Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials

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Summary

Background Quick administration of intravenous recombinant tissue plasminogen activator (rt-PA) after stroke improved outcomes in previous trials. We aimed to analyse combined data for individual patients to confirm the importance of rapid treatment.

Methods We pooled common data elements from six randomised placebo-controlled trials of intravenous rt-PA. Using multivariable logistic regression we assessed the relation of the interval from stroke onset to start of treatment (OTT) on favourable 3-month outcome and on the occurrence of clinically relevant parenchymal haemorrhage.

Findings Treatment was started within 360 min of onset of stroke in 2775 patients randomly allocated to rt-PA or placebo. Median age was 68 years, median baseline National Institute of Health Stroke Scale (NIHSS) 11, and median OTT 243 min. Odds of a favourable 3-month outcome increased as OTT decreased (p=0·005). Odds were 2·8 (95% CI 1·8–4·5) for 0–90 min, 1·6 (1·1–2·2) for 91–180 min, 1·4 (1·1–1·9) for 181–270 min, and 1·2 (0·9–1·5) for 271–360 min in favour of the rt-PA group. The hazard ratio for death adjusted for baseline NIHSS was not different from 1·0 for the 0–90, 91–180, and 181–270 min intervals; for 271–360 min it was 1·45 (1·02–2·07). Haemorrhage was seen in 82 (5·9%) rt-PA patients and 15 (1·1%) controls (p<0·0001). Haemorrhage was not associated with OTT but was with rt-PA treatment (p=0·0001) and age (p=0·0002).

Interpretation The sooner that rt-PA is given to stroke patients, the greater the benefit, especially if started within 90 min. Our results suggest a potential benefit beyond 3 h, but this potential might come with some risks.

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*Details at end of report; full list online at http://image.thelancet.com/extras/03art1122webappendix1.pdf

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Introduction

Thrombolysis with intravenous rt-PA is effective for strokes due to acute cerebral ischaemia when given within 3 h of symptom onset. In six large, multicentre, randomised, placebo-controlled trials researchers tested the benefits of rt-PA for acute stroke within 6 h of onset.[1–5] The investigators used similar doses of rt-PA and had common outcome measures, but the maximum time allowed to start rt-PA infusion ranged from 3 to 6 h. The most appropriate interval for beginning thrombolytic treatment remains to be clarified. Better understanding of the therapeutic window for intravenous rt-PA is important because the short time currently allocated for treatment is the greatest barrier to wider application of thrombolytic therapy.

The chance of benefit from intravenous rt-PA diminishes as time elapses during the first 3 h after onset of the stroke.[6] By combining individual patients' data from six trials, we have extended this analysis to 6 h. The trials were: two National Institute of Neurological Disorders and Stroke (NINDS) trials (parts 1 and 2, 3-h window), two ECASS trials (6-h window), and two ATLANTIS trials (part A, 6-h window and part B, 5-h window). We sought to determine whether time-to-treatment with intravenous thrombolytic therapy is a critical predictor of therapeutic benefit.

Methods

Patients

The trials we analysed represent all major investigations of rt-PA for acute stroke and more than 99% of all patients treated with intravenous rt-PA in randomised controlled clinical trials of acute ischaemic stroke identified in an ongoing cumulative meta-analysis.[7] From all investigations of rt-PA identified in that meta-analysis, the results of only one small (n=27) randomised pilot feasibility trial were not included because different endpoints were used.[8] For our combined analysis, a neuroradiologist (RvK) assessed all CT scans of patients with symptomatic or asymptomatic haemorrhage within 36 h to standardise the definition of intracerebral haemorrhage across trials.

Eligibility criteria

In all six trials, inclusion was based on a clinical diagnosis of ischaemic stroke determined by a focal neurological deficit measurable on either the National Institutes of Health Stroke Scale (NIHSS)[9] for NINDS and ATLANTIS, or the Scandinavian Stroke Scale for ECASS,[10] a clearly defined time of stroke onset, and CT scan of the head that excluded haemorrhage. All investigations had strict criteria for determination of time of stroke onset. Patients who awoke with symptoms of stroke were either excluded or time of onset was defined as the time they were last awake and had no symptoms of stroke. Informed consent was obtained for all patients.

The time allowed from stroke onset to start of treatment (OTT) varied between trials. In the NINDS studies, the

protocols dictated that treatment start within 3 h of onset of symptoms, and within 90 min for half the patients. Because the number of patients in the 91–180 min stratum could never exceed by more than two the number in the 0–90 min stratum, and because a permuted-block design was used, there were similar numbers of patients in both strata. In ECASS, patients were enrolled between 0–360 min from symptom onset with no stratification. Those in ATLANTIS A were enrolled from 0–360 min. ATLANTIS B initially recruited patients from 0–300 min. After the results of the NINDS trials became known, this was narrowed to 180–300 min from symptom onset.

