

EXPERT WORKING GROUP**ACTILYSE (ALTEPLASE) BALANCE OF BENEFITS AND RISKS WHEN USED IN THE TREATMENT OF ACUTE ISCHAEMIC STROKE**

Title of paper: Paper 4: Benefits and risks: new study data
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MAHs: Boehringer Ingelheim Limited	Previous Assessments: CHM May 2014
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1. Introduction

This paper will focus on data examining the benefits and risks of alteplase (rt-PA) within the current EU licensed indication.

The MAH was asked for an analysis of any clinical trials, observational study data, or meta-analyses not previously considered during the initial licensing of the stroke indication or during the extension of the time window for treatment which included important information on safety or efficacy. This was to include both MAH-sponsored and independently conducted studies.

The main clinical trial and observational study data used to support the extension to the indication to include treatment of acute ischaemic stroke within 3 hours of onset of symptoms in 2002 and the subsequent further variation in 2012 to extend the treatment window to 4.5 hours following onset of symptoms will first be summarised along with selected data already presented to the UK Commission for Human Medicines (CHM) in May 2014. This will primarily include data from the main randomised clinical trials NINDS parts 1 and 2 [NINDS 1995], ECASS I & II [Hacke 1995, 1998] and ATLANTIS A & B [Clark 2000, 1999] which were considered as part of the initial licensing application for use in stroke and ECASS III [Hacke 2008] which was assessed in the licensing extension to include treatment 3-4.5 hours after onset. This paper will also summarise a reanalysis of the NINDS trials [O'Fallon 2004], the IST-3 trial [IST-3 2012, 2013], and a further 2014 individual patient clinical trial meta-analysis by Emberson et al. [unpublished at the time of assessment by CHM in May 2014, Emberson 2014].

Further data contributed to the licensing extension but will not be summarised again here. These included an unpublished pooled analysis conducted by the MAH excluding ECASS I, interim data from the SITS-ISTR observational registry study [Wahlgren 2008], some early smaller observational cohort studies [Albers 2000, Lopez-Yunez 2001, and Koennecke 2001], and a 2010 meta-analysis of clinical trials conducted by Lees et al. [Lees 2010]. Observational data from the Oxfordshire community stroke project and the Lothian stroke register [Slot 2008] were presented to CHM in May 2014 (section 4.3) but again will not be summarised again here.

This paper will then summarise additional relevant data on the benefits and risks of rt-PA within the current EU approved indication of acute ischemic stroke that have not already been considered within regulatory procedures. This includes the latest data from the observational registry SITS-ISTR [Ahmed 2013] and the SITS-UTMOST cohort, the Get With The Guidelines-Stroke registry [Saver 2013], the Bade-Wuerttemberg Stroke registry [Gumbinger 2014], and the Canadian Alteplase for Stroke Effectiveness Study [Shobha 2011]. Additional aspects of some of these studies as well as those summarised earlier will be further addressed in Paper 4.

Data most specifically relevant to the benefits and risks of rt-PA outside of the licensed indication will be highlighted where appropriate but discussed in further detail within a subsequent paper to be presented to this group for discussion in January 2015.

2. Key results from studies used within licensing procedures

The studies that formed the basis of the initial application for the indication in the treatment of acute ischaemic stroke were NINDS part 1 and 2, ECASS I and II, and ATLANTIS part A and B. The main study supporting the extension to the time window for treatment up to 4.5 hours post-symptom onset was the ECASS III study. A high level summary of these trials (also provided in the May 2014 CHM paper, sections 3.1 and 3.2) is provided here.

NINDS part 1 and 2 (0-3 hours of symptom onset) [NINDS 1995]

These two studies were conducted in the US by the US National Institute of Neurological Disorders and Stroke (NINDS). Both studies were placebo-controlled, used a dose of 0.9mg/kg and treatment was within 0-3 hours of symptom onset. NINDS part 1 was a phase II study (n=291), and NINDS part 2 was phase III (n=333).

The primary endpoint for NINDS part 1 was neurological outcome after 24 hours measured as an improvement from baseline in the NIH stroke scale (NIHSS) of 4 or more points or complete resolution of neurologic deficit. The primary endpoint was not reached as there was no significant difference between the rt-PA and the placebo groups at 24 hours. However there was a benefit observed at 3 months after treatment in the rt-PA group.

NINDS part 2 was the pivotal randomised, placebo controlled trial supporting the application. The primary endpoint was clinical outcome at 3 months, according to scores on the Barthel index (BI), modified Rankin scale (mRS), Glasgow outcome scale (GOS) and NIHSS. The odds ratio for a favourable outcome (minimal or no disability at 3 months) in the rt-PA group compared with placebo was 1.7 (95% CI [1.2-2.6]). The absolute increase in number of patients with minimal disability was 12% at 90 days. Symptomatic intracranial haemorrhage (ICH) within 36 hours of stroke onset occurred in 6.4% of rt-PA treated patients vs. 0.6% of placebo patients. This did not translate into an increase in mortality. Overall mortality in the rt-PA group was 17%, vs. 21% in the placebo group. Stratifying patients by the time window for treatment suggested that the benefit of rt-PA over placebo is greater in the first 1.5 hours compared with the second 1.5 hours.

ECASS I (0-6 hours of symptom onset) [Hacke 1995]

The European Co-operative Acute Stroke Study (ECASS I) was a randomised double-blind placebo controlled trial in 14 European countries, designed to evaluate efficacy and safety of rt-PA in patients with acute ischaemic stroke with moderate to severe neurological deficit and with none or minimal early infarct signs on the initial CT scan. This was a phase III study, n=610.

The primary endpoints included BI and mRS at 90 days. Secondary endpoints included combined BI, mRS and Scandinavian stroke scale (SSS) at 90 days and 30 days mortality. The dose of rt-PA used was 1.1 mg/kg body weight within 6 hours of symptom onset.

There was no difference between the groups in the intention to treat (ITT) analysis of the primary endpoints. The secondary endpoint of combined BI and mRS demonstrated a difference in favour of rt-PA treatment. Mortality at 90 days was higher in the rt-PA population (22.4% vs. 15.8% for placebo) and parenchymal haemorrhages were significantly more frequent in the rt-PA group (ITT: n=62 for rt-PA vs. n=20 for the placebo group).

ECASS II (0-6 hours of symptom onset) [Hacke 1998]

The European-Australasian Acute Stroke Study (ECASS II) used a lower dose of rt-PA (0.9mg/kg body weight) to match that used in NINDS. This was a phase III study, n= 800. Treatment was given within 6 hours of symptom onset, stratified into 0-3 hours and 3-6 hours. Due to issues with patients receiving early treatment such as the time taken between onset of symptoms and arrival at hospital, only 81 out of 409 rt-PA treated patients were included in the early stratum.

The primary endpoint was the proportion of patients with a favourable outcome (score 0 or 1) on the mRS at day 90 after treatment. No significant difference was found between rt-PA and placebo for the primary endpoint. The study found no evidence that efficacy depends upon administration within 3 hours of symptom onset, however there were only a small number of patients in the 0-3 hour time window.

Symptomatic ICH occurred in 8.8% of rt-PA patients and in 3.4% of placebo patients, but no increase in morbidity or mortality at day 90 was observed in the rt-PA group compared with placebo.

ATLANTIS part B (3-5 hours of symptom onset) [Clark 1999]

The Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischaemic Stroke (ATLANTIS) study was a placebo-controlled, double-blind, randomised study conducted in North America. It was initially designed to assess rt-PA administered from 0-6 hours following onset of symptoms. Two years into the study the DSMB halted enrolment and the time-window for treatment was changed to 0-5 hours due to safety concerns in the 5-6 hour group. At this point the trial was re-started as part B, with the previously enrolled patients to be considered separately as part A. Part B was further modified 2 years later to a time window of 3-5 hours in light of the NINDS trial results for the 0-3 hour window. 31 patients in part B had been enrolled from 0-3 hours at the time of this change.

Part B was a phase III study, n=613. The dose of rt-PA used was 0.9mg/kg, as used in NINDS. This study was not included in the initial submission by the applicant for this indication. The trial endpoints were changed during the study¹ (for reasons unknown to this assessor), at the time of publication of part B the primary endpoint was the number of patients with an excellent neurological recovery at day 90 (score 0-1 on the NIHSS). Secondary endpoints were excellent recovery on BI, mRS and GOS scales at days 30 and 90.

For the primary outcome, 32% of placebo and 34% of rt-PA patients had an excellent recovery at 90 days. There were no differences in secondary outcome measures.

In the first 10 days following treatment, the rate of ICH was higher in the rt-PA treated group than in the placebo group (symptomatic ICH: 11.4% rt-PA vs. 4.7% placebo). Mortality at 90 days was 11% in the rt-PA group, vs. 6.9% in the placebo group.

This trial was stopped prematurely after a pre-planned interim analysis, as the DSMB considered a beneficial effect seemed unlikely.

Part A included 142 patients and also found no significant benefit for any of the planned efficacy endpoints, and an increased risk of ICH.

¹ The ATLANTIS part A publication states primary hypotheses as: 1. Significant difference between rt-PA and placebo groups in clinical improvement, (decrease of ≥ 4 points on the NIHSS or complete resolution of symptoms from baseline to 24 hours/30 days); 2. Significant difference between rt-PA and placebo groups in volume of cerebral infarction as measured by CT scanning at 30 days.

ECASS III (3 - 4.5 hours of symptom onset) [Hacke 2008]

The European Cooperative Acute Stroke Study III (ECASS III) was a randomised, multi-national, double-blind, placebo controlled trial in patients treated with rt-PA between 3 and 4.5 hours after stroke onset. The study took place between 2003 and 2008 and enrolled 821 patients. Inclusion and exclusion criteria were identical to the EU SmPC for rt-PA in ischaemic stroke, except for the time-window for treatment.

rt-PA was administered at a dose of 0.9 mg/kg body weight (the licensed dose). The primary outcome was mRS 0-1 at Day 90. The secondary outcome was a global measure combining Day 90 results for the mRS score 0-1, the BI score ≥ 95 , the NIHSS score of 0-1 and the GOS score of 1.

The safety endpoints included overall mortality at day 90, stroke-related and neurological deaths, all ICH, symptomatic ICH, and symptomatic brain oedema.

ECASS III results

Treatment with rt-PA was significantly associated with a favourable primary outcome (mRS = 0-1 at day 90) compared with placebo in the intention to treat population:

OR 1.34; 95% CI [1.02-1.76]

RR 1.16; 95% CI [1.01-1.34]

The more global secondary endpoint for the intention to treat population was also found to have a statistically significant difference in favour of rt-PA treatment:

OR 1.28; 95% CI [1.00-1.65].

The per-protocol results found similar, slightly greater ratios. The effect on the distribution of mRS scores is shown in the following figure.

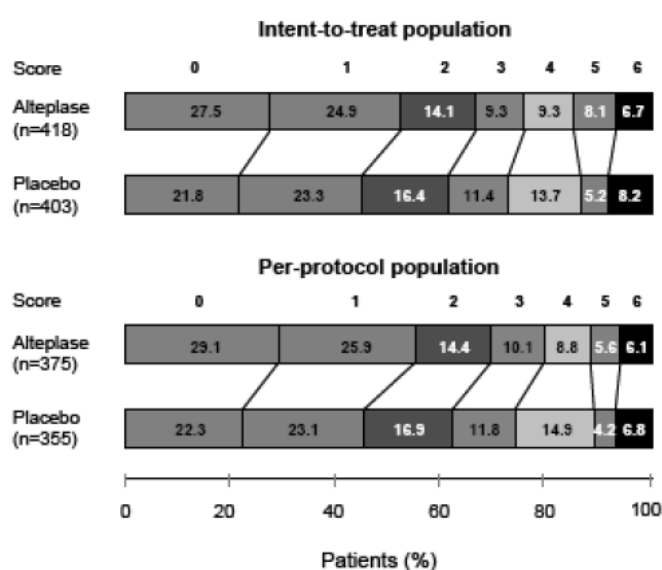


Figure 1: Overall distribution of scores on the mRS at the day 90 visit

A total of 113 patients (27%) in the rt-PA group had intracranial haemorrhages of which 3 were fatal. This compares with 71 patients (17.6%) with ICH in the placebo group of which 0 were fatal. Most ICH occurred within 24 hours of receiving treatment. The OR for any ICH was 1.73 95% CI [1.24-2.42]. Symptomatic ICH was defined as any blood in the brain or intracranial associated with a clinical deterioration of ≥ 4 points of the NIHSS for which haemorrhage has been identified as the dominating cause. All symptomatic ICH occurred within the first 22 to 36 hours

after initiation of treatment. Symptomatic ICH frequencies were also estimated using definitions from previous studies².

	Alteplase n (%)	Placebo n (%)	Odds Ratio (95% CI)	p value ¹
ITT population	418 (100.00)	403 (100.00)		
As per ECASS III definition	10 (2.39)	1 (0.25)	9.85 (1.26-77.32)	0.0076
As per ECASS II definition	22 (5.26)	9 (2.23)	2.43 (1.11-5.35)	0.0228
As per SITS-MOST definition	8 (1.91)	1 (0.25)	7.84 (0.98-63.00)	0.0219
As per NINDS definition	33 (7.89)	14 (3.47)	2.38 (1.25-4.52)	0.0064
PP population	375 (100.00)	355 (100.00)		
As per ECASS III definition	7 (1.87)	1 (0.28)	6.73 (0.82-55.01)	0.0398
As per ECASS II definition	19 (5.07)	9 (2.54)	2.05 (0.92-4.60)	0.0751
As per SITS-MOST definition	5 (1.33)	1 (0.28)	4.78 (0.56-41.15)	0.1157
As per NINDS definition	28 (7.47)	14 (3.94)	1.97 (1.02-3.80)	0.0410

Table 1: Overall incidence of symptomatic ICH in ECASS III (according to different definitions).

The percentage of patients with symptomatic ICH was found to remain the same for the rt-PA treated group across the three time periods of treatment (3-3.5, 3.5-4 and 4-4.5 hours) using NINDS criteria. For the placebo group, the rate of symptomatic ICH reduced with longer time to treatment.

Overall mortality rates were similar between the two groups, in the ITT population a total of 32 (7.7%) of patients in the rt-PA arm died whilst 34 (8.4%) in the placebo group died. A trend for increasing mortality with increasing time to treatment was found.

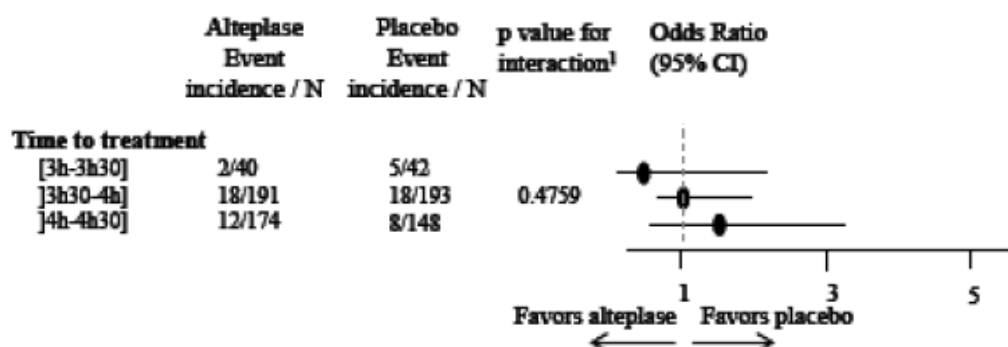


Figure 2: Subgroup analysis (time to treatment) for mortality (ITT population)

Elderly patients (≥ 65 years) were found to have a trend for increased mortality, an increased risk for symptomatic ICH and a trend to lower efficacy.

² Definition of sICH according to:

ECASS II: Any intracranial bleed and at least 4 points worsening on the NIHSS score (the same as the **ECASS III** protocol definition except that the causal relationship between haemorrhage and clinical deterioration was not required).

SITS-MOST: Local or remote parenchymal haematoma type 2 on the 22- to 36-hour posttreatment imaging scan, combined with a neurological deterioration of 4 points or more on the NIHSS from baseline, or from the lowest NIHSS value between baseline and 24 hours, or leading to death.

NINDS: A haemorrhage was considered symptomatic if it was not seen on a previous CT scan and there had subsequently been either a suspicion of haemorrhage or any decline in neurological status. To detect intracranial haemorrhage, CT scans were required at 24 hours and 7 to 10 days after the onset of stroke and when clinical finding suggested haemorrhage.

Assessor's comments:

A number of issues have been raised regarding these trials, including: baseline imbalances in stroke severity between the rt-PA treated arm and the placebo arm in the NINDS trials and ECASS III; possible centre effects in NINDS; NINDS study conduct (randomisation, blood pressure evaluation, pattern of onset to treatment time); ECASS III design and conduct (blinding of outcome assessments, slow recruitment). Other concerns that have been raised refer more generally to all of the main studies, including the appropriateness of the choice of primary outcome and the primary analyses; the accuracy of the 'time is brain' hypothesis; and the effect of rt-PA on short and long-term mortality.

These concerns are discussed in Paper 4.

3. Key results from the reanalysis of the NINDS trials [O'Fallon 2004]

The findings from the published re-analysis of the NINDS trials were reviewed in the May CHM paper, and some additional points are considered in paper 4. A summary of the findings are provided here.

The rt-PA review committee was established in May 2002 at the request of NINDS, and was asked to:
'address whether there is concern that eligible stroke patients may not benefit from rt-PA given according to the protocol used in the trials and, whether the subgroup imbalance (in baseline stroke severity) invalidates the entire trial as claimed by some of the critics'.

The committee evaluated the same outcome measures as used in the original trial (mRS, GOS, BI and NIHSS).

The principal remit of the committee, to assess whether the baseline imbalance in stroke severity measured by NIHSS was driving the positive results of the trial, was assessed by using sub-group analyses broken down across the baseline NIHSS quintiles (0-5, 6-10, 11-15, 16-20, >20). As expected, there were more favourable outcomes in the milder groups and very few favourable outcomes in the severe groups. However the impact of treatment was seen in the much steeper decline in favourable outcomes with severity in the placebo arm.

Data for mRS are shown here, all outcome scales are presented in the CHM paper.

Modified Rankin score by baseline NIHSS quintiles

Baseline NIHSS	n/N (%) Favourable outcome		Difference	95% CI
	t-PA	Placebo		
0-5	33/42 (79%)	13/16 (81%)	-2.7%	(-26.0, 20.6)
6-10	46/67 (69%)	38/83 (46%)	22.9%	(7.3, 38.4)
11-15	27/65 (42%)	15/66 (23%)	18.8%	(3.0, 34.6)
16-20	21/73 (29%)	14/70 (20%)	8.8%	(-5.3, 22.9)
>20	6/63 (10%)	3/77 (4%)	5.6%	(-2.9, 14.1)

The subgroup analyses make it clear that the overall benefit of rt-PA was not seen only because of the baseline imbalance.

The committee also reviewed a number of other issues including blood pressure assessment/management, intracerebral haemorrhage, onset to treatment time, centre effect, stroke subtype, pre-existing disability and diabetes mellitus

Overall, the committee's findings were that despite an increased incidence of symptomatic intracerebral haemorrhage in rt-PA treated patients, when rt-PA was administered according to the study protocol there was a statistically significant and clinically important benefit of treatment compared with placebo, measured by an adjusted odds ratio of 2.1, 95% CI [1.5-2.9] for a favourable outcome (using the global outcome measure) at 3 months. The analysis was adjusted for centre, time to treatment, study part, age, baseline NIHSS, diabetes and pre-existing disability.

4. Key results from IST-3 [IST-3 2012, 2013]

The third International Stroke Trial (IST-3) was reviewed by CHM in May 2014.

IST-3 was intended to determine whether a wider range of patients than the licensed population would benefit from thrombolysis, in particular patients >80 years of age and patients treated up to 6 hours after symptom onset.

IST-3 was an international, randomised, open-label trial. The initial phase was double-blind and placebo controlled (n=276), and in total for both phases of the trial 3035 patients were enrolled (rt-PA: n=1515; control: n=1520). The study period was from 2000 to 2011.

The primary trial hypothesis was that 0.9 mg/kg rt-PA within 6 hours of symptom onset increased the proportion of people who were alive and independent at 6 months, as measured by the Oxford Handicap Score (OHS). Patients with OHS of 0, 1 or 2 were classed as independent. 1007/3035 (33%) of patients were randomised between 4.5 and 6 hours after stroke onset.

The key results were:

Outcomes at 7 days...

- There was a statistically significant increase in the number of deaths in patients who received rt-PA (163, 11%) compared with control patients (107, 7%) by day 7 post-stroke (adj OR=1.6, 95% CI: 1.22-2.08).
- Fatal intracranial haemorrhage within 7 days of treatment was significantly increased in the rt-PA group compared with controls (adj OR=8.12, 95% CI: 3.68-17.9, p=0.013), as was fatal swelling of the original infarct (adj OR=1.89, 95% CI: 1.14-3.14, p<0.0001).

Outcomes at 6 months...

- In the rt-PA group at 6 months follow-up, 554 (37%) of patients were alive and independent in activities of daily living (OHS 0-2) compared with 534 (35%) in the control group (adj OR=1.13, 95% CI: 0.95-1.35, p=0.181).
- A secondary ordinal analysis found a favourable shift in distribution of OHS scores at 6 months. This analysis was adjusted for age, NIHSS, delay and presence/absence of visible acute ischaemic changes on baseline scan. With

OHS levels 4, 5 and 6 grouped and 0, 1, 2, 3 all discrete, the adjusted OR was 1.27 (95% CI: 1.10-1.47). The corresponding OR with all levels discrete was 1.17 (95% CI: 1.03-1.33).

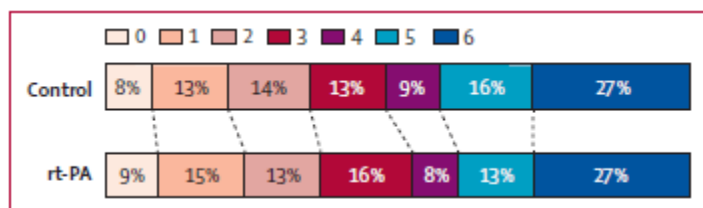


Figure 1: Outcome at 6 months, OHS by treatment group (IST-3 study)

- Pre-defined sub-analyses showed a trend towards a negative primary outcome (OHS 0-2 at 6 months) in those treated 3-4.5 hours after onset although this was not significant (adj OR 0.73, 99% CI: 0.50-1.07) and there was no evidence of a difference across the different treatment time groups (p=0.613).
- The imbalance in the number of deaths observed at 7 days was not found at the 6 month time point, with 408 (27%) rt-PA treated patients compared with 407 (27%) control patients having died by 6 months.

Outcomes at 18 months...

- The primary outcome measure (e.g. alive and independent, OHS score 0-2) was met at 18 months for 391 (35.0%) of patients in the rt-PA group, compared with 352 (31.4%) in the control group (adj OR 1.28, 95% CI: 1.03-1.57, p=0.024).

Assessor's comment: Full comments can be found in the report to CHM already provided to the group. Professor Peter Sandercock, co-Chief Investigator of the IST-3 trial, will be presenting at the meeting scheduled for 14th January 2015.

A summary of key previous Statistical Assessor comments...

Exposure: While the initial phase was double-blind and placebo-controlled the trial later became open label so it is possible that background care could have been influenced by knowledge of the treatment. In particular, in the open phase, patients allocated to the control group started aspirin immediately.

Timing of treatment: This trial was initiated before any licensing decisions with regards to an indication for acute ischaemic stroke were made therefore and the study was not powered to look at sub-groups based on time from symptom onset to treatment although these are now of more interest.

Endpoints: The primary endpoint is a subjective scale, which could be an issue given the open-label design of the trial. The 6 month data was collected via a postal questionnaire which was assessed by staff blinded to treatment allocation however patients were not blind to the allocation, so there is potential for recall bias, though the demarcation between categories 2 and 3 seems reasonably robust.

Analysis: The adjusted analysis is considered a reasonable supportive analysis. However it is a questionable choice as the primary analysis because the covariates seem to have been selected based upon the study data (albeit baseline data only).

and blinded to treatment allocation) rather than before the data were seen. The CHMP guideline on adjustment for baseline covariates states that stratification factors should usually be used as covariates in the statistical analysis. It would therefore have been easy to justify the choice if all the randomisation factors had been included (factors that were anticipated as being of importance) – the randomisation factors not included were region, use of anti-platelet agents and stroke subtype. An additional factor used in the analysis that was not used in the randomisation was degree of ischaemic change on baseline CT/MR. Given the data-driven choice of the covariates it will be important that the results are robust to the choice of covariates. In particular the unadjusted analysis for the primary endpoint should be looked at, as this is still valid despite the relationships between covariates noted by the company. The adjusted model will be necessary if comparing across sub-groups.

Follow up: The follow-up was good with a very high proportion of patients being assessed for the primary endpoint at month 6 and month 18, with no imbalance between the groups in terms of missing data. Therefore results should be fairly robust to the handling of missing data.

Randomisation: The groups were balanced for all the factors included in the treatment allocation algorithm, so the procedure performed well.

Results: The trial failed on its primary endpoint, the proportion of patients alive and independent at 6 months. After a failed primary analysis, the results of secondary endpoints should be treated with caution, but there does appear to be some evidence that treatment with rt-PA was generally associated with an improvement in OHS scores, but the clinical relevance of any improvement would have to be questioned.

Missing data: Patients with missing outcome data have been excluded. The assessor performed an analysis using missing=failure and this did not alter the results.

Subgroup analyses: It appears that overall prognosis in both treatment and control groups is better when administered later but this is likely due to confounding as those presenting earlier are more likely to have a more severe neurological deficit, be older, and be less likely to have a definitely visible ischaemic lesion. Looking at the difference between treatment groups there does seem to be evidence of a benefit in terms of being alive and independent when treatment is given within 3 hours. There is no evidence of a benefit for treating between 3 and 4.5 hours. However it should be noted there was no clear pattern for decreased efficacy across time.

Mortality: By around the 4 month point the proportion of patients dead has evened out between the treatment groups and it remains even for the rest of the study. There is no suggestion of a long-term mortality advantage.

Quality of life: The improvements in QoL as presented in the paper are not robust to the handling of patients who died in the analysis.

Statistical assessor's conclusions on IST-3: Based upon the pre-specified primary analysis, benefit of rt-PA when given within 6 hours of the occurrence of stroke symptoms has not been demonstrated. Therefore the trial is negative from a statistical perspective.

The primary analysis at 6 months did not show a difference between rt-PA and control in the proportion of patients alive and independent. The clearest finding was the disadvantage in early mortality, with a clear difference in mortality rates at 7 days.

The difference disappeared by 6 months, but some other advantage of treatment would be expected to compensate for this early mortality disadvantage, and this was not seen from the primary endpoint.

It is difficult to interpret secondary endpoints in the light of a failed primary analysis, but there was some suggestion of a shift in the OHS in favour of rt-PA but even if the finding were true the clinical relevance of the size of the shift would be questionable. The advantages claimed in QoL are not supported as the analysis excluded patients who died.

If evaluated in the context of the approved licence it might be possible to use the data from this trial to support the initial restriction to treat patients only within 3 hours of stroke symptoms emerging. In this sub-group there was an 8% difference in the proportion of patients alive and independent at 6 months which was maintained at 18 months. This could be weighed up in a risk-benefit discussion against the early mortality disadvantage. It would be difficult to make a case for the extension of the time-window to 4.5 hours based on these data, as no benefit was seen once the 3-4.5 hour group were included.

5. Emberson et al. meta-analysis of individual level clinical trial data [Emberson 2014]

Initial data from an unpublished meta-analysis was reviewed by CHM in May 2014. This study has now been published in full by Emberson et al. This meta-analysis includes data from 9 trials (ATLANTIS A/B, ECASS I/II/III, EPITHET, IST-3, NINDS part 1 and 2) and 6756 randomised patients (3391 treated with rt-PA).

The meta-analysis aims to assess:

- the extent to which treatment delay modifies the effect of rt-PA on stroke outcome
- the extent to which age or stroke severity modify these effects and
- the effects of rt-PA on risk of sICH and mortality.

The primary efficacy outcome is modified Rankin Score (mRS) 0-1 at 3-6 months post-stroke. Safety endpoints are 90 day mortality, sICH, fatal ICH within 7 days.

Multivariate logistic regression, stratified by trial, was used to model to log odds of each outcome adjusting for allocation to rt-PA, treatment delay, age, baseline stroke severity (NIHSS), plus interaction terms of each with allocation to rt-PA.

In summary, 2110 (31%) of 6,756 patients experienced a good outcome with rt-PA significantly increasing the odds of a good outcome (mRS \leq 1) at 3-6 months (p=0.016 for trend of increasing proportional benefit with earlier treatment) with a significant benefit of rt-PA within 3 hours if stroke (adj OR 1.75, 95% CI: 1.35-2.27) and within 3-4.5 hours (adj OR 1.26, 95% CI: 1.05-1.51). When this analysis was further stratified by age (\leq 80yrs vs $>$ 80 years) a significant benefit for treatment with rt-PA 3-4.5 hours after onset was seen only in patients \leq 80 years old (adj OR: 1.26, 95% CI: 1.04-1.54) and not in those aged $>$ 80 years (adj OR: 1.36, 95% CI: 0.87-2.14) although fewer patients aged $>$ 80 years were randomised within the trials and there was no evidence of a difference during which rt-PA could be effectively given across the two age groups (p=0.08). Further there was no evidence that stroke severity modified the effect of rt-PA (p=0.06).

The risk of sICH was increased with treatment compared with controls, both at 36 hours post-stroke (SITS-MOST criteria: adj OR=6.67, 95% CI: 4.11-10.84) and at 7 days (adj OR=5.55, 95% CI: 4.01-7.70). The risk of fatal ICH within 7 days was also significantly raised (adj OR=7.14, 95% CI: 3.98-12.8). Death within 90 days was numerically increased but not statistically significantly greater in the rt-PA group compared with controls (adj OR=1.11, 95% CI: 0.99-1.25).

Assessor's comments: This, now published, meta-analysis follows on from the pooled analysis by Lees et al. which included the same trials minus IST-3 and examined patients treated within 4.5 hours of stroke onset. The results will be discussed by the lead author, Dr Jonathan Emberson, at the meeting planned for the 20th November.

A summary of key previous Epidemiological Assessor comments...

Statistical methods: The methods chosen to analyse the data have not been fully specified in the protocol, although it seems likely that standard fixed or random effects models have been used. The Forest plots (not presented) do not show a huge amount of heterogeneity, so it seems unlikely that the statistical method chosen for the meta-analysis would alter the results.

Time to treatment: It is difficult to interpret the effect seen in the 3-4.5 hour time period. The data provided from ECASS III was only mildly positive while the comparative point estimate for IST-3 was against rt-PA yet the meta-analysis for this time period shows a statistically significant beneficial effect. Given that these studies contributed the majority of the data to this time period it is not clear why we are seeing a positive effect here.

Analysis: It is also unclear whether all surviving patients, or all patients randomised to treatment comprise the denominator in the individual studies that contribute to the analyses at 3-6 months. This could have an impact on the interpretation.

Epidemiological assessor's conclusions on meta-analysis: It would seem that the meta-analysis results support a beneficial effect of rt-PA up to 4.5 hours, whilst confirming an increased risk of ICH particularly within the first 7 days after treatment. This is in line with current understanding of rt-PA. However, the impact of each individual trial on the meta-analysis results needs to be carefully considered, given the differences in study design and results, in order to help understand, in particular, the sub-group analyses and to draw complete conclusions about the robustness of the results.

