A Review of the Exclusion Criteria for IV rtPA for Acute Ischaemic Stroke

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Background

• Criteria from NINDs trial – expert consensus
• Great deal of experience since – RCT’s / registry data/case series
• Evidence for IV thrombolysis has strengthened over time
• Rationale for avoiding therapy has reduced
• Low rates of thrombolysis – multifactorial but at least in part due to exclusion criteria
• AHA updated guidelines 2015
• Time for us regionally to review
South Yorkshire Regional Stroke Telemedicine Physicians Electronic Checklist

### Patient Demographics
- Patient initials and date of birth
- Patient Hospital number
- Current location and referring doctor
- Time and date last seen well
- On call Stroke Physician making decision
- Date and time of call

### Answer YES to the following questions to proceed with thrombolysis
- Symptoms suggestive of a stroke
- Seizure / migraine / Sub arachnoid bleed unlikely
- Confirmed onset < 4.5 hours (3 hrs - 4.5 hrs best evidence off licence)
- Age over 18 (Over 80 treated off licence or clinical judgement)

### Answer NO to the following questions to proceed with thrombolysis
- Stroke symptoms minor or rapidly improving (NIHSS < 2)
- Hypo or Hyperglycaemia (Blood glucose <2.8 or >22 mmol/l)
- LMW Heparin administered the past 24hrs or IV Heparin APTT ratio >1.0
- On warfarin INR > 2.5, or Non vit K antagonist (Dibigatran, Rivastigiba)
- Known bleeding source / tumour / clotting problem
- Recent Stroke in the past 6 weeks
- Major Surgery / trauma in past 3 months
- GI / Urinary tract bleeding past 3 weeks
- Previous CNS surgery, intracranial bleeds or known neoplasm
- Severe Liver disease
- Atrial puncture at a non compressible site less than 7 days ago
- Current systolic BP greater than 165 or diastolic BP greater than 110
- Significant head trauma less than 2 months ago
- History of Haemorrhagic retinopathy / pancreatitis / pericarditis
- Childbirth or prolonged CPR less than 10 days ago
- Known intracranial or extracranial aneurysm or AV malformation
- Significant functional dependence prior to stroke

### CT head scan reviewed by clinician on telemedicine screen
- No evidence of bleed
- No radiological contra indication to thrombolysis
- No clear clinical contra indication to thrombolysis

Updated 19/11/12

Version 1.6
Answer **NO** to the following questions to proceed with thrombolysis:

- Stroke symptoms minor or rapidly improving (NIHSS < 3)
- Hypo or Hyperglycaemia (Blood glucose < 2.8 or > 22 mmol/l)
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- Childbirth or prolonged CPR less than 10 days ago
- Known intracranial or extracranial aneurysm or AV malformation
- Significant functional dependance prior to stroke
AHA/ASA Scientific Statement

Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke
A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

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Agenda

• Stroke severity – severe/mild
• Resolving
• Early ischemic change on CT imaging
• Recent bleeding
• Blood glucose
• INR
• DOAC usage
• Previous ICH
• Intracranial aneurysms
• Malignancy
Stroke Severity
Severe

• Original FDA label, risks may be increased with NIHSS >22

• NINDS – max NIHSS 37 (few with NIHSS > 25)
  Mild stroke predicted good outcome but significant effect seen in strokes with NIHSS > 20.

• ECASS excluded pts with NIHSS >25
Stroke Severity
Severe

Pts achieving primary endpoint (alive and independent)
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

Jonathan Emberson, PhD, Prof Kennedy R Lees, MD, Prof Patrick Lyden, MD, Lisa Blackwell, BSc, Prof Gregory Albers, MD, Prof Erich Bluhmki, PhD, Prof Thomas Brott, MD, Geoff Cohen, MSc, Prof Stephen Davis, MD, Prof Geoffrey Donnan, MD, Prof James Grotta, MD, Prof George Howard, PhD, Prof Markku Kaste, MD, Masatoshi Koga, MD, Prof Ruediger von Kummer, MD, Maarten Lansberg, MD, Prof Richard I Lindley, MD, Prof Gordon Murray, PhD, Prof Jean Marc Olivot, MD, Prof Mark Parsons, MD, Prof Barbara Tilley, PhD, Danilo Toni, MD, Prof Kazunori Toyoda, MD, Prof Nils Wahlgren, MD, Prof Joanna Wardlaw, MBChB, William Whiteley, MD, Prof Gregory J del Zoppo, MD, Prof Colin Baigent, BM BCh, Prof Peter Sandercock, DM, Prof Werner Hacke, MD, for the Stroke Thrombolysis Trialists' Collaborative Group
Interpretation

