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ANALYSIS

Thrombolysis in acute ischaemic stroke: time for a rethink?

As the UK regulator reviews alteplase in ischaemic stroke, **Brian Alper and colleagues** interpret the evidence to suggest increased mortality with uncertain benefit for its use beyond three hours

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Systematic reviews and guidelines conclude that thrombolysis with alteplase (t-PA) up to 4.5 hours after the onset of ischaemic stroke is beneficial. It is reported to increase the likelihood of being functionally independent and not increase the 90 day risk of mortality. In the US the licence, or marketing authorisation, for alteplase is limited to 0-3 hours after onset of stroke,[1] but some other countries—including the UK and Australia—have extended the licence to 4.5 hours.[2-4] Irrespective of licensing, most major stroke guidelines support use of alteplase up to 4.5 hours after stroke onset,[5-16] although several emergency medicine associations do not recommend it (box).[17-21]

We believe that current guidance is based on uncertain evidence and that urgent reconsideration of the available data is essential to guide policy decisions on use of alteplase to manage acute stroke. In the UK the Medicines and Healthcare Regulatory Agency is planning to establish an expert working group to analyse all relevant sources of evidence and reassess the balance of benefits and risks for alteplase.[22]

We examined the most comprehensive sources of evidence and advice that working clinicians are likely to turn to for guidance on whether to use alteplase after stroke: a national clinical practice guideline published in 2013,[5] the Cochrane review updated in 2014,[23] and an individual patient data meta-analysis published in 2014.[24] Each of these sources suggests that alteplase is more beneficial than harmful when given 3-4.5 hours after the onset of ischaemic stroke. We tried to verify the data supporting these conclusions. We do not examine evidence or recommendations for the use of alteplase up to three hours after stroke.

Clinical practice guideline 2013

We evaluated the American Heart Association/American Stroke Association (AHA/ASA) guideline as the most recent authoritative national guideline.[5] The level of evidence is rated B, suggesting some uncertainty because it is based on either limited populations or data derived from a single randomised trial or non-randomised studies.[5] Nevertheless, the guideline gives a class I recommendation to use the drug (0.9 mg/kg, maximum dose 90 mg) 3-4.5 hours after onset of stroke. It says a class I recommendation means that "Benefit >>> Risk Procedure/Treatment **SHOULD** be performed/administered."[5]

To support their 3-4.5 hour recommendation, the guideline cites a 2004 individual patient data meta-analysis of six trials (801 patients treated at 3-4.5 hours) that reported increased likelihood of a "global favourable outcome" based on three stroke scales, including the modified Rankin score 0-1 at 3 months (adjusted odds ratio 1.40, 95% confidence interval 1.05 to1.85; unadjusted odds ratio 1.34, 1.04 to 1.72).[25] The modified Rankin scale is the most widely used outcome measure in trials of thrombolysis and is a patient oriented measure of function after stroke (table 1⇓).[26] The guideline cites the subsequent ECASS III trial[27] with 821 patients treated with alteplase or placebo 3-4.5 hours after stroke onset, which found a smaller benefit in the global favourable outcome (odds ratio 1.28, 1.00 to 1.65).[5]

ECASS III is the only trial to have reported benefit from use of alteplase in the 3-4.5 hour time frame as the primary outcome measure—a modified Rankin score 0-1 (freedom from any functional limitation) at 90 days.[27] It contributed the most data at 3-4.5 hours before 2012 and was the basis for some drug regulators and guidelines recommending extending use of alteplase from 3 hours to 4.5 hours after stroke onset. However, baseline differences are likely to have biased the results in favour of the alteplase group, which had a lower proportion of patients with a previous stroke (7.7% *v* 14.1%, P=0.003). A 2014 report including only the 89% (732/821) of patients without a prior stroke reported no significant difference in the primary outcome

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Major stroke guidelines and recommendations for alteplase at 3-4.5 hours after stroke onset

Guidelines presenting strong recommendation for ("is recommended" or highest recommendation rating)