6. Summary of additional observational data

SITS-ISTR [Ahmed 2013]

SITS-ISTR was a prospective multi-national registry study for patients given rt-PA following stroke. The most recent publication of data from this registry is from Ahmed et al. This updated analysis presented comparative analysis of benefits and risks in patients treated <3 hours following stroke onset and in 3-4.5 hours following onset. It additionally examined off-label use in patients treated 4.5-6 hours following stroke. It was based on data from SITS-ISTR during the period 2002-2011. Safety endpoints were sICH within 24 hours and mortality at day 90. Multivariate analyses were adjusted for age, sex, pre-stroke mRS score, atrial fibrillation, history of

hyperlipidaemia, previous stroke earlier than 3 months, antihypertensive therapy, signs of a recent infarction at baseline imaging, and baseline stroke severity measured by NIHSS score because these were statistically significant in univariate analyses at the 10% level.

Patients treated 3-4.5 hours after onset had a stroke severity 3 points lower on the NIHSS compared to patients treated within 3 hours.

For the 3-4.5 hour cohort compared with the 3 hour cohort:

Outcome	Patients treated within 3 hours (n=25 279)	Patients treated within 3-4.5 hours (n=4056)	Crude odds ratio (3-4.5hrs/<3 hrs)	95% CI (p-value)	Adjusted OR	Adjusted 95% CI, (p-value)
Rate of sICH (SITS-MOST definition)	1.5%	1.8%	1.16	0.89-1.49 (0.27)	1.22	0.92-1.61 (0.16)
Rate of sICH (ECASS II definition)	4.6%	4.5%	0.98	0.84-1.16 (0.85)	1.11	0.93-1.32 (0.26)
Rate of sICH (NINDS definition)	7.0%	6.5%	0.92	0.81-1.06 (0.24)	1.05	0.90-1.22 (0.54)
Mortality rate at 3 months	11.8%	11.1%	0.93	0.82-1.05 (0.21)	1.07	0.93-1.23 (0.31)
No or minimal disability (mRS ≤1 at 3 months)	42.1%	46.0%	1.17	1.08-1.26 (<0.01)	0.90	0.82-0.98 (0.02)
Independence (mRS ≤2 at 3 months)	58.4%	62.7%	1.19	1.10-1.29 (<0.01)	0.92	0.83-1.01 (0.09)

Table 1: sICH rates (SITS-ISTR registry)

Assessor's comments: Since the data from the SITS-ISTR registry were presented in 2008 minor changes have been seen. The study still suggests that the rate of sICH is comparable in patients treated 3-4.5 hours after treatment compared to those treated within 3 hours. However, the 3-month outcomes of no or minimal disability and independence were less favourable for those treated within 3-4.5 hours compared to those treated within 3 hours in the adjusted analyses. This trend had been seen in earlier analyses of this cohort but for the outcome of no or minimal disability statistical significance is now reached.

Analyses looking at these outcomes in patients treated 4.5-6 hours following onset compared to those treated within 3 hours were also conducted. No significant differences were found here although only 283 patients were treated 4.5-6 hours following onset so the power is greatly reduced. Further, this group is likely to be a highly selective subset of presenting patients so this does not provide robust evidence of safety and effectiveness in this group.

Given the observational nature of this study the results are much more vulnerable to confounding and other biases than randomised clinical trials. However, it is important to see how the benefits and risks of a product manifest when used in routine clinical practice. As this study is non-interventional the reasons for why a patient is treated or not treated with rt-PA can confound the outcomes seen. Therefore, the analyses that try to adjust for this confounding should be considered stronger than the crude analyses. In some cases, adjusting for confounding has had a considerable impact

on the estimated odds ratios. In particular, the crude analysis looking at “No or minimal disability (mRS≤1) at 3 months” is significantly in favour of later treatment (3-4.5 hours after symptom onset) while the adjusted analysis is significant in the opposite direction, with the better outcome now being seen in those treated within 3 hours. This is unsurprising given the trends already seen in trials whereby those presenting earlier are typically older with more severe neurological deficit. However, it is not clear if there is still any residual confounding and in turn, what impact that could be having on the results. Given how large the change in interpretation between the crude analysis and the adjusted analysis is, it seems likely that there is further confounding and the results should be interpreted with caution.

SITS-UTMOST

The Upper Time window Monitoring registry (SITS-UTMOST) is a prospective post-approval registry of intravenous rt-PA (0.9mg/kg) up to 4.5 hours post symptom onset in acute ischaemic stroke patients and is being conducted as part of the SITS-ISTR registry. The study is a regulatory requirement following the approval of the extended time window for treatment and the study started in May 2012.

The latest report on SITS-UTMOST was submitted to regulators in February 2014 with data to November 2013 and is summarised here. The final report will be available during the first quarter of 2015.

The study plans to recruit at least 1,000 patients treated in the 3-4.5 hour window. Currently 58 centres have recorded patients in the study and by November 2013 526 patients had been prospectively recruited while 1,442 comparator patients, treated within 3 hours of onset, had also been included (total 1,968 prospective patients). An additional 2,509 patients treated within 3 hours have been retrospectively recorded.

Of those patients prospectively recorded, those with time to treatment of 3 hours or less are less commonly female than those treated after 3-4.5 hours (40.2% vs. 45.6%, $p=0.031$), more likely to have hyperlipidaemia (30.5% vs. 24.6%, $p=0.011$), more likely to have atrial fibrillation (17.4% vs 12.4%, $p=0.008$), and have higher baseline NIHSS (median 10, IQR 6-16 vs. 8, 6-13, $p<0.001$). There were no other significant differences recorded in baseline characteristics between the two groups.

Between the prospective 0-3 hour and 3-4.5 hours treatment groups there is no statistical difference in sICH or mortality rates, or functional status at 3 months (Table 2).

Outcome	Prospectively identified patients treated within 3 hours: n/N (%)		Prospectively identified patients treated within 3-4.5 hours: n/N (%)		p-value (Pearson Chi-square test)	Retrospectively identified patients treated within 3 hours: n/N (%)	
	n/N	(%)	n/N	(%)		n/N	(%)
Rate of sICH (SITS-MOST definition)	24/1384	(1.73)	8/500	(1.60)	0.84	44/2391	(1.84)
Rate of sICH (ECASS II definition)	37/1368	(2.70)	20/505	(3.96)	0.16	95/2386	(3.98)
Rate of sICH (NINDS definition)	60/1387	(4.33)	26/510	(5.10)	0.47	136/2421	(5.62)

Mortality rate at 3 months	90/963	(9.4)	34/356	(9.6)	0.91	238/2142	(11.1)
No or minimal disability (mRS ≤1 at 3 months)	475/940	(50.5)	180/344	(52.3)	0.57	1037/2082	(49.8)
Independence (mRS ≤2 at 3 months)	631/940	(67.1)	232/344	(67.4)	0.92	1350/2082	(64.8)

Table 2: sICH rates (SITS-UTMOST registry)

Assessor's comments: This analysis presents interim results from the SITS-UTMOST registry study. At this stage, with no robust comparisons being made, it is difficult to say if there is any difference in either benefits or risks between those treated within 3 hours of onset and those treated within 3-4.5 hours since the approval of the extended time window.

If we compare the prospective data to the data seen in the full SITS-ISTR registry, which includes patients treated prior to the treatment time window extension, we are now seeing a trend towards lower rates of sICH according to both the ECASS II and NINDS definitions as well as mortality at 3 months. We are also seeing higher rates of benefits, in terms of both the proportion of patients with no or minimal disability at 3 months and the proportion with functional independence. These improvements are being seen regardless of the time to treatment window suggesting an overall improvement in general care with time although this study is at a preliminary stage and we cannot rule out that the SITS-UTMOST study consists of a select subset of potentially eligible patients. The complications around the confounding discussed with respect to the SITS-ISTR study are also relevant here and will need to be carefully considered when the full results are available.

Get with the guidelines [Saver 2013]

Get With The Guidelines-Stroke (GWTG) is a US national registry launched by the American Heart Association and the American Stroke Association (http://www.heart.org/HEARTORG/HealthcareResearch/GetWithTheGuidelines/Get-With-The-Guidelines-Stroke_UCM_306098_SubHomePage.jsp). It is part of an in hospital program designed to improve stroke care by promoting consistent adherence to the latest scientific treatment guidelines. Since its initiation in 2003, 1,656 hospitals have entered more than 2 million patient records in the GWTG-Stroke database and a range of scientific publications have been produced based on the data.

Using data from GWTG-Stroke, Saver et al. examined the relationship between onset to treatment time and in-hospital mortality, sICH within 36 hours, ambulatory status at discharge, and discharge destination. They analysed data from 58,353 patients treated with rt-PA within 4.5 hours of onset, April 2003-March 2012. Note, that there was no restriction on the age or baseline NIHSS of patients included. In summary, the relationship between time to treatment and the different outcomes of interest was examined using multivariate logistic regression, using generalised estimating equations (GEE) to account for within hospital clustering. Models were adjusted for a range of patient-level (age, ethnicity, sex, medical history, stroke severity, hospital arrival time and transport method, and exposure to vascular risk prevention medications) and hospital-level (hospital size, region, teaching status, rural location, stroke specialism, number of rt-PA treated patients, and number of stroke discharges) factors.

The median age of the included cohort was 72 years, 50.3% were women, median onset to treatment time was 144 minutes (interquartile range, 115-170), 9.3% (5404) had onset to treatment time of 0 to 90 minutes, 77.2% (45 029) had onset to treatment time of 91 to 180 minutes, and 13.6% (7920) had onset to treatment time of 181 to 270 minutes. Median pre-treatment National Institutes of Health Stroke Scale, documented in 87.7% of patients, was 11 (interquartile range, 6-17). Patient factors most strongly associated with shorter onset to treatment included greater stroke severity (OR=2.8, 95% CI: 2.5-3.1 per 5-point increase), arrival by ambulance (OR=5.9, 95% CI: 4.5-7.3), and arrival during regular hours (OR=4.6, 95% CI: 3.8-5.4).

Overall, there were 5,142 (8.8%) in-hospital deaths, 2,873 (4.9%) patients had sICH, 19,491 (33.4%) patients achieved independent ambulation at hospital discharge, and 22,541 (38.6%) patients were discharged to home. In adjusted analyses, faster onset to treatment time, in 15-minute increments, was associated with reduced in-hospital mortality (OR, 0.96; 95% CI, 0.95-0.98; $P < .001$), reduced sICH (OR, 0.96; 95% CI, 0.95-0.98; $P < .001$), increased achievement of independent ambulation at discharge (OR, 1.04; 95% CI, 1.03-1.05; $P < .001$), and increased discharge to home (OR, 1.03; 95% CI, 1.02-1.04; $P < .001$).

Focusing on the risk of sICH a significantly decreased risk is seen in adjusted analyses comparing the risk with treatment 3-4.5 hours after symptom onset to treatment to treatment within 1.5 hours (adj OR=0.72, 95% CI: 0.60-0.87) and treatment within 1.5-3 hours (adj OR=0.87, 95% CI: 0.76-0.99).

Assessor's comments: This equally large cohort is slightly older than that seen in the SITS-ISTR registry and a higher proportion are female.

This study suggests a significantly reduced sICH rate with earlier treatment. It should be noted that this risk has also been suggested in a further analysis of the SITS-ISTR data [Mazya 2012] which found that onset to treatment > 3 hours was an independent risk factor associated with an increased risk of sICH (adj OR 1.5, 95% CI: 1.2-2.0) although this study was primarily designed to devise a risk score for sICH. However, an increasing risk of large parenchymal haemorrhage with an increase in time to treatment was not seen in the pooled clinical trial analysis [Lees 2010]. Therefore, the risk observed here could be the result of residual confounding. Even if true, it is not clear how clinically meaningful this level of increase in risk is.

Mortality is also reduced with a short time to treatment although it should be noted that in this study only data on in-hospital mortality is available meaning that deaths that occur later after treatment are not included. A trend towards increased 90 day mortality with a longer time to treatment was also seen in an earlier pooled analysis of clinical trials data [Lee 2010] although this was no longer statistically significant after the inclusion of IST-3 [Emberson 2014]. Again, residual confounding may be present in this observational study.

The significant increased achievement of a mRS \leq 1 and/or a mRS \leq 2 with earlier treatment is again seen here. Again only in-hospital data is available in this study.

Baden-Wuerttemberg Stroke Registry [Gumbinger 2014]

Gumbinger et al. presented data from 84,439 patients treated for ischaemic stroke in 148 hospitals in Baden-Wuerttemberg, Germany January 2008 to December 2012. The primary analysis compared the odds of a mRS \leq 1 at discharge from hospital

following treatment with rt-PA compared to the odds without treatment with rt-PA using multivariate logistic regression adjusted for age, sex, premorbid mRS, NIHSS, diabetes, previous stroke, atrial fibrillation, ventilation, pneumonia, thrombosis or pulmonary embolism, level of stroke care and length of hospital stay. This study was not primarily designed for scientific research; therefore no follow up data after discharge was collected.

10,263 (12.2%) of patients were treated with rt-PA, with a considerably higher proportion of these admitted within 3 hours of onset compared to those not treated (88.5% vs 24.5%). 377 (3.7%) of those treated were admitted to hospital at least 6 hours following stroke onset, 2,365 (23.0%) had diabetes, 1,727 (16.8%) had a prior stroke, and 3,430 (33.4%) had atrial fibrillation. Those treated with rt-PA also had lower premorbid mRSs with 8,565 (83.5%) having a mRS ≤ 1 compared to 55,725 (67.0%) of those not treated.

Treatment with rt-PA was associated with an increased chance of a mRS ≤ 1 at discharge (overall adj OR 1.70, 95% CI 1.59-1.81, $p < 0.0001$). This benefit was greatest in the group treated within 90 mins of stroke onset (adj OR 2.49, 95% CI: 2.12-2.92) although a significant association was seen for treatment 91-180 mins following onset (adj OR=1.86, 95% CI: 1.71-2.02) and for treatment 181-270 mins following onset (adj OR 1.26, 95% CI: 1.08-1.46).

Assessor's comments: The data from this cohort is interesting to note as, unlike the other observational studies presented here, it includes patients not treated with rt-PA. It was also a mandatory registry meaning that it has very high population coverage and is not restricted to specialist stroke centres. This cohort was again older than the SITS-ISTR cohort (median age 74 years compared to ~68 years). There is potential for some crossover with the SITS-ISTR study which currently has 5,378 patients recruited from Germany.

The lack of follow up in this study is however a limitation. This is due to the fact that the registry is not designed primarily for scientific research purposes.

The authors present a comparison of their data to the pooled clinical trial analysis of Lees et al. [Lees 2010] and Emberson et al. [Emberson 2014, unpublished at time of this study]. The adjusted ORs they see are reasonably comparable to those seen in the meta-analyses with an association between earlier treatment and improved outcome (mRS ≤ 1). However, the same issues around confounding, as discussed for SITS-ISTR and the other studies, are still relevant here and are likely to impact on the results.

Canadian Alteplase for Stroke Effectiveness Study (CASES) [Shobha 2011]

The Canadian Alteplase for Stroke Effectiveness Study (CASES) was a prospective multicentre cohort study of stroke patients treated with rt-PA. At the time of the study, the Canadian licenced indication was only for treatment within 3 hours of onset. Shobha et al. presented analyses comparing the mRS at 90 days, mortality, and sICH in patients treated with rt-PA within 3 hours of symptom onset and those treated within 3-4.5 hours. Multivariate regression models, adjusting for age, sex, baseline NIHSS, baseline serum glucose and baseline ASPECTS (Alberta Stroke Registry Early CT Score), were used to compare outcomes in the two groups.

A total of 1,112 patients with complete data were included, 129 (11.6%) received rt-PA between 3 and 4.5 hours of onset while the rest received it within 3 hours. Those

in the 3-4.5 hour treatment group had more favourable baseline CT scans (median ASPECTS 9 vs 8, $p=0.02$). Of note, 36% of patients treated in the 3-4.5 hour window were treated off-label according to the current indication, primarily as they were >80 years old or had baseline NIHSS >25 . At 90 days, 50/127 (39.4%) of patients in the 3-4.5 hour treatment group and 352/965 (36.5%) in the under 3-hour group attained a mRS ≤ 1 (adj RR=0.98, 95% CI: 0.8-1.2). After adjustment there was a significant increase in the risk of both mortality (adj RR=1.53, 95% CI: 1.15-2.0) and sICH (adj RR=2.14, 95% CI: 1.09-4.2) in those treated within 3-4.5 hours compared to those treated within 3 hours although this was not seen in unadjusted comparisons.

Assessor's comments: The authors state that their results were concordant with those seen in ECASS III and the SITS-ISTR registry. However, there is a trend towards higher mortality and greater sICH rates in this cohort. They suggest this is because their cohort is highly selective and, even though the median time for treatment in the 3-4.5 hour group was 3 hours 10 minutes, patients were older and sicker than those included in other studies and this may explain poorer outcomes. This leads to the question of how representative this study is of the general rt-PA treated population. This study is also considerably smaller than other observational studies limiting its value.

Assessor's conclusions on recent observational studies: The observational data presented here suggest a benefit of rt-PA in achieving a mRS ≤ 1 , with the greatest benefit seen with earlier treatment. The risk of sICH seen in patients treated with rt-PA has not been compared to the risk in untreated patients in the additional observational studies and data is mixed on if there is any time-dependent risk. It is important to see how a product performs once used in routine clinical practice, away from the tighter clinical trial setting. However, these observational studies are likely to be subject to confounding and selection biases and so the results should be treated with caution and considered in light of the clinical trial data.

It should be noted that the observational studies presented here include patients treated off-label although they were not the main focus here. This should also be taken into consideration when discussing the relevance of these studies to examining the benefits and risks of rt-PA within the current licenced indication.

The following papers were referenced by the MAH but will be discussed further at the meeting in January 2015 as they focus primarily on the safety and effectiveness of rt-PA when used off-label compared to use according to the current licenced indication...

- 1) Meretoja et al. Off-label thrombolysis is not associated with poor outcome in patients with stroke. *Stroke*. 2010; 41: 1450-8.
- 2) Ford et al. Intravenous rt-PA for stroke in those older than 80 years old. *Stroke*. 2010; 41: 2568-74.
- 3) Mishra et al. Thrombolysis outcomes in acute ischaemic stroke patients with prior stroke and diabetes mellitus. *Neurology*. 2011; 77: 1866-72.
- 4) Frank et al. The effect of time to treatment in very elderly thrombolysed stroke patients. *Int. J. Stroke*. 2014; 9 (5): 591-6.
- 5) Cronin et al. Adherence to third European Cooperative Acute Stroke Study 3- to 4.5- exclusion and association with outcome: Data from Get with the Guidelines-Stroke. Time to treatment and outcome. *Stroke*. 2014; 45: 2745-9.
- 6) Frank et al. Thrombolysis in Stroke Despite Contraindications or Warnings? *Stroke*. 2013; 44 (3): 727-33.

7. Discussion

The balance of benefits and risks of rt-PA in the indication of acute ischaemic stroke has prompted extensive discussion and analysis since initial licensing of the indication in 2002. The main clinical trials that formed the basis of the initial application for the indication in the treatment of acute ischaemic stroke, and the variation to extend the time-window for treatment to 4.5 hours were NINDS parts 1 and 2, ECASS I and II, ATLANTIS A and B and ECASS III. The data from these trials have been extensively reviewed and debated both nationally and within the EU at the time of approval. A summary of the findings from these trials is provided in this paper as background, whilst specific concerns that have been raised relating to these trials are discussed in paper 4.

For several reasons, the balance of benefits and risks of rt-PA treatment for acute ischaemic stroke is perhaps particularly difficult to judge and achieve a consensus on. The efficacy of rt-PA in improving outcome has been demonstrated in some randomised controlled trials; however there are also RCTs that failed in their efficacy endpoints. Treatment with rt-PA carries an increased risk of intracranial haemorrhage, with potentially devastating consequences. Balancing the evidence for efficacy against the risk of intracranial haemorrhage, whilst giving consideration to all of the other variables involved, is not a straightforward task. Furthermore, a patient's perspective should be borne in mind, if possible, when considering this balance.

The current paper considers data that have become available since the grant of the extension to the time-window for treatment, or that have not previously been considered. Four additional observational studies have been reviewed for the first time. One of these studies [Gumbinger 2014] presents data suggesting an increased chance of achieving a mRS<1 with alteplase while all point towards increasing benefit with shorter times from onset to treatment. They also provide some evidence of a reduction in mortality with quicker treatment although this is not a consistent finding. Similarly, a reduction in the risk of sICH with shorter times to treatment is also inconsistently observed. These observational studies are all likely to be subject to residual confounding so the data should be considered in light of the results from the randomised clinical trials. However, they appear to be supportive of our current understanding on the benefits and risks of rt-PA within the current licensed indication.

8. Points to consider

Does the group consider that the new data discussed here have implications for the balance of benefits and risks of rt-PA as currently authorised in the EU?

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EXPERT WORKING GROUP

ACTILYSE (ALTEPLASE) BALANCE OF BENEFITS AND RISKS WHEN USED IN
THE TREATMENT OF ACUTE ISCHAEMIC STROKE

Title of paper: Paper 4: Benefits and risks: new study data – Addendum 1

Product: Actilyse 10,20, 50mg	Pharmacoepidemiology assessor: Dr [REDACTED]
Marketing Authorisation Holders: Boehringer Ingelheim Limited	
Active constituents: Alteplase (rt-PA)	
Therapeutic classification: Antithrombotic agent, ATC code B01AD02	

Paper 4: Addendum 1

SITS-UTMOST registry: Final report

Introduction

The Upper Time window Monitoring registry (SITS-UTMOST) is a prospective post-approval registry of intravenous rt-PA (0.9mg/kg) used up to 4.5 hours post symptom onset in acute ischaemic stroke patients according to the Summary of Product Characteristics (SmPC) and is being conducted as part of the SITS-ISTR registry. The study, which was a regulatory requirement following the approval of the extended time window for treatment, started in May 2012.

Paper 4 Section 6 contained a summary of the 3rd interim report for the SITS-UTMOST registry which included data up until November 2013. This Addendum summarises the results from the 4th and final report from this registry which is now available including data up until 2nd November 2014.

Final Results

Baseline characteristics

81 centres, out of 94 considered (based on their active participation in the SITS-ISTR registry), contributed data to this final analysis. In total 13,353 patients were entered in the SITS-ISTR registry study during the SITS-UTMOST study period. Of these, 7,611 patients were treated with alteplase (rt-PA) according to the EU SmPC criteria and therefore included in the SITS-UTMOST study: retrospective cohort: n = 3,454 (treated within 3 hours prior to extension) / prospective cohort (treated within 4.5 hours) n = 4,157. Within the prospectively registered cohort, 1,118 were treated within the 3-4.5 hour time window. The UK, Czech Republic, and Italy recruited the most patients: 30.4%, 20.5%, and 14.3% of the prospective cohort respectively.

There were some differences in the baseline and demographic characteristics between '3-4.5 hour' and 'within 3 hour' prospective cohorts. In the '3-4.5 hour' cohort, proportions of females were 4% higher (44.5% vs 40.8%, p=0.031), history of diabetes mellitus was 3% higher (19.4% vs 16.3%, p=0.020) and baseline clopidogrel treatment was 2% higher (7.7% vs 5.6%, p=0.012) compared to the 'within 3 hour' prospective cohort. Conversely, baseline median NIHSS (National Institute of Health Stroke Scale) score was 2 points lower (8 vs 10, p<0.001) and history of hyperlipidaemia (27.5% vs 31.2, p=0.027) and atrial fibrillation (13.1% vs 15.9%, p=0.029) were 3% lower in the '3-4.5 hour cohort' than in the 'within 3 hour' prospective cohort. These differences were already observed in the previous interim report. No other significant differences were found.

A statistical comparison was also done between the ≤ 3 hours prospective and retrospective cohort for comparison only. The retrospective cohort treated in ≤ 3 hours had a higher proportion of current and previous smokers, a higher proportion of patients with atrial fibrillation, greater use of dipyridamol and other anti-platelets (exc. Aspirin, dipyridamol, and

clopidogrel), less use of oral anti-hypertensives and statins, a lower median weight, and a higher median NIHSS score compared to those treated within 3 hours in the prospective cohort. However, in general the prospective and retrospective data for patients treated within 3 hours is very similar.

Time to treatment logistics

The times taken are given by treatment step in Table 1 according to total time to treatment category.

Table 1: Time logistics of patients

Time variables (in mins)	Prospective 3–4.5h (n=1,118)	Prospective within 3h (n=3,039)	p- values*	Retrospective within 3h (n=3,454)	p- values**
Stroke onset to door time	137 (100-171)	67 (50-90)	<0.001	65 (46-86)	<0.001
Door to imaging	29 (17-47)	22 (13-32)	<0.001	23 (14-35)	0.002
Imaging to treatment	45 (28-70)	32 (20-48)	<0.001	37 (24-55)	<0.001
Door to needle time	79 (54-111)	55 (40-75)	<0.001	63 (45-84)	<0.001
Stroke onset to treatment (OTT)	217 (200-240)	129 (105-155)	<0.001	135 (106-157)	<0.001

* Comparison between 3-4.5h and ≤3h for the prospective cohort and **between ≤3h prospective and ≤3h retrospective cohorts using Mann-Whitney U Test. Data are median (IQR).

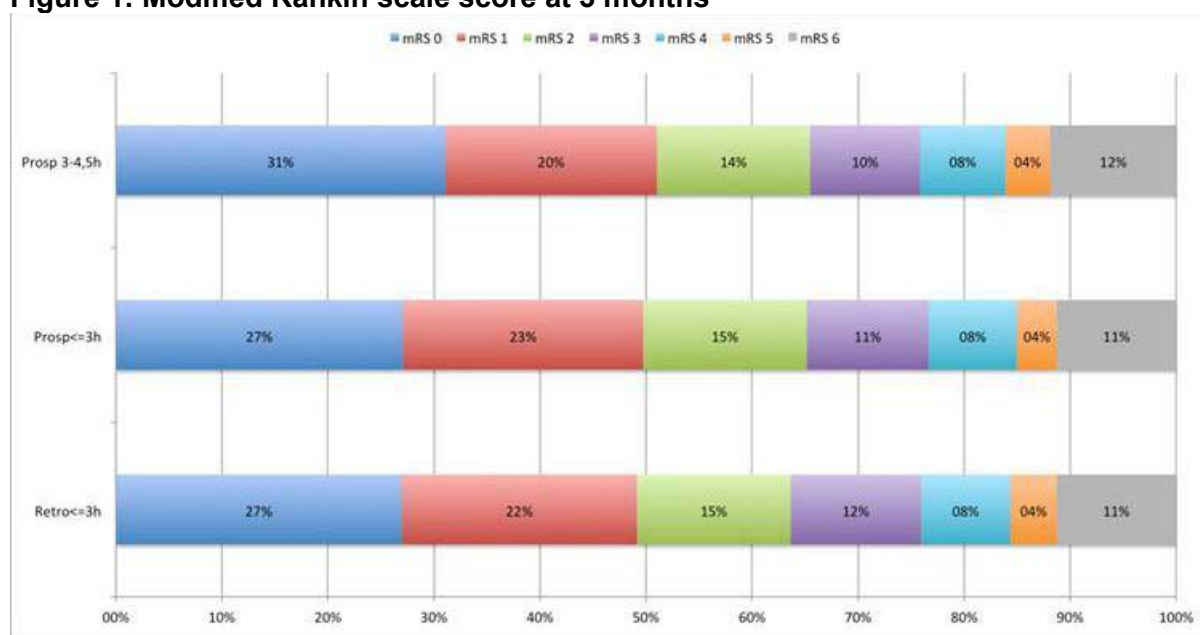
When time logistics are presented in hourly categories according to stroke to treatment time intervals (OTT: 0-1 hour, 1-2 hours, and 2-3 hours compared to 3-4.5 hours) there is a prolongation in the hospital management times with increasing onset to treatment times. For example, in the prospective cohort, those treated within 1 hour of onset have a median door to needle time of 33 minutes compared to 65 minutes for those treated within 2-3 hours of stroke onset.

When timings are stratified according to time from stroke onset to hospital presentation we see that management times are shorter for those who present later to hospital (3-4.5 hours following onset) compared to those who present sooner after their stroke. For example, again in the prospective cohort, those presenting 3-4.5 hours after stroke onset have a median door to needle time of 43 minutes compared to 61 minutes for those presenting within 1 hour of stroke onset.

Clinical outcomes

As in the 3rd interim analysis summarised in Paper 4 Section 6, this final report finds no statistically significant difference between symptomatic intracerebral haemorrhage (SICH) per any definition and 3-months mortality and functional outcome between '3-4.5 hour' and 'within 3 hour' cohorts using unadjusted analyses. The distributions of modified Rankin Scale scores at 3 months stratified by sub-cohort are presented in Figure 1.

Figure 1: Modified Rankin scale score at 3 months



In this final report, we now also have multivariate analyses, adjusting for baseline characteristics and comparing the rate of SICH and 3-months outcome in the prospective cohort treated within 3 hours with those treated with 3-4.5 hours. Multivariate analysis shows no difference in SICH per any definition and mortality between '3-4.5 hour' and 'within 3 hour' prospective cohorts (Table 2). There was a statistically significant lower adjusted odds ratio for functional independence at 3-months in the '3-4.5 hour' cohort compared to the 'within 3 hour cohort'. There was no statistically significant difference in any outcome parameters in the multivariate analysis for the prospective cohort within 3 hour compared to the retrospective cohort within 3 hours.

Table 2: Adjusted odd ratios of SICH and 3-months outcome (those treated 3-4.5 hours following onset compared to those treated within 3 hours)

Outcomes	Odds ratios (95% CI)*	p-values
SICH (SITS-MOST)	1.08 (0.61-1.90)	0.787
SICH (ECASS II)	1.46 (0.99-2.15)	0.053
SICH (NINDS definition)	1.35 (0.98-1.87)	0.068
No/minimal disability at 3 months (mRS 0-1)	0.87 (0.72-1.05)	0.159
Functional independence at 3 months (mRS 0-2)	0.81 (0.67-0.99)	0.044
Mortality at 3 months	1.30 (0.98-1.73)	0.066

* Multivariate analysis adjusted for age, sex, baseline NIHSS, history of diabetes mellitus, hyperlipidaemia and atrial fibrillation and treatment with Clopidogel at baseline.

Assessor's comments:

The SITS-UTMOST registry passed its target of 1,000 patients treated in 3-4.5 hours. Early data on use 3-4.5 hours after onset were used to support the licensing extension while later data on use in this time window have already been discussed in Section 6 of Paper 4.

Most of the statistically significant differences between the within 3h prospective and retrospective cohorts were likely due to large sample size and these differences were not clinically significant other than 1 point lower median NIHSS score in the within 3h prospective cohort than in the retrospective cohort. The lower baseline NIHSS score in both prospective cohorts (3-4.5h and ≤ 3 h) compared to the retrospective cohort reflects that more patients with milder stroke severity were treated in recent years compared to previous years.

