REVIEW ARTICLE

Intravenous Thrombolysis for Acute Ischemic Stroke — New Directions

James C. Grotta, M.D.[1]

SUMMARY

In the past 5 years, substantial changes have been made in the use of intravenous thrombolysis (IVT) in patients with acute ischemic stroke. Integrating IVT with endovascular thrombectomy, which improves outcomes in patients with stroke due to large cerebral vessel occlusion, has been a particular challenge. This review discusses the underlying vascular targets for IVT and thrombectomy, the increasing use of tenecteplase instead of alteplase, broadening indications for the use of IVT, and ancillary drugs and dosing methods that may augment the success of IVT.

Author affiliations are listed at the end of the article. James C. Grotta can be contacted at James.grotta@memorialhermann.org.

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Timely reperfusion of ischemic regions of the brain by intravenous thrombolysis (IVT) or endovascular thrombectomy (EVT) is a foundation of treating patients who have acute ischemic stroke. The modern era of treatment for acute ischemic stroke began with the advent of IVT and Food and Drug Administration (FDA) approval of the tissue plasminogen activator (tPA) alteplase in 1996. Because of its high fibrin affinity and specificity, tPA can lyse clots responsible for most acute ischemic strokes with low rates of cerebral and systemic bleeding. Over the ensuing two decades, randomized trials, pooled data, and clinical experience affirmed the favorable benefit-to-risk ratio of the initial trials. For example, in a meta-analysis published in 2014 of randomized trials of IVT administered within 3 hours after stroke onset, the percentage of patients who had a good outcome was 10 percentage points higher among patients who received IVT — 38% of patients recovered completely and 60% recovered without disability — than among those who received placebo.[1] The risk of intracerebral bleeding with IVT has varied across trials depending on the definitions used, but symptomatic worsening due to brain bleeding has consistently occurred in approximately 2 to 4% of patients treated with IVT.[1-3]

The development of stroke teams and stroke centers to support emergency department workflow, guideline adherence, telemedicine-guided treatment, and appropriate reimbursement gradually overcame the impediments to widespread adoption of IVT. The percentage of patients with acute ischemic stroke who were treated with IVT reached an estimated (but still inadequate) 15% in the United States in 2018.[4] Although the use of IVT treatment in many parts of the world and in rural areas has been lower than 15%,[5] training of local personnel and implementation of telemedicine to bypass infrastructure gaps is expected to reduce regional imbalances. The general recommendation is that published guidelines should be followed for clinical decision making in the treatment of acute ischemic stroke, and these guidelines have been recently updated,[6] a change that reflects advances in IVT research and treatment. A major challenge has been to integrate IVT with EVT, an effective treatment for large-vessel occlusions. This review discusses the underlying vascular targets for IVT as compared with EVT, the ascendancy

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of treatment with tenecteplase over alteplase, broadening of existing guidelines, and approaches that could potentially increase the success of IVT.

VASCULAR TARGETS FOR IVT

The target for IVT is a clot in a cerebral artery. Although not required before IVT, assessment with computed tomography (CT) angiography or magnetic resonance angiography (MRA) has become an essential element of the initial evaluation of acute stroke owing to the importance of identifying large cerebral-vessel occlusions. Large-vessel occlusion of the internal carotid, proximal (M1) middle cerebral, vertebral, and basilar arteries comprise approximately 30% of acute ischemic strokes, often have a cardioembolic origin, and are approachable by endovascular stent retrievers and aspiration devices. From 10 to 30% of large-vessel occlusions will lyse with IVT alone, but up to 90% can be recanalized by EVT. Therefore, identifying and triaging patients with large-vessel occlusion to an EVT center is warranted when practical, including for the potential use of EVT for basilar-artery occlusion, which is one of the changes in the recently updated guidelines.[6] However, most cerebral-artery occlusions are downstream of large-vessel occlusions (Fig. 1), involving medium or more-distal arterial branches, small penetrating arteries, or the microcirculation.

On the basis of several recent trials involving patients with occlusions of medium-size branch vessels, guidelines indicate moderate evidence of EVT benefit for larger-branch (M2) middle cerebral-artery occlusions, but no evidence of benefit for occlusions of smaller M2 and more-distal segments.[6] Further research and technical advances may extend the use of EVT to more of these medium-branch occlusions, particularly if there is a severe neurologic deficit that may indicate poor collateral flow. However, there is an anatomical limit to how far catheters can be deployed distally. Therefore, for more than half the patients who are eligible for IVT on the basis of criteria such as time from stroke onset, it remains the only reperfusion therapy available.

