n (%) | 7 (11.1) | 2 (6.7) | 0.71 |
| Angiotensin-converting enzyme inhibitors, n (%) | 11 (17.4) | 9 (30.0) | 0.19 |
| Angiotensin II receptor type AT1 blockers, n (%) | 9 (14.3) | 4 (13.3) | 0.99 |
| **Pre-hospital therapy (ambulance)** | | | |
| Acetylsalicylic acid, n (%) | 59 (93.6) | 28 (93.3) | 0.99 |
| Clopidogrel, n (%) | 44 (69.8) | 16 (53.3) | 0.16 |
| Ticagrelor, n (%) | 2 (3.2) | 3 (10.0) | 0.32 |
| Morphine, n (%) | 14 (22.5) | 5 (16.7) | 0.59 |
| **Platelet P2Y12 receptor blockers at hospital** | | | |
| Clopidogrel, n (%) | 5 (8.5) | 2 (7.7) | 0.99 |
| Ticagrelor, n (%) | 47 (79.7) | 23 (88.5) | 0.53 |
| Prasugrel, n (%) | 5 (8.47) | 1 (3.84) | 0.86 |
| **Clinical and procedure-related features** | | | |
| Acute STEMI, n (%) | 52 (82.5) | 23 (76.7) | 0.5 |
| Pain-to-balloon time, min, Me [IQR] | 225.0 [140.0; 430.0] | 367.5 [151.2; 518.7] | 0.87 |
| Door-to-balloon time, min, Me [IQR] | 34.0 [30.0; 42.0] | 36.0 [33.2; 40.0] | 0.99 |
| Angina pain at admission, n (%) | 49 (83.0) | 18 (66.7) | 0.1 |
| **Echocardiogram** | | | |
| LVEF, Me [IQR] | 52.0 [41.5; 57.0] | 60.0 [53.0; 60.0] | <0.01 |
| LVEDV, Me [IQR] | 112.0 [100.0; 142.0] | 120.0 [91.0; 137.5] | 0.89 |
| **Laboratory tests** | | | |
| Hemoglobin, g/L, Me [IQR] | 148.0 [138.0; 158.0] | 152.0 [145.0; 160.0] | 0.31 |
| Platelets, ×109/L, Me [IQR] | 233.0 [206.0; 278.0] | 223.0 [201.0; 298.0] | 0.82 |
| White blood cells, ×109/L, Me [IQR] | 10.3 [8.2; 12.2] | 8.7 [7.5; 10.5] | 0.04 |
| Creatinine, μmol/L, Me [IQR] | 95.0 [83.0; 107.0] | 92.5 [83.7; 104.5] | 0.69 |

Me, median; IQR, interquartile interval; IRA, infarct-related artery; MI, myocardial infarction;
PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume.

### *Thrombodynamics*

Thrombodynamics tests showed no statistically significant differences in thrombosis parameters between the patient groups.

### *Rotation thromboelastometry*

Patients with IRA TIMI 0–1 blood flow had shorter clotting time (CT, s – 602.0 [431.0; 745.0] vs. 728.0 [556.5; 821.5], p=0.04), larger clot size (A20, mm – 54.0 [51.0; 59.0] vs. 51.0 [44.7; 55.0], p=0.029; A30, mm – 58.0 [53.0; 62.0] vs. 54.5 [48.7; 57.2], p=0.01), and higher clot firmness (MCF, mm – 58.0 [55.0; 64.0] vs. 55.0 [49.7; 58.0], p=0.034). There was also a trend to lesser maximum clot lysis in this group (ML, % – 21.0 [18.0; 25.0] vs. 24.5 [20.0; 28.0], p=0.055) (Figure 1).

### *Impedance aggregometry*

Patients with IRA TIMI 0–1 blood flow had more intensive platelet aggregation induced by arachidonic acid (AUC Asa 26.0 [15.5; 43.5] vs. 16.0 [9.5; 20.5], p<0.01) and ADP (AUC ADP 43.0 [36.0; 56.0] vs. 35.0 [25.7; 42.2], p<0.01; Figure 2). There were no differences in TRAP-6-induced platelet aggregation.

### *EDV testing*

Patients with IRA TIMI 2–3 blood flow had higher EDV values (EDV, % – 4.0 [1.35; 5.8] vs. 6.0 [4.34; 9.5], p=0.011).

### *IRA blood flow predictors*

The analysis of logistic regression identified a statistically significant correlation of CT and AUC Asa with the IRA blood flow. These parameters also allowed quickly obtaining the test results.

