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Title: What are the risks of intracerebral haemorrhage due to alteplase after acute ischaemic stroke? Results from an individual patient data meta-analysis of randomised trials

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Abstract: Background: Randomised trials have shown that alteplase improves the odds of a good stroke outcome when delivered within 4.5 hours of acute ischaemic stroke. Alteplase also increases the risk of intracerebral haemorrhage, but the factors determining the proportional and absolute risks are uncertain.
Methods: We used data from the Stroke Thrombolysis Trialists' (STT) meta-analysis of individual patient data from 9 randomised trials of alteplase versus placebo (or open control) involving 6,756 patients. We pre-specified assessment of 3 definitions of intracerebral haemorrhage: type 2 parenchymal haemorrhage (PH-2) within 7 days; SITS-MOST haemorrhage within 24-36 hours (PH-2 with at least 4 point deterioration in NIHSS); and fatal intracerebral haemorrhage within 7 days. We used logistic regression, stratified by trial, to model the log odds of intracerebral haemorrhage on allocation to alteplase, treatment delay, age, and stroke severity. Exploratory analyses assessed mortality after intracerebral haemorrhage and examined the absolute risks of intracerebral haemorrhage in the context of functional outcome at 90-180 days.
Findings: Alteplase increased the odds of PH-2 haemorrhage (231/3391 [6.8%] among patients allocated alteplase vs 44/3365 [1.3%] among patients allocated control; odds ratio [OR] 5.55, 95% CI 4.01-7.70; absolute excess 5.5% [95% CI 4.6% - 6.4%]); SITS-MOST haemorrhage (124/3391 [3.7%] vs 19/3365 [0.6%]; OR 6.67, 4.11-10.84; absolute excess 3.1% [2.4% - 3.8%]); and of fatal intracerebral haemorrhage (91/3391 [2.7%] vs 13/3365 [0.4%]; OR 7.14, 3.98-12.79; absolute excess 2.3% [1.7% - 2.9%]). However defined, the proportional increase in intracerebral haemorrhage was similar irrespective of treatment delay, age or baseline stroke severity, but the absolute excess risk of intracerebral haemorrhage increased with increasing stroke severity: for SITS-MOST intracerebral haemorrhage the absolute excess risk ranged from 1.5% (95% CI 0.8-2.6%) for strokes with NIHSS 0-4 to 3.7% (95% CI 2.1-6.3%) for

NIHSS ≥22 (trend p=0.01). For those treated within 4.5 hours, the absolute increase in the proportion (6.8%) achieving a modified Rankin score of 0 or 1 (excellent outcome) exceeded the absolute increase in risk of fatal intracerebral haemorrhage (2.2%) and the increased risk of any death within 90 days (0.9%).
Interpretation: Among patients treated with alteplase the net outcome is predicted both by time to treatment (with faster time increasing the proportion achieving an excellent outcome) and stroke severity (with more severe stroke increasing the absolute risk of intracerebral haemorrhage). Although, on average, within 4.5 hours of stroke, the probability of achieving an excellent outcome clearly exceeds the risk of death, early treatment is especially important for those with severe strokes.

What are the risks of intracerebral haemorrhage due to alteplase after acute ischaemic stroke? Results from an individual patient data meta-analysis of randomised trials

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Abstract

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Introduction

The Stroke Thrombolysis Trialists' (STT) Collaboration has previously shown, in a meta-analysis of individual participant data from 9 trials of alteplase versus placebo (or open control), that alteplase significantly improves the odds of an excellent outcome (i.e., a modified Rankin score [mRS] of 0 or 1) when delivered within 4.5 hours of the onset of ischaemic stroke.[1] However, alteplase increases the risk of intracerebral haemorrhage within 48 hours of administration,[1] and variations in the absolute risks of such haemorrhage according to clinical presentation (eg, stroke severity) may influence the longer term outcome. Recent commentaries have drawn attention to a lack of reliable information about the hazards of alteplase and how they relate to benefits among different groups of patients, particularly those presenting more than 3 hours after stroke onset.[2,3] In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) expert working group considered, in strict confidence, these analyses from the STT Collaboration on the benefits and risks of alteplase as part of its review of the market authorisation for alteplase in acute ischaemic stroke.[4]

Since there are strong inter-relationships between prognostic variables among the trials included in the STT database (for example, patients treated earlier tended to be older and to have had more severe strokes), an assessment of benefit and harm can only be performed reliably using multivariable models applied to individual participant data. The STT's published protocol[5] outlined a range of secondary analyses that were to be conducted in addition to the main analysis.[1] The aim of the present report is to describe the results of secondary analyses assessing the proportional and absolute effects of alteplase on the risk of intracerebral haemorrhage and of mortality in different types of patients. We also explore how such variations might influence the net effects of alteplase by 90-180 days after stroke.

Methods

Study design

The methods of the Stroke Thrombolysis Trialists' (STT) Collaboration have been described in detail in the published protocol[5] and in the main report of the primary analysis.[1] Briefly, we sought individual participant data from all completed randomised phase 3 trials of intravenous alteplase in acute ischaemic stroke. Since a systematic review of trials of thrombolysis had been updated in 2013 [6] we identified potentially eligible trials from that review and by enquiry among active trialists and the manufacturer of alteplase used in all participating trials (Boehringer Ingelheim, Ingelheim, Germany).[5] We analysed participants in the group to which they were randomly allocated ('intention to treat').

Outcomes

The main outcome of interest in the current analysis was intracerebral haemorrhage, which was defined in three ways:

(i) *parenchymal haemorrhage type 2 (PH-2) by 7 days after randomisation*: defined as dense blood clot(s) exceeding 30% of the infarct volume with significant space-occupying effect seen on brain imaging, whether within or remote from the infarct.[7] For patients from IST-3,[8] in which PH-2 defined solely on radiological findings was not a pre-specified secondary outcome, we approximated it by a report from the IST-3 blinded CT-reading panel of 'significant brain parenchymal haemorrhage, local or remote from the infarct, or significant diffuse haemorrhagic transformation of an infarct on brain imaging';

(ii) *Safe Implementation of Thrombolysis in Stroke Monitoring Study's (SITS-MOST) haemorrhage*[9] defined as PH-2 on imaging with an increase of 4 NIHSS points or more from baseline (or the lowest point in the first 24 hours) or that led to death within 36 hours of treatment. In the third international stroke trial (IST-3), we approximated the SITS-MOST definition by the occurrence within 24 hours of 'clinically significant deterioration or death, together with evidence of either significant brain parenchymal haemorrhage (local or distant from the infarct) or significant haemorrhagic transformation of an infarct on brain imaging which, in the judgement of the blinded adjudication panel, was likely to have worsened mass effect or contributed to the burden of brain damage'; and

(iii) *fatal intracerebral haemorrhage*, defined as PH-2 (or its approximation in IST-3) confirmed by imaging (or autopsy) and death within 7 days of randomisation.

The timing of brain imaging to detect intracerebral haemorrhage varied slightly across the participating trials. The protocol of each trial mandated imaging at approximately 24 hours post-randomisation and additional brain imaging if neurological deterioration occurred. Further routine brain imaging was performed at 3-5 days in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET),[10] at 1 week in National Institutes of Neurological Diseases and Stroke (NINDS) A and B[11] and in European Cooperative Acute Stroke Study (ECASS) I, II, and III;[7,12,13], and at 23-37 days in Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischemic Stroke (ATLANTIS) A and B.[14,15]

Analyses of the effect of alteplase on death from all causes within 90 days, both overall and when separated by period of follow-up and treatment delay, have been published previously.[1] In post-hoc analyses of mortality for the current analysis, we subclassified deaths as: "deaths preceded by clinically significant intracerebral haemorrhage" (defined as fatal ICH within 7 days or death following SITS-MOST haemorrhage), and all other deaths.

We analysed the modified Rankin score (mRS) to define stroke outcome at 3-6 months. We defined an 'excellent' stroke outcome as mRS of 0–1 (ie, symptom-free or residual symptoms with no loss of activity), and a very poor stroke outcome as mRS of 5–6 (i.e. bed-bound or dead) at 3–6 months. In IST-3, mRS was reported at 6 rather than 3 months. Therefore, for consistency between the previously published analyses of 90-day mortality and the odds ratio estimates for mRS 0-5 vs 6 in the current analysis, we made the simplifying assumption that IST-3 patients who died between 91 days and 6 months (125 [4.1%] IST-3 participants) had an mRS of 5 at 90 days. [1]

Statistical analysis

We used logistic regression, stratified by trial, to model the common linear dependence of the log odds of intracerebral haemorrhage on allocation to alteplase, treatment delay, age, baseline stroke severity (National Institutes of Health Stroke Scale [NIHSS]) and interactions between allocation to alteplase and each of these other baseline covariates. Alternative hierarchical models that allowed for random effects to operate at the trial level gave virtually identical results. Treatment delay, age and stroke severity were all handled as linear variables. Analyses that considered quadratic risk-relationships for stroke severity were not informative over the models that simply considered a linear term, and are therefore not reported. In addition to such 'continuous' analyses, regression

models that handled each baseline covariate in pre-defined categories of treatment delay (≤3.0 hours, >3 to ≤4.5 hours, >4.5 hours), age (≤80, >80 years) and stroke severity (NIHSS ≤4, 5-10, 11-15, 16-21, ≥22) were also employed. Missing 6 month modified Rankin data in IST-3 were imputed from seven-day assessments using an algorithm that was found to work well among patients who had both measurements.[5] Assessment of whether treatment delay, age, stroke severity or trial modified (individually or jointly) the overall effect of alteplase on particular outcomes was based on the statistical significance of the relevant treatment interactions using likelihood ratio tests (i.e. through comparison of minus twice the log-likelihood statistic between appropriate "nested" models). Trial-by treatment interactions were used to assess whether there were important differences in the odds of intracerebral haemorrhage with alteplase between the 9 trials, and between IST-3 (with open control) and all other (placebo-controlled) trials combined.