No matter which artery is affected, the earlier after stroke onset that IVT is administered, the more likely a patient will recover without disability.[1] Irreversible brain infarction (the ischemic "core") starts developing 30 to 60 minutes after arterial occlusion.[7] Previous studies have shown that every 5 minutes saved within the first hour after stroke onset increases the odds of a nondisabling outcome from IVT by 3.5%.[8,9] Such treatment within the so-called golden hour is infrequently accomplished when patients must first be transported to an emergency department. Guidelines recommend the use of mobile stroke units that have the capability to initiate thrombolysis on the scene of a stroke when they are available.[10,11]

BROADENING INCLUSION CRITERIA FOR IVT

The initial trials of tPA established criteria aimed at identifying patients who had the most to gain from IVT (e.g., those with a disabling neurologic deficit), patients most likely to respond to IVT therapy (e.g., those who could be treated within the first 3 hours after onset of stroke), and patients least likely to have bleeding complications from IVT (e.g., those not being treated with anticoagulants). In the past 5 years, these original pillars of IVT management have been reexamined and expanded.

STROKE SEVERITY

The benefit versus risk of IVT in patients who have had mild strokes remains an area of uncertainty. Stroke severity has been measured in two ways. First, a mild stroke has been defined as a neurologic deficit that would not be disabling if it persisted; in such cases, guidelines recommend against IVT.[6] However, the extent of deficit that would be disabling for an individual patient is subjective and varies on the basis of age, activity level, and personal preference. Consequently, the decision to withhold IVT in patients with mild stroke is a frequent cause of disagreement, even among experienced clinicians.[12] Second, a more objective gauge of stroke severity is the National Institutes of Health Stroke Scale (NIHSS; scores range from 0 to 42, with higher scores representing greater neurologic deficit). The NIHSS score broadly correlates with the size of the artery affected, the volume of ischemic brain tissue, and, if reperfusion does not occur, eventual disability. If the NIHSS score is 5 or higher, hemiparesis or aphasia that would be considered by most persons to be disabling is almost always present. In contrast, an NIHSS score of 4 or lower usually indicates mild weak-

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ness, dysarthria, or sensory loss, and the deficit, if it persisted, may or may not be disabling. However, disabling hand weakness and gait difficulty may be present but are not appreciated by the NIHSS scoring system. In addition, among patients with NIHSS scores lower than 5, approximately 59% who do not receive IVT will have no important residual disability, as compared with 69% of those who receive IVT; this difference comes without an increased risk of bleeding in patients who receive IVT.[1] Despite these observations, a low NIHSS score is one of the most common reasons IVT is withheld.[13] Two recent trials explored the effect of administering IVT as compared with dual antiplatelet treatment in patients with low NIHSS scores and found no benefit with IVT.[14,15] However, given the poor precision of the NIHSS in predicting disability outcomes associated with low scores (≤5), guidelines recommend relying on a clinical assessment of whether a deficit would be disabling if it persisted rather than on an insensitive NIHSS score alone for deciding whether to administer or withhold IVT.[6]

