References and Literature Grading

tPA and Ischemic Stroke: Focused Update of 2010 Clinical Practice Advisory from the American Academy of Emergency Medicine

Appendix A - Literature Search Strategy

Three of the authors (WJM, BB, MA) independently performed expedited literature searches using the AAEM methodology previously described. They met and reached consensus on articles to include in the update.

Appendix 1 - Literature Search Strategy.

Using the AAEM methodology for literature search (included as Appendix 2) the following search was performed. All searches were limited to human studies, published in English
Search terms CVA AND (thromboly* OR alteplase), limited to 2010-2016, English language.
The clinical question: "Is intravenous thrombolysis safe and effective for stroke?"
Guideline statements and non-systematic reviews were excluded. Studies targeting differences between specific populations (i.e. males versus females) were excluded.

Tier 1: Systematic Reviews (Meta-Analysis) – Provided 227 citations. The abstracts were scanned, initially yielding 18 manuscripts, which were reduced to 7 relevant manuscripts after consensus discussion.

Tier 2: Clinical Trials, In Core Clinical Journals – Provided 95 citations and the abstracts were scanned. After consensus discussion, 3 relevant manuscripts were included.

Grading of evidence: The existing CPC process for evaluating the quality of included manuscripts will be used. For each reference identified above assign a grade of evidence using the following scale.

Grade A Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), directly addressing the review issue

Grade B Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), indirectly addressing the review issue

Grade C Prospective, controlled, non-randomized, cohort studies

Grade D Retrospective, non-randomized, cohort or case-control studies

Grade E Case series, animal / model scientific investigations, theoretical analyses, or case reports

Grade F Rational conjecture, extrapolations, unreferenced opinion in literature, or common practice

Then, assign a quality ranking for each above reference using the following scale.

Ranking	Design Considerations Present	Methodology Consideration Present	Both Considerations Present
Outstanding	Appropriate	Appropriate	Yes, Both Present
Good	Appropriate	Appropriate	No, Either Present
Adequate	Adequate with possible bias	Adequate	No, either present
Poor	Limited or Biased	Limited	No, either present
Unsatisfactory	Questionable / None	Questionable / None	No, either present

Recommendation:
The authors should provide a recommendation based on the clinical question in one of the following three categories (please note that the exact phrasing of the recommendation will vary whether a treatment, diagnostic or other type of clinical question is being addressed):

- Yes, the clinical question is supported positively by the available high quality evidence.
- No, the clinical question is not supported positively by the available high quality evidence or significant high quality evidence exists to the contrary of the clinical question.
- Neutral, the available high quality evidence is is conflicting and future additional data would be helpful to provide further guidance on this subject

Appendix B – Abstracts and Evidence Grading

Tier 1:

1. Stroke. 2015 May;46(5):1281-7. doi: 10.1161/STROKEAHA.115.009012. Epub 2015 Mar 19.

Safety of intravenous thrombolysis in stroke mimics: prospective 5-year study and comprehensive meta-analysis.

Tsivgoulis G(1), Zand R(1), Katsanos AH(1), Goyal N(1), Uchino K(1), Chang J(1), Dardiotis E(1), Putaala J(1), Alexandrov AW(1), Malkoff MD(1), Alexandrov AV(1).

BACKGROUND AND PURPOSE: Shortening door-to-needle time may lead to inadvertent intravenous thrombolysis (IVT) administration in stroke mimics (SMs). We sought to determine the safety of IVT in SMs using prospective, single-center data and by conducting a comprehensive meta-analysis of reported case-series.

METHODS: We prospectively analyzed consecutive IVT-treated patients during a5-year period at a tertiary care stroke center. A systematic review and meta-analysis of case-series reporting safety of IVT in SMs and confirmed acute ischemic stroke were conducted. Symptomatic intracerebral hemorrhage was defined as imaging evidence of ICH with an National Institutes of Health Stroke scale increase of ≥4 points. Favorable functional outcome at hospital discharge was defined as a modified Rankin Scale score of 0 to 1.

RESULTS: Of 516 consecutive IVT patients at our tertiary care center (50% men; mean age, 60±14 years; median National Institutes of Health Stroke scale, 11;range, 3-22), SMs comprised 75 cases. Symptomatic intracerebral hemorrhage occurred in 1 patient, whereas we documented no cases of orolingual edema o rmajor extracranial hemorrhagic complications. In meta-analysis of 9 studies (8942IVT-treated patients), the pooled rates of symptomatic intracerebral hemorrhage and orolingual edema among 392 patients with SM treated with IVT were 0.5% (95%confidence interval, 0%-2%) and 0.3% (95% confidence interval, 0%-2%),respectively. Patients with SM were found to have a significantly lower risk for symptomatic intracerebral hemorrhage compared with patients with acute ischemic stroke (risk ratio=0.33; 95% confidence interval, 0.14-0.77; P=0.010), with no evidence of heterogeneity or publication bias. Favorable functional outcome was almost 3-fold higher in patients with SM in comparison with patients with acute ischemic stroke (risk ratio=2.78; 95% confidence interval, 2.07-3.73; P<0.00001).