Irrespective of age or stroke severity, and despite an increased risk of fatal intracranial haemorrhage during the first few days after treatment, alteplase significantly improves the overall odds of a good stroke outcome when delivered within 4.5 h of stroke onset, with earlier treatment associated with bigger proportional benefits.
IV thrombolysis in very severe and severe ischemic stroke: Results from the SITS-ISTR Registry.

Mazya MV¹, Lees KR², Collas D², Rand VM², Mikulik R², Toni D², Wahlgren N², Ahmed N².

Abstract

OBJECTIVE: To study the safety of off-label IV thrombolysis in patients with very severe stroke (NIH Stroke Scale [NIHSS] scores >25) compared with severe stroke (NIHSS scores 15-25), where treatment is within European regulations.

METHODS: Data were analyzed from 57,247 patients with acute ischemic stroke receiving IV tissue plasminogen activator in 793 hospitals participating in the Safe Implementation of Thrombolysis in Stroke (SITS) International Stroke Thrombolysis Registry (2002-2013). Eight hundred sixty-eight patients (1.5%) had NIHSS scores >25 and 19,995 (34.9%) had NIHSS scores 15-25. Outcome measures were parenchymal hemorrhage, symptomatic intracerebral hemorrhage, mortality, and functional outcome.

RESULTS: Parenchymal hemorrhage occurred in 10.7% vs 11.0% (p = 0.79), symptomatic intracerebral hemorrhage per SITS-MOST (SITS-Monitoring Study) in 1.4% vs 2.5% (p = 0.052), death at 3 months in 50.4% vs 26.9% (p < 0.001), and functional independence at 3 months in 14.0% vs 29.0% (p < 0.001) of patients with NIHSS scores >25 and NIHSS scores 15-25, respectively. Multivariate adjustment did not change findings from univariate comparisons. Posterior circulation stroke was more common in patients with NIHSS scores >25 (36.2% vs 7.4%, p < 0.001), who were also more often obtunded or comatose on presentation (58.4% vs 7.1%, p < 0.001). Of patients with NIHSS scores >25, 26.2% were treated >3 hours from symptom onset vs 14.5% with NIHSS scores of 15-25.

CONCLUSIONS: Our data show no excess risk of cerebral hemorrhage in patients with NIHSS score >25 compared to score 15-25, suggesting that the European contraindication to IV tissue plasminogen activator treatment at NIHSS levels >25 may be unwarranted. Increased mortality and lower rates of functional independence in patients with NIHSS score >25 are explained by higher stroke severity, impaired consciousness on presentation due to posterior circulation ischemia, and longer treatment delays.

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CONCLUSIONS: Our data show no excess risk of cerebral hemorrhage in patients with NIHSS score >25 compared to score 15-25, suggesting that the European contraindication to IV tissue plasminogen activator treatment at NIHSS levels >25 may be unwarranted. Increased mortality and lower rates of functional independence in patients with NIHSS score >25 are explained by higher stroke severity, impaired consciousness on presentation due to posterior circulation ischemia, and longer treatment delays.
Stroke Severity

Severe

Recommendations

• Increased risk of haemorrhage should not be used as a reason not to treat.

• On the basis of available literature there should be no upper limit of NIHSS score for pts otherwise eligible for tPA within 3hrs

• FDA label has removed stroke severity (either “too mild” or NIHSS > 22)
Stroke Severity
Mild

• Disability among “mild” stroke pts is significant – not just motor
  - further stroke
  - deterioration
  - disability from problems not picked up on NIHSS
• Prediction difficult
• Risk of haemorrhagic transformation low
• Few mild pts in clinical trials therefore risk to benefit ratio unknown
• A number of case series and small clinical trials to suggest there may be benefit from thrombolysis especially if have vessel occlusion.

