



Off-label use of intravenous thrombolysis for acute ischemic stroke: a critical appraisal of randomized and real-world evidence

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Abstract: Intravenous thrombolysis (IVT) represents the only systemic reperfusion therapy able to reverse neurological deficit in patients with acute ischemic stroke (AIS). Despite its effectiveness in patients with or without large vessel occlusion, it can be offered only to a minority of them, because of the short therapeutic window and additional contraindications derived from stringent but arbitrary inclusion and exclusion criteria used in landmark randomized controlled clinical trials. Many absolute or relative contraindications lead to disparities between the official drug label and guidelines or expert recommendations. Based on recent advances in neuroimaging and evidence from cohort studies, off-label use of IVT is increasingly incorporated into the daily practice of many stroke centers. They relate to extension of therapeutic time windows, and expansion of indications in co-existing conditions originally listed in exclusion criteria, such as use of alternative thrombolytic agents, pre-treatment with antiplatelets, anticoagulants or low molecular weight heparins. In this narrative review, we summarize recent randomized and real-world data on the safety and efficacy of off-label use of IVT for AIS. We also make some practical recommendations to stroke physicians regarding the off-label use of thrombolytic agents in complex and uncommon presentations of AIS or other conditions mimicking acute cerebral ischemia. Finally, we provide guidance on the risks and benefits of IVT in numerous AIS subgroups, where equipoise exists and guidelines and treatment practices vary.

Keywords: alteplase, contraindications, intracranial bleeding, intravenous thrombolysis, ischemic stroke, large vessel occlusion, off-label, therapeutic window, tenecteplase

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Introduction

Intravenous thrombolysis (IVT) with tissue plasminogen activator (tPA), administered within 4.5 h from symptom onset, is the only approved systemic reperfusion treatment for acute ischemic stroke (AIS) that has proven effective in reversing neurological deficits and improving outcomes.¹ Apart from the 4.5 h narrow time window, numerous other relative or absolute contraindications considerably limit the widespread use of IVT. A recent survey of national scientific societies and stroke experts in 44 European countries reported

rates of IVT between 0% and 20%, with overall only 7.3% [95% confidence interval (CI), 5.4–9.1] of AIS patients receiving treatment in Europe.² Obviously, the heterogeneity in the efficacy of local health systems, and in the availability of stroke experts and resources, as well as variations in stroke awareness and geographical barriers account mainly for such great variations in IVT administration rates across different countries. One good example is the widespread use of alteplase in AIS patients aged >80 years over the last 15 years (which in some centers represents up

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to 40% of AIS patients), despite the fact that alteplase use was off-label in this specific patient subgroup until 2019 when the European Medicines Agency (EMA) label was revised and included the age group of >80 years. Current contraindications are derived largely from the inclusion and exclusion criteria used in the randomized controlled clinical trials (RCTs) of IVT, which aimed at selecting patients showing the clearest benefit with optimal safety.³ Moreover, the majority of these criteria were based on expert opinion, with scarce if any empirical support.³

Delayed patient presentation is the most common reason that renders AIS patients ineligible for IVT.⁴ Indeed, even in countries with well-organized stroke networks, presentation within the 4.5 h window occurs in less than half of AIS cases. Still, less than 60% of cases with in-time presentation receive IVT.⁵ Other commonly encountered factors that may prompt withholding IVT include minimal or very severe neurological deficits at presentation, anticoagulation pre-treatment, history of recent stroke or myocardial infarction, history of recent surgery or bleeding, and sometimes older age combined with pre-stroke morbidity. The list grows considerably when taking also into account the several relative contraindications of IVT. Adding to the complexity, a considerable discordance between the official drug prescribing instructions and the national or international guidelines, or expert recommendations is apparent.⁶ However, global experience from IVT has increased exponentially since the approval of alteplase by the Federal Drug Administration in 1996.⁷ The publication of numerous observational studies using registry data and meta-analyses of real-world evidence studies have resulted in questioning or even modification of many of the relative exclusion criteria for IVT.

It is noteworthy that the strict exclusion criteria, which had been implemented in the pivotal National Institute of Neurological Disorders and Stroke (NINDS) tPA stroke trials and subsequently were included in the official labeling of alteplase, are not the standard in other areas of systemic thrombolysis, such as pulmonary embolism or deep vein thrombosis. Indeed, the exclusion criteria in the NINDS tPA stroke trials were selected with the intention to maximize the potential benefits from IVT by avoiding patients with certain clinical, laboratory, or imaging characteristics that may either decrease efficacy or increase the risks of

IVT and in particular intracranial bleeding that represented the most feared complication of systemic thrombolysis for the indication of AIS. These exclusion criteria were adopted by the phase III trial and later the official labeling of the drug, influencing the design of subsequent studies and protocols.⁸

Besides patient selection, close monitoring within the stroke unit during and after IVT administration is of paramount importance. Treatment must be discontinued if the patient develops severe headache, nausea, vomiting, or neurological deterioration, and an urgent brain computed tomography (CT) scan obtained. Blood pressure measurements and neurological examination must be performed every 15 min during infusion, and drug administration must be discontinued if uncontrolled hypertension develops (>180/105 mmHg). Close monitoring is also suggested for the following 24 h. The placement of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters must be delayed, if possible. A follow-up brain imaging study is recommended at 24 h after IVT and before initiation of antiplatelets or anticoagulants.⁹

In the present narrative review, we summarize recent randomized trial and real-world data on the safety and efficacy of off-label use of IVT for AIS. We also make some practical recommendations to stroke physicians regarding the off-label use of thrombolytic agents in complex and uncommon presentations of AIS or other conditions mimicking acute cerebral ischemia. Finally, we provide guidance on the risks and benefits of IVT in numerous AIS subgroups, where equipoise exists and guidelines and treatment practices vary.

Therapeutic time window for IVT

IVT within 4.5 h of symptom onset is clearly beneficial, irrespective of age or stroke severity.¹⁰ The third International Stroke Trial (IST-3), the largest up-to-date RCT of IVT for AIS, randomized 3035 patients up to 6 h after symptom onset. At 6 months there was a non-significant absolute increase in the rates of functional independence in favor of the IVT-treated group [adjusted odds ratio (OR), 1.13; 95% CI, 0.95–1.35; $p=0.181$]. However, there was also a significant increase in the 7-day death rates in the IVT group (adjusted OR, 1.60; 95% CI, 1.22–2.08; $p=0.001$), but at

6 months death rates were not different between groups.¹¹

Without the use of advanced imaging, treatment effect of IVT is strictly time dependent. This is translated as increasing odds of 3-month favorable functional outcome [FFO; modified Rankin Scale (mRS) scores of 0–1] and neurological improvement [defined as a ≥ 4 points decrease in baseline National Institutes of Health Stroke Scale (NIHSS) score] with a number needed to treat (NNT) of eight and four, respectively, if treatment is given within 3 h of symptom onset. Accordingly, NNTs increase to 12 and eight for achieving FFO and neurological improvement, respectively, when IVT is initiated at 3–4.5 h from symptom onset.¹² However, after 4.5 h the overall net clinical benefit is no longer significant, while 3-month mortality appears to be increased.¹³

Early recanalization is crucial and determines the response to fibrinolytic treatment. It is shown that tPA-induced recanalization increases odds of good functional outcome (defined as 3-month mRS score of 0–2) by more than four-fold and reduces mortality by 76%.¹⁴ Moreover, every 15 min delay in recanalization is associated with a reduction in the odds of FFO of 16% (95%CI: 3–27%), and every 10 min delay in onset to treatment is associated with an increased elapsed time between tPA bolus and beginning of recanalization of 1.3 min (95%CI: 0.6–1.9).¹⁵

A recent RCT showed that extension of the therapeutic time window may be feasible using advanced imaging. The Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial randomized AIS patients presenting within 4.5–9 h from symptom onset to receive IVT or placebo, provided they fulfilled the following imaging criteria processed with the use of the RAPID automated software (IschemaView, Menlo Park, CA): perfusion/ischemic core mismatch > 1.2 , mismatch volume of at least 10 mL, and ischemic core < 70 mL. At 3 months, more patients in the IVT group achieved a FFO [adjusted risk ratio (RR), 1.44; 95%CI, 1.01–2.06; $p = 0.04$], whereas a statistically non-significant increase in symptomatic intracerebral hemorrhages (sICH; 6.2% with alteplase *versus* 0.9% with placebo) did not affect mortality rates at 3 months.¹⁶ Nevertheless, it should be mentioned that less than 2% of consecutive AIS patients may fulfill EXTEND

clinical and neuroimaging eligibility criteria for IVT.¹⁷

A subsequent individual patient data meta-analysis of three RCTs, EXTEND, European Cooperative Acute Stroke Study-4/Extending the time for thrombolysis in emergency neurological deficits (ECASS-4/EXTEND), and Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) that used perfusion imaging in the extended thrombolysis time window (> 4.5 h), demonstrated a benefit from IVT in achieving excellent functional outcomes (mRS 0–1) at 3 months (adjusted OR, 1.86; 95%CI, 1.15–2.99; $p = 0.011$), despite an increase in sICH (OR, 9.7; 95%CI, 1.23–76.55; $p = 0.031$), but not in mortality.^{16,18–20} Of 414 total patients, perfusion imaging was available for re-processing using the automated RAPID software in 405. Central adjudication of perfusion mismatch status found perfusion mismatch in 304 patients (73% in the alteplase group and 77% in the placebo group). Notably, excellent functional outcome at 3 months was significantly more common only in the IVT-treated subgroup with perfusion mismatch compared with placebo-treated patients with perfusion mismatch (OR, 2.06; 95%CI, 1.17–3.62; $p = 0.012$), but not in the IVT-treated subgroup without perfusion mismatch compared with placebo. Moreover, IVT in patients with perfusion mismatch significantly improved functional independence (FI) at 3 months (mRS scores 0–2), without significant increase in sICH rates. Among patients with perfusion mismatch, more than half were wake-up strokes and IVT was clearly beneficial for this subgroup, too (OR, 2.18; 95%CI, 1.05–4.54).²⁰

Specifically designed for AIS cases with unknown time of onset, including mainly wake-up strokes, the Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial was based on the observation that the identification of a visible ischemic lesion on diffusion-weighted-imaging (DWI) magnetic resonance imaging (MRI) along with absence of hyperintense signal in the same region on fluid-attenuated inversion recovery (FLAIR) MRI, predicts onset of stroke within the 4.5-h thrombolysis time window.²¹ The trial recruited 503 individuals 18–80 years old with stroke of unknown time onset, $> 90\%$ with wake-up strokes, including approximately 1/3 with large vessel occlusions (LVOs), not scheduled to undergo mechanical thrombectomy (MT). Although stopped prematurely, the trial was positive with FFO at 90 days observed in 53.3% in the

tPA group and 41.8% in the placebo group (adjusted OR, 1.61; 95%CI, 1.09–2.36; $p=0.02$), without significant increase in mortality or sICH.²² A subsequent pre-specified subgroup analysis of the trial data showed that patients with lacunar infarcts on brain MRI benefited equally from IVT compared with non-lacunar infarcts.²³ The safety of alteplase for cases with unknown time of stroke onset and DWI/FLAIR mismatch was demonstrated in the single-arm phase II MR-Witness study, too, which reported only one sICH among 80 patients treated.²⁴

