Low-Dose Intra-Arterial Prourokinase for Acute Ischaemic Stroke: A Systematic Review and Meta-Analysis

Prouroquinase Intra-Arterial em Baixa Dose para o Acidente Vascular Cerebral Isquêmico Agudo: Uma Revisão Sistemática e Meta-Análise

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ABSTRACT

Introduction: Despite advances in acute ischemic stroke (AIS) treatment, reperfusion remains suboptimal. This study evaluates the efficacy and safety of low-dose intra-arterial prourokinase as an adjunct to standard therapy.
Methods: A systematic search of PubMed and Embase was conducted up to January 18, 2025, to identify randomized controlled trials (RCTs) comparing low-dose intra-arterial prourokinase plus standard treatment versus standard treatment in adults with AIS. Primary outcomes included hemorrhages with clinical deterioration, overall hemorrhagic complications, and mortality. Secondary outcomes assessed functional recovery—using the modified Rankin Scale (mRS 0–1), Barthel Index (≥90), and NIHSS response—as well as complete and partial recanalization at 2 hours. Meta-analyses were performed using a random-effects model, with heterogeneity assessed via the I^2 statistic.
Results: Two RCTs were included. Prourokinase significantly increased the likelihood of complete recanalization (OR 5.523; 95% CI: 1.449–21.052; p = 0.012) and partial recanalization (OR 5.214; 95% CI: 2.382–11.411; p < 0.001), both with low heterogeneity. No significant differences were observed for mortality (RD 0.522; 95% CI: 0.271–1.007; p = 0.053) or hemorrhages with clinical deterioration (OR 1.954; 95% CI: 0.599–6.371; p = 0.267). Functional outcomes favored prourokinase without statistical significance: mRS 0–1 (OR 1.675; p = 0.151), Barthel Index ≥90 (OR 1.450; p = 0.216), and NIHSS response (OR 1.804; p = 0.172).
Conclusions: Low-dose intra-arterial prourokinase enhances early recanalization in AIS and suggests potential functional benefit without increasing adverse outcomes.

Keywords: Ischemic Stroke, Urokinase, Systematic Review, Meta-Analysis

RESUMO

Introduction: Apesar dos avanços no tratamento do acidente vascular cerebral isquêmico (AVCi) agudo, a reperfusão continua insatisfatória. Este estudo avalia a eficácia e segurança da prouroquinase de baixa dose intra-arterial como um complemento à terapia padrão.
Methods: Uma busca sistemática no PubMed e Embase foi realizada até 18 de janeiro de 2025, para identificar ensaios clínicos controlados randomizados comparando a prouroquinase intra-arterial de baixa dose associado ao tratamento padrão versus tratamento padrão em adultos com AVCi. Os desfechos primários incluíram hemorragias com deterioração clínica, complicações hemorrágicas gerais e mortalidade. Os desfechos secundários avaliaram a recuperação funcional — usando a Escala de Rankin modificada (mRS 0–1), Índice de Barthel (≥90) e resposta NIHSS — assim como a recanalização completa e parcial em 2 horas. Metanálises foram realizadas usando um modelo de efeitos aleatórios, com heterogeneidade avaliada pelo teste estatístico I^2.
Results: Dois estudos controlados randomizados foram incluídos. A prouroquinase aumentou significativamente a probabilidade de recanalização completa (OR 5,523; IC 95%: 1,449–21,052; p = 0,012) e recanalização parcial (OR 5,214; IC 95%: 2,382–11,411; p < 0,001), ambos com baixa heterogeneidade. Não foram observadas diferenças significativas para mortalidade (RD 0,522; IC 95%: 0,271–1,007; p = 0,053) ou hemorragias com deterioração clínica (OR 1,954; IC 95%: 0,599–6,371; p = 0,267). Os desfechos funcionais favoreceram o prouroquinase sem significância estatística: mRS 0–1 (OR 1,675; p = 0,151), Índice de Barthel ≥90 (OR 1,450; p = 0,216), e resposta NIHSS (OR 1,804; p = 0,172).
Conclusions: A prouroquinase intra-arterial em baixa dose melhora a recanalização precoce no AVCi agudo e com benefício funcional potencial sem aumentar os desfechos adversos.

Palavra-chave: Acidente Vascular Cerebral Isquêmico, Uroquinase, Revisão Sistemática, Meta-análise

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Authors' Contributions
J.V.A.F. led the study, conducted analyses, and drafted the manuscript. J.V.O.R. assisted with data collection and analysis. M.M.A.H. supervised and reviewed the work. All authors approved the final version.

