Original Contribution

Effect of Alteplase Within 6 Hours of Acute Ischemic Stroke on All-Cause Mortality (Third International Stroke Trial)

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Background and Purpose—Prompt thrombolytic therapy with intravenous alteplase reduces disability after acute ischemic stroke. In an exploratory analysis, we examined whether long-term survival varied by baseline characteristics after alteplase.

Methods—In this open-treatment, international, randomized, controlled trial, ischemic stroke patients were randomly allocated <6 hours of onset to intravenous alteplase (0.9 mg/kg) plus standard care (n=1515) or standard care alone (n=1520). We followed patients to death, censoring when last known to be alive. We grouped patients by delay to randomization, and good or poor predicted prognosis (calculated from baseline National Institutes of Health Stroke Scale [NIHSS] score and age). We present absolute mortality differences between treated and control groups at 7 days, 6 months, and 18 months poststroke.

Results—Alteplase was not associated with a significant increase in mortality within 18 months (0.6% [95% confidence interval (CI), −2.9% to +4.2] *P*=0.72] in all patients with complete vital status (99.9%, 3034/3035). In patients randomized <3 hours of stroke, 18-month mortality was lower in the alteplase-treated group than the control group (40.6% [95% CI, 42.6–52.7] versus 47.8% [95% CI, 35.5–45.3]; *P*=0.0434]. The difference in 18-month mortality between alteplase-treated and control patients was greater in patients who were randomized early (<3 hours) compared with late (3–6 hours; +9% [95% CI, 1–17]; *P*=0.0317). Alteplase led to a greater improvement in 18-month survival in patients with a poor prognosis than in patients with a good prognosis (+8% [95% CI, 2–14]; *P*=0.0091).

Conclusions—These exploratory analyses of the third International Stroke Trial (IST-3) trial support improving acute stroke patients' access to earlier alteplase treatment, treatment of patients with poor prognosis, and further randomized controlled trials in minor stroke to replicate these findings.

Clinical Trial Registration—URL: http://www.controlled-trials.com. Unique identifier: ISRCTN25765518.

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Key Words: mortality ■ randomized controlled trial ■ thrombolytic therapy

When given soon after onset of acute ischemic stroke, thrombolytic therapy with intravenous alteplase leads to an improvement in both short-term[1] and long-term[2] functional outcome. Although time to treatment is the key determinant of the effect of alteplase on functional outcome, the factors that modify the effect of alteplase on long-term mortality after stroke are less clear. Alteplase had no statistically significant effect on mortality by 90 days when studied in randomized, controlled trials.[1,3] However, by 7 days thrombolysis leads to an increase in the risk of death (22 per 1000 treated), principally because of intracranial hemorrhage (ICH).[1] These data suggest that stroke patients treated with alteplase who survive the acute phase are likely to gain a survival benefit from alteplase over the medium-term that offsets any early increase in mortality because of bleeding. This survival benefit may be because stroke survivors who are less disabled because of alteplase treatment live longer after stroke,[4] and it is possible that survival benefits accrue with time.

The balance between the early hazard of fatal ICH and potential long-term survival benefits may vary in different patients. In patients treated earlier, in whom the medium-term benefits of alteplase on functional outcome are larger, alteplase treatment may lead to a long-term survival benefit

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that is difficult to demonstrate in the medium-term. In ischemic stroke patients with a good prognosis, who are at a low absolute risk of death in the long-term without alteplase treatment, any early increase in mortality with alteplase (from ICH) may not be outweighed by a reduction in death in the longer term. To investigate whether the effect of alteplase on long-term survival in acute ischemic stroke patients was dependent on the delay to treatment or baseline prognosis, we performed an exploratory analysis of the third International Stroke Trial (IST-3), a large randomized trial of alteplase in ischemic stroke that collected data on survival ≤18 months of stroke.[2,5]

Methods

Ethics Statement

IST-3 was approved by the Multi-center Research Ethics Committees, Scotland (reference MREC/99/0/78), and by local ethical committees. Patients or a valid proxy gave written consent to participate. This trial was registered (ISRCTN25765518).

