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Review

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The Impact of the Fibrinolytic System on the Outcomes of Thrombolytic Therapy

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ABSTRACT Thrombolysis is one of the effectively used methods for treating patients with acute vascular pathology. Despite the high technical success of this therapy, some problems of fibrinolytic treatment still remain unresolved. Resistance to thrombolytic agents with subsequent unsatisfactory reperfusion of the vascular bed is the most important of them. Currently, despite advances in the pharmacotherapy of drugs used in thrombolysis and improvements in the technical basis for its performance, the predictors that influence its outcome are still not clearly defined. The use of fibrinolytic drugs during thrombolysis induces activation of the procoagulative component of hemostasis in the form of increased activity of thrombin, prothrombin fragments 1.2 and the thrombin-antithrombin III complex in response to excessive fibrinolysis caused by this treatment method. This paradoxical procoagulant activation of the hemostatic system may be the cause of the lack of initial reperfusion of the vascular bed in 15–25% of cases, and from 5% to 15% of cases of early thrombotic reocclusion after initially successful thrombolysis. In parallel with the activation of the coagulation link of hemostasis against the background of this type of treatment, changes occur in the functioning of the fibrinolysis system, which directly affects the outcomes of thrombolysis. This paper provides a comprehensive overview of the spectrum of major markers of the fibrinolytic system that have been studied in the context of thrombolysis outcomes in patients with acute vascular pathology. It was concluded that it is necessary to expand the determination of laboratory blood parameters by directly determining the values of plasminogen activator inhibitor-1, thrombin-activated fibrinolysis inhibitor, α_2-plasmin inhibitor in order to predict the outcome of thrombolysis.

Keywords: thrombolysis, fibrinolysis, hemorrhagic complications, thrombin-activated fibrinolysis inhibitor, plasminogen activator inhibitor-1, plasmin

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AMI — acute myocardial infarction
PAI-1 — plasminogen activator inhibitor-1
Plg — plasminogen
Pn — plasmin
PrC — protein C
rt-PA — recombinant tissue plasminogen activator
TAFI — thrombin-activatable fibrinolysis inhibitor
TAT — thrombin–antithrombin III complex
tPA — tissue-type plasminogen activator
u-PA — urokinase-type plasminogen activator
vWF — von Willebrand factor
α2-PI — α2-plasmin inhibitor

INTRODUCTION

Currently, vascular bed-specific thrombosis is the most common cause of disability and death in most industrialized countries [1]. Among the most common localizations of arterial lesions are the coronary bed, cerebral vessels, and lower limb arteries [2, 3]. One of the main causes of circulatory disorders in the arterial part of the vascular bed is the development of endothelial dysfunction against the background of atherosclerotic lesions, which in the literature is often called atherothrombosis. In the case of atherothrombosis, the blood supply to the thrombosed artery pool is interrupted, with subsequent tissue necrosis. This is why rapid restoration of blood flow in the affected vessel is a priority [4].

Today, thrombolytic therapy is a recognized method of treating patients with this pathology [5]. The main advantages of this type of treatment are less trauma to the endothelium of the vascular wall due to the absence of mechanical trauma, and a lower risk of developing infectious complications; dissolution of thrombotic masses in collateral branches of the vascular wall; direct possibility of visualization of the cause of thrombosis by performing angiography with subsequent use of appropriate methods of interventional treatment; shorter hospital stay [6].

However, failure to achieve reperfusion and the development of rethrombosis after successful thrombolysis remains an unsolved problem [7]. Treatment-related bleeding occurs in 6–8% of patients, potentially leading to worsening symptoms and may be fatal in approximately 1% of patients undergoing thrombolysis [8]. In some patients, arterial thrombi are lysed within a few hours during thrombolysis, whereas in others, lysis is ineffective, leading to re-thrombotic occlusion of the vascular bed [9].

Unfortunately, these problems cannot be solved by simply increasing the dose of thrombolytic drugs, as this is associated with an increased risk of serious bleeding [10]. The search for improved anticoagulant therapy using fibrin-specific plasminogen (Plg) activation is focused on thrombin and platelet aggregation inhibitors. Limiting platelet aggregation and thrombin-mediated coagulation is a key factor in achieving and maintaining arterial patency. Clinical studies with heparin, aspirin and agents specific to platelet receptors confirm these results [11, 12].

