# Intravenous thrombolysis for acute ischemic stroke

- Impact of Onset-to-Needle Time on the Risk of Early Neurological Deterioration in Patients with Acute Ischemic Stroke Receiving Intravenous Thrombolysis
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- From "time is brain" to "time is collaterals": updates on the role of cerebral collateral circulation in stroke
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Intravenous thrombolysis (IVT) is a treatment used for acute ischemic stroke (AIS) that involves the administration of a clot-dissolving medication to restore blood flow in the brain. The primary drug used for this treatment is tissue plasminogen activator (tPA), also known as alteplase.

## Mechanism

IVT works by breaking down the fibrin in blood clots, helping to dissolve the clot that is blocking blood flow to the brain. This can reduce the damage caused by a stroke and improve long-term outcomes.

## Time Window

The effectiveness of IVT is highly dependent on the time from stroke onset. It is typically administered within 4.5 hours of symptom onset. Beyond this window, the risks, particularly of bleeding, outweigh the benefits.

## Eligibility

Not all AIS patients are candidates for IVT. Some criteria for IVT include:

Diagnosis of AIS confirmed by imaging (e.g., CT or MRI)

Symptom onset within the 4.5-hour window

No evidence of intracranial hemorrhage (bleeding in the brain)

Blood pressure and other clinical factors within acceptable ranges

# Effectiveness

IVT can improve functional outcomes, reducing disability if given early and under appropriate conditions. It is often associated with better recovery, particularly in patients without large vessel occlusion (LVO), but it can still benefit some LVO patients, especially when used as a bridge to mechanical thrombectomy (MT).

Combination with Mechanical Thrombectomy (MT): For patients with LVO, IVT is sometimes administered before MT. This combination aims to provide an initial attempt at clot dissolution with IVT while preparing for mechanical clot retrieval through MT. Even if MT fails to completely restore blood flow, IVT can sometimes improve outcomes.

In summary, IVT for acute ischemic stroke is a time-sensitive, highly effective treatment that can significantly reduce stroke-related disability when administered promptly. However, careful patient selection and monitoring are critical to maximizing benefits and minimizing risks.

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Intravenous thrombolysis is associated with improved functional outcomes in acute ischemic stroke patients with large vessel occlusion despite unsuccessful mechanical thrombectomy [1].

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Ren et al. demonstrated national marked and sustainable improvement in adherence to door-to-needle time, door-to-puncture time, and successful reperfusion therapy from 2013 to 2017 in Japan in acute ischemic stroke thrombolysis. Adhering to the key Quality Indicators substantially affected in-hospital outcomes, underlining the importance of monitoring the quality of care using evidence-based Quality Indicators and the nationwide Close The Gap-Stroke program [2].

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Communication-type medical smartphone apps have the potential for shortening the time elapsed between admission and reperfusion therapy, especially image-to-needle time (INT) and image-to-puncture time (IPT).

# Complications

see Intravenous thrombolysis complications.

# Intraarterial recombinant human tissue plasminogen activator for ischemic stroke treatment

see Intraarterial recombinant human tissue plasminogen activator for ischemic stroke treatment.

## Meta-Analysis

The combination of mechanical thrombectomy (MT) and intravenous thrombolysis (IVT) is more effective than IVT alone in patients with large vessel occlusion, which has been proven in recent studies. However, there are still debates over whether IVT benefits patients treated with only direct mechanical thrombectomy (dMT).

PubMed, Embase, and Cochrane Library were searched on June 15, 2021, for randomized controlled trials (RCTs). Seven RCTs with 2,143 patients were enrolled in the study.

MT combined with IVT had comparable efficacy and safety outcome compared with dMT in proximal anterior circulation occlusion at 90 days. For the primary outcome, pooled data showed no significant difference in the modified Rankin Scale (mRS) 0-2 at 90 days between the dMT and MT+IVT groups (pooled odds ratio 0.96, 95% confidence interval, 0.79, 1.17, p = 0.39). As for the mRS score 0-1 at 90 days, the degree of benefit conferred by dMT was substantial: for every 100 patients treated, the number of patients which had an excellent outcome in the dMT group was 10 higher than that of the MT+IVT group.

In this meta-analysis including 7 RCTs, MT had comparable consequences to bridging treatment in efficacy and safety outcomes for patients with ischemic stroke caused by the occlusion of proximal anterior circulation, irrespective of geographical location. These findings support the adoption of dMT in acute ischemic stroke treatments and have higher cost-effectiveness in global applications [3].