AHA recommendation
Within 3 hours from symptom onset, treatment of patients with milder ischemic stroke symptoms that are judged as nondisabling may be considered. Treatment risks should be weighed against possible benefits; however, more studies are needed to further define the risk-to-benefit ratio
Stroke Severity
Rapidly Improving

• One of most common reasons for not thrombolysing
• Can be misinterpreted
• Many pts with initial rapid improvement remain disabled

• **Recommendations**: 
  • We should not be monitoring pts to see if improving
  • tPA remains reasonable for pts who despite rapid initial improvement remain disabled in the eyes of the examiner – “thrombolysé what’s in front of you”
CT findings of early stroke

• Controversy as to the degree of hypoattenuation that represents irreversible damage
• ECASS 2 – no evidence that tPA less effective in pts with EIC’s in >1/3 MCA territory
  reliability of application of 1/3 rule
• NINDS detailed review : 31% with EIC’s. No influence on treatment effect
• Post hoc analysis of NINDS using ASPECTS
  No treatment modifying effect for outcomes for ASPECTS > 7 vs <7
CT findings of early stroke

• No established extent or severity of EIC’s that should exclude someone from tPA

• HOWEVER

• Few trials with pts enrolled with very extensive EIC’s therefore safety and efficacy remains uncertain
CT findings of early stroke

• AHA Recommendations:
  1. Intravenous alteplase administration is recommended in the setting of EICs of mild to moderate extent (other than frank hypodensity) (Class I; Level of Evidence A).

  2. There remains insufficient evidence to identify a threshold of hypoattenuation severity or extent that affects treatment response to alteplase. However, administering intravenous alteplase to patients whose CT brain imaging exhibits extensive regions of clear hypoattenuation is not recommended. These patients have a poor prognosis despite intravenous alteplase, and severe hypoattenuation defined as obvious hypodensity represents irreversible injury (Class III; Level of Evidence A).
History of GI/GU bleeding in last 21 days

• Active bleeding = contraindication
• Recent bleeding = warning – relative CI on AHA guidelines
• Existing literature extremely limited.
• 21 days arbitrarily chosen
• Some studies with tPA used off licence included pts with “systemic disease with risk of bleeding”. Low numbers however.
• Risks and benefits likely to change depending on several factors
History of GI/GU bleeding in last 21 days

• AHA Recommendations:
Patients with a structural gastrointestinal malignancy or recent bleeding event within 21 days of their stroke event should be considered high risk, and intravenous alteplase administration is potentially harmful (Class III; Level of Evidence C).
Blood glucose

• Concern that hypo and hyperglycaemia can produce focal neurological deficits
• Account for <1% contraindications
• Hypoglycaemia rarely produces stroke like syndrome without other neuroglycopenic symptoms
• Hyperglycaemia can accelerate tissue infarction, reduce chances of successful recanalisation plus concerns over increased sICH.
  – Low number of pts with conflicting evidence SITS EAST vs VISTA
  – Persistent hyperglycaemia rather than initial hyperglycaemia may be more important
Blood Glucose

- Special diligence in making stroke diagnosis
- Treat blood glucose and reassess

- AHA recommendations

- 1. Intravenous alteplase is recommended in otherwise eligible patients within initial glucose levels >50 mg/dL (Class I; Level of Evidence A).
- 2. Treating clinicians should be aware that hypoglycemia and hyperglycemia may mimic acute stroke presentations and check blood glucose levels before intravenous initiation. Intravenous alteplase is not indicated for nonvascular conditions (Class III; Level of Evidence B).
- 3. Treatment with intravenous alteplase in patients with acute ischemic stroke who present with initial glucose levels >400 mg/dL that are subsequently normalized and who are otherwise eligible may be reasonable (Class IIb; Level of Evidence C).
INR level

• >1.7 within 3 hrs, and regardless of INR > 3hrs tPA contraindicated
• Numerous small studies of off label thrombolysis
• SITS registry
• AHA Get-With-The-Guidelines registry
Odds of more favorable outcome for thrombolyzed patients compared with controls, adjusted for age, and baseline National Institutes of Health Stroke Scale (NIHSS), within subgroups of patients with specified warnings and contraindications.