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INTRODUCTION

Acute ischemic stroke (AIS) is a leading cause of morbidity and mortality. Although standard treatments—such as intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) and mechanical thrombectomy—have improved outcomes, a significant proportion of patients still do not achieve adequate reperfusion or functional recovery[1-3]. This underscores the need to explore adjunctive strategies that could enhance current therapies without increasing adverse events[4,5].

Low-dose prourokinase, a fibrinolytic agent with high fibrin specificity, has been studied for its intra-arterial use, particularly in combination with heparin-based protocols. However, its role remains underexplored in the contemporary context of stroke care. To our knowledge, no meta-analysis has specifically evaluated low-dose intra-arterial prourokinase as an adjunct to conventional treatment strategies[6-10]. In this review, "standard therapy" refers exclusively to heparin-based regimens, as both included randomized controlled trials (RCTs) assessed the effect of intra-arterial prourokinase added to heparin and supportive care.

This systematic review and meta-analysis aim to assess the efficacy and safety of low-dose intra-arterial prourokinase in AIS by analyzing its effects on vessel recanalization, functional outcomes, and hemorrhagic complications. The findings provide preliminary evidence for its potential value and reinforce the need for further studies, especially evaluating its combination with modern reperfusion strategies such as rt-PA or mechanical thrombectomy.

METHODS

Protocol and Registration

This systematic review and meta-analysis was conducted following the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The study protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) under the identifier CRD420251002408.

Search Strategy Search Strategy and Eligibility Criteria

A thorough search was performed in the PubMed and Embase databases to identify relevant studies published up to January 18, 2025. The search strategy utilized a combination of keywords and Medical Subject Headings (MeSH) terms, such as "Prourokinase", "Stroke" and "Randomized Controlled Trial". Additionally, reference lists and discussion sections of relevant articles and reviews were manually screened to ensure no eligible studies were overlooked.

Eligible studies included RCTs enrolling adults with AIS, comparing low-dose intra-arterial prourokinase as an adjunct to standard treatment (e.g., intravenous thrombolysis or mechanical thrombectomy) versus standard treatment alone, with sufficient data on predefined primary and secondary outcomes. Exclusion criteria included non-randomized studies, animal research, and studies lacking adequate data for analysis.

Titles and abstracts were screened independently by two reviewers, followed by a full-text review for potentially relevant studies. Any disagreements were resolved through discussion or, if necessary, consultation with a third reviewer.

Search Strategy Search Strategy and Eligibility Criteria

Two reviewers independently extracted data using a standardized form in Microsoft Excel, and a third reviewer verified the extracted information to ensure consistency and accuracy. Collected data included study characteristics (e.g., author, publication year, sample size, and intervention details), participant demographics (e.g., age, sex, and cardiovascular risk factors), and outcomes.

Primary outcomes included hemorrhages with clinical deterioration, mortality, and all hemorrhagic complications. Functional recovery was assessed using the Modified Rankin Scale (mRS) scores of 0 or 1, the Barthel Index scores of 90 or 100, and NIHSS scores. Secondary outcomes focused on recanalization metrics, including complete recanalization at 2 hours and partial recanalization at 2 hours.

Odds Ratios (ORs) were used for dichotomous outcomes, including mRS scores of 0–1, all intracranial hemorrhages, and SAEs. Mean Differences (MDs) were calculated for continuous outcomes, such as changes in NIHSS scores at specified time points. Risk Differences (RDs) were used for mortality due to the absence of events in one of the comparison groups. Results were presented with 95% confidence intervals (CIs).

Heterogeneity was evaluated using the I^2 statistic, with values above 50% indicating substantial variability. A random-effects model using the Hartung–Knapp–Sidik–Jonkman method was applied to account for between-study differences, complemented by a fixed-effects model for sensitivity analyses. Statistical analyses were performed using the “meta” package in R Software (version 4.4.2, R Foundation for Statistical Computing, Austria). Statistical significance was set at a two-tailed p-value <0.05.

Risk of Bias Assessment

The Cochrane Collaboration’s tool for assessing the risk of bias was used to evaluate potential biases in selection, performance, detection, attrition, and reporting domains[11]. Given the limited number of included studies (<10), publication bias was not assessed.

RESULTS

Search Results

As shown in Figure 1, two RCTs were included in the analysis[12,13]. The study characteristics and demographic data of the included RCTs are summarized in Table 1.