A recent meta-analysis investigated the benefit of IVT given beyond 4.5 h of stroke onset, or in stroke of unknown time onset. The study analyzed four RCTs that used advanced neuroimaging (perfusion and/or MRI) for patient selection: EXTEND, ECASS IV, WAKE-UP, and a pilot single-center RCT from Switzerland.^{16,18,22,25} In the adjusted analyses, IVT increased odds of 3-month FFO (adjusted OR, 1.62; 95%CI, 1.20–2.20), functional improvement (adjusted common OR, 1.42; 95%CI, 1.11–1.81), and sICH (adjusted OR, 6.22; 95%CI, 1.37–28.26). However, there was no association between IVT and FI (adjusted OR, 1.61; 95%CI, 0.94–2.75) or all-cause mortality (adjusted OR, 1.75; 95%CI, 0.93–3.29) at 3 months.²⁶

The investigators of the Evaluation of unknown Onset Stroke thrombolysis trials (EOS) published recently an individual data meta-analysis of the trials EXTEND, ECASS IV, WAKE-UP, and THAWS, incorporating data only from patients that presented with AIS of unknown time of onset and received either alteplase or placebo after demonstration of viable brain tissue with perfusion-diffusion MRI, perfusion CT, or MRI with DWI-FLAIR mismatch.^{16,18,22,27} This pivotal study identified 843 individuals of whom 429 (51%) were assigned to alteplase and 414 (49%) to placebo. Patients were followed for 90 days.²⁸ IVT-treated patients had higher odds to achieve FFO (adjusted OR, 1.49; 95%CI, 1.10–2.03; $p=0.011$) and FI (adjusted OR, 1.50; 95%CI, 1.06–2.12; $p=0.022$). Rates of sICH (3% *versus* <1%; adjusted OR, 5.58; 95%CI, 1.22–25.50; $p=0.024$) and death (6% *versus* 3%; adjusted OR 2.06; 95%CI, 1.03–4.09; $p=0.040$) were higher in the alteplase group; however, numbers of patients ending up severely disabled or dead were similar between groups (adjusted OR, 0.76; 95%CI, 0.52–1.11; $p=0.15$). Notably, subgroup

analysis demonstrated significant benefits from IVT irrespective of the presence or not of LVO.²⁸

Since perfusion imaging or brain MRI are not readily available in many primary stroke centers, a retrospective multicenter stroke registry (Thrombolysis in Stroke With Unknown Onset Based on Non-Contrast Computed Tomography: TRUST-CT) compared 117 patients with unknown time of stroke onset, which were treated with IVT based on an initial Alberta Stroke Program Early Computerized Tomography score (ASPECTS) of ≥ 7 , with 112 propensity score matched, non-IVT-treated patients. Four sICHs occurred in the IVT-treated patients *versus* one in the non-IVT-treated group, a difference not statistically significant. FFO at 3 months was more common in the IVT group (33.3%) than the control (20.5%) group (adjusted OR, 1.94; 95%CI, 1.0–3.76; $p=0.05$).²⁹ However, the study was non-randomized, resulting in significant differences in the last-known-to-be-well to presentation times, as well as in the symptom-discovery to presentation times, both being more prolonged in the non-IVT-treated group, resulting in delays in the initiation of medical management. Additionally, more than 20% of patients in both groups eventually underwent MT, but when excluding MT-treated cases, median admission NIHSS scores were higher in the control than the IVT-treated group (10 *versus* 8, $p=0.03$). When patient selection is based solely on CT-ASPECT scores, additional studies, ideally RCTs, are needed to confirm the safety and efficacy of IVT in AIS of unknown time of onset.

In conclusion, based mainly on the WAKE-UP trial, the latest guidelines by the American Heart Association/American Stroke Association (AHA/ASA) recommend IVT for patients with unknown time of onset fulfilling the criteria of the WAKE-UP trial (Level IIA, Class B; Figure 1).³⁰ As the WAKE-UP protocol requires a baseline brain MRI scan, its applicability is still limited for many stroke centers that lack direct access to MRI scans. It is noteworthy that the MRI-DWI/FLAIR mismatch protocol does not impose significant time delays as it does not last longer than 10 min. No recommendation is given based on the EXTEND trial (Figure 2). However, perfusion mismatch-guided IVT for patients presenting up to 9 h after symptom onset, according to the EXTEND criteria, is routinely offered by many stroke centers and recommended by stroke

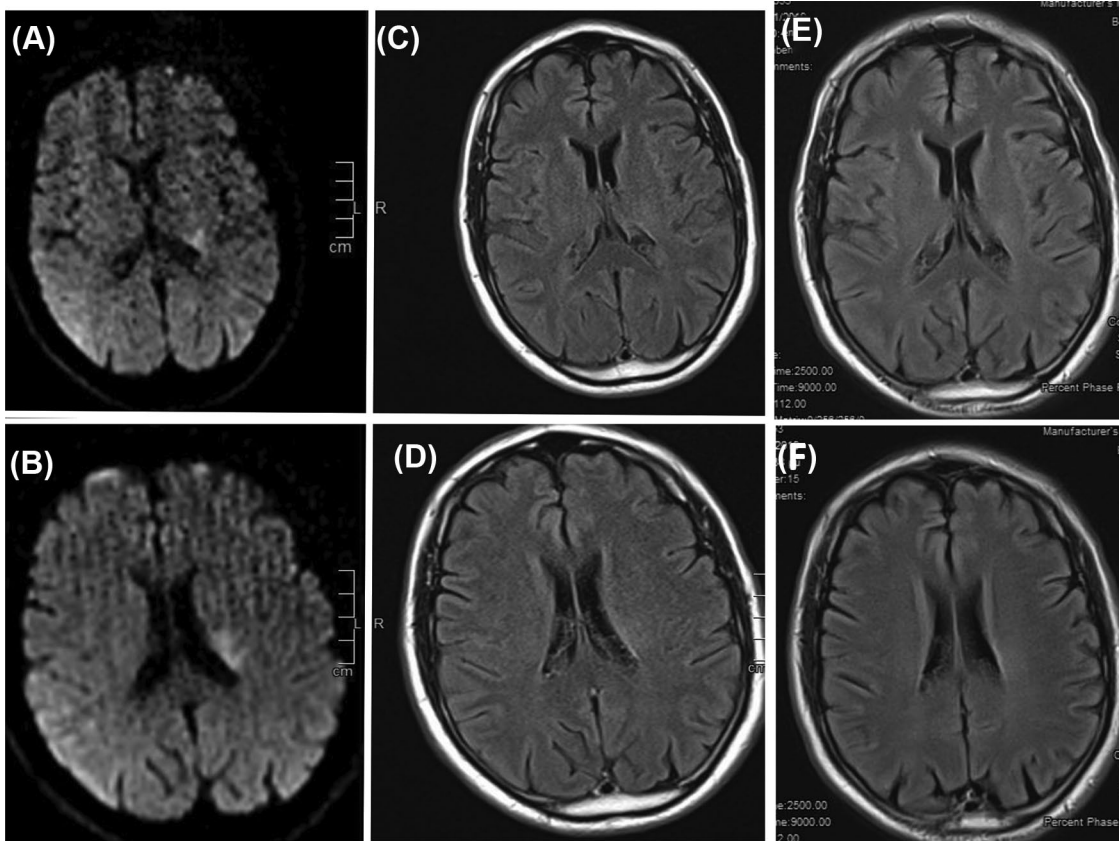


Figure 1. A 64-year-old man fell asleep without symptoms and woke up 5 h and 30 min later, with right-sided hemiparesis. He was admitted to the hospital 30 min later, with a National Institute of Health Stroke Scale score of 5 points. Urgent brain magnetic resonance imaging (MRI) revealed a left center semioval area of high signal intensity on Diffusion-Weighted-Imaging (DWI) sequences (Panels A and B), but no corresponding hyperintensity on Fluid-Attenuated Inversion Recovery (FLAIR) MRI sequences (Panels C and D), a finding consistent with DWI/FLAIR mismatch. The patient fulfilled the WAKE-UP trial criteria and received, 6 h and 15 min from last known to be well and 75 min after symptom discovery, intravenous thrombolysis with 0.9 mg/kg dose of alteplase. Full recovery of the neurological deficits was noticed at patient's discharge. Follow-up brain MRI (FLAIR sequences) at 3 months was negative for a corresponding ischemic infarct (Panels E and F).

specialists.³¹ Moreover, the meta-analysis from the EOS study group further supports IVT for AIS of unknown time of onset with salvageable brain tissue, demonstrated with advanced neuroimaging (perfusion imaging or DWI-FLAIR mismatch).²⁸ Although already implemented by some stroke centers, the potential utility of IVT for patients fulfilling the WAKE-UP or EXTEND criteria and scheduled to undergo MT, who either present directly in a thrombectomy-capable center or, more importantly, in the primary stroke center (drip and ship cases) currently remains unknown. In this direction, the subgroup analysis of the LVO cases with AIS of unknown time of onset from the EOS study group meta-analysis provides for the first time robust evidence for the efficacy of IVT in LVO-attributed AIS of

unknown time of onset, and thereby, potentially supports IVT administration for cases scheduled to undergo MT, particularly in drip and ship models.²⁸

Age limit

Although, with the exception of stroke of unknown time of onset fulfilling the WAKE-UP trial criteria, no upper age limit in the label of alteplase for AIS exists anymore, and alteplase administration is contraindicated only for patients <16 years old. Indeed, there are no RCTs, and only scarce retrospective series and case reports are available in the literature.³² The only randomized trial, the Thrombolysis in Pediatric Stroke (TIPS), was terminated early due to slow recruitment (many