There was a longer hospital management time in the 3-4.5h OTT time window compared to the ≤ 3 h OTT time window. There was also a longer hospital management time when patients arrived at hospital within 3 hours of symptom onset compared to later arrival to hospital. These results may suggest that late arrivals are handled more rapidly than earlier arrivals to hospital. However, this interpretation may not be the whole truth since the median hospital arrival to treatment time was 8 minutes shorter in the ≤ 3 h prospective cohort than the ≤ 3 h retrospective cohort according to OTT. These results may reflect that patients in the 3-4.5h cohort were a group of patients who might not have received treatment previously due to the ≤ 3 h time window restriction but after extension of the time window beyond 3 hours centres were able to treat these patients with IV thrombolysis and that hospital management times are reducing slightly.

With regard to safety, the study did not observe any difference in the SICH rate or the 3 month mortality and functional outcomes between the 3-4.5h and ≤ 3 h prospective cohort when using unadjusted analyses. In the adjusted analyses, no difference was seen in the risk of SICH when using the SITS definition, which is consistent with what was seen in the Emberson et al. meta-analysis (although of course comparisons made in that study were to placebo rather than between treated groups). However, there was a non-significant trend towards using an increased risk of SICH according to both the ECASS II and NINDS definitions in those treated 3-4.5 hours after onset compared to those treated within 3 hours. For effectiveness, after adjustment for baseline imbalances, there was a slightly lower but statistically significant odds ratio for functional independence (mRS 0-2) at 3-months in the 3-4.5h cohort compared to ≤ 3 h cohort and a trend towards a higher 3 month mortality rate. These findings are also consistent with the Emberson et al. meta-analysis.

In summary, this observational study demonstrated that treatment with IV thrombolysis between 3 and 4.5h after acute ischaemic stroke is of similar safety and efficacy compared to within 3h treatment. Although the longer hospital management time for patients in the 3-4.5h cohort is not optimal, the reason for these delays is not clear and did not result in considerably poorer outcome in the 3-4.5h cohort than in the ≤ 3 h. However, it is very important to note that there was a statistically significant lower odds ratio for functional independency in the 3-4.5h cohort than ≤ 3 h and results from the previous and updated pooled analyses consistently show that the shorter treatment window increases the odds for better outcome. The data presented with this report indicates that there may still be room for improvement of hospital management time and centres should put utmost effort into improving the hospital management.

EXPERT WORKING GROUP**ACTILYSE (A LTEPLASE) BALANCE OF BENEFITS AND RISKS WHEN USED IN THE TREATMENT OF ACUTE ISCHAEMIC STROKE**

Title of paper: Paper 5D: Benefit:risk of rt-PA administered between 3-4.5 hours post-symptom onset
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Product: Actilyse 10, 20, 50mg	Assessors: Scientific assessor: Dr [REDACTED] [REDACTED]
MAHs: Boehringer Ingelheim Limited	Previous Assessments: CHM May 2014 EWG: Nov 2014, Jan 2015
Active constituents: Alteplase (rt-PA)	Legal status: POM
Therapeutic classification: Antithrombotic agent, ATC code B01AD02	

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1. Introduction

Evidence for a favourable balance of benefits and risks of rt-PA treatment within 3 hours of stroke onset is robust. There is less evidence supporting treatment within 3-4.5 hours and the available data is also less positive than that for treatment between 0-3 hours, (efficacy decreases as time to onset increases). This paper therefore discusses all the available data relating to rt-PA treatment within 3-4.5 hours.

The current authorised indication for rt-PA highlights the need for treatment to be given as soon as possible after the onset of stroke symptoms.

“Fibrinolytic treatment of acute ischaemic stroke:

Treatment must be started as early as possible within 4.5 hours after onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques (e.g. cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage). The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.”

The SmPC also includes warnings about the time dependency of treatment and the negative benefit:risk ratio after 4.5 hours in several other sections:

In section 4.2 (Posology and method of administration):

“Actilyse should be given as soon as possible after symptom onset...”

... Treatment with Actilyse must be started as early as possible within 4.5 hours of the onset of symptoms. Beyond 4.5 hours after onset of stroke symptoms there is a negative benefit risk ratio associated with Actilyse administration and so it should not be administered (see section 5.1).”

In section 4.3 (Contraindications):

“Additional contra-indications in acute ischaemic stroke:

- *symptoms of ischaemic attack beginning more than 4.5 h prior to infusion start or symptoms for which the onset time is unknown and could potentially be more than 4.5 h ago”*

In section 4.4 (Special warnings and precautions for use):

“Special warnings / conditions with a decreased benefit/risk ratio:

Compared to other indications patients with acute ischaemic stroke treated with Actilyse have a markedly increased risk of intracranial haemorrhage as the bleeding occurs predominantly into the infarcted area. This applies in particular in the following cases:

...

- *with later time-to-treatment from onset of stroke symptoms the net clinical benefit is reduced and may be associated with a higher risk of ICH and death compared to patients treated earlier. Therefore, the administration of Actilyse should not be delayed.”*

In section 5.1 (Pharmacodynamic properties):

“The safety and efficacy of ACTILYSE for acute ischaemic stroke treatment up to 4.5 h time stroke onset time to start of treatment (OTT) has been assessed by an ongoing registry (SITS-ISTR: The Safe Implementation of Thrombolysis in Stroke registry). In this observational study safety outcome data of 21,566 treated patients in

the 0 to 3 h time window were compared with data from 2,376 patients treated between 3 to 4.5 h after onset of AIS.

The incidence of symptomatic intracranial haemorrhage (according to the SITS-MOST definition) was found to be higher in the 3 to 4.5 h time window (2.2%) as compared with the up to 3 h time window (1.7%). Mortality rates at 3 months were similar comparing the 3 to 4.5 h time window (12.0%) with the 0 to 3.0 h time window (12.3%) with an unadjusted OR 0.97 (95% CI: 0.84-1.13, p =0.70) and an adjusted OR 1.26 (95% CI: 1.07-1.49, p =0.005. The SITS observational data support clinical trial evidence of stroke onset time to start of treatment (OTT) as an important predictor of outcome following acute stroke treatment with alteplase.”

2. RCT data supporting extension of the time window to 4.5 hours

The data available on use of rt-PA during different time-windows for treatment has been presented in previous papers (paper 4 and paper 7). The time-dependence of successful treatment with rt-PA has long been recognised, and determining the maximum time to onset that can be considered to be associated with a positive balance of benefits and risks has been found to be challenging. Paper 1A provided explanation of the regulatory background to the initial decisions to approve the indication of acute ischaemic stroke, and the later decision to increase the time-window for treatment from 3 hours up to 4.5 hours.

The ECASS III trial was conducted as a condition of the original licence for rt-PA in the indication of acute ischaemic stroke and was used as the main basis, together with additional supporting information, for extending the time-window for treatment to include 3-4.5 hours in 2012.

ECASS III was a randomised, multi-national, double-blind, placebo controlled trial, which enrolled patients between 3-4.5 hours following onset of stroke symptoms (Hacke *et al*, 2008). The study was conducted between 2003 and 2008 and included 821 patients. ECASS III has been the only trial conducted to date that specifically enrolled patients treated only between 3-4.5 hours and therefore included the greatest number of patients enrolled in this time-window, with the exception of the open-label IST-3 trial – see below. As such, and as a randomised, double-blind trial, it arguably provides the most rigorous data available for treatment during this time-window. It should also be noted however, that as a licensing commitment this trial was supported by the MAH for rt-PA.

The results of the ECASS III trial demonstrated a positive effect of rt-PA treatment compared with placebo, with a favourable primary outcome for **mRS 0-1, OR 1.34; 95%CI [1.02-1.76]**. This trial used the licensed dose (0.9mg/kg body weight) and the inclusion/exclusion criteria mirrored the EU SmPC for rt-PA (the exception being the time-window, which was different from the authorised 0-3 hours window). A total of 113 patients (27%) in the rt-PA group had ICH, of which 3 were fatal. This compares with 71 patients (17.6%) in the placebo group, of which none were fatal. The frequency of sICH in the ECASS III trial varied depending on the definition chosen, but was similar to that observed in the NINDS trial when the NINDS definition was used: rt-PA: 7.9% and 6.4% in ECASS III and NINDS respectively, placebo: 3.5% and 0.6% in ECASS III and NINDS respectively.

ECASS III was the main study submitted to support the procedure for the extension of the time-window. Although initially the UK raised a number of issues relating to the results of the trial, in particular an apparent signal of increased mortality in the rt-PA arm compared with the placebo arm, these issues were mitigated by the provision of further data and analyses. Thus the initial presentation of mortality data had erroneously included additional deaths occurring during unequal follow-up time periods in the two study arms. Data from the SITS-ISTR registry and a pooled

analysis of clinical trial data also supported extension of the time-window for treatment.

The pooled analysis combined data from ECASS III with ECASS II, ATLANTIS A and B, and NINDS 1 and 2. The ECASS I trial was not included because it tested a higher dose. The NINDS trials enrolled patients between 0-3 hours following symptom onset and therefore contribute no data to the 3-4.5 hour time-window (NINDS stroke study group, 1995). The other trials included in the pooled analysis enrolled patients between 0-6 hours of symptom onset (ECASS II), and 3-5 hours of symptom onset (initially the ATLANTIS trial enrolled patients from 0-6 hours, this was then modified to 0-5 hours due to safety concerns, and then to 3-5 hours in light of the NINDS results).

The pooled analysis included a total of 2958 patients (1490 rt-PA and 1468 placebo) treated within 0-6 hours following stroke onset. Of these, 1355 patients were included in the 3-4.5 hour time-window. This analysis found a beneficial effect of rt-PA in the 3-4.5 hour time-window, for **mRS 0-1, OR 1.31, 95%CI [1.06-1.63], p=0.014**; and for patients treated within the licensing criteria other than time for treatment (n=1251), OR 1.42, 95%CI [1.13-1.78], p=0.002. The frequency of sICH in the 3-4.5 hour cohort was comparable with the results of the ECASS III trial, according to the SITS-MOST definition.

The pooled analysis of data for patients treated between 3-4.5 hours is more applicable to the discussion of this time-window than the overall findings from the individual trials (ECASS II and ATLANTIS A and B) because these studies enrolled patients treated beyond 4.5 hours, and in the case of ECASS II the data were stratified as 0-3 hours and 3-6 hours. Nevertheless, a trend towards a more favourable outcome was observed within each trial for the rt-PA group treated beyond 3 hours compared with placebo.

In the ECASS II trial, a total of 326 patients received rt-PA between 3-6 hours after symptom onset, and 309 were treated with placebo (Hacke *et al*, 1998). 40.2% of patients treated with rt-PA compared with 36.9% of patients treated with placebo in this time-window achieved mRS 0-1 day 90, a difference of 3.3% (p=0.42), OR 1.2, 95%CI [0.8-1.6].

In the ATLANTIS B trial (n=613) 547 patients were treated between 3-5 hours after symptom onset whilst 39 were treated within 3 hours and 24 were treated >5 hours after symptom onset (Clark *et al*, 1999). For the patients treated between 3-5 hours after symptom onset, 42.3% of patients treated with rt-PA had a mRS 0-1 at day 90, compared with 38.9% of placebo patients, a difference of 3.4% (p=0.42).

3. Data that have become available since the extension to the time-window to 4.5h

3.1 Observational data:

At the time of the variation to extend the treatment window up to 4.5 hours post-symptom onset, supporting data was presented from the SITS-ISTR registry, which collects data on patients treated with rt-PA for stroke. This included data collected on patients treated from 2002 to 2007, with a further update to 2008. Since the procedure completed, a further publication by Ahmed *et al* (2013) has provided updated data from SITS-ISTR of a comparative analysis of benefits and risks in patients treated <3 hours following onset of symptoms with those treated 3-4.5 hour following onset. The data presented were collected from 2002 to 2011, and included a total of 25,279 patients treated within 3 hours, and 4056 patients treated between 3-4.5 hours. For patients treated from 0-3 hours, 42.1% achieved mRS 0-1 at 3 months, this compared with 46.0% of patients treated from 3-4.5 hours, OR 1.17,

95%CI [1.08-1.26]. Although this crude result was in favour of later treatment, after adjustment for age, sex, pre-stroke mRS score, atrial fibrillation, history of hyperlipidaemia, previous stroke earlier than 3 months, antihypertensive therapy, signs of recent infarction at baseline imaging, baseline NIHSS score, the OR was statistically significantly in favour of earlier treatment (OR 0.90, 95%CI [0.82-0.98]). The data for sICH and mortality found no significant differences between the cohorts treated at 0-3 hours compared with 3-4.5 hours. The time-dependency of benefit of rt-PA is well recognised and therefore the odds ratio demonstrating improved outcomes in the 0-3 hour time-window compared with 3-4.5 hours was as expected. As the SITS-ISTR is a treatment registry, no comparison can be made with untreated/placebo patients.

A number of other observational studies have provided data on patients treated with rt-PA between 3-4.5 hours after symptom onset. The SITS-UTMOST registry was conducted as part of the SITS-ISTR registry as a regulatory commitment following approval of the extended time-window. This registry includes patients treated up to 4.5 hours post-symptom onset. Paper 4 described the results available from data up to November 2013. The final study report has now been received and the updated results are described in paper 4A addendum 1. The final prospective cohorts included a total of 1118 patients treated between 3-4.5 hours following stroke onset, 3039 treated within 3 hours and 3454 patients in the retrospective cohort treated within 3 hours. Multivariate analysis of the prospective cohorts showed a statistically significant lower adjusted odds ratio for functional independence (mRS 0-2) at 3 months in the 3-4.5 hour cohort compared with the <3 hour cohort (OR 0.81, 95%CI [0.67-0.99], $p=0.044$). The difference for mRS 0-1 was not significant however (OR 0.87, 95%CI [0.72-1.05], $p=0.159$). There was no statistical difference in rate of sICH (SITS-MOST, ECASS II or NINDS definition) or in mortality at 3 months between the prospective cohorts treated 3-4.5 hours following stroke onset and within 3 hours.

The Get With The Guidelines-Stroke registry is a US national registry, and since 2003 has recorded >2 million patients from 1656 hospitals. Saver *et al* (2013) used these data to analyse the relationship between time to treatment and stroke outcomes in 58,353 patients treated within 4.5 hours of symptom onset. Patients were treated between 2003 and 2012. The median time from symptom onset to treatment was 144 minutes (interquartile range 115-170), 9.3% (5404) were treated between 0-1.5 hours, 77.2% (45,029) were treated between 1.5-3 hours and 13.6% (7920) were treated between 3-4.5 hours. Factors that were associated with a shorter time from onset to treatment were greater stroke severity, arrival by ambulance, and arrival during regular hours.

A total of 19,491 (33.4%) patients achieved independent ambulation at discharge, and 22,541 (38.6%) were discharged to home. Faster onset to treatment time in 15 minute increments was associated with increased achievement of independent ambulation at discharge (OR 1.04, 95%CI [1.03-1.05], $p<0.001$) and increased discharge to home (OR 1.03, 95%CI [1.02-1.04], $p<0.001$).

A total of 5142 (8.8%) patients died in-hospital, and 2,873 (4.9%) had sICH. Faster onset to treatment time in 15 minute increments was associated with reduced in-hospital mortality (OR 0.96, 95%CI [0.95-0.98], $p<0.001$) and reduced sICH (OR 0.96, 95%CI [0.95-0.98], $p<0.001$). Although the risk of sICH was significantly reduced with earlier treatment (3-4.5 hours compared with either 0-1.5 hours or 1.5-3 hours), and this effect has also been observed in a further analysis of the SITS-ISTR registry (Mazya, 2012), it was not found in the pooled analysis of clinical trials by Lees, 2010 or in the meta-analysis by Emberson *et al*, 2014. There may therefore be residual confounding present.

An analysis of the Baden-Wuerttemberg stroke registry was conducted by Gumbinger *et al* (2014). This included 84,439 patients treated in 148 hospitals between 2008 and 2012. This registry has the advantage that it included both patients treated with rt-PA (n=10,263, 12.2%) and those not thrombolysed. After adjustment for baseline characteristics, treatment with rt-PA was found to be associated with an increased chance of mRS 0-1 at discharge compared with untreated patients, overall OR 1.70, 95%CI [1.59-1.81], p<0.0001). Whilst benefit was greatest in patients treated at the earliest time-points, a significant benefit was also seen for patients treated between 3 and 4.5 hours, **adjusted OR 1.26, 95%CI [1.08-1.46]**.

Shobha *et al* (2011) presented analyses from the Canadian Alteplase for Stroke Effectiveness Study (CASES), a multicentre cohort study of patients treated with rt-PA. Patients treated with rt-PA within 3 hours were compared with those treated between 3-4.5 hours. A total of 1112 patients were included, of which 129 (11.6%) were treated between 3 and 4.5 hours, the rest of the patients were treated at <3 hours. At 90 days, 39.4% of patients treated between 3 and 4.5 hours had achieved mRS 0-1, compared with 36.5% of patients treated <3 hours, a difference that was not statistically significant (adjusted RR 0.98, 95%CI [0.8-1.2]). After adjustment, there was a significantly increase risk in mortality and sICH in the 3-4.5 hour cohort compared with the <3 hour cohort. However, 36% of the patients included in the 3-4.5 hour group were treated off-label (primarily >80 years old or NIHSS>25). The size of this study is small, and in particular the number of patients treated between 3 and 4.5 hours is very small (n=129).

Overall the available observational data suggest that the greatest benefit (achieving mRS 0-1) from rt-PA is gained with earlier treatment, as has been found in clinical trials. Most of the registries did not include untreated patients and therefore it is generally not possible to comment on this comparison and overall balance of benefits and risks in this time-window from these data. However, although these data indicate, as expected, that earlier treatment has greater benefit, the reduction in benefit in the later 3-4.5 hour time-window was not excessive, and the results from the comparative German registry found significant benefit with rt-PA between 3 and 4.5 hours compared with non-thrombolysis.

3.2 Randomised trial:

IST-3 was an international, randomised, open-label trial, with an initial double-blind placebo controlled phase (n=276) (IST-3 collaborative group, 2012). The study enrolled a total of 3035 patients between 2000 and 2011. Patients were treated up to 6 hours post symptom onset.

The IST-3 trial was intended to determine whether a wider range of patients than the licensed population would benefit from thrombolysis. The CHM paper (May 2014) discussed the results of the IST-3 trial, paper 5 discusses a number of specific aspects of IST-3, and paper 6 discusses the relevance of the results of IST-3 to the balance of benefits and risks of rt-PA in actual clinical use in the UK. Enrolment into the trial was on the basis of the uncertainty principle – patients for whom rt-PA was clearly indicated, or was associated with a clearly negative benefit-risk were excluded. As a result, 95% of patients included in the trial did not meet the terms of the EU SmPC. In particular, over 50% of patients were >80 years of age, and a substantial number were treated beyond 4.5 hours after onset of symptoms.

The IST-3 trial was relatively large in comparison with the other randomised trials and contributed a substantial number of patients to the 3-4.5 hour time-window. The

primary outcome for the trial was OHS ≤ 2 at 6 months post stroke, and the subgroup results according to stroke onset to randomisation time-window were as follows:

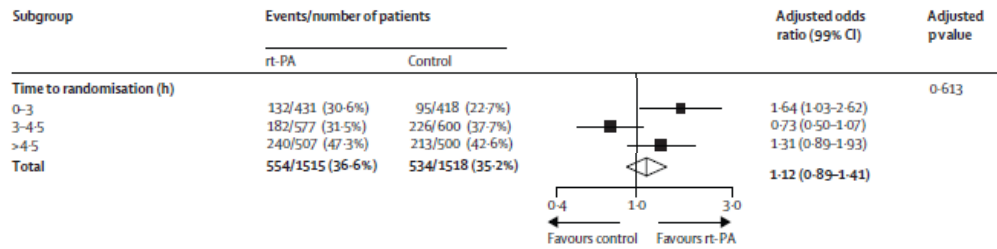


Figure: adjusted effect of treatment on the primary outcome in the IST-3 trial [taken from IST-3 collaborative group, 2012]

Overall prognosis in both rt-PA and control groups appeared to improve with treatment administered later, given the higher % response rates, however this effect is likely to be related to the confounding across covariates (for example, patients recruited earlier were more likely to have severe stroke and be older).

In the further subgroup analyses published by Lindley *et al* (2015), the results in this time-window were reported for the secondary outcome, an adjusted ordinal analysis of OHS at 6 months:

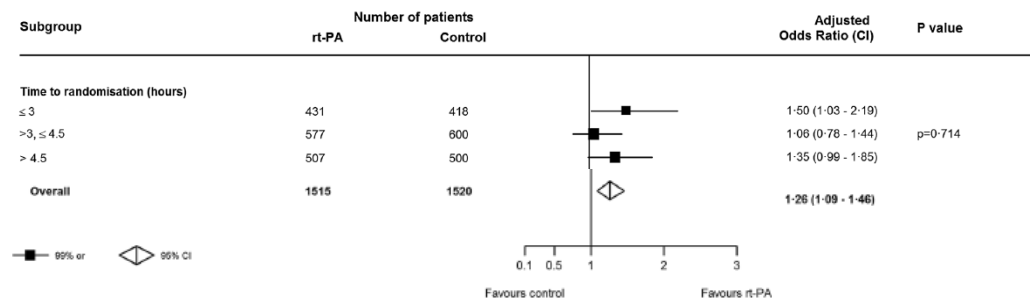


Figure: adjusted effect of treatment on the ordinal analysis of OHS (secondary outcome) [taken from Lindley *et al* 2015]

A similar pattern of results was found using both outcomes, with a significant benefit associated with rt-PA for patients randomised by 3 hours, and less favourable results for those patients randomised at 3-4.5 hours. In the secondary ordinal analysis the point estimate in this group favours rt-PA (**OR 1.06, 95%CI [0.78-1.44]**), whilst in the primary analysis it favours control (**OR 0.73, 95%CI [0.50-1.07]**). Counterintuitively, the results for patients randomised >4.5 hours have a more favourable point estimate for rt-PA treatment (non-significant) compared with patients randomised in the 3-4.5 hour group.

The pattern of the relationship between time to randomisation and effect of rt-PA was not plausible, and may have been influenced by the lack of power, as the trial sample size was revised to recruit approximately half the initially intended number of subjects. In addition, it should be noted that patients in IST-3 were categorised according to time from stroke onset to randomisation, rather than time to treatment. This was due to the lack of comparable treatment (i.e. placebo) provided to the control group – and therefore time to treatment could not be defined in this group. As a result, some of the patients in the time-window 0-3 hours would in fact have received rt-PA at >3 hours post-symptom onset, and some patients in the 3-4.5 hour subgroup would have received treatment at >4.5 hours post-symptom onset. The subsequent meta-analysis by Emberson *et al* (2014) has adjusted for this difference, as described in paper 5A.

As discussed in paper 6, as the patients included in IST-3 were generally treated outside of the EU licensing conditions, and were therefore likely to be a higher-risk population than the overall population of patients routinely treated in the clinic, the finding of less favourable results for rt-PA in this trial compared with some of the other randomised trials was perhaps not surprising.

The safety endpoints, mortality by day 7 and sICH by day 7, were also analysed for the time-window subgroups by Lindley *et al* (2015). There was no significant interaction between rt-PA and time-window to treatment for either of these endpoints. The results for sICH were similar across the three time-windows:

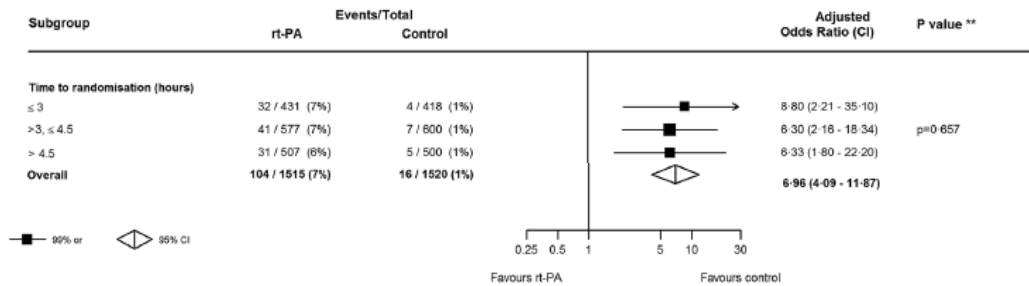


Figure: adjusted effect of treatment on sICH by day 7 [taken from Lindley *et al* 2015]

The results for mortality by day 7 are shown below. Whilst the result for 3-4.5 hours for rt-PA vs control would appear slightly worse than for 0-3 hours and >4.5 hours the confidence intervals for the three time periods substantially overlapped. Similarly to the findings relating to benefit, the pattern of the relationship for day 7 mortality with time to randomisation was not plausible.

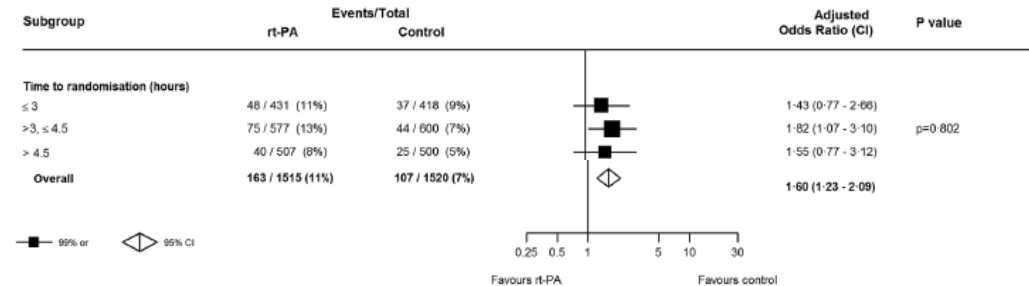


Figure: adjusted effect of treatment on mortality by day 7 [taken from Lindley *et al* 2015]

3.3 Meta-analyses:

An updated Cochrane review was published in July 2014 (Wardlaw *et al*, 2014) and concluded that 'Thrombolytic therapy given up to six hours after stroke reduces the proportion of dead or dependent people. Those treated within the first three hours derive substantially more benefit than with later treatment.'

The data included for the 3-4.5 hour time-window in the Cochrane review included only the ECASS III trial and a trial of streptokinase, these data were the only relevant available data for this time-window because the analysis was not conducted on individual patient data. The authors therefore conclude that the data available for 3-4.5 hours post-symptom onset was not sufficient to draw reliable conclusions and instead focus on results for the 0-3 hour and 3-6 hour time-windows.

The review found that the results from the 0-3 hour time-window demonstrated a statistically significant improvement in function independence, and no significant effect on mortality, whilst the 3-6 hour time-window demonstrated no significant effect on functional independence and a significant increase in mortality. As previously discussed in paper 5A, it is considered that the results found in the time-window 3-6

hours cannot be considered to contribute to any discussion of the 3-4.5 hour time-window, because it has previously been concluded that the balance of benefits and risks of rt-PA is negative beyond 4.5 hours.

As few trials have specifically studied the 3-4.5 hour time-window, the results from individual patient data meta-analyses are considered to be more robust when considering the benefits and risks of treatment between 3-4.5 hours.

The meta-analysis by Emberson *et al* (2014) is the most recent individual patient data meta-analysis, and included data from 9 trials (NINDS part 1 and 2, ATLANTIS A and B, ECASS I, II and III, EPITHET and IST-3), a total of 6756 randomised patients (3391 treated with rt-PA). The results from the meta-analysis were discussed in paper 4, and at the November 2014 and January 2015 EWG meetings where the data were presented by Professors Emberson and Baigent.

The primary efficacy outcome was mRS 0-1 at 3-6 months post-stroke. Safety outcomes were 90 day mortality, sICH and fatal ICH within 7 days. The results of the meta-analysis confirmed the expected relationship between time from stroke onset to treatment and benefit:

	Alteplase (n=3391)	Control (n=3365)		Odds ratio (95% CI)*
Treatment delay				
≤3-0 h	259/787 (32.9%)	176/762 (23.1%)		1.75 (1.35-2.27)
>3-0≤4.5 h	485/1375 (35.3%)	432/1437 (30.1%)		1.26 (1.05-1.51)
>4.5 h	401/1229 (32.6%)	357/1166 (30.6%)		1.15 (0.95-1.40)

*estimates were derived from a single logistic regression model stratified by trial, which enables separate estimation of the OR after adjustment for age and baseline NIHSS (but not for possible interactions with those characteristics)

Figure: Effect of rt-PA on good stroke outcome (mRS 0-1) by treatment delay [taken from Emberson *et al*, 2014]

The OR for patients treated between 3 and 4.5 hours post-symptom onset was significantly in favour of rt-PA treatment (**adj. OR 1.26, 1.05-1.51**). This favourable result was found despite the addition of the IST-3 data, which contributed a substantial portion of the patients in the 3-4.5 hour time-window (n=1148, 38%) and which had less favourable results for this time-window. This apparent discrepancy was discussed in detail in paper 5A, and was found to be related both to the pre-specified approach to the IST-3 data which involved converting 'time to randomisation' to 'time to treatment', in order for the data to be comparable with other trials and to the difference in the endpoints used in IST-3 (mRS 0-2) compared with the meta-analysis (mRS 0-1). Use of 'time to randomisation' in IST-3 was necessary because the time to treatment in the control arm of IST-3 was by definition unmeasurable as these patients received no treatment. The mean delay between randomisation and treatment in patients treated with rt-PA (18 minutes) was used to estimate the time to treatment in IST-3.

Using a regression model, the authors estimated that the time from onset of stroke at which rt-PA has no beneficial effect was 6.3 hours (95%CI 5.0-13.8), and the time at which the lower 95%CI first crossed 1 was 5.1 hours.

Time to treatment was not found to impact on the risk of fatal ICH within 7 days associated with rt-PA, which was similar (and raised in comparison to control patients) in all time-window categories.

	Alteplase (n=3391)	Control (n=3365)		Odds ratio (95% CI)*
Treatment delay				
≤3.0 h	22/787 (2.8%)	2/762 (0.3%)		10.86 (2.54-46.41)
>3.0≤4.5 h	35/1375 (2.5%)	7/1437 (0.5%)		5.63 (2.49-12.76)
>4.5 h	34/1229 (2.8%)	4/1166 (0.3%)		8.16 (2.88-23.11)

*estimates were derived from a single logistic regression model stratified by trial, which enables separate estimation of the OR after adjustment for age and baseline NIHSS (but not for possible interactions with those characteristics)

Figure: Effect of rt-PA on fatal ICH within 7 days by treatment delay [taken from Emberson et al, 2014]

A similar pattern of results were found for sICH (parenchymal haemorrhage type 2) within 7 days, whereby time to treatment was not found to impact on the risk associated with rt-PA, which was similar (and raised in comparison to control patients) in all time-window categories.

However there was a trend to increasing mortality at day 90 with increasing time to treatment, which was not statistically significant (p=0.22). Although as reported by the authors, the power to detect a true trend was limited by the number of deaths:

	Alteplase (n=3391)	Control (n=3365)		Hazard ratio (95% CI)*
≤3.0 h	175 (22.2%)	166 (21.8%)		1.00 (0.81-1.24)
>3.0≤4.5 h	232 (16.9%)	229 (15.9%)		1.14 (0.95-1.36)
>4.5 h	201 (16.4%)	161 (13.8%)		1.22 (0.99-1.50)
Total 90-day mortality	608 (17.9%)	556 (16.5%)		1.11 (0.99-1.25)

Test for linear trend of log HR with increasing treatment delay (p=0.22)

0.50 0.75 1.00 1.50 2.00
Alteplase better Alteplase worse

*estimated by Cox proportional hazards regression stratified by trial (and adjusted only for treatment allocation)

Figure: Effect of rt-PA on 90-day mortality by treatment delay [taken from Emberson et al, 2014]

For patients treated between 3-4.5 hours the authors conclude that rt-PA causes an average absolute increase in risk of early death from ICH of ~2% (rt-PA had no effect on risk of other early causes of death), but this is offset by an average absolute increase in disability-free survival (mRS 0-1) of ~5%.