Table 1. Studies Characteristics and Demographic Data

Author, year	del Zoppo, 1998		Furlan, 1999	
Study Design	RCT		RCT	
Follow up, days (total)	90		90	
Groups	Intervention 6mg rpro-UK + Heparin	Control Placebo + Heparin	Intervention 9mg rpro-UK + Heparin	Control Heparin
Sample size, n (total)	26	14	121	59
Female sex, %	46	64	42	39
Race (white), %	77	71	76	88
Age, y†	66.56 (11.0)	69.66 (11.1)	64 (14)	64 (14)
NIHSS†	17.0 (N/A)	19.0 (N/A)	17 (5-27)	17 (4-28)
Cardiac etiology, %	54	64	60	51
Angiography etiology, %	8	0	1	3
Atherosclerosis of ICA etiology, %	8	7	9	12
Unknown etiology, %	31	29	27	34
Time from stroke onset to randomization or treatment, h†	5.4 (N/A)	5.7 (N/A)	4.7 (4.0-5.3)	5.1 (4.2-5.5)

Legend: †, mean (SD) or median (IQR); rpro-UK, Recombinant Pro-Urokinase; RCT, Randomized Controlled Trial; n, number; y, year; NIHSS, National Institutes of Health Stroke Scale; ICA, Internal Carotid Artery; h, hours; N/A, Not Available

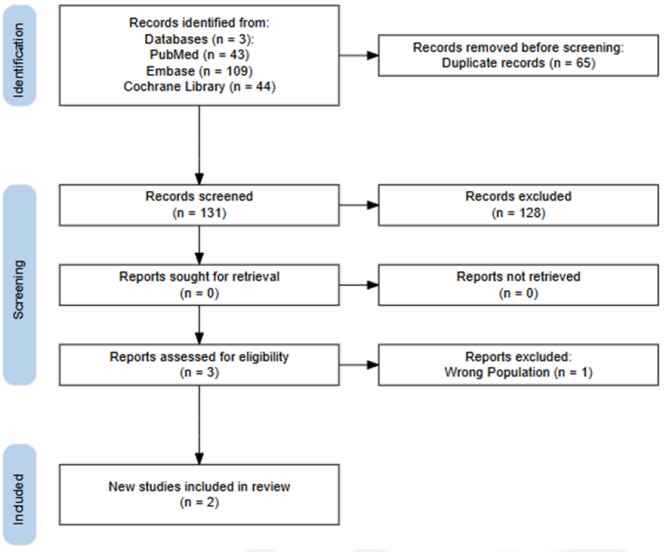

Figure 1. Prisma Flow Diagram

Legend: Diagram illustrating the study selection process, including the number of records identified, screened, assessed for eligibility, and included in the final systematic review and meta-analysis.

Efficacy Outcomes

Intra-arterial low-dose prourokinase demonstrated a significant benefit in early recanalization outcomes. Complete recanalization at 2 hours was achieved in 24 of 134 patients treated with prourokinase versus 2 of 64 in the heparin-treated control group, resulting in a pooled odds ratio (OR) of 5.523 (95% CI: 1.449–21.052; p = 0.012), with no heterogeneity (I^2 = 0.0%; Figure 2). Partial recanalization at 2 hours occurred in 62 of 134 patients in the intervention group compared to 9 of 64 heparin controls, with a pooled OR of 5.214 (95% CI: 2.382–11.411; p < 0.001; I^2 = 0.0%; Figure 2). Functional outcomes showed a favorable trend with prourokinase, although not statistically significant. mRS scores of 0 or 1 were reported in 39 of 147 patients in the prourokinase group versus 13 of 73 in the heparin control group (OR 1.675; 95% CI: 0.829–3.386; p = 0.151; I^2 = 0.0%; Figure 2). Barthel Index scores of 90 or 100 were observed in 61 of 147 prourokinase-treated patients and 24 of 73 heparin-treated controls (OR 1.450; 95% CI: 0.805–2.612; p = 0.216; I^2 = 0.0%; Figure 2). NIHSS improvement occurred in 27 of 147 patients in the prourokinase arm versus 8 of 73 in the heparin arm (OR 1.804; 95% CI: 0.773–4.210; p = 0.172; I^2 = 0.0%; Figure 2).

