Effects of Alteplase for Acute Stroke on the Distribution of Functional Outcomes

A Pooled Analysis of 9 Trials

Kennedy R. Lees, MD; Jonathan Emberson, PhD; Lisa Blackwell, BSc; Erich Bluhmki, PhD;
Stephen M. Davis, MD; Geoffrey A. Donnan, MD; James C. Grotta, MD; Markku Kaste, MD;
Rüdiger von Kummer, Drmed; Maarten G. Lansberg, MD; Richard I. Lindley, MD;
Patrick Lyden, MD; Gordon D. Murray, PhD; Peter A.G. Sandercock, DM; Danilo Toni, MD;
Kazunori Toyoda, MD; Joanna M. Wardlaw, MD; William N. Whiteley, MD;
Colin Baigent, BM BCh; Werner Hacke, MD; George Howard, DrPH;
on behalf of the Stroke Thrombolysis Trialists' Collaborators Group*

From the Institute of Cardiovascular and Medical Sciences, University of Glasgow, United Kingdom (K.R.L.); Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, United Kingdom (J.E., L.B., C.B.); Statistics Department, Boehringer Ingelheim, Germany (E.B.); Melbourne Brain Centre, The Royal Melbourne Hospital and University of Melbourne, Australia (S.M.D.); Stroke Division, Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, Australia (G.A.D.); Mobile Stroke Unit and Stroke Research Program, Memorial Hermann Hospital, Houston, TX (J.C.G.); Department of Neurology, Helsinki University Hospital and Clinical Neurosciences, University of Helsinki, Finland (M.K.); Department of Neuroradiology, Technische Universität, Dresden, Germany (R.v.K.); Stanford Stroke Center, Palo Alto, CA (M.G.L.); Discipline of Medicine, Westmead Hospital Clinical School, George Institute for Global Health, University of Sydney, NSW, Australia (R.I.L.); Department of Neurology, Cedars-Sinai, Los Angeles, CA (P.L.); Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, United Kingdom (G.D.M.); Centre for Clinical Brain Sciences, University of Edinburgh, United Kingdom (P.A.G.S., J.M.W., W.N.W.); Department of Neurology and Psychiatry, Sapienza University of Rome, Italy (D.T.); Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan (K.T.); Department of Neurology, University of Heidelberg, Im Neuenheimer Feld, Germany (W.H.); and Department of Biostatistics, UAB School of Public Health, Birmingham, AL (G.H.).

*A list of all Stroke Thrombolysis Trialists' Collaborators Group is given in the Appendix.

ABSTRACT

Background—Thrombolytic therapy with intravenous alteplase within 4.5 hours of ischemic stroke onset increases the overall likelihood of an excellent outcome (no, or nondisabling, symptoms). Any improvement in functional outcome distribution has value, and herein we provide an assessment of the effect of alteplase on the distribution of the functional level by treatment delay, age, and stroke severity.

Methods—Prespecified pooled analysis of 6756 patients from 9 randomized trials comparing alteplase versus placebo/ open control. Ordinal logistic regression models assessed treatment differences after adjustment for treatment delay, age, stroke severity, and relevant interaction term(s).

Results—Treatment with alteplase was beneficial for a delay in treatment extending to 4.5 hours after stroke onset, with a greater benefit with earlier treatment. Neither age nor stroke severity significantly influenced the slope of the relationship between benefit and time to treatment initiation. For the observed case mix of patients treated within 4.5 hours of stroke onset (mean 3 hours and 20 minutes), the net absolute benefit from alteplase (ie, the difference between those who would do better if given alteplase and those who would do worse) was 55 patients per 1000 treated (95% confidence interval, 13–91; P=0.004).

Conclusions—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 studied (top versus bottom fifth means: 22 versus 4); the earlier that treatment is initiated, the greater the benefit.