The formation of a relatively large amount of plasmin during thrombolytic therapy has an anticoagulant effect, since it is known that plasmin destroys key procoagulant cofactors such as fibrinogen, factors V and VIII of the blood coagulation system. At the same time, the use of thrombolytic treatment leads in some cases to the development of paradoxical procoagulant activation of the blood coagulation system, which may contribute to early re-thrombotic occlusion of the vascular bed. Results of clinical research indicate that pharmacological activation of Plg induces activation of the blood coagulation system and subsequent thrombin production [13, 14].

The outcome and safety of thrombolysis probably depend on factors that influence or regulate fibrinolysis, but the exact pathophysiological mechanism has not been fully determined. Activation of the fibrinolytic system aimed at the destruction of intravascular fibrin is a mechanism of response to vascular wall damage. The main component of this system is plasmin (Pn), which is formed from Plg under the action of tissue-type (t-PA) and urokinase-type (u-PA) activators. Plg activation, which occurs on fibrin and on cell surfaces, is a strictly regulated process [15]. Plasminogen activator inhibitor-1 (PAI-1) is the most potent inhibitor of t-PA and u-PA, while α2-plasmin inhibitor (α2-PI) directly inhibits Pn. The recombinant form (rt-PA) is used as a pharmacological therapy for dissolving thrombotic masses in patients with acute vascular pathology. As a result of coordinated reactions, the fibrinolytic

system functions as a highly effective and vital mechanism for maintaining homeostasis and adaptability of the body under various physiological and pathological conditions [16, 17]. The endothelium of the vascular wall plays a crucial role in maintaining the balance in the hemostasis and fibrinolysis system due to the synthesis of pro- and antithrombotic markers [18, 19]. For example, endothelial cells synthesize PAI-I, which forms a complex with coagulation factor XIa, blocking its activity, causing degradation of this factor [20]. During the development of acute thrombosis of the vascular bed, there is increased production of proinflammatory markers, such as TNF-alpha. This, in turn, leads to a decrease in the production of the anticoagulant marker thrombomodulin by the endothelium [21]. Endothelin-1 as a marker of endothelial dysfunction may influence blood coagulation by stimulating increased synthesis of von Willebrand factor (vWF), thereby increasing procoagulant potential [22].

The use of rt-PA pharmacological agents during thrombolysis has a direct effect on the activation and subsequent changes in the functioning of the fibrinolysis system, which affects the results of this treatment method. Thus, one study showed that an increase in the values of the thrombin-antithrombin III (TAT) complex, prothrombin fragment 1,2 (F1.2) and a marker of fibrinogenolytic activity (B beta 1-42) from 12 to 24 hours after thrombolysis can be a predictor of recurrent ischemia in patients with acute myocardial infarction (AMI) [23].

Ueda T. studied hemostatic parameters as prognostic markers of hemorrhagic complications after selective intra-arterial thrombolysis with urokinase. Thus, fibrinogen degradation product levels in the hemorrhagic transformation group increased significantly immediately and 1 hour after therapy. α2-PI activity decreased and plasmin-alpha-2-plasmin inhibitor (PIC) levels increased in both hemorrhagic transformation and control groups after treatment. At 24 hours after thrombolysis, D-dimer levels were higher in the hemorrhagic transformation group than in the control group. Furthermore, D-dimer levels were significantly higher in patients with complete recanalization compared with patients without or with partial recanalization [24].

In connection with the above, the study and systematization of research devoted to assessing the influence of blood fibrinolytic system indices on the results of thrombolysis in acute vascular pathology will be able to identify potential predictors of the development of unfavorable outcomes of this therapy.

Our **aim** was to summarize the results of scientific research devoted to the study of the impact of the fibrinolytic system on the outcomes of thrombolysis in acute vascular pathology.

MATERIAL AND METHODS

The query of "fibrinolysis and thrombolysis" was created in the search line of PubMed biomedical database. There were no restrictions on the year of publication. This query yielded 433 articles that were checked for relevant information. Additionally, the following keywords were used: plasminogen activator inhibitor-1, tissue plasminogen activator, thrombotic masses, plasmin activator inhibitor, thrombin-activatable fibrinolysis inhibitor, hemorrhagic complications, reperfusion. From these articles, 98 publications were selected and analyzed that were directly related to the practical activities of physicians. In writing this review, 54 literary sources were used, directly devoted to the study of the impact of the fibrinolytic system on the outcomes of thrombolysis in acute vascular pathology.