IST-3 Study Design and Participants

The details of the IST-3 study protocol,[6] statistical analysis plan,[7] and primary outcomes[5] have been published previously. In brief, ischemic stroke patients (with no upper age limit) who could start alteplase treatment within 6 hours of symptom onset, with no clear indication for, or clear contraindication to alteplase, and in whom the randomizing clinician was substantially uncertain about the risks and benefits of alteplase, were randomized 1:1 to standard care with an infusion of 0.9 mg/kg alteplase or standard care without alteplase between 2000 and 2011. Both groups were managed within a stroke unit with intravenous access and monitoring of blood pressure and other physiological variables. Treatment with alteplase was not blinded. Baseline data were collected by a web-based or telephone randomization system before treatment allocation. At 7 days, randomizing clinicians reported whether patients were independent of activities of daily living or not independent of daily living. The trial event adjudication committee defined symptomatic post-recombinant tissue-type plasminogen activator ICH (SICH) as a clinically significant deterioration or death within the first 7 days of treatment and evidence of either significant brain parenchymal hemorrhage (local or distant from the infarct) or significant hemorrhagic transformation of an infarct on brain imaging.[7]

The dates of death ≤18 months postrandomization were ascertained from central death registries in the United Kingdom, Norway, and Sweden. In other countries, dates of death were ascertained by contacting the patient's primary care physician or hospital co-ordinators. In a few cases, deaths were ascertained during the process of follow-up for disability at 6 and 18 months. Functional outcome was measured at 6 months with the Oxford Handicap Scale, which is similar to the modified Rankin Score.[8]

Statistical Analysis

In our survival analysis, we compared the survival of acute ischemic stroke patients treated with alteplase+standard care with patients managed with standard care alone (control) over 18 months, analyzed in their randomly allocated groups (ie, intention to treat analysis).

We examined the effect of delay to randomization on long-term survival in the subgroups 0 to 3 hours versus 3 to 6 hours and 0 to 4.5 hours versus 4.5 to 6 hours. These thresholds were chosen as the marketing authorization for the use of alteplase is within 3 hours of stroke onset in the United States and within 4.5 hours of stroke onset from Europe and other regions.[9]

We examined subgroups of patients defined by their probability of death or dependence at 3 months, calculated from their status at randomization with a previously developed and validated clinical prediction model based on the National Institutes of Health Stroke Scale (NIHSS) score and age,[10] at a threshold of predicted risk of 50%. The choice of this threshold was arbitrary but prespecified. We defined a predicted risk of death or dependence of <50% as good prognosis and a predicted risk of ≥50% as poor prognosis. To support this analysis, we separately explored the components of this predictive model, age (dichotomized at 80), and the NIHSS (dichotomized at 5) and performed sensitivity analyses at different thresholds of predicted risk (20% and 40%); in patients randomized within 4.5 hours; and in patients who received their allocated treatment (on-treatment analysis).

We used time from stroke onset to death within the first 548 days (18 months) of follow-up as the primary outcome and censored either at the end of follow-up or withdrawal of consent (for more details, please see Materials in the online-only Data Supplement).

Anticipating nonproportional hazards that would preclude Cox regression analysis, we calculated the cumulative mortality differences between alteplase and control at 7 days, 6 months, and 18 months, using Kaplan-Meier estimates. We tested interactions between treatment and delay by measuring the statistical significance of the difference in mortality differences between groups (eg, [$\text{mortality}_{\text{control}}$−$\text{mortality}_{\text{altepl as}}$] for patients <3 hours poststroke minus [$\text{mortality}_{\text{control}}$−$\text{mortality}_{\text{alteplas}}$] for patients 3–6 hours poststroke). The interactions between predicted prognosis and treatment were tested similarly. We adjusted further for the confounding effects of delay and predicted prognosis as continuous variables using Cox regression in different time periods (0–7, 7–183, and 183–548 days) and using logistic regression with death by 18 months as the dependent variable in those patients for whom follow-up ≤18 months was planned. We tested multiplicative interactions between treatment and delay or prognosis with a likelihood ratio test. We report *P* values with reference to a nominal 2-sided significance level of 0.05, although the type 1 error rate is unknown as the analyses are exploratory.

We wrote and published the statistical analysis plan for this work (available at http://www.dcn.ed.ac.uk/dcn/staff/displaystaff.asp?RecordId=174) before undertaking the analyses but after the publication of primary IST-3 report.[5]

Results

We analyzed all patients randomized in IST-3, bar one for whom we were unable to calculate a survival time (1520 control versus 1514 alteplase). Important prognostic factors were balanced between groups (Table I in the online-only Data Supplement). We were unable to calculate mortality hazard ratios between alteplase-treated and control patients as there was good evidence that the hazards of death over 18 months were nonproportional (test for nonproportionality *P*=0.0011), principally because of an excess of deaths within 7 days in the alteplase group.

By 7 days, in all patients, patients allocated to alteplase had an excess mortality over control of 3.5% (95% CI, 1.5–5.4), although no such excess at 6 months (0.1% [95% CI, −3.1 to +3.2]) or 18 months (−0.6% [95% CI, −4.1 to +2.9]; Table).