INR Level

• AHA recommendations:

• 1. Intravenous alteplase may be reasonable in patients who have a history of warfarin use and an INR ≤1.7 (Class IIb; Level of Evidence B).

• 2. Intravenous alteplase in patients who have a history of warfarin use and an INR >1.7 is not recommended (Class III; Level of Evidence B).
DOAC usage

- Currently there is very little data to support the thrombolysis of patients who are known to be taking DOACs.
- The below guidance is based on consensus and expert opinion.

- **No DOAC taken in the last 48hrs**
  - For apixaban and rivaroxaban, safe to proceed with thrombolysis if CrCl (NOT eGFR) >30ml/min. If CrCl <30ml/min, thrombolysis only recommended if greater than 72 hrs since last dose.
  
  - For Dabigatran can proceed if CrCl >50ml/min. If CrCl <50ml/min, thrombolysis only recommended if greater than 72 hrs since last dose.
DOAC usage

- Last dose of DOAC taken between 24 and 48 hours ago OR uncertain when last dose taken
- For patients on rivaroxaban and apixaban an urgent level can be obtained. No assay is available for dabigatran or edoxaban currently out of hours in Sheffield.

- If levels return <30ng/ml for rivaroxaban, apixaban or dabigatran then it will be safe to proceed with thrombolysis as that is below a detectable level.

- If levels come back >30ng/ml (i.e. showing anticoagulant activity) then not to proceed with thrombolysis.

- Last dose of DOAC taken within the last 24 hours
- We do not recommend thrombolysis
DOAC usage

• AHA Recommendations

The use of intravenous alteplase in patients taking direct thrombin inhibitors or direct factor Xa inhibitors has not been firmly established but maybe harmful (*Class III; Level of Evidence C*).

The use of intravenous alteplase in patients taking direct thrombin inhibitors or direct factor Xa inhibitors is not recommended unless laboratory tests such as aPTT, INR, platelet count, ecarin clotting time, thrombin time, or appropriate direct factor Xa activity assays are normal or the patient has not received a dose of these agents for >48 hours (assuming normal renal metabolizing function).
Previous ICH

• Previously CI
• Updated label – recent ICH “warning”
• Very low numbers in literature
• Evidence for thrombolysis in setting of cerebral microhaemorrhage
Bleeding Risk Analysis in Stroke Imaging Before ThromboLysis (BRASIL)

Pooled Analysis of T2*-Weighted Magnetic Resonance Imaging Data From 570 Patients

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Background and Purpose—There has been speculation that the risk of secondary symptomatic intracranial hemorrhage (SICH) may be increased after thrombolytic therapy in ischemic stroke patients who have cerebral microbleeds (CMBs) on T2*-weighted magnetic resonance imaging. Because of this concern, some centers withhold potentially beneficial thrombolytic therapy from these patients.

Methods—We analyzed magnetic resonance imaging data acquired within 6 hours after symptom onset from 570 ischemic stroke patients treated with intravenous tissue plasminogen activator in 13 centers in Europe, North America, and Asia. Baseline T2*-weighted magnetic resonance images were evaluated for the presence of CMBs. The primary end point was SICH, defined as clinical deterioration with an increase in the National Institutes of Health Stroke Scale score by ≥4 points, temporally related to a parenchymal hematoma on follow-up imaging.

Results—A total of 242 CMBs were detected in 86 of 570 patients (15.1%). The number of CMBs ranged from 1 to 77 in the individual patient, with ≥5 CMBs in 6 of 570 patients (1.1%). Proportions of patients with SICH were 5.8% (95% CI, 1.9 to 13.0) in the presence of CMBs and 2.7% (95% CI, 1.4 to 4.5) in patients without CMBs (P=0.170, Fisher’s exact test), resulting in no significant absolute increase in the risk of SICH of 3.1% (95% CI, –2.0 to 8.3).