- American Heart Association/American Stroke Association (Class I; Level of evidence B)[5]
- Canadian Stroke Network and Heart and Stroke Foundation of Canada (Evidence level A)[6]
- Chinese Stroke Therapy Expert Panel for Intravenous Recombinant Tissue Plasminogen Activator (Level 1 recommendation, Level A evidence)[7]
- European Stroke Organisation (Class I, Level A)[8]
- Haute Autorité de Santé (Professional agreement)[9]
- Japan Stroke Society (level of evidence Ia; grade of recommendation A)[10]
- National Institute for Health and Care Excellence ("is recommended")[11]
- National Stroke Foundation (Australia) (Grade A)[12]
- South African Stroke Society (Class I, Level A)[13]

Guidelines presenting weak recommendation for (lower recommendation rating)

- American College of Chest Physicians (Grade 2C)[14]
- American College of Emergency Physicians/American Academy of Neurology (Level B recommendation), currently being reconsidered by American College of Emergency Physicians[15]
- American College of Emergency Physicians (draft guideline in process) (Level B recommendation)[16]

Guidelines presenting weak recommendation against

- Canadian Association of Emergency Physicians (draft guideline in process) (Weak recommendation, moderate quality evidence)[17]

Statements that t-PA is controversial at all timeframes and should not be considered standard of care

- American Academy of Emergency Medicine[18]
- Australasian College for Emergency Medicine[19]
- Canadian Association of Emergency Physicians (currently posted policy)[20]
- New Zealand Faculty of the Australasian College for Emergency Medicine[21]

between the alteplase and placebo groups (odds ratio 1.19, 0.89 to 1.59; table 2⇓).[28]

The guideline also discusses another key trial, the Third International Stroke Trial (IST-3), which it describes as "the largest randomized, placebo-controlled trial to date of intravenous rtPA."[29] Although the subgroup of IST-3 patients treated 3-4.5 hours after stroke is the largest dataset for this time frame from any trial,[29] the guideline does not discuss results specific to 3-4.5 hours. IST-3 randomised patients who were treated 0-6 hours after stroke onset and used a primary outcome measure equivalent to a modified Rankin score of 0-2 (alive and independent) at six months. Outcomes are reported for 1177 patients who were treated between 3 and 4.5 hours.[29] The primary publication included a subgroup analysis of this group adjusted for age and baseline stroke severity. This found no significant benefit with a 99% confidence interval (adjusted odds ratio 0.73, 99% CI 0.5 to 1.07; table 2⇓).[29] The statistical analysis plan for IST-3 suggested subgroup analyses would be "interpreted without any consideration of multiple testing" and provided an example of how subgroup results would be reported using 95% confidence intervals.[30] The use of a 99% confidence interval in the subsequent publication was not explained. We performed an unadjusted analysis of the IST-3 results for patients treated between 3-4.5 hours using a 95% confidence interval and found a significant reduction in functional outcome (odds ratio 0.76, 95% CI 0.60 to 0.97, number needed to harm=16).

2014 Cochrane review

Cochrane reviews usually provide the most valid syntheses of evidence of effects of interventions; under 1% of Cochrane reviews have limitations in conduct and reporting that hinder the summary of best current evidence for clinical decision making.[31] But an update of the Cochrane review on thrombolysis for acute ischaemic stroke, published in July 2014, is confusing.[23] Key messages and conclusions seem inconsistent within the document and are unclear about the appropriate time window for using alteplase.

The conclusion of the abstract says, "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." However, in the Implications for Practice section, the authors state, "Despite the overall net benefit, the available data do not provide sufficient evidence to determine the duration of the therapeutic time window" and suggest "there is no evidence to withhold alteplase … if it can be administered within 4.5 hours." The plain language summary states that thrombolysis "definitely improves outcomes if given up to 4.5 hours after stroke."