Kaplan-Meier cumulative mortality curves during the first 90 days were calculated for patients allocated alteplase and patients allocated control (crudely pooling across all trials). Subsequently, trial-stratified Cox regression was used to estimate the average mortality hazard ratio within 90 days for 'deaths preceded by clinically significant intracerebral haemorrhage' and for all other deaths, with the time to event/censoring for both outcomes set as the earliest of day 90 or the date of death.

Stroke severity and treatment delay are both important determinants of stroke outcome for patients given alteplase. However, as previously reported, stroke severity and treatment delay were correlated in the included trials.[1] Therefore, to prevent treatment delay from confounding the observed mRS distribution when treated patients were subdivided by their baseline stroke severity (NIHSS ≤4; 5-10; 11-15; 16-21 and ≥22), we compared, for each baseline NIHSS group, the observed mRS distribution for control patients with the *expected* distribution if given alteplase within 3 or within 4.5 hours. This expected distribution was obtained by applying the *overall* odds ratios for each mRS dichotomy (ie, mRS 0 vs 1-6, mRS 0-1 vs 2-6, etc.) within a given time window (≤4.5 hours, <3 hours or 3-4.5 hours) to the *observed* mRS distribution at 3-6 months among control-allocated patients. Similarly, the estimates of absolute excess risk subdivided by a given characteristic (treatment delay, age or stroke severity) were obtained by applying the overall odds ratio estimates (and their confidence limits) to the control rates that *would have been expected* for that subgroup had average levels of the other two characteristics applied.

All estimates of treatment effect are provided with their 95% confidence intervals with p-values considered conventionally statistically significant, without allowance for multiple testing, at the 5% significance level. Analyses were done with SAS version 9.3 (SAS Institute, Cary) and R version 2.11.1 (www.R-project.org).

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The secretariat had full access to all the data and responsibility for the decision to submit for publication.

Results

Data were available from 6756 participants in 9 trials of intravenous alteplase versus control (webtable 1). Baseline data on treatment delay, age and baseline NIHSS were complete for almost all participants (6602/6756, 98%). Individual participant data were sought from an additional 5 trials[16–20] involving 270 participants, which reported a total of 18 patients with intracerebral haemorrhage (11 alteplase versus 7 control), but were either not available or, in one case,[18] the authors could not be contacted.

Overall, 275 participants had a PH-2 haemorrhage within 7 days of treatment (38% [39% alteplase vs 30% control] fatal within 7 days), of which 52% were SITS-MOST haemorrhages (41% [40% vs 47%] fatal within 7 days). After adjusting for age, treatment delay and stroke severity, alteplase increased the odds of intracerebral haemorrhage by a factor of about 6 to 7, depending on the definition used: PH-2 haemorrhage: 231/3391 (6.8%) vs 44/3365 (1.3%); OR 5.55, 95% CI 4.01–7.70; SITS-MOST haemorrhage 124/3391 (3.7%) vs 19/3365 (0.6%); OR 6.67, 4.11–10.84; and fatal intracerebral haemorrhage within 7 days 91/3391 (2.7%) vs 13/3365 (0.4%); OR 7.14, 3.98–12.79 (figure 1). These odds ratios were similar after adjusting for other baseline variables recorded and available in the data provided (prior stroke/TIA, prior diabetes, antiplatelet use, weight and systolic blood pressure at randomisation, data not shown). There was no evidence that the odds ratios for any of the definitions of intracerebral haemorrhage differed between trials, or between IST-3 (which had open control) and the 8 placebo-controlled trials (all heterogeneity p-values >0.05, webfigure 1). The proportion of patients with PH-2 haemorrhages who died by 7 days was also similar in IST-3 (62/159, [39%]) and in the other 8 (placebo-controlled) trials (42/116, [36%]).

For each type of intracerebral haemorrhage, the proportional effects of alteplase were similar irrespective of time to treatment, age or stroke severity (webfigures 2-4; p-values for interaction all >0.05). The estimated absolute excess risks were similar irrespective of time to treatment and age,

but there was a trend towards larger absolute excess risks with increasing stroke severity for PH-2 haemorrhage (p<0.0001; webfigure 5), fatal intracerebral haemorrhage (p=0.0002; webfigure 6) and SITS-MOST haemorrhage (p=0.0101; figure 2). For SITS-MOST intracerebral haemorrhages (ie, clinically significant bleeds in which there was both radiological evidence of bleeding and worsening symptoms within 24-36 hours after treatment), the absolute excess risk over control increased from 1.5% (95% CI 0.8-2.6%) among those with mild strokes (baseline NIHSS 0–4) to 3.7% (95% CI 2.1-6.3%) in patients with NIHSS ≥22 (figure 2).

Cause of death was not widely available in participating trials, but we conducted exploratory analyses to assess the 90-day risks of 'death preceded by clinically significant intracerebral haemorrhage' and of all other deaths. Among all trial participants, allocation to alteplase was associated with a significant increase in the risk of a death preceded by clinically significant intracerebral haemorrhage within 90 days (118 [3.5%] vs 14 [0.4%]; HR 8.52, 4.89-14.82; figure 3). Such deaths were, however, offset by non-significantly fewer deaths among people dying who had not experienced such a haemorrhage (490 [14.5%] vs 542 [15.9%]; HR 0.92, 95% CI 0.82-1.04; figure 3). An analysis that defined clinically significant haemorrhage by the radiological appearance of a PH2 haemorrhage, rather than by the SITS-MOST definition, gave similar results (webfigure 8).

Since the estimated absolute excess risk of intracerebral haemorrhage increased incrementally within the 5 pre-specified categories of stroke severity, we assessed the impact of this trend on the expected distribution of mRS scores at 90 days among all patients treated within 4.5 hours (on average, at 3 hours and 20 minutes) by applying the odds ratio for each mRS transition to the control population (figure 4 and 5). Among patients with the mildest strokes (NIHSS 0–4), alteplase would be expected to result in an absolute increase in excellent outcome of 8.0% (95% CI 4.5-11.1), and to reduce the absolute risk of very poor outcome by 0.1% (95% CI -0.6-0.8; 0.3% reduction in severe disability [mRS 5] and 0.2% excess of death). For the most severe strokes (NIHSS ≥22), the

corresponding amounts were a 1.0% (95% CI 0.5-1.5) absolute increase in excellent outcome and a 0.6% reduction in very poor outcome (95% CI -2.3-4.1; 2.8% reduction in severe disability and 2.1% excess of death).

Discussion

Within the 9 trials studied, alteplase resulted in approximately 6 to 7 times the odds of intracerebral haemorrhage within the first 7 days, which was similar irrespective of treatment delay, age and stroke severity. In these trials the underlying risk of intracerebral haemorrhage without alteplase increased with stroke severity, which is consistent with a systematic review of 55 observational studies in which each 1 point increment in the NIHSS was associated with an 8% (95% CI 6-11%) increase in the odds of intracerebral haemorrhage ($p<0.001$).[21] In the absence of heterogeneity of the odds ratio for haemorrhage, therefore, the absolute excess risk of intracerebral haemorrhage was higher among those with more severe strokes. Overall, among all patients, alteplase resulted in a 2.3% absolute excess of fatal intracerebral haemorrhage during the first week (Figure 1). After the first week, deaths preceded by ICH remained elevated among those allocated alteplase (Figure 3), perhaps due to conditions associated with chronic immobility (eg pneumonia). By contrast, during the first 90 days, there were non-significantly fewer other deaths among alteplase-allocated patients, perhaps owing to the beneficial effects of alteplase on functional outcome.

Taken together, the present analyses and our previous report show that, when given within 4.5 hours, alteplase is associated with an early hazard due to intracerebral haemorrhage but a later benefit in terms of less disability, and this study raises the hypothesis that there is a lower risk of death among those not experiencing an intracerebral haemorrhage. This pattern is analogous to many surgical procedures, eg carotid endarterectomy, where there is an early surgical hazard followed by a later survival benefit in selected patients[22,23] and the balance of hazard and benefit among particular types of patients determines their net clinical outcome.

The net effects of alteplase among particular types of patients are best represented by the predicted shift in the distribution of modified Rankin Scores among patients allocated to alteplase and control.

Our previous analyses indicated that the benefits of alteplase diminish with increasing treatment delay, whilst the present analyses indicate that the absolute excess risk of intracerebral haemorrhage increases with stroke severity. Our exploratory analyses suggest that these two variables help determine the net effects of alteplase in particular patients. In particular, they may help to explain the observation in our previous report[1] that there was a non-significant trend towards a larger relative increase in 90 day mortality among those treated later. Although there were limited data in the 3-4.5 hour group, it may be hypothesised that the observed patterns are due to the shifting balance between (i) an early increase in mortality from intracerebral haemorrhage (which is of similar magnitude irrespective of delay) and (ii) reduced mortality due to salvaged brain tissue among those treated early, with the magnitude of this benefit diminishing as delay increases (ie, 'time is brain').