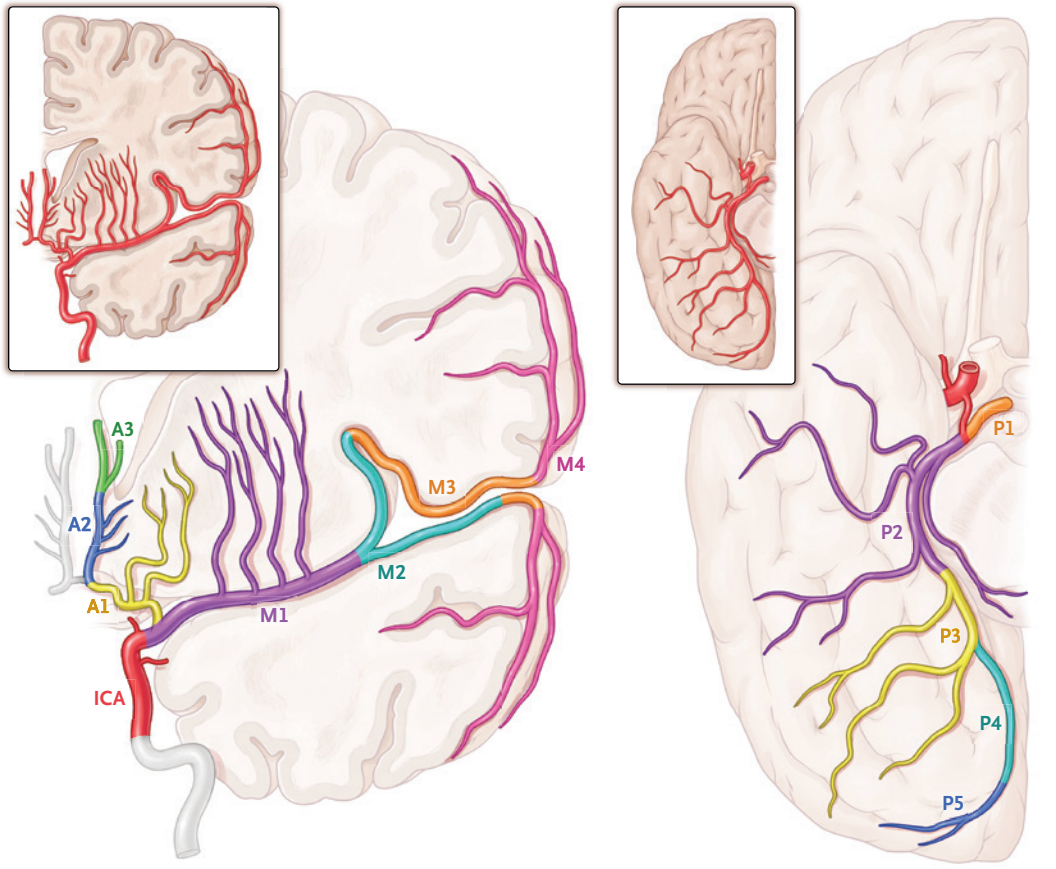


Figure 1. Cerebral Circulation.

Large-vessel occlusions occur in the internal carotid artery (ICA) and first segment of the middle cerebral artery (M1) and include the vertebral and basilar arteries, which are not shown; these occlusions collectively represent approximately 30% of acute ischemic strokes and are generally treated with endovascular thrombectomy (EVT) with or without intravenous thrombolysis (IVT). Medium-size vessel occlusions are the M2 and M3 branches of the middle cerebral artery, and the proximal anterior cerebral artery (A1) and its first branch (A2), the proximal posterior cerebral artery (P1) and its first branch (P2), which together represent approximately 20% of acute ischemic strokes and are generally treated with IVT and, in some M2 occlusions, with EVT. Distal-vessel occlusions represent the remaining arterial cerebrovascular occlusions, including penetrating vessels, arterioles, and microcirculation; these occlusions represent approximately 50% of acute ischemic strokes and are generally treated with IVT if the stroke is disabling.

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TREATMENT WITH IVT BEYOND 3 HOURS

Although treatment administered earlier rather than later has resulted in better outcomes with IVT, the time window of 3 hours that was derived from early trials of IVT has expanded to as long as 24 hours in special circumstances. This expansion began with trials that stretched the time for effective treatment from 3 hours to 4.5 hours after the onset of symptoms or after the time at which the patient was last known to be well. Depending on the size and location of the artery involved, substantial volumes of brain tissue distal to the occlusion may sustain viability if blood flow is restored or remains above the threshold for irreversible damage. These ischemic but still salvageable regions (penumbra) will become incorporated into an irreversibly infarcted core at a rate inversely proportional to the adequacy of collateral flow. Numerous trials and meta-analyses have confirmed that patients who awaken with symptoms (estimated to be up to one third of patients with acute ischemic stroke) or with uncertain time of onset may benefit from IVT administered within 24 hours if evidence of a salvageable region of ischemic penumbra (an area of ischemia that is larger than the irreversibly damaged core) is still present on magnetic resonance imaging (MRI) or CT perfusion imaging.[16,17] A trial of this tissue-based rather than time-based approach showed nondisabling outcome in 44% of patients with IVT as compared with 34% with placebo, and symptomatic hemorrhage in 2.8% and 0%, respectively.[18] These findings support more widespread availability and application of advanced brain imaging beyond the time window of 3 to 4.5 hours to identify potential candidates for IVT, but currently the availability of such imaging capability is limited outside major stroke centers.

