Effects of intravenous alteplase for acute ischaemic stroke on the distribution of functional outcomes: individual patient data meta-analysis of nine randomised trials

Kennedy R Lees MD[1], Jonathan Emberson PhD[2], Lisa Blackwell BSc[2], Erich Bluhmki PhD[3], Stephen M Davis MD[4], Geoffrey A Donnan MD[5], Markku Kaste MD[6], Rüdiger von Kummer Prof Drmed[7], Maarten G Lansberg MD[8], Richard Lindley MD[9], Gordon D Murray PhD[10], Peter AG Sandercock DM[11], Danilo Toni MD[12], Kazunori Toyoda MD[13], Joanna M Wardlaw MD[11], William N Whiteley MD[11], Colin Baigent BM BCh[2], Werner Hacke MD[14], George Howard DrPH[15]

On behalf of the Stroke Thrombolysis Trialists' Collaborators Group*

1   Institute of Cardiovascular & Medical Sciences, University of Glasgow, Glasgow, UK

2   Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, Oxford, UK

3   Boehringer Ingelheim, Ingelheim, Germany

4   The Royal Melbourne Hospital and University of Melbourne, Australia

5   Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville,3052, Australia

6   Clinical Neurosciences, University of Helsinki and Department of Neurology, Helsinki University Hospital, Helsinki, Finland

7   Institute of Neuroradiology, Technische Universität, Dresden, Germany

8   Stanford Stroke Center, 780 Welch Road, Suite 350, Palo Alto, CA 94304-5778, USA

9   Westmead Hospital Clinical School and George Institute for Global Health, University of Sydney, Sydney, NSW 2006, Australia

10   Usher Institute of Population Health Sciences and Informatics, University of

        Edinburgh, Edinburgh, UK

11   Centre for Clinical Brain Sciences, University of Edinburgh, UK

12   Department of Neurology and Psychiatry, Sapienza University of Rome, Italy

13   Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular

        Center, Suita, Osaka, Japan

14   University of Heidelberg Department of Neurology, Im Neuenheimer Feld 400,

        D69120 Heidelberg, Germany

15   Department of Biostatistics, UAB School of Public Health, Birmingham, AL, USA

Correspondence to:

Professor George Howard, Department of Biostatistics, UAB School of Public Health, 1665

University Blvd, Birmigham, AL, 35294-0022, USA.   email: ghoward@uab.edu

Word count:

Abstract – 337
Text (excl abstract, references, acknowledgement) – 2534

* See end of manuscript for full list of contributors.

2

Abstract

Importance: Thrombolytic therapy with intravenous alteplase within 4.5 hours of ischaemic stroke onset increases the overall likelihood of an excellent stroke outcome (no, or non-disabling, symptoms). Any improvement in functional outcome distribution has value, however.

Objective: To estimate how the effect of alteplase on the distribution of the functional level varies depending on treatment delay, age and stroke severity.

Data sources and study selection: We searched for all completed randomised phase 3 trials of intravenous alteplase for treatment of acute ischaemic stroke.

Data extraction and synthesis: Pre-specified individual-patient-data meta-analysis of 6756 patients from nine randomised trials comparing alteplase versus placebo/open control. Ordinal logistic regression models assessed treatment differences after adjustment for treatment delay, age, stroke severity (measured by National Institutes of Health Stroke Scale; NIHSS), and relevant interaction term(s).

Main outcome and measure: Ordinal analysis of the modified Rankin Score (mRS) at 3-6 months, on which improvement is represented by numerically lower scores.

Results: The maximum delay to treatment that was beneficial, when good outcome was defined as mRS categories 0, 0-1, 0-2 or 0-3, was at least 4.5 h after stroke onset. The 95% confidence interval around the common odds ratio for all dichotomisations of mRS remained above 1 provided that treatment was initiated within 4.5h, and there was greater benefit with earlier treatment. Neither age nor stroke severity significantly influenced the slope of the relation between benefit and time to treatment initiation. For the observed case mix of patients treated within 4.5 h of stroke onset, (mean 3h 20 min), the net absolute benefit of alteplase (ie, the difference between those who would do better if given alteplase and those who would do worse) was 55 patients per 1,000 treated (95% CI 13-91; p=0.004).

Conclusions and Relevance: Treatment with intravenous alteplase initiated within 4.5 hours of stroke onset increases the chance of achieving an improved level of function for all patients across the age spectrum including the over 80s and across all severities of stroke; the earlier that treatment is initiated, the greater the benefit.

Background

There are essentially two widely accepted approaches to the statistical analysis of acute stroke outcome data. One may focus solely on good versus bad outcome, disregarding further details of the patient's functional status. Thus, one may consider patients with an "excellent" outcome to be of equal value to those with a "good" outcome but otherwise patients left with only "fair" outcome, "poor" outcome or even death are all considered just as having a bad outcome. Alternatively, one could consider if treatment shifted the entire distribution of outcomes favourably, ie one seeks an increase in the average likelihood of achieving a better outcome.[1] The traditional measure for a good stroke outcome, mRS 0-1, considers the former whereas ordinal approaches generally consider the latter.

These two approaches are not mutually incompatible, however, and both should usually be considered. Indeed, a good clinician could incorporate elements of each approach when counselling patients or relatives prior to offering intravenous thrombolysis for stroke.