There is a need for improved representations of the benefits and risks of alteplase, building on those developed previously[24–27], to better equip clinicians in discussions with patients and their family members. Figure 4 and webfigures 7a and 7b have the inherent limitation that they do not directly represent the additional risks of fatal intracerebral haemorrhage. An alternative example of a possible representation of the expected effects of alteplase on the distribution of mRS scores, subdivided by stroke severity, is shown in Figure 5. Each cell represents a hypothetical group of 100 typical patients with an ischaemic stroke of given severity, with colours indicating a gradation of mRS scores at 3-6 months after stroke from excellent outcome (red circles, mRS 0-1) through to very poor outcome (mRS 5-6). Fatal intracerebral haemorrhage is marked by a purple circle with a cross. From this figure, a patient can see, in their particular case, the expected impact of being given alteplase, since a comparison of left (untreated) and right (treated) cells shows both the expected shift in mRS outcomes and the risk associated with intracerebral haemorrhage. Further development and refinement of the representation in figure 5 is now needed to provide a useful tool for clinicians.

Recent trials have demonstrated that intra-arterial thrombectomy in addition to intravenous thrombolysis leads to improved outcomes[28–32] among those with large artery ischaemic stroke and documented proximal arterial occlusion, which may help to improve the ratio of benefit to risk by magnifying benefit through improved salvage of brain tissue. Alternatively, it may be possible to improve this ratio by reducing the risk of intracerebral haemorrhage with intravenous thrombolytic therapy, for example, by the use of tenecteplase as an alternative to alteplase[33,34], use of a lower dose of alteplase (0.6mg/kg),[35] or by targeting thrombolysis based on neuroimaging appearances.[31]

Although our analyses provide a general guide to the effects of alteplase in different types of patients, there are a number of potential limitations: First, and most importantly, despite having access to individual participant data from 9 trials in almost 7000 patients with acute ischaemic stroke, there were relatively small numbers of outcomes with which to examine treatment effects in different patient subgroups.[32] Whilst recognising that there is a need to provide better information for doctors and patients, it is important that treatment decisions take account both of statistical uncertainty and of the possibility that different patients and their families may reach different decisions when presented with the same data on expected outcomes. The second limitation was that the methods employed by the Third International Stroke Trial (IST-3) differed in several respects to the other trials. It lacked a placebo control, raising the potential of biased reporting if there was a greater tendency to investigate possible intracerebral haemorrhage in the alteplase arm. However, alteplase increased the odds of intracerebral haemorrhage to a similar extent in IST-3 and in other trials (webfigure 1), suggesting that any bias due to the open nature of IST3 was small. The IST3 trial also did not record PH-2 haemorrhages or SITS-MOST haemorrhages, but defined equivalent categories. In the future, any such limitations caused by different symptomatic haemorrhage

definitions and classifications may be mitigated by the use of the recent Heidelberg classification of intracerebral bleeding events.[39]

A third limitation was that we did not have cause of death available, but could only examine the effects of alteplase on deaths that followed a haemorrhage. Our data strongly suggest, however, that most early deaths following a PH2 haemorrhage were likely to be due to the haemorrhage. In particular, the increased risk of death from any cause by 7 days (absolute excess 2.2%)[1] is virtually identical to the increased risk of those deaths that followed a PH2 haemorrhage (2.3%) (Figure 1). In addition, death preceded by clinically significant haemorrhage remained elevated after the first week (Figure 3). The most likely explanation for these large mortality differences is that haemorrhage led to death in almost all such cases (either directly, or after withdrawal of medical intervention), since the alternative explanation – that alteplase-allocated patients were at least 7 times more likely than control-allocated patients to die from causes unrelated to the bleed – seems highly implausible given their similar prognostic scores at randomization and the lack of any other known hazard of alteplase.

Finally, we were limited in the extent to which we could evaluate the effect of other potential risk factors, such as blood glucose and blood pressure control, that have previously been associated with increased bleeding risk after alteplase administration, and nor could we assess the effects of alteplase on less severe intracerebral haemorrhage since the requisite data were not consistently available.

Conclusion

Although alteplase increases the early risk of haemorrhagic stroke, when given within 4.5 hours the proportion of patients experiencing an excellent outcome exceeded the proportion dying from intracerebral haemorrhage. The greatest absolute risk of intracerebral haemorrhage after alteplase is experienced by those with the most severe strokes, among whom prompt treatment is essential in order to achieve worthwhile benefit.

Contributors

WH and EB had the original idea for this meta-analysis and implemented data definitions in 2004; KRL and EB refined the approach in 2010; CB, PS, and JW had the idea for this cycle of the meta-analysis and all authors contributed to the subsequent study protocol and statistical analysis plan. All authors contributed either to the acquisition of the original trial data or the creation of the combined dataset. JE and LB did the statistical analysis. WW wrote the first draft of the report. All authors contributed to the interpretation of the results, revision of the report, and have approved the final version of the manuscript.

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 Lees, Rüdiger von Kummer, Danilo Toni, Nils Wahlgren); EPITHET (Stephen Davis, Geoffrey Donnan, Mark Parsons); IST-3 (Peter Sandercock, Joanna Wardlaw, Richard Lindley, Geoff Cohen, William Whiteley); NINDS A and B (Thomas Brott, James Grotta, Patrick Lyden).

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.

Declaration of interests

CB, LB, and JE have not accepted fees, honoraria, or paid consultancies but are involved in clinical trials of lipid-modifying treatment funded by Merck to the University of Oxford, with the University the trial sponsor in all cases. KRL has received speaker fees from and has served on the data monitoring committee of trials for Boehringer Ingelheim; his department has received research grant support from Genentech. GA has received research grant support from Lundbeck, fees for consultancy and advisory board membership from Lundbeck, Covidien, Codman, and Genentech, fees for acting as an expert witness, and owns stock in iSchemaView. EB is employed by Boehringer Ingelheim. SD has received honoraria from Boehringer Ingelheim, EVER Pharma, and Sanofi and has received fees for consultancy and advisory board membership from Boehringer Ingelheim and Sanofi. GD has received research grant support from the NHMRC (Australia) and honoraria from Pfizer and Bristol-Myers Squibb. JG has received fees for consultancy and advisory board membership from Lundbeck. RvK has received speaker fees and honoraria from Penumbra and Lundbeck. RIL has received honoraria from Boehringer Ingelheim and Covidien. JMO has received speaker fees from Boehringer Ingelheim. MP has received travel support from Boehringer Ingelheim. DT has received speaker fees and fees for consultancy and advisory board membership from Boehringer Ingelheim and Bayer. KT has received research grant support from the Ministry of Health, Labour, and Welfare of Japan, and speaker fees from Mitsubishi Tanabe Pharma. JW has received research grant support from the UK Medical Research Council and from Boehringer Ingelheim to the University of Edinburgh for a research scanner bought more than 10 years ago. NW is chairman of SITS International which receives an unrestricted grant from Boehringer Ingelheim. WW has received research grant support from the UK Medical Research Council. PS has received honoraria for lectures which were paid to the department from Boehringer Ingelheim. WH has received research grant support from Boehringer Ingelheim, and speaker fees and fees for consultancy and advisory board membership from Boehringer Ingelheim. PL, TB, GC, GH, MKa, MKo, ML, NW, and GJdZ declare no competing interests.

Acknowledgments

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Figure legends

Figure 1: The effect within 7 days of alteplase on three types of intracerebral haemorrhage (ICH): parenchymal haemorrhage type 2 (PH-2), SITS-MOST haemorrhage, and fatal ICH.

Figure 2: The effect of alteplase on SITS-MOST intracerebral haemorrhage at 24 to 36 hrs by time to treatment, age and stroke severity.

Figure 3 The effect of alteplase on deaths following clinically significant intracerebral haemorrhage (fatal haemorrhage within 7 days or death following SITS-MOST haemorrhage), and all other deaths, during the first 90 days, overall and by period of follow up.

Figure 4 Expected proportions in each category of modified Rankin score at 3—6 months, with or without alteplase given within 4.5 hours of symptom onset. mRS 0–1 indicates survival symptom-free or with residual symptoms with no loss of activity; mRS 5-6 indicates bed-bound or dead at 3–6 months.

Figure 5 Expected stroke outcome at 3-6 months for groups of patients: i) not treated with alteplase; ii) treated with alteplase within 3 hours of stroke onset; and iii) treated with alteplase between 3 and 4.5 hours after stroke onset. mRS 0–1 indicates survival symptom-free or residual symptoms with no loss of activity; mRS 5-6 indicates bed-bound or dead at 3–6 months.

Research in Context

Evidence before this study

Meta-analyses have previously shown that alteplase increases the risk of intracerebral haemorrhage, but the extent to which the absolute excess risk differs by haemorrhage type, stroke severity, age, or treatment delay was uncertain, as was the balance between the risk of intracerebral haemorrhage and treatment benefit in different patients. We used individual participant data from 9 trials of alteplase versus control in the Stroke Thrombolysis Trialists' Collaboration to provide meta-analyses of the available evidence.

Added value of this study

This study provides estimates of symptomatic intracerebral haemorrhage risk, and benefits due to alteplase, in patients grouped by stroke severity, age and treatment delay. With the individual participant data, we were able to adjust for complex inter-correlations between variables to produce reliable estimates of absolute treatment effects.

Implications of all the available evidence

The absolute benefits of alteplase decline with treatment delay, and the absolute harms due to alteplase (from intracranial haemorrhage) increase with stroke severity. When delivered within 4.5 hours, the proportion of patients experiencing a good outcome exceeds those dying from intracranial haemorrhage. However, because the risk of haemorrhage is highest in those with the most severe stroke, prompt treatment of these patients is especially important. These absolute risk estimates will be useful to communicate the effects of alteplase to patients, families and clinicians.