INTRODUCTION

There are essentially 2 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 favorably, that is, one seeks an increase in the average likelihood of achieving a better outcome.[1] The traditional measure for a good stroke outcome, modified Rankin Scale (mRS) score of 0 to 1, considers the former, whereas ordinal approaches generally consider the latter.

These 2 approaches are not mutually incompatible, however, and both should usually be considered. Indeed, a good clinician could incorporate elements of each approach when counseling patients or relatives before offering intravenous thrombolysis for stroke.

The recent individual patient data pooled analysis of 6756 patients from 9 thrombolysis trials reported treatment differences that dichotomized outcomes into the excellent (mRS, 0–1) and bad (death: mRS 6 versus 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 hours of stroke onset. That analysis showed that earlier treatment resulted in larger benefit of treatment, with—at any given time delay—proportional treatment effects that were similar irrespective of age or stroke severity within the range studied. However, alteplase was also shown to increase the absolute risk of fatal intracranial hemorrhage 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 individual patient data 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 4.5 hours 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 to 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 dichotomized 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, and death) may be more discriminating for net benefit.[1,8] Because it is well established that later treatment (eg, 4.5–6 hours after stroke onset) is associated with reduced benefit and with a trend at least toward 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 score of 0 to 1.2 However, the more sensitive ordinal analysis offers the opportunity to refine the characterization of the time period when patients benefit from alteplase therapy. The aim of this report is to present the results from the predefined ordinal analyses9 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 score of 0 to 1 versus 2 to 6.[2,9] For each other dichotomy of mRS, that is, 0 versus 1 to 6, 0 to 2 versus 3 to 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 al11 that weights all steps of the mRS equally, 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 dichotomized outcomes were stratified by trial, were adjusted for allocation to alteplase, treatment delay, age, stroke severity (as measured by the pretreatment National Institutes of Health Stroke Scale [NIHSS]), and relevant interaction term(s).[9] Adjusted models are needed because of the strong inter-relationships between age, treatment delay, and stroke severity in the 9 included trials.[2,9] For example, patients treated earlier tended to be older and to have had more severe strokes than patients treated later. Eight trials assessed functional outcome after 3 months using the mRS, 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 score of 0 to 1 described functional outcome at 3 to 6 months, but mortality only at 3 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, NC) and R version 2.11.1 (https://www.Rproject.org).

Where relevant, the significance of 3-way interaction terms was assessed using the likelihood ratio test of the change in deviance between 2 nested models that differed only by the relevant interaction term. We made no adjustment for multiplicity: ordinal analysis was planned,[9] and the primary dichotomized analysis of mRS score of 0 to 1 achieved statistical significance.

Results

The baseline characteristics of the patient population are provided in Table. 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 hours) diminished as the selected cut point used to define better outcome shifted from asymptomatic (mRS, 0 versus 1–6; odds ratio, 1.40; 95% confidence interval [CI], 1.22–1.62) to greatest residual disability (mRS, 0–5 versus 6; odds ratio, 0.93; 95% CI, 0.82–1.06; Figure 1). The P value for the assumption of a common odds ratio is <0.0001, suggesting that there is heterogeneity of the odds ratios across the various dichotomies. This heterogeneity between mRS thresholds would seem to be attributable to a general downward shift in the odds of better outcome at higher mRS thresholds, whereas the pat-tern of poorer outcomes with longer delays in the time to treatment was relatively consistent across the mRS spectrum.

For each of the possible dichotomizations 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 to 1 versus 2 to 6 through to 0 to 4 versus 5 to 6, and, despite being qualitatively similar, with relatively few patients with mRS score of either 0 or 6 was not statistically significant for mRS score of 0 versus 1 to 6 or 0 to 5 versus 6 (Figure 2). 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 dichotomization of the mRS classify¬ing 0, 0 to 1, 0 to 2, or 0 to 3 as good outcome. For mRS score of 0 to 4 versus 5 to 6 or 0 to 5 versus 6 (death), it was not established that alteplase significantly increased the overall odds of a better outcome (Figure 1) nor that earlier treatment (even at 1 hour) was associated with a clear benefit (Figure 2).