All trials shared many exclusion criteria designed mainly to restrict the risk of bleeding. Thus, in the NINDS and ATLANTIS trials, patients were excluded if they had had stroke or serious head trauma within the preceding 3 months, major surgery within 14 days, gastrointestinal or genitourinary bleeding within 21 days, arterial puncture at a non-compressible site within 7 days, any history of intracranial haemorrhage or present symptoms suggestive of subarachnoid haemorrhage, or systolic blood pressure consistently more than 185 or diastolic more than 110 mm Hg (or patients needing aggressive treatment to lower their pressure to these levels). Patients taking oral anticoagulants, heparin within 48 h, and a raised partial thromboplastin time, and those with a prothrombin time more than 15 s or platelet count below 100 000 were also excluded. The ATLANTIS trials had slightly different allowed intervals from a previous stroke (6 weeks) and major surgery (30 days). ECASS had similar exclusions: conditions associated with gastrointestinal bleeding, trauma, surgery, or arterial puncture within 3 months; raised systolic or diastolic blood pressure; long-lasting partial thromboplastin time or prothrombin time; platelet count less than 100 000; and packed cell volume (haematocrit) less than 25.

There were no upper age limits during the later years of the NINDS part 1 trial or throughout the entire part 2 trial. ECASS and ATLANTIS excluded patients aged younger than 18 years or older than 80 years. The studies had important differences in exclusion of patients with mild or severe stroke. All investigations excluded patients who were rapidly improving. Individuals without significant deficit were excluded from NINDS parts 1 and 2 but there were no upper or lower limits of baseline NIHSS scores. In ECASS and ATLANTIS, patients with minor stroke (Scandinavian Stroke Scale >50 in ECASS, and NIHSS <4 in ATLANTIS) were excluded. Also, participants with complete hemispheric syndromes with hemiplegia and decreased consciousness or forced head and eye deviation were excluded from ECASS.

ECASS and ATLANTIS B also excluded those with extended early infarct signs on the baseline CT scan such as diffuse swelling and parenchymal hypodensity, with or without effacement of cerebral sulci in more than 33% of the middle cerebral artery territory. Detailed instructions for exclusion of such patients were provided to all of the ECASS and ATLANTIS sites. No such exclusion based on CT scan existed in the NINDS trials. To exclude possible stroke mimics, all studies excluded patients with seizure associated with stroke onset, or serum glucose below 500 mg/L or above 4000 mg/L. Patients were excluded from analysis if OTT could not be determined to be within 6 h.

Treatment

NINDS, ATLANTIS, and ECASS II gave a total intravenous study drug dose of 0·9 mg/kg bodyweight (90 mg maximum), whereas ECASS I used a total dose of 1·1 mg/kg (100 mg maximum). All studies gave 10% of the dose as a bolus during the first minute. The remainder was infused over 1 h. All trials allowed inclusion of patients who had taken antiplatelet agents before their stroke, but precluded the use of oral or intravenous anticoagulants or antiplatelet agents for the first 24 h after treatment. Specific guidelines for monitoring and treating raised blood pressure for the first 24 h after treatment were provided to all centres.

Outcome measures

The trials were similar in their outcome measures. Investigators in all studies measured NIHSS, modified Rankin Scale, and Barthel Index up to 3 months after stroke onset, calculated mortality, carefully determined the occurrence of haemorrhage with CT, and relied on clinical scales for their primary outcome measures. Measures of the Glasgow Outcome Scale and the Scandinavian Stroke Scale were not obtained in all studies and were not included. There were substantial differences between the trials in the definition of intracranial haemorrhage and in specific outcome scales and definitions of favourable outcomes that were chosen.

The trials differed in definition of primary outcome. In NINDS part 1, primary outcome was defined as the proportion of patients who improved from baseline by 4 or more points on the NIHSS scale at 24 h. In NINDS part 2, investigators assessed good outcome as low or no deficit at 90 days based on four measures (Barthel, Rankin, Glasgow Outcome, and NIHSS).[11–13] A global test statistic was used to simultaneously test for effect in all measures. ECASS I compared the median value of the Barthel and Rankin scales in the treated and control groups at 90 days. ATLANTIS A used change in NIHSS from baseline at 24 h and 30 days and the CT infarct volume at 30 days, and ATLANTIS B used the proportion at 90 days with NIHSS 0–1 as the primary outcome. The ECASS II primary endpoint was low or no deficit at 90 days with the Rankin scale.

Investigators in all studies went to great lengths to classify brain bleeding events with a central medical monitor or safety committee to review all CT scans and clinical data. The NINDS and ATLANTIS trials differentiated between symptomatic and asymptomatic intracranial haemorrhage. ECASS differentiated between four types of haemorrhagic infarction and parenchymal haemorrhage. Parenchymal hemorrhage II was defined as a dense blood clot exceeding 30% of the infarct volume with substantial space-occupying effect. Similar to the other studies, the ECASS protocol mandated CT scanning at 24 h, but also again between days 6 and 8 after stroke onset.