CONCLUSIONS: Our prospective, single-center experience coupled with the findings of the comprehensive meta-analysis underscores the safety of IVT in SM.
PMID: 25791717 [PubMed - indexed for MEDLINE]

Consensus Review: Grade B/D, Quality: Adequate

Comment: This was actually a 2-part study. The authors performed a retrospective chart analysis and then a meta-analysis. Complications were low in this non-stroke population. The single center portion is grade D, and the meta-analysis is grade B.
Recommendation: Neutral

2. PLoS One. 2015 Jan 8;10(1):e0116120. doi: 10.1371/journal.pone.0116120. eCollection 2015.

Intravenous versus intra-arterial thrombolysis in ischemic stroke: a systematic review and meta-analysis.

Ma QF(1), Chu CB(1), Song HQ(1).

BACKGROUND: Reperfusion following ischemic stroke can be attained by either intravenous thrombolysis (IVT) or intra-arterial thrombolysis (IAT). Only a limited number of randomized prospective studies have compared the efficacy andsafety of IVT and IAT. This meta-analysis investigated possible clinical benefits of IAT relative to IVT in patients with acute ischemic stroke.

METHODS: We searched the PubMed, Cochrane, and Google Scholar databases through October 2013 for manuscripts that describe the findings of randomized controlled or prospective studies that evaluated the outcomes of patients with ischemic stroke who were treated with IVT or IAT. The clinical outcome measures were score on the modified Rankin scale (mRS) and mortality at 90 days. A favorable outcome was defined as an mRS score of 0 to 2.

RESULTS: For the mRS, the combined odds ratio (OR) of 3.28 (95% confidence interval (CI), 1.91 to 5.65, $P < 0.001$) indicated that patients who received IAT had a significantly higher chance for a favorable outcome than did those who received IVT. For mortality, the OR indicated that IAT therapy significantly reduced the proportion of patients who died within 90 days of the procedure (combined OR, 0.40; 95%CI, 0.17 to 0.92; $P = 0.032$).

CONCLUSION: This meta-analysis determined that IAT conferred a significantly greater probability of achieving a favorable outcome compared with IVT. There was also a significant difference in mortality rates between IAT and IVT. The studies included in this analysis were small and heterogeneous; therefore, larger randomized prospective clinical studies are necessary to further investigate this issue.

PMCID: PMC4287629
PMID: 25569136 [PubMed - indexed for MEDLINE]

Consensus Review: Grade B Quality: Poor
Comment: This meta-analysis combined several trials dating back several years comparing intra-arterial therapy to intravenous thrombolysis. Some trials used urokinase. None used modern mechanical devices. As such this study does not inform the main clinical question.
Recommendation: Neutral

3. Med Sci Monit. 2014 Nov 2;20:2117-24. doi: 10.12659/MSM.892259.

Safety and outcome of thrombolysis in mild stroke: a meta-analysis.

Shi L(1), Zhang M(2), Liu H(2), Song B(2), Song C(1), Song D(2), Xu Y(1).

BACKGROUND: Whether patients presenting with mild stroke should or should not be treated with intravenous rtPA is still controversial. This systematic review aims to assess the safety and outcome of thrombolysis in these patients.
MATERIAL/METHODS: We systematically searched PubMed and Cochrane Central Register of Controlled Trials for studies evaluating intravenous rtPA in patients with mild or rapidly improving symptoms except case reports. Excellent outcome (author reported, mainly mRS 0-1), symptomatic intracranial hemorrhage (sICH) and mortality were analyzed.

RESULTS: Fourteen studies were included (n=1906 patients). Of these, 4 studies were comparative (2 randomized and 2 non-randomized). The remaining were single-arm studies. On the basis of 4 comparative studies with a total of 1006patients, the meta-analysis did not identify a significant difference in the odd sof excellent outcome (OR=0.86; 95% CI: 0.64-1.15; I2=0) between IV rtPA-treated minor stroke and those without rtPA treatment. Eleven studies involving 1083patients showed the pooled rate of excellent outcome was 76.1% (95% CI:69.8-81.5%, I2=42.5). Seven studies involving 378 patients showed the mortality rate was 4.5% (95% CI: 2.6-7.5%, I2=1.4). Twelve studies involving 831 patients showed the pooled rate of sICH was 2.4% (95% CI: 1.5-3.8, I2=0).

CONCLUSIONS: Although efficacy is not clearly established, this study reveals the adverse event rates related to thrombolysis are low in mild stroke. Intravenous rtPA should be considered in these patients until more RCT evidence is available.

PMCID: PMC4228861
PMID: 25362481 [PubMed - indexed for MEDLINE]

Consensus Review: Level of Evidence B, Quality: Adequate
Comment: Mild and improving stroke are different concepts, and have been lumped together in many previous studies. The authors of this study combined observational and small RCTs. Complications were lower than observed overall in trials that also included moderate and severe strokes. The studies included did not adequately account for pre-stroke disability status.
Recommendation: Neutral.