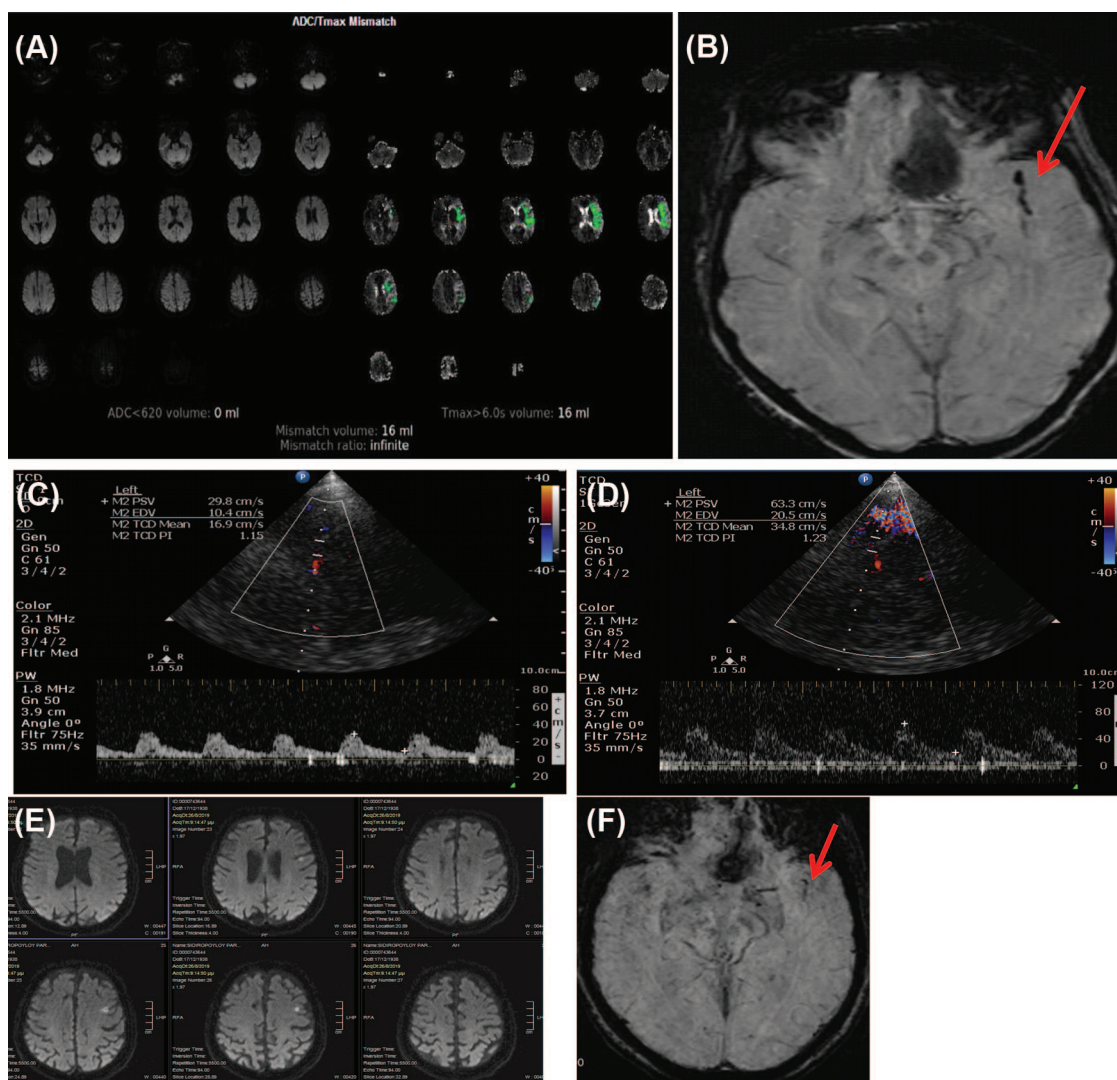


Figure 2. An 81-year-old woman with a history of non-coagulated paroxysmal atrial fibrillation presented to the emergency department 5h after the acute development of expressive aphasia with mild facial droop and right upper limb drift (National Institute of Health Stroke Scale score of 4 points). MR-Perfusion study (RAPID software, IschemaView, Menlo Park, CA) disclosed the absence of ischemic core (cerebral blood flow <30%), and identified a critically hypoperfused ($T_{max} > 6$ s) area of 16 mL (Panel A). Susceptibility-weighted imaging (SWI) brain magnetic resonance imaging (MRI) showed a left middle cerebral artery (MCA)-M2 segment thrombus (red arrow, Panel B), and transcranial duplex sonography (TCS) detected a sub-occlusive waveform corresponding to a Thrombolysis In Brain Ischemia (TIBI) grade III, in the left M2-MCA (Panel C). In accordance with the EXTEND trial eligibility criteria, the patient received intravenous thrombolysis with alteplase (0.9 mg/kg) at 6h following symptom onset. Immediately after the 1-h infusion of alteplase, a complete resolution of the patient's symptoms was noted. TCS disclosed restoration of a normal waveform within the left M2-MCA (TIBI grade V), (Panel D), and follow-up diffusion-weighted imaging (DWI) brain MRI showed small acute ischemic lesions within the left MCA territory (Panel E). MRI-SWI confirmed the complete resolution of the left M2-MCA thrombus (red arrow, Panel F).

pediatric stroke cases present outside the 4.5h time window).³³ However, data from children that received IVT treatment at centers scheduled to participate in the trial were published recently. Overall 26 children (age range, 1.1–17 years;

median, 14 years), with a median NIHSS of 14, were treated within 2–4.5h (median, 3.0h) after symptom onset. No sICH was reported.³⁴ Two additional retrospective studies of pediatric and adolescent IVT-treated stroke cases, with five and

10 patients, respectively, confirmed the feasibility and safety of IVT in this age group.^{35,36} Given the emerging literature data supporting the safety and efficacy of MT in childhood stroke treatment, but also the better functional outcomes of conservatively treated pediatric stroke in general compared with adult stroke, larger studies as well as international registries are needed to investigate the potential benefit in pediatric stroke from IVT.³⁷ Individualized patient management and close collaboration of Pediatricians with stroke specialists is necessary to take decisions regarding IVT administration, particularly for otherwise eligible for IVT pediatric patients, who present with significant neurological deficits within the 4.5 h time window.³⁸ With regard to the upper age limit of 80 years, the individual patient data meta-analysis of nine RCTs and a recent individual patient data meta-analysis combining both randomized and observational data have provided robust evidence that alteplase for AIS patients aged >80 years has a positive benefit–risk profile when administered according to the other regulatory criteria.^{10,39} Finally, this resulted in an amendment of the EMA label in 2019, while it should be kept in mind that the US label never included any upper age limits.

Stroke severity

European labeling of alteplase states that tPA administration for AIS is contraindicated for patients with minor neurological deficit or symptoms rapidly improving before initiation of infusion. On the contrary, the AHA/ASA expert guidelines distinguish minor-non-disabling from minor-disabling stroke and recommend IVT only for the latter.³⁰ This recommendation is based on the results of the Potential of rtPA for Ischemic Strokes With Mild Symptoms (PRISMS) trial, despite the fact that the trial was terminated early due to slow recruitment of 313 patients with minor (NIHSS <6) and not clearly disabling stroke, as was judged by the treating physician. Among 281 participants completing the trial, 122 (78.2%) in the IVT group and 128 (81.5%) in the aspirin group (control group) achieved a FFO at 3 months (adjusted risk difference, -1.1% ; 95%CI, -9.4% to 7.3%). There were five cases of sICHs (3.2%) defined as evidence of any neurological worsening according to the investigator following intracranial bleeding, all in the IVT group.⁴⁰ To assist with patient recruitment, non-disabling deficits were defined by the investigators

as those that, even without improvement, would not limit work capacity or the execution of basic activities of daily living. Typical eligible patients included cases with isolated mild aphasia, isolated facial droop, mild isolated hand weakness, mild hemiparesis, hemiataxia or hemisensory loss. Despite being the only currently available RCT on IVT for minor AIS, several limitations need to be acknowledged. First, due to slow recruitment, the study was terminated early, therefore lacks statistical power. Furthermore, almost two-thirds of patients in each group had “very” minor strokes with NIHSS <3, whereas the most prevalent deficits were sensory disturbances (46%), facial palsy (39%), and dysarthria (28%), therefore prognosis at any case was most likely very favorable. In addition, 12% of patients were diagnosed as stroke mimics, and in up to 10% of the enrolled sample, 3-month mRS evaluations were missing. Therefore, the study results should be interpreted with caution.

A recent analysis of the US National Inpatient Sample of hospitalizations identified 103,765 cases with mild (NIHSS <6) AIS, of whom 10,300 received IVT alone. As expected, patients treated with IVT had higher NIHSS scores compared with those that did not [$3.1 (\pm 1.5)$ versus $2.1 (\pm 1.6)$, $p < 0.001$]. However, IVT was associated with increased rates of excellent outcome (OR, 1.90; 95%CI, 1.71–2.13, $p < 0.001$), despite an increase in ICH (OR, 1.41; 95%CI, 1.09–1.83, $p < 0.001$).⁴¹ Consequently, physicians may refrain from administering IVT when patients are experiencing non-disabling symptoms, and in the same time, bear in mind that different deficits perceived as mild might have important impact on the lives of some people (for instance, mild aphasia may be disabling for a journalist, diplopia for a taxi driver, facial droop and dysarthria for a anchor man or an actor). In addition, impairments not captured by the NIHSS such as cognitive difficulties, visual problems, sleep disturbances and fatigue may lead to substantial disability, whereas IVT may be beneficial and safe in selected minor stroke cases.

Perhaps even more importantly, early neurological deterioration (END) is not uncommon in AIS and is associated with increased odds of poor outcome. Indeed, a recent large prospective study found prevalence of END of 14.6%, with the highest rates observed within the first 6 h after stroke onset. Older age, female sex, diabetes,

early arrival, large artery atherosclerosis as the cause of stroke, glucose level, systolic blood pressure, and leukocytosis at admission were, among others, factors related to END.⁴² Therefore, in patients with minor AIS presenting early after symptom onset with presumed high probability for END, administering IVT might be reasonable.

There are currently no RCTs addressing the benefit of IVT for minor (NIHSS score <6) non-disabling stroke attributed to LVO. The TNK-Tissue-Type Plasminogen Activator Evaluation for Minor Ischemic Stroke With Proven Occlusion (TEMPO-1) safety and feasibility trial administered tenecteplase in two different doses (0.1 and 0.25 mg/kg of body weight) in 50 patients with minor stroke (NIHSS ≤5) and LVO, presenting within 12 h after symptom onset, without the use of advanced imaging (perfusion imaging or MRI). Only one sICH occurred, whereas 66% of patients achieved FFO at 3 months. Importantly, recanalization rates were remarkably high, particularly with the higher dose (52% complete and 9% partial recanalization).⁴³ A retrospective comparison study of 336 minor AIS cases attributed to LVO or distal occlusions found that patients treated with IVT had higher odds of improving at discharge and better 3-month functional outcomes, without increase in sICH compared with patients that did not receive IVT, after adjustment for potential confounders, including MT.⁴⁴ Similarly, another observational study reported that, among 598 AIS patients with LVO treated with either IVT alone or bridging with MT, 74% and 83% of those who received only IVT achieved FFO and FI at 3 months, respectively, while only 3% experienced sICH.⁴⁵ However, these studies did not distinguish between disabling and non-disabling stroke. Although not currently proven whether non-disabling AIS with LVO benefits from IVT, the presence of a symptomatic LVO is generally regarded as an important prognostic factor for END, and therefore IVT is justified.⁴⁶

Despite most recent guidelines stating that the benefit from IVT in AIS presenting with NIHSS scores >25 is unclear, data from the individual patient data meta-analysis by Emberson *et al.*,¹⁰ the third International Stroke Trial (IST-3), and the Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Registry (SITS-ISTR) provide evidence for a

significant benefit of IVT in patients with severe stroke, without significant increase in the risk of sICH when compared with lower severity AIS.^{11,30,47} Additionally, AIS cases with extensive ischemic changes on baseline imaging were excluded from RCTs. Indeed, extensive and clear hypoattenuation on baseline CT, or extensive hyperdense DWI areas on baseline MRI represent irreversibly damaged brain tissue, and therefore IVT is of limited value. Although the degree of extension of these ischemic areas that may render IVT futile or even harmful is not well known, an ASPECTS <7 is associated with increased risk of sICH.⁴⁸ Still, IVT in such cases might be justified as a life-saving intervention. Considering the fact that no global consensus exists on the extent of irreversible ischemic changes that should prompt cancellation of IVT, this decision may be individualized. For instance, when MT is readily available, when managing older patients within the 3–4.5 h window, or patients with significant leukoaraiosis, diabetes, or cerebral microbleeds on susceptibility-weighted imaging (SWI), IVT may be withheld in favor of MT. Perfusion imaging may also provide complementary information regarding this decision-making process, as the presence of severe hypoperfusion on pre-treatment perfusion imaging increases risk of sICH (Figure 3).⁴⁹

Seizure presentation at stroke onset

Epileptic seizures are common stroke mimics, but seizures may also represent the initial manifestation of stroke as a symptomatic seizure (Figure 4). Current European labeling of alteplase considers seizures at stroke onset as a contraindication for IVT. A multicenter study investigated outcomes as well as the risk of sICH after IVT in cases with seizures at stroke onset. The authors identified 146 patients (1.5% of all IVT-treated cases), who had relatively higher initial NIHSS scores and higher pre-stroke dependency compared with AIS cases without seizures at stroke onset.⁵⁰ After adjustments, IVT in this patient group was not associated with worse 3-month outcomes, neither sICH, while in 39% of the study population seizures eventually proved to be stroke mimics.⁵⁰

Stroke mimics

Other common stroke mimics in addition to seizures include migraine and functional disorders.