Figure 2A

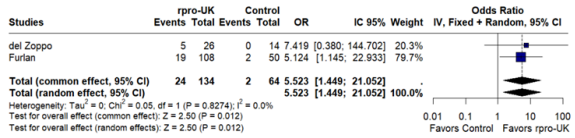

Figure 2B

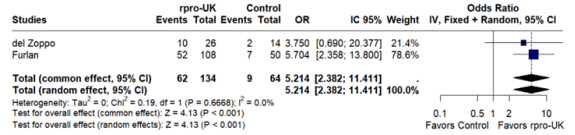

Figure 2C

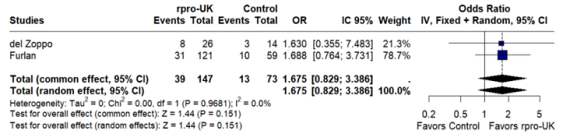

Figure 2D

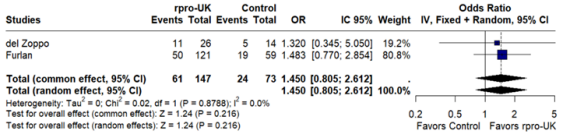

Figure 2E

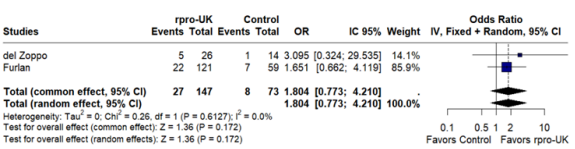

Figure 2. Forest Plots of Efficacy Outcomes

Legend: Figure 2A shows complete recanalization at 2 hours; Figure 2B displays partial recanalization at 2 hours; Figure 2C presents the proportion of patients with a modified Rankin Scale (mRS) score of 0 or 1; Figure 2D shows the proportion of patients with a Barthel Index score of 90 or 100; and Figure 2E illustrates NIHSS improvement.

Safety Outcomes

In terms of safety, no significant differences were identified between groups. Hemorrhages with clinical deterioration were reported in 15 of 134 patients receiving intra-arterial prourokinase and in 4 of 68 in the control group, with a pooled OR of 1.954 (95% CI: 0.599–6.371; p = 0.267; I^2 = 0.0%; Figure 3A). All hemorrhagic complications occurred in 86 of 134 patients in the prourokinase group compared to 36 of 68 in the control group, with a pooled risk difference of 1.596 (95% CI: 0.875–2.911; p = 0.128; I^2 = 0.0%; Figure 3B). Mortality was recorded in 27 of 147 patients who received prourokinase and in 22 of 73 control patients, resulting in a pooled risk difference of 0.522 (95% CI: 0.271–1.007; p = 0.053; I^2 = 0.0%; Figure 3C), showing no significant increase in death risk.

Figure 3A

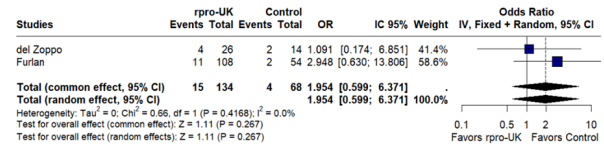

Figure 3B

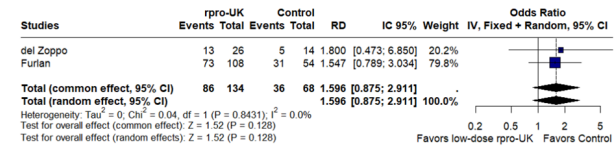

Figure 3C

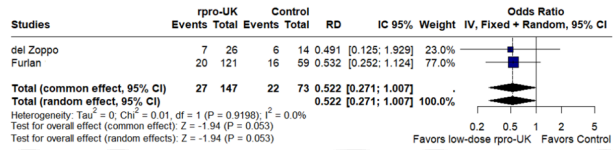

Figure 3. Forest Plots of Safety Outcomes

Legend: Figure 3A presents the occurrence of hemorrhages with clinical deterioration; Figure 3B shows the total number of hemorrhagic complications; and Figure 3C displays all-cause mortality.

Risk of Bias Assessment

The overall risk of bias assessment indicated some concerns for both included studies. Figure 4 details the evaluation across the assessed domains.

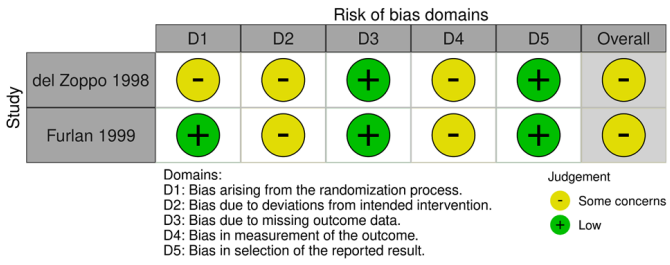

Figure 4. Risk of Bias Assessment

Legend: Summary of the risk of bias judgments across five domains for the two included randomized controlled trials. D1: bias arising from the randomization process; D2: bias due to deviations from intended intervention; D3: bias due to missing outcome data; D4: bias in measurement of the outcome; D5: bias in selection of the reported result. Judgments are indicated as "Low" or "Some concerns".

DISCUSSION

This systematic review and meta-analysis provides a focused synthesis of available randomized evidence on the use of low-dose intra-arterial prourokinase as an adjunct to standard care, defined in this review as heparin and supportive management, in patients with AIS. The findings suggest that this strategy offers a meaningful improvement in early recanalization rates without significantly increasing the risk of hemorrhagic complications or mortality. Although functional recovery outcomes trended favorably toward prourokinase, they did not reach statistical significance in the pooled analysis. These results support the potential of intra-arterial prourokinase to enhance early reperfusion and possibly improve long-term outcomes in selected AIS patients.