USE OF DIRECT ORAL ANTICOAGULANT (DOAC) THERAPY

A common reason for withholding IVT is concurrent use of a DOAC, because these agents are used for stroke prevention in persons with atrial fibrillation, a major risk factor for acute ischemic stroke. DOAC use was previously considered to be an absolute contraindication to IVT because of a potentially increased risk of bleeding, but recent guidelines regard DOAC use within 48 hours before acute ischemic stroke as only a relative contraindication to IVT.[6] In patients who have received a DOAC, a number of factors influence the advisability of treatment with IVT, including the interval since the last dose (most DOACs have a half-life of about 12 hours), renal impairment that prolongs the half-life, the availability of DOAC-specific assays, stroke severity, and the availability and suitability of an alternative treatment such as EVT. Several developments may help clinicians safely administer IVT to patients receiving DOACs. For example, point-of-care assays are under development to quickly identify patients who have nontherapeutic levels of DOAC anticoagulation.[19] Pooled data from nonrandomized trials involving 1342 patients (at 28 comprehensive stroke centers) who had taken DOACs within 24 hours before acute ischemic stroke have been reassuring with respect to the safety of administering IVT; the incidence of symptomatic intracranial hemorrhage was approximately 3% with IVT and 6% when IVT was withheld, and major bleeding occurred in 2.3% of patients in both groups.[20] A randomized trial to test for superiority of IVT over non-IVT treatment of patients with acute ischemic stroke taking DOACs is underway (ClinicalTrials.gov number, NCT06571149).

COORDINATING THE USE OF IVT AND EVT

A common question in practice is whether IVT should be administered before EVT in patients who are eligible for both treatments, an approach known as bridging IVT. IVT can lyse up to 30% of large-vessel occlusions but may complicate subsequent EVT by causing clot fragmentation. In parts of the world where EVT is not available, the initiation of IVT without delay would be appropriate regardless of whether a large-vessel occlusion is suspected. Trials have shown a significant but modest overall benefit in rates of functional independence with bridging IVT when the duration between IVT and EVT is brief (median, 16 minutes) and there is little time for the thrombolytic agent to act on the clot.[21,22] The IVT-to-EVT interval can be this brief if patients first present to a center that has capability for EVT. At least half the patients with acute stroke in the United States and other developed countries present to a primary stroke center where EVT is not available; these patients are usually transported to a comprehensive stroke center for EVT.[23] If treated with IVT at the

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initial contact in a center that does not offer EVT, such patients would have the theoretical advantage of a longer "dwell time" of the thrombolytic agent on the clot. Observational studies suggest that transferred patients benefit from IVT before or during transport, with little added risk.[24,25] Even when the patient presents first to a center that offers EVT, the time it takes to evaluate and treat the patient with EVT is unpredictable, and IVT can be given during this interval. Therefore, guidelines recommend that bridging IVT be administered before EVT in most IVT-eligible patients.[6]

Table 1. Recommended Doses of Tenecteplase for Persons with Acute Ischemic Stroke.

Body Weight	Tenecteplase Dose	
	mg	*ml*
<60 kg	15.0	3.0
60 to <70 kg	17.5	3.5
70 to <80 kg	20.0	4.0
80 to <90 kg	22.5	4.5
≥90 kg	25.0	5.0

TENECTEPLASE VERSUS ALTEPLASE

Among the biggest changes in IVT practice in the past 5 years has been the increased use of tenecteplase over alteplase. Tenecteplase, a slightly modified form of tPA, has more fibrin specificity and longer half-life than alteplase and therefore can be given more conveniently as a single bolus rather than the one-hour infusion needed for alteplase. In the past decade, tenecteplase has been tested in comparison with alteplase in patients with acute ischemic stroke. Although tenecteplase may result in higher rates of recanalization, trials have shown that clinical outcomes are essentially equivalent between the two drugs — or at least the conclusion can be made that tenecteplase is noninferior to alteplase in terms of benefit and safety.[26,27] Largely on the basis of these noninferiority results, in 2025, the FDA approved the use of tenecteplase in patients with acute ischemic stroke. Although accurate patient weight is important to establish doses for both alteplase and tenecteplase, the tiered dosing of tenecteplase that was approved by the FDA (Table 1) makes rapid determination of the appropriate dose easier. Tenecteplase is replacing alteplase for IVT in clinical practice because it eliminates maintaining an infusion of alteplase during transport and thus is more convenient and simplifies the transfer of patients who have received IVT to centers where they can receive EVT.