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Table

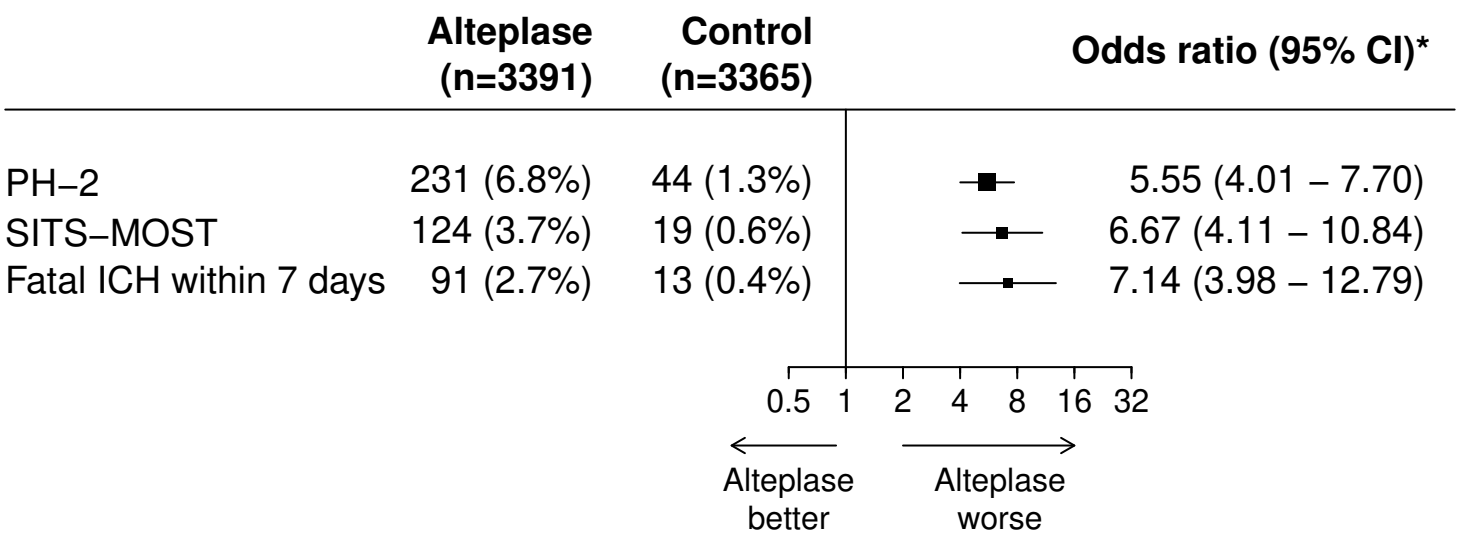
Table 1: Baseline characteristics of participating trials

Variable	NINDS A[11]	NINDS B[11]	ECASS I[7]	ECASS II[12]	ATLANTIS A[15]	ATLANTIS B[14]	ECASS III[13]	EPITHET[10]	IST-3[8]	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.

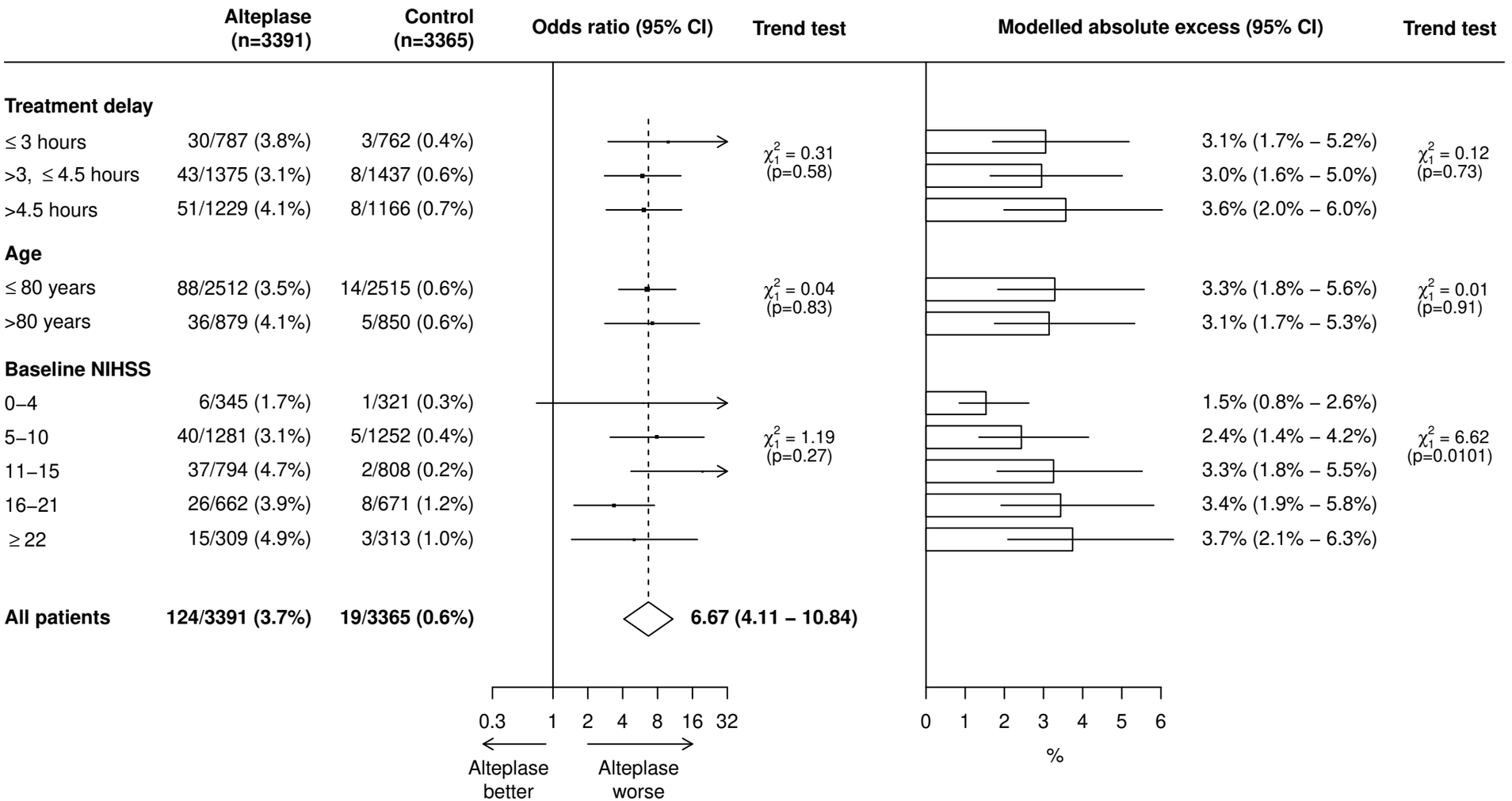
Figure
Click here to download Figure: 2016-04-28 Figures 1-5.pdf

Figure 1: The effect within 7 days of alteplase on three types of intracerebral haemorrhage (ICH): parenchymal haemorrhage type 2 (PH–2), SITS–MOST haemorrhage, and fatal ICH



* Estimated from a trial–stratified logistic regression model adjusted only for treatment allocation

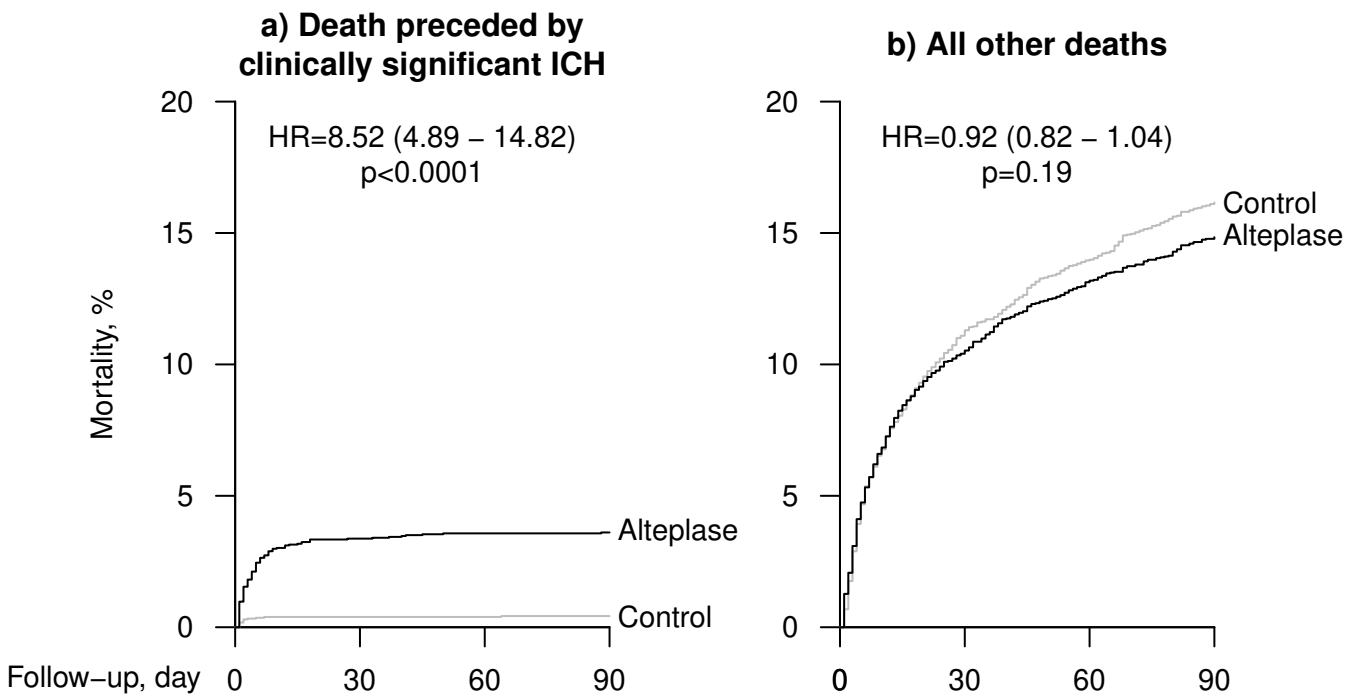
Figure 2: The effect of alteplase on SITS–MOST intracerebral haemorrhage at 24 to 36 hrs by time to treatment, age and stroke severity



* For each of the three baseline characteristics shown, the odds ratio subgroup estimates shown are derived from a single trial–stratified logistic regression model which allows for separate estimation of the OR in each of the subgroups after adjustment for the other two baseline characteristics (but not possible interactions with those characteristics). The overall effect in all patients (indicated by the open diamond) is the trial–stratified logistic regression estimate adjusted only for treatment allocation.