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 3). Given treatment delay, neither patient age nor baseline stroke severity significantly altered the proportional effect of alteplase on the odds of an improved outcome (Figure I in the online-only Data Supplement) nor did stroke severity significantly alter the relationship between treatment delay and the odds of an improved outcome with alteplase (P=0.72). The test for a 3-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 (Figure II in the online-only Data Supplement). The window remains open until at least 4.5 hours for both younger and more elderly (ie, >80-year old) 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 Figures III and IV in the online-only Data Supplement.

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 1 or more divisions of the mRS, found that a net 55 patients (95% CI, 13–91) per 1000 treated were better with alteplase, P=0.004. Earlier treatment was better: within 3 hours (average 2 hours 20 minutes) net benefit was 122 patients (95% CI, 61–171) per 1000 treated, whereas initiating treatment beyond 4.5 hours (mean 5 hours 20 minutes) revealed a net benefit of only 20 patients (95% CI, −31 to 75) per 1000 treated, P=0.45.

Discussion

Patients with acute ischemic stroke show wide variation in the severity and range of their symptoms at presentation. Their functional outcomes are also diverse. The categories of the mRS capture this diversity well. Dichotomization of the scale at mRS score at 0 to 1 (excellent outcome) versus 2 to 6 (poorer outcome) or at 0 to 2 (independent) versus 3 to 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 whether treatment will make a noticeable difference to their functional outcome: many would regard an improvement by any step in mRS level as worthwhile, although 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.

Although all trials except IST-3 excluded patients with the most minor symptoms, 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, although earlier treatment is better and by 4.5 hours, the benefit is becoming small. Although generalizing these findings to those with the most minor symptoms (who were excluded from most trials) should be done with caution, our data cover a range of NIHSS from 4 (mean in bottom fifth of distribution) to 22 (top fifth mean). Within this, the uniformity of the proportional treatment effect across the spectrum of severity suggests a consistent effect. The absolute risk of bleeding is lower among patients with low NIHSS scores. Treatment with intravenous alteplase initiated within 4.5 hours reduces the proportion of patients with mRS score of ≥4: there will be fewer patients who cannot walk independently or require help with basic toileting. We neither found that intravenous alteplase alters mRS score of 0 to 4 versus 5 to 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 (Figures 1 and 2). Thus, intravenous alteplase seems 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, although the odds ratios diminish as the criterion for good outcome drops toward 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 toward 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 shortens the treatment time window for any relative benefit. Note that the 9 trials that we analyzed include many patients who would fall out with the labels for marketing authorizations that apply in the United States, Europe, and many other regions.

Because the magnitude of the treatment effect seems to decrease at higher thresholds (ie, 2 higher dichotomies show no significant benefit from intravenous alteplase irrespective of treatment initiation delay), it was anticipated that the ordinal analysis may not confirm benefit until 4.5 hours. 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 score of 0 to 4 versus 5 to 6 and on survival, there is still a strong trend toward a time-related effect for these mRS divisions, such that the treatment initiated within 3 hours seems more useful than the 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 (Figures IV and V in the online-only Data Supplement) 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.

We also note that the design of the IST differed from other trials in 3 major ways: (1) it was open label treatment, whereas other trials were placebo controlled, (2) it assessed outcome after 6 months, rather than 3 months, and (3) it had a broader eligibility criteria and included patients outside of usual treatment guidelines. However, as previously reported, the results from IST-3 were consistent with those from the other trials, both for measures of benefit and for measures of harm (eg, for mRS, 0–1 versus 2–6, the P value for inconsistency between IST-3 and the other trials was 0.92).[19]

Our current results extend our previous reports[2,19] and are consistent with the conclusions of the individual trials that showed benefit within 4.5 hours of stroke onset, but especially within 3 hours.[12,15] They also support the conclusions of the European Stroke Organisation Guidelines on stroke management.[20] We have not discussed here the early risk of fatal bleeding that is a well-recognized complication of intravenous alteplase treatment,[2,19] because it has an impact neither on assessment of the outcome distribution nor, in the absence of a reliable means of identifying patients who will suffer an unacceptably high risk of bleeding, on the decision to treat. This does not detract from the importance of weighing risks and benefits when counseling patients.