We examined the Cochrane review analyses for the 3-4.5 hour time window but they were too limited to be useful. They include one trial of alteplase (ECASS III) and one of streptokinase (showing harm). They do not report subgroup data for 3-4.5 hours from the larger number of trials that used a wider time window that included 3-4.5 hours—for example, those that randomised patients between 0 and 6 hours. The review also did not include the individual patient data meta-analysis, and such meta-analyses are not typically performed in Cochrane reviews.

The Cochrane review does report outcomes for alteplase use between 3 and 6 hours and finds no benefit for thrombolysis.[23] Subgroup analyses of alteplase at 3-6 hours (both by time randomised and by time treated) suggest no significant effect on functional independence (odds ratio 0.97, 95% CI 0.85 to 1.09 and 0.93, 0.83 to 1.04, respectively) but suggest a marginally significant increase in mortality (odds ratio 1.17, 1.00 to 1.38 and 1.16, 1.00 to 1.35, respectively). These results are opposite to those of subgroup analyses of alteplase at 0-3 hours.

With such differences in functional independence and mortality by time windows, an overall conclusion on use from 0-6 hours no longer appears valid for informing clinical decision making.

At this point, the subgroup analyses covering 3-6 hours may be the best approximate view of the 3-4.5 hour time window, but a focused view on 3-4.5 hours would be ideal.

Individual patient data meta-analysis 2014

Arguably the most valid and comprehensive approach to determine treatment effects is an individual patient data meta-analysis. This involves the central collection, validation, and re-analysis of the primary data from each trial. In August 2014, the Stroke Thrombolysis Trialists' Collaborative Group published an updated meta-analysis including individual patient data from all nine completed alteplase trials for which data were available.[24]

The previous 2010 meta-analysis included eight trials with 1620 patients in the 3-4.5 hour time window.[32] More than half of the data for this analysis comes from the ECASS III trial.[27] The prespecified primary functional outcome (a modified Rankin score of 0-1 at three months) was reached by 44.6% in the alteplase group and 37.7% in the placebo group (adjusted odds ratio 1.34, 95% CI 1.06 to 1.68). This was consistent with benefit from the drug: number needed to treat for one additional beneficial outcome=15. The 2014 update included data from IST-3, which had 1177 patients in the 3-4.5 hour time window and reported a primary functional outcome of modified Rankin score 0-2 at six months (adjusted odds ratio 0.73, 99% CI 0.5 to 1.07, table 2⇓).[29]

The reader might have expected that combining the odds ratio of 1.34 from the 2010 analysis with the 0.73 in the subgroup analysis from IST-3 would result in an odds ratio close to 1.00 and confidence intervals extending above and below 1.00 showing no significant benefit from the drug. However, the 2014 meta-analysis concluded "alteplase significantly improves the overall odds of a good stroke outcome when delivered within 4.5 hours of stroke onset." Of those randomised within 3-4.5 hours, 35.3% receiving alteplase achieved modified Rankin score 0-1 compared with 30.1% of controls (adjusted odds ratio 1.26, 95% CI 1.05 to 1.51).[24]

The discrepancy in the summary statistics might be explained by differences in the outcome analysed; the meta-analyses used modified Rankin score 0-1 and IST-3 used modified Rankin score 0-2. Could excluding participants with modified Rankin score 2 (slight disability) from the functional outcome explain the result? If this was the case, it would suggest that data from IST-3 show benefit for modified Rankin score 0-1 but harm for modified Rankin score 0-2. Further analysis of the 2014 data to explore whether this is the case, and to quantify the effect for both modified Rankin score 0-1 and 0-2 groups, seems appropriate and relevant to clinical decision making.

Alternatively the unexpected, positive result of the 2014 meta-analysis could be related to which participants were included in the analysis.[24] Different methods for defining the 3-4.5 hour subgroup, counting time from symptom onset to alteplase administration, or counting time from symptom onset to randomisation may have resulted in the meta-analysis not including the same patients as the subgroups in the original studies.