Statistical analysis

We focused primarily on the 3-month favourable outcome defined by three neurological function scores of modified Rankin Scale (0 or 1), Barthel Index (95 or 100), and NIHSS (0 or 1). For all three outcomes the dichotomies were chosen to represent minimal or no poststroke disability (favourable, not favourable). Of particular interest was whether the odds of a favourable outcome increased as OTT decreased (ie, whether there is an OTT by treatment interaction). We tested for this interaction with a global statistical test. We used generalised estimating equations to estimate the odds ratio, 95% CIs , and p values calculated from correlated binary outcomes in a logistic regression model.

All trials were missing one or more of these outcome measures at 90 days for some patients. A conservative algorithm assigning outcomes based on measurement made earlier than 90 days for these patients was

Potential confounders

Age (years)
Weight (kg)
Sex
Baseline diastolic blood pressure (mm Hg) at start of treatment
Baseline systolic blood pressure (mm Hg) at start of treatment
Blood glucose comcentration at baseline (mg/L)
NIHSS on admission
History of stroke or transient ischaemic attack
History of diabetes
History of angina
Previous or current atrial fibrillation
History of myocardial infarction
History of congestive heart failure
History of hypertension
On aspirin at time of index stroke

developed and applied to all investigations. If no measurements were available after baseline, the worst score for the modified Rankin Scale, NIHSS, or Barthel Index was assigned. The algorithm allowed all patients with known OTT to be included in the final intention-to-treat (ITT) analysis. 12, 11, 33, 37, 83, and 47 patients from NINDS part 1, NINDS part 2, ECASS I, ECASS II, ATLANTIS A, and ATLANTIS B, respectively, were missing one or more outcomes at 3 months based on the ITT algorithm and were given the worst outcomes. In the original report on the NINDS trials only one patient in part 1 and four in part 2 were reported as having missing outcomes. For the other 18 patients, outcomes after 90 days were available.

To obtain maximum study power to establish whether the benefit of rt-PA changes with OTT, we tested for an interaction between the two, treating OTT as a continuum in a logistic regression model, after validating the linearity of log-odds for the OTT variable. Since there might be potential confounders that mask or exaggerate the treatment by OTT interaction, the other baseline variables associated with stroke outcome from previous publications (panel) were considered for inclusion into a multivariate logistic regression model. To be a potential confounder, a variable had to be associated with either treatment or with OTT, and also associated with the outcome of interest.

To identify potential confounders, we used Spearman's correlation for testing the association between OTT and the other baseline continuous variables and likelihood-ratio tests for testing the association between treatment and the other baseline continuous or categorical variables. A potential association was regarded as present if $p \leq 0{\cdot}2$. All baseline variables with a potential association with treatment or OTT and associated with the outcome would be included into the first step multivariable model. A continuous variable as potential confounder was further tested for linearity of log-odds before inclusion in a multivariable model to determine whether transformations were needed. As a result, all continuous variables were kept as continuous and were centralised (subtracted mean and divided by SD).

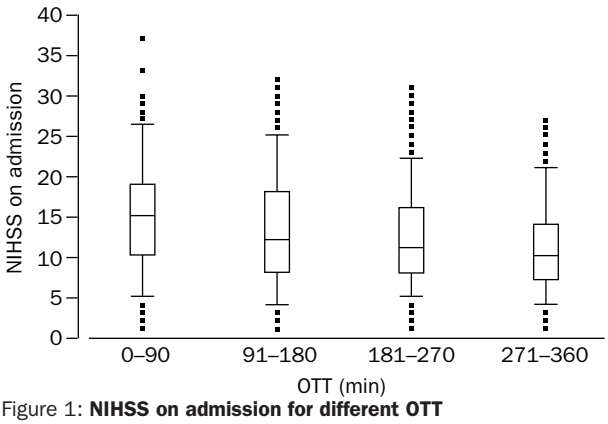

Figure 1: **NIHSS on admission for different OTT**
89 patients without baseline measurements for NIHSS were excluded from this analysis.

Dummy variables representing a trial (NINDS, ECASS, or ATLANTIS) could not be included in the logistic regression model. Trial is collinear with OTT since OTT is defined by trial. When there is a high degree of collinearity, the logistic regression model will not converge to a solution. Trial also defines continent, ethnic background, and dose (the administered dose was higher in the ECASS I trial [planned 1·1 mg/kg] than in all others [planned 0·9 mg/kg]). Thus, these three variables were also collinear with OTT, by design, and therefore could not be considered for inclusion into the multivariate logistic regression model.