3.4 Subgroups of particular interest

3.4.1 Patients with mild stroke

The SmPC for rt-PA contraindicates use in “Minor neurological deficit or symptoms rapidly improving before start of infusion”. The benefits and risks of rt-PA treatment in mild stroke were discussed in paper 7, concluding that whilst an overall positive effect of rt-PA was found compared with control in the Emberson *et al* (2014) meta-analysis, an individual patient with only mild symptoms might consider the balance of benefits and risks to be negative, as a positive outcome is more likely regardless of whether they are treated with rt-PA, and a risk of sICH or fatal ICH remains. In terms of the 3-4.5 hour treatment window, a large observational study by Romano *et al* (2015) found no significant differences in rates of outcomes (sICH, death, life-threatening or serious systemic haemorrhage, other serious complications, independent ambulation and discharge to home) between patients treated <3 hours and those treated between 3-4.5 hours with baseline NIHSS ≤5. There were a greater proportion of patients with ‘complications of undetermined cause’ in the 3-4.5 hour subgroup compared with the 3 hour subgroup however. The absolute frequencies of sICH, death, and serious haemorrhage were found to be low, and

overall these data were reassuring regarding the benefits and risks in patients with mild stroke treated at the later time point compared with <3 hours.

3.4.2 Patients with severe stroke

The relationship between stroke severity and outcome is complex and many studies have found that patients with severe strokes tend to present earlier and are therefore treated earlier than less severe strokes. As discussed in paper 7, Emberson *et al* showed that the efficacy of rt-PA did not vary with stroke severity within the 0-4.5 hour treatment window, and the proportional increase in risk of fatal ICH due to rt-PA was similar regardless of stroke severity although the absolute excess risk increased with increasing severity (Emberson *et al*, 2014). The number of patients treated with baseline NIHSS \geq 22 and included in the meta-analysis was small (n=309 in the rt-PA group, vs. n=313 in the control group).

The efficacy data for rt-PA in the 3-4.5 hour window is less robust compared with the <3 hour time window, and therefore the balance of benefits and risks in patients with adverse prognostic factors (such as severe stroke) is not clear but may be negative. The development of predictive tools for individual use may aid the assessment of the balance of benefits and risks should rt-PA be considered for use in this patient group (see paper 9).

The SmPC for rt-PA contraindicates use in “severe stroke as assessed clinically (e.g. NIHSS >25) and/or by appropriate imaging techniques”.

3.4.3 Elderly patients

The benefits and risks of rt-PA treatment in elderly patients (>80 years) have been discussed in paper 6 and 7, and the currently available data suggest that the benefits of rt-PA are not age-related. The Emberson *et al* (2014) meta-analysis found a statistically significant result in favour of rt-PA treatment for mRS 0-1 in patients aged >80 years treated within 3 hours of onset of stroke (OR 1.86, 95%CI [1.11-3.13]) and for the dataset overall (OR 1.56, 95%CI [1.17-2.08]). The data for 3-4.5 hours and >4.5 hours for patients aged >80 years found a non-significant favourable OR for rt-PA treatment (for 3-4.5 hours: OR 1.36, 95%CI [0.87-2.14]). Treatment of patients aged >80 years is currently contraindicated in the EU SmPC, although the MAH has indicated that they are intending to submit a review of data in this patient subgroup to determine whether it is acceptable for the contraindication to be lifted. The review will consider whether there are any subgroups of patients aged >80 years for whom the balance of benefits and risks of rt-PA treatment would be unfavourable.

4. Conclusion on benefit:risk of rt-PA at 3-4.5 hours

At the time of the decision to increase the time-window for treatment with rt-PA to 4.5 hours, the most relevant data source was the ECASS III trial which provided randomised, controlled data specifically in the 3-4.5 hour time-window. This was supported by observational data and a pooled analysis of the clinical trials available at that time. Since then, further information has become available, the most notable source being the IST-3 trial which included a large number of patients in the 3-4.5 hour time window. Additional observational data have also become available, which are generally supportive of the use of rt-PA in routine clinical practice between 3 and 4.5 hours. The majority of these observational data do not include untreated patients and therefore no comparison with control can be made from these.

More recently, a meta-analysis by Emberson *et al* (2014) has been published. As an individual patient data meta-analysis which includes all of the main trials available to date, it is considered to be the most comprehensive and rigorous summary of the available data on the 3-4.5 hour time-window. The results of the meta-analysis demonstrate a statistically significant beneficial effect of rt-PA compared with non-

thrombolysed patients when treatment is given in the 3-4.5 hour time-window. The results confirm that the earlier the treatment is given, the greater the odds of a good outcome. The risk of sICH associated with rt-PA does not appear to increase with increasing time to treatment, although a non-significant trend to increase in overall mortality by day 90 as time to treatment increases has been observed.

Patients with mild stroke are contraindicated for use of rt-PA and this is considered to be appropriate (see paper 7 for further discussion of mild stroke). Data for patients with mild stroke are limited due to their exclusion from the main clinical trials, however a large observational study of patients with NIHSS ≤ 5 has recently been published which found similar outcomes for patients treated 3-4.5 hours after symptom onset compared with those treated up to 3 hours post-symptom onset.

The efficacy of rt-PA was not found to vary according to stroke severity within the 0-4.5 hour time-window and the risk of sICH associated with rt-PA was similarly unaffected, however the absolute excess risk of sICH increased with increasing stroke severity. The efficacy data for rt-PA in the 3-4.5 hour window is less robust compared with the <3 hour time window, and therefore the balance of benefits and risks in patients with adverse prognostic factors (such as severe stroke) is unclear but may be negative. The development of predictive tools for individual use may aid the assessment of the balance of benefits and risks should rt-PA be considered in this patient group (see paper 9). Patients with severe stroke NIHSS >25 are contraindicated in the SmPC, and this is considered appropriate particularly given the lack of data available in this subgroup (see paper 7).

The data now available for patients aged >80 years suggests that treatment effect is not influenced by age. Increasing age is a risk for poor outcome, both with or without rt-PA treatment. The balance of benefits and risks in patients >80 years may be more favourable in those treated <3 hours post-symptom onset than those treated between 3-4.5 hours. The MAH has indicated that they are intending to submit a review of data in this patient subgroup to determine whether it is acceptable for the contraindication to be lifted. The review will consider whether there are any subgroups of patients aged >80 years for whom the balance of benefits and risks of rt-PA treatment would be unfavourable, and therefore whether restrictions should be imposed in the event of lifting of the contraindication in this population.

In summary, the data available in the 3-4.5 hour time-window are supportive of a positive balance of benefits and risks when used within the conditions of the licence. However, it is clear that benefit decreases with increasing onset to treatment time, and therefore efforts to reduce this time are paramount to improving outcomes. The current SmPC highlights, in several relevant sections including the indication, the need for treatment to be provided as soon as possible following the onset of stroke symptoms and the relationship between decreasing efficacy with increasing onset-to-treatment time (see Introduction).

Points for discussion for the EWG

- Is the EWG satisfied that the balance of benefits and risks has been demonstrated to be positive in the 3-4.5 hour treatment time-window?

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EXPERT WORKING GROUP**ACTILYSE (ALTEPLASE) BALANCE OF BENEFITS AND RISKS WHEN USED IN THE TREATMENT OF ACUTE ISCHAEMIC STROKE**

Title of paper: Paper 6: Clinical use of rt-PA in the UK and feasibility of treating within the conditions of the marketing authorisation
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Product: Actilyse 10, 20, 50mg	Assessors: Scientific assessor: Dr [REDACTED] [REDACTED]
MAHs: Boehringer Ingelheim Limited	Previous Assessments: CHM May 2014 EWG: Nov 2014, Jan 2015
Active constituents: Alteplase (rt-PA)	Legal status: POM
Therapeutic classification: Antithrombotic agent, ATC code B01AD02	

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1. Introduction

This paper discusses the clinical use of rt-PA for acute ischaemic stroke in the UK and the relevance of clinical trial data to the understanding of benefits and risks in actual clinical use. It also considers whether current levels of off-label use raise concerns and the feasibility of complying with the conditions of the marketing authorisation during routine clinical use.

2. Clinical use of rt-PA in the UK

Paper 7 discusses available outcome data in patients who are treated outside of the conditions of the marketing authorisation for rt-PA. Paper 3 (Usage of rt-PA in acute ischaemic stroke) previously described the available data on patients treated with rt-PA in the UK, and found that ~70% of use is within the conditions of the marketing authorisation. The remaining ~30% of use which occurs off-label most commonly involves treatment of patients >80 years of age (SITS registry data from January 2012 to July 2014 suggests ~29% of patients were aged over 80 years), with some use (~2%) beyond the 4.5 hour time-window for treatment.

Data from the latest SSNAP report for July- September 2014 (RCP, 2014) suggests that overall nearly 40% of patients admitted for stroke (haemorrhagic or ischaemic) in England, Wales and N Ireland, were aged over 80 years, and ~75% had one or more co-morbidity (including congestive heart failure, hypertension, diabetes, stroke/TIA, atrial fibrillation). Despite the relatively high proportion of patients >80 years of age, age was provided as a reason for not treating with thrombolysis in only 0-3% of cases – this is in agreement with the data from SITS and suggests that older age is not considered in the clinic to be a barrier to treatment despite the contraindication in the marketing authorisation for patients >80 years. The use of rt-PA in over 80 year olds is endorsed in the current National Clinical Guidelines¹, most clearly if treatment is initiated within 3 hours, whilst for patients <80, treatment is recommended ≤4.5 hours after symptom onset. Between 3-6 hours, patients are to be considered for treatment on an individual basis and it would therefore be of interest to know how many 80 year olds are treated between 3 and 4.5 hours.

The main reasons for not thrombolysing patients (SSNAP report July – September 2014) were given as: patient arrived outside of the time window for thrombolysis (~29%), wake up time unknown (~30%), stroke too mild/severe (~15%), haemorrhagic stroke (~11%). Other reasons included that the patient's condition was improving, the patient had other co-morbidities, and 'other medical reasons' (each accounting for 5-7%). A small proportion of patients (0-3%) were not thrombolysed due to concomitant medications or patient refusal (or as mentioned above, patient age). This information provides some insight into the treatment decisions in the clinic, with the most common reason for not administering rt-PA being related to the time from onset of symptoms being either too long or unknown (~60%). The proportion of patients who were not thrombolysed due to other co-morbidities and 'other medical reasons' was much smaller (between 10-14% in total), and may include patients with other contraindications to treatment such as history of prior stroke and concomitant diabetes, very low/very high blood glucose, very high blood pressure, and general contraindications to rt-PA that are associated with increased risk of haemorrhage. Other medical conditions that are not contraindicated but are likely to be reasons for not thrombolysing a patient include severe dementia

¹ The UK National Clinical Guideline for stroke recommends use in: a) all patients regardless of age or stroke severity where treatment can be started within 3 hours of onset of symptoms, and who have been shown not to have an intracerebral haemorrhage or other contraindications b) between 3 and 4.5 hours of known symptom onset, patients under 80 years who have been shown not to have an intracerebral haemorrhage or other contraindication and c) patients between 3 and 6 hours of symptom onset to be considered for treatment on an individual basis

and major pre-stroke disability [personal communication, Professor Gary Ford.] It is not clear from these data however whether patients with these conditions are being treated with rt-PA regardless, or whether this proportion is reflective of the number of patients presenting with such conditions.

Whilst the National Clinical Guidelines recommend that patients of any age and any stroke severity should be considered for thrombolysis with rt-PA when treatment may be started within 3 hours, and patients <80 years of age should be considered for treatment between 3-4.5 hours of symptom onset, these recommendations also carry the caveat that this is providing intracerebral haemorrhage or other contraindications have been ruled out. It is difficult to comment on the overall level of use of rt-PA for stroke in patients with contraindications relating to concomitant medical conditions/treatments. The contraindications in place specifically relating to use in ischaemic stroke concerning blood glucose and blood pressure cover the more extreme ends of the spectrum of these measures – as a result these thresholds may be more likely to be up-held by HCPs, and particularly given the advice provided in the guidelines.

2.1 Relevance of clinical trial data to balance of benefits and risks in actual clinical use in the UK

The most common off-label use of rt-PA for acute ischaemic stroke appears to be in patients aged >80 years. The level of off-label use in other contraindicated populations (e.g. patients with mild/severe stroke, other contraindicated conditions) is more difficult to ascertain, however it appears that use beyond 4.5 hours only occurs in a small minority of cases.

The majority of clinical trials applied exclusion criteria similar to the contraindications in place in the current rt-PA product information, with the exception that some trials allowed treatment up to 6 hours following symptom onset, and as a result most clinical trial data are of relevance to patients treated within the licence conditions. Only a very small number of patients aged >80 years were included in clinical trials until IST-3 was conducted (IST-3 collaborative group, 2012).

The IST-3 trial and results were discussed in the CHM paper (May 2014) and by Professor Sandercock at the January 2015 EWG meeting. In addition specific aspects of the trial were discussed in paper 5. Further details of the results of subgroups from IST-3 are provided in papers 7 and 5D.

The majority of patients enrolled in the IST-3 trial (95%) reportedly did not meet the terms of the EU licence, as trial eligibility was based on the uncertainty principle – patients for whom rt-PA treatment was clearly indicated or was associated with a clearly negative benefit-risk were excluded. As a result, the implications of the findings of the IST-3 trial for patients treated within the terms of the EU licence are unclear, particularly as the trial population might reasonably be expected to include higher risk patients. Since the national guidelines recommend treatment for patients over the age of 80 within 3 hours if they have no other contraindications, the over 80s included in IST-3 may be expected to have additional contraindications, or at least risk factors, to treatment.

The IST-3 trial findings are of more relevance to the understanding of the benefit-risk of rt-PA in actual clinical use than use strictly within the terms of the marketing authorisation, given that more than 50% of patients enrolled were aged >80 years and SITS/SSNAP data suggest that a high proportion of rt-PA treated stroke patients may be aged over 80. IST-3 provides more information in this sub-group of patients than the other previously conducted clinical trials. Patients in IST-3 also likely fell outside of the licence conditions with regards to a variety of different measures

including blood pressure, blood glucose, stroke severity and delay in randomisation (4.5-6 hours) for example (see table 2 of May 2014 CHM paper).

As the IST-3 trial was a large randomised, open trial of rt-PA in patients for whom rt-PA is not currently indicated it can be considered to be the best quality evidence currently available in these particular subgroups of patients. Whilst the trial failed in the overall primary outcome (OHS 0-2 at 6 months post-treatment) with an adjusted OR 1.13 95%CI [0.95-1.35], benefit was found in the subgroup of patients treated <3 hours after randomisation (adjusted OR 1.64, 95%CI [1.03-2.62]), and the secondary endpoint ordinal analysis found an overall positive result (OR1.27, 95%CI [1.10-1.47]). The subgroup results of patients aged >80 years were more favourable, albeit not statistically significant), than the results for patients aged ≤80 years.

Considering that the population included in the IST-3 trial may be expected to be higher risk than the actual population treated routinely in the clinic, given the uncertainty principle under which patients were enrolled, and that the study was underpowered due to the failure to meet the original recruitment target (and therefore the subgroup analyses are also underpowered), the failure of the primary endpoint to demonstrate a significant benefit is perhaps not too unexpected.

The meta-analysis by Emberson *et al* (2014) included data from nine clinical trials (NINDS A and B, ECASS I, II, III, ATLANTIS A and B, EPITHET and IST-3), and provides the most current summary of all clinical trial data available on rt-PA. As might be expected, the majority of information available in patients aged >80 years was contributed by the IST-3 trial (n=1617), with a small number from the other 8 trials (combined n=112). The primary outcome in this meta-analysis was mRS 0-1 at 3-6 months, and the result in patients aged >80 years was positive. The meta-analysis provides some data on other contraindicated populations, for example patients with mild or very severe stroke and as might be expected, much of these data are contributed by the IST-3 trial (see paper 7 for further details of the results of the meta-analysis).

3. Level of concern regarding off-label use and implications for product licence

Given the available information on actual use of rt-PA in the clinic, it would seem that most stroke units are using rt-PA in accordance with the guidelines and broadly in line with the SmPC and that the main discrepancy is with respect to age over 80 years. Given the inconsistency of the recommendation for patients over 80 between the guideline and the SmPC the balance of benefits and risks in this subgroup of patients is the most important to consider. The information from IST-3 and from observational sources as well as the overall results from the Emberson *et al* meta-analysis (as discussed in paper 7), do not raise concerns in terms of benefits or risks of treatment, and if anything the IST-3 trial suggests improved benefit in this sub-population, compared with younger patients. However the limitations of the data sources should be appreciated (e.g. the open nature of the IST-3 trial).

The last formal regulatory assessment of use of rt-PA in patients >80 years of age was conducted during the variation to extend the time-window for treatment to 4.5 hours post-symptom onset. This assessment included data from ECASS III (Hacke *et al*, 2008) and a pooled analysis of the clinical trial data available at that time (prior to IST-3), as well as linear modelling of the pooled data using age as a continuum to assess the effect of rt-PA on a good outcome and day 90 mortality. The assessment concluded that there is a continuing decline in favourable outcome with increasing age and an upward trend with respect to mortality with increasing age. As a result, a warning was included in section 4.4 of the SmPC, as follows:

“Data available from ECASS III and the pooled analysis indicate that the net clinical benefit becomes smaller in elderly with increasing age compared to younger patients as benefit from treatment with Actilyse appears to decrease and the risk of mortality appears to increase with increasing age.”

Since then much additional data has become available, mainly through IST-3. In the current review of rt-PA the MAH has indicated that they intend to submit a review of the benefits and risks of rt-PA treatment in patients aged >80 years, with a view to lifting the contraindication in this population. As rt-PA is licensed via the mutual recognition procedure, the assessment of these data will be led by Germany. The MAH has indicated that their submission will consider the impact of the newly available data from IST-3, and overall findings from meta-analyses to determine whether it is acceptable for the contraindication to be lifted. It will also consider whether there are any subgroups of patients aged >80 years who are unsuitable for rt-PA treatment and therefore whether different restrictions should be introduced. The MAH comments that as a result, if the contraindication is lifted, the current level of use in patients >80 years may in fact be reduced because the appropriate elderly population can be more specifically defined.

For the purposes of this review, it is concluded that the body of evidence now available does not raise concerns about the balance of benefits of risks associated with widespread use of rt-PA in patients aged >80 years.

4. Feasibility of treating acute ischaemic stroke with rt-PA strictly within the conditions of the marketing authorisation

The contraindications for treatment with rt-PA in the setting of acute ischaemic stroke are fairly extensive (see paper 7). This inevitably raises questions regarding the feasibility of complying with all of these conditions when it is essential that the treatment concerned is administered as quickly as possible.

The requirement to rule out intracranial haemorrhage via CT (or MRI) scan is so essential that this contraindication will always be applied appropriately. Several of the other contraindications that relate to the immediate assessment of the patient, for example, stroke severity, blood pressure, seizure at onset of stroke would also seem relatively easy to comply with. Regarding time of stroke onset, the available data suggests that where time of onset is unknown or >4.5 hours, the patient would not be treated with rt-PA, except in a very small number of cases.

Other contraindications require accurate patient history, for example, history of prior stroke and concomitant diabetes, prior stroke within the last 3 months, information on concomitant medications (anticoagulants), other medical history that entails a high risk of bleeding e.g. ulcerative gastrointestinal disease during the last 3 months, severe liver disease, neoplasm with increased bleeding risk. This information may or may not be easily accessible depending upon the patient's location and condition on admission, and whether information is available from anyone accompanying the patient. If the patient is unable to communicate, it is likely that it will not be possible to determine the existence or otherwise of all of these conditions.

Patient age is another piece of information that may or may not be easily ascertained, depending upon the condition of the patient at admission. However, as previously discussed, much of the current off-label use is in patients aged >80 years, and this is understood to be intentional off-label use, in accordance with clinical guidelines.

Finally, other contraindications rely on the results of tests, for example, blood glucose levels <2.8 or >22.2 mmol/l, platelet count below 100,000/mm³, INR in patients anticoagulated with warfarin and thromboplastin time in patients treated recently with

heparin. At present, tests such as INR cannot be performed at the bedside and therefore may result in delay to treatment if they are deemed necessary. It is likely therefore that INR testing will only be ordered in cases where the patient is known or suspected to be anticoagulated with e.g. warfarin. Cases of patients suffering stroke whilst already admitted to hospital may well have results for these parameters and therefore these restrictions will be simpler to apply in such cases.

It is considered likely that in many cases it will not be possible to obtain every relevant piece of information and still treat the patient in the shortest possible time. Therefore it is expected that physicians would apply their clinical judgement regarding the need for particular investigations prior to administration of rt-PA. From a regulatory point of view it remains appropriate to include all relevant contraindications, as different pieces of information will be available for different patients.

The feasibility of administering rt-PA within the conditions of the MA in terms of practical issues and medication errors is discussed in paper 7.

5. Discussion and conclusion

The data available suggests that the main area of off-label use of rt-PA in acute ischaemic stroke is in patients aged >80 years. Data from SITS and supported by SSNAP suggests that ~30% of thrombolysed patients are aged >80 years. Off-label use beyond the approved time-window for treatment of 4.5 hours appears to be low (~2%) and it is difficult to ascertain the level of off-label use in other contraindicated subgroups. Use of rt-PA in patients aged over 80 years is supported by national guidelines and therefore this high level of off-label use is not unexpected.

The majority of clinical trials had exclusion criteria that were similar to the contraindications in the current SmPC, and therefore these data are most relevant to patients treated within the conditions of the marketing authorisation. The IST-3 trial is the best source of randomised trial data on patients treated outside of the licence, and the meta-analysis by Emberson *et al* provides the most current summary of all clinical trial data available on rt-PA in acute ischaemic stroke including IST-3.

The contraindications for treatment with rt-PA for acute ischaemic stroke are extensive and therefore the feasibility of complying with all of the conditions for use whilst ensuring treatment is given as quickly as possible can be questioned. However, several of the contraindications can be immediately assessed (e.g. blood pressure). Others may be subject to clinical judgement, for example the need for INR measurement, or investigations to rule out medical conditions that increase the risk of bleeding. This will also depend upon the ability of the patient to communicate, or whether they have family/carers with them. The most frequently disregarded contraindication is likely to be use in patients aged over 80 years, this off-label use is intentional and in accordance with clinical guidelines. The currently available data are not considered to raise concerns regarding the off-label use of rt-PA in these patients. Although it may not be feasible to check that all contraindications are complied with in every case, it is considered that it remains appropriate to include all relevant contraindications, as different information will be available for different patients.

Points for discussion for the EWG:

- Does the EWG have any comments regarding the feasibility or otherwise of complying with the contraindications to treatment and whether these raise any issues that should be addressed e.g. using national communications? For example the need for, and difficulty obtaining information on patient medical history or test results.

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EXPERT WORKING GROUP**ACTILYSE (A LTEPLASE) BALANCE OF BENEFITS AND RISKS WHEN USED IN THE TREATMENT OF ACUTE ISCHAEMIC STROKE**

<p>Title of paper: Paper 7: Benefits and risks of rt-PA in clinical practice, including in off-label use, and the occurrence of medication errors</p>
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<p>Product: Actilyse 10, 20, 50mg</p>	<p>Assessors: Medical assessor: Dr [REDACTED] Scientific assessors: Dr [REDACTED] Dr [REDACTED] Epidemiological assessors: Dr [REDACTED]</p>
<p>MAHs: Boehringer Ingelheim Limited</p>	<p>Previous Assessments: CHM May 2014 EWG: Nov 2014, Jan 2015</p>
<p>Active constituents: Alteplase (rt-PA)</p>	<p>Legal status: POM</p>
<p>Therapeutic classification: Antithrombotic agent, ATC code B01AD02</p>	

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7. Benefits and risks of alteplase in clinical practice, including off-label use and medication error

Introduction

This paper will discuss the benefit-risk balance for alteplase when used in clinical practice for the treatment of acute ischaemic stroke. This includes relevant examples of off-label use.

The paper will also assess whether recent evidence on the efficacy and harms of alteplase in specific patient sub-groups is appropriately reflected in the relevant sections of the current Summary of Product Characteristics (SmPC). Published data on key variables that may alter the benefit-risk balance of alteplase will also be evaluated.

Through review of evidence for and nature of any medication/administration errors that have been reported with alteplase, we will also consider whether there is any evidence of harm in everyday use resulting from a lack of clarity in the current marketing authorisation.

Some of these topics have already been discussed in different contexts during the EWG meetings, therefore this paper is intended to consolidate these discussions and provide a more formal record of the evidence.

The indication for alteplase in acute ischaemic stroke is as follows:

Fibrinolytic treatment of acute ischaemic stroke

Treatment must be started as early as possible within 4.5 hours after onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques (e.g. cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage). The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.

The contraindications for the use of alteplase in acute ischaemic stroke are extensive and include a large number that apply to all authorised indications. Many of these relate to the risk of bleeding with alteplase.

The SmPC also lists a number of additional contraindications specific to the indication of acute ischaemic stroke:

- symptoms of ischaemic attack beginning more than 4.5 hours prior to infusion start or symptoms for which the onset time is unknown and could potentially be more than 4.5 hours ago
- minor neurological deficit or symptoms rapidly improving before start of infusion
- severe stroke as assessed clinically (e.g. NIHSS >25) and/or by appropriate imaging techniques
- seizure at onset of stroke
- evidence of intracranial haemorrhage (ICH) on the CT-scan
- symptoms suggestive of subarachnoid haemorrhage, even if CT-scan is normal

- administration of heparin within the previous 48 hours and a thromboplastin time exceeding the upper limit of normal for laboratory
- patients with any history of prior stroke and concomitant diabetes
- prior stroke within the last 3 months
- platelet count of below 100,000/mm³
- systolic blood pressure >185 or diastolic BP >110 mmHg, or aggressive management (intravenous pharmacotherapy) necessary to reduce BP to these limits
- blood glucose <50 or >400 mg/dl [<2.8 or >22.2 mM].
- Use in children and adolescents:

Alteplase is not indicated for the treatment of acute stroke in paediatric patients under 18 years.

- Use in elderly patients

Alteplase is not indicated for the treatment of acute stroke in adults over 80 years of age.

Prognosis of ischaemic stroke without thrombolysis

Little is known about the natural history of ischaemic stroke if it is strictly defined as the untreated course of the disorder because patients with stroke usually receive some form of medical or nursing therapy.

A review of 142 prognostic studies conducted before the licensing of alteplase for ischaemic stroke identified the following predictors of functional recovery: age, previous stroke; urinary incontinence; level of consciousness within the first 48 h after a stroke; disorientation in time and place; severity of motor weakness; sitting balance; level of disability on admission; level of perceived social support; and metabolic rate of glucose outside the infarcted area in hypertensive patients (measured by positron emission tomography of fluorodeoxyglucose) (Kwakkel et al. 1996). The following radiological findings have been shown to be statistically significant ($p<0.05$) independent predictors of poor survival and/or poor functional outcome after stroke in at least one study including more than 100 patients: large stroke lesion; site of brain lesion; mass effect; intraventricular bleeding and visible infarction (Counsell 1998).

The risk of dying within the first 7 days of a first-ever ischaemic stroke depends on infarct size and location. The mortality rate at 7 days ranges from 2% for a partial anterior circulation or lacunar infarct to 17% for a total anterior circulation infarct. At 30 days the mortality rate remains at 2% for a lacunar infarct, doubles to 4% for a partial anterior circulation infarct but increases to 39% for a total anterior circulation infarct (Oxfordshire Community Stroke Project, Bamford et al. 1991). The early mortality rate for a complete middle cerebral artery (MCA) territory infarct can be as high as 80% (Hacke et al. 1996).

The causes of death following an ischaemic stroke vary over time. Early deaths in the first days following a stroke may be due to: direct damage to vital brain regions by infarction or oedema; intracranial haemorrhage (ICH) or haemorrhagic transformation (HT); or co-morbidities such as ischaemic heart disease or cancer that may be associated with or may have caused the stroke. The rates of symptomatic ICH (sICH) derived from control patients in clinical studies of alteplase ranged from 0% in certain sub-groups (Hacke et al. 2004; Lees et al. 2010) to 11.6% from pooled trial data

(Wahlgren et al. 2007). Most studies had sICH rates below 5%. The baseline stroke severity (measured using the National Institutes of Health Stroke Scale [NIHSS] score) correlated with the risk of HT in a study of 229 untreated patients with ischaemic stroke presenting within 12 hours (h) of onset (median NIHSS score 14 (interquartile range [IQR: 9-20]; n=55 in those with HT versus median NIHSS score of 10 [IQR: 7-15]; n=174 in those without HT, $p = 0.002$) (Leira et al. 2012).

After the first few days, patients may die from complications related to immobility such as pneumonia, thromboembolic disease, urinary tract infection, pressure sores, and even renal failure from dehydration if supportive care is inadequate. Other potentially fatal complications include injuries from falls, drug reactions and stroke recurrence.

A number of prognostic models for use in acute ischaemic stroke have been developed using data derived from clinical trials and registries. Accurate prognostic information is useful for allocating and planning appropriate care (including palliative and rehabilitation services) and helpful when advising patients or their carers (table 1). All of these models contain age and stroke severity as independent prognostic factors. The reliability and usefulness of clinical prediction scores can be measured using the C statistic which is a function of the specificity and sensitivity of the prediction model for discriminating between outcomes. The C statistic ranges from 0.5 (equivalent to chance) to 1.0 (perfect discrimination). The models in table 1 had C values ranging from 0.80 to 0.89 indicating very good discrimination (Rempe 2014). These prediction models have a number of limitations: they are derived from historical data and new treatments may alter the prognosis; they may not incorporate all relevant factors if they were collected in a registry; a small proportion of patients may have been thrombolysed; and to be clinically useful each model should have been validated in several patient populations or registries. Only the iScore model has been shown to be better than an experienced physician at predicting outcomes using data derived from 1415 patients (11% thrombolysed) in the Registry of the Canadian Stroke Network (Saposnik et al. 2013a).

The risks of alteplase therapy may be modified by certain adverse prognostic factors for ischaemic stroke and these factors may be inter-related. For example, stroke severity or conscious state may be related to lesion size on CT scan and/or patient co-morbidities.

The hazards of intravenous alteplase for acute ischaemic stroke may be overestimated if the prognosis of severe cerebral infarction is not appreciated or if functional outcomes are not used to define sICH (Saver 2007). Most of the clinical risk factors for ICH and cerebral oedema after alteplase treatment are also associated with a poor prognosis after untreated stroke (Veerbeek et al. 2011).

The main risks of alteplase therapy for acute ischaemic stroke are symptomatic and fatal haemorrhagic transformation of the infarcted brain tissue and cerebral oedema. It therefore follows that the presence of any factors which have been shown to alter the frequency of beneficial and harmful outcomes after ischaemic stroke may also alter the benefit-risk profile of alteplase.

Table 1: Outcome prediction models for acute ischaemic stroke (Rempe 2014).