4. Lancet. 2014 Nov 29;384(9958):1929-35. doi: 10.1016/S0140-6736(14)60584-5. Epub 2014 Aug 5.

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 randomized trials. Emberson J(1), Lees KR(2), Lyden P(3), Blackwell L(1), Albers G(4), Bluhmki E(5),Brott T(6), Cohen G(7), Davis S(8), Donnan G(9), Grotta J(10), Howard G(11),Kaste M(12), Koga M(13), von Kummer R(14), Lansberg M(4), Lindley RI(15), Murray G(7), Olivot JM(4), Parsons M(16), Tilley B(10), Toni D(17), Toyoda K(13),Wahlgren N(18), Wardlaw J(7), Whiteley W(7), del Zoppo GJ(19), Baigent C(20),Sandercock P(7), Hacke W(21); Stroke Thrombolysis Trialists' Collaborative Group.

BACKGROUND: Alteplase is effective for treatment of acute ischaemic stroke but debate continues about its use after longer times since stroke onset, in older patients, and among patients who have had the least

or most severe strokes. We assessed the role of these factors in affecting good stroke outcome in patients given alteplase.

METHODS: We did a pre-specified meta-analysis of individual patient data from6756 patients in nine randomized trials comparing alteplase with placebo or open control. We included all completed randomized phase 3 trials of intravenous alteplase for treatment of acute ischaemic stroke for which data were available. Retrospective checks confirmed that no eligible trials had been omitted. We defined a good stroke outcome as no significant disability at 3-6 months, defined by a modified Rankin Score of 0 or 1. Additional outcomes included symptomatic intracranial haemorrhage (defined by type 2 parenchymal haemorrhage within 7 days and, separately, by the SITS-MOST definition of parenchymal type 2 haemorrhage within 36 h), fatal intracranial haemorrhage within 7 days, and 90-day mortality.

FINDINGS: Alteplase increased the odds of a good stroke outcome, with earlier treatment associated with bigger proportional benefit. Treatment within 3·0 h resulted in a good outcome for 259 (32·9%) of 787 patients who received alteplase versus 176 (23·1%) of 762 who received control (OR 1·75, 95% CI 1·35-2·27); delay of greater than 3·0 h, up to 4·5 h, resulted in good outcome for 485 (35·3%) of1375 versus 432 (30·1%) of 1437 (OR 1·26, 95% CI 1·05-1·51); and delay of more than 4·5 h resulted in good outcome for 401 (32·6%) of 1229 versus 357 (30·6%) of1166 (OR 1·15, 95% CI 0·95-1·40). Proportional treatment benefits were similar irrespective of age or stroke severity. Alteplase significantly increased the odds of symptomatic intracranial haemorrhage (type 2 parenchymal haemorrhage definition 231 [6·8%] of 3391 vs 44 [1·3%] of 3365, OR 5·55, 95% CI 4·01-7·70,p<0·0001; SITS-MOST definition 124 [3·7%] vs 19 [0·6%], OR 6·67, 95% CI4·11-10·84, p<0·0001) and of fatal intracranial haemorrhage within 7 days (91[2·7%] vs 13 [0·4%]; OR 7·14, 95% CI 3·98-12·79, p<0·0001). The relative increase in fatal intracranial haemorrhage from alteplase was similar irrespective of treatment delay, age, or stroke severity, but the absolute excess risk attributable to alteplase was bigger among patients who had more severe strokes. There was no excess in other early causes of death and no significant effect on later causes of death. Consequently, mortality at 90 days was 608 (17·9%) in the alteplase group versus 556 (16·5%) in the control group (hazard ratio 1·11, 95%CI 0·99-1·25, p=0·07). Taken together, therefore, despite an average absolute increased risk of early death from intracranial haemorrhage of about 2%, by 3-6months this risk was offset by an average absolute increase in disability-free survival of about 10% for patients treated within 3·0 h and about 5% for patients treated after 3·0 h, up to 4·5 h.

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.

FUNDING: UK Medical Research Council, British Heart Foundation, University of Glasgow, University of Edinburgh.

PMCID: PMC4441266
PMID: 25106063 [PubMed - indexed for MEDLINE]

Consensus Review: Level of Evidence A, Quality Good Comment:
This was a pooled analysis of individual patient level data from a number of clinical trials, therefore methodologically stronger than a typical meta-analysis. The large number of patients from the IST-3 trial, which only included patients that the treating neurologists felt would not benefit, means that selection bias

was likely present in this group; although presumably they were selecting a group that had a poorer prognosis and lower likelihood of good outcome. They found improvement with alteplase versus control (placebo or no-treatment depending on the trial) was much more likely earlier from the onset of symptoms up to 4.5 hours, and that it was not modified by age or severity. There was a higher odds of sICH in tPA treated patients.
Recommendation: Supports treatment

5. Cochrane Database Syst Rev. 2014 Jul 29;7:CD000213. doi: 10.1002/14651858.CD000213.pub3.

Thrombolysis for acute ischaemic stroke.

Wardlaw JM(1), Murray V, Berge E, del Zoppo GJ.