## Retrospective cohort studies

Elawady et al. in a retrospective cohort study included acute ischemic stroke patients who underwent mechanical thrombectomy for anterior circulation large vessel occlusion with failed recanalization modified treatment in cerebral ischemia score ≤ 2A. Patients who received IVT before MT were compared to those who received MT alone. Propensity score matching used demographic, clinical, radiographic, and procedural variables to match patients with and without IVT. The primary outcome was a favorable 90-day good functional outcome (defined as a modified Rankin scale of 0-2), and secondary outcomes included intracranial hemorrhage (ICH), symptomatic ICH (sICH), and 90-day mortality.

A total of 610 AIS patients with unsuccessful MT were included. After propensity matching, 219 patients were identified in each group. Median age was 70 years and 73 years in the IVT + MT and MT alone groups, respectively. In the IVT + MT group, final mTICI scores of 0, 1, and 2A were achieved in 92 (42.0%), 33 (15.1%), and 94 (42.9%) patients, respectively, versus 76 (34.7%), 29 (13.2%), and 114 (52.1%) in the MT alone group. The IVT + MT group had greater odds of a 90-day good functional outcome (adjusted odds ratio 2.54, 95% confidence interval 1.53-4.32). There were no significant differences in secondary outcomes.

Intravenous thrombolysis is associated with improved functional outcomes in acute ischemic stroke patients with large vessel occlusion despite unsuccessful mechanical thrombectomy [4].

## Case series

Patient data registered in the Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Register (SITS-ISTR) between 2005 and 2021 were used. Acute ischemic stroke (AIS) patients who developed symptomatic intracerebral hemorrhage (SICH) following intravenous thrombolysis (IVT) according to the SITS-Monitoring Study definition were analyzed to identify predictors of functional outcomes.

A total of 1,679 patients with reported SICH were included, out of which only 2.8% achieved good functional outcomes modified Rankin Scale (mRS) scores of 0-2, while 80.9% died at 3 months. Higher baseline-NIHSS and 24-hour-ΔNIHSS scores were independently associated with a lower likelihood of achieving both good and excellent functional outcomes at 3 months. Baseline-NIHSS and hematoma location (presence of both SICH, defined as remote- and local-SICH concurrently; n=478) were predictors of early mortality within 24 hours. Independent predictors of 3-month mortality were age, baseline-NIHSS, 24-hour-ΔNIHSS, admission serum glucose values, and hematoma location (both-SICH). Age, baseline-NIHSS-score, 24-hour-ΔNIHSS, hyperlipidemia, prior stroke/TIA, antiplatelet treatment, diastolic blood pressure at admission, glucose values on admission, and SICH location (both SICH) were associated with reduced disability at 3 months (≥1-point reduction across all mRS scores). Patients with remote-SICH (n=219) and local-SICH (n=964) had comparable clinical outcomes, both before and after propensity score matching.

SICH presents an alarmingly high prevalence of adverse clinical outcomes, with no difference in clinical outcomes between remote- and local-SICH [5].

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In a prospective cohort study conducted at Helsinki University Hospital, Virta et al. identified intravenous thrombolysis-treated patients with concurrent saccular unruptured intracranial aneurysms admitted to a comprehensive stroke center between 2005 and 2019 using 2 overlapping methods. For each UIA patient, a control patient was identified and matched (1:1) for age, sex, admission year, and stroke severity. The primary outcome was an unfavorable outcome at 3 months, defined as a modified Rankin Scale (mRS) score of 3 to 6. The secondary outcomes were an excellent outcome (mRS score 0-1) at 3 months and mRS difference in shift analysis.

In total, 118 UIA patients and 118 matched control patients were identified. The UIA patients were more often current smokers, and their admission systolic blood pressure was higher. The rate of hemorrhagic complications did not differ between the groups. UIAs were not associated with an unfavorable outcome in the conditional logistic regression analysis (odds ratio, 1.41 [95% CI, 0.79-2.54]; P=0.25). However, the UIA patients were less likely to have excellent outcomes (odds ratio for non-excellent outcome, 2.09 [95% CI, 1.13-3.85]; P=0.02). In shift analysis, UIAs were associated with higher mRS (odds ratio, 1.61 [95% CI, 1.03-2.49]; P=0.04).

The intravenous thrombolysis-treated stroke patients with unruptured intracranial aneurysms were more often current smokers and had higher systolic blood pressure than the matched patients without UIAs. They were as likely to have unfavorable outcomes at 3 months but seemed less likely to

achieve excellent outcomes and were more likely to have higher mRS in shift analysis [6].

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