Summary and Conclusions

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

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 with earlier initiation of treatment;
3. neither age nor stroke severity has a detectable impact on the relationship 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 optimize 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.

Figures

Figure 1. Relative odds of a good stroke outcome with alteplase, for each alternative definition of good outcome, among all randomized patients. CI indicates confidence interval. *Estimated from a logistic regression model stratified by trial and adjusted only for treatment allocation. **Primary prespecified modified Rankin Scale comparison. International Stroke Trial-3 (IST-3) applied the Oxford Handicap Scale to patients at 6 months of 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.

Figure 2. 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. CI indicates confidence interval; and mRS, modified Rankin Scale.

Figure 3. Effect of alteplase on any upwards shift in modified Rankin Scale (mRS), by treatment delay. The solid line represents the best linear fit between the log odds ratio for an improved stroke outcome among patients given alteplase compared with patients given control (vertical axis) and treatment delay (horizon-tal 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 International Stroke Trial-3 [IST-3]) had a time from stroke onset to treatment of >6 h. The point at which the estimated treatment effect crosses 1 is, therefore, an extrapolation from the data. CI indicates confidence interval.

Appendix

Included Trials

ATLANTIS A and B: Gregory Albers, James Grotta, Maarten Lansberg, Jean Marc Olivot; ECASS-1, ECASS-2, ECASS-3: Erich Bluhmki, Werner Hacke, Markku Kaste, Kennedy R Lees, Ruediger von Kummer, Danilo Toni, Nils Wahlgren; EPITHET: Stephen Davis, Geoffrey Donnan, Mark Parsons; IST-3: Peter Sandercock, Joanna Wardlaw, Richard Lindley, Gordon Murray, Geoff Cohen, William Whiteley; NINDS A and B: Thomas Brott, James Grotta, Patrick Lyden, John Marler, Barbara Tilley). STT Statistical Analysis Centre and Secretariat: Colin Baigent, Lisa Blackwell, Erich Bluhmki, Kelly Davies, Jonathan Emberson, Heather Halls, Lisa Holland, George Howard, Clare Mathews, Samantha Smith, Kate Wilson.

STT Collaborative Group

Gregory Albers, Colin Baigent, Lisa Blackwell, Erich Bluhmki, Thomas Brott, Geoffrey Cohen, Stephen Davis, Geoffrey Donnan, Jonathan Emberson, James Grotta, Werner Hacke, George Howard, Markku Kaste, Masatoshi Koga, Ruediger von Kummer, Maarten Lansberg, Kennedy R Lees, Richard I Lindley, Patrick Lyden, Gordon Murray, Jean Marc Olivot, Mark Parsons, Peter Sandercock, Barbara Tilley, Danilo Toni, Kazunori Toyoda, Nils Wahlgren, Joanna Wardlaw, William Whiteley, Gregory J del Zoppo.