To test the consistency of treatment and OTT effect on the 3-month outcome of interest, we also did an analysis that included two-way interactions (age by NIHSS at baseline, by systolic blood pressure, and by diastolic blood pressure) taken from a previous report[14] in the final multivariate logistic regression model with their associated main effects. We used backward stepwise model selection by testing the interactions and then, if interactions were not detected, we tested main effects. Interactions with $p<0{\cdot}1$, and their associated main effects, and main effects (cut-off $p<0{\cdot}05$) based on the likelihood ratio statistic were retained in the final model.

The final logistic regression model was developed on the basis of only recorded data—ie, participants missing any data item were excluded. We then applied the model to the total population using the ITT approach described previously. The analyses with only observed data (n=2552) and analyses of ITT (n=2775) gave similar results; therefore ITT results are presented. Similar analytical approaches were used to study treatment and OTT effect on 3-month favourable outcomes individually, and treatment and OTT effect on modified Rankin Scale (0, 1, or 2) as defined in ECASS post-hoc analyses,[3] respectively. Analyses of recorded data and ITT datasets gave results that were much the same. Epi Info 2000 was used to do the sample size calculation, assuming $\alpha=0{\cdot}05$, two-sided, and power=90%. Cox regression adjusting for NIHSS at baseline was used to calculate hazard ratios for death.

	Treatment	n	Odds ratio (95% CI)*	
			Adjusted	Unadjusted
Interval (min)				
0–90	rt-PA	161	2·81 (1·75–4·50)	1·96 (1·30–2·95)
	Placebo	150		
91–180	rt-PA	302	1·55 (1·12–2·15)	1·65 (1·23–2·22)
	Placebo	315		
181–270	rt-PA	390	1·40 (1·05–1·85)	1·34 (1·04–1·72)
	Placebo	411		
271–360	rt-PA	538	1·15 (0·90–1·47)	1·04 (0·84–1·29)
	Placebo	508		

3-month favourable outcomes include Rankin (0–1), Barthel (95–100), and NIHSS (0–1). One, eight, nine, and six patients from NINDS part I, ECASS I, ECASS II, and ATLANTIS B, respectively, were excluded from this analysis since they were randomised after 360 min or OTT was not reported. *Odds ratios calculated from global statistical approach[13] by ITT analysis. Adjusted odds ratios were calculated adjusting for age, baseline glucose concentration, baseline NIHSS, baseline diastolic blood pressure, previous hypertension, and interaction between age and baseline NIHSS.

Table 1: **Odds ratio for a favourable outcome at 3 months after stroke**

Role of the funding source
For the ATLANTIS trials, Genentech provided full support for the study and Genentech employees participated to some extent in study design, data collection, data analysis, and data interpretation, writing of the report, and in the decision to submit the manuscript for publication. For the ECASS trials, Boehringer Ingelheim provided full support. Employees of Boehringer Ingelheim participated in study design, in data collection, data analysis, data interpretation, writing of the report, and in the decision to submit the report for publication. For the NINDS trials, Genentech provided only the drug and additional study monitoring to ensure compliance with requirements of the US Food and Drug Administration. All support for the investigators and for data collection, analysis, and interpretation were provided by NINDS. For this combined analysis, Genentech and Boehringer Ingelheim provided data from the ATLANTIS and ECASS trials. Statistical support was provided by Boehringer Ingelheim and NINDS.

Results

The ITT analysis included 2775 patients treated at more than 300 hospitals from 18 countries. All trials included some community hospitals. Median age was 68 years, IQR 60–74 years, and 84·6% were reported as white (non-Hispanic), 9·1% as black (non-Hispanic), 2·0% as Hispanic, 0·9% as Asian, and 0·6% as being from other ethnic backgrounds. Ethnic background was not reported for 2·8%. Median baseline NIHSS score was 11, and median OTT 243 min. 1847 patients (67%) were treated for longer than 3 h after symptom onset. Of 928 treated within 3 h, 306 (33%) were treated in trials other than NINDS. Excluded from all trials were eight patients randomised after 6 h from stroke onset and 16 patients whose OTT was not reported. Figure 1 shows the inverse correlation of baseline NIHSS with OTT.

Of 15 potential confounders related to outcome and OTT or treatment (panel), five variables and one interaction between the variables met the criteria for inclusion in the final model. The final multivariable model of favourable outcome included treatment, OTT, age, blood glucose concentrations at baseline, NIHSS on admission, baseline diastolic blood pressure, previous hypertension, interaction between age and NIHSS on admission, and interaction between OTT and treatment. Interaction between OTT and treatment remained significant (p=0·005) in the final multivariable model. In this model, the benefit from treatment increased as OTT decreased. Thus, we undertook separate analyses at four OTT periods (table 1). Figure 2 shows the odds ratios by NIHSS categories within OTT intervals. Figure 3 shows OTT by treatment interaction through estimation of global odds ratio at different times from stroke onset. Assuming a fixed value for the other variables, we plotted the global odds ratio and 95% CIs predicted by the final model for different OTT.