Conclusions—The data suggest that if there is any increased risk of SICH attributable to CMBs, it is likely to be small and unlikely to exceed the benefits of thrombolytic therapy. No reliable conclusion regarding risk in the rare patient with multiple CMBs can be reached. (Stroke. 2007;38:2738-2744.)
ABSTRACT

Background  Intracerebral haemorrhage (ICH) remains the most devastating yet unpredictable complication of intravenous thrombolysis for acute ischaemic stroke. We performed a systematic review and meta-analysis, to assess whether the presence of cerebral microbleeds (CMBs) on prethrombolysis MRI scans is associated with an increased risk of ICH.

Methods  We searched PubMed for studies assessing ICH risk in patients with acute ischaemic stroke treated with thrombolysis, in relation to the presence of pre-treatment CMBs.

Results  We identified five studies including 790 patients and pooled data in a meta-analysis. The CMB (+) versus CMB (−) groups were not significantly different in age, gender or stroke severity. The overall prevalence of CMBs was 135/790 (17.1%). Amongst patients with CMBs, 10/135 (7.4%) experienced a symptomatic ICH after thrombolysis, compared to 29/655 (4.4%) patients without CMBs. The pooled relative risk of ICH was 1.90 (95% CI 0.92 to 3.93; p=0.082).

Conclusions  The available evidence does not demonstrate a statistically significant increased risk of symptomatic ICH after thrombolysis for ischaemic stroke in patients with CMBs. However, in view of the methodological limitations of the studies included, the clinical relevance of any potential hazard associated with CMBs remains uncertain. Further studies are warranted to evaluate whether the risk of ICH might outweigh the benefit of thrombolysis, especially in patients with multiple lobar CMBs suggestive of cerebral amyloid angiopathy.
Previous ICH

• AHA Recommendations
  1. Intravenous alteplase has not been shown to increase sICH rates in patients with CMBs. Intravenous alteplase administration in these patients is therefore reasonable (Class IIa; Level of Evidence B).

  2. Intravenous alteplase administration in patients who have a history of intracranial hemorrhage is potentially harmful (Class III; Level of Evidence C).
Unruptured Intracranial aneurysm

• Unruptured aneurysm occurs in 2-3% of general population

• Data from case reports and series and more recent meta-analysis of case series
Systemic thrombolysis in acute ischemic stroke patients with unruptured intracranial aneurysms.

Goyal N¹, Tsivgoulis G¹, Zand R¹, Sharma VK¹, Barlinn K¹, Male S¹, Katsanos AH¹, Bodechtel U¹, Iftikhar S¹, Arthur A¹, Eliovich L¹, Alexandrov AW¹, Alexandrov AV².

Author information

Abstract

OBJECTIVE: We sought to determine the safety of IV thrombolysis (IVT) in acute ischemic stroke (AIS) patients harboring unruptured intracranial aneurysm (UIA) in a multicenter study and a comprehensive meta-analysis of available case series.

METHODS: We analyzed prospectively collected data from consecutive AIS patients treated with IVT during a 4-year period at 4 tertiary-care stroke centers. All patients routinely underwent CT or magnetic resonance angiography during hospitalization. The presence of UIA was documented on the basis of neuroradiology reports. Symptomatic intracranial hemorrhage (sICH) was defined as imaging evidence of ICH combined with an increase in NIH Stroke Scale score of ≥4 points. A systematic meta-analysis of case series reporting safety of IVT in AIS with concomitant UIA was conducted according to PRISMA recommendations.

RESULTS: Among 1,398 AIS patients treated with IVT, we identified 42 cases (3.0%) harboring a total of 48 UIAs. The rates of symptomatic and asymptomatic ICH were 2.4% (95% confidence interval [CI] by adjusted Wald method: 0%-12.6%) and 7.1% (95% CI: 1.8%-19.7%), respectively. A total of 5 case series met our inclusion criteria for meta-analysis, and the pooled rate of sICH among 120 IVT-treated AIS patients harboring UIA was 6.7% (95% CI: 3.1%-13.7%). In the overall analysis of 5 case-series studies, the risk ratio of sICH did not differ between AIS patients with and without UIA (risk ratio = 1.60; 95% CI: 0.54-4.77; p = 0.40) with no evidence of heterogeneity across included studies (I²(2) = 22% and p = 0.27 for Cochran Q test).