BACKGROUND: Most strokes are due to blockage of an artery in the brain by a blood clot. Prompt treatment with thrombolytic drugs can restore blood flow before major brain damage has occurred and improve recovery after stroke in some people. Thrombolytic drugs, however, can also cause serious bleeding in the brain, which can be fatal. One drug, recombinant tissue plasminogen activator (rt-PA), islicensed for use in selected patients within 4.5 hours of stroke in Europe and within three hours in the USA. There is an upper age limit of 80 years in some countries, and a limitation to mainly non-severe stroke in others. Forty per cent more data are available since this review was last updated in 2009.

OBJECTIVES: To determine whether, and in what circumstances, thrombolytic therapy might be an effective and safe treatment for acute ischaemic stroke.

SEARCH METHODS: We searched the Cochrane Stroke Group Trials Register (last searched November 2013), MEDLINE (1966 to November 2013) and EMBASE (1980 to November 2013). We also hand searched conference proceedings and journals, searched reference lists and contacted pharmaceutical companies and trialists.

SELECTION CRITERIA: Randomized trials of any thrombolytic agent compared withcontrol in people with definite ischaemic stroke.

DATA COLLECTION AND ANALYSIS: Two review authors applied the inclusion criteria, extracted data and assessed trial quality. We verified the extracted data with investigators of all major trials, obtaining additional unpublished data if available.

MAIN RESULTS: We included 27 trials, involving 10,187 participants, testing urokinase, streptokinase, rt-PA, recombinant pro-urokinase or desmoteplase. Four trials used intra-arterial administration, while the rest used the intravenous route. Most data come from trials that started treatment up to six hours after stroke. About 44% of the trials (about 70% of the participants) were testing intravenous rt-PA. In earlier studies very few of the participants (0.5%) were aged over 80 years; in this update, 16% of participants are over 80 years of age due to the inclusion of IST-3 (53% of participants in this trial were aged over80 years). Trials published more recently utilized computerized randomization, so there are less likely to be baseline imbalances than in previous versions of the review. More than 50% of trials fulfilled criteria for high-grade concealment, there were few losses to follow-up for the main outcomes. Thrombolytic therapy, mostly administered up to six hours after ischaemic stroke, significantly reduced the proportion of participants who

were dead or dependent (modified Rankin 3 to6) at three to six months after stroke (odds ratio (OR) 0.85, 95% confidence interval (CI) 0.78 to 0.93). Thrombolytic therapy increased the risk of symptomatic intracranial haemorrhage (OR 3.75, 95% CI 3.11 to 4.51), early death (OR 1.69, 95% CI 1.44 to 1.98; 13 trials, 7458 participants) and death by three to six months after stroke (OR 1.18, 95% CI 1.06 to 1.30). Early death after thrombolysis was mostly attributable to intracranial haemorrhage. Treatment within three hours of stroke was more effective in reducing death or dependency (OR 0.66, 95% CI 0.56 to 0.79) without any increase in death (OR 0.99, 95% CI0.82 to 1.21; 11 trials, 2187 participants). There was heterogeneity between the trials. Contemporaneous antithrombotic drugs increased the risk of death. Trials testing rt-PA showed a significant reduction in death or dependency with treatment up to six hours (OR 0.84, 95% CI 0.77 to 0.93, P = 0.0006; 8 trials,6729 participants) with significant heterogeneity; treatment within three hours was more beneficial (OR 0.65, 95% CI 0.54 to 0.80, P < 0.0001; 6 trials, 1779participants) without heterogeneity. Participants aged over 80 years benefited equally to those aged under 80 years, particularly if treated within three hours of stroke.

AUTHORS' CONCLUSIONS: Thrombolytic therapy given up to six hours after stroke reduces the proportion of dead or dependent people. Those treated within the first three hours derive substantially more benefit than with later treatment. This overall benefit was apparent despite an increase in symptomatic intracranial haemorrhage, deaths at seven to 10 days, and deaths at final follow-up (except for trials testing rt-PA, which had no effect on death at final follow-up).Further trials are needed to identify the latest time window, whether people with mild stroke benefit from thrombolysis, to find ways of reducing symptomatic intracranial haemorrhage and deaths, and to identify the environment in which thrombolysis may best be given in routine practice.

PMCID: PMC4153726
PMID: 25072528 [PubMed - indexed for MEDLINE]

Consensus Review: Level of Evidence A, Quality Good
Comment: This is an incremental update of a large meta-analysis to include results of IST-3. The authors conclude alteplase is beneficial, but increases the short term risk of death while reducing the long term risk of death/dependency. Many more older adults are now included in this meta-analysis, but substantial questions remain regarding environment, mild stroke, and time window. Some analyses combined IV, IA and alternative lytics, but analyses limited to IV tPA alone are provided.
Recommendation: Supports treatment.

6. Stroke. 2012 Nov;43(11):2904-9. doi: 10.1161/STROKEAHA.112.665331. Epub 2012 Sep 20.

Risk factors for intracranial hemorrhage in acute ischemic stroke patients treated with recombinant tissue plasminogen activator: a systematic review and meta-analysis of 55 studies.

