https://doi.org/10.15360/1813-9779-2026-1-2628

Comparison of Alteplase and Forteplase Efficacy in Reperfusion Therapy of Ischemic Stroke: a Retrospective Cohort Study

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For citation: *Alexey R. Avidzba, Vitaliy A. Saskin, Anton M. Nikonov, Ayyaz Hussain, Mikhail Y. Kirov.* Comparison of Alteplase and Forteplase Efficacy in Reperfusion Therapy of Ischemic Stroke: a Retrospective Cohort Study. *Obshchaya Reanimatologiya = General Reanimatology.* 2026; 22 (1): 41–48. https://doi.org/10.15360/1813-9779-2026-1-2628 [In Russ. and Engl.]

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Summary

The aim of the study. To compare the effectiveness of thrombolytic therapy in patients with ischemic stroke with forteplase and alteplase in clinical practice.

Materials and methods. A single-center retrospective cohort study was conducted using data from the reperfusion interventions registry at the Arkhangelsk regional vascular center. The primary endpoint was patients' functional recovery at discharge from the hospital. The incidence of type 2 intracranial hemorrhages according to the Heidelberg bleeding classification, mortality, and the duration of hospital stay were analyzed as the secondary endpoints. Descriptive statistics were used. Simple and multivariate multiple linear and logistic regression models were constructed to assess the relationship of forteplase use with functional recovery and length of hospital stay.

Results. The study involved 213 patients with the mean age of 68 (60; 76) years, including 111 (52.1%) men. Forteplase was used in 91 (42.7%) patients. Modified Rankin scale scores of 0–2 were documented in 52 (57.14%) and 51 (41.8%) patients in the forteplase and alteplase groups, respectively, $p=0.019$. After correction for potential confounders, no relationship was found between achieving good functional recovery and the use of forteplase: adjusted odds ratio was 1.04 [95% CI 0.54–2.01], $p=0.91$. The incidence of type 2 parenchymal hemorrhages was 3.3% in the forteplase group vs 0.8% in the alteplase group, $p=0.315$, and the mortality rates were 6.59% vs 11.48%, respectively, $p=0.247$. The use of forteplase did not affect the length of hospital stay in a multivariate analysis: B = –0.54 [95% CI –3.74–2.66], $p=0.741$.

Conclusion. Thrombolysis with forteplase is an effective and safe method of treatment in the acute period of ischemic stroke. Rates of achieving good functional recovery, incidence of intracranial hemorrhage, and length of hospital stay were comparable in groups treated with forteplase and alteplase after correction for significant confounders.

Keywords: alteplase; forteplase; ischemic stroke; systemic thrombolysis

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Intravenous thrombolysis (IVT) is at the forefront of acute ischemic stroke (AIS) current management in the «therapeutic window» [1–3]. The use of IVT and mechanical recanalization techniques can improve patients' functional recovery after AIS [4, 5]. Given the high prevalence of ischemic stroke (IS) in the adult population and the significant disability caused by intracranial accidents, extending reperfusion therapy in management of patients with AIS is a crucial task for current practice [6, 7]. In addition, stroke is a major economic challenge in countries with aging populations, leading to a high burden on health care and social protection systems and increasing already high financial and societal costs [8–10].

One of the most promising areas for increasing the number of reperfusion procedures is a widespread use of advanced neuroimaging techniques to select patients for reperfusion outside the classic «therapeutic window» of 4.5 to 6 hours after the onset of symptoms [7, 11].