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Disclosures

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Behring, and he has received grant support within the past 3 years from Haemonetics and Medtronics. Dr Kaste reports fees and expenses from Lundbeck A/S, Mitsubishi Pharma Europe, Siemens AG. R. von Kummer reports fees from H. Lundbeck A/S, Boehringer Ingelheim, Covidien, Brainsgate, Synarc, and Penumbra, Inc. Dr Lindley has received honoraria from Boehringer Ingelheim, Covidien, and Pfizer for lectures given in the past 3 years. P.A.G. Sandercock has received honoraria for lectures, which were paid to the department from Boehringer Ingelheim. Dr Toni reports hono¬raria from Boehringer Ingelheim, Bayer, and Pfizer. Dr Toyoda has received research grant support from the Japan Agency for Medical Research and Development, and fees from Mitsubishi Tanabe Pharma. Dr Wardlaw declares trial funding from the Medical Research Council, Efficacy and Mechanism Evaluation Programme, Stroke Association and Health Foundation. Dr Whiteley is funded by a Medical Research Council Clinician Scientist Fellowship (G0902303). Dr Hacke reports honoraria from Boehringer Ingelheim, Daiichi Sankyo, and Bayer, receipt of an unrestricted research grant from Boehringer Ingelheim to perform the European Cooperative Acute Stroke Study 4 (ECASS 4) EXTEND trial, and past chairmanship of the ECASS 1–3 thrombolysis trials. The other authors report no conflicts.

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Table 1: Baseline Characteristics of Included Trials

Variable	NINDS A	NINDS B	ECASS I	ECASS II	ATLANTIS A	ATLANTIS B	ECASS III	EPITHET	IST-3	TOTAL
Number randomized	291	333	620	800	142	613	821	101	3035	6756
Alteplase	144 (49%)	168 (50%)	313 (50%)	409 (51%)	71 (50%)	301 (49%)	418 (51%)	52 (51%)	1515 (50%)	3391 (50%)
Control	147 (51%)	165 (50%)	307 (50%)	391 (49%)	71 (50%)	312 (51%)	403 (49%)	49 (49%)	1520 (50%)	3365 (50%)
Treatment delay (hours)	2.0 (0.6)	2.0 (0.6)	4.4 (1.1)	4.3 (1.1)	4.3 (1.1)	4.4 (0.8)	4.0 (0.4)	4.9 (0.8)	4.2 (1.2)	4.0 (1.2)
>0, ≤3	290 (>99%)	333 (100%)	87 (14%)	158 (20%)	22 (15%)	39 (6%)	-	-	620 (20%)	1549 (23%)
>3, ≤4.5	1 (<1%)	-	233 (38%)	265 (33%)	53 (37%)	249 (41%)	788 (96%)	31 (31%)	1148 (38%)	2768 (41%)