The recent individual patient data (IPD) meta-analysis of 6756 patients from nine thrombolysis trials reported treatment differences that dichotomised outcomes into the "excellent" (mRS 0-1) and "bad" (death: mRS 6 versus mRS 0-5) ends of the scale.[2] In those analyses, intravenous alteplase was shown to improve significantly the overall odds of an excellent stroke outcome (mRS 0-1) when delivered within 4·5 h of stroke onset. That analysis showed that earlier treatment resulted in larger benefit of treatment, with – at any given time delay - treatment advantages that were similar irrespective of age or stroke severity. However, alteplase was also shown to increase the absolute risk of fatal intracranial haemorrhage within the first week by about 2%, with no significant effect on other early causes of death but perhaps partly offset by later causes of death.

An earlier IPD analysis carried out in 2010, which included data from 8 of the same 9 trials, suggested that 3 month mortality was increased when treatment was initiated beyond 4.5h

after stroke onset,[3] but in the updated analysis this trend with treatment delay lost statistical significance. However, death is just one potential adverse outcome: severe or even moderate disability will be considered by some patients to be as undesirable as death, or perhaps worse;[4] and others still may consider any loss of dependence as a poor outcome.[5] In addition, differences in the length of hospital stay, and the cost of care, increase substantially and monotonically with measures of disability.[6]   To help clinicians to discuss with their patients the pros and cons of a treatment that carries both potential risks and benefits, we now report various analyses that consider the full range of functional states 90-180 days after stroke.

For most circumstances in which the outcome measure involves a series of 3 or more levels of ordinal outcomes, ordinal analysis is generally considered a statistically powerful approach by expert groups for circumstances where treatment effects are not expected to concentrate at one end of the disability scale.[1,7] For treatments that may have a dual effect (the extreme example would be 'kill or cure'), risk and benefit may each be more reliably detected by a dichotomised analysis ("symptom-free survival"), but if survival despite continued symptoms is a desirable health state to some patients, then an analysis that considers all categories (symptom-free survival, symptomatic survival, severe disability, death) may be more discriminating for net benefit.[1,8] Since it is well established that later treatment (eg 4.5 to 6 hours after stroke onset) is associated with reduced benefit and with a trend at least towards lower 90-day survival, we can surmise that the greatest treatment delay at which net benefit persists may be shorter than the ~5 hour window when indexed by defining a good outcome as mRS 0-1.[2] However, the more sensitive ordinal analysis offers the opportunity to refine the characterisation of the time period when patients benefit from alteplase therapy. The aim of this report is to present the results from the pre-defined ordinal analyses,[9] and to put them in context with the already published main dichotomous ones.[2]

Methods

The data sources and analysis methods have been described in detail previously, particularly the approach used to determine the influence of time from stroke onset on the outcome mRS 0-1 versus 2-6.[2,9] For each other dichotomy of mRS, ie 0 versus 1-6, 0-2 versus 3-6 etc, we repeated that approach. We also examined the full range of the mRS to assess the common odds of better outcome with intravenous alteplase versus control, using ordinal logistic regression.[10] The use of the common odds ratio invokes assumptions about the consistency of the treatment effect across the spectrum of outcome scores, but carries advantages over its alternatives in terms of greater statistical power and ease of adjustment for baseline prognostic factors.[1,8] However, we also applied the ordinal approach of Howard et al (2012)[11] to estimate the net benefit of treatment (ie, the expected number who would do better if given alteplase minus the expected number who would do worse), among a cohort with the case mix included in the pooled trials.

As described previously, regression models, which for dichotomised outcomes were stratified by trial, were adjusted for allocation to alteplase, treatment delay, age, stroke severity (as measured by the National Institutes of Health Stroke Scale; NIHSS), and relevant interaction term(s).[9] Eight trials assessed functional outcome after 3 months using the modified Rankin Scale whereas the third international stroke trial, IST-3, applied the Oxford Handicap Scale to patients at 6 months' follow-up.[12-18] Whereas our publication on mRS 0-1 described functional outcome at 3-6 months but mortality only at three months, for the present analyses we have used mortality and functional outcome at 6 months for IST-3 patients but at 3 months for all other trials' patients (noting that a 3-month assessment was not performed in IST-3).[2] Analyses were performed using SAS version 9.3 (SAS Institute, Cary) and R version 2.11.1 (www.R-project.org).

Where relevant, the significance of 3-way interaction terms was assessed using the likelihood ratio test of the change in deviance between two nested models that differed only

by the relevant interaction term. We made no adjustment for multiplicity: ordinal analysis was

planned[9] and the primary dichotomised analysis of mRS 0-1 achieved statistical significance.

Results

The baseline characteristics of the patient population have been published previously.[2] There were 6756 patients with mean (SD) age 71 ± 13 years, NIHSS 12 ± 7 and onset to treatment delay 4.0 ± 1.2 hours.

The average odds of achieving a better stroke outcome in alteplase-allocated compared with control-allocated patients across the whole 6-hour window (mean delay 4.0 h) diminished as the selected cutpoint used to define "better" outcome shifted from least symptomatic (mRS 0, OR 1.40, 95% CI: 1.22–1.62) to greatest residual disability (mRS 5, OR 0.93, 95% CI: 0.82–1.06; eFigure 1). The p-value for the assumption of a common odds ratio is <0.0001, suggesting there is heterogeneity of the odds ratios across the various dichotomies. This heterogeneity between mRS thresholds would appear to be attributable to a general downward shift in the odds of better outcome at higher mRS thresholds, while the pattern of poorer outcomes with longer delays in the time to treatment was relatively consistent across the mRS spectrum.