Currently, computed tomography (spiral CT) or magnetic resonance (MRI) perfusion imaging of the brain is actively studied in clinical trials and has already been included in the up-to-date national

and international guidelines and treatment protocols for patients with AIS [3]. Another available neuroimaging option that can expand the therapeutic window is diffusion weighted imaging – fluid attenuation inversion recovery — DWI/FlAIR mismatch MRI [12, 13]. Currently, this modality is used not only to select patients for reperfusion procedures in cases with unknown symptom onset, but also in cases with large ischemic core volume outside the therapeutic window [14, 15]. Hence, advanced neuroimaging techniques enable expansion of indications for using reperfusion therapy. On the other hand, wider use of reperfusion can be associated with higher rates of symptomatic intracranial hemorrhages (sICH) in this patient cohort due to extended therapeutic window compared to traditional approaches [13, 16]. For these reasons, search for ways to reduce the risk of hemorrhagic transformations (HTs) in the ischemic zone becomes more than relevant, offering employment of innovative thrombolytic agents with adequate safety profile as one of potential solution.

Use of fibrinolysin on January 22, 1986 for management of progressive vertebrobasilar stroke in Marshal of the Soviet Union G. K. Zhukov was one of the first documented cases of systemic thrombolysis in AIS [17]. Routine use of thrombolysis for AIS was not feasible until the end of the 20th century due to the lack of CT scanners in healthcare, which made it difficult to accurately differentiate between different types of stroke. It was not until 1996 that the first thrombolytic drug for the treatment of AIS, alteplase, was approved in the United States [4]. Representing the 2nd generation of fibrinolytic drugs, safe and highly effective alteplase has become the gold standard for managing AIS, although in the meantime, new thrombolytics have emerged in routine clinical practice in the last decade.

Between 2010 and 2025 a number of third-generation thrombolytic tenecteplase (TNK) studies have been conducted, expecting that its higher fibrin affinity would decrease the incidence of hemorrhagic complications associated with IVT. However, the results of these studies showed that TNK efficacy and safety profiles were comparable to those of alteplase [18–20]. According to the results of a systematic review and meta-analysis by the authors of the European Stroke Organization (ESO) clinical guidelines, which included data from three randomized studies, the efficacy and safety of tenecteplase and alteplase in AIS reperfusion therapy are comparable [1].

Forteplase, a recombinant protein containing staphylokinase amino acid sequence is another novel thrombolytic agent [21]. After publication in Lancet Neurology in 2021 the results of FRIDA RCT evaluating clinical effectiveness of IVT with forteplase compared to alteplase in AIS [22], the Russian MoH approved and included the use of forteplase for management of AIS in clinical guidelines [3]. Accumulated since 2021 clinical experience with forteplase substantiates its' compilation and sharing the overview of the results coming from observational studies.

The aim of this work was to compare clinical effectiveness of IVT with forteplase and alteplase in patients with AIS.

Materials and Methods

Data from the reperfusion therapy registry of the Arkhangelsk Regional vascular center (RVC) based at E. E. Volosevich First City Clinical Hospital (Arkhangelsk), which provides medical care to 1,300–1,400 patients with acute cerebrovascular accidents every year, were used for this single-center retrospective cohort study. The analysis included data from January 1, 2023, to July 1, 2025.

The study results were presented according to the EQUATOR network guidance for cohort studies [23].

The protocol for the registry set up was approved by the local ethics committee of the E. E. Volosevich First City Clinical Hospital of the Arkhangelsk Region (Arkhangelsk) on September 21, 2023. Data collection was carried out without obtaining informed consent due to the observational nature of the registry, which does not require additional medical or diagnostic interventions other than routine ones (the «waived informed consent» procedure, which allows for a deviation from the requirement to obtain informed consent).

The registry included patients aged over 18 years with AIS treated with reperfusion procedures (IVT and mechanical recanalization interventions) at the RVC. For the purposes of this study, patients who underwent IVT (either single or staged reperfusion) were included in the analysis. Cases with no data on functional recovery or whatever outcomes at discharge were excluded from the analysis.