There was evidence to suggest that the absolute effect of alteplase on mortality varied by time to randomization. There was modification of the difference in 18-month mortality between alteplase and control patients in the direction of improved survival in those randomized <3 hours. A test for interaction, the difference in 18-month mortality differences with alteplase between early and late groups (+8.8% [95% CI, 0.8–16.9]; *P*=0.03; Figure 1), suggested improved long-term mortality with earlier alteplase treatment. However, when comparing patients treated 0 to 4.5 hours with patients treated >4.5 hours the difference of effect was in the same direction but not statistically significant (+3.2% [95% CI, −3.9 to 10.4]; *P*=0.38).

There was evidence to suggest that the absolute effect of alteplase on 18-month mortality varied by baseline prognosis. There was modification of the difference in 18-month mortality in the direction of greater survival with alteplase in poor

Table. Kaplan-Meier Estimates of Mortality With 95% CIs at 7 Days, 6 Months, and 18 Months Poststroke, With Absolute Difference Between Treatment Arms at Each Time Point (Control Minus Alteplase)

	Control, %		Alteplase, %		Difference (Control-Alteplase), %*	
Days Since Enrolment	Deaths (n)	K-M Estimate (95% CI)	Deaths (n)	K-M Estimate (95% CI)	Estimate (95% CI)	*P* Value
All patients						
7	102	6.71 (5.44 to 7.96)	154	10.17 (8.64 to 11.68)	−3.46 (−5.44 to −1.49)	0.0006
183	407	26.80 (24.54 to 29.00)	407	26.90 (24.63 to 29.10)	−0.10 (−3.25 to 3.06)	0.9510
548	539	36.56 (34.03 to 38.99)	529	35.93 (33.41 to 38.35)	0.63 (−2.86 to 4.13)	0.7235
Delay to randomization						
Time to randomization, <3 h						
7	35	8.86 (6.01 to 11.62)	41	10.10 (7.12 to 12.98)	−1.24 (−5.29 to −2.82)	0.5497
183	142	35.95 (31.04 to 40.51)	130	32.02 (27.33 to 36.41)	3.93 (−2.63 to 10.49)	0.2401
548	184	47.84 (42.55 to 52.65)	161	40.62 (35.54 to 45.30)	7.22 (0.21 to 14.23)	0.0434
Time to randomization, ≥3 h						
7	67	5.96 (4.56 to 7.33)	113	10.20 (8.40 to 11.96)	−4.24 (−6.50 to −1.99)	0.0002
183	265	23.59 (21.06 to 26.03)	277	25.03 (22.43 to 27.54)	−1.44 (−5.00 to 2.12)	0.4287
548	355	32.58 (29.72 to 35.33)	368	34.20 (31.29 to 37.00)	−1.62 (−5.62 to 2.38)	0.4270
Time to randomization, <4.5 h						
7	74	7.44 (5.80 to 9.06)	110	11.19 (9.20 to 13.14)	−3.75 (−6.30 to −1.19)	0.0041
183	306	30.81 (27.88 to 33.62)	297	30.22 (27.29 to 33.03)	0.59 (−3.47 to 4.65)	0.7753
548	398	41.12 (37.91 to 44.16)	379	39.42 (36.23 to 42.45)	1.70 (−2.70 to 6.11)	0.4489
Time to randomization, ≥4.5 h						
7	28	5.32 (3.39 to 7.22)	44	8.29 (5.91 to 10.60)	−2.96 (−5.99 to 0.07)	0.0552
183	101	19.23 (15.79 to 22.53)	110	20.76 (17.23 to 24.13)	−1.53 (−6.35 to 3.30)	0.5353
548	141	27.89 (23.84 to 31.72)	150	29.41 (25.31 to 33.28)	−1.52 (−7.12 to 4.08)	0.5941
Predicted prognosis						
Predicted risk of death or dependence by 3 months <0.5 (good prognosis)						
7	8	1.49 (0.46 to 2.50)	14	2.69 (1.29 to 4.07)	−1.21 (−2.93 to 0.52)	0.1713
183	36	6.71 (4.57 to 8.81)	45	8.67 (6.22 to 11.06)	−1.96 (−5.18 to 1.26)	0.2323
548	55	10.71 (7.99 to 13.36)	74	15.03 (11.80 to 18.15)	−4.32 (−8.48 to −0.17)	0.0415
Predicted risk of death or dependence by 3 months ≥0.5 (poor prognosis)						
7	94	9.57 (7.71 to 11.39)	140	14.08 (11.89 to 16.22)	−4.51 (−7.35 to −1.67)	0.0018
183	371	37.78 (34.67 to 40.74)	362	36.42 (33.36 to 39.35)	1.36 (−2.90 to 5.62)	0.5330
548	484	50.60 (47.30 to 53.70)	455	46.78 (43.52 to 49.85)	3.82 (−0.67 to 8.32)	0.0956

Note 1 patient was excluded from all analyses as follow-up time was missing.