In terms of efficacy, the observed improvement in both complete and partial recanalization rates reinforces the thrombolytic capacity of prourokinase when delivered intra-arterially[14-17]. Compared to intravenous alteplase—currently the standard pharmacologic reperfusion strategy—prourokinase via intra-arterial route may offer greater fibrin-specific thrombolysis directly at the clot site, facilitating rapid vessel reopening[9,18–20]. Mechanical thrombectomy has revolutionized AIS care, but is limited by access, operator dependency, and incomplete recanalization in a subset of cases[21-25]. In this context, pharmacologic augmentation with intra-arterial agents such as prourokinase becomes particularly attractive. The trends toward improved scores on mRS, Barthel Index, and NIHSS suggest possible downstream functional benefits, although underpowered to confirm superiority in these domains.

Given that both included studies evaluated prourokinase in combination with heparin rather than modern reperfusion therapies, the findings suggest that intra-arterial low-dose prourokinase may provide additional benefit in AIS patients managed with heparin alone. This highlights its potential as an adjunct in contexts where rt-PA or mechanical thrombectomy are unavailable or contraindicated. Regarding safety, the findings are reassuring. Despite increased rates of total hemorrhagic events numerically, there were no statistically significant differences in clinically relevant hemorrhages or mortality between groups. This is important when evaluating any fibrinolytic agent, particularly one delivered intra-arterially, which may raise concerns about local vessel damage or hemorrhagic transformation[26-32]. Compared to historical data from the PROACT II trial—which used higher doses of intra-arterial prourokinase with increased bleeding risks—this meta-analysis indicates that low-dose administration may balance efficacy and safety more favorably[13,33-35].

From a physiopathological and pharmacological standpoint, prourokinase is a proenzyme converted to urokinase at the thrombus site, promoting targeted fibrinolysis with high affinity for fibrin-bound plasminogen[6,36-39]. In AIS, where rapid restoration of

perfusion is essential to minimize infarct core expansion and preserve penumbral tissue, intra-arterial delivery ensures high local concentration while minimizing systemic exposure[40-46]. This mechanism aligns with the pathobiology of AIS, where clot composition and location determine recanalization success[47-53]. By acting directly within the occluded vessel, intra-arterial prourokinase potentially circumvents some limitations of systemic thrombolytics, especially in large-vessel occlusions. Nonetheless, intra-arterial administration presents inherent limitations, including the need for specialized infrastructure, longer preparation and procedural times, and higher technical complexity. These factors may restrict its applicability to high-resource settings or delay time-to-treatment in emergency contexts.

Despite the favorable findings, this study has limitations that must be acknowledged. The inclusion of only two RCTs restricts the robustness of the evidence and limits the ability to explore heterogeneity or perform subgroup analyses[12,13]. The relatively small sample sizes reduce the statistical power to detect differences in functional outcomes and safety endpoints, especially those that are less frequent, such as symptomatic hemorrhages or mortality. Additionally, variation in treatment protocols may have introduced clinical heterogeneity, potentially influencing the magnitude of the observed effects. The functional outcomes assessed, although relevant, were secondary endpoints in the original trials and may not have been adequately powered or uniformly measured across studies, limiting the confidence in conclusions regarding long-term recovery. Additionally, both included RCTs are from previous decades, reflecting an earlier era of AIS management. These factors suggest that while the current data are promising, they should be interpreted as exploratory and hypothesis-generating rather than definitive.

Future research should focus on larger, multicenter RCTs evaluating low-dose intra-arterial prourokinase in combination with contemporary endovascular techniques. Subgroup analyses stratifying patients by occlusion site, stroke severity, time to treatment, and imaging profiles (e.g., perfusion mismatch) could help refine candidate selection. Additionally, head-to-head comparisons with other intra-arterial fibrinolytics or direct comparison with tenecteplase-based regimens would further inform clinical decision-making. Investigation into the optimal dosing strategy and timing relative to thrombectomy would also be valuable.

CONCLUSION

This study suggests that low-dose intra-arterial prourokinase enhances recanalization rates in AIS but does not significantly improve functional recovery or mortality while increasing hemorrhagic risks. These findings are based on trials in which the control groups received only heparin and supportive care, and highlight the need for further research to optimize the balance between efficacy and safety in thrombolytic strategies for acute ischemic stroke. Future trials should aim to refine patient selection criteria and dosing strategies to maximize clinical benefits while mitigating hemorrhagic complications.