IVT was performed based on indications and according to the current Russian MoH national and international clinical guidelines [3, 24]. When onset of AIS symptoms could not be established, patients were selected for the procedure based on DWI/FLAIR mismatch in brain MRI imaging. In all cases, the relevance of IVT was confirmed by joint decision of a neurologist and anesthesiologist-intensivist. All patients included in the registry received alteplase at a recommended dose of 0.9 mg/kg or 0.6 mg/kg for patients aged over 80 years for systemic thrombolysis according to the standard regimen (10% of the calculated dose was administered intravenously as a bolus within the first 60 seconds, and the remaining 90% was administered within 1 hour), or forteplase 10 mg i/v bolus injection. The use of forteplase relative to alteplase was considered as an exposure variable

For the purposes of subsequent analysis, the following potential confounders were selected from the registry: gender, age, concomitant pathology, the interval between AIS onset and IVT initiation, glycemia level on

admission, maximum systolic blood pressure (SBP) on the first post IVT day, use of staged reperfusion (IVT combined with mechanical recanalization procedures), and the severity of neurological deficit on admission according to National Institutes of Health Stroke Scale (NIHSS) [25]. Of the above factors, effect-modifying potential can be attributed to staged reperfusion, but stratified analysis was not done due to the small number of dual interventions in the sample.

Brain imaging was done using Revolution EVO (General Electric, USA), Brilliance CT 64 (Philips, Netherlands), or Sytec-S 2000i (General Electric, USA) spiral tomographs. Hemodynamic parameters were monitored using GE PROCARE B40 (USA) or Comen WQ-002 (China) monitors. Blood pressure was managed according to national and international guidelines: SBP was maintained at less than 180 mmHg. Diastolic blood pressure was adjusted if it exceeded 110 mmHg. Intravenous urapidil and azamethonium bromide were used to control patients' blood pressure.

The primary endpoint was functional recovery on discharge from the hospital, assessed by modified Rankin scale (mRS). The rehabilitation diagnosis and potential were assessed by a multidisciplinary team in all cases. Good functional recovery was defined as a score of 0–2 on the mRS. The secondary endpoints included hospital mortality, the rate of intracranial hemorrhages (ICH) and type 2 parenchymal hematomas (PH class 2) according to Heidelberg bleeding classification [26] separately, along with severe allergic reactions and length of hospital stay.

Statistical analysis of the data. Quantitative variables were presented as the mean (*M*) and standard deviation (*SD*) for variables with normal distribution, and the median (*Me*) and 25th and 75th quartiles for variables with skewed distribution. The normality of distribution was assessed using the Shapiro–Wilk test. Dichotomous variables were presented as absolute values and percentages. The differences between unrelated samples were assessed using the Mann–Whitney test due to non-normal distribution of the variables. Fisher's exact test was used to analyze the differences in qualitative variables.

Univariate and multivariate regression models were used to assess the relationship between the use of forteplase (relative to alteplase) and the attainment of good functional recovery (mRS 0–2 vs mRS 3–6). Univariate models were constructed to select significant confounders by evaluating the association between all demographic, clinical, and laboratory parameters and the functional outcome. The results of this analysis identified the following variables which were significantly associated with the functional outcome: patient age, NIHSS score on admission, maximum SBP in the first 24 hours after IVT, and the use of staged reperfusion. Multivariate regression models were constructed based on the results of this analysis, and all variables were entered into the model simultaneously. The results were presented as odds ratios (ORs) and adjusted ORs (aORs) with 95% confidence intervals (CIs).

To assess the relationship between the use of forteplase and length of hospital stay, we constructed simple and multivariate linear regression models. To select confounders that were significantly associated with the duration of hospital stay, we conducted a univariate analysis, testing all potential confounders. According to the results, only the severity of neurological deficits on admission assessed by the NIHSS, was associated with the dependent variable. We included the variables in the final model simultaneously. The results were presented as regression coefficients B with 95% confidence intervals.

The STATA 14 MP software (StataCorp, USA) was used for statistical analysis.