The absolute excess risk (and its 95% CI) for each subgroup is estimated by applying the odds ratio seen among all randomised patients (or its confidence limits) to the average expected risk among control–allocated patients for that subgroup (estimated from a logistic regression model among all participants adjusted for trial, treatment allocation, the subgroup of interest and average levels of the other two baseline characteristics).

Figure 3: Effect of alteplase on: a) deaths preceded by clinically significant intracerebral haemorrhage (SITS–MOST or fatal haemorrhage within 7 days); and b) all other deaths, within the first 90 days



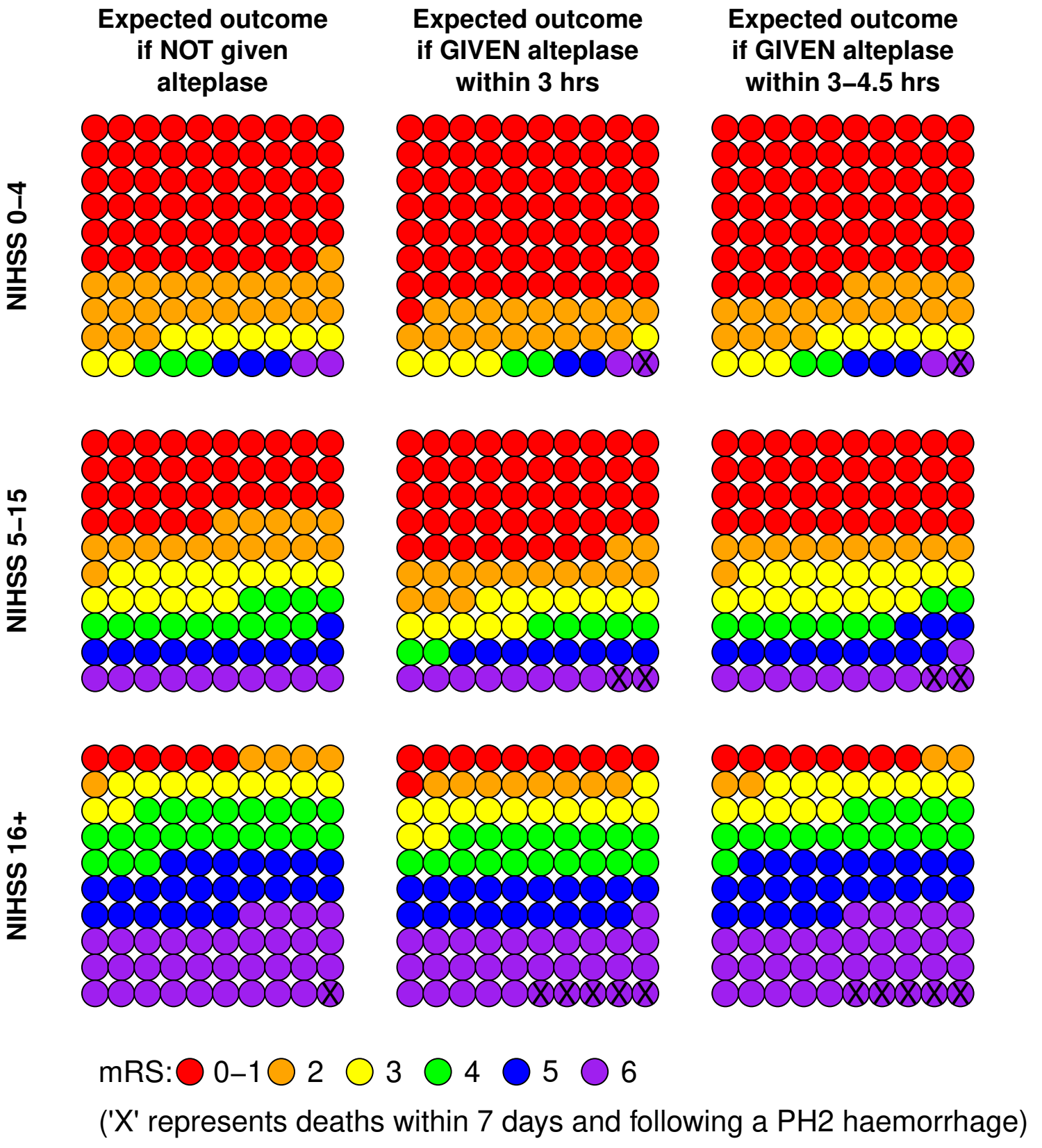
Number dead								
Alteplase	0	111	117	118	0	349	436	490
Control	0	13	13	14	0	379	469	542

Average hazard ratio estimated by Cox proportional hazards regression stratified by trial, with adjustment only for treatment allocation

Figure 4: Expected proportions in each category of modified Rankin score at 3—6 months, with or without alteplase given within 4.5 hours of symptom onset (mean 3 hrs 20 min)

mRS 0/1='Excellent' outcome; In IST–3, 125 (4.1%) patients died between 3 and 6 months. For comparability of mRS 6 between IST–3 and the other trials (which had 3 month mRS), these patients were reassigned an mRS of 5 for this analysis.

Figure 5: EXPECTED stroke outcome at 3–6 months for groups of patients: i) not treated with alteplase; ii) treated with alteplase within 3 hours of stroke onset; and iii) treated with alteplase between 3 and 4.5 hours after stroke onset.

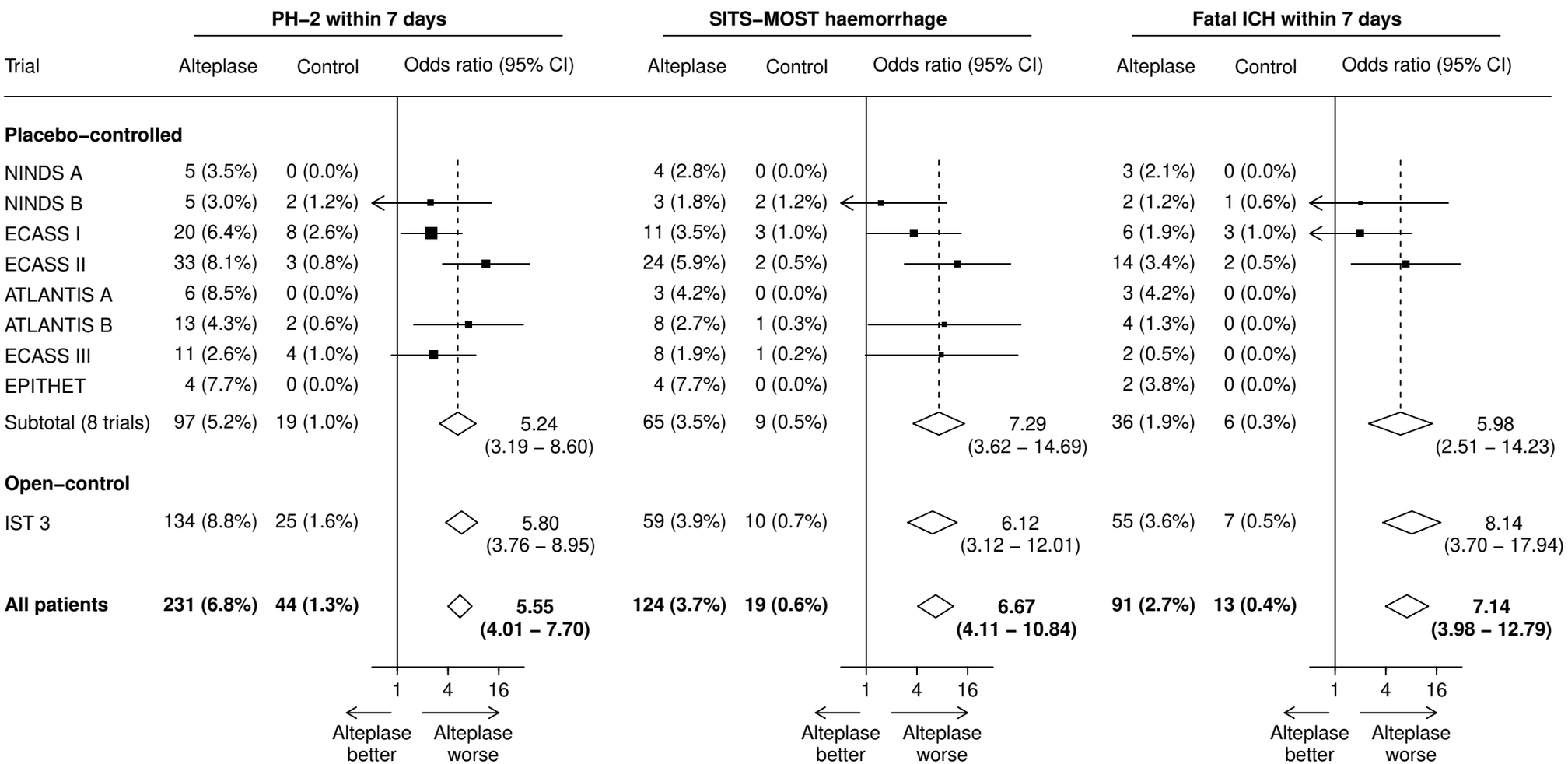


Each 10 x 10 grid represents 100 hypothetical patients who have experienced a stroke with severity 0–4 NIHSS points (top row), 5–15 points (middle row) or 16+ points (bottom row). Each circle in each grid represents a single patient with the colour of the circle reflecting their expected mRS outcome at 3–6 months if: a) not given alteplase (left column); b) given alteplase within 3 hours (middle column); or c) given alteplase between 3 and 4.5 hours (right column).