For each of the possible dichotomisations of mRS, earlier treatment was associated with bigger proportional benefits; this interaction with treatment delay was conventionally statistically significant (p<0.05) for each of the comparisons 0-1 v 2-6 through to 0-4 v 5-6, and, despite being qualitatively similar, with relatively few patients with mRS of either 0 or 6 was not statistically significant for mRS 0 vs 1-6 or mRS 0-5 vs 6 (Figure 1). The maximum delay between stroke onset and treatment that was associated with a significantly positive treatment effect was at least 4.5 hours for each dichotomisation of the mRS scale classifying 0, 0-1, 0-2 or 0-3 as good outcome. For mRS 0-4 versus 5-6 or 0-5 versus 6 (death), it was not established that alteplase significantly increased the overall odds of a better outcome (eFigure 1) nor that earlier treatment (even at 1 hour) was associated with a clear benefit (Figure 1).

After combining the results of the alternative dichotomous analyses to model the average odds ratio for any upwards shift in mRS, treatment initiation within 4.5 hours was associated with statistically significant net benefit, with earlier treatment resulting in bigger proportional benefits (Figure 2). Given treatment delay, neither patient age or baseline stroke severity significantly altered the effect of alteplase on the odds of an improved outcome (eFigure 2); nor did stroke severity significantly alter the relationship between treatment delay and the odds of an improved outcome with alteplase (p = 0.12). The test for a three-way interaction among treatment, treatment delay and age as a continuous variable had a p value of 0.0019, in the direction of older age lengthening the window during which intravenous alteplase may be effective (eFigure 3). The window remains open until at least 4.5 hours for both younger and more elderly patients.

The observed frequencies of patients in various outcome strata according to treatment delay and baseline stroke severity, without adjustment for other characteristics, are shown in eFigures 4 and 5.

An ordinal analysis, avoiding the proportionality assumption,[11] of the patients treated within 4.5 hours of stroke onset (mean delay 3 hours 20 minutes), where benefit is expressed as any improvement in one or more divisions of the mRS, found that a net 55 patients (95% CI 13, 91) per 1,000 treated were better with alteplase, p=0.004. Earlier treatment was better: within 3 hours (average 2 h 20 m) net benefit was 122 patients (95% CI 61, 171) per 1,000 treated whereas initiating treatment beyond 4.5 hours (mean 5 hours 20 minutes) revealed a net benefit of only 20 patients (95% CI -31, 75) per 1,000 treated, p=0.45.

Discussion

Patients with acute ischaemic stroke show wide variation in the severity and range of their symptoms at presentation. Their functional outcomes are also diverse. The categories of the modified Rankin Scale capture this diversity well. Dichotomisation of the scale at mRS 0-1 (excellent outcome) versus 2-6 (poorer outcome), or at 0-2 (independent) versus 3-6 (dependent or dead) simplifies the presentation of the impact of treatment but implying cure or near cure oversimplifies clinical reality for most patients. Patients want to know if treatment will make a noticeable difference to their functional outcome: many would regard an improvement by any step in mRS level as worthwhile, though they would not necessarily weight all transitions as equal.[5]

In addition, such simplification tends to lead to situations where clinicians are eager to identify the "good responders", whereas the reality may well be that the majority of patients improve somewhat, with a few showing a major improvement (or major deterioration and early death). An overemphasis on only treating those likely to have a major improvement may lead to the situation where the net benefit of thrombolysis would be lost.

Our analysis reveals that if good outcome is represented by any contiguous group of mRS levels from 0 (asymptomatic) down to 3 (requiring help for activities of daily living), then the onset to treatment time window in which benefit is statistically more likely with alteplase is at least 4.5 hours, though earlier treatment is better and by 4.5 hours the benefit is becoming small. Treatment with intravenous alteplase initiated within 4.5 hours reduces the proportion of patients with mRS 4 or higher: there will be fewer patients who cannot walk independently or require help with basic toileting. We did not find that intravenous alteplase alters mRS 0-4 versus 5-6, nor, as we have previously shown and examined in greater detail,[2] did we have evidence that it alters survival excepting the small excess of early fatal bleeding (Figure 1 and eFigure 1). Thus, intravenous alteplase appears to enhance chances of achieving a good outcome by more than it improves the chances of achieving a merely acceptable

outcome, which may be attractive to patients. Analysis that relies on a common odds ratio to combine all possible dichotomies of mRS is compromised by violation of the assumption that these ratios are similar. However, though the odds ratios diminish as the criterion for good outcome drops towards greater disability, we do not have evidence that they invert.

We found that if all categories of mRS are given equal weight and any net movement towards better outcome is regarded as desirable, then the onset to treatment window for benefit from intravenous alteplase is at least 4.5 hours, although earlier treatment is better than later treatment within this window. The ordinal approach[11] that avoids the proportionality assumption gives a comparable result. Neither age nor baseline stroke severity modifies this relation, or if age does so it is to lengthen slightly rather than shorten the available time for treatment.

Since the magnitude of the treatment effect appears to decrease at higher thresholds (i.e., two higher dichotomies show no significant benefit from iv alteplase irrespective of treatment initiation delay), it was anticipated that the ordinal analysis may not confirm benefit until 4.5h. However, there was a clear benefit for lower mRS thresholds, and only a lack of effect for higher mRS thresholds. In contradistinction, although alteplase has a neutral effect on mRS 0-4 versus 5-6 and on survival, there is still a strong trend towards a time-related effect for these mRS divisions such that treatment initiated within 3 hours appears more useful than treatment initiation after 3 hours. This has biological plausibility.