THROMBIN-ACTIVATABLE FIBRINOLYSIS INHIBITOR, PLASMINOGEN ACTIVATOR INHIBITOR-1

Plasminogen activator inhibitor-1 (PAI-1) is a serine protease inhibitor that acts on the Plg system by inhibiting u-PA and t-PA. Elevated PAI-1 levels were identified in the world literature as a risk factor for cardiovascular diseases [25–27].

Thrombin-activatable fibrinolysis inhibitor (TAFI) is a plasma procarboxypeptidase that, after conversion to the active enzyme TAFIa, removes the C-terminal lysine from partially degraded fibrin, thereby reducing the binding of t-PA and Pg in the clot. It is mainly synthesized by the liver, although extrahepatic pathways also exist (endothelial cells, macrophages, and megakaryocytes). The thrombin-thrombomodulin complex is suggested to be one of the physiological activators of TAFI. Plasmin was also shown to activate TAFI in vitro and in vivo in the

immediate vicinity of the thrombus. It was suggested that TAFIa generation represents a mechanism of thrombus resistance to thrombolytic therapy. However, the ability of TAFI to inhibit fibrinolysis by pharmacological concentrations of t-PA was not properly studied [28–30].

In experimental models of pharmacological thrombolysis, administration of TAFI inhibitors together with a fibrinolytic agent results in a marked improvement in thrombus lysis, highlighting the potential of TAFI inhibitors as adjuvants in thrombolytic therapy [31].

In a study by Alessi et al., TAFIa levels were shown to increase significantly at the end of thrombolysis lasting up to 4 hours in patients with ischemic stroke. Higher TAFIa levels were associated with higher NIHSS scores on day 2 after thrombolysis and an unfavorable modified Rankin Scale (mRS) score at day 90 of follow-up [32].

Fernandez-Cadenas et al. assessed the effect of two polymorphisms of the PAI-1 and TAFI genes on the rate of middle cerebral artery recanalization in patients with stroke who received rt-PA. The study did not reveal a relationship between the PAI-1 4G/5G polymorphism and the rate of recanalization. However, the TAFI Thr325Ile polymorphism was significantly associated with resistance to vascular recanalization during thrombolytic therapy. The combination of two polymorphisms doubled the risk of unsuccessful recanalization during thrombolysis [33]. At the same time, Szegedi I. et al. showed that patients with the PAI-15G/5G genotype had a tendency to increase the volume of intracerebral hemorrhage after lysis compared to PAI-1 4G carriers. Moreover, the risk of hemorrhagic transformation after thrombolysis in patients with acute ischemic stroke, conditioned by the PAI-15G/5G genotype, increased 5-fold (OR: 4.75, 95% CI: 1.18–19.06, p=0.028) [34].

However, Cruden N.L. et al. managed to prove in their study that such indicators as TAFI, soluble CD40L ligand (sCD40L), and C-reactive protein in blood plasma do not affect reperfusion in patients receiving thrombolytic therapy for AMI with ST segment elevation [35]. Kim S.H. et al. did not find differences in the baseline TAFI level between groups of patients with successful and ineffective thrombolysis in acute ischemic stroke. Although elevated plasma PAI-1 values before treatment were associated with thrombolysis failure based on control angiography [36]. Sinkovic A. showed in his study that the initial PAI-1 level of more than 4 U/ml is associated with the ineffectiveness of thrombolysis in patients with AMI [37].

At the same time, Paganelli F. in turn found that PAI-1 values after thrombolysis with streptokinase in patients with AMI are associated with vascular patency. It was shown that elevated plasma PAI-1 levels 6 and 18 hours after thrombolysis are associated with re-occlusion of the infarct-related artery. This research showed that the increase in PAI-1 levels was more pronounced after streptokinase treatment than after the use of rt-PA [38]. Therapeutic approaches aimed at suppressing PAI-1 activity after thrombolysis may be of interest for increasing the effectiveness of thrombolysis in acute vascular pathology.