Webmaterial: What are the risks of intracerebral haemorrhage due to alteplase after acute ischaemic stroke? Results from an individual patient data meta-analysis of randomised trials

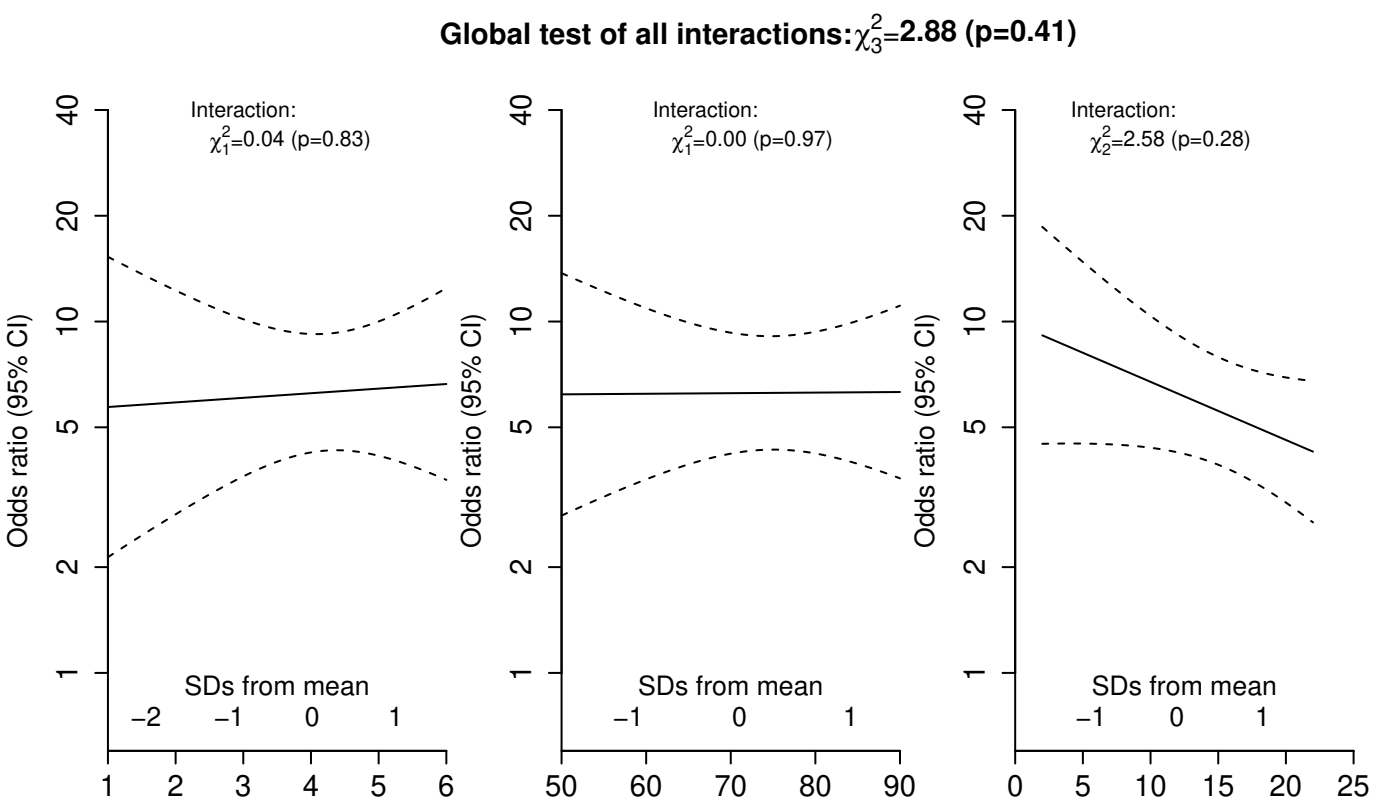
Webfigures **Pg**

Webfigure 1: Effect of alteplase on intracerebral haemorrhage in each trial



Where estimable, individual trial estimates above correspond to the simple odds ratio and its 95% confidence interval. The summary diamonds, and their 95% CIs, are derived from trial–stratified logistic regression models (which allow trials with zero events in the control arm to contribute information). There was no evidence that the proportional effect of allocation to alteplase on ICH differed between the placebo–controlled trials and IST–3 (p=0.76 for PH–2 within 7 days, p=0.72 for SITS–MOST haemorrhage and p=0.61 for fatal ICH within 7 days. Nor was there any evidence of significant heterogenity between all 9 trials (test for trial–by–treatment interaction: p=0.57 for PH–2 within days, p=0.87 for SITS–MOST haemorrhage and p=0.88 for fatal ICH within 7 days).

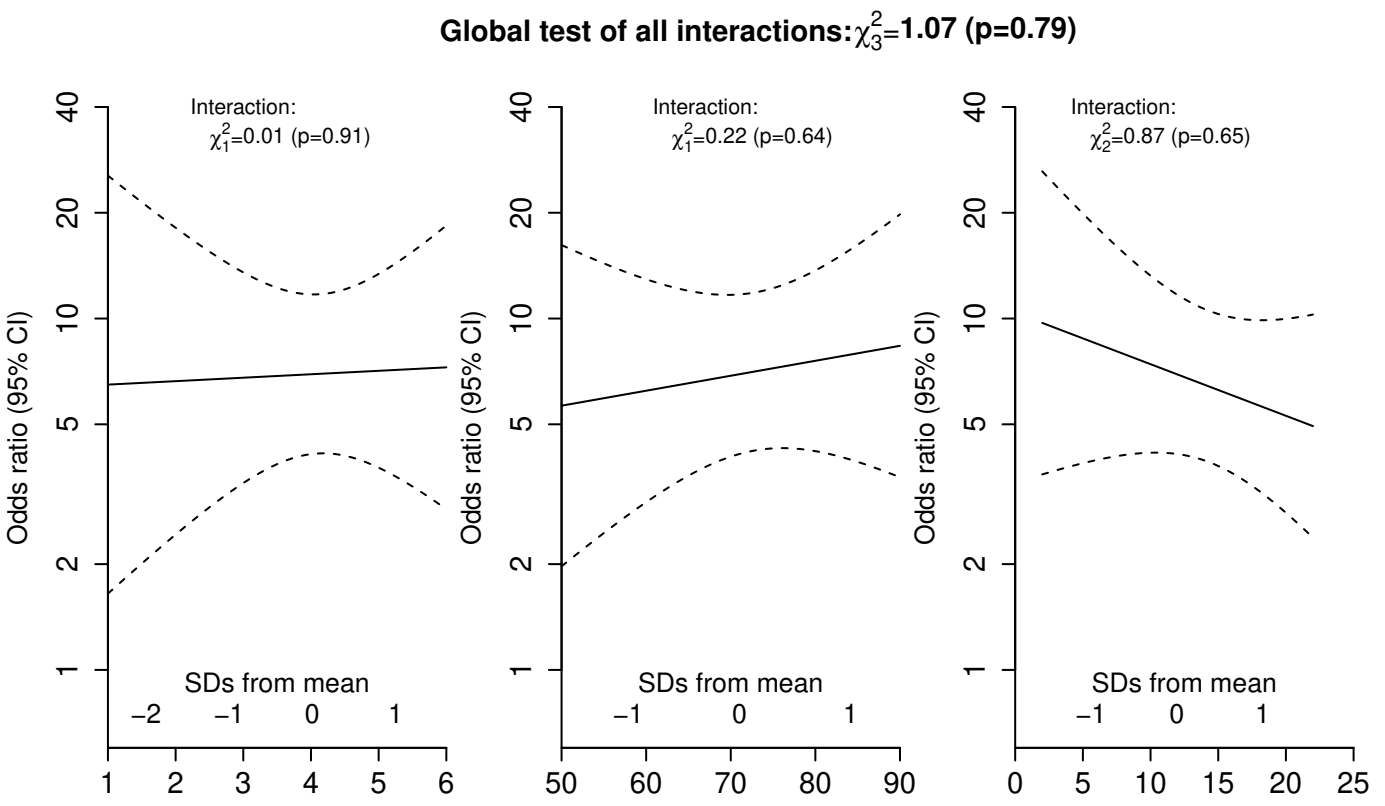
Webfigure 2: Treatment–modifying effects of time to treatment, age and stroke severity on parenchymal haemorrhage type 2 within 7 days



The solid line on each plot shows how the estimated odds ratio associated with allocation to alteplase varies with, respectively, time, age and baseline NIHSS, so its slope provides a test for interaction between that characteristic and allocation to alteplase. Each panel is adjusted for treatment delay, age, and baseline NIHSS (as linear main effects), and all three treatment–interaction terms (ie, all three panels derive from the same regression model).