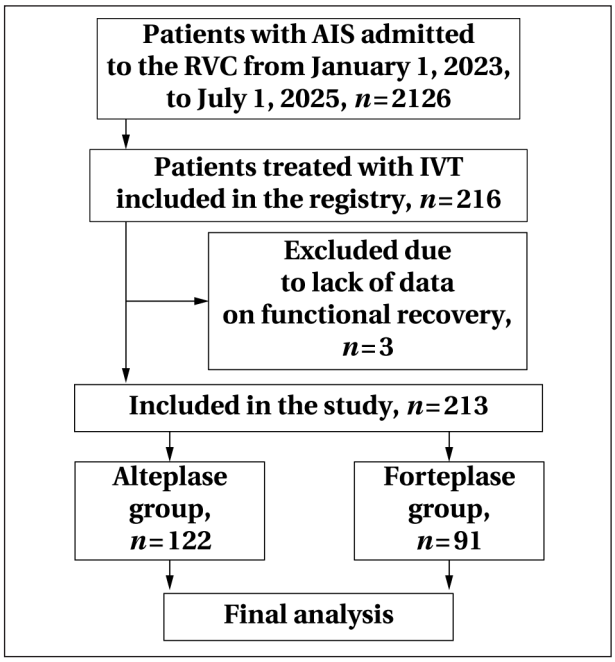

Fig. 1. Patient selection scheme for the study.

Results

During the study, out of 2126 patients with AIS admitted to the RVC 216 patients were treated with IVT (10.2%) and included in the registry. A total of 213 patients were included in the final analysis (Fig. 1).

Of the 213 patients included in the final analysis, 111 (52.1%) were men. The median age was 68 (60; 76) years, and forteplase was used in 91 (42.7%) cases. Detailed clinical and demographic characteristics are presented in Table 1

The median mRS score at discharge in the sample was 3 (1;4), and 103 (48.36%) patients achieved good functional recovery. In the forteplase group, the mRS score at discharge was 2 (1;3) versus 3 (1; 4) in patients who received alteplase, $p=0.016$. Good functional recovery was recorded in 52 (57.14%) and 51 (41.8%) cases in the forteplase and alteplase groups, respectively, $p=0.019$. Assessment of the relationship between the use of forteplase and functional recovery is presented in Table 2.

The mortality rate in the sample was 20 (9.39%). In the forteplase group 6 (6.59%) cases were fatal,

Table 1. Clinical and demographic characteristics of patients.

Parameters	Parameter values in the entire sample and in the groups			*p**
	Entire sample, *n* = 213	Alteplase, *n* = 122	Forteplase, *n* = 91	
Gender, men, *n* (%)	111 (52.11)	68 (55.74)	43 (47.25)	0.267
Age, years, *Me* (*Q1*; *Q3*)	68 (60; 76)	68 (60; 76)	68 (60; 76)	0.978
Time since AIS symptoms onset on admission, minutes, *Me* (*Q1*; *Q3*)	180 (140; 230)	176 (133; 220)	185 (153; 230)	0.128
NIHSS on admission, scores, *Me* (*Q1*; *Q3*)	8 (5; 17)	11 (6; 19)	6 (5; 10)	$p < 0.001$
Max SBP within first 24 hrs, mm Hg., *Me* (*Q1*; *Q3*)	169 (152; 180)	170 (152; 180)	165 (150; 179)	0.221
Glycemia level on admission, mmol/l	6.5 (5.6; 8)	6.5 (5.7; 7.6)	6.3 (5.6; 8.3)	0.863
Staged reperfusion, *n* (%)	19 (8.92)	16 (13.1)	3 (3.3)	0.014
Comorbidities				
Arterial hypertension, *n* (%)	204 (95.77)	115 (94.26)	89 (97.8)	0.306
Diabetes mellitus, *n* (%)	34 (15.96)	18 (14.75)	16 (17.58)	0.577
Arial fibrillation, *n* (%)	45 (21.13)	26 (21.31)	19 (20.88)	1.0

Note. Here and Table 2: NIHSS is the National Institutes of Health Stroke Scale, SBP is systolic blood pressure; * — is the significance of a difference between the Forteplase and Alteplase groups.