REFERENCES

1. Gottula AL, Barreto AD, Adeoye O. Alteplase and adjuvant therapies for acute ischemic stroke. Semin Neurol. 2021 Feb;41(1):16-27. doi:10.1055/s-0040-1722720.
2. Dorado L, Millán M, Dávalos A. Reperfusion therapies for acute ischemic stroke: an update. Curr Cardiol Rev. 2014 Nov;10(4):327-35. doi:10.2174/1573403x10666140320144637.
3. Bhatia K, Bhagavan S, Bains N, French B, Siddiq F, Gomez CR, Qureshi AI. Current endovascular treatment of acute ischemic stroke. Mo Med. 2020 Sep-Oct;117(5):480-9.
4. Molina CA, Alvarez-Sabín J. Recanalization and reperfusion therapies for acute ischemic stroke. Cerebrovasc Dis. 2009;27 Suppl 1:162-7. doi:10.1159/000200455.
5. Fan S, Yang L, Ji X. Reperfusion therapy for acute ischemic stroke: where we are and where to go. J Transl Int Med. 2025 Mar 19;13(1):1-3. doi:10.1515/jtim-2025-0001.
6. Ding BS, Hong N, Murciano JC, Ganguly K, Gottstein C, Christofidou-Solomidou M, Albelda SM, Fisher AB, Cines DB, Muzykantov VR. Prophylactic thrombolysis by thrombin-activated latent prourokinase targeted to PECAM-1 in the pulmonary vasculature. Blood. 2008 Feb 15;111(4):1999-2006. doi:10.1182/blood-2007-07-103002.
7. Adivitiya, Khasa YP. The evolution of recombinant thrombolytics: current status and future directions. Bioengineered. 2017 Jul 4;8(4):331-58. doi:10.1080/21655979.2016.1229718.
8. Nikitin D, Choi S, Mican J, Toul M, Ryu WS, Damborsky J, Mikulik R, Kim DE. Development and testing of thrombolytics in stroke. J Stroke. 2021 Jan;23(1):12-36. doi:10.5853/jos.2020.03349.
9. Fox D, Ouriel K, Green RM, Stoughton J, Riggs P, Cimino C. Thrombolysis with prourokinase versus urokinase: an in vitro comparison. J Vasc Surg. 1996 Apr;23(4):657-66. doi:10.1016/s0741-5214(96)80047-4.
10. Gurewich V. Thrombolysis: a critical first-line therapy with an unfulfilled potential. Am J Med. 2016 Jun;129(6):573-5. doi:10.1016/j.amjmed.2015.11.033.
11. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct 18;343:d5928. doi:10.1136/bmj.d5928.
12. del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism. Stroke. 1998 Jan;29(1):4-11. doi:10.1161/01.str.29.1.4.
13. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, Pessin M, Ahuja A, Callahan F, Clark WM, Silver F, Rivera F. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. JAMA. 1999 Dec 1;282(21):2003-11. doi:10.1001/jama.282.21.2003.
14. Li S, Gu HQ, Feng B, Li H, Wang X, Dong Q, Fan D, Xu Y, Zhu S, Dai H, Wei Y, Wang Z, Lu G, Ma Y, Li Z, Wang Y, Meng X, Zhao X, Liu L, Wang Y; PROST-2 investigators. Safety and efficacy of intravenous recombinant human prourokinase for acute ischaemic stroke within 4·5 h after stroke onset (PROST-2): a phase 3, open-label, non-inferiority, randomised controlled trial. Lancet Neurol. 2025 Jan;24(1):33-41. doi:10.1016/S1474-4422(24)00436-8.