>4.5	-	-	295 (48%)	370 (46%)	67 (47%)	321 (52%)	6 (1%)	69 (68%)	1266 (42%)	2394 (35%)
Missing	-	-	5 (1%)	7 (1%)	-	4 (1%)	27 (3%)	1 (1%)	1 (<1%)	45 (1%)
Age (years)	66 (11)	68 (12)	65 (12)	66 (11)	66 (13)	66 (11)	65 (12)	72 (13)	77 (12)	71 (13)
≤ 80	279 (96%)	289 (87%)	615 (>99%)	792 (99%)	142 (100%)	608 (>99%)	805 (98%)	76 (75%)	1418 (47%)	5024 (74%)
>80	12 (4%)	44 (13%)	5 (1%)	8 (1%)	-	3 (<1%)	15 (2%)	25 (25%)	1617 (53%)	1729 (26%)
Missing	-	-	-	-	-	2 (<1%)	1 (<1%)	-	-	3 (<1%)
Stroke severity (NIHSS)	14 (7)	15 (7)	12 (6)	12 (6)	13 (7)	11 (6)	10 (5)	13 (6)	12 (7)	12 (7)
>0, ≤4	16 (5%)	13 (4%)	34 (5%)	47 (6%)	10 (7%)	47 (8%)	98 (12%)	1 (1%)	400 (13%)	666 (10%)
>4, ≤10	78 (27%)	98 (29%)	189 (30%)	339 (42%)	57 (40%)	279 (46%)	389 (47%)	40 (40%)	1064 (35%)	2533 (37%)
>10, ≤15	68 (23%)	63 (19%)	183 (30%)	232 (29%)	28 (20%)	128 (21%)	163 (20%)	22 (22%)	601 (20%)	1488 (22%)
>15, ≤21	76 (26%)	78 (23%)	146 (24%)	113 (14%)	25 (18%)	106 (17%)	142 (17%)	29 (29%)	618 (20%)	1333 (20%)
>21	45 (15%)	74 (22%)	28 (5%)	43 (5%)	20 (14%)	33 (5%)	18 (2%)	9 (9%)	352 (12%)	622 (9%)
Missing	8 (3%)	7 (2%)	40 (6%)	26 (3%)	2 (1%)	20 (3%)	11 (1%)	-	*	114 (2%)
Female	120 (41%)	142 (43%)	231 (37%)	331 (41%)	45 (32%)	250 (41%)	325 (40%)	43 (43%)	1570 (52%)	3057 (45%)
History of hypertension	188 (65%)	220 (66%)	258 (42%)	412 (52%)	87 (61%)	364 (59%)	514 (63%)	71 (70%)	1954 (64%)	4068 (60%)
History of stroke	49 (17%)	34 (10%)	83 (13%)	158 (20%)	31 (22%)	89 (15%)	89 (11%)	11 (11%)	699 (23%)	1243 (18%)
History of diabetes mellitus	64 (22%)	67 (20%)	81 (13%)	169 (21%)	27 (19%)	130 (21%)	129 (16%)	23 (23%)	388 (13%)	1078 (16%)
History of atrial fibrillation	55 (19%)	60 (18%)	113 (18%)	188 (24%)	37 (26%)	97 (16%)	108 (13%)	42 (42%)	914 (30%)	1614 (24%)
Antiplatelet use	78 (27%)	93 (28%)	87 (14%)	196 (25%)	59 (42%)	211 (34%)	201 (24%)	30 (30%)	1306 (43%)	2261 (33%)
Weight (kg)	78 (17)	78 (19)	74 (12)	75 (14)	80 (20)	79 (18)	78 (15)	75 (19)	72 (15)	75 (16)
Systolic blood pressure (mmHg)	154 (21)	152 (21)	154 (23)	152 (21)	152 (24)	152 (21)	153 (21)	148 (19)	155 (24)	154 (22)
Diastolic blood pressure (mmHg)	85 (13)	85 (14)	87 (13)	84 (13)	81 (14)	82 (14)	84 (14)	78 (13)	82 (15)	83 (14)