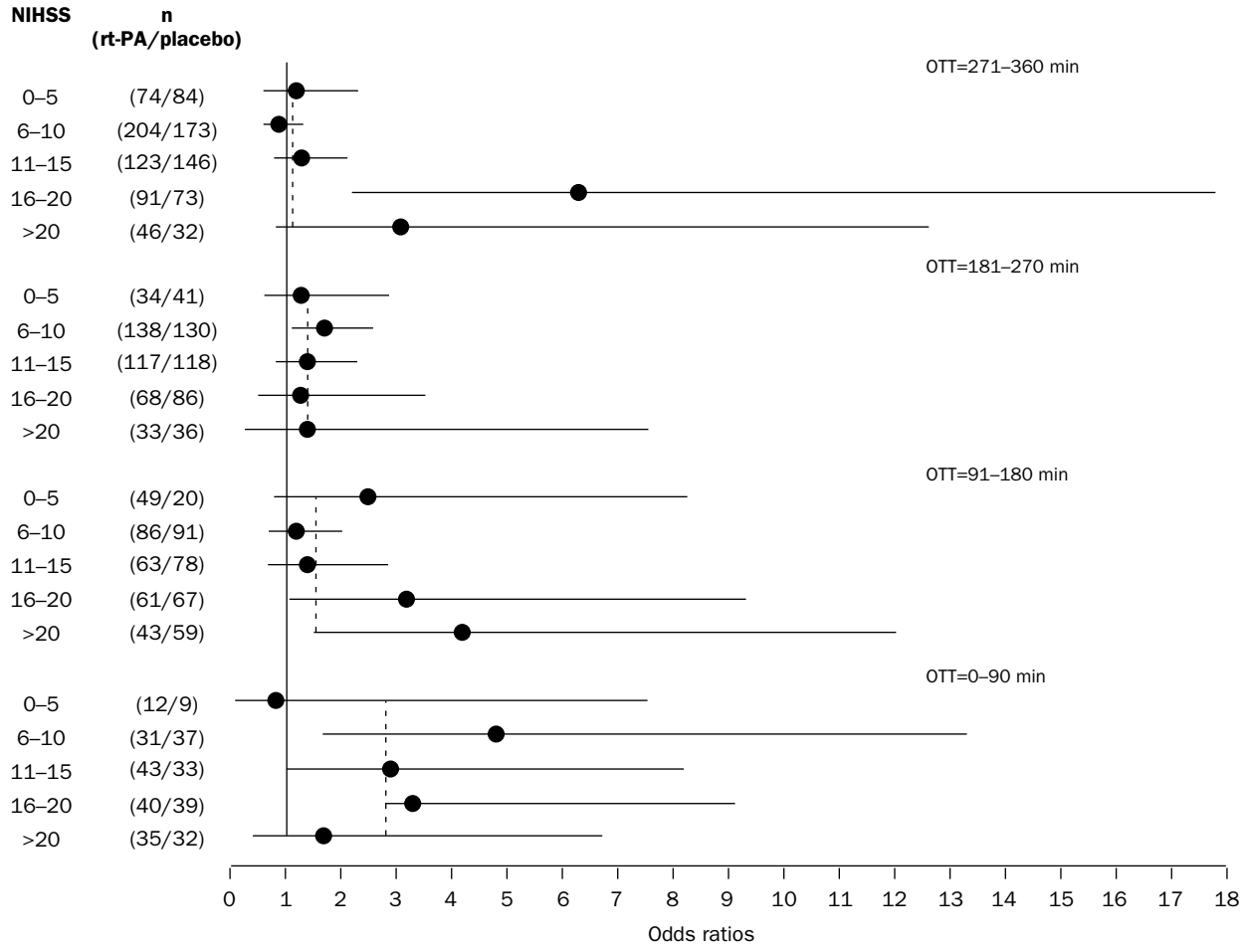

Figure 2: **Odds ratios for favourable outcome at 3 months by OTT and NIHSS category**
Odds ratios were calculated with adjustment for age, baseline glucose concentration, baseline diastolic blood pressure, and previous hypertension. The short dash lines are the overall estimates of odds ratios for each time stratum. 3-month favourable outcomes include Rankin (0–1), Barthel (95–100), and NIHSS (0–1). One, eight, nine, and six patients from NINDS part I, ECASS I, ECASS II, and ATLANTIS B, respectively, were excluded from this analysis because they were randomised after 360 min or OTT was not reported.