The odds ratio in each panel corresponds to patients with AVERAGE levels of the other 2 baseline characteristics. The OR for alteplase was 6.26 at the mean values of age (71 years), NIHSS (12 points) and time to treatment (4 hours). The significance of each interaction, as well as the global test of all interactions, 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).

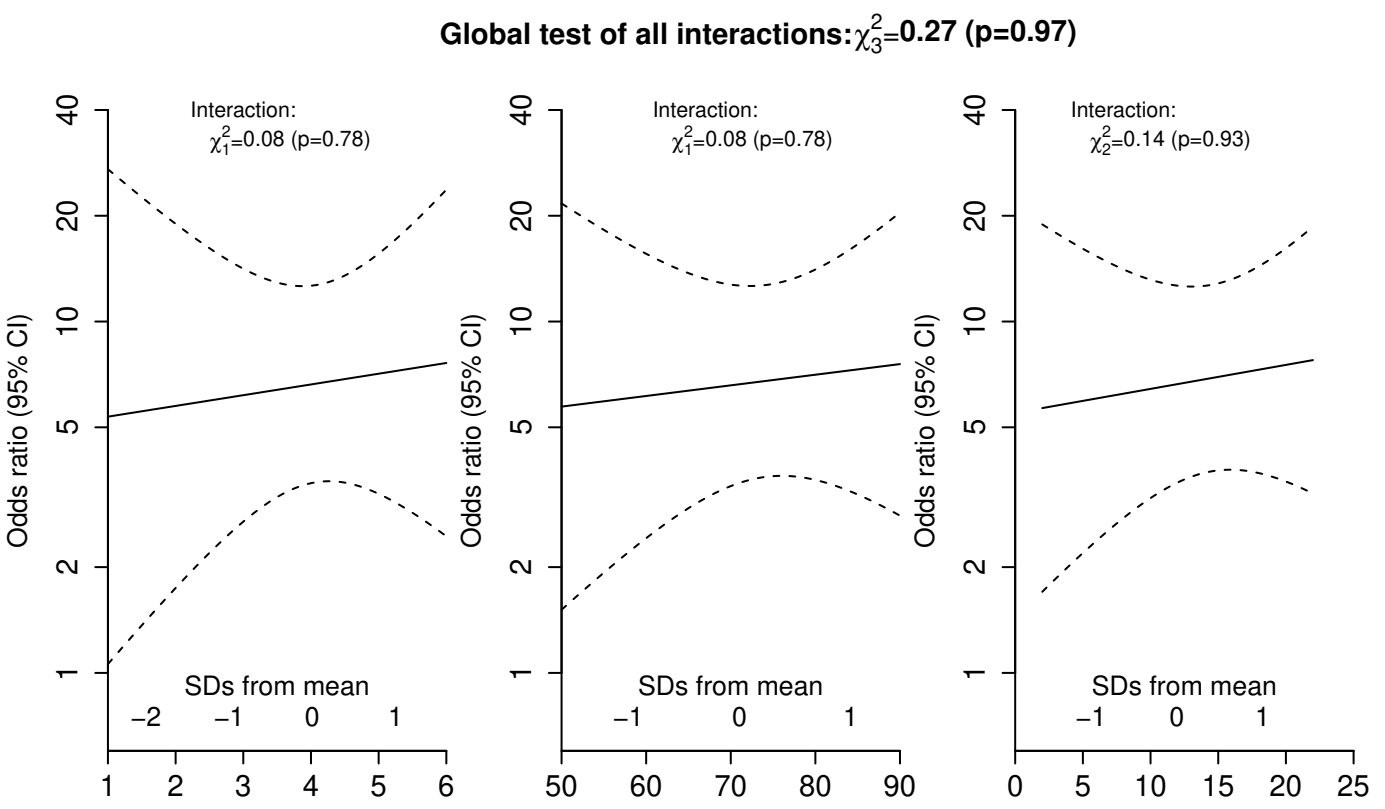
Webfigure 3: Treatment–modifying effects of time to treatment, age and stroke severity on SITS–MOST intracerebral haemorrhage at 24–36 hours



The solid line on each plot shows how the estimated odds ratio associated with allocation to alteplase varies with, respectively, time, age and baseline NIHSS, so its slope provides a test for interaction between that characteristic and allocation to alteplase. Each panel is adjusted for treatment delay, age, and baseline NIHSS (as linear main effects), and all three treatment–interaction terms (ie, all three panels derive from the same regression model).

The odds ratio in each panel corresponds to patients with AVERAGE levels of the other 2 baseline characteristics. The OR for alteplase was 6.94 at the mean values of age (71 years), NIHSS (12 points) and time to treatment (4 hours). The significance of each interaction, as well as the global test of all interactions, 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).

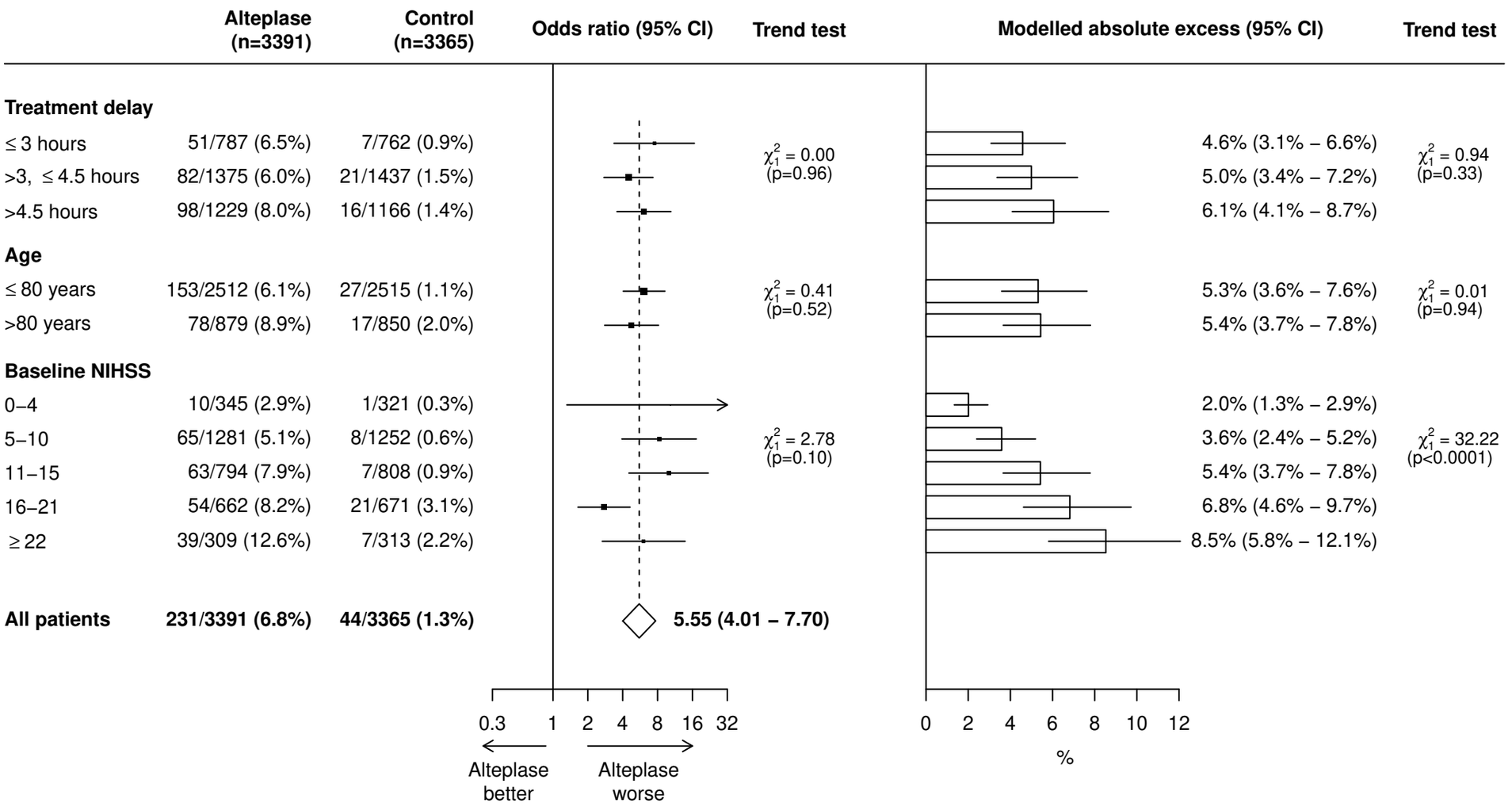
Webfigure 4: Treatment–modifying effects of time to treatment, age and stroke severity on fatal intracerebral haemorrhage within 7 days



The solid line on each plot shows how the estimated odds ratio associated with allocation to alteplase varies with, respectively, time, age and baseline NIHSS, so its slope provides a test for interaction between that characteristic and allocation to alteplase. Each panel is adjusted for treatment delay, age, and baseline NIHSS (as linear main effects), and all three treatment–interaction terms (ie, all three panels derive from the same regression model).

The odds ratio in each panel corresponds to patients with AVERAGE levels of the other 2 baseline characteristics. The OR for alteplase was 6.63 at the mean values of age (71 years), NIHSS (12 points) and time to treatment (4 hours). The significance of each interaction, as well as the global test of all interactions, 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).