OTHER THROMBOLYTIC AGENTS AND ALTERNATIVE APPROACHES TO FIBRINOLYSIS

Newer approaches to IVT are needed to overcome the failure of IVT to achieve the target levels of arterial recanalization and distal reperfusion; this failure results in disability at 90 days in approximately half of patients treated with IVT after acute ischemic stroke. IVT failure may be due to treatment that is too late to rescue the ischemic core, but other factors include failure to lyse the clot, successful thrombolysis followed by reocclusion, partial thrombolysis with distal clot embolization, or failure to reperfuse the microcirculatory system. The last of these has been attributed to endothelial swelling, capillary constriction, microthrombi, or embolic fragments clogging the microvascular network.[28,29] These vascular events may be targets for new IVT strategies.

In patients who were randomly assigned to receive two sequential doses of intravenous reteplase (18-mg bolus followed 30 minutes later by a second 18-mg bolus) or standard-dose tPA, the dual-reteplase group had better outcomes and no greater amount of bleeding than the tPA group in one trial.[30] Alternative approaches to enhance endogenous fibrinolysis are under investigation. These include von Willebrand factor inhibition (NCT06226805), alpha-2–antiplasmin antagonism (NCT05948566), and induction of conformational changes in plasminogen to increase fibrin affinity (NCT06990867). Phase 2 trials are targeting patients who receive treatment late in the target window of time for treatment after stroke; the appropriate strategy for how such later treatment might complement or substitute for IVT or EVT remains uncertain.

IVT COMBINED WITH ANTITHROMBOTIC OR ANTIPLATELET AGENTS

One logical approach to prevent reocclusion of vessels after successful thrombolysis and to augment distal reperfusion has been to couple IVT with antithrombotic or antiplatelet therapies. In general, adding antiplatelet agents or anticoagulants to IVT has resulted in increased risk without benefit. A phase 3 trial showed no benefit and possibly increased risk of hemorrhage when

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KEY POINTS

INTRAVENOUS THROMBOLYSIS FOR ACUTE ISCHEMIC STROKE — NEW DIRECTIONS

- Intravenous thrombolysis remains the most common reperfusion therapy for patients with acute ischemic stroke.
- Intravenous thrombolysis and endovascular thrombectomy have complementary vascular targets, and appropriate treatment should consider both options.
- Updated published guidelines provide new evidence-based recommendations pertaining to intravenous thrombolysis administration for treating patients who have had minor strokes, who are receiving endovascular thrombectomy, who present more than 4.5 hours after symptom onset, or who are receiving direct-acting anticoagulant therapy.
- Tenecteplase is replacing the tissue plasminogen activator alteplase because of its convenience and equivalent benefit and safety.
- Newer fibrinolytic drugs and alternate dosing strategies may yield improved outcomes.

the direct thrombin inhibitor argatroban or the glycoprotein IIb–IIIa antagonist eptifibatide was administered with or immediately after IVT, as compared with IVT alone.[2] In contrast, a trial in which tirofiban was added after IVT showed a higher percentage of patients with excellent functional outcomes in that group than in the group that received IVT alone, and tirofiban did not increase bleeding risk when started within 60 minutes after IVT.[31] Further study of antiplatelet drugs in conjunction with IVT seems to be appropriate.

ALTERNATIVE DOSING STRATEGIES

Providing sustained thrombolytic activity by administering multiple doses of a thrombolytic agent either intravenously or intraarterially is another strategy to achieve higher rates of recanalization and resolve persistent distal or microcirculatory occlusions. In two trials, alteplase or tenecteplase was infused intraarterially after successful EVT; patients who also received bridging IVT before EVT were included. Outcomes were better among patients treated with intraarterial thrombolytic drugs, without increased rates of bleeding, although deaths were inexplicably numerically higher than in those who did not receive this treatment.[32,33] The use of two sequential IVT doses has been investigated in a nonrandomized study in which MRA was repeated 1 hour after administration of a full dose of alteplase; if arterial occlusion was still present, a full dose of tenecteplase was administered. As compared with matched patients receiving only a single dose of alteplase, a greater percentage of the patients who received the additional dose of tenecteplase had 24-hour recanalization (82% vs. 65%) and excellent nondisabling outcomes at 90 days (69% vs. 44%) without a greater incidence of bleeding.[34] The pharmacokinetic features of tenecteplase[35] suggest that a second full dose might be safe if it is administered after an initial dose; this dose scenario is under investigation (NCT06801054).[36] Because the circulatory half-life of tenecteplase is 22 minutes — and given that the second tenecteplase dose would not be given until at least 60 minutes (approximately 2.7 half-lives) after the first dose — only approximately 15% of the initial dose would remain circulating. This amount would be equivalent to a second dose of 0.288 mg per kilogram of body weight, which is within the approved dose range.