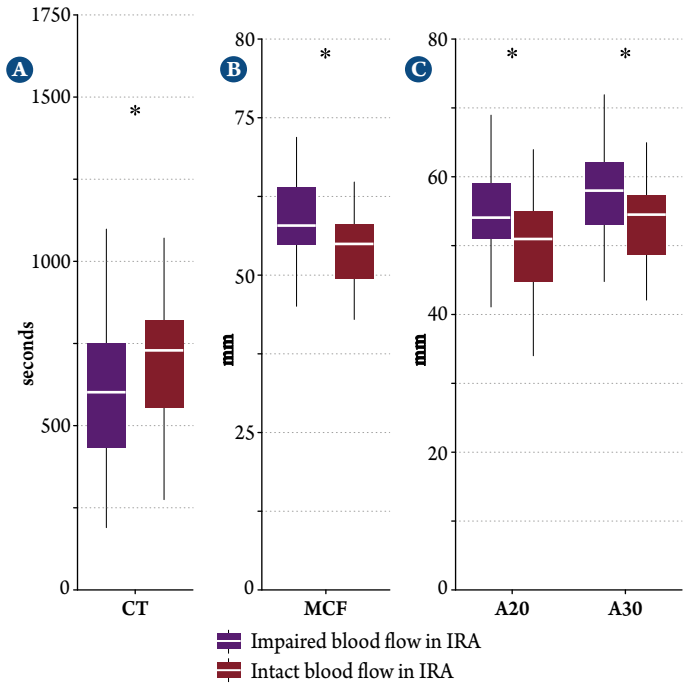
The combined use of these two parameters makes it easier to distinguish patients with TIMI 0–1 blood flow in IRA with the area under the ROC curve of 80% (sensitivity 76%, specificity 71%; Figure 3). Adding ST segment changes to the mentioned parameters did not improve their predictive accuracy.

### *Hospital-acquired complications of AMI and the long-term course of the disease*

Patients with TIMI 0–1 blood flow in IRA achieved the primary endpoint more frequently: 26 (41.3%) vs. 5 (16.7%), p=0.015 (Table 2).

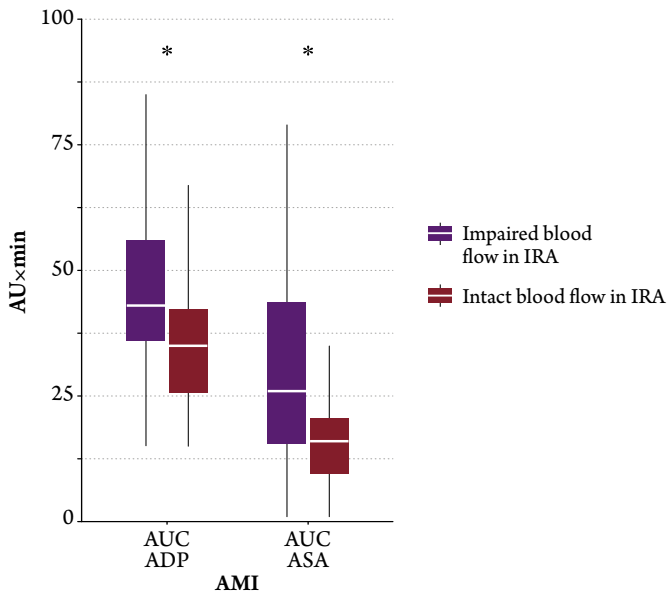
The final analysis of the long-term course of the disease included 55 patients. No significant differences were found in the incidence of the secondary endpoint in the patient groups (Table 3, Figure 4A). Patients with TIMI 2–3 blood flow in IRA had minor bleeding (BARC 1–2) significantly more frequently (8.5% vs. 30.4%; p=0.045; see Table 3, Figure 4B).

**Figure 1.** Comparison of rotation thromboelastometry parameters between the groups of patients with impaired (TIMI 0–1) and intact (TIMI 2–3) blood flow in IRA




A – clotting time (CT, s); B – clot firmness (MCF, mm); C – clot size at minute 20 and minute 30 of the test (A20, mm; A30, mm); * – p<0.05. AMI, acute myocardial infarction; IRA, infarct-related artery.

**Figure 2.** Comparison of impedance aggregometry parameters between the groups of patients with impaired (TIMI 0–1) and intact (TIMI 2–3) blood flow in IRA




AU×min, platelet aggregation units per minute; AMI, acute myocardial infarction; IRA, infarct-related artery; AUC ADP, adenosine diphosphate-induced platelet aggregation; AUC Asa, arachidonic acid-induced platelet aggregation; * = p<0.05.