15. Robinson T, Zaheer Z, Mistri AK. Thrombolysis in acute ischaemic stroke: an update. Ther Adv Chronic Dis. 2011 Mar;2(2):119-31. doi:10.1177/2040622310394032.
16. Takano K, Carano RA, Tatlisumak T, Meiler M, Sotak CH, Kleinert HD, Fisher M. Efficacy of intra-arterial and intravenous prourokinase in an embolic stroke model evaluated by diffusion-perfusion magnetic resonance imaging. Neurology. 1998 Apr;50(4):870-5. doi:10.1212/wnl.50.4.870.
17. Xavier AR, Siddiqui AM, Kirmani JF, Hanel RA, Yahia AM, Qureshi AI. Clinical potential of intra-arterial thrombolytic therapy in patients with acute ischaemic stroke. CNS Drugs. 2003;17(4):213-24. doi:10.2165/00023210-200317040-00001.
18. Nguyen TN, Babikian VL, Romero R, Pikula A, Kase CS, Jovin TG, Norbash AM. Intra-arterial treatment methods in acute stroke therapy. Front Neurol. 2011 Mar 8;2:9. doi:10.3389/fneur.2011.00009.
19. Rehan R, Virk S, Wong CCY, Passam F, Layland J, Keech A, Yong A, White HD, Fearon W, Ng M. Intracoronary thrombolysis in ST-elevation myocardial infarction: a systematic review and meta-analysis. Heart. 2024 Jul 10;110(15):988-96. doi:10.1136/heartjnl-2024-324078.
20. Wardlaw JM, Koumellis P, Liu M. Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke. Cochrane Database Syst Rev. 2013 May 31;2013(5):CD000514. doi:10.1002/14651858.CD000514.pub3.
21. Neumann A, Schildhauer P, Weiler SM, Schramm P, Schacht H, Royl G, Jensen-Kondering U. Mechanical thrombectomy failure in anterior and posterior circulation stroke: current results from a high-volume comprehensive center. Neurol Sci. 2025 Feb;46(2):807-17. doi:10.1007/s10072-024-07881-2.
22. Aroor SR, Zevallos CB, Asif KS, Singh N, Potter-Vig J, Rodriguez-Calienes A, et al. Mechanical Thrombectomy Access Score: a systematic review and modified Delphi of global barriers to endovascular therapy. Stroke. 2025 Jan;56(1):158-67. doi:10.1161/STROKEAHA.124.047805.
23. Wrona P, Wróbel D, Mizera P, Jóźwik J, Jakobschy K, Zdrojewska K, et al. The benefit of optimizing recanalization during mechanical thrombectomy in patients with acute ischemic stroke depends on preprocedural tissue-level collateralization. Neuroradiology. 2024 Nov;66(11):2023-31. doi:10.1007/s00234-024-03443-7.
24. Sommer KN, Bhurwani MMS, Mokin M, Ionita CN. Evaluation of challenges and limitations of mechanical thrombectomy using 3D printed neurovascular phantoms. Proc SPIE Int Soc Opt Eng. 2021 Feb;11601:116010B. doi:10.1117/12.2580962.
25. Aroor SR, Asif KS, Potter-Vig J, Sharma A, Menon BK, Inoa V, et al. Mechanical thrombectomy access for all? Challenges in increasing endovascular treatment for acute ischemic stroke in the United States. J Stroke. 2022 Jan;24(1):41-8. doi:10.5853/jos.2021.03909.
26. Chapin JC, Hajjar KA. Fibrinolysis and the control of blood coagulation. Blood Rev. 2015 Jan;29(1):17-24. doi:10.1016/j.blre.2014.09.003.
27. Lapointe M, Haines S. Fibrinolytic therapy for intraventricular hemorrhage in adults. Cochrane Database Syst Rev. 2002;2002(3):CD003692. doi:10.1002/14651858.CD003692.
28. Moore HB, Moore EE, Neal MD, Sheppard FR, Kornblith LZ, Draxler DF, et al. Fibrinolysis shutdown in trauma: historical review and clinical implications. Anesth Analg. 2019 Sep;129(3):762-73. doi:10.1213/ANE.0000000000004234.
29. Wang D, Liu J, Norton C, Liu M, Selim M. Local fibrinolytic therapy for intraventricular hemorrhage: a meta-analysis of randomized controlled trials. World Neurosurg. 2017 Nov;107:1016-1024.e1. doi:10.1016/j.wneu.2017.07.135.
30. Mularczyk T, Kostewicz W. Fibrinolytic intra-arterial therapy in treatment of arterial occlusion in femoropopliteal segment. Int Angiol. 2008 Aug;27(4):313-8.
31. Eckert B, Kucinski T, Neumaier-Probst E, Fiehler J, Röther J, Zeumer H. Local intra-arterial fibrinolysis in acute hemispheric stroke: effect of occlusion type and fibrinolytic agent on recanalization success and neurological outcome. Cerebrovasc Dis. 2003;15(4):258-63. doi:10.1159/000069493.
32. van Solinge TS, Muskens IS, Kavouridis VK, Gormley WB, Mekary RA, Broekman MLD, Arnaout O. Fibrinolytics and intraventricular hemorrhage: a systematic review and meta-analysis. Neurocrit Care. 2020 Feb;32(1):262-71. doi:10.1007/s12028-019-00786-5.