The observed outcomes of the isolated cohorts of patients within each treatment delay window or severity category (eFigures 5 and 6) give a less reliable picture of treatment effects than the models that incorporate all data together, because case mix varies between cohorts and this has a strong influence on outcome and because smaller samples deliver lower statistical power.

Our results are consistent with those of the dichotomised IPD analysis[2] and with the conclusions of individual trials that show benefit within 4.5 hours of stroke onset, but especially within 3 hours.[12,15] They support the conclusions of the European Stroke Organisation Guidelines on stroke management.[19] We have not discussed here the early risk of fatal bleeding that is a well recognised complication of intravenous alteplase treatment,[2] because it neither has an impact on assessment of the outcome distribution nor, in the absence of a reliable means of identifying patients who will suffer such bleeding, on the decision to treat.

The implications of our analysis that considers all levels of functional outcome including survival after stroke are clear:

1) on average, there is an increased chance of achieving an improved level of function if treatment with intravenous alteplase is initiated within 4.5 hours of stroke onset;

2) treatment benefit is greater the earlier that it is initiated;

3) neither age nor stroke severity has a detectable impact on the relation between delay and treatment benefit, and particularly not on the duration of the clinically justifiable treatment window; and

4) any patient who fulfils the criteria for treatment with alteplase and who wishes to optimise his chance of survival with optimal function should be offered treatment with intravenous alteplase as a matter of extreme urgency, ideally within a maximum initiation delay of 4.5 hours.

References

1. Bath PMW, Lees KR, Schellinger PD et al for the European Stroke Organisation Outcomes Working Group. Statistical Analysis of the Primary Outcome in Acute Stroke Trials. Stroke 2012; 43: 1171-1178

2. Emberson J, Lees KR, Lyden P, 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; 379: 2352-63.

3. Lees KR, Bluhmki E, von Kummer R 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.

4. Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. Arch Int Med 1996; 156: 1829-1836

5. Hong KS, Saver JL. Quantifying the value of stroke disability outcomes: WHO global burden of disease project disability weights for each level of the modified Rankin Scale. Stroke. 2009;40:3828 –3833.

6. Dawson J, Lees JS, Chang TP, Walters MR, Ali M, Davis SM, et al. Association between disability measures and healthcare costs after initial treatment for acute stroke. Stroke; a journal of cerebral circulation. 2007 Jun;38(6):1893-8. PubMed PMID: 17446431.

7. Lees KR, Bath PMW, Schellinger PD et al and for the European Stroke Organisation Outcomes Working Group. Contemporary Outcome Measures in Acute Stroke Research: Choice of Primary Outcome Measure. Stroke 2012; 43: 1163-U451

8.   Rahlfs VW, Zimmermann H, Lees KR. Effect size measures and their relationships in stroke studies. Stroke 2014; 45: 627-633

9.   Stroke Thombolysis Trialists' Collaboration. Details of a prospective protocol for a collaborative meta-analysis of individual participant data from all randomized trials of intravenous rt-PA vs. control: statistical analysis plan for the Stroke Thrombolysis Trialists' Collaborative meta-analysis. International Journal of stroke 2013; 8(4): 278-83.

10.   McCullagh P (1980). Regression models for ordinal data (with discussion). J R Statist Soc B; 42: 109-142

11.   Howard G, Waller JL, Voeks JH et al. A Simple, Assumption-Free, and Clinically Interpretable Approach for Analysis of Modified Rankin Outcomes. Stroke 2012. doi: 10.1161/STROKEAHA.111.632935

12.   The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med, 1995. 333(24): 1581-7

13.   Hacke W, Kaste M, Fieschi C et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA, 1995. 274(13): 1017-25.

14.   Hacke W, Kaste M, Fieschi C et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II).

Second European-Australasian Acute Stroke Study Investigators. Lancet, 1998. 352(9136): 1245-51.

15. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med, 2008. 359(13): 1317-29.

16. Clark WM, Wissman, S, Albers GW et al. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. JAMA, 1999. 282(21): p. 2019-26.

17. Davis SM, Donnan GA, Parsons MW et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. Lancet Neurol, 2008. 7(4): 299-309.

18. Sandercock P, Wardlaw JM, Lindley RI, et al and the IST-3 collaborative group. 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 randomised controlled trial. Lancet, 2012. 379(9834): 2352-63.

19. The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee. Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008. Cerebrovasc Dis 2008; 25: 457-507

Contributors:

Figure 1

Relative odds of a good stroke outcome with alteplase by time to treatment, for each alternative definition of 'good' outcome

Figure 2

Effect of alteplase on any upwards shift in mRS, by treatment delay

eFigure 1

Relative odds of a good stroke outcome with alteplase, for each alternative definition of 'good' outcome, among all randomised patients

eFigure 2

Effect of alteplase on any upwards shift in mRS, by treatment delay, age and stroke severity

eFigure 3

Effect of alteplase on any upwards shift in mRS by age and treatment delay

eFigure 4

Actual distribution of mRS* at 3−6 months by randomised treatment allocation, overall and by treatment delay

eFigure 5

Actual distribution of mRS* at 3−6 months by randomised treatment allocation, by stroke severity (among all randomised patients)