Table 2. Relationship between the use of forteplase and attainment of good functional recovery (mRS 0–2).

Predictor	Univariate analysis			Adjusted analysis		
	OR	95% CI	*p*	aOR	95% CI	*p*
Use of forteplase	1.86	1.07–3.22	0.027	1.04	0.54–2.01	0.91
Age	0.95	0.93–0.98	< 0.001	0.96	0.94–0.99	0.006
NIHSS score on admission	0.85	0.81–0.9	< 0.001	0.87	0.82–0.93	< 0.001
Max SBP first 24 hrs	0.98	0.96–0.99	0.002	0.99	0.97–1.0	0.17
Staged reperfusion	0.1	0.02–0.48	0.004	0.36	0.07–1.9	0.232

compared to 14 (11.48%) in the alteplase group, $p = 0.247$.

Three (3.3%) PH 2cases were documented in the forteplase group, compared to 1 case (0.8%) in the alteplase group, $p = 0.315$. The incidence of all ICH types according to Heidelberg bleeding classification is presented in Table 3.

The rate of severe allergic reactions did not differ between the groups: 1 (0.82%) vs. 2 (2.2%) cases among patients who received alteplase and forteplase, respectively, $p = 0.577$.

The duration of hospital stay was 15 (11; 23) days in the alteplase group and 12 (10; 16) days in the forteplase group, $p = 0.005$. The use of forteplase was not associated with shorter hospital stay in a multivariate analysis adjusted for the severity of neurological deficits on admission: B = –0.54 [95% CI –3.74–2.66], $p = =0.741$ (Fig. 2).

Table 3. Incidence of intracranial hemorrhage in the groups.

Parameters	Values in the groups, *n* (%)	
	Alteplase, *n* = 122*	Forteplase, *n* = 91*
No ICH	100 (81.97)	81 (89.01)
Class 1a	5 (4.10)	4 (4.40)
Class 1b	10 (8.2)	2 (2.20)
Class 1c	6 (4.92)	1 (1.10)
Class 2	1 (0.82)	3 (3.30)

Note. ICH — intracranial hemorrhage; * — $p = 0.1$.

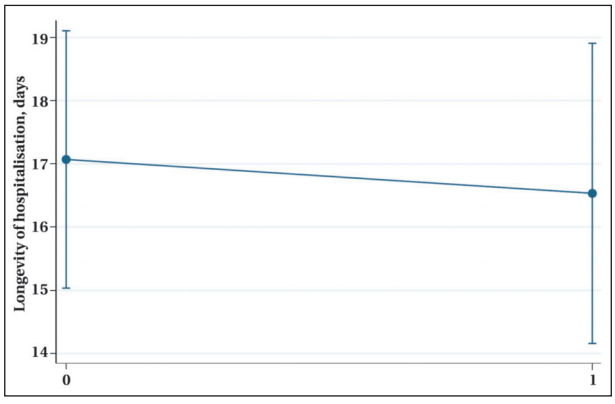

Fig. 2. Marginal average hospital stays by thrombolytic used, obtained in a multivariate linear regression model.

Discussion

The analysis of reperfusion therapy registry of the Arkhangelsk Regional vascular center (RVC) based at E. E. Volosevich First City Clinical Hospital (Arkhangelsk) suggests that forteplase is comparable in efficacy and safety to alteplase in IVT management of AIS.

Less severe cases in terms of neurological deficits on admission in the forteplase group can be attributed to two factors. The first relates to patient screening algorithm for IVT, as the on-call staff selected less severe cases for reperfusion procedure during implementation phase of forteplase bolus administration. The second — to restricted use of forteplase as until December 2024 it was not approved for staged reperfusion based on prescribing information, while clinical guidelines envisaged alteplase-based thrombolysis followed by interventional treatment in patients with large vessel oc-

clusion (LVO) and severe neurological deficits, explaining evermore the difference in rates of staged reperfusion in two study groups.