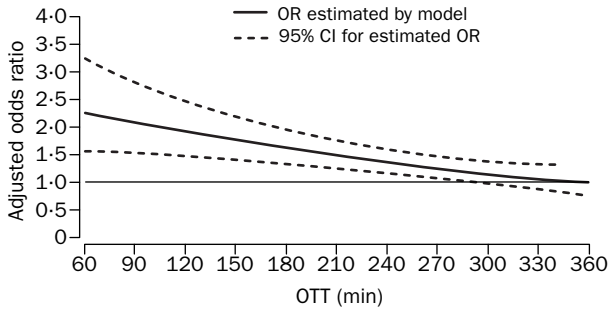

Figure 3: **Model estimating odds ratio for favourable outcome at 3 months in rt-PA-treated patients compared with controls by OTT**

Adjusted for age, baseline glucose concentration, baseline NIHSS measurement, baseline diastolic blood pressure, previous hypertension, and interaction between age and baseline NIHSS measurement.

Figure 4 shows measurements on the modified Rankin Scale at four OTT periods for placebo and rt-PA groups. After 3 months in the ITT analysis, 390 (14·0%) of 2775 patients were dead or had the worst score assigned, and 707 (25·5%) were severely disabled (modified Rankin 4–5). Fewer rt-PA patients treated within 90 min died compared with controls, but assuming all patients with missing data were alive at last follow-up the 95% CIs for the hazard ratio, adjusted for baseline NIHSS, included 1·0 (0·88, 0·54–1·46). Adjusted hazard ratios for the OTT strata 91–180 and 181–270 exceeded 1·0, but 95% CIs were not significant (1·15 [0·77–1·70]; 1·24 [0·84–1·84]). For the OTT interval 271–360, the adjusted hazard ratio exceeded 1·0 (1·45 [1·02–2·07]).

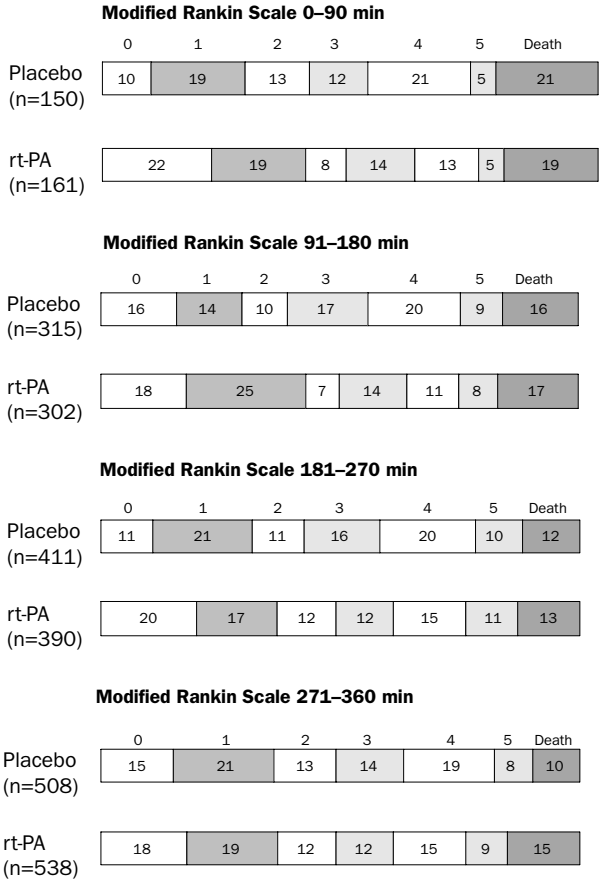

Figure 4: **Modified Rankin Scale measurement at day 90**

0–90 min, n=311; 91–180 min, n=618; 181–270 min, n=801; 270–360 min, n=1046. Values do not equal 100% because of rounding.

	Placebo		rt-PA	
	n*	Patients with parenchymal haematoma (90%, 95% CI)	n	Patients with parenchymal haematoma (90%, 95% CI)
OTT (min)				
0–90	150	0 (0, ··)	161	5 (3·1, 1·6–5·6)
91–180	315	3 (1·0, 0·4–2·0)	302	17 (5·6, 3·9–7·9)
181–270	411	7 (1·7, 1·0–2·9)	390	23 (5·9, 4·3–8·0)
271–360	508	5 (1·0, 0·5–1·8)	538	37 (6·9, 5·3–8·7)

Parenchymal haematoma is defined as a dense blood clot exceeding 30% of the infarct volume with significant space-occupying effect. *One, eight, nine, and six patients from NINDS part I, ECASS I, ECASS II, and ATLANTIS B, respectively, were excluded from this analysis because they were randomised after 360 min or OTT was not reported.