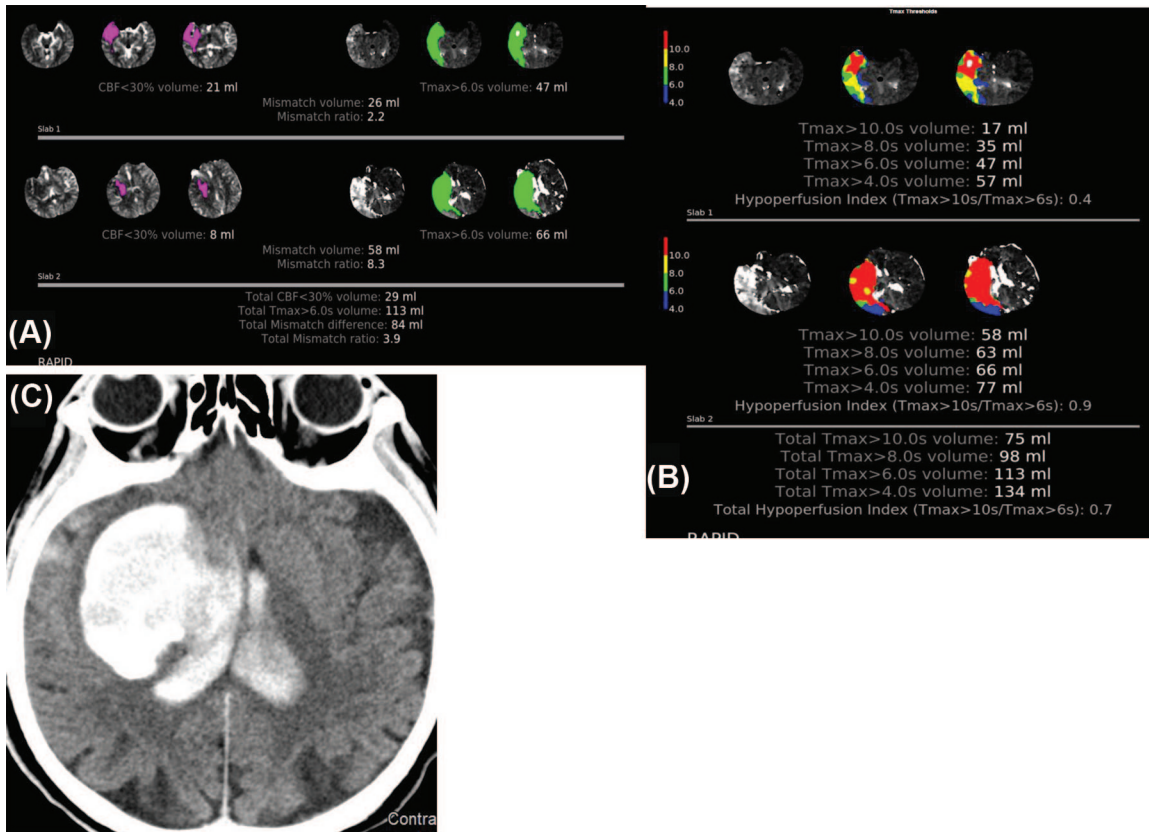


Figure 3. An 89-year-old man presented within 1 h of symptom onset with severe AIS [National Institute of Health Stroke Scale (NIHSS) score of 18 points] due to tandem (right internal carotid artery and middle cerebral artery) arterial occlusion. CT-Perfusion study (RAPID software, IschemaView, Menlo Park, CA) showed a critically hypoperfused area within the right middle cerebral artery territory of 113 mL (Tmax > 6 s), and an ischemic core volume of 29 mL (Cerebral Blood Flow < 30%), with a mismatch difference of 84 mL (Panel A). However, 75 mL of the total 113 mL of the hypoperfused tissue showed Tmax values > 10s, resulting in a hypoperfusion index of 0.7 that indicates the presence of an extensive and severely hypoperfused cerebral volume (Panel B). The patient received intravenous thrombolysis and was transferred to the angiography suite, where significant extravasation of contrast was detected in the right hemisphere that corresponded to the formation of a large parenchymal hematoma type II and intraventricular hemorrhage confirmed on brain CT (Panel C). Substantial neurological deterioration was documented during the first 24 h following tPA bolus (NIHSS score 26).

A retrospective analysis of IVT-treated stroke mimics from the SITS-ISTR found parenchymal hematoma rates of 1.2%, and sICH according to NINDS, ECASS II, and SITS-MOST (SITS Monitoring Study) definitions in 0.5%, 0.2%, and 0%, respectively, significantly lower than IVT-treated true strokes. In addition, 3-month outcomes were better and death rates were lower, thus underscoring the safety of IVT in such cases and highlighting the fact that in case of suspicion of a stroke mimic there is no need to withhold or postpone treatment in order to obtain further investigations.⁵¹ Similar results were reported from another study of 75 IVT-treated stroke

mimics, with the investigators documenting only one case of sICH and no case of orolingual edema or major extracranial hemorrhage.⁵² In addition, a meta-analysis of all available cohort studies estimated a pooled rate of sICH of 0.5% (95%CI, 0–2%).⁵² Another recent meta-analysis also reported that patients presenting with acute motor functional neurological disorders and receiving IVT for presumed stroke have good functional outcomes at discharge and at 3-month follow-up.⁵³ Perfusion imaging may further assist in treatment decisions and in the differential diagnosis of stroke mimics from acute cerebral ischemia, without considerable treatment delays.⁵⁴ Last, it

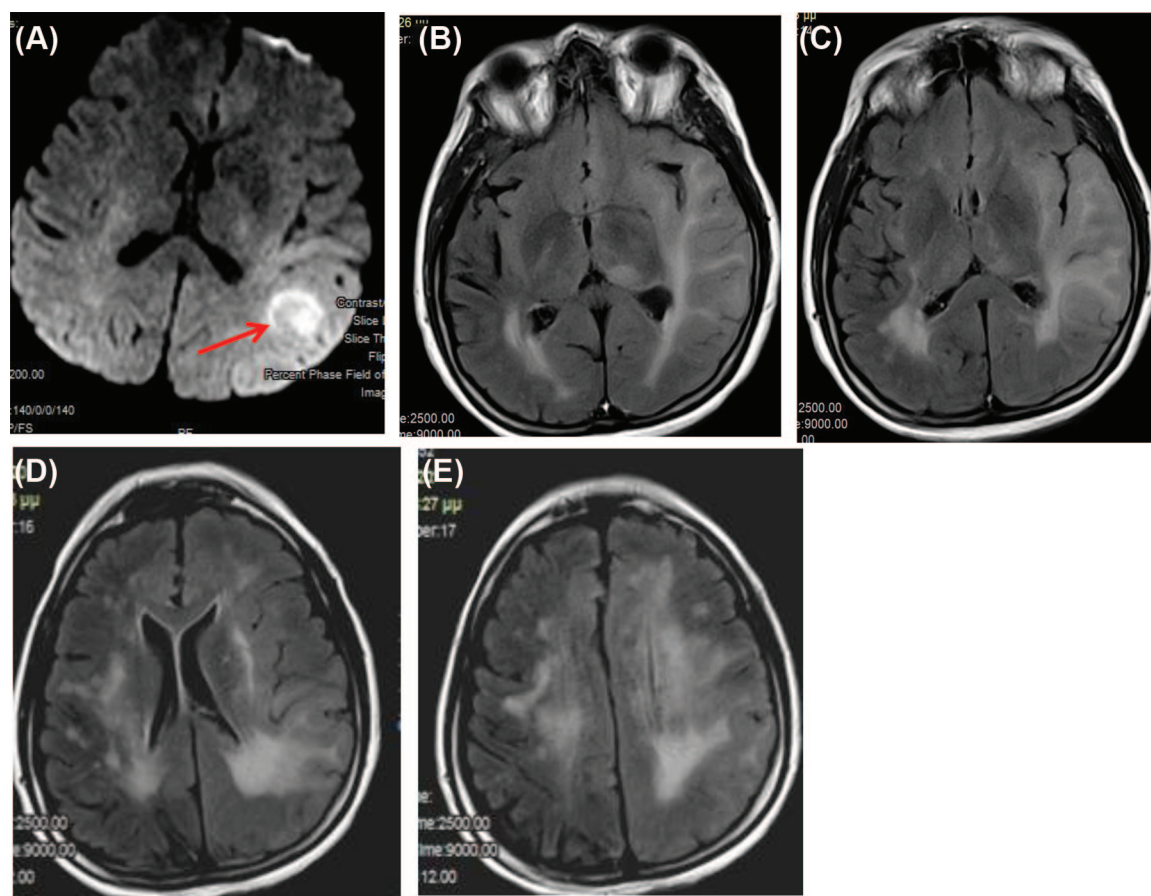


Figure 4. A 68-year-old woman was admitted to a primary stroke center within 4 h of acute onset of aphasia and right hemiparesis [National Institute of Health Stroke Scale (NIHSS) score of 7 points]. The patient received intravenous alteplase (0.9 mg/kg). During the infusion, she developed two episodes of generalized tonic-clonic seizures. A second urgent brain CT scan did not reveal brain hemorrhage. The patient was transferred to a comprehensive stroke center. Diffusion-weighted-imaging brain MRI sequences showed a left temporo-parietal acute ischemic lesion (red arrow, Panel A). Fluid-attenuated inversion recovery brain MRI sequences revealed extensive left temporo-parietal vasogenic edema that was attributed to a hyperperfusion syndrome with clinical epileptic seizures, an uncommon complication following successful recanalization with intravenous thrombolysis (Panels B–E).

should be noted that IVT should not be administered in cases of isodense subdural hematoma mimicking AIS, since it may be complicated with devastating intracranial bleeding complications (Figure 5).⁵⁵

Anticoagulation pre-treatment

IVT is contraindicated for patients who have received full dose of low molecular weight heparin (LMWH) within the previous 24 h or have a thromboplastin time exceeding the upper limit of normal values.³⁰ In a multicenter study comprising 1482 IVT-treated patients, 21 had received LMWH. After adjustment for potential confounders,

LMWH pre-treatment was associated with higher mortality (OR, 5.3, 95%CI, 1.8–15.5; $p=0.002$), risk of sICH (OR, 8.4, 95%CI, 2.2–32.2; $p=0.002$) and lower likelihood of 3-month FI (OR, 0.3, 95%CI, 0.1–0.97; $p=0.043$).⁵⁶ A recent analysis from the SITS registry identified 1411 patients who had received thromboprophylactic LMWH doses before IVT, but did not find increased risk of sICH or death within 7 days.⁵⁷ Therefore, IVT may not be rejected for patients under prophylactic doses of LMWH, but its safety remains uncertain for cases receiving therapeutic LMWH doses, and evidence is extremely scarce on the safety of IVT following heparin reversal with protamin sulfate.⁵⁸ Direct MT may be the optimal reperfusion strategy