We reviewed the protocol for the IPD meta-analysis since neither explanation seemed sufficient. The protocol says[33]:

> It has already been established that thrombolysis with iv alteplase (rt-PA) is both effective and safe when administered to particular types of patient within 4.5 h of stroke onset, and that treatment benefit diminishes with increasing treatment delay. Consequently, any estimate of the overall effect for all patients randomised to rt-PA within six-hours of stroke onset provided by the analyses described in this document should not necessarily be used to guide the future use of treatment (or to revisit efficacy in presently recommended subgroups) because of the possibility that such an estimate might be diluted substantially by the results from IST-3 (which, through use of the "uncertainty principle" in its design, recruited substantial numbers of patients in whom the effect of treatment may be proportionally smaller than that observed in previous trials, or even nonexistent).

The prespecified analysis plan does not clearly describe an analysis to determine if alteplase is effective at 3-4.5 hours after stroke. The authors seem concerned about the potential for IST-3 to "dilute substantially" the previous meta-analysis results.[33] The authors seem to wish to avoid "revisiting efficacy" for the "established use" within 4.5 hours of stroke onset.[33] However, the "uncertainty principle"—the concept that patients in IST-3 were appreciably different from patients in previous trials—does not clearly apply to the enrolment of patients in IST-3 at 3-4.5 hours after stroke. This time frame was not considered an indication for alteplase for most of the time of IST-3 enrolment (2000 through 2011).

The functional benefit reported in the 2014 individual patient data meta-analysis for use of alteplase at 3-4.5 hours has too many open questions for us to consider the result a reliable summary of the underlying data. More transparent analysis and reporting are needed to determine the effect on functional outcome estimated by existing trials.

Meanwhile alteplase 3-4.5 hours after stroke onset has clearly established harms. The 2014 meta-analysis found that the risk of fatal intracranial haemorrhage at seven days was increased (adjusted odds ratio 5.63, 95% CI 2.49 to 12.76, estimated number needed to harm=44).[24] This rounds up to a 2% absolute increase in mortality at seven days, and the authors stated "by 90 days this 2% excess remained but was no longer statistically significant." Although critics might argue that the harms including mortality are included in a global disability endpoint, patients may not weigh all outcomes similarly; using an "overall disability measure" to discount the effect of mortality therefore seems inappropriate for decision making.

Full data must be made available

We have summarised data for the 3-4.5 hour time window from the most comprehensive and relevant sources above (table 3⇓). The evidence on the effects of alteplase at 3-4.5 hours after stroke on functional outcomes is inconsistent. Some data support an increase in good functional outcome at three months, and others show a worse functional outcome at six months; any single estimate of effect from currently available data is therefore likely to be unreliable. However, data from the same trials show a clear increase in the risks of symptomatic intracranial haemorrhage and fatal intracranial haemorrhage and suggest an increase in mortality at 90 days (table 3⇓).

The key to resolving uncertainty about the benefits and harms of alteplase 3-4.5 hours after stroke lies in publishing more of the underlying data forming the basis of the 2014 meta-analysis and reanalysing them transparently. Individual trial results for patients treated between 3 and 4.5 hours (including modified Rankin scores) are needed to enable evaluation of heterogeneity and determine consistency across these data. This would show whether meta-analysis is warranted (or at least inform the statistical approach applied to a meta-analysis). Realistically,

considering the overall volume of data, complexity, and inconsistencies, an independent analysis of the available data may not "settle" the issue and is more likely to result in the conclusion of insufficient evidence and a call for additional research.

Unless and until there are data showing unequivocal benefits to outweigh known harms, we believe that there should not be any strong recommendation or encouragement for use of alteplase beyond three hours after stroke.