PAI-1 and TAFI levels on admission in patients with ischemic stroke (middle cerebral artery occlusion) receiving sequential rt-PA therapy were studied by Ribo et al. In patients with hemorrhagic transformation, they observed lower baseline PAI-1 values with higher TAFI levels. The combination of baseline PAI values less than 21.4 ng/ml and TAFI greater than 180% could be considered as a prognostic model for the risk of symptomatic intracranial hemorrhage. The sensitivity and specificity of the model were 75% and 97.6%, respectively [39]. Using ROC analysis, Ribo M. showed that the initial PAI-1 value over 34 ng/ml is associated with resistance to recanalization of the middle cerebral artery in patients with acute ischemic stroke during thrombolysis. The sensitivity of the method was 84.6% and specificity was 70% [40].

Takazoe K. studied the indices of protein C (PrC), TAT complex, and PAI-I in blood plasma of patients with AMI who underwent thrombolysis. At admission, PrC levels were significantly elevated in patients with AMI compared with the control group (2.5±0.4 vs. 1.2±0.2, p<0.01). On discharge, the plasma levels of PrC in patients with AMI decrease to values that are insignificantly different from those in the control group. TAT levels differed in the compared groups similarly to PrC level. The values of PAI-I activity in patients with AMI were higher at

admission than on discharge, and higher than in patients of the control group (p<0.01). Thirty-two patients with AMI were divided into two groups based on the results of thrombolysis: a group with successful thrombolysis (group 1), and a group with ineffective thrombolysis (group 2). The levels of PrC and TAT were higher in group 2 than in group 1 (5.1±0.7 versus 1.6±0.2, p<0.01). Moreover, the levels of PAI-I activity were lower in group 2 than in group 1. Correlations were also found between PrC and TAT levels both upon admission (r=0.75, p<0.0001) and upon discharge (r=0.71, p<0.0001) [41].

In contrast to the above studies, Cocho D. showed that none of the hemostatic markers (fibrinogen, F1.2, factors XIII and VII, α2-PI, PAI-1 and TAFI) predicted symptomatic cerebral hemorrhage in patients with ischemic stroke who received t-PA [42].

In an experimental study on rats, Rupin A. showed that the use of PAI-1 significantly reduces the lysis time compared to the control group (123±30 sec compared to 169±33 sec, p<0.05), with a decrease in the volume of thrombotic masses by 56±7% [43]. A number of studies showed that residual mural thrombi after thrombolysis can contribute to the development of atherosclerosis due to the synthesis of platelet-derived growth factor, which stimulates the proliferation of smooth muscle cells in the vascular wall [44]. Farrehi RM studied the role of PAI-1 in endogenous clearance of arterial thrombi in mice with a deficiency of this biomarker PAI-1(-). It was shown that residual thrombotic masses were detected in 64.7% of mice with normal PAI-1(+) content and in 33.9% of mice with PAI-1(-) deficiency. Computerized planimetric analysis showed that the average cross-sectional area of the thrombus was 0.033±0.02 mm^2 in PAI-1(+) mice versus 0.016±0.02 mm^2 in PAI-1(-) mice. The author concluded that PAI-1 is an important factor determining thrombolysis at the sites of vascular wall damage [45]. Colucci M. used an in vitro clot lysis model in 103 healthy donors, studying the individual response to pharmacological concentration of rt-PA and the influence of physiological changes in hemostatic parameters on this response. Multivariate analysis showed that both PAI-1 antigen and Plg independently predicted poor response to rt-PA. However, surprisingly, not only PAI-1, but also Plg was negatively correlated with rt-PA-induced clot lysis. The observation that neutralization of PAI-1 by specific antibodies, either in plasma or within the clot, does not enhance clot lysis suggests that inhibition of PAI-1 is insufficient to weaken the thrombolytic activity of the pharmacological concentration of rt-PA, and that its increase, similar to the increase in plasminogen, is not the cause of clot stability, but rather an accidental discovery. It was concluded that the in vitro thrombus lysis test can help identify patients who may be resistant to thrombolytic therapy [46]. At the same time, Vaughan D.E. proved that elevated levels of active PAI-1 can neutralize the thrombolytic effects of rt-PA in vivo and refute the possibility that t-PA can dissociate from PAI-1 and restore its activity in the presence of a thrombus [47]. Sakamoto T. showed that additional use of PrC after successful thrombolysis in the form of intravenous infusion leads to a lower percentage of repeated thrombotic occlusion of the infarction-related coronary artery, as well as hemorrhagic complications. This may be due to the fact that PrC suppresses the increased PAI-1 activity in plasma after thrombolysis in patients with AMI [48].