Prediction Model	What is predicted	Prognostic Factors	Scoring system
ASTRAL (Ntaios 2012)	mRS score >3 or death at 30 days	Age NIHSS score Time to presentation Visual field defect Glucose Level of consciousness (LOC)	Every 5 years = 1 point Every NIHSS point = 1 point Presentation >3 h from onset = 2 points Visual field defect = 2 point Glucose >131 (7.3 mM) or <66 mg/dl (3.7 mM) = 1 point LOC reduced = 3 points
IScore (Saposnik 2011)	30 day mortality; 1 year mortality; 30 day death or mRS score >3; 30 day mortality or institutionalisation at discharge	Age Sex *Canadian Neurological Scale Score Stroke subtype Vascular risk factors Co-morbidities Pre-admission disability Admission glucose	1 point for each year of age Male = 10 points Female = 0 points 0 = 105 points <4 = 65 points 5-7 = 40 points >8 = 0 points Lacunar = 0 points Nonlacunar = 30 points Undetermined = 35 points Atrial fibrillation = 10 points Heart failure = 10 points Cancer = 10 points Renal dialysis = 35 points Independent = 0 points Dependent = 15 points <135 mg/dl (7.5 mM) = 0 points >135 mg/dl = 15 points
PLAN (O'Donnell 2012)	30 day mortality; death or severe disability at discharge (mRS score 5-6); 1 year mortality; mRS score 0-2 at discharge	Age Stroke severity Co-morbidities	1 point per decade Severe arm weakness = 2 points Severe leg weakness = 2 points Neglect or aphasia = 1 point Atrial Fibrillation = 1 point Heart failure = 1 point Cancer = 1.5 points Dependence = 1.5 points

Prediction Model	What is predicted	Prognostic Factors	Scoring system
PLAN		Level of consciousness	LOC reduced = 5 points
BOAS (Muscari 2011)	mRS score >2 or death at 6 months	Age NIHSS score Persistent arm weakness Paralysis at discharge Oxygen required Urinary catheter	>78 years = 1 point >10 = 1 point If present = 1 point If present = 1 point If necessary = 1 point If present = 1 point
Get With the Guidelines Stroke Risk Model (Smith 2010)	In-hospital mortality	Age NIHSS score Mode of arrival Sex History of vascular risk factors	< 60 years = 0 points 60-70 years = 1 point 70-80 years = 5 points > 80 years = 9 points 0-2 = 0 points 3-5 = 10 points 6-10 = 21 points 11-15 = 37 points 16-20 = 48 points 21-25 = 56 points > 25 = 65 points Private transport = 0 points Did not present through A&E = 16 points Ambulance from scene = 12 points Female = 3 points No prior stroke/TIA = 2 points Diabetes mellitus = 2 points Hyperlipidaemia = 2 points Atrial fibrillation = 2 points Ischaemic heart disease = 5 points No hyperlipidaemia = 2 points

Key: ASTRAL=age, severity of stroke, stroke onset to admission time, range of visual fields, acute glucose, and level of consciousness score; BOAS=Bologna outcome algorithm for stroke; iScore= ischaemic stroke predictive risk score; PLAN= preadmission comorbidity, level of consciousness, age and neurological deficit score; mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; TIA=transient ischaemic attack.

* The Canadian Neurological Scale (CNS) score is a validated stroke scale that predicted functional status measured by the Katz ADL scale at 6 months. The CNS assesses: mentation (level of consciousness, orientation and speech); motor function (power of facial and proximal/distal limb muscles based on a patient's ability to understand and co-operate with the motor examination. The maximum score is 11.5 for normal neurological function (Cote et al. 1989). A CNS score of 1 to 4 equals an NIHSS score of 14 to 22 (severe), a CNS score of 5 to 7 equals an NIHSS score of 9 to 13 (moderate), a CNS score of ≥ 8 equals an NIHSS score of ≤ 8 (mild), and a CNS score of 0 equals an NIHSS score of >22 (Saposnik et al. 2011).

Summary of presentation from Professor Baigent on new analyses and Group discussion at Alteplase EWG meeting in January 2015

Dr Emberson presented the data from this Stroke Thrombolysis Trialists' Collaborative Group (STT) meta-analysis at the Alteplase Expert Working Group (EWG) meeting in November 2014 and further analyses of the individual patient data were requested.

The additional analyses using the STT meta-analysis data were presented by Professor Baigent. The EWG noted that all of the trials for alteplase had limitations, and therefore it was important to assess to what extent each trial might impact on the overall meta-analysis result, and whether they were consistent with one another. With respect to the latter, none of the trials were found to be outliers, all were consistent.

The EWG was informed that it was not possible to conduct a simple meta-analysis to determine the effects of age, treatment delay and baseline stroke severity because there were strong interactions between these three characteristics and that therefore multivariable regression analysis of the data was conducted. The analyses found that younger patients presented later, that older patients had more severe strokes and that less severe strokes were more likely to be randomised later. The EWG heard that there was a significant interaction between time to onset of treatment and odds of a good outcome (mRS 0-1), supporting the "time is brain" hypothesis. The result for interaction between baseline stroke severity and odds of a good outcome (mRS 0-1) was not significant ($p=0.06$, significance pre-specified as $p=0.05$), but as the result was borderline, it warranted further consideration. There was no significant interaction between odds of a good outcome (mRS 0-1) and patient age.

The EWG also noted that there were no statistically significant interactions between age, time to onset of treatment and baseline severity with risk of sICH, or fatal ICH. Although there were similarly no significant interactions for day 90 mortality, subgroup analyses of 0-3 h vs 3-4.5 h vs >4.5 h suggested that there may be a relationship between increasing mortality and time to onset of treatment.

The results of the STT meta-analysis were qualitatively the same, although less robust, when data from the NINDS trials was removed. There was a higher rate of fatal ICH in the IST-3 trial (4%) compared with the meta-analysis overall (3%) but the population enrolled in IST-3 had a higher baseline risk of ICH. The Group was informed that the absolute rate of ICH that was observed in the National Stroke Audit was ~2-3%, i.e. slightly lower than that suggested by the trial data.

7.1. Benefits and risks of alteplase in different patient sub-groups

In this section we examine the benefits and risks of alteplase in different patient sub-groups including key contraindications for which relevant data are available. This includes:

- stroke severity
- time to onset of treatment
- age
- comorbidities including high blood pressure, prior history of stroke and concomitant diabetes, hyperglycaemia/high blood glucose and
- concomitant anticoagulants and antiplatelets.

Contraindications for alteplase have generally been implemented based on the exclusion criteria of the clinical trials of alteplase (apart from IST-3), and therefore good quality RCT data is relatively limited in these subgroups. However a number of relevant analyses have been conducted using data from the VISTA¹ and SITS registries and from other observational studies.

Other populations that are contraindicated specifically for treatment of acute ischaemic stroke and which are not considered are 'symptoms suggestive of subarachnoid haemorrhage, even if CT scan is normal', 'platelet count of below 100,000 /mm³', and 'prior stroke within the last 3 months'. For these groups of patients, the contraindication relates directly to the patient's risk of bleeding and so it is appropriate that these remain as contraindications. Similarly the general contraindications for use of alteplase in MI and PE relate to risk factors for bleeding and are also not discussed.

Usage of alteplase in the UK and EU, both on and off-label has been described in paper 3. It is estimated from the SITS-UK registry that off-label use in UK accounts for ~30% of total use, although much of this use is within the National clinical guidelines for treatment of stroke². SITS-UK data estimates that the majority of off-label use relates to treatment of patients aged over 80 years (~29%). About 2% of off-label use relates to patients treated outside of 4.5 h from the onset of symptoms.

In their response to the question requesting a discussion of benefits and risks in off-label populations, the MAH has mainly focused on the criteria of age and time from onset of symptoms to define 'off-label use'. There is little discussion of other categories of off-label use, or of patients with more than one contraindicated condition

7.1.1. Stroke severity

A multivariate analysis of the SITS-MOST registry results (adjusted for baseline variables) compared registry data of 6483 patients treated with alteplase, with data from 464 patients treated with alteplase within 3 h of stroke onset from pooled RCTs (Wahlgren et al. 2008). Baseline stroke severity and disability before current stroke were the strongest predictors for mortality and functional recovery at 3 months. The adjusted outcomes for the Registry data were almost identical to those from relevant RCTs.

Emberson et al. (2014) reported the effects of treatment delay, age, and stroke severity on the efficacy and safety of intravenous alteplase for ischaemic stroke using a meta-analysis of the individual patient data of 6756 patients from 9 randomised trials: ATLANTIS A and B; ECASS I to III; EPITHET; IST-3; and NINDS A and B. All completed randomised phase 3 trials of alteplase were included but individual patient data were not available for 5 trials involving 270 subjects (Haley et al. 1993; Mori et al. 1992; Wang et al. 2003; Yamaguchi et al. 1993; Hemmen et al. 2010). The baseline patient characteristics are shown in table 2. The primary measure of

¹ VISTA: the Virtual International Stroke Trials Archive; database of data from completed clinical trials (<http://www.vista.gla.ac.uk/>)

² The UK National Clinical Guideline for stroke recommends use in: a) all patients regardless of age or stroke severity where treatment can be started within 3 hours of onset of symptoms, and who have been shown not to have an intracerebral haemorrhage or other contraindications [treatment of patients >80 years or <18 years, those with minor deficit or severe stroke are contraindicated] b) between 3 and 4.5 hours of known symptom onset, patients under 80 years who have been shown not to have an intracerebral haemorrhage or other contraindication and c) patients between 3 and 6 hours of symptom onset to be considered for treatment on an individual basis [treatment with rt-PA is approved up to 4.5 hours following symptom onset]

Table 2: Baseline characteristics of patients in participating trials
(Emberson et al. 2014)

	NINDS A	NINDS B	ECASS I	ECASS II	ATLANTIS A	ATLANTIS B	ECASS III	EPITHET	IST-3	TOTAL
Number randomised	291	333	620	800	142	613	821	101	3035	6756
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)
≤3.0	290 (>99%)	333 (100%)	87 (14%)	158 (20%)	22 (15%)	39 (6%)	--	--	620 (20%)	1549 (23%)
>3.0≤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%)
5-10	78 (27%)	98 (29%)	189 (30%)	339 (42%)	57 (40%)	279 (46%)	389 (47%)	40 (40%)	1064 (35%)	2533 (37%)
11-15	68 (23%)	63 (19%)	183 (30%)	232 (29%)	28 (20%)	128 (21%)	163 (20%)	22 (22%)	601 (20%)	1488 (22%)
16-21	76 (26%)	78 (23%)	146 (24%)	113 (14%)	25 (18%)	106 (17%)	142 (17%)	29 (29%)	618 (20%)	1333 (20%)
≥22	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%)
Aspirin 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)

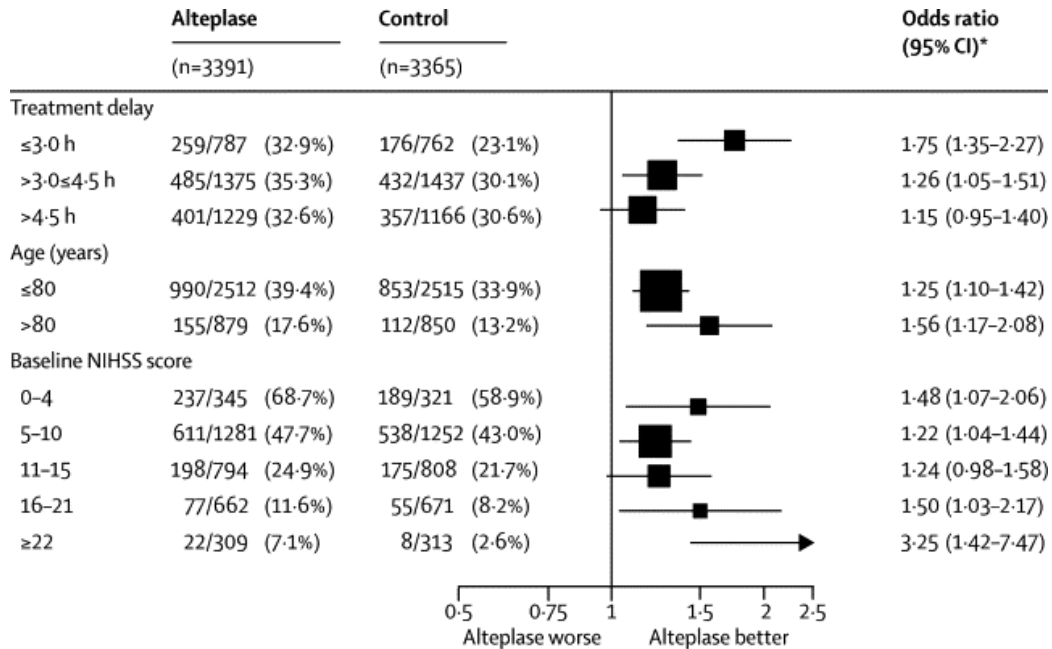
Categorical data presented as n (%), continuous data presented as mean (SD). NINDS=National Institute of Neurological Disorders and Stroke; ECASS=European Cooperative Acute Stroke Study; ATLANTIS=Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; EPITHET=Echoplanar Imaging 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.

treatment efficacy was the proportion of patients with a good stroke outcome defined as a modified Rankin score (mRS) of 0-1 at 3 to 6 months (IST-3 only had a 6 month assessment). The Oxford Handicap Scale score used in IST-3 was converted to the equivalent mRS category. The key secondary outcomes were: fatal ICH within 7 days; any sICH (defined as parenchymal haemorrhage [PH] type 2 within 7 days (Hacke et al. 2008) or 36 h (Wahlgren et al. 2007); and 90-day mortality. The IST-3 definition of ICH was approximated to fit these criteria. The statistical analysis used logistic regression, stratified by trial, to model the common linear dependence of the log odds of a particular outcome on: allocation to alteplase, treatment delay, age and baseline stroke severity NIHSS score (modelled by both linear and quadratic terms), and interactions between allocation to alteplase and each of these other baseline covariates. All estimates of treatment effect compared patients allocated alteplase to those who were not allocated alteplase (ie placebo or open control). All of the statistical analyses and imputation of missing data were pre-specified in a published statistical analysis plan (Stroke Thrombolysis Trialists' Collaborative Group 2013).

Ninety eight percent of 6756 patients (n=6620) had complete baseline data for treatment delay, age and stroke severity. Alteplase significantly increased the odds of a good outcome (defined as mRS 0-1) at 3 to 6 months across the range of NIHSS scores (the lower limit of the 95% CI for the OR for baseline NIHSS scores of 11-15 crosses unity but the point estimate was 1.25) (figure 1). The effect of alteplase was related to treatment delay as baseline stroke severity did not contribute any additional predictive value after controlling for delay. The odds of a good stroke outcome were improved when alteplase was started within 4.5 h of stroke onset. The efficacy of alteplase did not vary with stroke severity within the 4.5 h treatment

window. The proportional increase in the risk of fatal ICH was similar regardless of treatment delay, age or stroke severity but the absolute excess risk attributable to alteplase increased with increasing stroke severity.

Figure 1: Effect of alteplase on good stroke outcome (mRS 0-1), by treatment delay, age and stroke severity (Emberson et al. 2014)



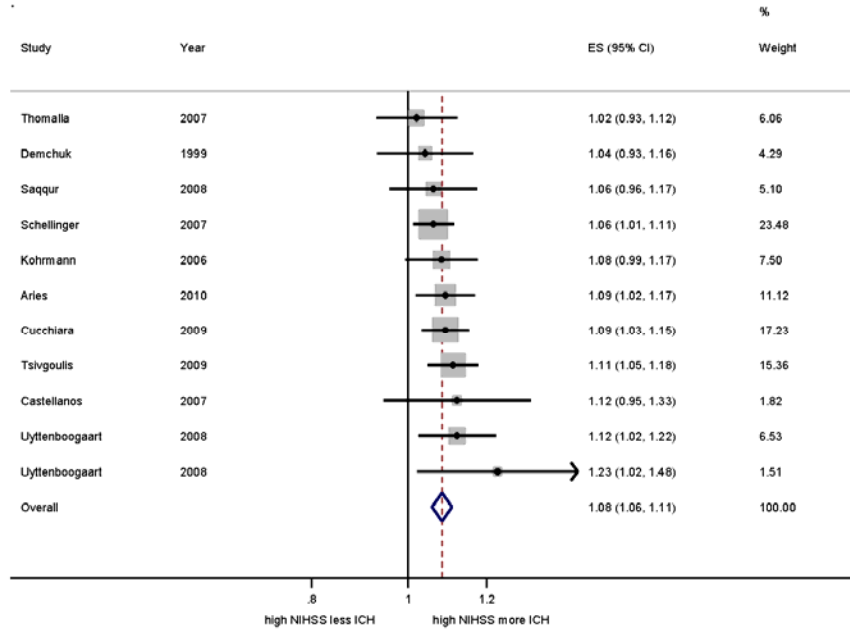
*For each of the 3 baseline characteristics, estimates were derived from a single logistic regression model stratified by trial, which enables separate estimation of the OR for each subgroup after adjustment for the other baseline characteristics (but not for possible interactions)

A subgroup analysis of the NINDS trial showed that the presence of a severe neurological deficit was associated with an increased risk of sICH (17% [11/63] with NIHSS score >20; vs 3% [3/110] with NIHSS score <10; vs 0.6% [2/312] on placebo) (the NINDS t-PA stroke study group 1997). An increased risk of sICH was also associated with increasing NIHSS scores (OR 1.09 per point [95% CI: 1.03-1.15, $p = 0.002$]) in 965 patients receiving alteplase within 3 h of stroke onset (Cucchiara et al. 2009). However, the baseline NIHSS score did not predict the risk of sICH in the ECASS II study (n=409 allocated alteplase, Larrue et al. 2001).

Whiteley et al. (2012) conducted a meta-analysis of 55 studies (11 RCTs and 44 prospective cohort studies; n=65,264) that assessed 43 baseline variables and reported ICH rates after alteplase for ischaemic stroke. ICH was variably defined as 'any visible haemorrhage with any neurological deterioration' in 26 studies; 12 used 'any visible haemorrhage with significant neurological deterioration'; 9 used 'parenchymal haemorrhage with or without neurological deterioration'; and 8 used 'parenchymal haemorrhage with significant neurological deterioration'. All of these definitions were used to characterise clinically important ICH for the meta-analysis. There was also variation in the timing of assessments for each ICH definition. A weighted estimate of the proportions of patients with each definition of ICH was calculated by meta-analysing the inverse variance-weighted proportions from each study. The natural log of the OR and the standard error of the log ratio were also calculated. The summary OR and 95% CIs were estimated using a random-effects meta-analysis which assumed that the true underlying effect size varied between studies. Random-effects meta-regression explored the extent to which study design,

degree of adjustment for confounding factors, and definition of ICH explained between-study heterogeneity for those associations with >10 studies. Eleven studies reported the relationship between changes in the NIHSS score and the risk of ICH:

Figure 2: A meta-analysis of 11 studies of the association between a 1 point increase in the NIHSS score and risk of post-alteplase ICH (Whiteley et al. 2012)



Key: ES=Odds ratio per unit increase in NIHSS score

Higher stroke severity as measured by the NIHSS score was associated with a higher risk of clinically important ICH following alteplase treatment with low heterogeneity when modelled as a continuous variable (OR 1.08 per point increase) or when categorised as a dichotomised or trichotomised variable. The association between baseline stroke severity and the risk of ICH after alteplase appeared modest and the authors concluded that it is unlikely that stroke severity alone is a reliable way to predict the risk of post-thrombolysis ICH on an individual basis.

Mild stroke

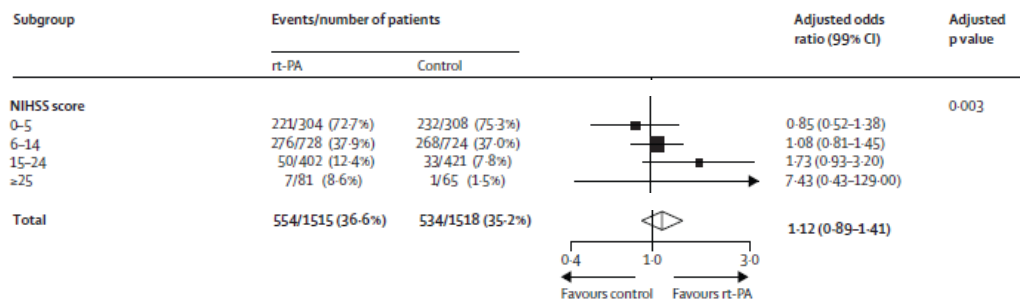
The use of rt-PA in mild stroke is a contraindication in the EU SmPC, stated as “Minor neurological deficit or symptoms rapidly improving before start of infusion”. There is also a related warning in section 4.4 of the SmPC, “In patients with very mild stroke, the risks outweigh the expected benefit (see section 4.3 [contraindications])”. NIHSS score 0-5 is commonly considered to constitute mild stroke (Romano et al, 2015). However, as discussed previously in paper 5, patients experiencing sometimes significant stroke may still have an NIHSS of zero, particularly in the case of infarct occurring in the brainstem or cerebellum.

The contraindication in the SmPC reflects the exclusion criteria of the majority of the main clinical trials (NINDS, ECASS I, II, III, ATLANTIS A and B), and as a result these trials did not include a high proportion of patients with mild stroke at baseline. Table 2 above (Emberson et al. 2014) provides the numbers of patients with different baseline stroke severity according to NIHSS in the different trials, with the mildest category defined as NIHSS 0-4. The IST-3 trial had a less strict exclusion criterion of ‘symptoms considered likely to resolve completely within the next few hours (i.e. a

TIA)', and although the proportion of patients included with NIHSS 0-4 at baseline was quite low (13%), this equated to 400 patients due to the larger size of this trial (and a total of 612 patients with NIHSS 0-5).

The primary outcome results from IST-3 for patients with NIHSS 0-5 at baseline were less favourable for rt-PA than patients with more severe stroke. The primary outcome (OHS 0-2 at 6 months post-stroke) favoured control, although this was not statistically significant:

Figure 3: Primary (dichotomised) outcome in IST-3 (mRS 0-2 at 6 months) according to NIHSS subgroups. OR adjusted for age and time (The IST-3 collaborative group 2012).



The results for the secondary ordinal analysis in IST-3 (Lindley et al. 2015) for NIHSS 0-5, were however numerically in favour of rt-PA treatment, albeit not statistically significant (adj OR 1.14 [95% CI: 0.79-1.65]). The risk of death within 7 days was increased in the rt-PA group compared with the controls for NIHSS 0-5 (adj OR 2.38 [95%CI: 0.40-14.24]), and the OR favoured control for all NIHSS groups, however was significant only for NIHSS 16-24. The wide confidence intervals for the result in mild stroke reflects the small number of deaths (n=7 in the rt-PA group vs n=3 in the control group). For sICH in the mild stroke subgroup, there were no events in the control arm, and 9 (3%) in the rt-PA group.

Overall, the IST-3 results do not appear to support the use of rt-PA in patients with mild stroke. However, as the IST-3 trial enrolled patients according to the uncertainty principle, it is likely that the trial population were higher risk than patients treated routinely in the clinic (see paper 6).

In contrast the meta-analysis by Emberson et al (2014), which includes the IST-3 data, found a favourable result for the primary outcome mRS 0-1 in rt-PA treated patients with baseline NIHSS 0-4 compared with controls (OR 1.48 [95%CI: 1.07-2.06]), see figure 1. As discussed above, rt-PA effect was related to treatment delay, as baseline stroke severity did not contribute additional predictive value after controlling for delay and as such rt-PA efficacy was not found to vary with stroke severity. Similarly the risk of fatal ICH varied little with stroke severity, although the absolute risk increased with increasing severity.

A large observational study on rt-PA treatment of mild acute ischaemic stroke was recently published by Romano et al. (2015). This was a retrospective analysis of the Get With the Guidelines-Stroke registry which included patients with NIHSS ≤5 treated with rt-PA within 4.5 h of stroke onset between 2010 and 2012. A total of 33,995 patients were treated with rt-PA within 4.5 h during this time period, of which 7621 had a baseline NIHSS ≤5, and 5910 had a complete data and were included in the analysis. The outcomes considered were sICH (defined as brain haemorrhage confirmed by CT within 36 h of i.v. rt-PA and physician's notes indicating clinical

deterioration due to the haemorrhage), life-threatening or serious systemic haemorrhage, other serious complications/undetermined complications, in-hospital mortality, discharge to home, independent ambulation at discharge and length of stay.

Of the 5910 patients included, 79% were treated between 0-3 h, and 21% were treated between 3-4.5 h. Patients treated within 3 h were found to be older, more likely to be men, non-Hispanic white, have atrial fibrillation, dyslipidemia, to be taking prophylactic medications e.g. anticoagulants, antihypertensives, and more likely to arrive by ambulance. The NIHSS score was similar in patients treated within 3 h and between 3-4.5 h. The outcomes for the two treatment windows are also shown:

Table 3: Outcomes and treatment complications by treatment window (Romano et al. 2015)

Outcome	Total Population (n = 5910)	%		Univariate P Value
		Treatment Window		
		0-3 h (n = 4643)	3-4.5 h (n = 1267)	
Death	1.3	1.3	1.3	.79
Discharge home	70.6	70.3	71.6	.39
Independent ambulation ^a	69.7	69.6	70.2	.72
LOS				
Median (IQR), d	3 (2-5)	3 (2-5)	4 (2-5)	.37
≥3 d	73.0	73.1	72.6	.70
Symptomatic ICH	1.8	2.0	1.4	.20
Life-threatening or serious systemic hemorrhage	0.2	0.2	0.1	.27
Other serious complications	1.8	1.8	1.8	.10
Complications of undetermined cause	2.4	2.1	3.3	.01

IQR=interquartile range; LOS=length of stay; ^aRestricted to those with documented ability to ambulate independently at baseline (n=4221)

The rates of outcomes and treatment complications were mainly found to be similar between the group of patients treated within 3 h and those treated between 3-4.5 h. The average rate of sICH for patients with NIHSS ≤5 was 1.8%, and 1.3% for death. The risk of sICH was found to increase with age, (OR 1.35 [95% CI: 1.12-1.63] for each 10 years of age). Longer-term (3 month) outcomes such as mRS were not measured.

This study did not include a non-thrombolysed comparator group, because the authors considered that it would not be possible to sufficiently adjust for selection bias. Therefore it is not possible to comment from these data on the efficacy of rt-PA in patients with mild stroke. However, the rate of sICH was found to be relatively low and lower than the overall absolute rates reported by the Emberson et al (2014) meta-analysis for patients with any NIHSS at baseline (type 2 parenchymal haemorrhage within 7 days occurred in 6.8% of rt-PA patients and SITS-MOST defined type 2 parenchymal haemorrhage within 36h occurred in 3.7%). The rate of death was also found to be low (1.3%), which compared with an overall rate of 8.3% for mortality within the first 7 days (any NIHSS at baseline) in the Emberson et al. (2014) meta-analysis.

A number of other observational studies have considered thrombolysis in mild stroke patients, however these have involved small numbers of patients. Urra et al. (2013) found an improved shift in the mRS at 3 months (OR 2.66 [95% CI: 1.49-4.74]), in a

small series of 203 patients (119 treated with rt-PA, 84 not treated). Hassan et al. (2010) compared outcomes in 27 patients with NIHSS ≤ 6 treated with rt-PA with 24 historical controls and found an improved mRS at discharge in the rt-PA treated group, with no significant difference in risk of ICH. Huisa et al. (2012) compared 59 patients treated with rt-PA with 74 untreated patients with NIHSS ≤ 5 . At 90 days, a smaller proportion of the rt-PA patients had an outcome of mRS 0-1 compared with the untreated patients, however the difference was not significant (OR 0.93 [95% CI: 0.39-2.2]). Greisenegger et al (2014) conducted a matched analysis using the Austrian Stroke Unit registry. A total of 445 matched pairs of rt-PA treated and untreated patients with NIHSS ≤ 5 were compared. In 41% of pairs, the rt-PA treated case had a better functional outcome at 3 months than the untreated case, in 29% the untreated case had a better outcome and in 30% of cases the mRS outcome was the same. This corresponded to a shift towards better outcome in rt-PA treated patients (OR 1.49 [95% CI: 1.17-1.89]).

Comments on the data

The available data in patients with mild stroke (NIHSS ≤ 5) is limited, with most of the randomised clinical trials excluding these patients. The IST-3 trial enrolled some patients with NIHSS ≤ 5 however (n=612). The subgroup results for these patients were non-significant, with an unfavourable trend for rt-PA treatment in the primary outcome (mRS 0-2 at 6 months) and a favourable trend in the secondary ordinal analysis. However, the subgroups in the IST-3 trial were underpowered. The meta-analysis by Emberson et al. (2014) which included the IST-3 data as well as data from patients in the other main clinical trials found a positive result for mRS 0-1 in patients with baseline NIHSS ≤ 4 . The meta-analysis found that rt-PA efficacy did not vary according to stroke severity, and the risk of sICH attributable to rt-PA was unchanged by stroke severity (although the absolute risk of sICH increased with increasing stroke severity).

The recently published, large observational study by Romano et al. (2015) provided reassurance from a relatively large cohort of patients with NIHSS ≤ 5 that outcomes were similar in patients treated < 3 h and in those treated between 3-4.5 h. The study did not include a comparator untreated group and therefore cannot provide any information on efficacy of rt-PA compared with no treatment in this group, however the absolute rates of death and sICH were relatively low. Other observational studies have found mixed results, though the size of the patient groups in these studies was small. The analysis of 445 matched pairs by Greisenegger et al. was one of the larger of these small studies and found a positive result for rt-PA treatment.

A limitation of these analyses that should be considered is the use of NIHSS ≤ 5 to define mild stroke – because as stated previously this may not necessarily be the case.

The meta-analysis by Emberson et al. provides the most comprehensive summary of available randomised controlled data in this subgroup of patients and suggests that the efficacy of rt-PA is unaffected by stroke severity and that rt-PA treatment in mild stroke has a positive effect. The rates of serious outcomes such as sICH and death were found to be low in the study by Romano et al. however non-treated patients were not included in this analysis.

Whilst the balance of benefits and risks of rt-PA treatment in patients with mild stroke (as defined by NIHSS) appears to be positive at a population level, the balance for individual patients is less clear. This is due to the higher likelihood of a positive outcome in this group of patients, regardless of whether treatment with rt-PA is given, which alters the perception of acceptable risk in a population, and the fact that risk of sICH or fatal ICH associated with rt-PA persists in patients with mild stroke. Therefore whilst overall in this sub-population, rt-PA may result in better outcomes

than in untreated patients, individuals themselves may be less willing to accept any risk. The level of risk deemed acceptable by patients with mild stroke is therefore likely to differ markedly on an individual basis.

Ongoing randomised controlled clinical studies such as PRISMS (Potential for rtPA to Improve Stroke with Mild Symptoms study) and TEMPO-2 (TNK-tPA evaluation for minor ischemic stroke with proven occlusion) a study of tenecteplase in patients with NIHSS ≤ 5 , may provide important new information in this subgroup of patients.

