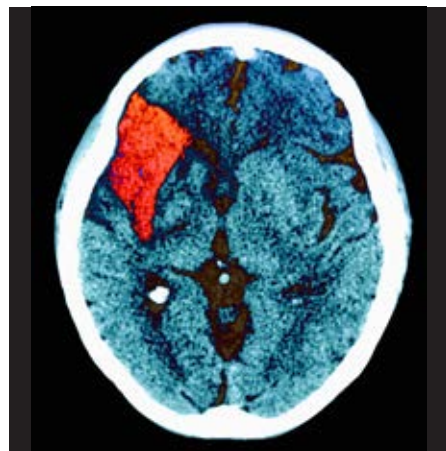


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- Research News: Lives lost with every 15 minute delay in thrombolysis after acute stroke (*BMJ* 2013;346:f3962)
- Clinical Review: Diagnosis and management of transient ischaemic attack and ischaemic stroke in the acute phase (*BMJ* 2011;342:d1938)
- Analysis: Getting the priorities right for stroke care (*BMJ* 2009;338:b2083)



# Thrombolysis in acute ischaemic stroke: time for a rethink?

As the UK regulator reviews alteplase in ischaemic stroke, **Brian Alper and colleagues** question the evidence for its use beyond three hours

**S**ystematic 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,<sup>1</sup> but some other countries—including the UK and Australia—have extended the licence to 4.5 hours.<sup>2-4</sup> Irrespective of licensing, most major stroke guidelines support use of alteplase up to 4.5 hours after stroke onset,<sup>5-16</sup> although several emergency medicine associations do not recommend it (see box on thebmj.com).<sup>17-21</sup>

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.<sup>22</sup>

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,<sup>5</sup> the Cochrane review updated in 2014,<sup>23</sup> and

an individual patient data meta-analysis published in 2014.<sup>24</sup> 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.

## Clinical practice guideline 2013

We evaluated the American Heart Association/American Stroke Association (AHA/ASA) guideline as the most recent authoritative national guideline.<sup>5</sup> 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.<sup>5</sup> 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.”<sup>5</sup>

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 to 1.85; unadjusted odds ratio 1.34, 1.04 to 1.72).<sup>25</sup> 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, see thebmj.com).<sup>26</sup> The guideline cites the subsequent ECASS III trial<sup>27</sup> 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).<sup>5</sup>

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.<sup>27</sup> 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 between the alteplase and placebo groups (odds ratio 1.19, 0.89 to 1.59; table 2).<sup>28</sup>

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.”<sup>29</sup> 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,<sup>29</sup> 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

## 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

treated between 3 and 4.5 hours.<sup>29</sup> 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).<sup>29</sup> 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.<sup>30</sup> 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.<sup>31</sup> But an update of the Cochrane review on thrombolysis for acute ischaemic stroke, published in July 2014, is confusing.<sup>23</sup> 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 “defi-

### Alteplase 3-4.5 hours after stroke onset has clearly established harms

nately 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.<sup>23</sup> 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.<sup>24</sup>

The previous 2010 meta-analysis included eight trials with 1620 patients in the 3-4.5 hour time window.<sup>32</sup> More than half of the data for this analysis comes from the ECASS III trial.<sup>27</sup> The pre-specified 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).<sup>29</sup>

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).<sup>24</sup>

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

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

Trial	ECASS III <sup>27</sup>	IST-3 <sup>29</sup>
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.<sup>28</sup> 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 <sup>27</sup>	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 <sup>29</sup>	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 <sup>24</sup>	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 <sup>27</sup>	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 <sup>32</sup>	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 <sup>24</sup>	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 <sup>24</sup>	IPD MA (subgroup)§	Moderate††	16.9 (232/1375)	15.9 (229/1437)	HR: 1.14 (0.95 to 1.36)	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)<sup>29</sup>; 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. \*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.

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.

Alternatively the unexpected, positive result of the 2014 meta-analysis could be related to which participants were included in the analysis.<sup>24</sup> 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<sup>33</sup>:

*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 and to wish to avoid “revisiting efficacy”

for the “established use” within 4.5 hours of stroke onset.<sup>33</sup> 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.

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).<sup>24</sup> 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 mortality is 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

The evidence on the effects of alteplase at 3-4.5 hours after stroke on functional outcomes is inconsistent (table 3). 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, 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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