Categorical data presented as n (%), continuous data presented as mean (SD). NINDS=National Institute of Neurological Disorders and Stroke; ECASS=European Cooperative Acute Stroke Study; ATLANTIS=Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; EPITHET=Echoplanar Imaging Thrombolytic Evaluation Trial; IST=International Stroke Trial. *In IST-3, 244 patients had their baseline NIHSS score predicted from other measurements recorded at their baseline assessment. Ignoring these patients, the numbers of IST-3 patients in each category of baseline NIHSS score above would be 385, 972, 531, 559 and 344 respectively.

Figure 1

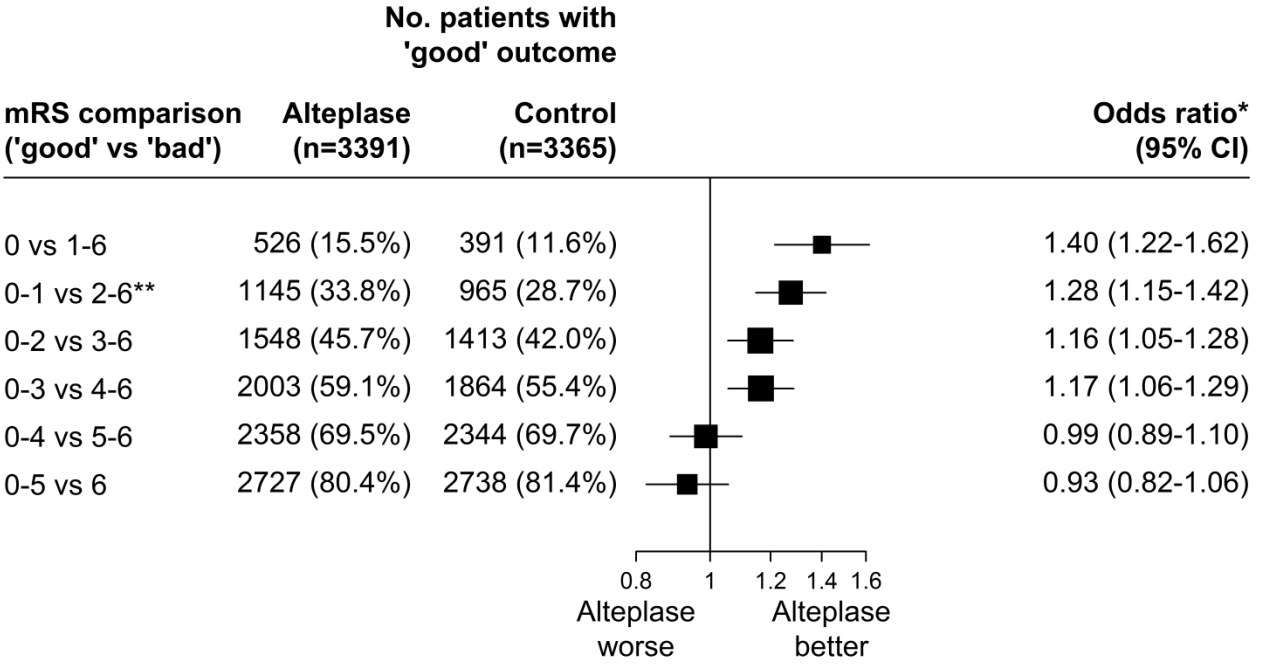

No. patients with 'good' outcome
mRS comparison ('good' vs 'bad')
Alteplase (n=3391)
Control (n=3365)
Odds ratio* (95% CI)
0 vs 1-6
526 (15.5%)
391 (11.6%)
1.40 (1.22-1.62)
0-1 vs 2-6**
1145 (33.8%)
965 (28.7%)
1.28 (1.15-1.42)
0-2 vs 3-6
1548 (45.7%)
1413 (42.0%)
1.16 (1.05-1.28)
0-3 vs 4-6
2003 (59.1%)
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 worse
Alteplase better