CONCLUSIONS: Our prospectively collected multicenter data, coupled with the findings of the meta-analysis, indicate the potential safety of IVT in AIS patients with UIA.
Systemic thrombolysis in acute ischemic stroke patients with unruptured intracranial aneurysm

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Author information

Abstract

OBJECTIVE: We sought to determine the safety of IV thrombolysis (IVT) in acute ischemic stroke patients harboring unruptured intracranial aneurysm (UIA) in a multicenter study and a comprehensive meta-analysis.

METHODS: We analyzed prospectively collected data from 336 patients harboring UIA during a 4-year period at 4 tertiary-care stroke centers. All patients routinely underwent CT or magnetic resonance imaging to ensure UIA confirmation. The presence of UIA was documented on the basis of neuroradiology reports. Symptomatic intracerebral hemorrhage (sICH) was defined as imaging evidence of ICH combined with an increase in NIH Stroke Scale score of 4 points or more. A prospective case-series reporting safety of IVT in AIS with concomitant UIA was conducted according to PRISMA guidelines.

RESULTS: Among 336 patients harboring UIA, 42 cases (3.0%) harboring a total of 48 UIAs. The rates of symptomatic and asymptomatic ICH were estimated by adjusted Wald method: 0%-12.6% and 7.1% (95% CI: 1.8%-19.7%), respectively. A total of 120 patients harboring UIA were included in the meta-analysis, and the pooled rate of sICH among 120 IVT-treated AIS patients harboring UIA was estimated as 5.1% (95% CI: 3.1%-7.9%).

Overall analysis of 5 case-series studies, the risk ratio of sICH did not differ between AIS patients with and without UIA (RR: 0.54-4.77; p = 0.40) with no evidence of heterogeneity across included studies (I^2 = 22% and p = 0.27 for heterogeneity).

CONCLUSIONS: Our prospectively collected multicenter data, coupled with the findings of the meta-analysis, indicate the potential safety of IVT in AIS patients harboring UIA.

No absolute increase in risk
Unruptured Intracranial aneurysm

- AHA Recommendations
  1. For patients presenting with acute ischemic stroke who are known to harbor a small or moderate-sized (<10 mm) unruptured and unsecured intracranial aneurysm, administration of intravenous alteplase is reasonable and probably recommended (Class IIa; Level of Evidence C).

  2. Usefulness and risk of intravenous alteplase in patients with acute ischemic stroke who harbor a giant unruptured and unsecured intracranial aneurysm are not well established (Class IIb; Level of Evidence C).
Major Surgery Within 14 Days

- FDA label
- NINDS -14 days, ECASS 3 months.

- Concern over bleeding at operation site

- Paucity of data
Off-label intravenous thrombolysis in acute stroke


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See editorial by Martin-Schild, on page 359.

**Keywords:** ischaemic stroke, off label, Stroke Unit, thrombolysis, tPA

**Background and purpose:** Therapy for stroke with intravenous tissue plasminogen activator (IV-tPA) is hampered by tight licensing restrictions; some of them have been discussed in recent literature. We assessed the safety and effectiveness of off-label IV-tPA in the clinical settings.

**Methods:** Retrospective analysis of all the patients treated with IV-tPA at our Stroke Unit. Patients were divided into two groups by licence criteria (on-label group [OnLG], off-label group [OffLG]). Primary outcome measures were symptomatic intracranial haemorrhages (sICH), major systemic haemorrhages, modified Rankin scale (mRS) and mortality rate at 3 months.