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**Table 2.** Hospital-acquired complications of AMI, n (%)

| Parameter | Patients with IRA blood flow TIMI 0–1 (n = 63) | Patients with IRA blood flow TIMI 2–3 (n = 30) | p |
|---|---|---|---|
| Clinical death, n (%) | 3 (5.0) | 2 (6.6) | 0.99 |
| Death, n (%) | 0 | 0 | — |
| ALVF, n (%) | 11 (18.3) | 2 (6.7) | 0.2 |
| Platelet IIb/IIIa inhibitor infusion, n (%) | 11 (18.3) | 2 (6.6) | 0.2 |
| MV, n (%) | 3 (5.0) | 0 | — |
| Mechanical circulatory support, n (%) | 2 (3.3) | — | — |
| Stent thrombosis, n (%) | 2 (3.17) | 1 (3.3) | 0.96 |
| AV block, n (%) | 2 (3.4) | 1 (3.3) | 0.99 |
| Major bleeding, n (%) | 0 | 0 | — |
| Primary endpoint, n (%) | 26 (41.3) | 5 (16.7) | 0.015 |

AMI, acute myocardial infarction; ALVF, acute left ventricular failure; MV, mechanical ventilation; AV, atrioventricular; IRA, infarct-related artery.

**Table 3.** Long-term course of the disease in patients with AMI, n (%)

| Outcome | Patients with IRA blood flow TIMI 0–1 (n = 34) | Patients with IRA blood flow TIMI 2–3 (n = 21) | p |
|---|---|---|---|
| Death, n (%) | 1 (2.9) | 0 | — |
| Death from cardiovascular causes, n (%) | 0 | 0 | — |
| Recurrent PCI, n (%) | 0 | 1 (4.8) | — |
| Repeat emergency revascularization, n (%) | 4 (11.7) | 1 (4.8) | 0.36 |
| Stent thrombosis, n (%) | 2 (5.9) | 0 | — |
| Major bleeding (BARC 3–5), n (%) | 0 | 0 | — |
| Minor bleeding (BARC 1–2), n (%) | 3 (8.5) | 7 (30.4) | 0.045 |

AMI, acute myocardial infarction; IRA, infarct-related artery.

## Discussion

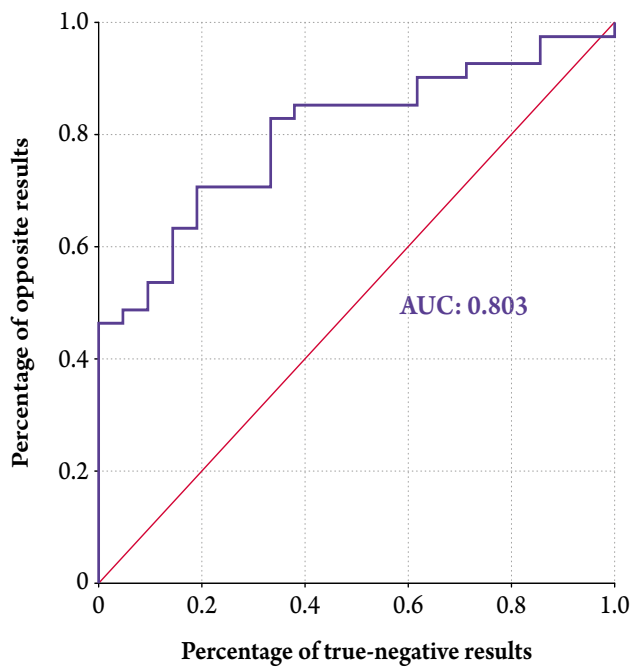
Patients with spontaneous IRA reperfusion have a more favorable prognosis of the disease [12, 13]. In this study, we confirmed once again that patients with TIMI 2–3 blood flow in IRA, with and without ST segment elevation, are less likely to have hospital-acquired complications of AMI.

There are predisposing factors for intact blood flow in IRA [14–16]. The correlation between clotting, endogenous fibrinolysis, and IRA blood flow was described [17–20]. Several studies demonstrated the effect of an inflammatory setting on the state of IRA [21, 22]. According to our findings, patients with TIMI 0–1 blood flow in IRA have more intense clotting due to greater platelet aggregation and plasma hemostasis. It should be noted that the outpatient and pre-hospital treatment did not affect the parameters of interest and the course of the disease. It is also noteworthy that a small number of patients had increased platelet reactivity, despite the load doses of antiplatelet agents, which may be characteristic of hemostasis in patients of this group. Moreover, there was a trend to more active endogenous fibrinolysis in patients with TIMI 2–3 blood flow in IRA. In this study, we also demonstrated higher EDV values in patients with TIMI 2–3 blood flow in IRA.