*Positive numbers indicate less mortality with alteplase. We estimated the standard error for the difference in survivorship functions using the individual standard errors of the K-M estimates for control and alteplase and calculated the 95% point-wise confidence bands and associated *P* values.

prognosis patients. The test for interaction, the difference of 18-month mortality differences with alteplase between good and poor prognosis groups, was statistically significant (−8.1% [95% CI, 2.0–14.2; *P*=0.0091; Figure 2). The direction of this difference was similar, although not consistently statistically significant, with different thresholds of predicted risk of poor outcome to define good prognosis (<20% −2.2 [95% CI, −8.9 to 4.5]; *P*=0.5178, and <40% −8.15 [95% CI, −14.3 to −2.0]; *P*=0.0090); in patients randomized <4.5 hours after stroke (−6.2% [95% CI, −31.8 to 19.5]; *P*=0.1307) and in an on-treatment analysis (−9.4% [95% CI, −15.8 to −2.9]; *P*=0.00470). When patients were grouped by components of the prognostic score, the difference of differences in 18-month mortality between alteplase and control groups was smaller and not statistically significant (NIHSS <5 versus ≥5=−4.0 [95% CI, −10.6 to 2.7; *P*=0.2412], age ≤80 versus >80=−1.8 [95% CI, −8.5 to 4.8; *P*=0.5879]; please see Table II in the online-only Data Supplement).

We further adjusted for the confounding effects of prognosis and delay in Cox regression models in different periods. After adjustment, the hazard ratio of early death (0–7 days) was increased by alteplase (hazards ratio, 1.54; 95% CI, 1.19–2.00), with no evidence of modification by time to randomization ($P_{interaction}$=0.2371) or predicted prognosis ($P_{interaction}$=0.9386). For late death (183–548 days), there was evidence that worse predicted prognosis reduced the hazard ratio of later death with alteplase treatment ($P_{interaction}$=0.0066), but the reduction in late death with earlier treatment was not significant ($P_{interaction}$=0.1994; Table III in the online-only Data Supplement). In an adjusted logistic regression analysis of all patients followed up until 18 months (n=2348), alteplase led to lower odds of all deaths by 18 months in patients with a poorer

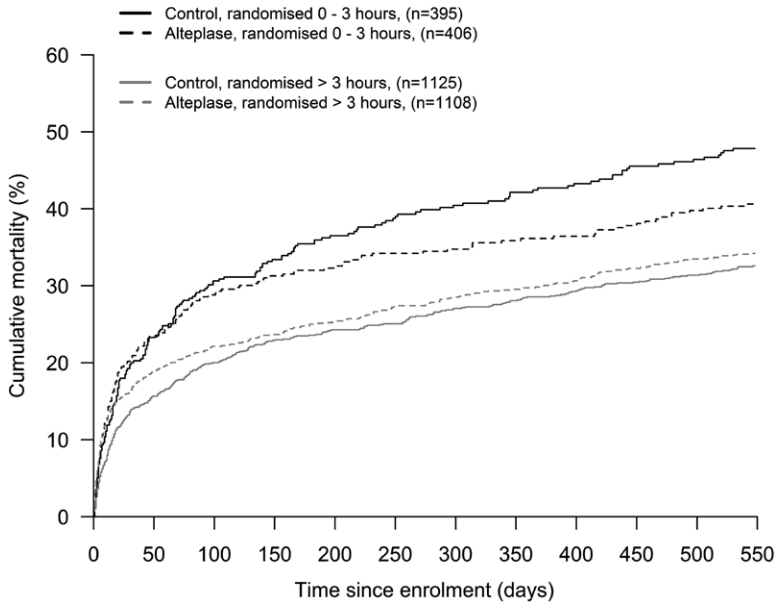

Figure 1. Cumulative mortality plots of alteplase-treated versus control patients split by onset time to randomization (0–3 hours vs >3 hours). The difference of the differences in 18-month mortality in the 0=3 hours and the >3 hours groups was 8.8% (95% confidence interval [CI], 0.8–16.9, *P* value = 0.0317).

compared with better predicted prognosis ($P_{interaction}$=0.005) and nonsignificantly lower odds of death by 18 months in patients treated earlier rather than later after stroke ($P_{interaction}$=0.499).

There were no important differences in 18-month mortality when comparing patients allocated alteplase and those allocated control between men and women (*P* for difference of difference 0.901) or between different baseline stroke subtypes classified with the Oxford Community Stroke Project scale.

The early excess mortality with alteplase compared with control was largely because of SICH. By 18 months, in patients who avoided ICH, the survival benefit of alteplase compared with control was +4.13% (95% CI, 0.43–7.83; *P*=0.0287). However, this comparison is nonrandomized and should be interpreted with caution.