**Results:** Five hundred and five patients were registered, 269 (53.2%) were assigned to OnLG and 236 (46.9%) to OffLG. Inclusion criteria for the OffLG were aged > 80 years (129 patients), time from onset of symptoms to treatment over 3 h (111), prior oral anticoagulant treatment with International Normalised Ratio ≤ 1.7 (41), combination of previous stroke and diabetes mellitus (14), surgery or severe trauma within 3 months of stroke (13), National Institutes of Health Stroke Scale score over 25 (11), intracranial tumours (5), systemic diseases with risk of bleeding (7) and seizure at the onset of stroke (2). No significant differences were identified between both groups regarding the proportion of sICH (OnLG 2.2% vs. OffLG 1.6%, P = 0.78) or the 3-month mortality rate (11.1% vs. 19%; odds ratio [OR], 1.49; 95% CI, 0.86–2.55; P = 0.14). Multivariate analysis showed no significant differences in functional independence at 3 months between both groups (mRS < 3: 64.3% vs. 50.4%; OR mRS > 2: 1.7; 95% CI, 0.96–2.5; P = 0.07).

**Conclusion:** Intravenous thrombolysis may be safe and efficacious beyond its current label restrictions.
13 patients with major surgery in last 3 months.
3 haemorrhages – systemic.
No long term consequences
Off-Label Thrombolysis Is Not Associated With Poor Outcome in Patients With Stroke

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Background and Purpose—Numerous contraindications included in the license of alteplase, most of which are not based on scientific evidence, restrict the portion of patients with acute ischemic stroke eligible for treatment with alteplase. We studied whether off-label thrombolysis was associated with poorer outcome or increased rates of symptomatic intracerebral hemorrhage compared with on-label use.

Methods—All consecutive patients with stroke treated with intravenous thrombolysis from 1995 to 2008 at the Helsinki University Central Hospital were registered (n=1104). After excluding basilar artery occlusions (n=119), the study population included 985 patients. Clinical outcome (modified Rankin Scale 0 to 2 versus 3 to 6) and symptomatic intracerebral hemorrhage according to 3 earlier published criteria were analyzed with a logistic regression model adjusting for 21 baseline variables.

Results—One or more license contraindications to thrombolysis was present in 51% of our patients (n=499). The most common of these were age >80 years (n=159), mild stroke National Institutes of Health Stroke Scale score <5 (n=129), use of intravenous antihypertensives prior to treatment (n=112), symptom-to-needle time >3 hours (n=95), blood pressure >185/110 mm Hg (n=47), and oral anticoagulation (n=39). Age >80 years was the only contraindication independently associated with poor outcome (OR, 2.18; 95% CI, 1.27 to 3.73) in the multivariate model. None of the contraindications were associated with an increased risk of symptomatic intracerebral hemorrhage.

Conclusions—Off-license thrombolysis was not associated with poorer clinical outcome, except for age >80 years, nor with increased rates of symptomatic intracerebral hemorrhage. The current extensive list of contraindications should be re-evaluated when data from ongoing randomized trials and observational studies become available. (Stroke. 2010;41:1450-1458.)

Key Words: acute stroke  •  cerebral infarct  •  contraindications  •  ICH  •  off-label  •  thrombolysis  •  thrombolytic Rx  •  tPA
Off-Label Thrombolysis Is Not Associated With Poor Outcome in Patients With Stroke

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Background and Purpose—Numerous contraindications included in the license of alteplase, most of which are not based on evidence from randomized controlled trials. The purpose of this study was to evaluate the accuracy of the current contraindications to thrombolysis in a large, unselected, consecutive cohort of patients with acute ischemic stroke.

Methods—We included all consecutive patients presenting to the emergency department with acute ischemic stroke and treated with thrombolysis, as well as the 21 baseline variables adjusted for. The accuracy of the license was evaluated using logistic regression models.

Results—One or more license contraindications to thrombolysis was present in 51% of our patients (n=499). The most common contraindication was age >80 years (n=159), followed by NIH Stroke Scale score <5 (n=129), use of intravenous antiplatelet agents prior to treatment (n=112), symptom-to-needle time >3 hours (n=95), blood pressure >185/110 mm Hg (n=47), and oral anticoagulation (n=39). Age >80 years was the only contraindication independently associated with poor outcome (OR, 2.18; 95% CI, 1.27 to 3.73) in the multivariate model. None of the contraindications were associated with an increased risk of symptomatic intracerebral hemorrhage.