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1 Genentech. Activase (alteplase).www.gene.com/download/pdf/activase_prescribing.pdf.
2 European Agency for the Evaluation of Medicinal Products. Summary information on a referral opinion following an arbitration pursuant to article 29 of directive 2001/83/EC, for Actilyse. www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Actilyse_29/WC500010327.pdf.
3 Electronic Medicines Compendium. Summary of product characteristics—actilyse. www.medicines.org.uk/EMC/medicine/308/SPC/Actlyse.
4 Australian Government Department of Health, Therapeutic goods administration. Product and consumer medicine information—actilyse. www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=&q=Actilyse&r=https://www.ebs.tga.gov.au/.
5 Jauch EC, Saver JL, Adams HP, Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44:870-947.
6 Casaubon LK, Suddes M, on behalf of the Acute Stroke Care Writing Group. Hyperacute stroke care. In: Lindsay MP, Gubitz G, Bayley M, Phillips S, eds. Canadian best practice recommendations for stroke care: 2013. http://strokebestpractices.ca/wp-content/uploads/2013/05/Ch3_SBP2013_Hyper-Acute-_23MAY13_EN_-FINAL4.pdf.
7 Xu AD, Wang YJ, Wang DZ, Chinese Stroke Therapy Expert Panel for Intravenous Recombinant Tissue Plasminogen Activator. Consensus statement on the use of intravenous recombinant tissue plasminogen activator to treat acute ischemic stroke by the Chinese Stroke Therapy Expert Panel. *CNS Neurosci Ther* 2013;19:543-8.
8 European Stroke Organisation Executive Committee, ESO Writing Committee. Ischaemic stroke and transient ischaemic attack. In: Gilhus NE, Barnes MP, and Bainin M, eds. European handbook of neurological management. Vol 1. 2nd ed. ESO, 2011:101-58.
9 Haute Autorité de Santé. Stroke: early management (alert, prehospital phase, initial hospital phase, indications for thrombolysis). Clinical practice guideline. 2009. www.has-sante.fr/portail/upload/docs/application/pdf/2010-03/stroke_early_management_-_guidelines_-_english_version.pdf.
10 Minematsu K, Toyoda K, Hirano T, Kimura K, Kondo R, Mori E, et al. Guidelines for the intravenous application of recombinant tissue-type plasminogen activator (alteplase), the second edition, October 2012: a guideline from the Japan Stroke Society. *J Stroke Cerebrovasc Dis* 2013;22:571-600.
11 National Institute for Health and Care Excellence. Final appraisal determination—alteplase for treating acute ischaemic stroke (review of technology appraisal guidance 122). 2012. www.nice.org.uk/guidance/ta264/documents/stroke-acute-ischaemic-alteplase-review-of-ta122-final-appriasal-determination-guidance2.
12 National Stroke Foundation (Australia). Clinical guidelines for stroke management. 2010. http://strokefoundation.com.au/site/media/clinical_guidelines_stroke_managment_2010_interactive.pdf.
13 Bryer A, Connor M, Haug P, Cheyip B, Staub H, Tipping B, et al. South African guideline for management of ischaemic stroke and transient ischaemic attack 2010: a guideline from the South African Stroke Society (SASS) and the SASS writing committee. *S Afr Med J* 2010;100:747-78.
14 Lansberg MG, O'Donnell MJ, Khatri P, Lang ES, Nguyen-Huynh MN, Schwartz NE, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141(2 suppl):e601-36S.
15 American College of Emergency Physicians, American Academy of Neurology. Clinical policy: use of intravenous tPA for the management of acute ischemic stroke in the emergency department. *Ann Emerg Med* 2013;61:225-43.
16 American College of Emergency Physicians. Clinical policy: use of intravenous tPA for the management of acute ischemic stroke in the emergency department [draft]. 2015. www.acep.org/Clinical-Policy-Comment-form-Intravenous-tPA/.
17 Canadian Association of Emergency Physicians. Position statement on acute ischemic stroke [draft]. 2014. http://caep.ca/sites/caep.ca/files/caep/comment_on_stroke_position_statement.pdf.
18 American Academy of Emergency Medicine Work Group on Thrombolytic Therapy in Stroke. Position statement on the use of intravenous thrombolytic therapy in the treatment of stroke. 2002. www.aaem.org/em-resources/position-statements/2002/thrombolytic-therapy.
19 Australasian College for Emergency Medicine. Statement on intravenous thrombolysis for ischaemic stroke.2014. www.acem.org.au/getattachment/1636cfd5-3829-4fc6-9eb2-91742f3d250b/Statement-on-Intravenous-Thrombolysis-for-Ischaemi.aspx.
20 Canadian Association of Emergency Physicians Committee on Thrombolytic Therapy for Acute Ischemic Stroke. Thrombolytic therapy for acute ischemic stroke. http://caep.ca/resources/position-statements-and-guidelines/thrombolytic-therapy-acute-ischemic-stroke.
21 New Zealand Faculty of the Australasian College for Emergency Medicine. Consensus statement on thrombolysis for acute ischaemic stroke. 2013. www.acem.org.nz/files/2013/Consensus%20Statement%20on%20Thrombolysis%20for%20Acute%20Ischaemic%20Stroke%20-June%202013.pdf.
22 Hudson I. Alteplase for ischaemic stroke—responses. *Lancet* 2014;384:662-3.
23 Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev* 2014;7:CD000213.
24 Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014;384:1929-35.
25 Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 2004;363:768-74.
26 Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry* 1991;54:1044-54.
27 Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317-29.
28 Shy BD. Implications of ECASS III error on emergency department treatment of ischemic stroke. *J Emerg Med* 2014;46:385-6.
29 IST-3 Collaborative Group, Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 hours of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet* 2012;379:2352-63.
30 Sandercock P, Lindley R, Wardlaw J, Whiteley W, Murray G, IST-3 Collaborative Group. Statistical analysis plan IST-3. IST-3 SAP v5.3.2. 2012. *Int J Stroke* 2012;7:186-7.
31 Alper BS, Fedorowicz, Z, van Zuuren, EJ. Limitations in conduct and reporting of Cochrane reviews rarely inhibit the determination of the validity of evidence for clinical decision making. *J Evid Based Med* (forthcoming).
32 Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010;375:1695-703.
33 Stroke Thrombolysis Trialists' Collaborative Group. Details of a prospective protocol for a collaborative meta-analysis of individual participant data from all randomised trials of intravenous rt-PA vs. control: statistical analysis plan for the Stroke Thrombolysis Trialists' Collaborative meta-analysis. *Stroke* 2013;8:278-83.
34 Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med* 1999;18:1293.
35 Altman DG, Deeks JJ. Meta-analysis, Simpson's paradox, and the number needed to treat. *BMC Med Res Methodol* 2002;2:3.
36 Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999;319:1492-5.