CONCLUSION AND FUTURE PROSPECTS

The approaches to the use of IVT, the most common treatment for acute ischemic stroke, have evolved and will continue to do so. More patients will probably receive IVT owing to easing of existing exclusions, expanded availability of imaging and treatment up to (and possibly beyond) 24 hours after onset of symptoms if there is salvageable tissue, enhanced prehospital diagnosis and treatment, and extension of resources to remote or underdeveloped regions. IVT outcomes may be improved by resolving persistent arterial occlusion and impaired microcirculatory flow by the addition of new fibrinolytic agents and multiple dosing strategies.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

AUTHOR INFORMATION

[1]Houston Mobile Stroke Unit, Memorial Hermann Hospital, Houston.

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REFERENCES

1. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014;384:1929-35.
2. Adeoye O, Broderick J, Derdeyn CP, et al. Adjunctive intravenous argatroban or eptifibatide for ischemic stroke. N Engl J Med 2024;391:810-20.
3. Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369:275-82.
4. Asaithambi G, Tong X, Lakshminarayan K, Coleman King SM, George MG. Current trends in the acute treatment of ischemic stroke: analysis from the Paul Coverdell National Acute Stroke Program. J Neurointerv Surg 2020;12:574-8.
5. Khatib R, Arevalo YA, Berendsen MA, Prabhakaran S, Huffman MD. Presentation, evaluation, management, and outcomes of acute stroke in low- and middle-income countries: a systematic review and meta-analysis. Neuroepidemiology 2018; 51:104-12.
6. Prabhakaran S, Gonzalez NR, Zachrison KS, et al. 2026 Guideline for the early management of patients with acute ischemic stroke: a guideline from the American Heart Association/American Stroke Association. Stroke 2026;2026:26.
7. Jones TH, Morawetz RB, Crowell RM, et al. Thresholds of focal cerebral ischemia in awake monkeys. J Neurosurg 1981; 54:773-82.
8. Tanaka K, Reeves MJ. Mobile stroke units and pursuit of intravenous tissue-type plasminogen activator treatment in the golden hour. Stroke 2023;54:426-9.
9. Mackey J, Yamal JM, Parker SA, et al. Golden hour treatment with tPA (tissue-type plasminogen activator) in the BEST-MSU study. Stroke 2023;54:415-25.
10. Grotta JC, Yamal J-M, Parker SA, et al. Prospective, multicenter, controlled trial of mobile stroke units. N Engl J Med 2021; 385:971-81.
11. Turc G, Hadziahmetovic M, Walter S, et al. Comparison of mobile stroke unit with usual care for acute ischemic stroke management: a systematic review and meta-analysis. JAMA Neurol 2022;79:281-90.
12. Ramadan A-R, Denny MC, Vahidy F, et al. Agreement among stroke faculty and fellows in treating ischemic stroke patients with tissue-type plasminogen activator and thrombectomy. Stroke 2017; 48:222-4.
13. Smith EE, Fonarow GC, Reeves MJ, et al. Outcomes in mild or rapidly improving stroke not treated with intravenous recombinant tissue-type plasminogen activator: findings from Get With The Guidelines-Stroke. Stroke 2011;42:3110-5.
14. Sykora M, Krebs S, Miksova D, et al. IV thrombolysis vs early dual antiplatelet therapy in patients with mild noncardioembolic ischemic stroke. Neurology 2023; 101(9):e933-e939.
15. Fei Z-X, Yin Y, Cui Y, Nguyen TN, Chen H-S. Dual antiplatelet therapy versus alteplase for mild stroke with admission NIHSS score 0-3 versus 4-5: a secondary analysis of the ARAMIS randomized trial. CNS Drugs 2025;39:1037-46.
16. Ma H, Campbell BCV, Parsons MW, et al. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. N Engl J Med 2019;380:1795-803.