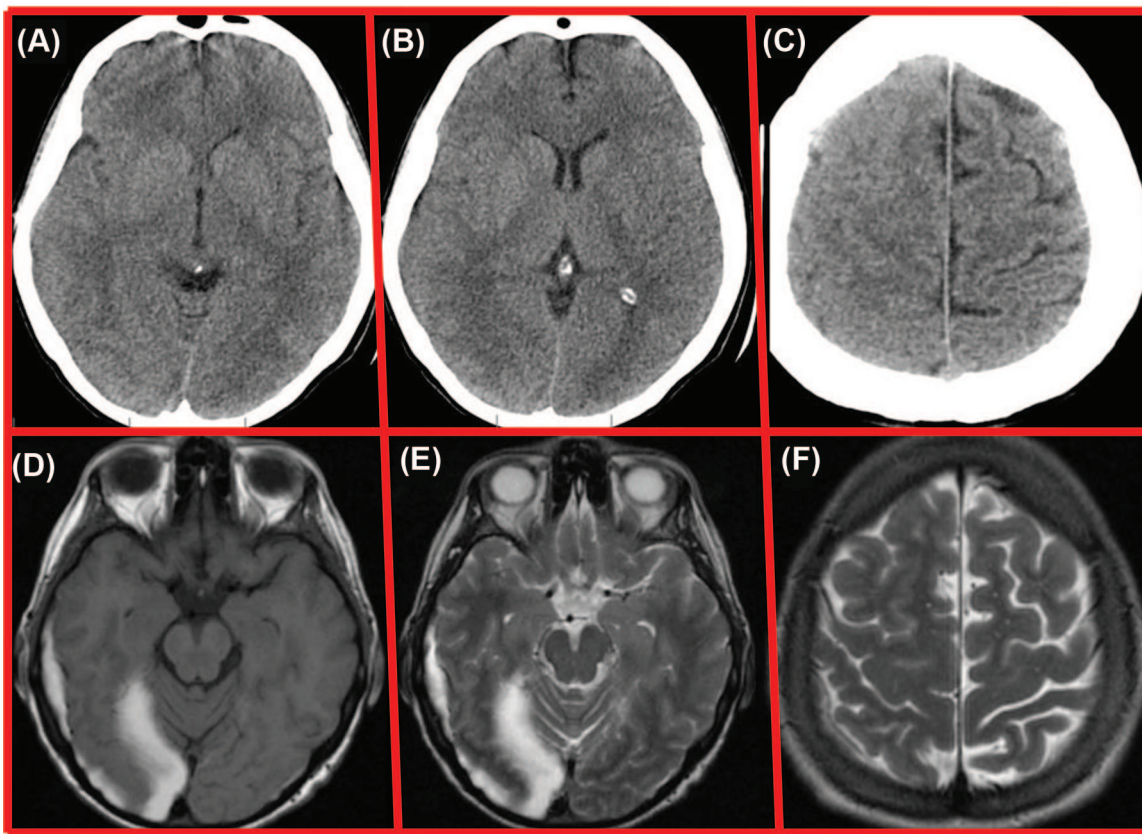


Figure 5. A 36-year-old woman with history of migraine presented in the Emergency Room with acute left homonymous hemianopsia (National Institute of Health Stroke Scale score of 2 points) within the time window of intravenous thrombolysis (onset-to-door time: 59 min). The patient had a history of PFO (patent foramen ovale) closure 12 days ago due to chronic migraine. She was receiving aspirin 100 mg qd following PFO closure and was also taking nimesulide 100 mg bid during the past 5 days. Brain CT (Panels A–C) disclosed sulcal effacement in right frontal and parietal lobes and loss of gray–white matter differentiation in the right hemisphere. The suspicion of isodense subdural hematoma was raised and intravenous thrombolysis was averted. Brain MRI was performed the following day and disclosed the presence of a right occipital subdural lesion that was hyperintense on axial T1 (Panel D) and axial T2 (Panel E) sequences. These findings confirmed the diagnosis of subacute subdural hematoma. Sulcal effacement in right frontal and parietal lobes was also noted on brain MRI (Panel F).

in AIS patients due to LVO and pre-treatment with therapeutic LMWH.

IVT is also contraindicated in patients taking oral anticoagulants. More specifically, IVT should be withheld in AIS patients pre-treated with vitamin K antagonists and International Normalized Ratio levels >1.6 due to the increased perceived risk of bleeding intracranial and systemic complications.^{59,60} Similar, AIS patients with normal renal function, pre-treated with thrombin or factor Xa inhibitors [non-vitamin K antagonist oral anticoagulants (NOACs)] within 48h from symptom onset, are not eligible for IVT unless thrombin time is <60 s or dabigatran levels are <50 ng/mL

in case of dabigatran pre-treatment, and factor Xa inhibitor levels are <50 ng/mL or anti-Xa is <0.5 U/mL in case of factor Xa inhibitors.^{61,62} A systematic review and meta-analysis of six studies that included 366 patients on NOACs and 2133 on warfarin pre-treatment that received IVT, did not detect any additional risk of sICH in selected AIS patients pre-treated with NOACs compared with patients on warfarin or to patients without prior anticoagulation.⁶³ Similarly, a literature review documented rates of sICH following IVT of 4.3% in selected AIS patients pre-treated with NOACs, despite a median time interval from the last dose of the anticoagulant to IVT of only 8h. Moreover, the administration of idarucizumab

before IVT in 44 dabigatran pre-treated patients resulted in numerically fewer sICHs (4.5% *versus* 7.4%) and deaths (4.5% *versus* 12.0%).⁶⁴ Although both reviews conclude that in selected patients with NOAC pre-treatment IVT may not increase sICH, more data are needed to clarify the safety of IVT in this group of patients, particularly when specific coagulation assays to assess residual anticoagulant activity at patient presentation are not available.

Regarding pre-treatment with dabigatran, several case reports and case series support the urgent administration of idarucizumab before IVT to reverse the anticoagulant effect of dabigatran. A retrospective case series of 55 patients that had received dabigatran within the previous 48 h, reported benefit from IVT, defined as a NIHSS reduction of at least 5 points, in 82% of patients. Only one asymptomatic ICH occurred, and one had early stroke recurrence.⁶⁵ From a national registry of IVT-treated patients in New Zealand, 51 idarucizumab pre-treated cases were identified. Despite idarucizumab pre-treated patients having longer door-to-needle times, sICHs and death rates were similar to other IVT-treated cases, and no thrombotic complications were reported.⁶⁶ The largest case series published to date comes from Germany, comprising 80 idarucizumab pre-treated patients subsequently receiving IVT for AIS. The majority of the cases (78%) showed a median improvement of 7 points in NIHSS, and no bleeding complications were reported.⁶⁷ In the absence of randomized data, dabigatran reversal with idarucizumab before IVT in AIS patients pre-treated with dabigatran appears to be safe and feasible, while it may also be associated with early neurological improvement. In AIS cases with LVO (large part of cardioembolic strokes) and readily available MT, it is preferable to take the patients swiftly to the angio suite for direct endovascular therapy and to withhold idarucizumab for dabigatran reversal and IVT.

Recently, andexanet alfa has been approved as an antidote for factor Xa inhibitors.⁶⁸ One case has been described so far in the literature, reporting on a patient successfully treated with IVT after having received a bolus dose followed by 2-h of infusion 880 mg of andexanet alfa.⁶⁹ Notably, alteplase was administered immediately following andexanet alfa bolus, while a rebound effect of anti-Xa activity was recorded at 10 h following

symptom onset. The concerns about andexanet alfa pre-administration include the cost of treatment, the long duration of andexanet alfa infusion, and the transiency of the anticoagulant reversal followed by a rebound of the anticoagulant activity within a few hours after treatment.

Platelet count < 100,000/ μ L

Conversely, despite low platelet count (<100,000/ μ L) being an exclusion criterion for IVT in the pivotal RCTs, observational studies have disclosed acceptable sICH rates in AIS patients with low platelet count following treatment with IVT. A prospective multicenter European cohort study of IVT-treated AIS patients identified 44 thrombolyzed patients with platelet count below 100,000/mcL. The incidence of sICH (7%), poor outcome, and mortality was not significantly different from that of patients with platelet count >100,000/mcL.⁷⁰ Since in this study every 10,000/ μ L decrease in platelet count was associated with increasing risk of sICH (adjusted OR, 1.03; 95%CI, 1.02–1.05), the lowest acceptable limit of 100,000/ μ L may be challenged to perhaps 70,000/ μ L or even 50,000/ μ L, although additional data from real-world evidence studies are required to confirm this hypothesis. Similar rates of sICH in IVT-treated patients with thrombocytopenia were reported by a single-center North-American study.⁷¹ In accordance with current guidelines, for patients without a known hematological disorder, withholding IVT while pending results of platelet count is not justified.

Admission hyperglycemia

Under European labeling, severe hyperglycemia (>400 mg/dL) is listed as a contraindication to IVT. Indeed, admission hyperglycemia is associated with END and worse functional outcomes in patients treated with IVT.^{72,73} A propensity score matching analysis, using data from the SITS-ISTR Registry, documented blood glucose levels between 181 mg/dL and 200 mg/dL to increase risk of sICH after IVT compared with levels between 80 mg/dL and 120 mg/dL (OR, 2.86; 95%CI, 1.69–4.83, $p < 0.001$). Hyperglycemia was associated with worse outcomes both in diabetic and non-diabetic patients, too.⁷³ Other IVT studies that assessed the effects of higher admission glucose levels, >400 mg/dL, >216 mg/dL, and >200 mg/dL, respectively, reported also an

increased risk of sICH complicating IVT for AIS.^{74–76} Interestingly, since increased glycosylated hemoglobin A1 levels were also predictors of sICH, it is argued that IVT-related sICH in diabetics might be related to chronic vascular injury.⁷⁷ However, the combination of diabetes and previous ischemic stroke does not seem to further increase risk of sICH, and such cases are typically not excluded from IVT.⁷⁸ Strict glycemic control rather than withholding IVT is suggested by guidelines and experts for patients with hyperglycemia and/or diabetes, even for cases presenting with severe hyperglycemia (>400 mg/dL). Conversely, low blood glucose levels, although may manifest as a stroke mimic, do not appear to represent a risk factor for sICH.⁷⁴

Increased blood pressure levels

Increased blood pressure (BP) levels should always be treated aggressively before the initiation and during the infusion of intravenous thrombolytics, to a target of less than 185/110 mmHg before the bolus dose and to a target below 180/105 mmHg during alteplase infusion and during the first 24 h following alteplase administration. Pre-IVT infusion BP protocol violations are linked to higher sICH rates, whilst not maintaining low BP levels after IVT is linked to worse functional outcomes and to sICH with a linear association.^{74,79,80} Accordingly, a systematic review and meta-analysis showed that increased pre-IVT (adjusted OR, 1.08; 95% CI, 1.01–1.16) and post-IVT (adjusted OR, 1.13; 95% CI, 1.01–1.25) systolic BP levels were associated with increased risk of sICH, but also with lower likelihood of FI at 3 months (pre-treatment adjusted OR, 0.91; 95% CI, 0.84–0.98, and post-treatment adjusted OR, 0.70; 95% CI, 0.57–0.87).⁸¹ A recent open-label with blinded-endpoint trial investigated whether acute intensive BP lowering (targeting systolic BP <140 mmHg within 1 h) in patients receiving IVT is safer compared with progressive BP lowering within 72 h according to guidelines. Any ICH development was less common in the intensive group, but there was no significant reduction in sICH. However, the two groups had relatively small mean systolic BP (over 24 h) differences (144.3 mmHg in the intensive group and 149.8 mmHg in the guideline group) that may have limited the possibility to detect significant treatment effects between groups.⁸² Nevertheless, over-treating increased BP levels appears safe and is probably preferred to protocol violations that allow levels >180/105 mmHg

within the first 24 h after IVT for AIS. More specifically, a *post-hoc* analysis of a phase III RCT of sonothrombolysis that implemented a robust BP control protocol using serial BP recordings before during and after alteplase infusions has recently reported a high rate (34%) of BP excursions above the pre-specified thresholds among AIS patients treated with IVT. Notably, the BP excursions above guideline thresholds were associated with adverse clinical and imaging outcomes in the group of patients treated with tPA monotherapy.⁸³

History of ischemic stroke within the previous 3 months or history of intracranial hemorrhage