Figure 1: Relative odds of a good stroke outcome with alteplase by time to treatment, for each alternative definition of 'good' outcome
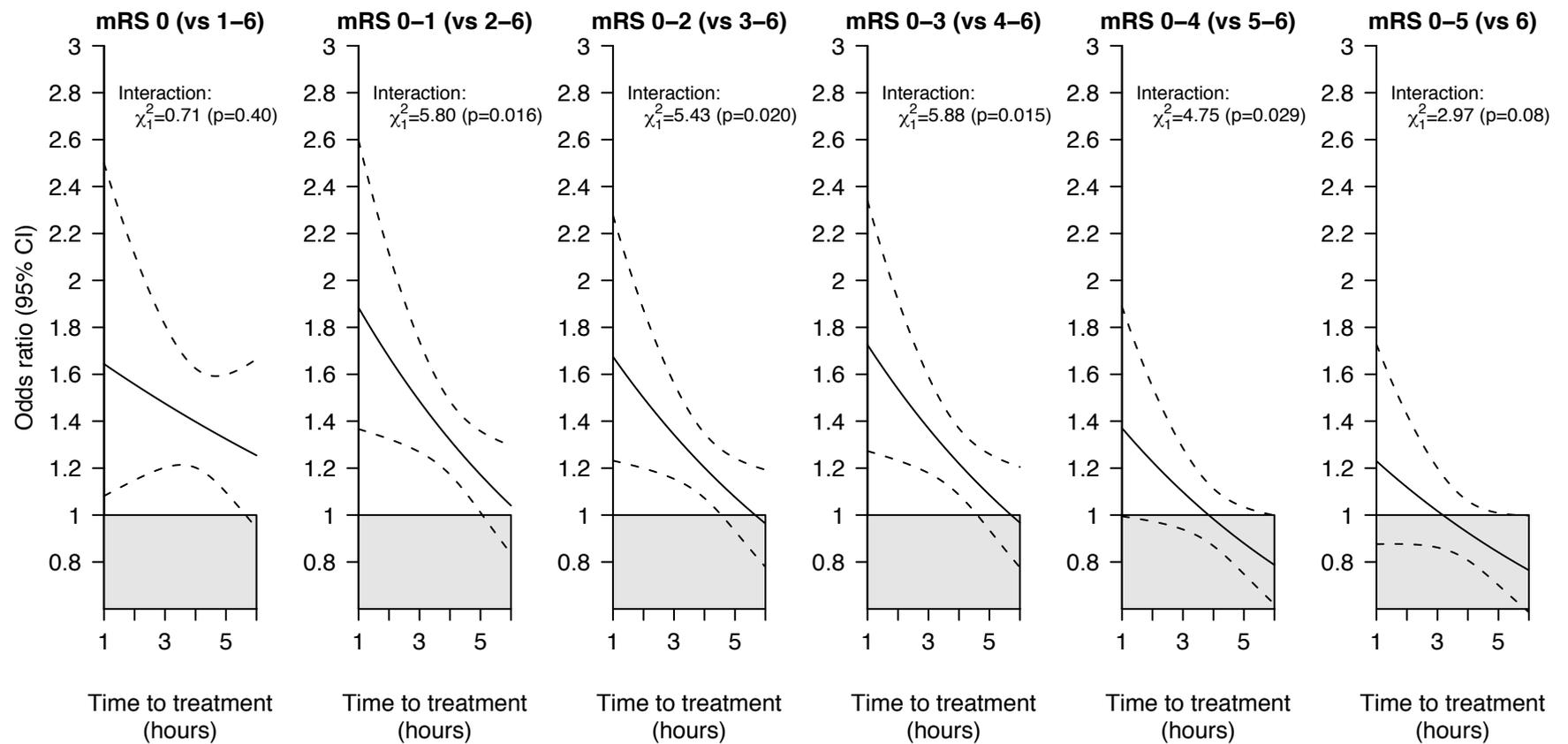
In each panel the solid line represents the best linear fit between the log odds ratio for each mRS outcome among patients given alteplase compared with patients given control (vertical axis) and treatment delay (horizontal axis).

Estimates are derived from a regression model in which alteplase, time to treatment, age and stroke severity (handled in a quadratic manner) are included as main effects but the only treatment interaction included is with time to treatment.

Figure 2: Effect of alteplase on any upwards shift in mRS, by treatment delay
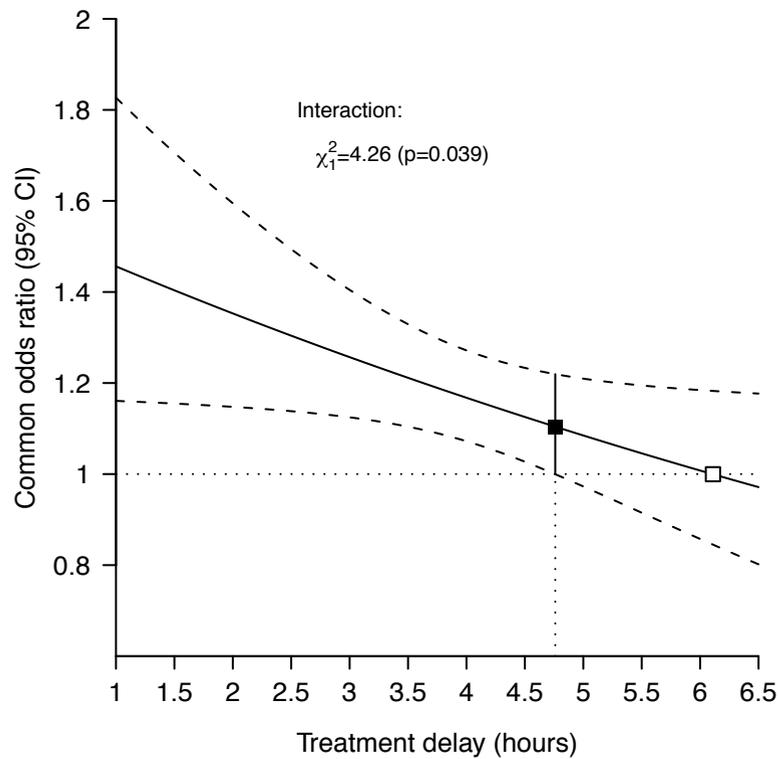
The solid line represents the best linear fit between the log odds ratio for a good stroke outcome among patients given alteplase compared with patients given control (vertical axis) and treatment delay (horizontal axis).