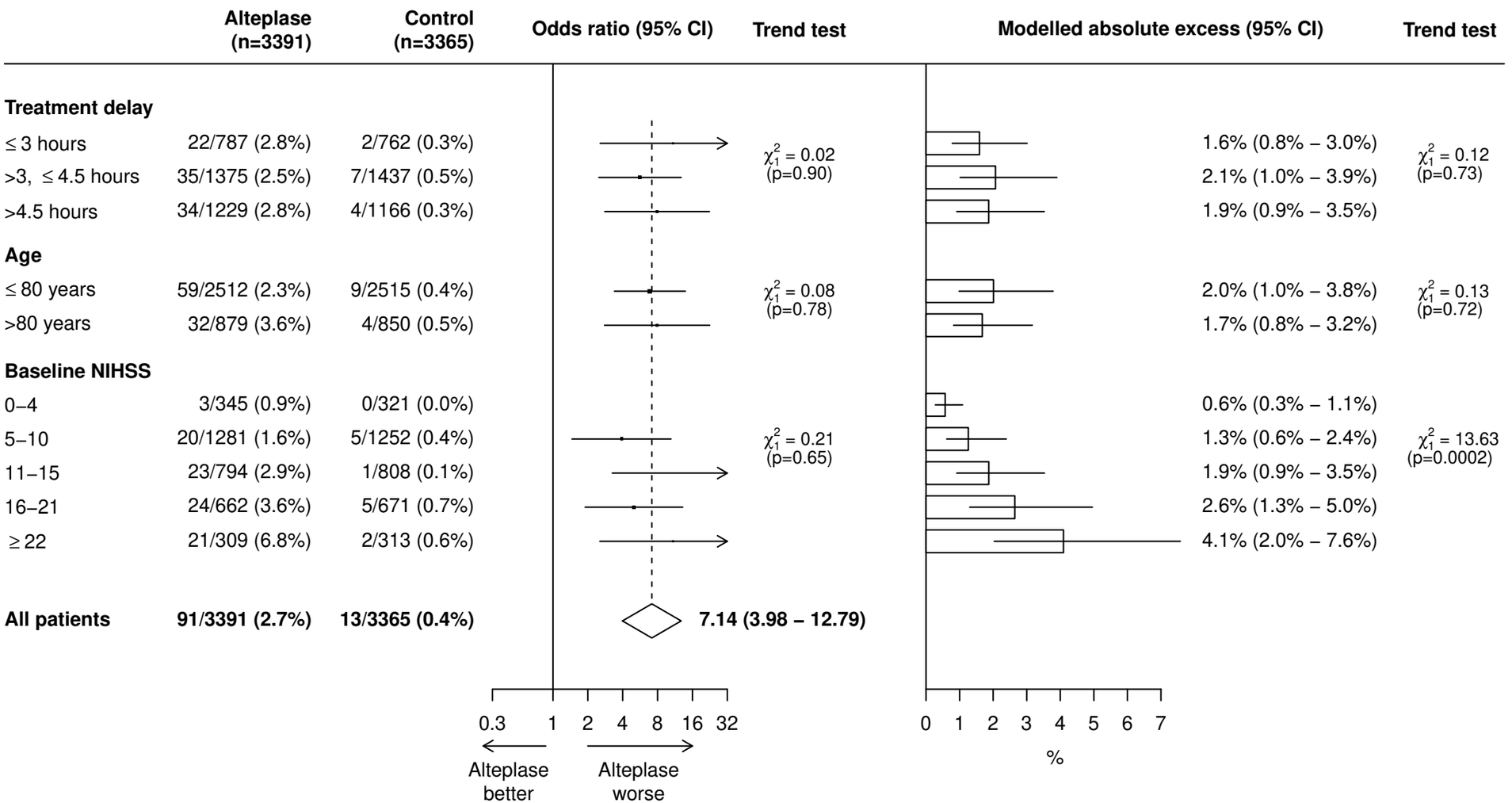
Webfigure 5: The effect of alteplase on parenchymal haemorrhage type 2 within 7 days by time to treatment, age and stroke severity



* For each of the three baseline characteristics shown, the odds ratio subgroup estimates shown are derived from a single trial–stratified logistic regression model which allows for separate estimation of the OR in each of the subgroups after adjustment for the other two baseline characteristics (but not possible interactions with those characteristics). The overall effect in all patients (indicated by the open diamond) is the trial–stratified logistic regression estimate adjusted only for treatment allocation.

The absolute excess risk (and its 95% CI) for each subgroup is estimated by applying the odds ratio seen among all randomised patients (or its confidence limits) to the average expected risk among control–allocated patients for that subgroup (estimated from a logistic regression model among all participants adjusted for trial, treatment allocation, the subgroup of interest and average levels of the other two baseline characteristics).

Webfigure 6: The effect of alteplase on fatal intracerebral haemorrhage within 7 days by time to treatment, age and stroke severity



* For each of the three baseline characteristics shown, the odds ratio subgroup estimates shown are derived from a single trial–stratified logistic regression model which allows for separate estimation of the OR in each of the subgroups after adjustment for the other two baseline characteristics (but not possible interactions with those characteristics). The overall effect in all patients (indicated by the open diamond) is the trial–stratified logistic regression estimate adjusted only for treatment allocation.

The absolute excess risk (and its 95% CI) for each subgroup is estimated by applying the odds ratio seen among all randomised patients (or its confidence limits) to the average expected risk among control–allocated patients for that subgroup (estimated from a logistic regression model among all participants adjusted for trial, treatment allocation, the subgroup of interest and average levels of the other two baseline characteristics).

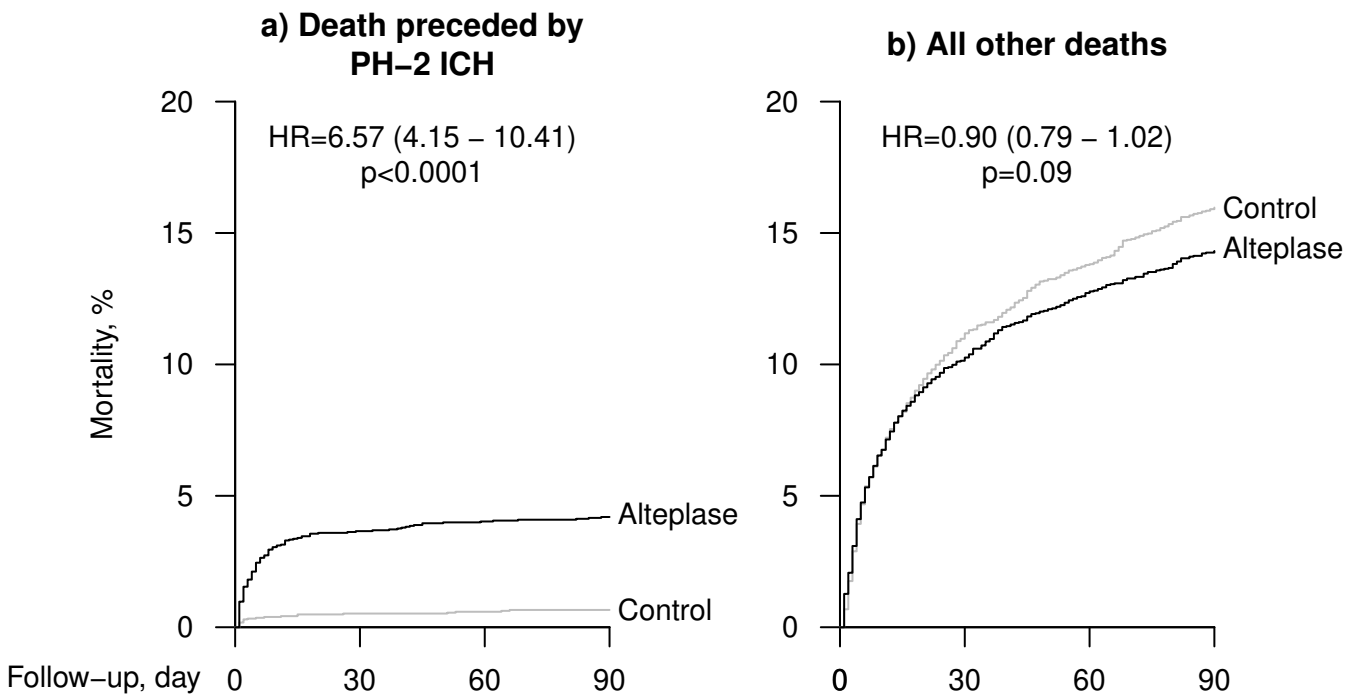
Webfigure 7a: Expected proportions in each category of modified Rankin score at 3—6 months, with or without alteplase given within 3 hours of symptom onset (mean 2 hrs 20 min)

mRS 0/1='Excellent' outcome; In IST–3, 125 (4.1%) patients died between 3 and 6 months. For comparability of mRS 6 between IST–3 and the other trials (which had 3 month mRS), these patients were reassigned an mRS of 5 for this analysis.

Webfigure 7b: Expected proportions in each category of modified Rankin score at 3—6 months, with or without alteplase given within 3–4.5 hours of symptom onset (mean 3 hrs 50 min)

mRS 0/1='Excellent' outcome; In IST–3, 125 (4.1%) patients died between 3 and 6 months. For comparability of mRS 6 between IST–3 and the other trials (which had 3 month mRS), these patients were reassigned an mRS of 5 for this analysis.

Webfigure 8: Effect of alteplase on: a) deaths preceded by PH–2 haemorrhage; and b) all other deaths, within the first 90 days



Number dead								
Alteplase	0	120	131	136	0	340	422	472
Control	0	17	19	21	0	375	463	535

Average hazard ratio estimated by Cox proportional hazards regression stratified by trial, with adjustment only for treatment allocation