Despite the lack of robust evidence, history of previous ischemic stroke within the preceding 3 months is considered by national guidelines as a contraindication for IVT. A meta-analysis of six studies with almost 900 IVT-treated patients with a history of prior stroke within the preceding 3 months did not find statistical significant differences in the incidence of sICH and death compared with patients without history of prior stroke within the previous 3 months. Moreover, the odds for early neurological improvement and 3-month FI were similar between the two groups.⁸⁴ However, there was substantial heterogeneity across included studies, while the elapsed time interval between the index and the previous ischemic stroke was not specified in the included studies. In a multicenter study of 568 patients who received IVT and had a history of stroke within the previous 3 months, although rates of sICH were similar to patients without history of recent stroke, mortality and unfavorable discharge rates were increased when alteplase was administered in AIS patients with recent history of ischemic stroke.⁸⁵ These discrepancies in the results of different studies reflect the complexity of the issue. First, the studies did not take into account the size or severity of previous stroke, obviously an important determinant of the final functional outcome and of the risk of sICH. Second, the risk of hemorrhagic transformation varies according to stroke etiology, being highest in cardioembolic stroke type.⁸⁶ Third, the time elapsed between previous and current stroke is important, too. This is pointed out by a recent retrospective study from the Get With The Guidelines (GWTG)-Stroke hospitals that identified 293 IVT-treated patients with prior stroke within 3 months. Although in this multicenter

study outcomes were worse for patients with previous stroke, rates of sICH were excessively increased only in the group of patients with previous stroke within 14 days (6.3%).⁸⁷ Notably, the Japanese National guidelines for IVT application have set prior stroke in the previous 1 month as an exclusion criterion for IVT administration.⁸⁸ Therefore, an individualized approach is needed when managing otherwise eligible for IVT AIS patients with a recent prior stroke and significant new-onset neurological deficits. The degree of pre-existing disability, previous stroke severity and etiology, as well as time elapsed between the two strokes are factors to be considered before excluding patients from IVT. On the other hand, IVT appears to be safe for cases with recent silent infarcts detected on brain MRI, according to a recent study comparing 115 IVT-treated patients with recent silent infarcts with 866 patients without recent silent infarcts.⁸⁹

Patients with AIS and a history of ICH were excluded from the RCTs of IVT, and guidelines do not encourage administration of alteplase in such cases. In addition, a limited number of patients with previous ICH receiving IVT have been described in the literature. A multicenter study identified seven cases, with none developing sICH. All prior ICHs were of deep location.⁹⁰ A more recent study did not find significant differences in sICH, mortality rates, and outcomes between 12 patients with a history of ICH and 793 without a history of ICH that received IVT. However, among patients with a history of ICH, those receiving IVT had better functional outcomes at 3 months compared with those without IVT treatment, whereas sICH and mortality rates were similar between the two groups.⁹¹ Factors that may be considered when managing otherwise eligible for IVT, non-minor AIS patients with a history of previous ICH are etiology and location of the ICH, as well as time elapsed from the event. IVT may be considered for cases with deep location of the prior ICH or when a reversible etiology was detected and treated (for instance aneurysm, arteriovenous malformation, drug-related) and provided that a long time period has elapsed since the ICH (>12 months). However, the accuracy of such assumptions needs to be confirmed in future real-world evidence studies.

Patients hospitalized for or having very recently suffered a transient ischemic attack (TIA) have been typically excluded from RCTs. One study

that analyzed IVT-treated AIS patients with a history of TIA within the previous month (60 cases), did not report any significant differences in functional outcomes or complications compared with patients without a history of recent TIA.⁹² Similarly, hospitalized patients for TIA with stroke recurrence during hospitalization may be safely treated with IVT, as shown in a retrospective analysis of 25 cases. In this study, median time-to-symptom recurrence was 24h, and FI was achieved by 84% of patients, with no sICH reported. Notably, outcomes were better if IVT was started within 90min of symptom onset, which may be a feasible goal for inpatients hospitalized for TIA that manifest AIS during hospitalization.⁹³

History of myocardial infarction within the previous 3 months

History of recent myocardial infarction (MI) is not an official contraindication for IVT. Instead, international guidelines include recent (within the previous 3 months) ST-elevation MI (STEMI) in the relative contraindications for IVT due to the risk of hemopericardium and catastrophic cardiac tamponade, and of recurrent embolization from cardiac thrombi.^{94,95} Two relevant studies have been published recently: A case series and literature review compared 47 IVT-treated AIS patients with a history of recent MI with 55 non-IVT-treated cases with also a history of recent MI. The authors describe four (8.5%) cases complicated with hemopericardium in the IVT-treated group, all with a history of STEMI within the preceding week, *versus* one in the non-IVT-treated group. Importantly, no complications were described in cases with a history of recent non-STEMI or in cases with concurrent acute MI and AIS. No significant differences were detected in the incidence of cardiac embolization between IVT-treated and non-treated groups.⁹⁶

However, the largest study to date retrieved data that were collected within a 6-year period from the GWTC–Stroke hospitals in the USA. There were 241 patients with recent MI that received IVT for AIS, of which 19.5% had STEMI. Patients with recent MI had higher rates of mortality compared with patients without past MI (17.4% *versus* 9.0%; adjusted OR, 1.60; 95%CI, 1.10–2.33; $p=0.014$). However, no significant differences were found regarding IVT-related

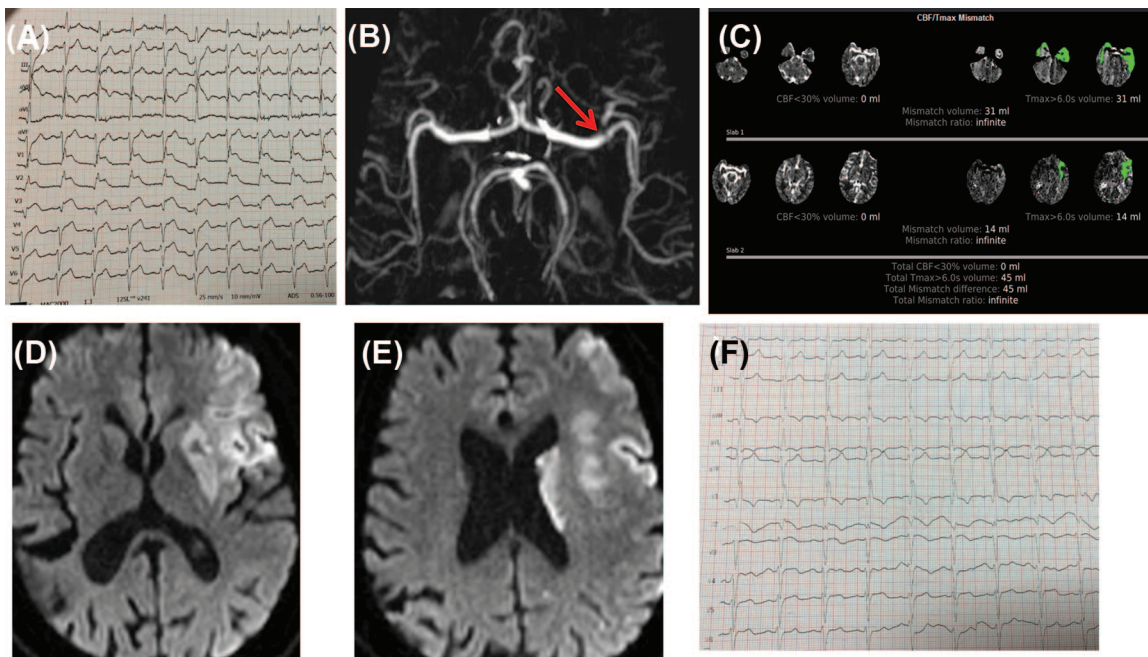


Figure 6. A 63-year-old man presented 3.5h after the acute onset of severe aphasia and right hemiplegia with left gaze deviation [National Institute of Health Stroke Scale (NIHSS) score of 18]. Admission troponin levels were increased (0.56 ng/mL, positive >0.1 ng/mL) and the electrocardiogram showed ST elevations in leads V1 to V4 (Panel A), consistent with anterior wall acute myocardial infarction (MI). Brain CT-Angiography and Perfusion study (RAPID software, IschemaView, Menlo Park, CA) revealed a distal left middle cerebral artery (MCA) M1-segment sub-occlusion (red arrow, Panel B), and a critically hypoperfused cerebral area (Penumbra, $T_{max} > 6$ s) of 45 mL, without detectable ischemic core (Panel C). The patient received intravenous alteplase (0.9 mg/kg) 4 h after symptom onset, bridged with mechanical thrombectomy with complete recanalization 5.5 h after symptom onset. Brain MRI showed an acute left MCA infarct (Panel D and E). A few hours later, troponin levels increased dramatically (120 ng/mL) and later decreased to normal ranges within the next few days, whereas ST elevations subsided (Panel F). These findings were consistent with recanalization of the anterior coronary artery that was verified later with coronary angiography. The patient was discharge with a NIHSS score of 5 points.

complications. Hemopericardium developed in one patient with recent MI. Notably, recent STEMI but not non-STEMI was associated with higher risk of death and IVT-related complications. On the other hand, even in non-IVT-treated AIS patients, recent MI was still linked to increased mortality and poor outcomes. Subgroup analysis according to time elapsed from MI to IVT for AIS revealed a trend for increasing mortality rates as time between MI occurrence and IVT became shorter.⁹⁷

In view of the former considerations, withholding IVT is reasonable for cases with STEMI within the preceding week of the AIS. If the STEMI has occurred between 1 week and 3 months before the AIS, the decision for IVT treatment should be individualized. Size of the STEMI and efficacy of the acute treatment that had been applied for the

MI are factors to be considered. Recent (<3 months) non-STEMI and acute (within 6 h) concurrent MI in patients presenting with symptoms of acute cerebral ischemia may not represent absolute contraindications to IVTs (Figure 6).

Chronic renal failure

Renal failure is not listed as a contraindication for IVT. Those patients have multiple comorbidities, creating concerns about potentially higher bleeding risks. Analysis of 44,410 IVT-treated patients from the GWTG-Stroke hospitals identified 15,191 (34%) IVT-treated patients with chronic renal disease (CKD), defined as glomerular filtration rate <60 mL/min per 1.73 m². In multivariable analysis, CKD was linked to increased risk of mortality and unfavorable functional outcome.⁹⁸ Similarly, in a *post-hoc* analysis of the Enhanced

Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) increased mortality rates were found in IVT-treated patients with severe CKD ($<30\text{ mL/min per }1.73\text{ m}^2$) compared with patients with normal renal function. However, there was no effect on sICH rates or disability. Interestingly, mortality showed a linear increase following the worsening of renal function: every decrease of $10\text{ mL/min per }1.73\text{ m}^2$ in estimated glomerular filtration rate was associated with an adjusted 9% increase in odds of death.⁹⁹ On the contrary, a systematic review and pairwise meta-analysis showed that moderate to severe CKD was also associated with increased risk of sICH in AIS patients treated with IVT compared with IVT-treated patients without CKD.¹⁰⁰

Since there are no available studies comparing outcomes between IVT-treated and non-IVT-treated AIS patients with CKD, the worse outcomes reported after IVT in patients with CKD compared with those without CKD may be attributed to comorbidities rather than the IVT itself. Hence, omitting IVT treatment in all AIS patients with significant CKD, even in those undergoing hemodialysis, is currently not justified. At the same time and given the overall increased risk of sICH and death after IVT in CKD patients, skipping IVT may be also reasonable in specific cases, such as minor stroke, uncontrolled BP levels before alteplase bolus, proximal LVO with readily available MT, and coexistence of multiple other relative contraindications for IVT.