Estimates are derived from a regression model in which alteplase, time to treatment, age and stroke severity (handled in a quadratic manner) are included as main effects but the only treatment interaction included is with time to treatment.

Only 198 patients (159 of whom were from IST–3) had a time from stroke onset to treatment of more than 6 hours. The point at which the estimated treatment effect crosses 1 is therefore an extrapolation from the data.

Supplementary material: Effects of intravenous alteplase for acute ischaemic stroke on the distribution of functional outcomes: individual patient data meta-analysis of nine randomized trials

eFigure 1: Relative odds of a good stroke outcome with alteplase, for each alternative definition of 'good' outcome, among all randomized patients

mRS comparison ('good' vs 'bad')	No. patients with 'good' outcome			Odds ratio* (95% CI)
	Alteplase (n=3391)	Control (n=3365)		
0 vs 1–6	526 (15.5%)	391 (11.6%)		1.40 (1.22–1.62)
0–1 vs 2–6**	1145 (33.8%)	965 (28.7%)		1.28 (1.15–1.42)
0–2 vs 3–6	1548 (45.7%)	1413 (42.0%)		1.16 (1.05–1.28)
0–3 vs 4–6	2003 (59.1%)	1864 (55.4%)		1.17 (1.06–1.29)
0–4 vs 5–6	2358 (69.5%)	2344 (69.7%)		0.99 (0.89–1.10)
0–5 vs 6	2727 (80.4%)	2738 (81.4%)		0.93 (0.82–1.06)

```
        0.8    1   1.2  1.4 1.6
     Alteplase       Alteplase
       worse           better
```

* Estimated from a logistic regression model stratified by trial and adjusted only for treatment allocation.

** Primary pre–specified mRS comparison.

IST–3 applied the Oxford Handicap Scale to patients at 6 months' follow–up. We have used mortality and functional outcome at 6 months for IST–3 patients but at 3 months for all other trials' patients.

eFigure 2: Effect of alteplase on any upwards shift in mRS, by treatment delay, age and stroke severity

Global test of all interactions:χ^2_4=5.27 (p=0.26)

The solid line on each plot represents the interaction between alteplase with one of time, age or baseline NIHSS. Each is adjusted for treatment delay (linear), age (linear) and baseline NIHSS (quadratic), and interactions between alteplase with the other main effects (i.e. two of age, time and baseline NIHSS).

The estimated odds ratio is plotted for patients with AVERAGE levels of the other 2 baseline characteristics. The OR for alteplase was 1.14 at the mean values of age (71 years), NIHSS (12 points) and time to treatment (4 hours). The significance of each interaction is tested by comparing the change in deviance between two nested models that differ only by the interaction term(s) (ie, the likelihood ratio test).

eFigure 3: Effect of alteplase on any upwards shift in mRS by age and treatment delay

In each panel, the solid line represents the best linear fit between the log of the common odds ratio (vertical axis) and treatment delay (horizontal axis). The estimates and their confidence intervals are derived from a proportional odds logistic regression model which adjusts for allocation to rtPA, age, treatment delay and stroke severity and, through inclusion of appropriate interaction terms, allows the log odds ratio to vary by treatment delay and for that relationship to itself differ between patients aged 80 years or younger and patients aged over 80 years.

eFigure 4: Actual distribution of mRS* at 3–6 months by randomized treatment allocation, overall and by treatment delay

a) Treatment delay ≤ 3 hours (n=1549)

	13.7%	19.2%	9.7%	13.1%	11.1%	9.5%	23.8%

Alteplase (n=787)

3–6 month mRS: 0 / 1 / 2 / 3 / 4 / 5 / 6

Control (n=762)

Mean treatment delay = 2.3 hours
Mean NIHSS = 13.8

	9.4%	13.6%	9.3%	14.8%	16.1%	12.2%	24.4%

b) Treatment delay 3–4.5 hours (n=2812)

	17.4%	17.9%	11.0%	13.3%	9.8%	12.4%	18.3%

Alteplase (n=1375)

3–6 month mRS: 0 / 1 / 2 / 3 / 4 / 5 / 6

Control (n=1437)

Mean treatment delay = 3.9 hours
Mean NIHSS = 11.9

	12.5%	17.6%	13.9%	12.1%	13.6%	12.0%	18.3%

c) Treatment delay >4.5 hours (n=2395)

	14.6%	18.1%	14.3%	13.8%	10.8%	10.1%	18.4%

Alteplase (n=1229)

3–6 month mRS: 0 / 1 / 2 / 3 / 4 / 5 / 6

Control (n=1166)

Mean treatment delay = 5.3 hours
Mean NIHSS = 11.0

	12.0%	18.6%	15.2%	14.1%	13.9%	11.0%	15.3%

All patients (n=6756)

	15.5%	18.3%	11.9%	13.4%	10.5%	10.9%	19.6%

Alteplase (n=3391)