Table 2: **Frequency of parenchymal haematoma between 0 and 360 min after treatment**

Substantial intracerebral haemorrhage (parenchymal haematoma, type II) was seen in 5·9% of the rt-PA patients compared with 1·1% of placebo patients ($p<0·0001$). 59·8% of those with parenchymal haematoma died within 3 months (62·2% for rt-PA and 46·7% for placebo). Median age of patients with haematoma was 72 years (IQR 65–76). Median OTT in patients with the haematoma was 261 min (180–300), and median baseline NIHSS score was 12 (8–16). Table 2 shows the frequency of parenchymal haematoma by OTT. In the multivariate model for haematoma, including treatment, OTT, age, and NIHSS score, the OTT-treatment interaction was not significant ($p=0·48$). Subsequent analyses showed that the occurrence of such haematoma was associated with rt-PA treatment ($p=0·0001$) and age ($p=0·0002$), but not with OTT ($p=0·71$) or baseline NIHSS score ($p=0·10$).

Further details of results available at http://image.thelancet.com/extras/03art1122webappendix2.pdf.

Discussion

Our results confirm that rapid treatment is associated with better outcomes at 3 months. Previously, NINDS Stroke Study investigators reported that the probability of benefit from intravenous rt-PA in the combined data from the two NINDS trials diminishes as time elapses during the first 3 h after onset of the stroke.[6] Our results confirm and expand on this finding. For example, the odds ratio of a favourable outcome for patients treated with rt-PA compared with controls was 2·81 (1·75–4·50) for those treated within 90 min and 1·55 (1·12–2·15) for those treated within 91–180 min. The adjusted hazard ratio for death was not significantly different from 1·0 (HR [95% CI]) for patients treated within 0–270 min and exceeded 1·0 (1·45 [1·02–2·07]) in the interval 271–360. Our findings suggest that the beneficial effect of rt-PA might extend beyond 3 h since the odds ratio for a favourable outcome was 1·40 (1·05–1·85) for those treated within 181–270 min. However, the beneficial effect might not extend to 6 h. Our analysis did not provide strong evidence to support exclusion of patients from treatment based on their initial NIHSS for any OTT.

Definition of the limits of the treatment window for rt-PA in acute ischaemic stroke has been difficult. Based on the results of the two NINDS trials, approval for use of the drug has been restricted to within 3 h of stroke onset. Our results suggest that the benefit of rt-PA could extend beyond 3 h, a finding that is compatible with results of secondary analyses from the other rt-PA investigations.[2,3,5] Figure 3 shows that the point estimate of the odds of a

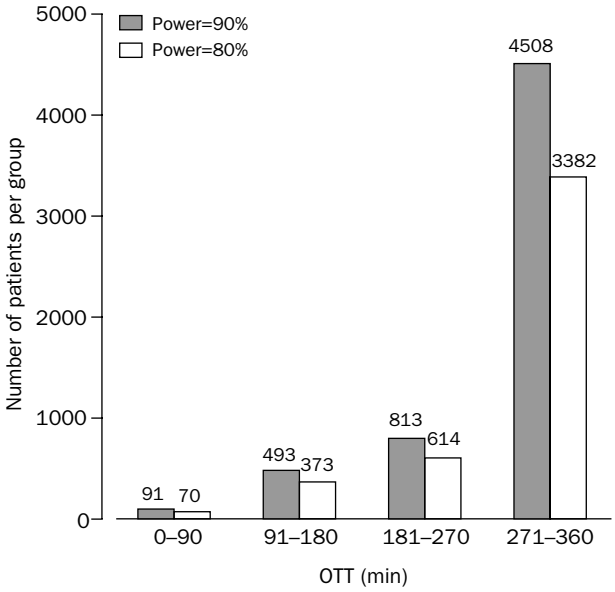

Figure 5: **Sample size by OTT**
Projected number of patients needed for ischaemic stroke studies of thrombolysis based on odds ratios recorded within intervals of OTT.

favourable outcome is close to 1·0 at 360 min, suggesting reduced probability of benefit beyond this time. The apparent reduction in benefit from rt-PA at later periods does not seem to be explained by an increased rate of parenchymal haematoma. We suspect that a progressive disappearance of the ischaemic penumbra is the major factor that accounts for the declining benefit with time.

Patients who continue to have potentially viable ischaemic brain tissue at later times might have substantial treatment benefits.[15,16] Our results are consistent with those from a previous trial in which investigators used transcranial doppler to correlate time to arterial recanalisation with neurological recovery at 24 h after administration of intravenous rt-PA. No individual had early complete recovery if an occlusion persisted for more than 300 min. Complete or part recanalisation of the occluded artery took place within 60 min of the start of treatment in 75% of those in whom recanalisation was seen. A third of these had recanalisation within 30 min of the start of treatment.[17] These data are also consistent with a therapeutic window from stroke symptom onset to start of intravenous rt-PA treatment of 240–270 min.