17. Wang Z, Li J, Wang X, Yuan B, Li J, Ma Q. Tenecteplase for acute ischemic stroke at 4.5 to 24 hours: a meta-analysis of randomized controlled trials. Stroke 2026;57: 50-62.
18. Ma G, Mo R, Zuo Y, et al. Tenecteplase for acute non-large vessel occlusion 4.5 to 24 hours after ischemic stroke: the OPTION randomized clinical trial. JAMA 2026;335:1137-47.
19. Tan PS, Park PSW, Cody R, et al. Assessment of direct oral anticoagulant status using the DOASENSE dipstick in thrombolysis eligible patients with stroke: proof-of-concept study. Stroke 2023;54(4): e142-e144.
20. Meinel TR, Bücke P, D'Anna L, et al. Intravenous thrombolysis in patients with recent intake of direct oral anticoagulants: a target trial analysis and comparison with reversal agent use. Stroke 2025; 56:2836-45.
21. Majoie CB, Cavalcante F, Gralla J, et al. Value of intravenous thrombolysis in endovascular treatment for large-vessel anterior circulation stroke: individual participant data meta-analysis of six randomised trials. Lancet 2023;402:965-74.
22. Qiu Z, Li F, Sang H, et al. Intravenous tenecteplase before thrombectomy in stroke. N Engl J Med 2025;393:139-50.
23. Venema E, Groot AE, Lingsma HF, et al. Effect of interhospital transfer on endovascular treatment for acute ischemic stroke. Stroke 2019;50:923-30.
24. Katsanos AH, Sarraj A, Froehler M, et al. IV thrombolysis initiated before transfer for endovascular stroke thrombectomy: a systematic review and meta-analysis. Neurology 2023;100(14):e1436-e1443.
25. Seners P, Mlynash M, Ter Schiphorst A, et al. Intravenous thrombolysis use before inter-facility transfer for thrombectomy: association with efficacy and safety outcomes. Ann Neurol 2025;98:871-80.
26. Menon BK, Buck BH, Singh N, et al. Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. Lancet 2022;400:161-9.
27. Palaiodimou L, Katsanos AH, Turc G, et al. Tenecteplase vs alteplase in acute ischemic stroke within 4.5 hours: a systematic review and meta-analysis of randomized trials. Neurology 2024;103(9): e209903.
28. Tudor T, Spinazzi EF, Alexander JE, et al. Progressive microvascular failure in acute ischemic stroke: a systematic review, meta-analysis, and time-course analysis. J Cereb Blood Flow Metab 2024;44: 192-208.
29. Rivet S, Churilov L, Yassi N, et al. Persistent tissue-level hypoperfusion (no-reflow) negates the clinical benefit of successful thrombectomy. Stroke 2025;56: 1451-9.
30. Li S, Gu HQ, Li H, et al. Reteplase versus alteplase for acute ischemic stroke. N Engl J Med 2024;390:2264-73.
31. Tao C, Liu T, Cui T, et al. Early tirofiban infusion after intravenous thrombolysis for stroke. N Engl J Med 2025;393: 1191-201.
32. Renú A, Millán M, San Román L, et al. Effect of intra-arterial alteplase vs placebo following successful thrombectomy on functional outcomes in patients with large vessel occlusion acute ischemic stroke: the CHOICE randomized clinical trial. JAMA 2022;327:826-35.
33. Writing Committee for the PEARL Investigators, Yang X, He X, et al. Intra-arterial alteplase after successful endovascular reperfusion in acute stroke: the PEARL randomized clinical trial. JAMA 2025;334:1728-39.
34. Chausson N, Olindo S, Laborne F-X, et al. Second-dose intravenous thrombolysis with tenecteplase in alteplase-resistant medium-vessel-occlusion strokes: a retrospective and comparative study. Eur Stroke J 2024;9:943-51.
35. Keyt BA, Paoni NF, Refino CJ, et al. A faster-acting and more potent form of tissue plasminogen activator. Proc Natl Acad Sci U S A 1994;91:3670-4.
36. Grotta JC. Administering a second dose of intravenous tenecteplase in acute ischemic stroke: rationale and design of a pilot clinical trial. Stroke Vasc Interv Neurol 2025;5(6):e002022.

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