Whiteley WN(1), Slot KB, Fernandes P, Sandercock P, Wardlaw J.

BACKGROUND AND PURPOSE: Recombinant tissue plasminogen activator (rtPA) is aneffective treatment for acute ischemic stroke but is associated with an increased risk of intracranial hemorrhage (ICH). We sought to identify the risk factors for ICH with a systematic review of the published literature. METHODS: We searched for studies of rtPA-treated stroke patients that reported an association between a variable measured before rtPA infusion and clinically important ICH (parenchymal ICH or ICH associated

with clinical deterioration). We calculated associations between baseline variables and ICH with random-effect meta-analyses.

RESULTS: We identified 55 studies that measured 43 baseline variables in 65 264acute ischemic stroke patients. Post-rtPA ICH was associated with higher age(odds ratio, 1.03 per year; 95% confidence interval, 1.01-1.04), higher stroke severity (odds ratio, 1.08 per National Institutes of Health Stroke Scale point; 95% confidence interval, 1.06-1.11), and higher glucose (odds ratio, 1.10 per mmol/L; 95% confidence interval, 1.05-1.14). There was approximately a doubling of the odds of ICH with the presence of atrial fibrillation, congestive heart failure, renal impairment, previous antiplatelet agents, leukoaraiosis, and avisible acute cerebral ischemic lesion on pretreatment brain imaging. Little of the variation in the sizes of the associations among different studies was explained by the source of the cohort, definition of ICH, or degree of adjustment for confounding variables.

CONCLUSIONS: Individual baseline variables were modestly associated with post-rtPA ICH. Prediction of post-rtPA ICH therefore is likely to be difficult if based on single clinical or imaging factors alone. These observational data do not provide a reliable method for the individualization of treatment according to predicted ICH risk.

PMID: 22996959 [PubMed - indexed for MEDLINE]

Consensus Review: Level of evidence C, Quality Adequate
Comment: Several factors were associated with post-alteplase symptomatic ICH, yet a variety of adjustments were used in the included trials. The authors were not able to provide a reliable way to individualize treatment based on predicted ICH risk.
Recommendation: Neutral.

7. J Neurol Neurosurg Psychiatry. 2011 Jul;82(7):712-7. doi: 10.1136/jnnp.2010.223149. Epub 2011 Feb 3.

Intravenous thrombolysis in acute ischaemic stroke: a systematic review and meta-analysis to aid decision making in patients over 80 years of age.

Bhatnagar P(1), Sinha D, Parker RA, Guyler P, O'Brien A.

Introduction: Patients ≥ 80 years of age are increasingly receiving intravenous thrombolysis for acute ischaemic stroke (AIS) despite lack of firm evidence. This systematic review assesses the safety and efficacy of intravenous thrombolysis with alteplase in ≥ 80 versus < 80 year old patients with AIS. Methods Theexisting literature was systematically analysed for outcome measures of mortality, functional recovery by modified Rankin scale and symptomatic intracranial haemorrhage (SICH) at 3 months following intravenous thrombolysis with alteplase in <80 and ≥ 80 year old patients with AIS. Statistical tests were performed for heterogeneity and publication bias. A detailed sensitivity analysis was performed and Forest plot was constructed for each of the outcome measures.

Results: 13 studies were identified. The overall OR was 2.77 (95% CI 2.25 to 3.40)for death, 0.49 (95% CI 0.40 to 0.61) for achieving a favorable outcome and 1.31(95% CI 0.93 to 1.84) for SICH in ≥ 80 year old patients compared with those < 80years old. The total number of events contributing to the estimates of effect for each outcome was: death 199, favorable outcome 141 and SICH 49.

Conclusion: Patients ≥ 80 years of age appear to have a lower probability of gaining a favorable outcome and a higher mortality rate compared with patients < 80 years old; however, the rate of SICH was not significantly increased. This supports recruitment of patients aged ≥ 80 years into ongoing trials comparing thrombolysis with controls. For patients who refuse or cannot be randomized, it provides information on risks and benefits of using alteplase off-licence.

PMID: 21292789 [PubMed - indexed for MEDLINE]

Consensus Review: Level of Evidence B, Quality: Poor
This study compared older adults, treated with tPA to younger patients treated with tPA. Older adults were at greater risk of death and had a lower likelihood of a good outcome. It is unclear how useful this comparison is because it did not address the relative benefits in each group (i.e. are older adults treated with tPA better off than older adults not treated with tPA).
Recommendation: Neutral.

Tier 2:

8. Stroke. 2014 Apr;45(4):1000-6. doi: 10.1161/STROKEAHA.113.004362. Epub 2014 Mar 6.

Targeting recombinant tissue-type plasminogen activator in acute ischemic stroke based on risk of intracranial hemorrhage or poor functional outcome: an analysis of the third international stroke trial.

Whiteley WN(1), Thompson D, Murray G, Cohen G, Lindley RI, Wardlaw J, Sandercock P; IST-3 Collaborative Group.