Patients who were dependent at 7 days follow-up had greater mortality by 18 months days after stroke than patients who were independent at 7 days (proportion of 7-day survivors dead at 548 days, 44% versus 11%). Patients with less disability in the medium-term (6 months) had better survival than patients with more disability (Figure 3). For patients with a 6-month Oxford Handicap Scale of 0, 1, 2, 3, 4, and 5, the proportion who died over the next 12 months were 3%, 5%, 9%, 12%, 12%, and 40%, respectively.

Discussion

We have shown that alteplase given within 6 hours of ischemic stroke does not lead to any significant change in overall mortality at 18 months. Although there was some evidence in our exploratory analysis that the effect of alteplase on mortality differed by time to randomization. Consistent with previous findings that earlier treatment leads to better functional outcome at 3 to 6 months (although no clear difference in

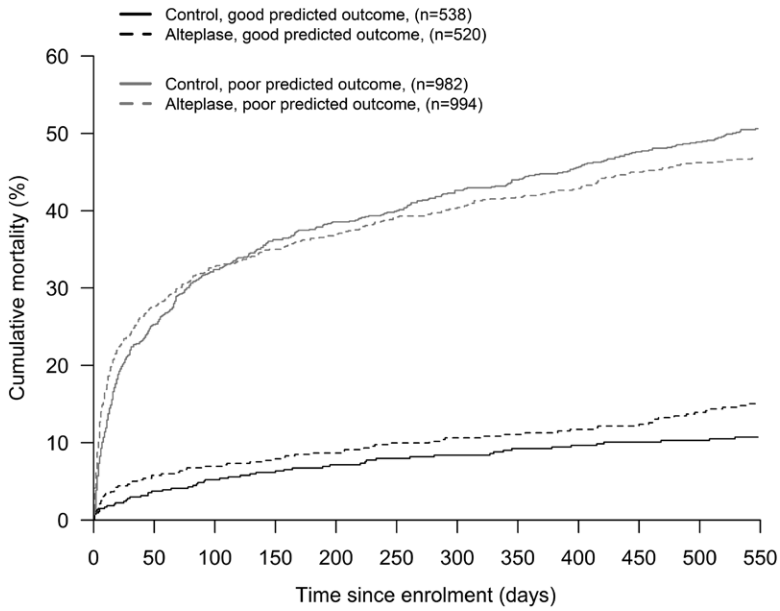

Figure 2. Cumulative mortality plots of alteplase-treated versus control patients split by predicted functional outcome (good <50% vs poor ≥50%). The difference of the differences between alteplase-treated and control patients in the good prognosis and poor prognosis groups was –8.1% (95% confidence interval [CI], 2.0–14.2 *P*=0.0091) at 18 months. Numbers indicate cumulative deaths at 7 days, 6 months and 18 months.

mortality is evident at that time point),[11] treatment <3 hours after stroke was associated with better 18-month survival than later treatment, although this association was attenuated after adjustment for predicted prognosis and could have been attributable to confounding or chance.

There was support for our hypothesis that patients with a good prognosis after acute stroke might not gain a survival advantage from alteplase. In our analysis, patients with a poor prognosis had greater reduction in long-term mortality than patients with a good prognosis, and there was some evidence for a small increase in 18-month mortality with alteplase treatment in patients with a good prognosis. A plausible explanation is that early hazard owing to SICH is outweighed by a survival advantage because of a small reduction in severe disability in patients with a poor prognosis, although not in patients with a good prognosis.

The strengths of this study are the large number of patients randomized, the inclusion of older patients, and those with more severe stroke, and the length and completeness of follow-up. We have studied all-cause mortality where the ascertainment of the outcome and its timing is objective, so bias in outcome ascertainment is unlikely and the lack of blinding is not relevant.

The study has several limitations. Although we studied 1068 deaths in 3034 stroke patients, it is likely that the study was underpowered to determine all the important factors that modify the effect of alteplase on mortality. The Stroke Thrombolysis Trialists' Collaboration individual patient data meta-analysis of all patients randomized in trials of intravenous alteplase has important information on short- and medium-term mortality, to which we add with longer term mortality estimates.[1] IST-3 was an open-label study; this aspect has been discussed in great detail before,[12] and while this may have biased the observed estimate of effects on functional outcome, it is hard to conceive how an open design might bias estimates of effect on late mortality. The effects of alteplase on disability in IST-3 were entirely consistent with the effects of alteplase in previous trials,[11] and our observations in this study run counter to the expected direction of information bias. Although using survivor functions may have reduced statistical power to examine the effect of factors modifying mortality, our conclusions are supported by more powerful Cox and logistic regression modeling. These analysis adjusted for the well-recognized confounding of time to randomization by stroke severity (ie, patients with more severe strokes tend to be randomized into trials earlier).[1] We only collected cause of death ≤7 days after stroke, so cause-specific differences in long-term mortality were not available. While a protocol was used for this statistical analysis, this was written after knowledge of the primary results of IST-3, and therefore, these results are exploratory (ie, there is a risk of a type 1 error) and should be put in the context of several secondary analyses of the data; a P value of <0.05 should not be taken as strong evidence that the results were not because of chance. These finding therefore should be replicated before they lead to a change in practice. This may be achieved through studying long-term data in other studies: the only other existing study with long-term follow-up, the National Institute of Neurological Disorders and Stroke (NINDS) trial, did not report an early increased risk of death with alteplase, so may be less generalizable to clinical practice where fatal SICH is not infrequent.[13,14]