3–6 month mRS: 0 / 1 / 2 / 3 / 4 / 5 / 6

Control (n=3365)

Mean treatment delay = 4.0 hours
Mean NIHSS = 12.0

	11.6%	17.1%	13.3%	13.4%	14.3%	11.7%	18.6%

% 0 10 20 30 40 50 60 70 80 90 100

* mRS score ascertained at 6 months for IST–3 and 3 months for other trials.

eFigure 5: Actual distribution of mRS* at 3–6 months by randomized treatment allocation, by stroke severity (among all randomized patients)

a) NIHSS 0–4 (n=666)
- Alteplase (n=345): 0 = 33.6%, 1 = 35.1%, 2 = 13.6%, 3 = 7.8%, 4 = 1.2%, 5 = 3.8%, 6 = 4.9%
- Control (n=321): 0 = 26.8%, 1 = 32.1%, 2 = 23.7%, 3 = 9.0%, 4 = 3.4%, 5 = 1.9%, 6 = 3.1%
- Mean treatment delay = 4.3 hours, Mean NIHSS = 3.3

b) NIHSS 5–10 (n=2533)
- Alteplase (n=1281): 0 = 23.5%, 1 = 24.2%, 2 = 14.6%, 3 = 13.7%, 4 = 8.1%, 5 = 7.3%, 6 = 8.5%
- Control (n=1252): 0 = 18.3%, 1 = 24.7%, 2 = 17.8%, 3 = 14.6%, 4 = 8.7%, 5 = 6.9%, 6 = 9.0%
- Mean treatment delay = 4.2 hours, Mean NIHSS = 7.4

c) NIHSS 11–15 (n=1602)
- Alteplase (n=794): 0 = 9.8%, 1 = 15.1%, 2 = 11.7%, 3 = 16.6%, 4 = 14.5%, 5 = 12.2%, 6 = 20.0%
- Control (n=808): 0 = 7.2%, 1 = 14.5%, 2 = 12.3%, 3 = 16.5%, 4 = 19.4%, 5 = 13.2%, 6 = 17.0%
- Mean treatment delay = 4.0 hours, Mean NIHSS = 12.9

d) NIHSS 16–21 (n=1333)
- Alteplase (n=662): 0 = 4.1%, 1 = 7.6%, 2 = 9.1%, 3 = 13.9%, 4 = 15.0%, 5 = 16.6%, 6 = 33.8%
- Control (n=671): 0 = 2.5%, 1 = 5.7%, 2 = 6.1%, 3 = 12.5%, 4 = 22.7%, 5 = 18.6%, 6 = 31.9%
- Mean treatment delay = 3.8 hours, Mean NIHSS = 18.1

e) NIHSS 22+ (n=622)
- Alteplase (n=309): 0 = 1.3%, 1 = 5.8%, 2 = 5.2%, 3 = 9.1%, 4 = 10.7%, 5 = 17.8%, 6 = 50.2%
- Control (n=313): 0 = 0.3%, 1 = 2.2%, 2 = 2.9%, 3 = 7.0%, 4 = 16.3%, 5 = 22.4%, 6 = 48.9%
- Mean treatment delay = 3.5 hours, Mean NIHSS = 24.9

% 0 10 20 30 40 50 60 70 80 90 100

* mRS score ascertained at 6 months for IST–3 and 3 months for other trials.

Supplementary material: Effects of intravenous alteplase for acute ischaemic stroke on the distribution of functional outcomes: individual patient data meta-analysis of nine randomised trials

eFigure 1: Relative odds of a good stroke outcome with alteplase, for each alternative definition of 'good' outcome, among all randomized patients

mRS comparison ('good' vs 'bad')	No. patients with 'good' outcome			Odds ratio* (95% CI)
	Alteplase (n=3391)	Control (n=3365)		
0 vs 1–6	526 (15.5%)	391 (11.6%)		1.40 (1.22–1.62)
0–1 vs 2–6**	1145 (33.8%)	965 (28.7%)		1.28 (1.15–1.42)
0–2 vs 3–6	1548 (45.7%)	1413 (42.0%)		1.16 (1.05–1.28)
0–3 vs 4–6	2003 (59.1%)	1864 (55.4%)		1.17 (1.06–1.29)
0–4 vs 5–6	2358 (69.5%)	2344 (69.7%)		0.99 (0.89–1.10)
0–5 vs 6	2727 (80.4%)	2738 (81.4%)		0.93 (0.82–1.06)

```
        0.8    1   1.2 1.4 1.6
      Alteplase      Alteplase
        worse          better
```

* Estimated from a logistic regression model stratified by trial and adjusted only for treatment allocation.

** Primary pre–specified mRS comparison.

IST–3 applied the Oxford Handicap Scale to patients at 6 months' follow–up. We have used mortality and functional outcome at 6 months for IST–3 patients but at 3 months for all other trials' patients.

eFigure 2: Effect of alteplase on any upwards shift in mRS, by treatment delay, age and stroke severity

Global test of all interactions: χ^2_4=5.27 (p=0.26)

The solid line on each plot represents the interaction between alteplase with one of time, age or baseline NIHSS. Each is adjusted for treatment delay (linear), age (linear) and baseline NIHSS (quadratic), and interactions between alteplase with the other main effects (i.e. two of age, time and baseline NIHSS).