It should be noted that greater proportion of patients attained functional recovery at discharge in the forteplase group, i. e. 52 (57.14%) patients with mRS 0–2 score versus 51 (41.8%) in the alteplase group, OR 1.86 [95% CI 1.07–3.22], $p=0.027$. Most likely, this is associated with less severe neurological deficit on admission in the forteplase group, as evidenced by NIHSS 6 scores (5; 10) vs 11 (6; 19) scores in the alteplase group. After adjustment for potential confounders (NIHSS on admission, patient age, maximum SBP on the first day after IVT, and the use of staged reperfusion), no association was found between the use of forteplase and achievement of good functional outcome: aOR 1.04 [95% CI 0.54–2.01], $p=0.91$. These findings are consistent with previously published results of other studies [27]. According to Alasheev A. M. et al, patient functional recovery does not depend on the type of thrombolytic used [28]. The results of the only RCT comparing the effects of staphylokinase amino acid sequence-based recombinant protein and alteplase showed that 50% of patients in the forteplase group achieved excellent functional recovery (mRS 0–1), compared to 40% in the alteplase group, but the difference was not statistically significant ($p=0.1$) [22].

The results of M. Yu. Volodyukhin et al. study published in 2023 indicate that efficacy and safety of forteplase in staged reperfusion are comparable to those of alteplase [29]. The results of this study are consistent with the above mentioned with regard to adjusted for the use of endovascular recanalization procedures multivariate analysis, which demonstrated that IVT with forteplase had no significant influence on patient functional outcomes compared to alteplase: aOR 1.04 [95% CI 0.54–2.01] $p=0.91$.

Published data on mortality rates from FRIDA randomized trial were 10% in the forteplase group compared to 14% in the alteplase group, $p=0.032$ [22]. Similar trend is obvious in the presented analysis, with 11.5% mortality in the alteplase group compared to 6.6% in the forteplase group, although the difference was not statistically significant, $p=0.247$.

ICH was reported in 11 (11%) and 22 (18%) patients form forteplase (recombinant protein containing staphylokinase amino acid sequence) and alteplase groups, respectively. According to R. S. Maksimov et al, ICH was reported in forteplase and alteplase groups in equal proportions [27], which is consistent with the results of this study. Published data indicate close to 6% incidence of PH 2 class hemorrhage in patients receiving IVT with forteplase [29]. The 3.3% rate of PH2 in our study can be explained by small sample size. No statistically significant differences in rates of PH 2 and symptomatic ICH between the two thrombolytic agents was found either in this study, or published data from other studies [30]. The incidence of severe allergic reactions did not differ in the groups, which is also consistent with the results of a previously published study [30].

Shorter median hospital stay was reported after treatment with forteplase compared to alteplase — 12 vs. 15 days, respectively, $p=0.005$. Similar results were reported in the study of A. A. Kulesh et al., with 1 day difference in favor of forteplase, $p<0.005$ [31]. However, after adjustment for the severity of neurological deficit on admission, this initial statistically significant difference between the groups in length of hospital stay was lost and became statistically insignificant: B = –0.54 [95% CI –3.74–2.66], $p=0.741$.

The study is limited by its retrospective, single-center design, which makes it difficult to generalize the results onto entire AIS population. Additionally, due to the specific nature of the reperfusion intervention registry, patients' functional recovery was assessed upon discharge from the hospital rather than at 90 days, which is not optimal from the perspective of standardized approaches to assessing outcomes in studies on this topic. However, the sufficient sample size allowed for statistically significant results to be obtained after appropriate statistical analysis.

Conclusion

IVT with forteplase is an effective and safe method of a precise therapy in the acute period of ischemic stroke. Rates of achieving good functional recovery, ICH incidence, and the duration of hospital stay for IVT with forteplase are comparable to those obtained with alteplase.

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PMID: 39113454.

Received 13.10.2025
Accepted 14.01.2026
Online First 26.01.2026