The main cause of increase in early mortality with alteplase treatment is SICH. There is no reliable way to detect a group of patients at a high risk of ICH who do not benefit from alteplase using clinical or simple imaging biomarkers.[14] A future blood or imaging marker that reliably identified a group of patients at high risk of ICH and who did not benefit from alteplase, or a new thrombolysis agent or treatment regimen with similar or increased benefits to alteplase with a reduced risk of ICH, would therefore be extremely useful.

In a meta-analysis of all available data, there was no evidence that the relative effects of alteplase on 90 day mortality or functional outcome (modified Rankin scale 0–1) or on 18 month quality of life were materially different across the range of the components of the prognostic score (NIHSS and

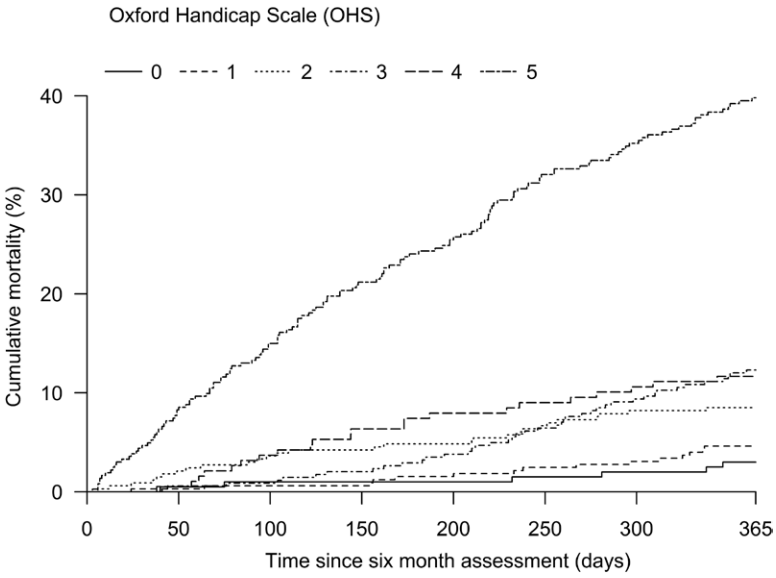

Figure 3. The cumulative mortality of 6-month survivors, grouped by Oxford Handicap Scale (OHS) measured at 18 months.

age).[1,3] In conclusion, in patients with a good prognosis, the balance between a modest absolute improvement in disability with alteplase versus a potential small increase in mortality in the long-term needs to be further investigated. These results therefore support the rationale for further randomized trials of alteplase versus control in patients with good prognosis, such as the Potential of recombinant tissue-type plasminogen activator for Ischemic Strokes with Mild Symptoms (PRISMS) study, which is recruiting patients <3 hours poststroke (http://www.clinicaltrials.gov, NCT02072226). Our data support the use of alteplase in patients with a poor prognosis, despite their increase risk of ICH, as it does not lead to increased mortality in the long-term and leads to an improvement in functional outcome.

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Disclosures

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ONLINE SUPPLEMENT

ONLINE SUPPLEMENTARY METHODS

Censoring scheme: For patients not known to have died by 548 days, the date of censoring was determined by: in Australia, UK, Norway, and Sweden where reporting of death was prompt, we censored all at 548 days; in Portugal and Switzerland, where follow up was to cease at 6 months, at 183 days if the 6 month follow up form was available, or at date last known alive if the 6 month form was unavailable; and in other countries we censored at 548 days if the 18 month form was returned; otherwise at 183 days if the 6 month follow up form was available and no further contact had been made, or at the date last known alive if the 6 month form was unavailable or if a contact had been made between 183 and 548 days

Table I Prognostic factors at baseline.