The estimated odds ratio is plotted for patients with AVERAGE levels of the other 2 baseline characteristics. The OR for alteplase was 1.14 at the mean values of age (71 years), NIHSS (12 points) and time to treatment (4 hours). The significance of each interaction is tested by comparing the change in deviance between two nested models that differ only by the interaction term(s) (ie, the likelihood ratio test).

eFigure 3: Effect of alteplase on any upwards shift in mRS by age and treatment delay

In each panel, the solid line represents the best linear fit between the log of the common odds ratio (vertical axis) and treatment delay (horizontal axis). The estimates and their confidence intervals are derived from a proportional odds logistic regression model which adjusts for allocation to rtPA, age, treatment delay and stroke severity and, through inclusion of appropriate interaction terms, allows the log odds ratio to vary by treatment delay and for that relationship to itself differ between patients aged 80 years or younger and patients aged over 80 years.

eFigure 4: Actual distribution of mRS* at 3–6 months by randomized treatment allocation, overall and by treatment delay

a) Treatment delay ≤ 3 hours (n=1549)

	13.7%	19.2%	9.7%	13.1%	11.1%	9.5%	23.8%

Alteplase (n=787)

3–6 month mRS: 0 / 1 / 2 / 3 / 4 / 5 / 6

Control (n=762)

9.4%	13.6%	9.3%	14.8%	16.1%	12.2%	24.4%

Mean age = 73 years
Mean treatment delay = 2.3 hours
Mean NIHSS = 13.8

b) Treatment delay 3–4.5 hours (n=2812)

17.4%	17.9%	11.0%	13.3%	9.8%	12.4%	18.3%

Alteplase (n=1375)

3–6 month mRS: 0 / 1 / 2 / 3 / 4 / 5 / 6

Control (n=1437)

12.5%	17.6%	13.9%	12.1%	13.6%	12.0%	18.3%

Mean age = 71 years
Mean treatment delay = 3.9 hours
Mean NIHSS = 11.9

c) Treatment delay >4.5 hours (n=2395)

14.6%	18.1%	14.3%	13.8%	10.8%	10.1%	18.4%

Alteplase (n=1229)

3–6 month mRS: 0 / 1 / 2 / 3 / 4 / 5 / 6

Control (n=1166)

12.0%	18.6%	15.2%	14.1%	13.9%	11.0%	15.3%

Mean age = 70 years
Mean treatment delay = 5.3 hours
Mean NIHSS = 11.0

All patients (n=6756)

15.5%	18.3%	11.9%	13.4%	10.5%	10.9%	19.6%

Alteplase (n=3391)

3–6 month mRS: 0 / 1 / 2 / 3 / 4 / 5 / 6

Control (n=3365)

11.6%	17.1%	13.3%	13.4%	14.3%	11.7%	18.6%

Mean age = 71 years
Mean treatment delay = 4.0 hours
Mean NIHSS = 12.0

% 0 10 20 30 40 50 60 70 80 90 100

* mRS score ascertained at 6 months for IST–3 and 3 months for other trials.

eFigure 5: Actual distribution of mRS* at 3–6 months by randomized treatment allocation, by stroke severity (among all randomized patients)

a) NIHSS 0–4
(n=666)

Alteplase (n=345): 33.6% | 35.1% | 13.6% | 7.8% | 1.2% | 3.8% | 4.9%

3–6 month mRS: 0 | 1 | 2 | 3 | 4 | 5 | 6

Control (n=321): 26.8% | 32.1% | 23.7% | 9.0% | 3.4% | 1.9% | 3.1%

Mean age = 69 years
Mean treatment delay = 4.3 hours
Mean NIHSS = 3.3

b) NIHSS 5–10
(n=2533)

Alteplase (n=1281): 23.5% | 24.2% | 14.6% | 13.7% | 8.1% | 7.3% | 8.5%

3–6 month mRS: 0 | 1 | 2 | 3 | 4 | 5 | 6

Control (n=1252): 18.3% | 24.7% | 17.8% | 14.6% | 8.7% | 6.9% | 9.0%

Mean age = 70 years
Mean treatment delay = 4.2 hours
Mean NIHSS = 7.4

c) NIHSS 11–15
(n=1602)

Alteplase (n=794): 9.8% | 15.1% | 11.7% | 16.6% | 14.5% | 12.2% | 20.0%

3–6 month mRS: 0 | 1 | 2 | 3 | 4 | 5 | 6

Control (n=808): 7.2% | 14.5% | 12.3% | 16.5% | 19.4% | 13.2% | 17.0%

Mean age = 70 years
Mean treatment delay = 4.0 hours
Mean NIHSS = 12.9

d) NIHSS 16–21
(n=1333)

Alteplase (n=662): 4.1% | 7.6% | 9.1% | 13.9% | 15.0% | 16.6% | 33.8%

3–6 month mRS: 0 | 1 | 2 | 3 | 4 | 5 | 6

Control (n=671): 2.5% | 5.7% | 6.1% | 12.5% | 22.7% | 18.6% | 31.9%

Mean age = 73 years
Mean treatment delay = 3.8 hours
Mean NIHSS = 18.1

e) NIHSS 22+
(n=622)

Alteplase (n=309): 1.3% | 5.8% | 5.2% | 9.1% | 10.7% | 17.8% | 50.2%

3–6 month mRS: 0 | 1 | 2 | 3 | 4 | 5 | 6

Control (n=313): 0.3% | 2.2% | 2.9% | 7.0% | 16.3% | 22.4% | 48.9%

Mean age = 76 years
Mean treatment delay = 3.5 hours
Mean NIHSS = 24.9

% 0 10 20 30 40 50 60 70 80 90 100

* mRS score ascertained at 6 months for IST–3 and 3 months for other trials.