MAH's response

The MAH has provided summaries for a selection of articles and concluded that the *severity of stroke at baseline is not associated with an unknown risk and the use of Actilyse. The evaluation of the publications related to severity of stroke does not show any new findings with respect to an unknown risk or harm.*

Summaries of the following references were provided by the MAH: Berger et al. 2001; Wardlaw et al. 2003; Sylaja et al. 2006; Bluhmki et al. 2009; Alonso de Lecinana et al. 2012; Matute et al. 2012; Seet et al. 2012; Chen et al. 2013; Kunisawa et al. 2013; Sledzinska-Dzwigal et al. 2013; Sobolewski et al. 2013; Jang et al. 2014.

Concluding comments:

The MAH has concluded that the severity of stroke is associated with a known risk of developing ICH and no new risks related to stroke severity have been identified.

Overall, the available evidence shows that baseline stroke severity, as measured using the NIHSS score, is an independent predictor of symptomatic and fatal ICH following alteplase treatment given within the 4.5 h window. The effectiveness of alteplase within the 4.5 h window does not vary according to stroke severity although there is little data concerning patients with NIHSS scores >22 .

Implications for the marketing authorisation

Severe stroke

The SmPC (Section 4.3) lists “*severe stroke as assessed clinically (e.g. NIHSS >25) and/or by appropriate imaging techniques*” as an additional contraindication for use of alteplase in acute ischaemic stroke.

In addition Section 4.4 of the SmPC warns that “*In stroke patients the likelihood of good outcomes decreases with increasing age, **increasing stroke severity** and increased levels of blood glucose on admission while the likelihood of severe disability and death or relevant intracranial bleedings increases, independently from treatment. Patients over 80, patients with severe stroke (as assessed clinically and/or by appropriate imaging techniques) and patients with blood glucose levels <50 mg/dl (<2.8 mM) or >400 mg/dl (>22.2 mM) at baseline should not be treated with Actilyse.*”

The recommendations in the SmPC remain appropriate for severe stroke on the basis of the current evidence.

Mild stroke

There is currently no evidence to suggest that the balance of benefits and risks of rt-PA treatment in patients with mild stroke is negative; however, because of the nature

of mild stroke each case would need be considered on an individual basis. At present, the SmPC contraindication (“Minor neurological deficit or symptoms rapidly improving before start of infusion”) and warning are considered to be appropriate. It is noted that this contraindication would not rule out treatment with rt-PA in patients with more severe stroke symptoms who have a low NIHSS.

7.1.2. Time to treatment

This topic was considered in *Paper 4: Benefits and risks from new study data* which is summarised here:

A meta-analysis of individual patient level clinical trial data (Emberson et al. 2014)

The aims and outcome measures have already been described for this meta-analysis which assessed the extent to which treatment delay modifies the effect of alteplase on stroke outcomes.

Multivariate logistic regression, stratified by trial, was used to model to log odds of each outcome adjusting for allocation to alteplase, treatment delay, age, baseline stroke severity (NIHSS), plus interaction terms of each with allocation to alteplase.

In summary, 2110 (31%) of 6756 patients experienced a good outcome with alteplase significantly increasing the odds of a good outcome (mRS ≤ 1) at 3-6 months ($p = 0.016$ for trend of increasing proportional benefit with earlier treatment) with a significant benefit of alteplase within 3 h of stroke (adj OR 1.75 [95% CI: 1.35-2.27]) and within 3-4.5 h (adj OR 1.26 [95% CI: 1.05-1.51]). When this analysis was further stratified by age (≤ 80 years vs > 80 years) a significant benefit for treatment with alteplase 3-4.5 h after onset was seen only in patients ≤ 80 years (adj OR: 1.26 [95% CI: 1.04-1.54]) and not in those aged > 80 years (adj OR: 1.36 [95% CI: 0.87-2.14]) although fewer patients aged > 80 years were randomised within the trials and there was no evidence of a difference during which alteplase could be effectively given across the two age groups ($p = 0.08$). Further there was no evidence that stroke severity modified the effect of alteplase ($p = 0.06$).

The risk of sICH was increased with treatment compared with controls, both at 36 h post-stroke (SITS-MOST criteria: adj OR 6.67 [95% CI: 4.11-10.84]) and at 7 days (adj OR 5.55 [95% CI: 4.01-7.70]). The risk of fatal ICH within 7 days was also significantly raised (adj OR 7.14 [95% CI: 3.98-12.8]). Overall mortality within 90 days was numerically increased but not statistically significantly greater in the alteplase group compared with controls (adj OR 1.11 [95% CI: 0.99-1.25]). The relative increase in fatal ICH from alteplase was similar irrespective of treatment delay, age, or stroke severity, but the absolute excess risk attributable to alteplase was bigger among patients who had more severe strokes. There was no excess in other early causes of death and no significant effect on later causes of death.

Additional observational data from SITS-ISTR (Ahmed et al. 2013)

SITS-ISTR was a prospective multi-national registry study for patients given alteplase following stroke. The most recent publication of data from this registry is from Ahmed et al. 2013. This updated analysis presented comparative analysis of benefits and risks in patients treated < 3 h following stroke onset and in 3-4.5 h following onset. It additionally examined off-label use in patients treated 4.5-6 h following stroke. It was based on data from SITS-ISTR during the period 2002-2011. Safety endpoints were sICH within 24 h and mortality at day 90. Multivariate analyses were adjusted for age, sex, pre-stroke mRS score, atrial fibrillation, history of hyperlipidaemia, previous

stroke earlier than 3 months, antihypertensive therapy, signs of a recent infarction at baseline imaging, and baseline stroke severity measured by NIHSS score because these were statistically significant in univariate analyses at the 10% level.

Patients treated 3-4.5 h after onset had a stroke severity 3 points lower on the NIHSS compared to patients treated within 3 h.

For the 3-4.5 h cohort compared with the 3 h cohort:

Outcome	Patients treated within 3 h (n=25,279)	Patients treated within 3-4.5 h (n=4056)	Crude odds ratio (3-4.5h/ <3 h)	95% CI (p-value)	Adjusted OR	Adjusted 95% CI: (p value)
Rate of sICH (SITS-MOST definition)	1.5%	1.8%	1.16	0.89-1.49 (0.27)	1.22	0.92-1.61 (0.16)
Rate of sICH (ECASS II definition)	4.6%	4.5%	0.98	0.84-1.16 (0.85)	1.11	0.93-1.32 (0.26)
Rate of sICH (NINDS definition)	7.0%	6.5%	0.92	0.81-1.06 (0.24)	1.05	0.90-1.22 (0.54)
Mortality rate at 3 months	11.8%	11.1%	0.93	0.82-1.05 (0.21)	1.07	0.93-1.23 (0.31)
No or minimal disability (mRS ≤1 at 3 months)	42.1%	46.0%	1.17	1.08-1.26 (<0.01)	0.90	0.82-0.98 (0.02)
Independence (mRS ≤2 at 3 months)	58.4%	62.7%	1.19	1.10-1.29 (<0.01)	0.92	0.83-1.01 (0.09)

Since the data from the SITS-ISTR registry were presented in 2008 minor changes have been seen. The study still suggests that the rate of sICH is comparable in patients treated 3-4.5 h after treatment compared to those treated within 3 h. However, the 3 month outcomes of no or minimal disability and independence were less favourable for those treated within 3-4.5 h compared to those treated within 3 h in the adjusted analyses. This trend had been seen in earlier analyses of this cohort but for the outcome of no or minimal disability statistical significance is now reached.

Analyses looking at these outcomes in patients treated 4.5-6 h following onset compared to those treated within 3 h were also conducted. No significant differences were found here although only 283 patients were treated 4.5-6 h following onset so the power is greatly reduced. Further, this group is likely to be a highly selective subset of presenting patients so this does not provide robust evidence of safety and effectiveness in this group.

Given the observational nature of this study the results are much more vulnerable to confounding and other biases than RCTs. However, it is important to see how the benefits and risks of a product manifest when used in routine clinical practice. As this study is non-interventional the reasons for why a patient is treated or not treated with alteplase can confound the outcomes seen. Therefore, the analyses that try to adjust for this confounding should be considered stronger than the crude analyses. In some cases, adjusting for confounding has had a considerable impact on the estimated odds ratios. In particular, the crude analysis looking at “No or minimal disability (mRS ≤1) at 3 months” is significantly in favour of later treatment (3-4.5 h after symptom onset) while the adjusted analysis is significant in the opposite direction, with the better outcome now being seen in those treated within 3 h. This is unsurprising given the trends already seen in trials whereby those presenting earlier are typically older

with more severe neurological deficits. However, it is not clear if there is still any residual confounding and in turn, what impact that could be having on the results. Given how large the change in interpretation between the crude analysis and the adjusted analysis is, it seems likely that there is further confounding and the results should be interpreted with caution.

Update from SITS-UTMOST Registry

The Upper Time window Monitoring Registry (SITS-UTMOST) is a prospective post-approval registry of intravenous alteplase (0.9mg/kg) up to 4.5 h post symptom onset in acute ischaemic stroke patients which is being conducted as part of the SITS-ISTR registry. The study is a regulatory requirement following the approval of the extended time window for treatment and the study started in May 2012.

The latest report on SITS-UTMOST was submitted to regulators in February 2014 with data to November 2013 and is summarised here. The final report has now been received and the updated results are described in paper 4 addendum 1A. The final prospective cohorts included a total of 1118 patients treated between 3-4.5 h following stroke onset, 3039 treated within 3 h and 3454 patients in the retrospective cohort treated within 3 h. Multivariate analysis of the prospective cohorts showed a statistically significant lower adjusted odds ratio for functional independence (mRS 0-2) at 3 months in the 3-4.5 h cohort compared with the <3 h cohort (OR 0.81 [95% CI: 0.67-0.99, $p=0.044$]). The difference for mRS 0-1 was not significant however (OR 0.87 [95%CI: 0.72-1.05, $p=0.159$]). There was no statistical difference in rate of sICH (SITS-MOST, ECASS II or NINDS definition) or in mortality at 3 month between the prospective cohorts treated 3-4.5 h following stroke onset and within 3 h.

Get With The Guidelines-Stroke (Saver et al. 2013)

Using data from the US national Registry, GWTG-Stroke, Saver et al. (2013) examined the relationship between onset to treatment time and in-hospital mortality, sICH within 36 h, ambulatory status at discharge, and discharge destination. They analysed data from 58,353 patients treated with alteplase within 4.5 h of onset, April 2003-March 2012. Note, that there was no restriction on the age or baseline NIHSS score of patients included. In summary, the relationship between time to treatment and the different outcomes of interest was examined using multivariate logistic regression, using generalised estimating equations to account for within hospital clustering. Models were adjusted for a range of patient-level (age, ethnicity, sex, medical history, stroke severity, hospital arrival time and transport method, and exposure to vascular risk prevention medications) and hospital-level (hospital size, region, teaching status, rural location, stroke specialism, number of alteplase treated patients, and number of stroke discharges) factors.

The median age of the included cohort was 72 years, 50.3% were women, median onset to treatment time was 144 minutes (interquartile range, 115-170), 9.3% (5404) had onset to treatment time of 0 to 90 minutes, 77.2% (45,029) had onset to treatment times of 91 to 180 minutes, and 13.6% (7920) had onset to treatment times of 181 to 270 minutes. Median pre-treatment NIHSS score, documented in 87.7% of patients, was 11 (interquartile range, 6-17). Patient factors most strongly associated with shorter onset to treatment included greater stroke severity (OR 2.8 [95% CI: 2.5-3.1 per 5-point increase]).

Overall, there were 5142 (8.8%) in-hospital deaths, 2873 (4.9%) patients had sICH, 19,491 (33.4%) patients achieved independent ambulation at hospital discharge, and 22,541 (38.6%) patients were discharged to home. In adjusted analyses, faster onset to treatment time, in 15 minute increments, was associated with reduced in-hospital mortality (OR, 0.96 [95% CI: 0.95-0.98; $p<0.001$]), reduced sICH (OR 0.96 [95% CI: 0.95-0.98; $p<0.001$]), increased achievement of independent ambulation at discharge

(OR 1.04 [95% CI: 1.03-1.05; $p < 0.001$]), and increased discharge to home (OR 1.03 [95% CI: 1.02-1.04; $p < 0.001$]).

Focusing on the risk of sICH a significantly decreased risk was seen in adjusted analyses comparing the risk with treatment 3-4.5 h after symptom onset to treatment to treatment within 1.5 h (adj OR 0.72 [95% CI: 0.60-0.87]) and treatment within 1.5-3 h (adj OR 0.87 [95% CI: 0.76-0.99]).

This equally large cohort is slightly older than that seen in the SITS-ISTR registry and a higher proportion are female.

This study suggests a significantly reduced sICH rate with earlier treatment. It should be noted that this risk has also been suggested in a further analysis of the SITS-ISTR data which found that onset to treatment > 3 h was an independent risk factor associated with an increased risk of sICH (adj OR 1.5 [95% CI: 1.2-2.0]) although this study was primarily designed to devise a risk score for sICH (Mazya et al. 2012). However, an increasing risk of large parenchymal haemorrhage with an increase in time to treatment was not seen in the pooled clinical trial analysis (Lees et al. 2010). Therefore, the risk observed here could be the result of residual confounding. Even if true, it is not clear how clinically meaningful this level of increase in risk is.

Mortality is also reduced with a short time to treatment although it should be noted that in this study only data on in-hospital mortality is available meaning that deaths that occur later after treatment are not included. A trend towards increased 90 day mortality with a longer time to treatment was also seen in an earlier pooled analysis of clinical trials data (Lees et al. 2010) although this was no longer statistically significant after the inclusion of IST-3 (Emberson et al. 2014). Again, residual confounding may be present in this observational study.

The significant increased achievement of a mRS ≤ 1 and/or a mRS ≤ 2 with earlier treatment is again seen here. Again only in-hospital data is available in this study.

The Baden-Wuerttemberg Stroke Registry (Gumbinger et al. 2014)

Gumbinger et al. (2014) presented data from 84,439 patients treated for ischaemic stroke in 148 hospitals in Baden-Wuerttemberg, Germany from January 2008 to December 2012. The primary analysis compared the odds of a mRS ≤ 1 at discharge from hospital following treatment with alteplase compared to the odds without treatment with alteplase using multivariate logistic regression adjusted for age, sex, premorbid mRS, NIHSS, diabetes, previous stroke, atrial fibrillation, ventilation, pneumonia, thrombosis or pulmonary embolism, level of stroke care and length of hospital stay. This study was not primarily designed for scientific research; therefore no follow up data after discharge was collected.

10,263 (12.2%) of patients were treated with alteplase, with a considerably higher proportion of these admitted within 3 h of onset compared to those not treated (88.5% vs 24.5%). 377 (3.7%) of those treated were admitted to hospital at least 6 h following stroke onset, 2365 (23.0%) had diabetes, 1727 (16.8%) had a prior stroke, and 3430 (33.4%) had atrial fibrillation. Those treated with alteplase also had lower premorbid mRSs with 8565 (83.5%) having a mRS ≤ 1 compared to 55,725 (67.0%) of those not treated.

Treatment with alteplase was associated with an increased chance of a mRS ≤ 1 at discharge (overall adj OR 1.70 [95% CI: 1.59-1.81, $p < 0.0001$]). This benefit was greatest in the group treated within 90 mins of stroke onset (adj OR 2.49 [95% CI: 2.12-2.92]) although a significant association was seen for treatment 91-180 mins following onset (adj OR 1.86 [95% CI: 1.71-2.02]) and for treatment 181-270 mins following onset (adj OR 1.26 [95% CI: 1.08-1.46]).

The data from this cohort is interesting to note as, unlike the other observational studies presented here, it includes patients not treated with alteplase. It was also a mandatory registry meaning that it has very high population coverage and is not restricted to specialist stroke centres. This cohort was again older than the SITS-ISTR cohort (median age 74 years compared to ~68 years). There is potential for some crossover with the SITS-ISTR study which currently has 5378 patients recruited from Germany.

The lack of follow up in this study is however a limitation. This is due to the fact that the registry is not designed primarily for scientific research purposes.

The authors present a comparison of their data to the pooled clinical trial analysis of Lees et al. (2010) and Emberson et al. (2014, unpublished at time of this study). The adjusted ORs they see are reasonably comparable to those seen in the meta-analyses with an association between earlier treatment and improved outcome (mRS ≤ 1). However, the same issues around confounding, as discussed for SITS-ISTR and the other studies, are still relevant here and are likely to impact on the results.

The Canadian Alteplase for Stroke Effectiveness Study (CASES) (Shobha et al. 2011).

The Canadian Alteplase for Stroke Effectiveness Study (CASES) was a prospective multicentre cohort study of stroke patients treated with alteplase. At the time of the study, the Canadian licenced indication was only for treatment within 3 h of onset. Shobha et al. (2011) presented analyses comparing the mRS at 90 days, mortality, and sICH in patients treated with alteplase within 3 h of symptom onset and those treated within 3-4.5 h. Multivariate regression models, adjusting for age, sex, baseline NIHSS, baseline serum glucose and baseline ASPECTS (Alberta Stroke Registry Early CT Score), were used to compare outcomes in the two groups.

A total of 1112 patients with complete data were included, 129 (11.6%) received alteplase between 3 and 4.5 h of onset while the rest received it within 3 h. Those in the 3-4.5 h treatment group had more favourable baseline CT scans (median ASPECTS 9 vs 8, $p = 0.02$).

Of note, 36% of patients treated in the 3-4.5 h window were treated off-label according to the current indication, primarily as they were >80 years old or had baseline NIHSS score >25 .

At 90 days, 50/127 (39.4%) of patients in the 3-4.5 h treatment group and 352/965 (36.5%) in the under 3 h group attained a mRS ≤ 1 (adj RR 0.98 [95% CI: 0.8-1.2]). After adjustment there was a significant increase in the risk of both mortality (adj RR 1.53 [95% CI: 1.15-2.0]) and sICH (adj RR 2.14 [95% CI: 1.09-4.2]) in those treated within 3-4.5 h compared to those treated within 3 h although this was not seen in unadjusted comparisons.

The authors state that their results are concordant with those seen in ECASS III and the SITS-ISTR registry. However, there is a trend towards higher mortality and greater sICH rates in this cohort. They suggest this is because their cohort is highly selected and, even though the median time for treatment in the 3-4.5 h group was 3 h 10 minutes, patients were older and sicker than those included in other studies and this may explain poorer outcomes. This leads to the question of how representative this study is of the general alteplase treated population. This study is also considerably smaller than other observational studies limiting its value.

The observational data presented here suggest a benefit of alteplase in achieving a mRS ≤ 1 , with the greatest benefit seen with earlier treatment. The risk of sICH seen in patients treated with alteplase has not been compared to the risk in untreated patients in the additional observational studies and data is mixed on if there is any time-dependent risk.

It is important to see how a product performs once used in routine clinical practice, away from the tighter clinical trial setting.

However, these observational studies are likely to be subject to confounding and selection biases and so the results should be treated with caution and considered in light of the clinical trial data.

It should be noted that the observational studies presented here include patients treated off-label although they were not the main focus. This should also be taken into consideration when discussing the relevance of these studies to examining the benefits and risks of alteplase within the current licenced indication.

In addition, the latest Cochrane review reported that the risk of sICH was similar for the 0-3 h (OR 4.55 [95% CI: 2.92-7.09]; 6 trials, n=1779) and 3-6 h (OR 3.73 [95% CI: 2.86-4.86]; 7 trials, n=4935) time windows (Wardlaw et al. 2014). The risks of death or dependency at the end of follow-up were also similar when analysed according to time to randomisation: <3 h (OR 0.65 [95% CI: 0.54-0.80; 6 trials, n=1779]; 3-6 h (OR 0.93 [95% CI: 0.83-1.04; 7 trials, n=4950]). These findings were supported by the meta-analysis of individual patient data from randomised trials (Emberson et al. 2014). The Cochrane review (2014) concludes:

“there was no clear increase in hazard (ICH or death) with increasing time up to six hours after stroke, although there was some evidence of decreasing benefit (reduction in death and dependency). Therefore, increasing time to treatment may reduce benefit more than it increases the hazard of thrombolysis.”

Guidance

The National stroke guidelines recommend:

- *any patient, regardless of age or stroke severity, where treatment can be started within 3 hours of known symptom onset and who has been shown not to have an intracerebral haemorrhage or other contraindications should be considered for treatment using alteplase.*
- *between 3 and 4.5 hours of known stroke symptom onset, patients under 80 years who have been shown not to have an intracerebral haemorrhage or other contraindication, should be considered for treatment with alteplase*
- *between 3 and 6 hours of known stroke symptom onset, patients should be considered for treatment with alteplase on an individual basis, recognising that the benefits of treatment are likely to be smaller than those treated earlier, but that the risks of a worse outcome, including death, will on average not be increased.*

The American Heart Association stroke guidelines advise that the eligibility criteria for the 3-4.5 h period are similar to those for patients treated within 3 h but that patients with 1 or more of the following factors that increase the risks of thrombolysis should be excluded: patients aged >80 years; oral anticoagulant therapy (regardless of INR); severe stroke (NIHSS score >25); those with imaging evidence of ischaemic injury involving more than a third of the MCA territory; or those with a history of both stroke and diabetes mellitus (Jauch et al. 2013). This recommendation is supported by the available evidence.

MAH's response

The MAH has provided summaries for a selection of articles that address the benefits and harms of alteplase according to the time to treatment (Clark et al. 2000; Marler et al. 2000; Brown et al. 2004; Saposnik et al. 2004; Mateen et al. 2009; Wardlaw et al. 2009; Lees et al. 2010; Muchumpurath et al. 2011; Karlinski et al. 2012; Mazighi et al. 2012; Cronin et al. 2013; Cronin et al. 2014; Ebinger et al. 2014; Frank et al. 2014; Muchada et al. 2014).

The MAH concludes *the identified published literature did not reveal any new risks associated with time to treatment and reflects the current recommendations given by the approved time to treatment interval.*

Concluding comments:

The benefit-risk balance of alteplase changes with increasing time-to-treatment from onset. There is robust evidence that treatment within the 0-3 h window is effective with an acceptable risk of ICH and mortality. The benefits of alteplase therapy appear to reduce with time up to 4.5 h after onset with similar risks. The benefit-risk balance of alteplase beyond 4.5 h appears to be negative on the basis of available evidence.

Implications for the marketing authorisation

The MAH has failed to mention that a number of recent publications have provided essential information on this topic that supports the licensed onset to treatment time of up to 4.5 h. Nevertheless, the conclusion provided by the MAH. is still valid; we have not identified any new risks associated with time to treatment. The SmPC includes the following relevant information:

Section 4.1 Therapeutic indication states:

Treatment must be started as early as possible within 4.5 h after onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques (e.g. cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage). The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.

Section 4.2 Posology and method of administration states:

Acute ischaemic stroke

Treatment with Actilyse must be started as early as possible within 4.5 h of the onset of symptoms. Beyond 4.5 h after onset of stroke symptoms there is a negative benefit risk ratio associated with actilyse administration and so it should not be administered

Section 4.3 Contraindications states:

Additional contra-indications in acute ischaemic stroke:

- *symptoms of ischaemic attack beginning more than 4.5 h prior to infusion start or symptoms for which the onset time is unknown and could potentially be more than 4.5 h ago*

Section 4.4 Special warnings and precautions for use states:

Special warnings / conditions with a decreased benefit/risk ratio:

Compared to other indications patients with acute ischaemic stroke treated with Actilyse have a markedly increased risk of intracranial haemorrhage as the bleeding occurs predominantly into the infarcted area. This applies in particular in the following cases:

- with later time-to-treatment from onset of stroke symptoms the net clinical benefit is reduced and may be associated with a higher risk of ICH and death compared to patients treated earlier. Therefore, the administration of Actilyse should not be delayed.*

Section 5.2 Pharmacodynamic properties states:

The safety and efficacy of ACTILYSE for acute ischaemic stroke treatment up to 4.5 h time stroke onset time to start of treatment (OTT) has been assessed by an ongoing registry (SITS-ISTR: The Safe Implementation of Thrombolysis in Stroke registry). In this observational study safety outcome data of 21,566 treated patients in the 0 to 3 h time window were compared with data from 2,376 patients treated between 3 to 4.5 h after onset of AIS.

The incidence of symptomatic intracranial haemorrhage (according to the SITS-MOST definition) was found to be higher in the 3 to 4.5 h time window (2.2%) as compared with the up to 3 h time window (1.7%). Mortality rates at 3 months were similar comparing the 3 to 4.5 h time window (12.0%) with the 0 to 3.0 h time window (12.3%) with an unadjusted OR 0.97 (95% CI: 0.84-1.13, p =0.70) and an adjusted OR 1.26 (95% CI: 1.07-1.49, p =0.005. The SITS observational data support clinical trial evidence of stroke onset time to start of treatment (OTT) as an important predictor of outcome following acute stroke treatment with alteplase.

The information and recommendations provided in the SmPC remain appropriate on the basis of the current evidence.

7.1.3. Age

Most of the clinical trials of alteplase for acute ischaemic stroke included patients in the licensed age range for Actilyse (18 to 80 years). However, the benefit-risk profile of alteplase in those outside the approved age range is not as well characterised so will be discussed here.

Children

Childhood acute ischaemic stroke is rare making large clinical trials impractical although there have been numerous case reports describing successful intravenous thrombolysis in young patients (Amlie-Lefond et al. 2009). Nevertheless, the underlying causes of stroke, haemostatic mechanisms and suitable doses of alteplase may be different in children (Balami et al. 2013).

One multicentre observational cohort study of 687 children with acute ischaemic stroke enrolled in the International Pediatric Stroke Study reported that only 15 (2%) children received alteplase (9 intravenous; 6 intra-arterial) (Amlie-Lefond et al. 2009). A single child had a basilar artery thrombosis and the others had anterior circulation infarcts. The median time to treatment for intravenous alteplase was 3.3 h (mean 10.5 h; range 2 to 52 h). After intravenous alteplase: 2 children had asymptomatic ICH, 1 child died of brain herniation; and 8 had residual neurological deficits. This study did not use any validated measures for the reported clinical outcomes. The authors concluded that children with ischaemic stroke are thrombolysed infrequently and often at later times than are specified in stroke guidelines for adult patients. Poor

neurological outcome was common but no alteplase-related deaths or sICH were observed.

Another study examined in-patient data relating to paediatric ischaemic stroke and outcomes following alteplase use from 2001 to 2010 (Nasr et al. 2014). Alteplase was given to 99 patients (1.4% of 7044 included) with 4.9% of those thrombolysed developing ICH vs 1.6% not thrombolysed ($p = 0.01$) but no in-patient deaths occurred in those thrombolysed (vs 4.5% not thrombolysed). Again clinical outcomes were not reported using validated measures or standard definitions for ICH. The authors concluded: the risk of death was increased in those children with strokes due to mitochondrial diseases and hypercoagulable states; paediatric patients receiving alteplase have a low risk of fatal ICH; and alteplase is increasingly used in children with ischaemic stroke.

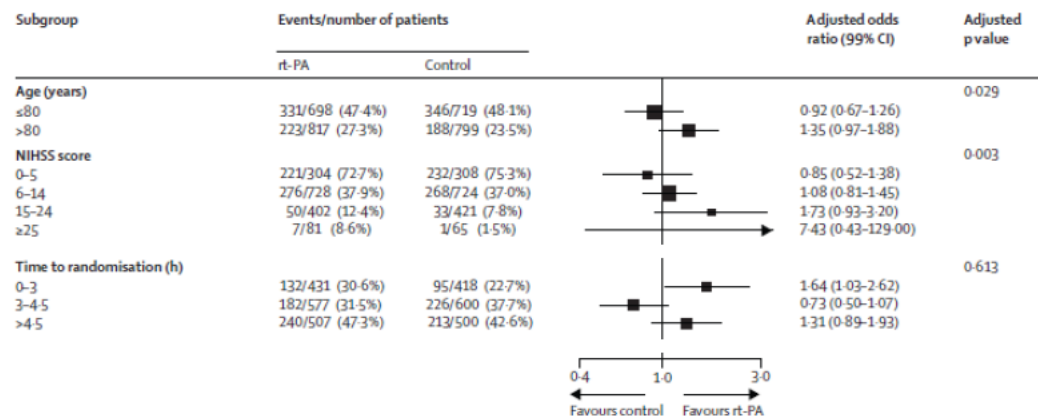
Older people

Few clinical trials of alteplase for ischaemic stroke have included patients aged over 80 years. Only 2 trials of alteplase for ischaemic stroke started with no upper age limit (Davis et al. 2008; The IST-3 collaborative group 2012). The EPITHET study included 25 patients aged over 80 years and IST-3 included 1617 participants aged over 80 years (Wardlaw et al. 2014). The NINDS trial protocol was amended to include 69 patients aged over 80 years after 188 subjects had been recruited in Part A (The NINDS rt-PA Stroke Study Group 1995).

The IST-3 trial

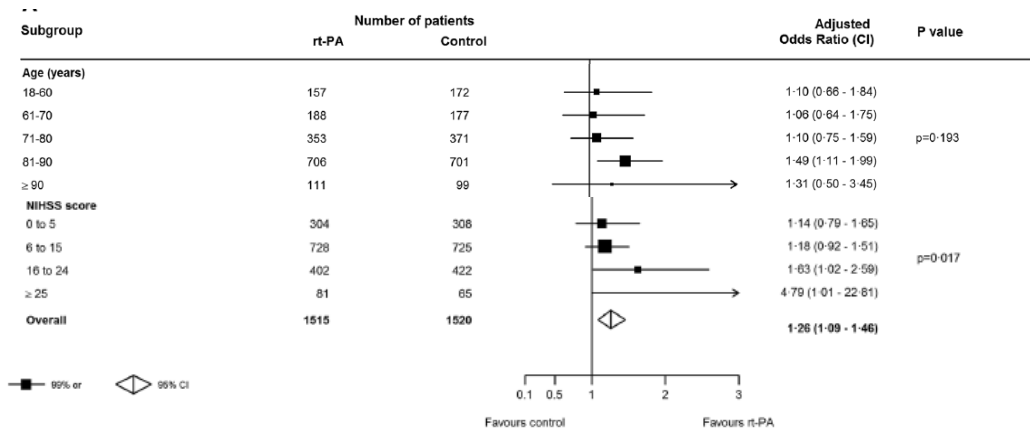
Whilst IST-3 failed in its overall primary outcome of alive and independent (OHS 0-2) at 6 months follow-up, the subgroup analyses of patients aged >80 years and patients with severe stroke (NIHSS score 15-24 and ≥ 25) found more favourable results (albeit not statistically significant) than the subgroups of patients aged <80 years and with milder stroke:

Figure 4: Selected subgroup analyses of the primary (dichotomised) outcome in IST-3 (alive and independent at 6 months); OR adjusted for age, NIHSS and time (IST-3 collaborative group 2012).