Baseline variables collected before treatment allocation	Alteplase (1514)	Control (1520)
Age (> 80yr)	816 (54%)	800 (53%)
NIHSS (per point)		
0-5	304 (20%)	308 (20%)
6-10	422 (28%)	430 (28%)
11-15	306 (20%)	295 (19%)
> 15	482 (32%)	487 (32%)
Time to randomisation		
0-3hrs	430 (28%)	418 (28%)
3-4.5hrs	577 (38%)	600 (39%)
> 4.5hrs	507 (33%)	502 (33%)
Sex, female	781 (52%)	788 (52%)
Stroke Syndrome		
TACI	639 (42%)	666 (44%)
PACI	595 (39%)	551 (36%)
LACI	168 (11%)	164 (11%)
POCI	110 (7%)	136 (9%)
Other	2 (<1%)	3 (<1%)
Country		
Northwest Europe	792 (52%)	797 (52%)
Scandinavia	251 (17%)	250 (16%)
Australasia	89 (6%)	90 (6%)
Southern Europe	203 (13%)	204 (13%)
Eastern Europe	174 (11%)	173 (11%)
Americas	5 (<1%)	6 (<1%)
Expert reader's assessment of acute ischaemic change[1]		
Scan completely normal	140 (9%)	129 (9%)
Scan not normal but no sign of acute ischaemic change	742 (49%)	781 (52%)
Signs of acute ischaemic change	624 (41%)	600 (40%)

Abbreviations: NIHSS – National Institute of Health Stroke Scale; Alteplase - recombinant tissue plasminogen activator; LACI - lacunar circulation infarcts; PACI - partial anterior circulation infarcts; POCI - posterior circulation infarcts; and TACI - total anterior circulation infarcts. 1 – Alteplase with 8 missing and control 10 missing

Table II Kaplan Meier estimates of mortality with 95% CIs at 7 days, 6 months and 18 months post stroke, with absolute difference between treatment arms at each time point (control minus alteplase).

	Control (%)		Alteplase (%)		Difference (control-alteplase) (%)*	
Days since enrolment	**Deaths (n)**	**K-M estimate (95% CI)**	**Deaths (n)**	**K-M estimate (95% CI)**	**Estimate (95% CI)**	**P-value**
Age ≤ 80						
7	36	5.00 (3.39 to 6.58)	61	8.74 (6.62 to 10.81)	-3.74 (-6.37 to -1.11)	0.0053
183	107	14.87 (12.23 to 17.44)	112	16.07 (13.29 to 18.75)	-1.19 (-4.96 to 2.58)	0.5357
548	152	21.79 (18.65 to 24.81)	147	21.71 (18.53 to 24.77)	0.08 (-4.30 to 4.46)	0.9700
Age > 80						
7	66	8.25 (6.32 to 10.14)	93	11.40 (9.19 to 13.55)	-3.15 (-6.04 to -0.25)	0.0332
183	300	37.54 (34.09 to 40.81)	295	36.15 (32.77 to 39.36)	1.39 (-3.31 to 6.10)	0.5624
548	387	49.98 (46.28 to 53.42)	382	48.05 (44.43 to 51.44)	1.92 (-3.08 to 6.92)	0.4511
NIHSS < 5						
7	3	0.97 (0.00 to 2.06)	7	2.30 (0.60 to 3.97)	-1.33 (-3.34 to 0.68)	0.1954
183	16	5.21 (2.69 to 7.66)	24	7.93 (4.83 to 10.92)	-2.71 (-6.64 to 1.21)	0.1758
548	30	10.41 (6.80 to 13.88)	37	12.87 (8.90 to 16.68)	-2.46 (-7.72 to 2.80)	0.3586
NIHSS ≥ 5						
7	99	8.17 (6.61 to 9.70)	147	12.15 (10.29 to 13.97)	-3.98 (-6.38 to -1.58)	0.0012
183	391	32.28 (29.60 to 34.86)	383	31.66 (28.99 to 34.23)	0.62 (-3.09 to 4.34)	0.7418
548	509	43.14 (40.22 to 45.92)	492	41.65 (38.75 to 44.41)	1.49 (-2.52 to 5.51)	0.4662

Note one patient wasexcluded from all analyses as follow up time was missing. * positive numbers indicate less mortality with alteplase. We estimated the standard error for the difference in survivorship functions using the individual standard errors of the K-M estimates for control and alteplase and calculated the 95% point-wise confidence bands and associated P-values

Table III Estimate of mortality hazard ratios with alteplase by delay to randomization and baseline predicted prognosis from a Cox regression model with interactions with delay to randomization and predicted prognosis.