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Key messages

- Use of alteplase 3-4.5 hours after stroke is supported by guidelines and meta-analyses based on analyses that do not directly examine treatment in this time frame
- Direct comparisons of alteplase with no alteplase at 3-4.5 hours after stroke suggest an absolute increase in mortality of 2% and no clear benefit
- Recommendations to use alteplase 3-4.5 hours after stroke should be re-evaluated

Tables

Table 1| **Modified Rankin scale**

Score	Description	Classification
0	No symptoms	Not disabled
1	No significant disability, able to carry out all duties	Not disabled
2	Unable to carry out some previous activities but able to look after own affairs without assistance	Slight disability
3	Requiring some help but able to walk without assistance	Moderate disability
4	Unable to walk without assistance and unable to meet bodily needs without assistance	Moderately severe disability
5	Bedridden, incontinent, and requiring constant nursing care	Severe disability

Table 2| Functional outcome data specific to 3-4.5 hour time window in two largest trials

Trial	ECASS III[27]	IST-3[29]
Primary outcome	mRS 0-1 at 90 days	mRS 0-2 at 6 months
% (No) with primary outcome:		
Alteplase	52.4 (219/418)	31.5 (182/577)
Control	45.2 (182/403)	37.7 (226/600)
Reported summary statistic	OR=1.34 (95% CI 1.02 to 1.76)	Adjusted OR=0.73 (99% CI 0.5 to 1.07)
Interpretation of summary statistic	Significant benefit	Non-significant harm
Major bias affecting results	Baseline differences in history of stroke	Uncertain effects of adjustments for baseline differences; use of 99% CI for reporting despite this not being in statistical analysis plan
Analysis method that subtracts these biases	Analysis limited to patients without history of stroke (89% participants)*	Unadjusted analysis of results using 95% CI
Revised summary statistic	OR=1.19 (95% CI 0.89 to 1.59)	OR=0.76 (95% CI 0.60 to 0.97)
Revised interpretation	No significant effect (or small non-significant benefit)	Significant harm