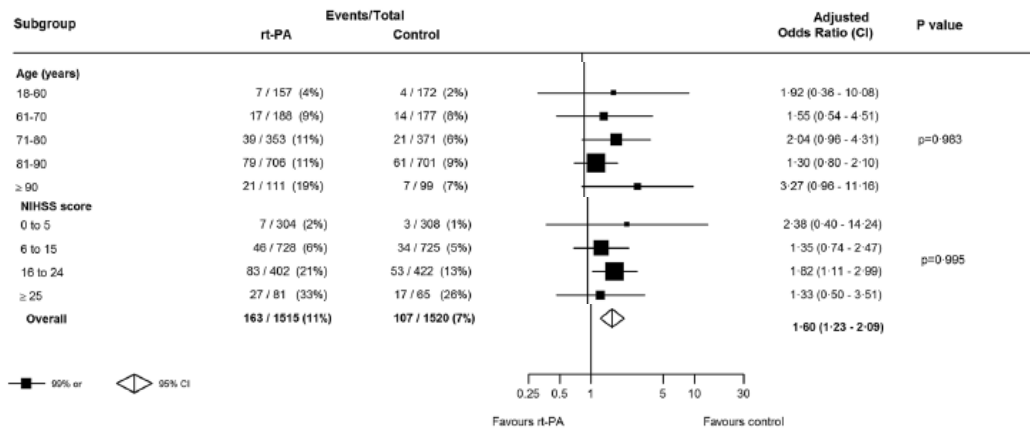


The recent analysis by Lindley et al. (2015) of many subgroups of patients in the IST-3 trial attempted to identify any subgroups of patients with an unacceptably high risk of sICH or low chance of benefit. This publication considered benefit using the secondary outcome (ordinal analysis of OHS at 6 months; adjusted for age, NIHSS and time of randomisation), on account of the greater power associated with this analysis to detect clinically important interactions – due to the overall significant result for the trial found with this outcome. The benefit results for the subgroups of

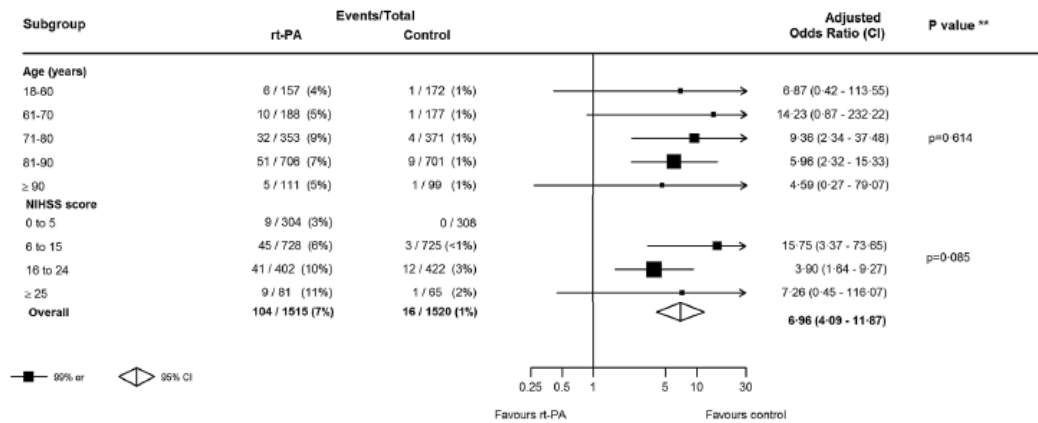
patients (aged >80 years or with severe stroke) were similar to the above, though the confidence intervals no longer crossed 1 for patients aged 81-90 years and for NIHSS score ≥ 16 , as shown below:



The results for day 7 mortality in these subgroups were as follows:



The results for sICH within 7 days for these subgroups were as follows:



The results from IST-3 for subgroups of patients >80 years of age and patients with severe stroke do not raise concerns either in terms of benefits (the subgroup

analyses if anything indicate a greater benefit in these groups), nor in terms of mortality or sICH – for which the results were similar across subgroups.

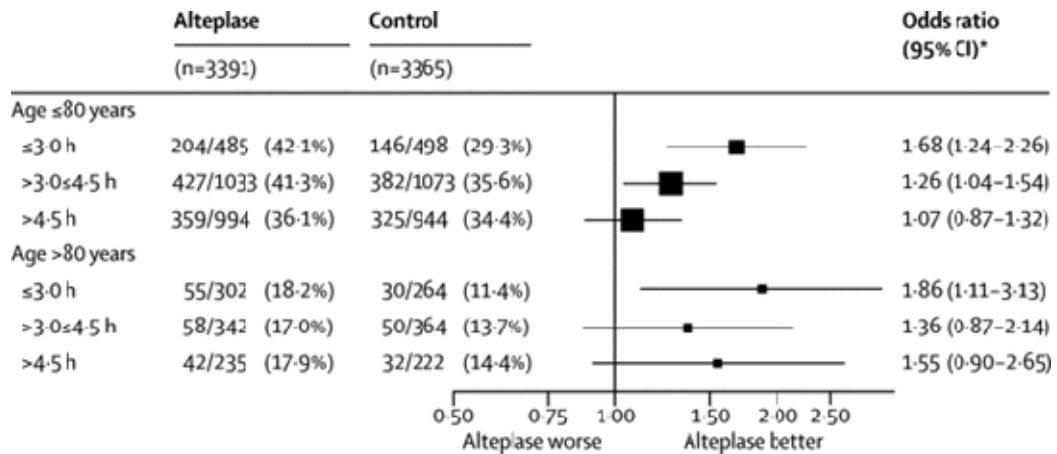
The other subgroups from IST-3 considered by Lindley et al. (2015) encompass a number of the other contraindications for treatment with rt-PA, and have been discussed in other sections, e.g. blood pressure, blood glucose, pre-trial treatment for diabetes or hypertension. The results in these subgroups were not found to raise concerns compared with the overall trial results, and there were no clearly significant ($p < 0.01$) interactions between rt-PA and any baseline clinical characteristics.

Meta-analysis of individual patient data from randomised trials

Emberson et al. (2014) provided data on the benefit-risk balance of alteplase in the elderly in their meta-analysis of individual patient data from randomised trials. Patients in IST-3 were older than those in the previous 8 trials by an average of at least 5 years (mean age [SD] was 77 years [12]) and they received thrombolysis approximately 20 minutes later but their mean (SD) baseline NIHSS scores were identical (mean NIHSS scores 12 [7]).

In the meta-analysis the effect of alteplase on a good stroke outcome by age according to time from onset to treatment was categorised into 3 time intervals (≤ 3 h; >3 to ≤ 4.5 h; and >4.5 h):

Figure 5: Effect of alteplase on a good stroke outcome (mRS 0-1) by age, with different treatment delays (Emberson et al. 2014).



Effect of age on the interaction between treatment delay and treatment effect $p = 0.08$ (ie, not significant but, if anything, in the direction of it lengthening, not shortening, the period during which alteplase is effective in older people). *All six estimates derived from a single stratified logistic regression model that enables the odds ratio to be estimated separately for each group (also adjusted for baseline National Institutes of Health Stroke Scale score). mRS=modified Rankin Scale.

Alteplase significantly increased the odds of a good outcome (mRS 0-1) when given within 3 h to those aged over 80 years (OR 1.86 [95% CI: 1.11-3.13]).

Age did not change the effect of alteplase on the odds of a good outcome (mRS 0-1, $p = 0.53$). The effect of alteplase treatment was similar for patients aged 80 years or younger (mean treatment delay 4.1 h; 990 [39%] vs 853 untreated [34%]; OR 1.25 [95% CI: 1.10–1.42, $p < 0.0001$]) and for those older than 80 years (mean treatment delay 3.7 h; 155 [18%] vs 112 untreated [13%]; OR 1.56 [95% CI: 1.17–2.08, $p = 0.0023$]).

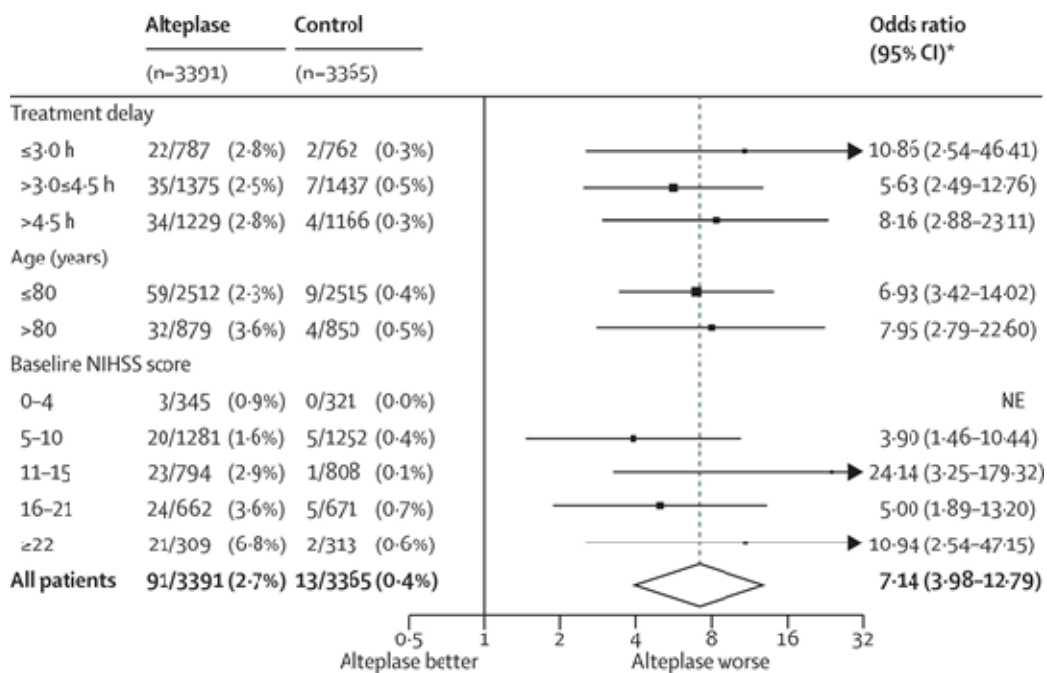
There was no evidence that alteplase was less effective in those patients aged over 80 years with the most mild or severe strokes or that age shortened the time window

for the beneficial effects of alteplase (figure 5). Alteplase increased the likelihood of sICH using the ECASS or SITS-MOST definitions to the same extent in those patients aged ≤ 80 years as in those aged >80 years.

In all patients, parenchymal haemorrhage type 2 within 7 days occurred in 231 (6.8%) of 3391 patients assigned to alteplase versus 44 (1.3%) of 3365 assigned to control (OR 5.55 [95% CI: 4.01–7.70; $p < 0.0001$]) and type 2 parenchymal haemorrhage within 36 h occurred in 124 (3.7%) of 3391 with alteplase versus 19 (0.6%) of 3365 of controls (OR 6.67 [95% CI 4.11–10.84; $p < 0.0001$]).

The proportional increase in risk of fatal intracranial haemorrhage was much the same, irrespective of treatment delay, age, or stroke severity ($p_{\text{interaction}} > 0.7$ for all) but the absolute excess risk increased with increasing stroke severity. For patients ≤ 80 years of age, fatal ICH occurred in 59 (2.3%) of alteplase treated patients, versus 9 (0.4%) of control patients (OR 6.93 [95% CI: 3.42-14.02]); and for patients >80 years of age, fatal ICH occurred in 32 (3.6%) of alteplase treated patients, versus 4 (0.5%) of control patients (OR 7.95 [95% CI: 2.79-22.60]):

Figure 6: Effect of alteplase on fatal intracranial haemorrhage within 7 days by treatment delay, age, and stroke severity (Emberson et al. 2014).



*For each of the three baseline characteristics, estimates were derived from a single logistic regression model stratified by trial, which enables separate estimation of the OR for each subgroup after adjustment for the other two baseline characteristics (but not possible interactions with those characteristics). The overall effect in all patients is the trial-stratified logistic regression estimate adjusted only for treatment allocation. NE=not estimable.

Alteplase did not increase early or late mortality from other causes as the hazard ratio for total 90 day mortality for all patients treated was 1.11 (95% CI: 0.99-1.25).

The authors concluded that there was no evidence that age modified the proportional benefits or hazards of alteplase with clear evidence of overall benefit for a good stroke outcome (mRS 0-1) among the 1729 patients aged over 80 years at randomisation.

Cochrane meta-analysis of randomised trials of alteplase for acute ischaemic stroke

Wardlaw et al. (2014) have also presented efficacy data according to age and time from onset to treatment for the NINDS, EPITHET and IST-3 studies. No age-related data on the hazards of alteplase were presented in this systematic review apart from partial reporting of the numbers of deaths captured within the mRS outcome data.

For treatment with alteplase up to 3 h after stroke onset, the proportion of patients aged >80 years who were dead or dependent (mRS 3-6) (OR 0.56 [95% CI: 0.40-0.78, $p=0.0007$; $n=726$]) was the same as in younger patients ≤ 80 years (OR 0.66 [95% CI: 0.52-0.85, $p=0.001$; $n=1039$]). For treatment with alteplase up to 6 h after stroke onset, the proportion of patients aged over 80 years who were dead or dependent (mRS 3 to 6) (OR 0.80 [95% CI: 0.64-0.99, $p=0.04$; $n=1696$]) was the same as in younger patients ≤ 80 years (OR 0.85 [95% CI: 0.76-0.95, $p=0.004$; $n=5175$]).

The proportions of those aged under or over 80 years who were alive and independent (mRS 0-2) after alteplase whether treated within 3 h ($n=1779$ treated), between 3 and 6 h ($n=4971$ treated) or up to 6 h ($n=6885$ treated) were also similar (Wardlaw et al. 2014).

Observational studies

Mishra et al. (2010a) compared the clinical outcomes of 23,334 thrombolysed patients from the SITS-ISTR from 2002 to 2009 to those of 6166 untreated stroke patients from negative trials of neuroprotective agents in the Virtual International Stroke Trials Archive* (VISTA; from 1998 to 2007).

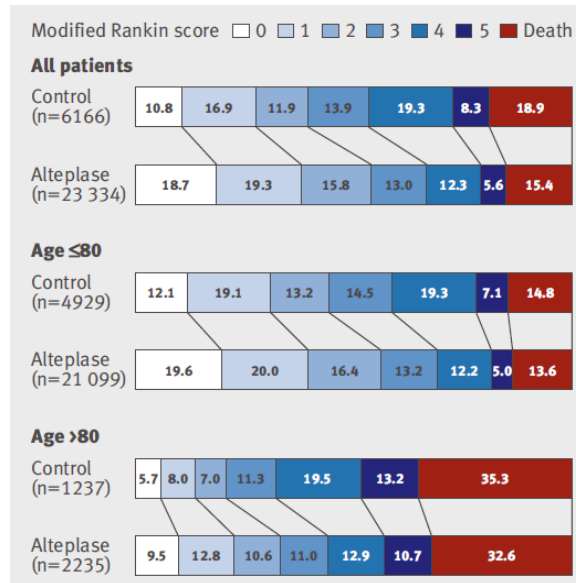
The controls comprised patients who had received placebo or potentially neuroprotective drugs which did not alter clotting or have any vasoactive properties. The controls were therefore patients who did not receive alteplase.

The main outcome measure was functional outcome as measured by the mRS at 3 months. Shift analysis of the mRS was adjusted for baseline imbalances in age and stroke severity (NIHSS score). Reliable data on sICH was not available from the VISTA subjects as post-treatment imaging was not usually required. All stroke patients were treated according to routine clinical practice.

The baseline characteristics for alteplase-treated and control groups were similar (alteplase-treated median NIHSS 12 [range 0-42]; control 12 [2-37], $p=0.14$). Independently, baseline NIHSS scores accounted for 25.5% and age for 7.4% of the variation in the 3 months outcome by mRS. There were 3439 patients aged over 80 years and the median time from stroke onset to treatment for those over 80 years was not significantly different to that for younger patients (median time 145 mins, $p=0.25$).

* VISTA is a register of stroke trials that contained information from 21 interventional trials up to Sep 2006 including the following interventions: anicrod (an anticoagulant); clomethiazole; alteplase (NINDS, ECASS I and II); gavestinel (non-competitive NMDA antagonist); magnesium sulphate; lubeluzole (indirect NMDA antagonist); nimodipine; selfotel (competitive NMDA antagonist); streptokinase; heparinoids; and repinotan (5HT_{1A} receptor agonist). VISTA also includes data from non-interventional studies (Ali et al. 2007).

Figure 7: Scores on mRS at 3 months for patients treated with alteplase vs controls (Mishra et al. 2010)

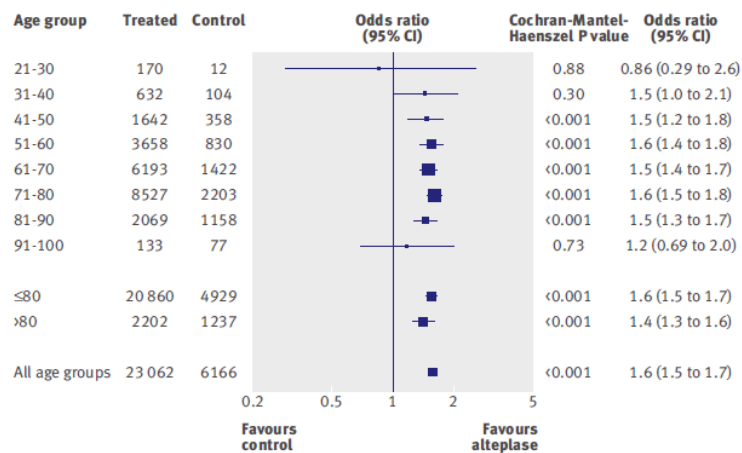


Numbers within white or coloured cells are percentages

Treatment with alteplase in patients aged over 80 years was associated with a significantly better distribution of mRS scores at 3 months compared with placebo (Figure 7, adj OR 1.4 [95% CI: 1.3-1.6, $p < 0.001$, $n = 3439$]). The OR was 2.1 (95% CI: 1.7-2.5) for a favourable outcome (mRS 0-2) when the mRS was dichotomised.

The outcome by age was further assessed by calculating the adjusted ORs in those given alteplase according to 10 year age groups:

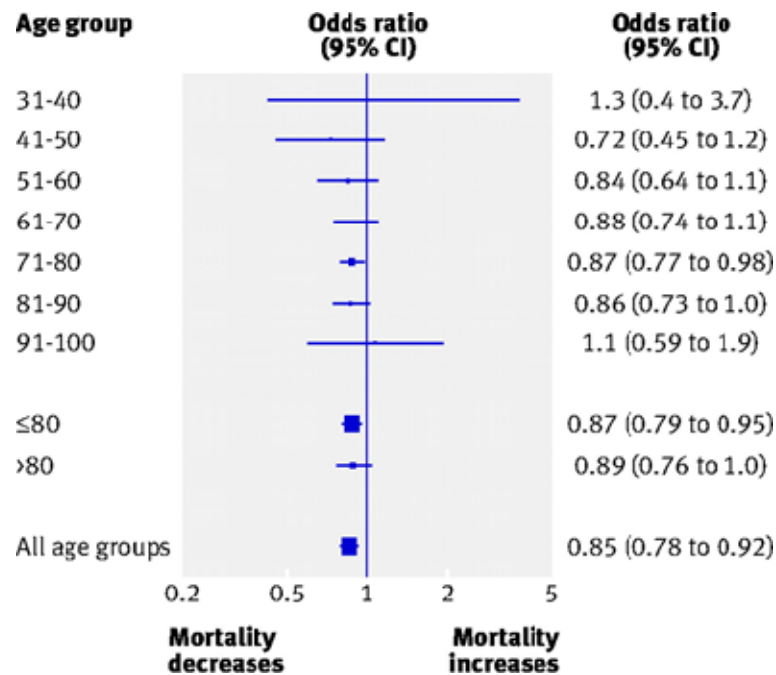
Figure 8: Shift towards better outcomes on mRS at 3 months adjusted for age and baseline severity (NIHSS score) (Mishra 2010)



Number of patients shown for age groups do not add up to 29228 because numbers of patients ages <21 ($n = 38$) and >100 ($n = 2$) were too low to allow any comparison. All patients aged <21 were from SITS and underwent thrombolysis; 15 patients reached a 90 day modified Rankin score of 0, 10 patients attained a score of 1, eight patients reached a score of 2, one patient achieved a score of 3, and two a score of 4; two died. Two patients aged 101 did not undergo thrombolysis in VISTA neuroprotection trials; they achieved modified Rankin score of 0 and 4 at 90 days

The odds ratios for a score of 0-1 on the mRS at 3 months were significantly better than controls for all age groups from 40 to 90 years and the point estimate for the 91 to 100 year group was similar to other age groups although the small sample sizes for the oldest and youngest age ranges produced 95% CIs that covered unity. The adj ORs for mortality at 3 months for those receiving thrombolytic therapy were also similar across the age groups:

Figure 9: Odds ratios for mortality at 3 months adjusted for age and baseline NIHSS score in those receiving thrombolysis (Mishra et al. 2010a)



The rate of sICH within 24 h using the SITS-MOST definition was 2.5% (54/2163) among those aged over 80 years receiving alteplase compared with 1.9% (398/20,759) among those aged ≤80 years receiving alteplase (OR 1.3 [95% CI: 0.96-1.8; $p=0.07$]). However, the sICH rate using the NINDS criteria was significantly higher in those aged over 80 years: 11.0% (229/2087) vs 8.3% (1670/20,220); (OR 1.4 [95% CI: 1.2-1.6; $p<0.001$]).

The authors concluded that the effectiveness of alteplase is similar in patients aged over 80 years despite generally poorer outcomes in older patients. The outcome results were similar to those reported from RCTs.

Ford et al. (2010) compared the effectiveness and harms of alteplase in patients aged over 80 years ($n=1831$) with younger patients ($n=19,411$) using a slightly smaller dataset from the SITS-ISTR. All patients were treated according to the conditions of the EU marketing authorisation except for the upper age restriction of 80 years (the treatment time-window for alteplase was then <3 h post-symptom onset).

There were baseline imbalances in the following for those over 80 years (all $p<0.005$): more females (59.3% >80 years, 39.4% ≤80 years); independence (mRS 0-1) before stroke (82.1% >80 years, 92.8% ≤80 years); more common previous stroke (14.9% >80 years, 10.3% ≤80 years), hypertension (75.7% over 80 years, 60.3% ≤80 years)

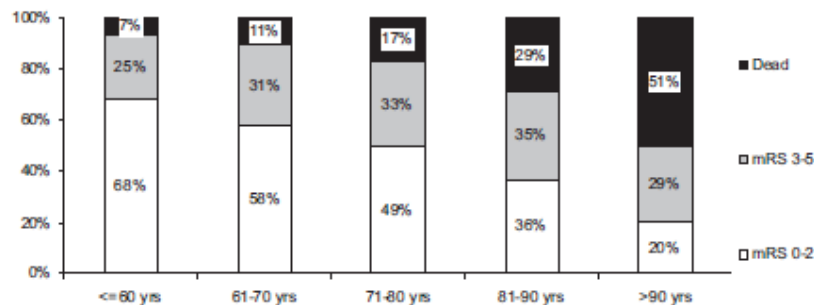
years), atrial fibrillation (44.6% >80 years, 21.9% ≤80 years), heart failure (16.1% >80 years, 7.3% ≤80 years), and aspirin use at stroke onset (48.8% >80 years, 29.7% ≤80 years) and they were also less likely to be current or previous smokers. Median stroke severity was higher in those >80 years with a NIHSS score excluding distal motor function of 14 (range 9-19) versus 12 (7-17) for younger patients ($p < 0.005$). The median (IQR) time for stroke onset to treatment was 135 mins (110-160) in those over 80 years and 140 mins (115-165, $p = 0.01$) although there was no difference in the percentage of patients thrombolysed at ≤90 mins (11.4% >80 years vs 10.8% ≤80 years, $p = 0.5$). A greater proportion of strokes were due to cardiac embolism in those aged over 80 years (49.7% vs 31.6%). Those aged >80 years weighed less than younger patients and received a lower average dose of alteplase. The main outcomes are shown in table 4 and figure 10.

Table 4: Proportion (%) and adjusted OR of main outcomes for patients >80 years compared with younger patients treated with alteplase (Ford et al. 2010)

Outcomes	Protocol Adhered no./No., % (95% CI)				P
	Patients >80 Years	Patients ≤80 Years	P	Adjusted OR	
SICH per SITS-MOST	32/1768 1.8 (1.26–2.58)	316/19 084 1.7 (1.49–1.85)	0.70	0.90 (0.73–1.09)	0.28
SICH per NINDS	162/1707 9.5 (8.16–11.00)	1407/18 598 7.8 (7.2–7.96)	0.005	0.96 (0.87–1.06)	0.42
Mortality at 3 months	456/1510 30.2 (27.9–32.6)	2038/16 742 12.2 (11.7–12.7)	<0.005	1.53 (1.43–1.65)	<0.005
Independence at 3 months (mRS 0–2)	527/1499 35.2 (32.8–37.7)	9468/16 504 57.4 (56.6–58.1)	<0.005	0.73 (0.68–0.78)	<0.005
Complete recovery at 3 months (mRS 0–1)	370/1499 24.7 (22.5–27.0)	6704/16 504 40.6 (39.9–41.4)	<0.005	0.81 (0.75–0.87)	<0.005

A progressive reduction in good functional outcomes (mRS 0-1 or 0-2) with increasing age in treated patients was seen (table 4). The sICH rate was not significantly increased in those over 80 years compared with younger patients after adjustment for other risk factors (SITS-MOST criteria 1.8% vs 1.7%, $p = 0.70$, adj OR: 0.90 [95% CI: 0.73-1.09; $p = 0.28$]; NINDS criteria 9.5% versus 7.8%, $p < 0.005$, adj OR, 0.96 [95% CI: 0.87-1.06, $p = 0.42$]). Patients aged over 80 years had a higher mortality rate at 3 months (30% versus 12%; $p < 0.005$; adj OR 1.53 [95% CI: 1.43-1.65; $p < 0.005$]).

Figure 10: Functional outcome in alteplase treated patients at 3 months measured by mRS according to age (Ford et al. 2010).



The Canadian Alteplase for Stroke Effectiveness Study (CASES) also reported that the incidence of sICH did not differ between patients aged <80 years (4.6% [95% CI: 3.3-6.2, n=865]) or ≥80 years (4.4% [95% CI: 2.3-7.6, n=270, $p = 1.0$]) (Sylaja et al. 2006).

A meta-analysis of 55 cohort studies involving a total of 65,264 alteplase-treated patients reported that older age was associated with an increased risk of ICH after alteplase therapy across all studies when age was modelled as a continuous variable (OR 1.03 per year) (Whiteley et al. 2012). However, age did not significantly predict ICH after alteplase when it was divided into 2 categories at 80 years (pooled OR from 5 studies was 1.25 [95% CI: 0.82-1.90, $p = 0.31$]).

Many smaller observational studies have generally reported similar outcomes in elderly patients treated with alteplase and have concluded that its benefit-risk profile is positive in older people despite the expected higher mortality and poorer outcomes seen in this age group (Tanne et al. 2000; Simon et al. 2004; Engelter et al. 2005; Ringleb et al. 2007; Pundik et al. 2008; Mateen et al. 2010).

MAH's response

The MAH has provided summaries for a selection of articles that address the benefits and harms of alteplase according to age (Tanne et al. 2000; Engelter et al. 2005; Pundik et al. 2008; Toni et al. 2008; Mateen et al. 2009; Kim et al. 2012; Willey et al. 2012; Balestrino et al. 2013; Richard et al. 2013; Liu et al. 2014; Ong et al. 2014).

The MAH concludes that *overall, none of the identified published literature did present any new findings with respect to risk related to age of patients.*

Concluding comments:

Children

The MAH has not discussed alteplase use in paediatric stroke. The UK clinical guideline for paediatric stroke noted in 2004 that there were no studies specifically examining the efficacy of acute treatments for arterial ischaemic stroke in children. The guideline states there is currently no evidence to support the use of thrombolytic agents such as alteplase in the acute treatment of arterial ischaemic stroke in children (Paediatric Stroke Working Group 2004).

Implications for the marketing authorisation - children

Section 4.2 Posology and method of administration of the alteplase SmPC states:

The experience in children and adolescents is limited. Actilyse is contraindicated for the treatment of acute stroke in children and adolescents.

Section 4.3 Contraindications of the alteplase SmPC states:

Use in children and adolescents

Actilyse is not indicated for the treatment of acute stroke in paediatric patients under 18 years.

The current SmPC wording concerning the use of alteplase in children is acceptable in the absence of any positive findings from RCTs including children with acute ischaemic stroke.

Older people

The safety and effectiveness of thrombolysis in older patients is an important issue: patients aged over 80 years make up almost a third of stroke admissions in developed countries (Ford et al. 2010); primary and secondary stroke preventative measures are increasingly effective in middle-aged people; and the number of people aged over 80 has doubled in the UK since 1982 (Mishra et al. 2010). The MAH has failed to note the findings from a number of recent studies including the IST-3 study that have provided reassuring data on the efficacy and risks of unlicensed alteplase use in older patients and the conclusion provided by the MAH is not considered valid.

It should be noted that the MAH has changed the contraindication in patients over 80 years to a special warning and precaution in their Company Core Data Sheet (CCDS)* dated 14 July 2009. The CCDS now states:

ACTILYSE is not indicated for the therapy of acute stroke in children and adolescents under 18 years. For use in patients above 80 years of age please refer to “special warnings and precautions.”

Compared to other indications, patients with acute ischemic stroke treated with ACTILYSE have a markedly increased risk of intracranial haemorrhage as the bleeding occurs predominantly into the infarcted area. This applies in particular in the following cases:

- *late time-to-treatment onset*
- *patients over 80 years of age may have an increased risk of intracerebral haemorrhage and a reduced net benefit from treatment compared to younger patients.*

Therefore, the use of ACTILYSE should be weighed carefully against anticipated risks on an individual patient basis.

The available evidence appears to indicate that the benefits of alteplase therapy are not age-related particularly when patients are treated early, and that, although the risks of fatal and sICH may be increased in those aged over 80 years, elderly patients should not be denied thrombolysis on the basis of age alone as their prognosis is worse.

Implications for the marketing authorisation – older people

Section 4.3 Contraindications of the SmPC for alteplase states:

Use in elderly patients

Actilyse is not indicated for the treatment of acute stroke in adults over 80 years of age

Section 4.4 Special warnings and precautions for use of the SmPC states

In stroke patients the likelihood of good outcomes decreases with increasing age, increasing stroke severity and increased levels of blood glucose on admission while.

Note: *Companies often prepare a Company Core Data Sheet (CCDS) which includes sections relating to safety, indications, dosing, pharmacology, and other information concerning a medicinal product. The CCDS is used as the reference product information for both the risk sections of the periodic safety reports as well as the main approved indications for which benefit is evaluated on a world-wide basis.

the likelihood of severe disability and death or relevant intracranial bleedings increases, independently from treatment. Patients over 80, patients with severe stroke (as assessed clinically and/or by appropriate imaging techniques) and patients with blood glucose levels <50 mg/dl or >400 mg/dl at baseline should not be treated with Actilyse (see section 4.3).

Data available from ECASS III and the pooled analysis indicate that the net clinical benefit becomes smaller in elderly with increasing age compared to younger patients as benefit from treatment with Actilyse appears to decrease and the risk of mortality appears to increase with increasing age.

The MAH has recently indicated that they intend to review the contraindication in patients aged >80 years based on an up to date review of the benefits and risks of alteplase treatment in this age group. Until such time the wording in the current SmPC remains appropriate.

7.1.4. Hy pertension

Hypertension in stroke

The risk of haemorrhagic transformation in acute ischaemic stroke with acute and chronic hypertension has been assessed in a number of studies.

Transient acute increases in blood pressure that settle spontaneously are frequently observed in the initial h after the onset of ischaemic stroke (Broderick et al. 1993).