			Predicted poor prognosis (log odds)	
Delay (hours)	20% (-1.39)	50% (0.00)	70% (0.85)	90% (2.20)
Death at 0 to 7 days				
2	1.94 (0.92 to 4.11)	1.91 (1.09 to 3.34)	1.88 (1.18 to 3.00)	1.85 (1.26 to 2.73)
3	1.74 (0.89 to 3.41)	1.71 (1.07 to 2.73)	1.69 (1.17 to 2.43)	1.66 (1.25 to 2.19)
5	1.40 (0.73 to 2.66)	1.37 (0.87 to 2.17)	1.36 (0.93 to 1.97)	1.33 (0.94 to 1.88)
Death at 183 to 548 days				
2	1.38 (0.69 to 2.78)	1.03 (0.60 to 1.75)	0.86 (0.54 to 1.36)	0.64 (0.41 to 1.00)
3	1.47 (0.83 to 2.60)	1.09 (0.74 to 1.61)	0.91 (0.67 to 1.25)	0.68 (0.50 to 0.94)
5	1.66 (0.99 to 2.79)	1.24 (0.85 to 1.80)	1.03 (0.73 to 1.46)	0.77 (0.51 to 1.18)

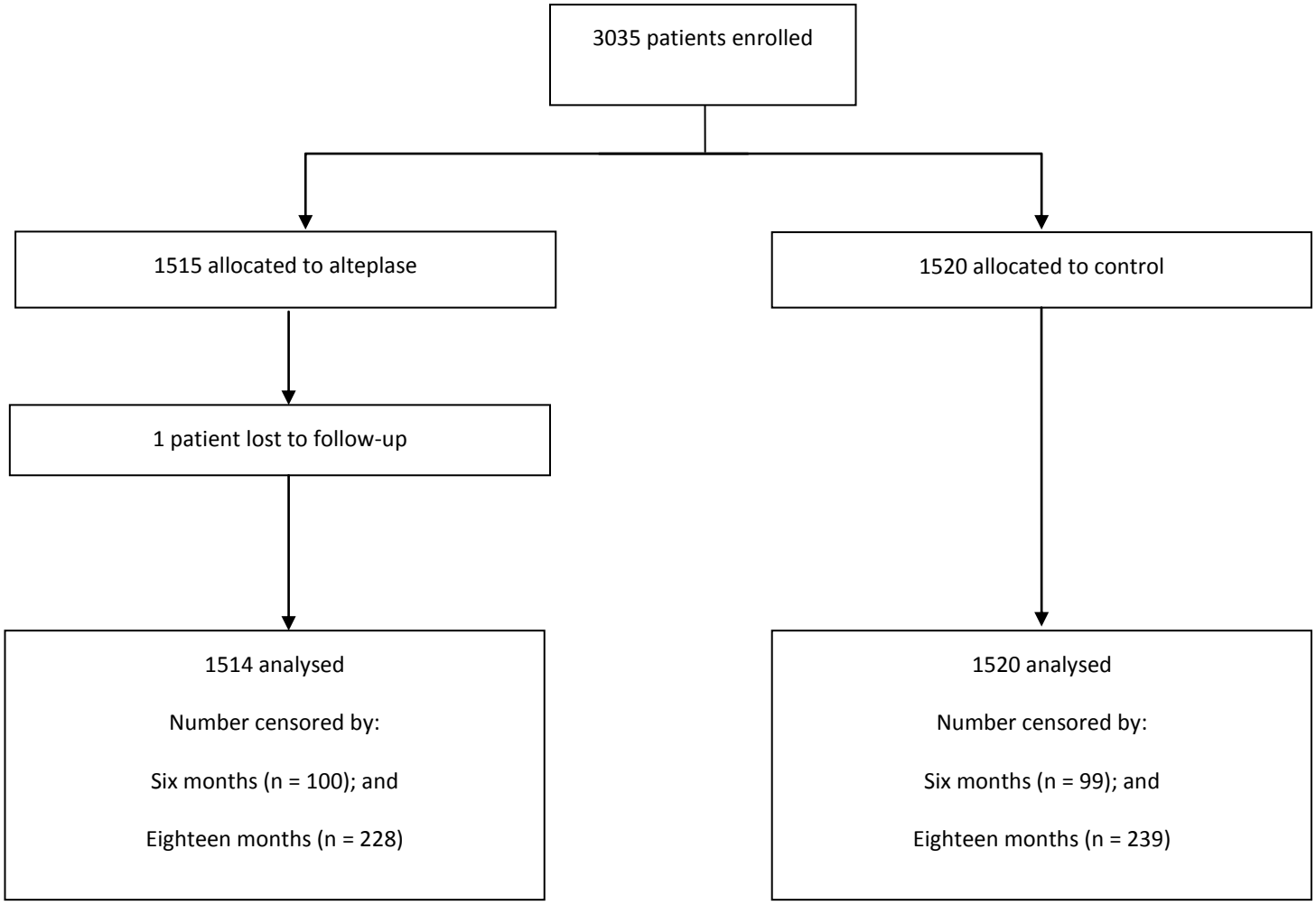

Figure I. CONSORT diagram