BACKGROUND AND PURPOSE: Intravenous recombinant tissue-type plasminogen activator(r-tPA), despite a risk of early symptomatic intracranial hemorrhage (sICH), is of net clinical benefit to acute stroke patients. We tested if predictive models could identify patients least likely to be harmed by sICH or those who gained no net benefit.

METHODS: We used the Third International Stroke Trial (IST-3) trial data set, an international, multicenter, open treatment randomized trial of 0.9 mg/kg r-tPA versus control in 3035 patients with acute ischemic stroke. We compared the discrimination and calibration of previously developed predictive models for ICH and post stroke poor outcome and developed a new model using variables selected by systematic review. We calculated the absolute and relative risk reduction of death or dependency with r-tPA in patients at a low, medium, or high predicted risk of sICH or poor functional outcome.

RESULTS: Prediction models for sICH or poor outcome (Hemorrhage After Thrombolysis [HAT]; Sugar, Early Infarct Signs, Dense Artery, Age, National Institutes of Health (NIH) Stroke Score (SEDAN); Glucose Race Age Sex Pressure Stroke Severity [GRASPS]; Stroke Thrombolytic Predictive Instrument; Dense Artery, Rankin Score, Age, Glucose, Onset to Treatment Time, NIHSS [DRAGON];Totaled Health Risks in Vascular Events [THRIVE]; our new model; and a model with National Institutes of Health Stroke Scale and age) had similar area under receiver operator characteristic curves (AUROCC) to predict sICH (P for difference >0.05). The simplest model (with covariates National Institutes of Health Stroke Scale and age) predicted both sICH (AUROCC, 0.63; 95% CI,0.58-0.68) and post stroke poor functional outcome

(AUROCC, 0.80; 95% CI,0.77-0.82) similarly to complex models. There was no evidence that the effect of r-tPA in patients at high predicted risk of sICH or poor functional outcome after stroke was less than in those at lower risk.

CONCLUSIONS: There is a clinically relevant net positive effect of r-tPA in patients with acute stroke at a high predicted risk of sICH or poor functional outcome.
CLINICAL TRIAL REGISTRATION URL: http://www.controlled-trials.com.
Unique identifier: ISRCTN25765518.

Consensus Review: Level of Evidence: D Quality Adequate
Comment: This was a secondary analysis of the IST-3 trial, which was subject to selection bias. Investigators here evaluated whether patients who were at higher risk, based on a variety of plausible external models (including simply NIHSS and age, well known to be strongest predictors of functional outcome), had more or less benefit from intravenous tPA. In short, a model based approach demonstrated that patients in all risk categories benefited from tPA within the IST-3 trial. This finding may not be applicable to general practice, as most patients in the IST-3 trial were older, and/or were treated with intravenous alteplase after 4.5 hours.
Recommendation: Neutral.

9. Stroke. 2014 Dec;45(12):3612-7. doi: 10.1161/STROKEAHA.114.006890. Epub 2014 Nov 4.

Effect of alteplase within 6 hours of acute ischemic stroke on all-cause mortality (third International Stroke Trial).

Whiteley WN(1), Thompson D(2), Murray G(2), Cohen G(2), Lindley RI(2), Wardlaw J(2), Sandercock P(2); IST-3 Collaborative Group.

BACKGROUND AND PURPOSE: Prompt thrombolytic therapy with intravenous alteplase reduces disability after acute ischemic stroke. In an exploratory analysis, we examined whether long-term survival varied by baseline characteristics after alteplase.

METHODS: In this open-treatment, international, randomized, controlled trial, ischemic stroke patients were randomly allocated <6 hours of onset to intravenous alteplase (0.9 mg/kg) plus standard care (n=1515) or standard care alone(n=1520). We followed patients to death, censoring when last known to be alive. We grouped patients by delay to randomization, and good or poor predicted prognosis (calculated from baseline National Institutes of Health Stroke Scale[NIHSS] score and age). We present absolute mortality differences between treated and control groups at 7 days, 6 months, and 18 months post stroke.

RESULTS: Alteplase was not associated with a significant increase in mortality within 18 months (0.6% [95% confidence interval (CI), -2.9% to +4.2] P=0.72] in all patients with complete vital status (99.9%, 3034/3035). In patients randomized <3 hours of stroke, 18-month mortality was lower in the alteplase-treated group than the control group (40.6% [95% CI, 42.6-52.7] versus 47.8% [95% CI, 35.5-45.3]; P=0.0434]. The difference in 18-month mortality between alteplase-treated and control patients was greater in patients who were randomized early (<3 hours) compared with late (3-6 hours; +9% [95% CI, 1-17];P=0.0317). Alteplase led to a greater improvement in 18-month survival in patients with a poor prognosis than in patients with a good prognosis (+8% [95%CI, 2-14]; P=0.0091).

CONCLUSIONS: These exploratory analyses of the third International Stroke Trial(IST-3) trial support improving acute stroke patients' access to earlier alteplase treatment, treatment of patients with poor prognosis, and further randomized controlled trials in minor stroke to replicate these findings.