Conclusions—Off-license thrombolysis was not associated with poorer clinical outcome, except for age >80 years, nor with increased rates of symptomatic intracerebral hemorrhage. The current extensive list of contraindications should be re-evaluated when data from ongoing randomized trials and observational studies become available. (Stroke. 2010;41:1450-1458.)

Key Words: acute stroke ■ cerebral infarct ■ contraindications ■ ICH ■ off-label ■ thrombolysis ■ thrombolytic Rx ■ tPA
Major Surgery in Last 14 days

• AHA recommendations:
Use of intravenous alteplase in carefully selected patients presenting with acute ischemic stroke who have undergone a major surgery in the preceding 14 days may be considered, but the potential increased risk of surgical-site hemorrhage should be weighed against the anticipated benefits of reduced stroke related neurological deficits (Class IIb; Level of Evidence C).
Malignancy

• Neither FDA label nor AHA guidelines contraindicate tPA
• Independent predictor of poor outcome in stroke pts
• Only small case series – no cases of brain metastases

• **Masrur S, Risk of Thrombolytic Therapy for AIS in Patients with Current Malignancy, Journal of Stroke and Cerebrovascular Diseases, 2009.**

18 pts with current malignancy. 26 with remote history.
No brain mets.

Current malignancy was associated with increased in-hospital mortality. Mortality was attributable largely to medical comorbidities, not to symptomatic ICH. Our data suggest that thrombolysis may be a reasonable option for patients with malignancy who have acceptable medical comorbidities and performance status
Thrombolysis for Acute Ischemic Stroke in Patients With Cancer
A Population Study

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Background and Purpose—The safety of thrombolysis for acute stroke in patients with cancer is not well established. Our aim is to study the outcomes after thrombolysis in patients with stroke with cancer.

Methods—Patients with acute ischemic stroke who received thrombolysis were identified from the 2009 and 2010 Nationwide Inpatient Sample. Patients with cancer-associated strokes and noncancer strokes were compared based on demographics, comorbidities, and outcomes.

Results—Of the 32576 strokes treated with thrombolysis, cancer-associated strokes had significantly higher comorbidity indices overall, but fewer vascular risk factors than noncancer strokes. There was no difference in the rates of home discharge and in-hospital mortality, after adjusting for confounders. Subgroup analysis showed that compared with liquid cancers, patients with solid tumors had worse home discharge (odds ratio, 0.178; 95% confidence interval, 0.109–0.290; P<0.001) and higher in-hospital mortality (odds ratio, 3.018; 95% confidence interval, 1.37–6.646; P=0.006) after thrombolysis. Metastatic cancers had poorest outcomes, but intracerebral hemorrhage rates were similar.

Conclusions—Thrombolytic therapy for acute stroke in patients with cancer is not associated with increased risk of intracerebral hemorrhage or in-hospital mortality. However, careful consideration of the cancer subtype may help delineate the subset of patients with poor response to thrombolysis. Prospective confirmation is warranted. (Stroke. 2013;44:3573-3576.)
Malignancy

• AHA recommendations:
The safety and efficacy of alteplase in patients with current malignancy are not well established (Class IIb; Level of Evidence C). Patients with systemic malignancy and reasonable (>6 months) life expectancy may benefit from intravenous alteplase if other contraindications such as coagulation abnormalities, recent surgery, or systemic bleeding do not coexist.
Summary

• A number of “contraindications” have remained for historical reasons
• A wealth of experience has been gained with thrombolysis since NINDS
• We can be reassured by the evidence that thrombolysis in a number of previously “contraindicated” areas is likely beneficial
• AHA have reviewed the evidence behind the exclusion criteria and recently updated their guidelines – it’s time to do this ourselves!
Recommendations

• Network meeting to review current inclusion/exclusion criteria

• Division of criteria into “absolute contraindication” and “caution/warning” for clarity

• Education of those involved in thrombolysis rota at all levels

• ? Regional audit of all complications
Thank You

Questions and Discussion