33. Roberts HC, Dillon WP, Furlan AJ, Wechsler LR, Rowley HA, Fischbein NJ, et al. Computed tomographic findings in patients undergoing intra-arterial thrombolysis for acute ischemic stroke due to middle cerebral artery occlusion: results from the PROACT II trial. Stroke. 2002 Jun;33(6):1557-65. doi:10.1161/01.str.0000018011.66817.41.
34. Wechsler LR, Roberts R, Furlan AJ, Higashida RT, Dillon W, Roberts H, et al. Factors influencing outcome and treatment effect in PROACT II. Stroke. 2003 May;34(5):1224-9. doi:10.1161/01.STR.0000068782.15297.28.
35. Rahme R, Yeatts SD, Abruzzo TA, Jimenez L, Fan L, Tomsick TA, et al. Early reperfusion and clinical outcomes in patients with M2 occlusion: pooled analysis of the PROACT II, IMS, and IMS II studies. J Neurosurg. 2014 Dec;121(6):1354-8. doi:10.3171/2014.7.JNS131430.
36. Blasi F, Vassalli JD, Danø K. Urokinase-type plasminogen activator: proenzyme, receptor, and inhibitors. J Cell Biol. 1987 Apr;104(4):801-4. doi:10.1083/jcb.104.4.801.
37. Lin H, Xu L, Yu S, Hong W, Huang M, Xu P. Therapeutics targeting the fibrinolytic system. Exp Mol Med. 2020 Mar;52(3):367-79. doi:10.1038/s12276-020-0397-x.
38. Fears R. Binding of plasminogen activators to fibrin: characterization and pharmacological consequences. Biochem J. 1989 Jul 15;261(2):313-24. doi:10.1042/bj2610313.
39. Mican J, Toul M, Bednar D, Damborsky J. Structural biology and protein engineering of thrombolytics. Comput Struct Biotechnol J. 2019 Jul 2;17:917-38. doi:10.1016/j.csbj.2019.06.023.
40. van der Knaap N, Franx BAA, Majoie CBLM, van der Lugt A, Dijkhuizen RM; CONTRAST consortium. Implications of post-recanalization perfusion deficit after acute ischemic stroke: a scoping review of clinical and preclinical imaging studies. Transl Stroke Res. 2024 Feb;15(1):179-94. doi:10.1007/s12975-022-01120-6.
41. Yang SH, Liu R. Four decades of ischemic penumbra and its implication for ischemic stroke. Transl Stroke Res. 2021 Dec;12(6):937-45. doi:10.1007/s12975-021-00916-2.
42. Chalet L, Boutelier T, Christen T, Raguenes D, Debatisse J, Eker OF, et al. Clinical imaging of the penumbra in ischemic stroke: from the concept to the era of mechanical thrombectomy. Front Cardiovasc Med. 2022 Mar 9;9:861913. doi:10.3389/fcvm.2022.861913.
43. Saver JL. Intra-arterial thrombolysis. Neurology. 2001;57(5 Suppl 2):S58-60. doi:10.1212/wnl.57.suppl_2.s58.
44. Marzelle J, Combe S, Gigou F, Samama M. Results of thrombolysis in the treatment of arterial ischemia of the limbs according to mode of administration. Int Angiol. 1989 Oct-Dec;8(4):179-87.
45. Bansal S, Sangha KS, Khatri P. Drug treatment of acute ischemic stroke. Am J Cardiovasc Drugs. 2013 Feb;13(1):57-69. doi:10.1007/s40256-013-0007-6.
46. Nam J, Jing H, O'Reilly D. Intra-arterial thrombolysis vs. standard treatment or intravenous thrombolysis in adults with acute ischemic stroke: a systematic review and meta-analysis. Int J Stroke. 2015 Jan;10(1):13-22. doi:10.1111/j.1747-4949.2012.00914.x.
47. Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. Trends Neurosci. 1999 Sep;22(9):391-7. doi:10.1016/s0166-2236(99)01401-0.

48. Deb P, Sharma S, Hassan KM. Pathophysiologic mechanisms of acute ischemic stroke: an overview with emphasis on therapeutic significance beyond thrombolysis. Pathophysiology. 2010 Jun;17(3):197-218. doi10.1016/j.pathophys.2009.12.001.
49. Yenari MA. Pathophysiology of acute ischemic stroke. Cleve Clin J Med. 2004 Jan;71 Suppl 1:S25-7. doi:10.3949/ccjm.71.suppl_1.s25.
50. Vandelanotte S, De Meyer SF. Acute ischemic stroke thrombus composition. Neuroscience. 2024 Jul 9;550:11-20. doi:10.1016/j.neuroscience.2023.12.010.
51. Singh P, Kaur R, Kaur A. Clot composition and treatment approach to acute ischemic stroke: the road so far. Ann Indian Acad Neurol. 2013 Oct;16(4):494-7. doi:10.4103/0972-2327.120433.
52. Desilles JP, Di Meglio L, Delvoye F, Maïer B, Piotin M, Ho-Tin-Noé B, et al. Composition and organization of acute ischemic stroke thrombus: a wealth of information for future thrombolytic strategies. Front Neurol. 2022 Jul 6;13:870331. doi:10.3389/fneur.2022.870331.