CLINICAL TRIAL REGISTRATION URL: http://www.controlled-trials.com.
Unique identifier: ISRCTN25765518.DOI: 10.1161/STROKEAHA.114.006890

PMCID: PMC4282176

PMID: 25370587 [PubMed - indexed for MEDLINE]

Consensus Review: Level of Evidence: D Quality Adequate
Comment: The IST-3 trial was subject to selection bias. In this long term follow up study, the investigators evaluated 18 month mortality. Overall, 18 month mortality was not increased or decreased by alteplase in IST-3. In the subgroup of patients randomized under 3 hours (likely to be mostly aged over 80 as younger adults in Europe were likely to be treated under the alteplase package insert outside IST-3) mortality was decreased from 47 to 40%, a significant finding.
Recommendation: Neutral, overall / Supports treatment (when given under 3 hours)

10. Lancet. 2012 Jun 23;379(9834):2352-63. doi: 10.1016/S0140-6736(12)60768-5. Epub 2012 May 23.

The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomized controlled trial.

IST-3 collaborative group, Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, Innes K, Venables G, Czlonkowska A, Kobayashi A, Ricci S, Murray V, Berge E, Slot KB, Hankey GJ, Correia M, Peeters A, Matz K, Lyrer P, Gubitz G,Phillips SJ, Arauz A.

BACKGROUND: Thrombolysis is of net benefit in patients with acute ischaemic stroke, who are younger than 80 years of age and are treated within 4·5 h of onset. The third International Stroke Trial (IST-3) sought to determine whether a wider range of patients might benefit up to 6 h from stroke onset.

METHODS: In this international, multicentre, randomized, open-treatment trial, patients were allocated to 0·9 mg/kg intravenous recombinant tissue plasminogen activator (rt-PA) or to control. The primary analysis was of the proportion of patients alive and independent, as defined by an Oxford Handicap Score (OHS) of0-2 at 6 months. The study is registered, ISRCTN25765518.

FINDINGS: 3035 patients were enrolled by 156 hospitals in 12 countries. All of these patients were included in the analyses (1515 in the rt-PA group vs 1520 in the control group), of whom 1617 (53%) were older than 80 years of age. At 6months, 554 (37%) patients in the rt-PA group versus 534 (35%) in the control group were alive and independent (OHS 0-2; adjusted odds ratio [OR] 1·13, 95% CI 0·95-1·35, p=0·181; a non-significant absolute increase of 14/1000, 95% CI -20 to48). An ordinal analysis showed a significant shift in OHS scores; common OR 1·27(95% CI 1·10-1·47, p=0·001). Fatal or non-fatal symptomatic intracranial haemorrhage within 7 days occurred in 104 (7%) patients in the rt-PA group versus16 (1%) in the control group (adjusted OR 6·94, 95% CI 4·07-11·8; absolute excess58/1000, 95% CI

44-72). More deaths occurred within 7 days in the rt-PA group(163 [11%]) than in the control group (107 [7%], adjusted OR 1·60, 95% CI1·22-2·08, p=0·001; absolute increase 37/1000, 95% CI 17-57), but between 7 days and 6 months there were fewer deaths in the rt-PA group than in the control group, so that by 6 months, similar numbers, in total, had died (408 [27%] in the rt-PA group vs 407 [27%] in the control group).

INTERPRETATION: For the types of patient recruited in IST-3, despite the early hazards, thrombolysis within 6 h improved functional outcome. Benefit did not seem to be diminished in elderly patients.

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Consensus Review: Level of Evidence B, Quality Poor
Comment: Patients, mostly older adults (>80) and patients in an extended time window (over 4.5 hours), were enrolled in an open-label, randomized trial of tPA, if the bedside clinicians felt there was reasonable uncertainty as to whether the individual patient would benefit. Other work from similar and larger databases has suggested one cannot predict well who will benefit from tPA using multivariable modeling, therefore clinician intuition was likely to be rather ineffective. As such, it is unclear how the patients were selected. Almost two thirds were dead or dependent across tPA versus no tPA. On the primary outcome, tPA was neutral even when adjusting for age and severity. On a planned ordinal shift analysis, there appeared to be an effect. While this was the largest randomized trial of thrombolysis, the inclusion bias, lack of blinding and concealment, and other issues make it a challenge to use these results to make decisions about individual patients.
Recommendation: Neutral.

Additional Requested References:
Reviewed Inclusion of Decision Aids as in 2010 statement. None of computerized aids from that statement were still available. Reviewed impact of institutional organization of post-ED (inpatient) stroke care.

One meta-analysis was identified in 2016. This addressed the accuracy of prognostic models in stroke. A second meta-analysis addressed organized stroke unit care.

11. Acta Neurol Scand. 2016 Jan;133(1):41-8. doi: 10.1111/ane.12421. Epub 2015 May 13.

Prognostic indices for early mortality in ischaemic stroke - meta-analysis.

Mattishent K(1), Kwok CS(1), Mahtani A(1), Pelpola K(2), Myint PK(3), Loke YK(1).

OBJECTIVES: Several models have been developed to predict mortality in ischaemic stroke. We aimed to evaluate systematically the performance of published stroke prognostic scores.