Unruptured intracranial aneurysms and vascular malformations

The recommendations provided from international guidelines concerning IVT in patients harboring unruptured intracranial aneurysms (UIA) are typically based on the size of the aneurysm, in a way that the presence of aneurysms with maximal diameter larger than 10 mm may render IVT potentially harmful.³⁰ Official labeling of alteplase also refers to the presence of UIA as a contraindication for treatment. However, there is absence of robust literature data supporting these statements. Several case series have not disclosed any excessive hemorrhagic risk from IVT in patients with UIA compared with patients without UIA.^{101–104} A case series and meta-analysis of IVT-treated AIS patients harboring UIA found incidence of sICH of 6.7%, not significantly

different from AIS patients without UIA (RR, 1.60; 95%CI, 0.54–4.77; $p = 0.40$).¹⁰⁵ Therefore, withholding IVT due to incidental finding or known UIA of less than 10 mm is not justified. Moreover, in cases with UIAs exceeding 10 mm in maximal diameter, IVT may be reasonable if patients present with significant neurological deficits attributed to the AIS and MT is not indicated or unavailable.

Concerning unruptured cerebral vascular malformations (arteriovenous malformations arteriovenous fistulas, cavernous malformations), literature data are scarce, and thus IVT decision should be individualized. Noteworthy, higher risk of sICH appears to be largely related to the coexistence of cerebral cavernous malformations with AIS.³⁸

Pregnancy

To the best of our knowledge, there are no indications of a teratogenic or mutagenic effect of alteplase in animal embryos, and the drug does not cross the placenta.¹⁰⁶ Currently, there are 20 cases described in the literature of pregnant women receiving IVT, alone or in combination with MT, for AIS.^{1,38,107–109} Two patients developed sICH, but with favorable outcomes, one case developed intrauterine hematoma. Most neonatal outcomes were favorable, with very few medically terminated pregnancies or intrauterine deaths that were unrelated to alteplase infusion. Off-label IVT may be considered for selected pregnant women with AIS, provided a close collaboration with a gynecologist is feasible.

Cerebral microbleeds

The presence of cerebral microbleeds (CMBs) on SWI or T2* sequences of brain MRI may signal the presence of various pathophysiological processes, that are being related to increased bleeding risk.¹¹⁰ In a multicenter study, among 672 IVT-treated patients, 103 harbored CMBs, with 10 having >10 CMBs. Patients with >10 CMBs developed sICH in rates of 30%, indicating a statistical significant increase in the risk of sICH (OR, 13.4; 95%CI, 3.2–55.9).¹¹¹ Another study found, additionally, increased mortality rates after IVT in patients with >10 CMBs.¹¹² Finally, a meta-analysis of available cohorts reported an excessively high rate of sICH (47%) among the small subgroup of AIS with >10 CMBs on brain MRI (0.8% of all AIS patients with available brain

MRI).¹¹³ However, since the probability of harboring >10 CMBs is low (0.6–2.7%), obtaining MRI scans before IVT is not justified, a statement also adopted by the AHA/ASA guidelines.³⁰

Intracranial tumors

The presence of intra-axial intracranial tumors represents an absolute contraindication to IVT because it may be associated with an excessive risk of sICH based on limited case series or case reports.^{38,114} Conversely, the detection of extra-axial brain tumors on brain imaging should not result in withholding IVT in patients with symptoms of acute cerebral ischemia. Limited research lends support to these recommendations, deriving mainly from IVT-treated AIS cases with co-existent meningiomas, in which no sICH has been documented (31 cases).^{115,116} In view of the previous considerations, an individual decision making is probably warranted when managing patients with known intra-axial tumors. In such cases, obtaining a pre-IVT brain MRI is crucial to search for microhemorrhages within the tumor on SWI-MRI or to appreciate the extent of peritumoral edema.

Recent diagnosis of gastrointestinal malignancy or recent gastrointestinal bleeding, recent surgery, recent severe head trauma

Recent major surgery or head trauma, and recent diagnosis of gastrointestinal (GI) malignancy or recent GI bleeding are all considered as potential contraindications to IVT. However, there are variations in the guidelines and the official drug labeling of alteplase regarding the minimum required time interval between the pre-mentioned conditions and AIS onset for off-label use of IVT to be permitted. Limited data exist in the literature about the risks of IVT in such situations. Two retrospective studies, examining the safety of IVT after recent diagnosis (within 1 year) of GI malignancy (96 patients), recent (within 21 days) GI bleeding (43 patients), and recent (<3 months) surgery or head trauma (13 patients) did not report excessive bleeding complications from IVT in these AIS subgroups.^{117,118} In the absence of robust data, IVT may be averted in AIS patients with recent (<21 days) GI bleeding or known conditions substantially increasing GI bleeding

risk, as well as with history of recent major head trauma (<3 months), but the time interval for this restriction depends on the severity and the imaging findings attributed to the trauma.

Cases with recent surgery may not be denied IVT universally. Conversely, the bleeding risk must be appreciated with the aid of the treating surgeon in order to weigh benefits from IVT against the potential hemorrhagic hazards, particularly for cases that are not eligible or do not have access to MT and sustain substantial neurological deficits.

Uncommon causes of acute cerebral ischemia: cardiac myxoma, cardiac thrombus, aortic arch dissection, infective endocarditis, intracranial arterial dissection

Several case reports have described patients with cardiac myxoma-associated AIS treated with IVT. Overall, an increased rate of parenchymal hematoma type-2 formation (18.2%) has been reported, but no death has been documented.¹¹⁹ The concern derives from the known association of cardiac myxoma-related cerebral embolism with cerebral aneurysmal formation and cerebral microbleeds.¹²⁰

Similarly, in infective endocarditis the generation and release of septic emboli, causing pyogenic arteritis and cerebral mycotic aneurysms, are well-known mechanisms predisposing to ICH. A systematic review identified 52 patients with AIS due to infective endocarditis that received IVT, MT, or combined IVT–MT therapy. The risk of ICH was 4.14 times higher in IVT-treated patients and 4.67 times higher in patients receiving both IVT and MT. A trend for more favorable outcomes was observed when patients underwent MT alone.¹²¹ Stroke clinicians should always bear in mind the rare probability of AIS caused by an underlying infective endocarditis, and if suspicion is high withholding IVT is justified (Figure 7).

The risk from IVT in AIS cases with intracardiac mobile thrombi is associated with the probability of partial degradation of the thrombi, leading to recurrent cerebral or peripheral embolism. Although such complications have been described in the literature, early detection of a floating intracardiac thrombus in an AIS patient with

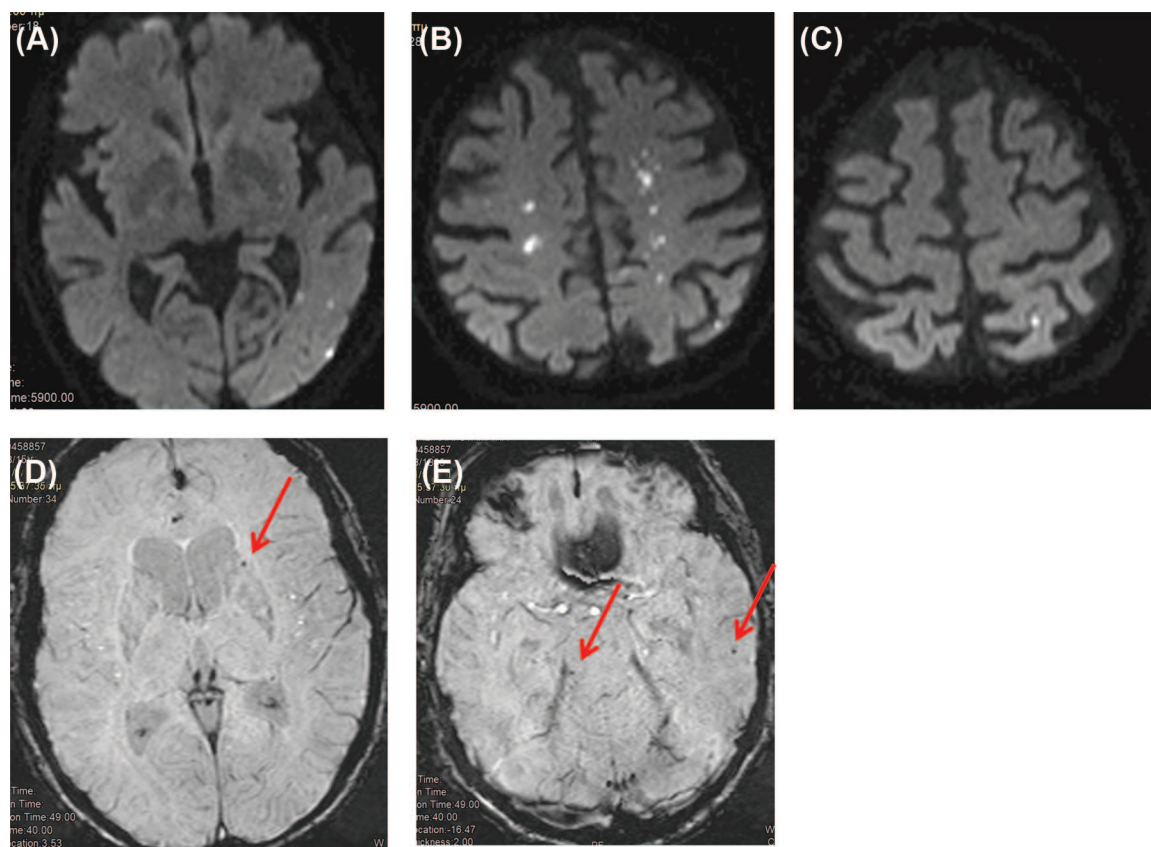


Figure 7. An 85-year-old woman, with a history of degenerative mitral valve disease and a recent diagnosis of melanoma, presented with fever and reduced level of consciousness. Admission inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) were increased. Urgent diffusion-weighted-imaging brain MRI sequences showed multiple small embolic-type acute infarcts in different arterial distributions including left middle cerebral artery, left anterior cerebral artery and right anterior cerebral artery (Panels A–C). Susceptibility-weighted imaging MRI showed multiple periventricular and subcortical cerebral microbleeds (Panels D and E, arrows). Echocardiography revealed valve vegetations and blood cultures were positive for *Staphylococcus aureus*, establishing the diagnosis of infective endocarditis due to contamination of the skin lesion (melanoma), which is an absolute contraindication for intravenous thrombolysis.

potentially severe disability does not justify withholding IVT.^{122–124}

Aortic arch dissection may manifest as AIS. Although few case reports have reported the uncomplicated administration of IVT, aortic dissection represents an absolute contraindication to IVT because of the risk of aortic rupture and systemic hemorrhagic complications.¹²⁵ Carotid ultrasound, performed easily at the bedside, may swiftly detect aortic dissection extending into the common carotid arteries and potentially avert the use of IVT in this uncommon AIS subgroup (Figure 8).¹²⁶

IVT for AIS due to intracranial artery dissection may not be routinely recommended because of the

perceived risk of subarachnoid hemorrhage that may complicate intracranial dissections especially when located in the vertebrobasilar circulation. Again, limited case reports have been published so far, including one case series comprising five IVT-treated patients with intracranial dissections, none of which developed sICH.¹²⁷

Intravenous thrombolysis with low-dose alteplase

Aiming to enhance safety without reducing efficacy of IVT, the ENCHANTED trial randomized 3310 AIS patients to receive IVT within 4.5 h of symptom onset with either a lower (0.6 mg/kg) or the standard dose of alteplase (0.9 mg/kg). The majority of patients included