Figure 2

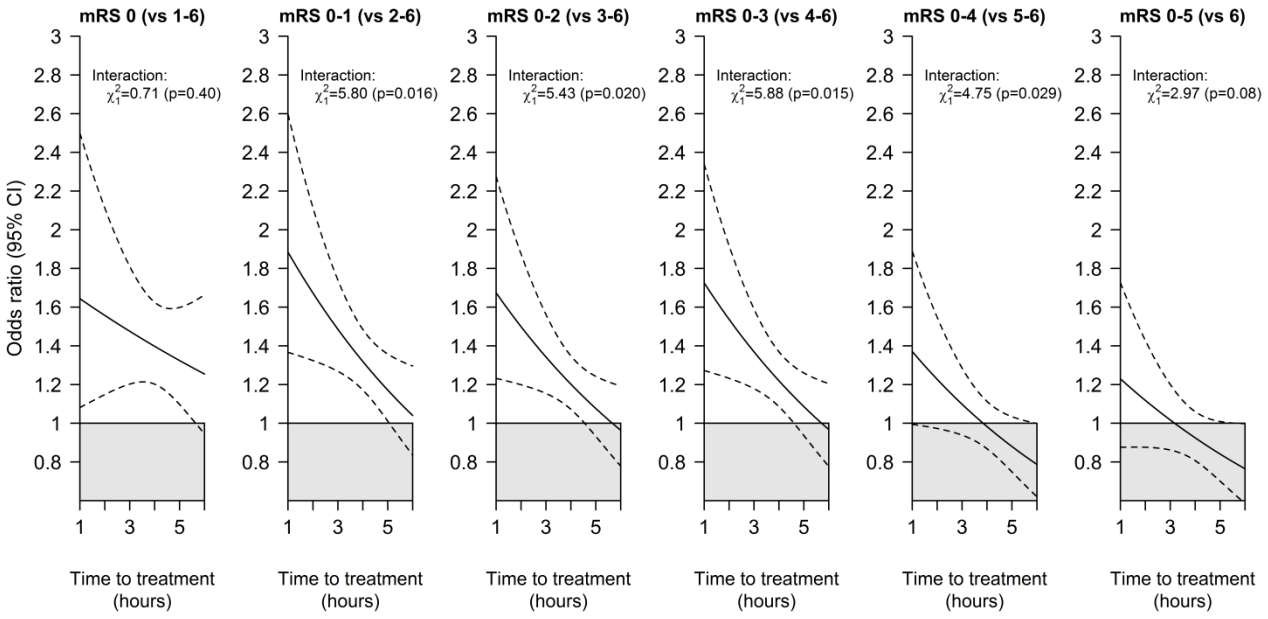
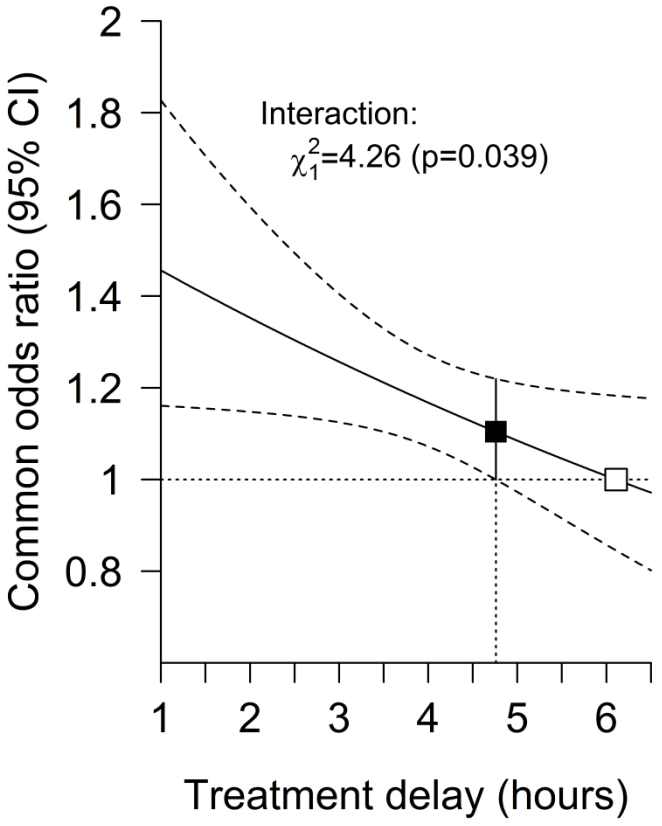

mRS 0 (vs 1-6)
Interaction: χ^2_1=0.71 (p=0.40)
mRS 0-1 (vs 2-6)
Interaction: χ^2_1=5.80 (p=0.016)
mRS 0-2 (vs 3-6)
Interaction: χ^2_1=5.43 (p=0.020)
mRS 0-3 (vs 4-6)
Interaction: χ^2_1=5.88 (p=0.015)
mRS 0-4 (vs 5-6)
Interaction: χ^2_1=4.75 (p=0.029)
mRS 0-5 (vs 6)
Interaction: χ^2_1=2.97 (p=0.08)
Odds ratio (95% CI)
Time to treatment (hours)

Figure 3


Common odds ratio (95% CI)
2
1.8
1.6
1.4
1.2
1
0.8
Interaction:
χ^2_1=4.26 (p=0.039)
1
2
3
4
5
6
Treatment delay (hours)