METHODS: We searched MEDLINE and EMBASE in February 2014 for prognostic models (published between 2003 and 2014) used in predicting early mortality (<6 months) after ischaemic stroke. We evaluated discriminant ability of the tools through meta-analysis of the area under the curve receiver

operating characteristic curve (AUROC) or c-statistic. We evaluated the following components of study validity: collection of prognostic variables, neuroimaging, treatment pathways and missing data.

RESULTS: We identified 18 articles (involving 163 240 patients) reporting on the performance of prognostic models for mortality in ischaemic stroke, with 15 articles providing AUC for meta-analysis. Most studies were either retrospective, or post hoc analyses of prospectively collected data; all but three reported validation data. The iSCORE had the largest number of validation cohorts (five) within our systematic review and showed good performance in four different countries, pooled AUC 0.84 (95% CI 0.82-0.87). We identified other potentially useful prognostic tools that have yet to be as extensively validated as iSCORE - these include SOAR (2 studies, pooled AUC 0.79, 95% CI 0.78-0.80), GWTG (2 studies, pooled AUC 0.72, 95% CI 0.72-0.72) and PLAN (1 study, pooled AUC 0.85, 95% CI 0.84-0.87).

CONCLUSIONS: Our meta-analysis has identified and summarized the performance of several prognostic scores with modest to good predictive accuracy for early mortality in ischaemic stroke, with the iSCORE having the broadest evidence base.

Review:
Level of Evidence B; Quality Adequate
The use of prognostic scores to aid in decision making has not been proven superior to the usual process in a randomized trial. However, these scores may aid clinicians in estimating short term prognosis and may serve as a guide for discussing benefits and risks of tPA. The iScore is available online at http://www.sorcan.ca/iscore/ (There is also an iOS app). The scores did not appear to be prospectively applied, however they were applied to derivation and validation cohorts of prospectively identified stroke patients from registries. Future studies should determine how patients who have discussions facilitated by these tools do with and without tPA and how accurate the predictions are.
Recommendation: Neutral (risk scores may be accurate but use at bedside prospectively not yet proven).

12. Cochrane Database Syst Rev. 2013 Sep 11;(9):CD000197. doi:10.1002/14651858.CD000197.pub3.

Organised inpatient (stroke unit) care for stroke.

Stroke Unit Trialists' Collaboration(1).

Update of Cochrane Database Syst Rev. 2007;(4):CD000197.

BACKGROUND: Organized stroke unit care is provided by multidisciplinary teams that exclusively manage stroke patients in a ward dedicated to stroke patients, with a mobile stroke team or within a generic disability service (mixed rehabilitation ward).

OBJECTIVES: To assess the effect of stroke unit care compared with alternative forms of care for people following a stroke.

SEARCH METHODS: We searched the trials registers of the Cochrane Stroke Group (January 2013) and the Cochrane Effective Practice and Organization of Care (EPOC) Group (January 2013), MEDLINE (2008 to September 2012), EMBASE (2008 to September 2012) and CINAHL (1982 to September 2012). In an effort to identify further published, unpublished and ongoing trials, we searched 17 trial registers (January

2013), performed citation tracking of included studies, checked reference lists of relevant articles and contacted trialists.

SELECTION CRITERIA: Randomized controlled clinical trials comparing organized inpatient stroke unit care with an alternative service. After formal risk of bias assessment, we have now excluded previously included quasi-randomized trials.

DATA COLLECTION AND ANALYSIS: Two review authors initially assessed eligibility and trial quality. We checked descriptive details and trial data with the coordinators of the original trials.

MAIN RESULTS: We included 28 trials, involving 5855 participants, comparing stroke unit care with an alternative service. More-organized care was consistently associated with improved outcomes. Twenty-one trials (3994 participants) compared stroke unit care with care provided in general wards. Stroke unit care showed reductions in the odds of death recorded at final (median one year) follow-up (odds ratio (OR) 0.87, 95% confidence interval (CI) 0.69 to 0.94; P = 0.005), the odds of death or institutionalized care (OR 0.78, 95% CI 0.68 to 0.89; P = 0.0003) and the odds of death or dependency (OR 0.79, 95% CI 0.68 to 0.90; P = 0.0007). Sensitivity analyses indicated that the observed benefits remained when the analysis was restricted to securely randomized trials that used unequivocally blinded outcome assessment with a fixed period of follow-up. Outcomes were independent of patient age, sex, initial stroke severity or stroke type, and appeared to be better in stroke units based in a discrete ward. There was no indication that organized stroke unit care resulted in a longer hospital stay.

AUTHORS' CONCLUSIONS: Stroke patients who receive organized inpatient care in a stroke unit are more likely to be alive, independent, and living at home one year after the stroke. The benefits were most apparent in units based in a discrete ward. We observed no systematic increase in the length of inpatient stay.

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Review: Level of evidence A: Quality Fair
This meta-analysis looked at trials evaluating organized stroke unit care versus usual care on a medical ward. Blinding and randomization of such trials is challenging. However, more organized stroke care appears to reduce death and disability on a scale that is larger than benefits of tPA.
Recommendation: Supportive (of stroke units).