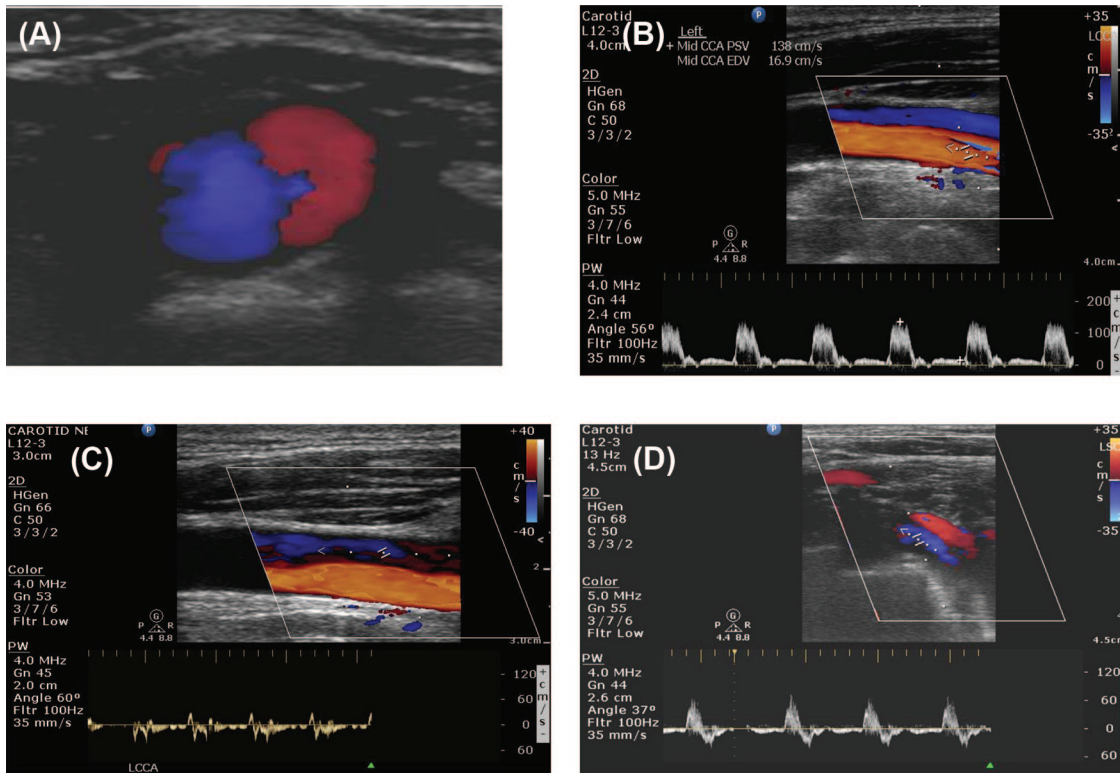


Figure 8. A 53-year-old man presented with acute onset of dysarthria and right arm weakness (National Institute of Health Stroke Scale score of 4 points). Carotid ultrasound examination disclosed double lumen appearance within the right common carotid artery (Panel A), with opposite flow directions within each lumen, (Panels B and C). Double lumen appearance was also evident in the right subclavian artery (Panel D). The patient suffered an aortic arch dissection that extended into the innominate, right CCA, and right subclavian arteries. The decision was made to withhold IVT.

were Asian, and the trial is the only RCT to date to investigate the potential non-inferiority of lower compared with standard doses of alteplase for AIS. Non-inferiority was not documented, since unfavorable functional outcome (defined as mRS scores 2–6) was reported in 53.2% in the low-dose and 51.1% in the standard-dose group (OR, 1.09; 95%CI, 0.95–1.25; p for non-inferiority=0.51). Although rates of sICH were decreased in the low-dose group (1.0% *versus* 2.1%, $p=0.01$), 3-month mortality rates were comparable between groups (8.5% and 10.3%, respectively, $p=0.07$).¹²⁸ In a pre-specified subgroup analysis, patients with prior antiplatelet treatment had better functional outcomes with low *versus* standard alteplase dose, compared with patients not receiving antiplatelets, although difference was non-statistically significant (OR 0.84; 95%CI, 0.62–1.12 *versus* OR, 1.16; 95%CI, 0.99–1.36; p for interaction = 0.053).¹²⁹

Analysis of individual patient data from nine acute stroke Asian registries with 6250 participants, including 1610 receiving off-label low alteplase dose, did not disclose significant differences between the low and the standard alteplase dose in terms of efficacy and rates of sICH. A trend for lower mortality rates was seen in the low-dose-treated patient group (OR, 0.77; 99%CI, 0.59–1.01).¹³⁰ Several other observational registry data involving exclusively Asian stroke populations have been published with conflicting results.^{131,132}

Based mainly on the high quality of evidence from the ENCHANTED trial, low-dose alteplase use for IVT in AIS is currently not justified. Limited data deriving from subgroup RCT analysis or observational registries describing potential benefit from low-dose IVT in patients on antiplatelet treatment, or lower rates of sICH

and death in general, must be interpreted with caution, primarily because they derive exclusively from Asian stroke populations, and therefore cannot be generalized.

Intravenous thrombolysis with tenecteplase

Tenecteplase (TNK) is being increasingly used by stroke physicians due to its higher fibrin specificity, increased resistance to plasminogen activator inhibitor-1 activity, and longer half-life compared with alteplase, permitting its administration as a single bolus injection (Table 1).¹³³ Although AIS treatment is not included in the official drug labeling indications, the latest AHA/ASA guidelines encompass a statement regarding the possible use of TNK for AIS attributed to LVO.³⁰ The recommendation is based on the results of the Tenecteplase *versus* Alteplase Before Endovascular Therapy for Ischemic Stroke trial (EXTEND-IA TNK) that randomized LVO-related AIS patients, presenting within 4.5 h from symptom onset, to alteplase or TNK. Complete reperfusion was achieved in 22% *versus* 10% ($p=0.03$) in the TNK and alteplase groups, respectively. Moreover, TNK-treated patients had better 3-month functional outcomes without differences in the sICH rates.¹³⁴ Subsequently, the EXTEND-IA TNK Part 2 trial confirmed the relatively high reperfusion rates with TNK bolus injection in patients with LVO, and, additionally, did not find significant differences between the 0.40 mg/kg or the 0.25 mg/kg doses of TNK.¹³⁵ A network meta-analysis also found better efficacy and imaging outcomes with the 0.25 mg/kg dose of TNK compared with the higher doses.¹³⁴

Five randomized trials compared different TNK doses with alteplase.^{135–140} The largest, the Norwegian Tenecteplase Stroke Trial, did not find significant differences in efficacy and safety between the 0.4 mg/kg dose of TNK and the standard dose of alteplase; however, the trial included mostly patients with low stroke severity.^{137,141} Only the Tenecteplase *versus* Alteplase for Acute Ischaemic Stroke trial (TAAIS) showed significant early neurological improvement from TNK compared with alteplase, coupled with higher recanalization rates.¹³⁸ Notably, the higher efficiency of TNK in LVO recanalization is most consistent among trials. A recent meta-analysis of the five randomized trials confirmed the

non-inferiority of TNK compared with alteplase in terms of functional outcomes and safety.¹⁴²

Due to the enhanced recanalization rates in LVO-attributed stroke, the rapid infusion protocol, and the comparative efficacy with alteplase, TNK may be used in cases with proximal LVO, particularly when scheduled to undergo MT. Moreover, recent data support the cost effectiveness of TNK over alteplase before MT for LVO-attributed AIS.¹⁴³ Finally, the advantages of tenecteplase compared with alteplase related to shortening workflow time metrics of IVT support the use of tenecteplase to reduce the emergency department spread of Coronavirus 2019 Disease (COVID-19) and facilitate the bridging of IVT and MT during the COVID-19 pandemic.¹⁴⁴

Conclusion

IVT is a highly effective reperfusion therapy for AIS that should be offered to all eligible patients. Due to the uncertainties regarding the absolute and the numerous relative contraindications of IVT for AIS between official drug labeling of alteplase in different countries, and also due to different and sometimes divergent international guidelines, there is often uncertainty about the eligibility of many patients, which contributes to the universally low IVT rates. Tables 2 and 3 summarize the authors' personal views regarding absolute contraindications to IVT in specific conditions mimicking acute cerebral ischemia or in AIS patients with uncommon causes associated to high perceived risk of systemic or intracranial complication. In contrast, we favor tPA administration in conditions that were originally included in the list of IVT contraindications (e.g. low platelet count, increased stroke severity, age >80 years, previous ischemic stroke with an elapsed time interval of >14 days, previous history of diabetes coupled with onset to treatment time >3 h, etc).

In real-world daily practice many of the official contraindications are violated, either inadvertently as a result of human error or deliberately from informed patient decision after detailed discussion with treating physicians. The present narrative review provides some insight into the safety repercussions of off-label tPA use in the real world by summarizing systematically the available

Table 1. Comparative evaluation of tenecteplase and alteplase agents for the therapeutic indication of intravenous thrombolysis (IVT) for acute ischemic stroke (AIS).

Variable	Alteplase	Tenecteplase
Pharmacological properties		
Fibrin selectivity	Moderate	High
Half-life, min	4–8	10–20
Inhibition of tPA due to binding with PAI-1	High	Low
IVT workflow characteristics		
Time to prepare	Longer	Shorter
Single bolus injection	No	Yes
Infusion following bolus	Yes (1 h)	No
Intravenous infusion pump (required)	Yes	No
Second intravenous catheter (required)	Yes	No
Needle to groin puncture time*	Longer	Shorter
Efficacy in AIS**		
3-month favorable functional outcome (mRS score 0–1), %	35%	46%
3-month functional independence (mRS score 0–2), %	46%	58%
Safety in AIS**		
Symptomatic intracranial hemorrhage, %	3	2
3-month mortality, %	17	13
Efficacy in AIS due to large vessel occlusion***		
Successful reperfusion, % [#]	10	22
3-month favorable functional outcome (mRS score 0–1), %	43	51
3-month functional independence (mRS score 0–2), %	51	64
Safety in AIS due to large vessel occlusion***		
Symptomatic intracranial hemorrhage, %	1	1
3-month mortality, %	18	10
*in patients eligible for endovascular thrombectomy. **data reported in the meta-analysis by Burgos & Saver. ¹³⁴ ***Patients eligible for endovascular thrombectomy; data reported in EXTEND-IA TNK Trial. ¹²⁶ [#] Before initiation of endovascular thrombectomy. mRS, modified Rankin Scale; PAI-1, plasminogen activator inhibitor type I; tPA, tissue plasminogen activator.		

data. Current guidelines and AIS protocols should be modified to accommodate recent real-world experience in numerous conditions that were originally considered absolute or relative tPA contraindications. The potential of

tenecteplase as an alternative thrombolytic agent that can be administered as a single bolus dose with at least similar safety and efficacy compared with alteplase deserves further investigation in the setting of RCTs and in the LVO subgroup in

Table 2. Uncommon conditions mimicking acute ischemic stroke (AIS) with absolute contraindications to intravenous thrombolysis (IVT; authors' personal opinion).

Uncommon conditions mimicking AIS with absolute contraindication to IVT	Potential complication related to IVT for AIS
Isodense subdural hematoma	Symptomatic intracranial bleeding
Intra-axial brain tumors	Symptomatic intracranial bleeding
Transient focal neurological episodes due to underlying cerebral amyloid angiopathy	Symptomatic intracranial bleeding
Symptomatic cerebral cavernous malformation	Symptomatic intracranial bleeding
Spinal cord epidural hematoma	Symptomatic intraspinal bleeding

Table 3. Uncommon causes of acute ischemic stroke (AIS) with absolute contraindication to intravenous thrombolysis (IVT; authors' personal opinion).

Uncommon causes of AIS with absolute contraindication to IVT	Potential Complication related to IVT for AIS
Aortic arch dissection	Aortic rupture
Infective endocarditis	Symptomatic intracranial bleeding
Recent (>6 h and <7 days) anterior ST-elevation myocardial infarction	Cardiac tamponade
Intracranial thrombosed giant aneurysm	Symptomatic intracranial bleeding
Vasospasm due to previously undiagnosed aneurysmal subarachnoid hemorrhage	Symptomatic intracranial bleeding

particular, before it can be recommended as the primary fibrinolytic standard of care taking over from rt-PA.

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