An interesting study was conducted by Zhang S., who showed that circulating neutrophils can contribute to resistance to the use of rt-PA. After thrombolysis, a significant increase in the number of circulating neutrophils was noted in patients with acute ischemic stroke without improvement, while in patients with improvement, the changes were insignificant. In addition, circulating neutrophils activate platelets, endothelial cells and increase the procoagulant state of the blood by increasing vWF and PAI-1 production. At the same time, the use of activated PrC significantly inhibits these effects. A treatment strategy aimed at inhibiting the synthesis of circulating neutrophils may represent a promising therapeutic approach to improve the efficacy of thrombolysis in patients with acute ischemic stroke [49]. The results of studies on the impact of fibrinolysis biomarkers on thrombolysis outcomes are presented in the table.

Table

The results of studies on the impact of fibrinolysis biomarkers on thrombolysis outcome

Study/First author of the study	Number of patients in the study	Timing of blood collection for fibrinolysis biomarker studies	Drugs used for thrombolysis	Thrombolysis outcomes	p-value for the association between fibrinolysis biomarker levels and thrombolysis outcomes
Szegedi I. et al. [34]	131 patients with acute myocardial infarction	Evaluation of PAI-1 4G/5G polymorphism	rt-PA	Intracerebral hemorrhage	Patients with the PAI-1 5G/5G genotype showed a tendency toward increased intracerebral hemorrhage volume after lysis compared with carriers of the PAI-1 4G/4G genotype (p=0.028)
Ribo M. et al. [39]	77 patients with acute myocardial infarction	Baseline PAI-1 and TAFI values	rt-PA	Intracerebral hemorrhage	Baseline TAFI >180% and PAI-1 <21.4 ng/mL were associated with the risk of intracerebral hemorrhage (p<0.05)
Fernandez-Cadenas I. et al. [33]	139 patients with acute myocardial infarction	Evaluation of PAI-1 4 G/5 and TAFI Thr325Ile polymorphisms	rt-PA	The rate of recanalization of the vascular bed during thrombolysis	1. The PAI-1 4 G/5 G polymorphism did not affect the rate of vascular recanalization. 2. TAFI Thr325Ile polymorphism is associated with resistance to vascular recanalization by the end of rt-PA infusion (p=0.003)
Martí-Fàbregas J. et al. [50]	63 patients with acute myocardial infarction	Baseline PAI-1, TAFI and 2-antiplasmin values	rt-PA	Functional outcome (mRS score >2) 3 months after thrombolysis	None of the fibrinolysis biomarkers were associated with functional outcome 3 months after thrombolysis (p>0.05)
				The rate of recanalization of the vascular bed during thrombolysis	Initially low 2-antiplasmin level was a prognostic indicator of vascular recanalization (p=0.038)
Ribo et al. [39]	44 patients with acute myocardial infarction	Baseline PAI-1 and TAFI values	rt-PA	Efficiency of thrombolysis	PAI-1 level > 34 ng/ml is an independent predictor of thrombolysis resistance and poor functional outcome after 3 months (p=0.014)
				Functional outcome (mRS score>2) 3 months after thrombolysis	
Park S.Y. et al. [26]	175 patients with acute myocardial infarction	PAI-1 values within 24 hours after acute ischemic stroke	rt-PA	Functional outcome (mRS score>2) 3 months after thrombolysis	No correlation was found
Zeng L. et al. [27]	105 patients with acute myocardial infarction	PAI-1, t-PA values 72 hours after acute ischemic stroke	rt-PA	Functional outcome (mRS score>2) 3 months after thrombolysis	Reduced PAI-1 values are associated with good functional outcome (p=0.026)
Sinkovic A. et al. [37]	60 patients with acute myocardial infarction	Baseline PAI-1	Streptokinase	Efficiency of thrombolysis	Baseline PAI-1 level > 4.0 U/ml was associated with thrombolysis failure (p<0.05)
Alessi M.C. et al. [32]	109 patients with acute myocardial infarction	Baseline, day 1, then days 2–4, days 7, and days 90 post-thrombolysis TAFI values	rt-PA	Clinical outcome according to NIHSS on day 2 and clinical outcome according to mRS on day 90 of observation	High TAFIa levels were associated with higher NIHSS score on day 2 after thrombolysis and unfavorable mRS score on day 90 of follow-up
Martí-Fàbregas J. et al. [29]	40 patients with acute myocardial infarction	TAFI, 2-antiplasmin, fibrinogen values before and 30 minutes after the end of rt-PA infusion	rt-PA	1. The degree of vascular bed recanalization 2. Likelihood of rehospitalization	None of the studied parameters were associated with vascular recanalization and the likelihood of rehospitalization (p>0.05)
Brouns R. et al. [30]	12 patients with acute myocardial infarction	TAFI values were determined before, during and after thrombolysis	Urokinase	Efficiency of thrombolysis	Higher TAFI values negatively affect the efficacy and safety of thrombolysis (p<0.05)