*This analysis method is not the optimal method for adjusting for baseline differences but was available through a subsequent publication.[28] A reanalysis adjusting for baseline differences including history of previous stroke would be a more valid approach.

Table 3| Data on functional outcome data and harm specific to 3-4.5 hour time window

Outcome	Study	Study type	GRADE quality of evidence	% with alteplase	% no alteplase	Odds ratio (95% CI)	NNTB/NNTH (95% CI)
Functional outcome							
mRS 0-1 at 90 days	ECASS III[27]	RCT	Low*†	52.4 (219/418)	45.2 (182/403)	1.34 (1.02 to 1.76)	NNTB 14 (7 to 254)
mRS 0-2 at 6 months	IST-3[29]	RCT (subgroup)	Moderate‡	31.5 (182/577)	37.7 (226/600)	0.76 (0.60 to 0.97)	NNTH 16 (9 to 146)
mRS 0-1 at 90 days	Emberson[24]	IPD MA (subgroup)§	Low¶	35.3 (485/1375)	30.1 (432/1437)	Adjusted: 1.26 (1.05 to 1.51)	NNTB 20 (11 to 97)
Harm							
Symptomatic intracranial haemorrhage:							
NINDS definition	ECASS III [27]	RCT	High†	7.9 (33/418)	3.5 (14/403)	2.38 (1.25 to 4.52)	NNTH 22 (13 to 80)
Parenchymal type 2	Lees [32]	IPD MA (subgroup)§**	High	4.3 (35/809)	1.2 (10/811)	Adjusted: 3.61 (1.76 to 7.38)	NNTH 33 (14 to 112)
Fatal intracranial haemorrhage	Emberson [24]	IPD MA (subgroup)§	High	2.5 (35/1375)	0.5 (7/1437)	Adjusted: 5.63 (2.49 to 12.76)	NNTH 44 (18 to 136)
Death at 90 days	Emberson [24]	IPD MA (subgroup)§	Moderate††	16.9 (232/1375)	15.9 (229/1437)	HR: 1.14 (0.95 to1.36)	NNTH 49 (NNTH 19 to ∞ to NNTB 137)

Abbreviations: GRADE= Grading of Recommendations Assessment, Development and Evaluation; IPD MA= individual patient data meta-analysis; mRS=modified Rankin score (relabelled as Oxford Handicap Score 0-2 in IST-3 trial report)[29]; NNTB= number needed to treat for one patient to benefit; NNTH= number needed to treat for one patient to be harmed. HR=hazard ratio; NINDS=National Institute of Neurological Disorders and Stroke.

We calculated the NNTB and NNTH using the absolute difference in event rates for outcomes from individual trials (and 95% confidence intervals using the Newcombe-Wilson method without continuity correction[34] using a confidence interval calculator from www.pedro.org.au/wp-content/uploads/CIcalculator.xls), and the odds ratio and control event rates for outcomes from meta-analyses,[35] and the hazard ratio and control survival rate for survival data from meta-analyses using time-to-event measures.[36]

*Confidence intervals include small differences (NNTB > 100)

†Baseline differences favouring alteplase group for stroke severity and history of stroke substantially downgrade quality of evidence for functional outcome but not for symptomatic intracranial hemorrhage due to direction of confounding bias.

‡Lack of blinding.

§Individual trial results for 3-4.5 hour time window not reported.

¶High degree of inconsistency in results (IST-3 compared to other trials), mRS 0-2 outcome analysis listed in protocol but not presented in IPD MA report.

**Does not include data from IST-3.