We were first to show that the use of a combination of two simple hemostasis assessment methods allows estimating the degree of IRA blood flow impairment. It should be noted that these parameters assess the degree of impaired IRA blood flow without taking into consideration the ST-segment changes on the ECG. Our results make it possible to identify patients who are very likely to have IRA occlusion. This may be relevant for the rate of myocardial revascularization in patients with NSTEMI, since it can be delayed up to 24 hours from the time of hospitalization according to the current guidelines [23].

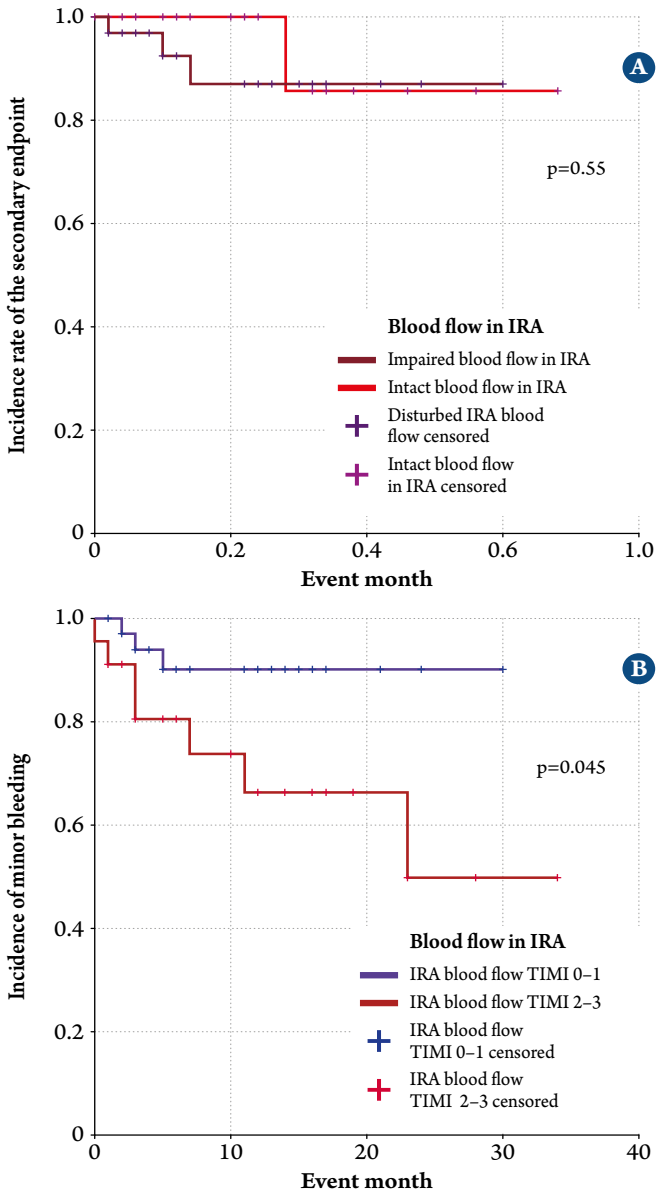
The analysis of the long-term course of the disease showed a more frequent development of minor bleeding in patients with TIMI 2–3 blood flow in IRA in the acute

**Figure 3.** Concomitant use of AUC Asa and CT as predictors of IRA blood flow in patients with AMI




AMI, acute myocardial infarction; IRA, infarction-related artery; AUC Asa, platelet aggregation induced by arachidonic acid; CT, clotting time.

**Figure 4.** Kaplan-Meier curves: incidence of secondary endpoint (A) and incidence of minor bleeding (B) in patient with impaired (TIMI 0–1) and intact (TIMI 2–3) blood flow in infarct-related artery




phase of the disease. These patients have less intense clotting, which makes them more prone to hemorrhagic complications during dual antiplatelet therapy. It seems that patients of this group should be supervised more carefully due to possible hemorrhagic complications and possibly with de-escalation of antiplatelet therapy, which was shown to be safe in the TROPICAL-ACS trial [24].

### *Limitations*

The main limitation of the study is the small sample size and low incidence of various hospital-acquired and delayed complications of AMI, which allows analyzing then only as a part of the composite point. The relatively low incidence of delayed complications of AMI and major bleeding is due to the study design, which did not include patients at very high risk (cardiogenic shock, mechanical complications of AMI).

## Conclusion

Patients with acute myocardial infarction and TIMI 0–1 blood flow in the infarct-related artery are characterized by the deteriorated functional state of the endothelium, more intensive clotting and platelet aggregation processes compared to patients with intact blood flow. It was shown for the first time that the concomitant use of two simple criteria of hemostasis assessment (AUC Asa; CT) allows estimating the degree of blood flow impairment in the infarct-related artery in patients with acute myocardial infarction. The data obtained can be used as a ground for further randomized trials to develop the best possible management strategy for patients with acute myocardial infarction depending on coronary blood flow.

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