Notes: PAI-1 — plasminogen activator inhibitor-1; rt-PA — recombinant tissue plasminogen activator; TAFI — thrombin-activatable fibrinolysis inhibitor

ALPHA-2 PLASMIN INHIBITOR

Alpha-2 plasmin inhibitor (α2-PI) is a serine protease that forms a stable complex with plasmin, thereby neutralizing its activity. Little is known about the factors that modify α2-PI incorporation into the fibrin clot, and whether this has clinical significance [51].

A number of studies found that α2-PI levels correlate well with the rate of recanalization in patients with ischemic stroke who received rt-PA. In a work of Marti-Fabregas et al. it was shown that the initially low level of α2-PI is an independent predictor of vascular recanalization in patients with acute ischemic stroke. However, its level is not associated with long-term outcome in patients receiving rt-PA within the first 3 hours [51].

In other studies, although a decrease in α2-PI levels was found after lysis, α2-PI values did not show a relationship with the occurrence of hemorrhagic transformation or adverse outcomes after thrombolysis [42].

Bagoly Z. showed in his study that an elevated factor XIII level increases the incorporation of α2-PI into the fibrin clot. The incorporation of α2-PI into the fibrin clot in the control group and in patients with a favorable outcome did not differ statistically significantly (49.4±4.6% vs. 47.4±6.7%, p=1.0) after rt-PA administration, however, it was significantly lower in patients who had intracranial hemorrhage after thrombolysis. The author concluded that in stroke patients undergoing intravenous thrombolysis, α2-PI incorporation into the fibrin clot demonstrated a relationship with the outcome of therapy, especially with thrombolysis-associated intracranial hemorrhage. It was also found that the α2-PI p.Arg6Trp polymorphism did not affect either the outcomes of thrombolytic therapy or the degree of α2-PI incorporation into fibrin clots in any of the study groups [52].

Reed G.L. demonstrated in vitro that inhibition of human α2-PI by a monoclonal antibody markedly enhanced clot lysis by Plg activators in a rabbit jugular vein thrombosis model. These experiments suggest that the combination of α2-PI and a plasminogen activator may be a more effective thrombolytic strategy [53].

Another study showed that higher α2-PI levels correlated with more severe ischemic brain injury, cerebral edema, and decreased middle cerebral artery thrombus dissolution. At the same time, α2-PI deficiency increased the lysis of thrombotic masses with improved cerebral blood flow against the background of a reduced risk of infarction and cerebral edema. Inactivation of α2-PI within a few hours after middle cerebral artery thrombosis reduces the risk of cerebral infarction ($p<0.001$) and bleeding ($p<0.05$) [54].

CONCLUSION

Understanding the mechanisms underlying resistance to thrombolytic therapy, which lead to a low incidence of revascularization, is of crucial importance for increasing the effectiveness of this type of treatment. The results of the studies presented in this review show that the development of adverse outcomes after thrombolysis is associated with changes in the fibrinolytic system. Evaluation of fibrinolysis biomarkers can provide an opportunity to differentiate patients at risk of hemorrhagic complications or ineffectiveness of this therapy. It is necessary to expand the definition of standard laboratory blood parameters by directly determining PAI-I, TAFI, α2-PI values in patients with acute vascular pathology at different timing of thrombolysis in order to predict its effectiveness. In a number of patients with repeated episodes of acute thrombotic events, it is essential to conduct genetic analysis for polymorphism of fibrinolysis marker genes to select the optimal treatment strategy.

In the presented studies, heterogeneity of the patient sample size, different time points of sampling and studying various fibrinolysis markers, the use of a variety of pharmacological agents and routes of administration during lysis do not provide clear recommendations as to which fibrinolysis biomarkers are predictive of clinical outcomes after this therapy. Nevertheless, some biomarkers show promising results, and require further study and validation in larger populations with well-defined study designs.

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