One trial, ATLANTIS B, specifically addressed the issue of the benefit or risk of such treatment within 3–5 h. This trial enrolled 79% of the participants in the 4–5 h interval and failed to show efficacy. These results are consistent with ours. In the later intervals, consistent with results from ECASS and ATLANTIS, the benefit is small in unselected patients. The sample size needed for a trial of rt-PA would vary by OTT (figure 5). Based on these power analyses, none of the individual trials that treated patients with OTT longer than 3 h had sufficient power to detect the effects of the magnitude recorded. Although these findings suggest that the therapeutic window could extend beyond 3 h, large prospective randomised trials need to confirm this idea. Additional trials are underway: IST 3 (6000 patients); ECASS III (800 patients); DIAS (630 patients); EPITHET (100 patients).

Another important finding in this study is the relation between stroke severity and time to presentation. Patients with more severe strokes arrived earlier in the emergency department, than did those whose condition was less severe (figure 1). Thus, mortality and disability are high in early treatment intervals. This trend is best seen in controls, of whom those treated earlier had greater rates of death and severe disability (modified Rankin Score 4 or 5) than did those treated in later intervals. This finding has implications for the timing of thrombolytic therapy because these patients represent those with the most to gain from treatment, since earlier treatment significantly enhances the likelihood of keeping long-term disability to a minimum. The effect of rt-PA is greatest in those treated early despite greater stroke severity.[18] This result also indicates the potential difficulties in comparing stroke treatment trials in which the time-to-treatment differs substantially, without adjustment for differences in baseline stroke severity.

The relation between time-to-treatment and effectiveness of thrombolytic therapy for stroke confirms previous findings in acute myocardial infarction. The Fibrinolytic Therapy Trialists[19] reported that the absolute difference in 30-day mortality between fibrinolytic and control therapy steadily diminished from 3·5% in patients treated at 0–1 h to 1·6% in those treated within 7–12 h. The CORE investigators[20] reported a strong relation between time-to-treatment with thrombolytic therapy and 35-day mortality. They recorded a mortality of 5·7% in individuals treated in less than 2 h and 12·5% for those treated after 6 h. The GUSTO-IIb investigators[21] reported that the time from enrolment to first balloon inflation for coronary angioplasty was a significant predictor of 30-day mortality, with 1% mortality for patients treated within 60 min and 6·4% mortality for those treated after 90 min.

Our combined analysis indicates that time-to-treatment with thrombolytic therapy is also important for acute stroke (figure 3). However, the therapeutic window for thrombolytic treatment seems to be shorter than that for acute myocardial infarction. The protocols of all trials included measures that were intended to overestimate OTT. For instance, for patients who awoke with stroke symptoms stroke onset was assumed to be at the time they were last known to be healthy. If OTT is an overestimate, the actual therapeutic window could be even shorter.

Our study is limited by differences in trial methodologies such as dose of rt-PA. The total study population was 2775, smaller than that in many acute myocardial infarction trials.[22] However, the magnitude of the differences in outcome is large compared with such trials, especially at early times. Since quicker treatment with rt-PA greatly improves the odds of a favourable outcome, particularly within 90 min, treatment without delay is paramount. Yet, doctors and other health-care personnel might take more time to begin treatment when time limits are longer.[6,23] An acute stroke intervention team can increase the speed and quality of assessment given to a stroke patient before treatment and after arrival in an emergency department. We urge setting a target of 1 h from time of presentation to intravenous treatment for patients with acute ischaemic stroke.[24] This goal could be a challenge for many institutions and might need reorganisation of resources, but it can be achieved.[25]

Our results confirm the strong association between rapid treatment and favourable outcome. Although not as effective as early treatment, our findings suggest a potential benefit from treatment after 3 h. The next step would be to identify patients who are likely to respond to treatment when they present at the later end of the suggested therapeutic interval. The success of acute stroke treatment will be dictated largely by how we use the time we have.

Writing Committee
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All investigators made contributions to one or more of the six trials and have seen and approved the final version of the manuscript. G Albers, G Donnan, and C Fieschi did not contribute to the first draft, but did review the draft for accuracy. Two corporate sponsors, Boehringer Ingelheim and Genentech, co-operated in preparation of the document by providing access to the data from the ECASS and ATLANTIS trials for which they were the sole support.

Conflict of interest statement
Genentech provided active and placebo drug for the NINDS trials, but provided no financial support to investigators during the trials. G Albers, J P Broderick, and M Frankel (only after NINDS trials publication), C Fieschi, W Hacke, S Hamilton, M Kaste, and R von Kummer have received funding from corporate sponsors. E C Haley Jr has a Research Supply Agreement with Genentech that supplies study drug to an NIH-funded clinical trial. S Hamilton has received more than US$10 000 from one of the corporate sponsors. None of the authors has an equity or ownership interest in a corporate sponsor. G Biegert and M Wilhelm are employees of Boehringer Ingelheim.

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