There was a U-shaped relationship between admission systolic and diastolic blood pressures and mortality at 1 and 12 months in 1121 patients admitted within 24 h of ischaemic or haemorrhagic stroke onset. The systolic blood pressure at admission associated with the lowest mortality rate was 130 mmHg (the corresponding admission diastolic blood pressure was 81-90 mmHg after adjustment for known outcome predictors; Vemmos et al. 2004). Death due to cerebral oedema was significantly ($p=0.005$) more frequent in patients with high admission systolic blood pressure and deaths due to cardiovascular disease were more common in those with low systolic blood pressures ($p=0.004$). A moderate increase in blood pressure might improve cerebral perfusion of ischaemic tissue or it may worsen cerebral oedema and haemorrhagic transformation (Vemmos et al. 2004). Normal cerebral autoregulation mechanisms may fail in the ischaemic penumbral region so that cerebral perfusion pressure is directly related to systemic blood pressure. Systolic blood pressure was reported to exceed 139 mmHg in 69% of 563,704 patients with acute stroke arriving at hospital and was more than 184 mmHg in 13% and may be higher in those with chronic hypertension, but it typically starts to drop spontaneously within 90 minutes of stroke onset (Qureshi et al. 2007; Jauch et al. 2013). It is likely that an optimal blood pressure range exists for each patient during ischaemic stroke but it has not been defined.

Chronic hypertension is associated with a number of structural alterations in the cerebral arterioles that may lead to a failure or shifting of cerebral autoregulation to a higher blood pressure, damage to the integrity of the blood-brain barrier and radiological markers of small vessel ischaemia (Pantoni et al. 2010).

The impact on stroke outcome of blood pressure lowering would not necessarily be expected to be the same in patients treated with rt-PA and those that are not treated, given the increased risk of ICH attributable to rt-PA.

Effect of hypertension on rt-PA outcome

Clinical trial data (treatment with rt-PA)

ECASS I: A post-hoc analysis of the ECASS I study (Yong et al. 2005) examined the blood pressure profile of 615 patients from randomisation until 72 h later (every 2 h for the first 20 h, then every 4 h up to 72 h post-randomisation). Blood pressure profiles were considered by baseline, maximum, minimum, mean and successive variation (serial variability of successive blood pressure measurements, measured as the average squared difference between any two successive blood pressure measurements) of the profile. The endpoint was favourable outcome defined as mRS 0-1 at day 90.

Patients with systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg prior to study entry were excluded and so the study cannot provide any useful information on the appropriateness or otherwise of the contraindication.

Nevertheless, the effect of blood pressure within these limits was evaluated. At baseline ~80% of patients had elevated blood pressure, i.e. systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Mean systolic and diastolic blood pressure values gradually decreased with time in all subgroups, treated and untreated, favourable and unfavourable outcome.

Treatment assignment, gender, age, baseline body weight, onset to treatment time, initial stroke severity, specific disease histories e.g. atrial fibrillation, previous stroke, TIA, hypertension, coronary heart disease, valvular disease and diabetes, aspirin treatment at baseline, and findings on CT at baseline were considered as potential confounders of outcome. Significant predictors were included in the final logistic regression model.

Decreased successive variation in diastolic blood pressure appeared to be an independent predictor of day 90 favourable outcome (mRS 0-1). Successive variation in systolic blood pressure however was not an independent predictor after adjustment for confounders. This was consistent in both rt-PA treated and untreated patients.

Higher baseline systolic or diastolic blood pressure was an independent predictor of favourable outcome at day 90. However, in the hours following admission, the mean blood pressure profiles of patients with favourable outcome were generally lower than those in patients with unfavourable outcome, particularly for systolic blood pressure, as can be seen in the following figures.

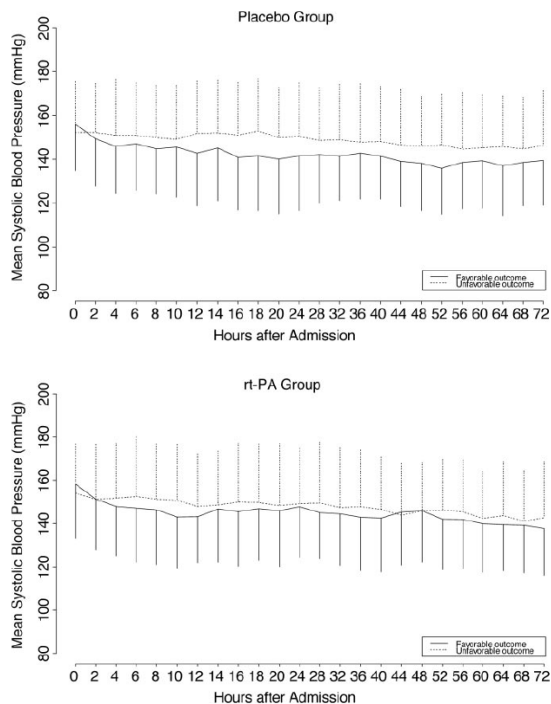


Figure 11: Sample mean profiles of systolic blood pressure with 95%CI according to favourable (mRS 0-1) [solid line]; and unfavourable (mRS 2-6), [dotted line] outcome (Yong et al. 2005)

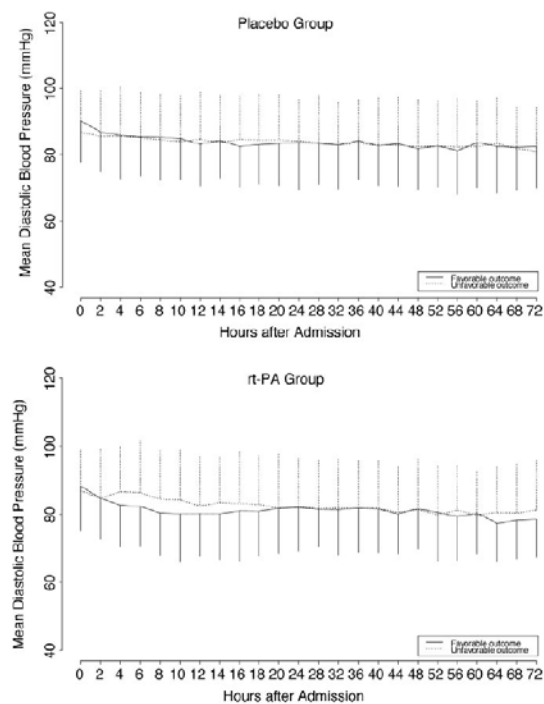


Figure 12: Sample mean profiles of diastolic blood pressure with 95%CI according to favourable (mRS 0-1) [solid line]; and unfavourable (mRS 2-6), [dotted line] outcome (Yong et al. 2005).

The limitations of this analysis include its post-hoc nature, that patients with minor stroke symptoms who were rapidly improving were excluded, as were patients with systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg. Therefore the impact of very high blood pressure may have been underestimated. In addition, the ECASS I trial used a higher dose of alteplase (1.1 mg/kg body weight) than the licensed dose (0.9 mg/kg body weight).

ECASS II: A post-hoc analysis of the ECASS II study (Yong and Kaste 2008) examined the blood pressure profile of 793 patients from randomisation until 24 h later (every 15 minutes for the first 2 h, then every 30 minutes up to 8 h, and thereafter every h up to 24 h). Patient blood pressure profiles were considered by baseline, maximum, minimum and mean blood pressure and successive variation of the profile. The endpoints were: favourable outcome defined as mRS 0-1 at day 90, all-cause mortality at day 90 and haemorrhagic transformation within the first 7 days.

Patients with systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg prior to study entry were excluded. At baseline, almost 80% of patients had elevated blood pressure, i.e. systolic blood pressure \geq 140 mmHg or diastolic blood pressure \geq 90 mmHg.

After adjustment (for age, gender, time from stroke onset to treatment, initial stroke severity, history of hypertension, aspirin use before stroke and extent of hypodensity on baseline CT), within-patient maximum, mean, and successive variation of systolic blood pressure were inversely associated with favourable outcome at day 90 in both placebo and rt-PA treatment groups. There was also an inverse association with baseline systolic blood pressure but only in the rt-PA group. Death within 90 days was not associated with blood pressure profile in either group.

Table 5: Characteristics of within-patient systolic blood pressure profiles and their impact on favourable outcome (mRS 0-1) and mortality according to treatment assignment (Yong and Kaste 2008).

	Placebo		rtPA	
	Crude OR	Adjusted OR†	Crude OR	Adjusted OR†
90-day favorable outcome				
Baseline SBP	0.96 (0.87–1.06)	0.91 (0.80–1.03)	0.89 (0.80–0.98)	0.84 (0.74–0.94)
0–24 hours SBP maximum	0.81 (0.73–0.89)	0.76 (0.66–0.86)	0.82 (0.75–0.90)	0.82 (0.73–0.91)
0–24 hours SBP minimum	0.86 (0.76–0.97)	0.92 (0.79–1.06)	0.91 (0.81–1.02)	0.90 (0.79–1.02)
0–24 hours SBP mean	0.79 (0.70–0.89)	0.76 (0.65–0.89)	0.82 (0.73–0.92)	0.81 (0.71–0.93)
0–24 hours SBP SV	0.58 (0.36–0.95)	0.41 (0.22–0.76)	0.51 (0.33–0.79)	0.57 (0.35–0.92)
0–24 hours SBP change	1.16 (1.05–1.28)	1.10 (0.98–1.23)	1.04 (0.96–1.14)	0.99 (0.90–1.10)
90-day mortality				
Baseline SBP	1.02 (0.87–1.19)	1.02 (0.85–1.22)	1.02 (0.87–1.19)	0.99 (0.84–1.18)
0–24 hours SBP maximum	0.96 (0.83–1.11)	0.94 (0.79–1.11)	1.10 (0.96–1.27)	1.15 (0.99–1.34)
0–24 hours SBP minimum	1.03 (0.86–1.24)	1.07 (0.87–1.32)	1.07 (0.89–1.28)	1.08 (0.89–1.31)
0–24 hours SBP mean	1.01 (0.85–1.20)	1.03 (0.83–1.27)	1.10 (0.92–1.32)	1.16 (0.94–1.43)
0–24 hours SBP SV	1.72 (0.86–3.43)	1.81 (0.85–3.87)	1.56 (0.85–2.87)	1.67 (0.88–3.18)
0–24 hours SBP change	0.95 (0.82–1.09)	0.92 (0.79–1.09)	0.97 (0.84–1.12)	0.96 (0.83–1.11)

OR for an increase of 10 mm Hg; 95% CIs in parentheses.

†Adjusted for age, gender, initial stroke severity, time from symptom onset to needle, hypertension and acetylsalicylic acid, medication history, extent of hypodensity of middle cerebral artery on CT; statistically significant associations in bold.

After adjustment, high baseline systolic blood pressure, within-patient maximum, mean and successive variation of systolic blood pressure were associated with increased risk of parenchymal haemorrhage within 7 days, but only in rt-PA treated patients and not placebo patients. Haemorrhagic infarction (defined as petechiae without space-occupying effect ranging from small petechiae along the margins of the infarct to confluent petechiae within the infarct area) was not associated with blood pressure profiles in either placebo or rt-PA treated patients, except for 0-24 h systolic blood pressure change in rt-PA treated patients:

Table 6: Characteristics of within-patient systolic blood pressure profiles and their impact on parenchymal haemorrhage and haemorrhagic infarction according to treatment assignment (Yong and Kast 2008).

	Placebo		rtPA	
	Crude OR	Adjusted OR†	Crude OR	Adjusted OR†
Parenchymal hemorrhage				
Baseline SBP	1.08 (0.81–1.43)	1.15 (0.84–1.56)	1.23 (1.05–1.43)	1.27 (1.07–1.51)
0–24 hours SBP maximum	1.04 (0.80–1.33)	1.08 (0.83–1.42)	1.46 (1.26–1.69)	1.49 (1.27–1.75)
0–24 hours SBP minimum	0.98 (0.71–1.35)	1.01 (0.72–1.41)	1.07 (0.90–1.27)	1.08 (0.90–1.29)
0–24 hours SBP mean	1.06 (0.78–1.44)	1.13 (0.81–1.58)	1.51 (1.25–1.82)	1.52 (1.23–1.87)
0–24 hours SBP SV	1.46 (0.43–5.01)	1.71 (0.47–6.25)	2.61 (1.50–4.55)	2.62 (1.40–4.87)
0–24 hours SBP change	1.03 (0.79–1.33)	1.05 (0.80–1.38)	1.04 (0.90–1.19)	1.02 (0.88–1.18)
Haemorrhagic infarction				
Baseline SBP	0.88 (0.80–0.98)	0.93 (0.82–1.06)	0.94 (0.85–1.04)	1.01 (0.90–1.13)
0–24 hours SBP maximum	0.98 (0.89–1.07)	1.02 (0.91–1.14)	0.98 (0.90–1.07)	1.01 (0.91–1.11)
0–24 hours SBP minimum	1.01 (0.90–1.14)	1.04 (0.91–1.20)	1.03 (0.92–1.16)	1.10 (0.97–1.25)
0–24 hours SBP mean	0.98 (0.87–1.09)	1.03 (0.90–1.19)	0.97 (0.86–1.08)	1.00 (0.88–1.15)
0–24 hours SBP SV	0.91 (0.57–1.46)	1.06 (0.62–1.83)	1.10 (0.73–1.65)	1.08 (0.69–1.70)
0–24 hours SBP change	0.92 (0.84–1.01)	0.99 (0.88–1.10)	0.91 (0.83–0.99)	0.94 (0.85–1.04)

OR for an increase of 10 mm Hg; 95% CIs in parentheses.

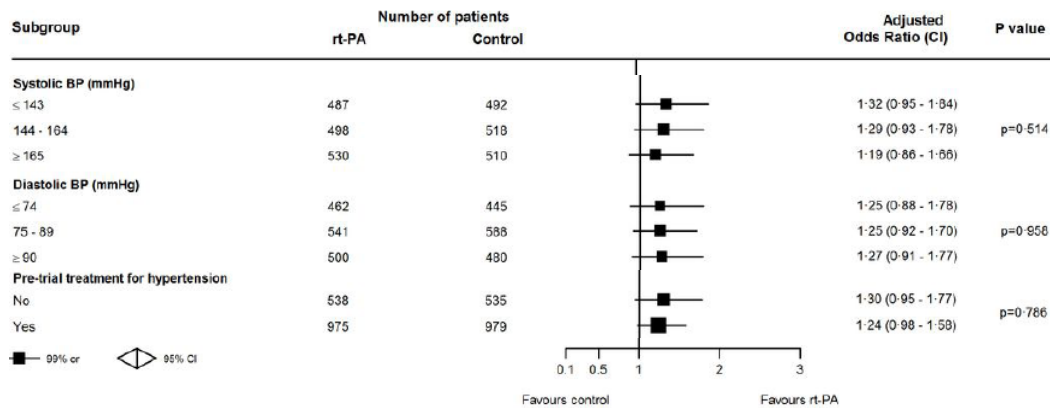
†Adjusted for age, gender, initial stroke severity, time from symptom onset to needle, hypertension and acetylsalicylic acid medication history, extent of hypodensity of middle cerebral artery on CT; statistically significant associations are in bold.

The limitations of this analysis are the same as described for ECASS I. Therefore the impact of very high blood pressure may have been underestimated. There may also be variation in blood pressure measurements between centres, although there was a standardised study protocol. In addition although adjustments were made for known confounders, residual confounding is possible.

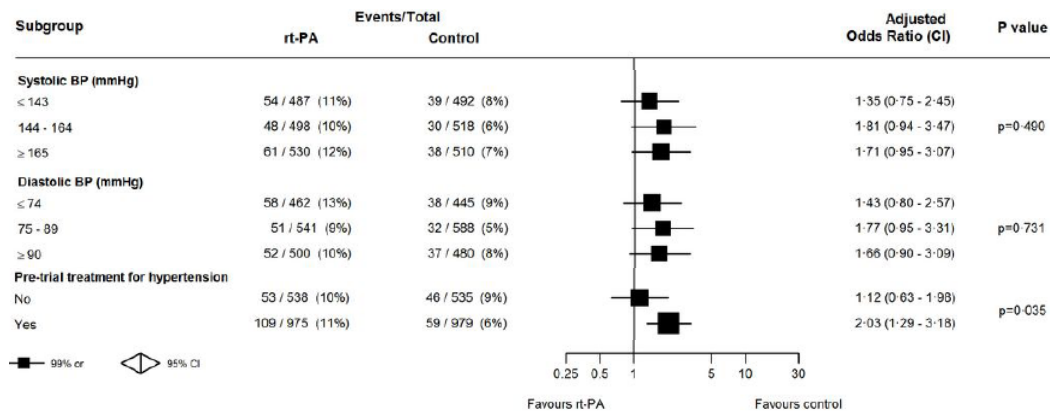
IST-3: Subgroups of patients with different blood pressures and subgroups either previously treated or not with antihypertensives were considered in the recent analyses by Lindley *et al* (2015). See section 6.1.5 for a description of these analyses.

Information on blood pressure was collected at randomisation, and was analysed in sub-groups of systolic blood pressure ≤ 143 ; 144-164, and ≥ 165 mmHg and diastolic blood pressure ≤ 74 , 75-89, and ≥ 90 mmHg. Patients with systolic blood pressure < 90 or > 220 mmHg or diastolic blood pressure < 40 or > 130 mmHg were excluded. Information on treatment for hypertension prior to the onset of stroke was also collected.

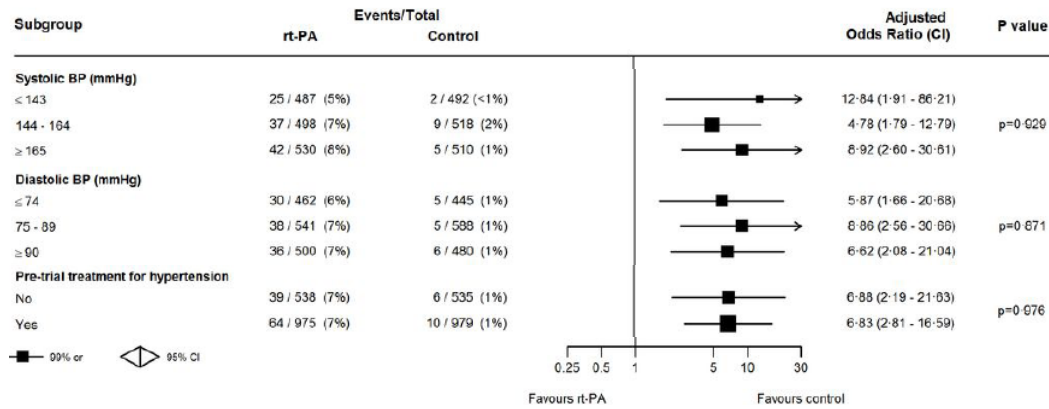
The results for functional outcome at 6 months (adjusted ordinal analysis of the OHS), for sub-groups with different blood pressures, and treated/not treated with antihypertensives are shown below:



The results for day 7 mortality for these subgroups are shown below:



The results for sICH within 7 days for these subgroups are shown below:



None of the sub-groups studied by Lindley et al. demonstrated significant interactions at the $p < 0.01$ level. An interaction at the $p < 0.05$ level can be seen for day 7 mortality and history of treatment of hypertension ($p = 0.035$), however there was no evidence for an interaction on sICH or six month functional outcome. The authors consider that the effect on day 7 mortality appears to be related to a lower than expected death rate in the control patients treated with antihypertensive.

EPITHET: A subgroup analysis of the EPITHET trial reported an association between mean systolic blood pressure at 24 h post-thrombolysis and the risk of parenchymal haemorrhage in patients thrombolysed within 3-6 h of stroke onset (Butcher et al. 2010).

Observational studies (treatment with rt-PA)

Early blood pressure variation and outcomes of thrombolysis:

SAMURAI: A sub-study of the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA registry investigated the association between early blood pressure variability and outcomes of thrombolysis (Endo et al, 2013).

The SAMURAI registry is a multi-centre retrospective observational registry, and 527 patients with acute ischaemic stroke treated with i.v. rt-PA at 0.6 mg/kg body weight (dose recommended by Japanese guidelines) were included in the analysis. Blood pressure was measured at baseline, and at 0, 4, 8, 12, 16, 20 and 24 h post treatment. Use of antihypertensives was permitted if required according to the guidelines.

Maximum, minimum and average blood pressure was calculated, as well as difference between maximum and minimum, standard deviation, coefficient of variation and successive variation (square root of the average difference in blood pressure between each of the measurements). Outcomes were sICH, mRS 0-1, death at 3 months.

Systolic blood pressure amongst patients with sICH tended towards being higher than those without sICH ($p = 0.083$), and was significantly lower in patients with mRS 0-1 than those with mRS 2-6 ($p < 0.001$). Variability in blood pressure profile was greater in patients with sICH and those that died, and lower in patients with mRS 0-1 compared with 2-6 (significantly lower for Δ BP, numerically lower for successive variation ($p = 0.081$)). The following table illustrates the associations between systolic blood pressure profiles and outcomes, giving adjusted ORs per 10mmHg.

Table 7: Associations between systolic blood pressure profiles and outcomes (Endo et al. 2013)

		sICH		mRS 0-1		Death	
Initial	1.08	0.86-1.35	0.96	0.86-1.06	1.03	0.83-1.27	
0 h	1.28	0.99-1.66	0.87	0.78-0.97	0.98	0.79-1.23	
4 h	1.24	0.99-1.57	0.89	0.80-0.99	1.05	0.86-1.30	
8 h	1.02	0.82-1.27	0.92	0.83-1.02	1.05	0.85-1.29	
12 h	1.16	0.93-1.46	0.91	0.82-1.005	0.90	0.74-1.11	
16 h	1.14	0.92-1.41	1.02	0.92-1.13	0.93	0.76-1.14	
20 h	1.05	0.84-1.32	0.90	0.81-1.001	0.93	0.76-1.14	
24 h	0.98	0.80-1.21	0.93	0.84-1.03	0.93	0.77-1.12	
Max	1.36	1.07-1.73	0.82	0.73-0.93	1.19	0.93-1.50	
Min	0.91	0.69-1.18	0.92	0.81-1.04	0.74	0.57-0.94	
Mean	1.24	0.89-1.75	0.86	0.74-0.99	0.94	0.70-1.27	
ΔBP	1.33	1.08-1.66	0.88	0.77-0.99	1.40	1.14-1.75	
SD	2.52	1.26-5.12	0.73	0.48-1.09	2.85	1.47-5.65	
CV	3.15	1.12-8.84	0.77	0.43-1.34	4.67	1.78-12.6	
SV	1.82	1.04-3.10	0.76	0.56-1.03	1.99	1.20-3.25	

BP indicates blood pressure; CV, coefficient of variation; Max, maximum; Min, minimum; mRS, modified Rankin Scale; SBP, systolic BP; sICH, symptomatic intracerebral hemorrhage; SD, standard deviation; and SV, successive variation.

Odds ratio per 10 mm Hg with 95% confidence interval for each SBP profile adjusted for sex, age, baseline National Institutes of Health Stroke Scale score, onset-to-treatment interval, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, intravenous antihypertensives just before recombinant tissue plasminogen activator, and ASPECTS on first computed tomography scan. Bold indicates, $P < 0.05$.

SITS MOST: An analysis of the SITS-MOST study was conducted by Wahlgren et al (2008), to compare the results of this observational study with the results from active arms of rt-PA randomised clinical trials, using multivariable analysis to adjust the SITS-MOST outcome results for the most important baseline prognostic variables. The study included 6483 patients treated with rt-PA from SITS-MOST, and these were compared with 464 patients treated with rt-PA in randomised clinical trials. High systolic blood pressure was demonstrated to be a prognostic variable for sICH (SITS-MOST definition; OR 1.33 [95% CI: 1.06-1.65] vs BP one standard deviation below [20.5 mmHg]), whilst diastolic blood pressure was not. However, high diastolic blood pressure (>90 mmHg) was a predictor of poor outcome of independence (mRS 0-2; OR 0.82 [95% CI: 0.70-0.95]) and of increased mortality (OR 1.52 [95% CI: 1.23-1.87]).

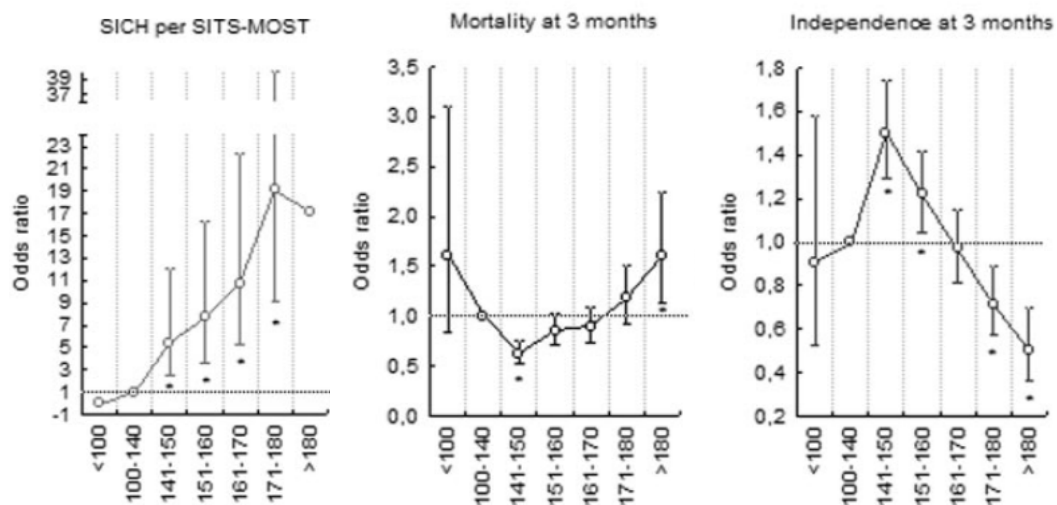
SITS-ISTR: Further investigation of the relationship between management of blood pressure and outcomes after treatment with rt-PA for acute ischaemic stroke was carried out by Ahmed et al. (2009) in an analysis of the SITS-ISTR registry. The registry included 11,080 treatments between 2002 and 2006, 6483 of whom were included in SITS-MOST. Blood pressure was recorded at baseline, 2 h and 24 h following thrombolysis. The outcomes evaluated were sICH, mortality and independence (mRS 0-2) at 3 months. Patients were also categorised by history of hypertension and use of antihypertensives in the 7 days following thrombolysis:

- Group 1: patients with history of hypertension, treated with antihypertensives, n=5612; median (interquartile range IQR) blood pressure at baseline: systolic 160 (142-170), diastolic: 84 (75-93)
- Group 2: patients with history of hypertension, not treated with antihypertensives, n=1573; median (interquartile range IQR) blood pressure at baseline: systolic 150 (135-165), diastolic: 80 (71-90)
- Group 3: patients without history of hypertension treated with an antihypertensive, n=995; median (interquartile range IQR) blood pressure at baseline: systolic 154 (140-168), diastolic: 84 (77-90)

- Group 4: patients without history of hypertension and not treated with antihypertensives, n=2632
median (interquartile range IQR) blood pressure at baseline:
systolic 140 (130-157), diastolic: 80 (71-90)

Using a multivariable analysis, high systolic blood pressure at 2 – 24 hours after thrombolysis was associated with worse outcome, and was associated with increased frequency of sICH. Using systolic blood pressure as a categorical variable with 100-140mmHg as the reference group for calculation of odds ratios, the relationship with sICH was approximately linear whilst for mortality and independence (mRS 0-2 at 3 months) it was U-shaped, with the best outcomes in patients with blood pressure of 141-150 mmHg:

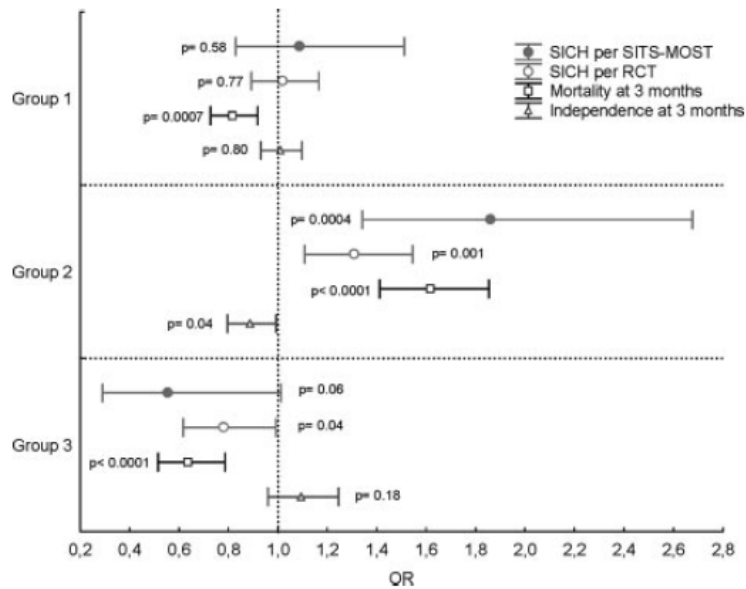
Figure 13: adjusted ORs and 95% CI from multivariable analysis for main outcomes categorised by average post-thrombolysis systolic blood pressure within 24 hours (* denotes statistically significant difference at p<0.05 between category and reference blood pressure [100-140mmHg]) (Ahmed et al. 2009).



sICH per SITS-MOST was defined by NIHSS score deterioration 4 points within 24 hours plus intracerebral haemorrhage Type 2

Odds ratios were derived using multivariable analysis of outcomes for the hypertension groups (groups 1-4), using group 4 as the reference group (patients without history of hypertension and not treated with antihypertensive in the 7 days following stroke). Patients with history of hypertension and not treated with antihypertensive (group 2) had the worst outcomes in terms of sICH, mortality and independence at 3 months. Patients in group 3 (patients without a history of hypertension and treated with antihypertensives) had the best outcomes – with lower rates of mortality and sICH and higher functional independence rate.

Figure 14: ORs for the main outcomes categorised by history of hypertension and antihypertensive treatment within 7 days following stroke, with group 4 as the reference group (Ahmed et al. 2009).



Adjusted OR, the midpoints, and their 95% CIs (horizontal errors bars) derived from multivariable analysis of outcome. For sICH and mortality, OR <1.0 means outcome was better (lower sICH and mortality) than Group 4. For independence, OR <1.0 means outcome was worse (lower independence) than Group 4.

The limitations of this analysis include a) that it is a retrospective analysis of an observational study and therefore it may be subject to reporting biases; b) as expected for a non-randomised study, the patient groups with and without a history of hypertension or antihypertensive treatment were imbalanced at baseline and although multivariable analyses were conducted, this may not account for all imbalances; c) it is not known when antihypertensive therapy was administered within the 7 days post-thrombolysis, and d) the type of antihypertensive drug administered was not recorded – some may have been administered for other indications such as congestive heart failure.

Meta-analysis

The meta-analysis of 55 studies of rt-PA-treated patients by Whiteley et al. (2012) reported that a prior history of hypertension was significantly associated with ICH (OR 1.50 [95%CI: 1.18-1.89, $p=0.001$]) using data from 11 studies although there was no increased risk of ICH with systolic blood pressure (per mmHg).

Effect of rt-PA on blood pressure:

As discussed above, Kerr et al. (2012) analysed data from the VISTA database on the effect of rt-PA thrombolysis on blood pressure and blood glucose compared with non-thrombolysis. Patients included were from trials of neuroprotectant agents, in many of which ~50% of subjects received rt-PA as part of normal practice. Data were collected for patients with admission and 24 hour recordings of blood pressure or blood glucose, where rt-PA use (or not) was recorded and information was

available on baseline prognostic variable and NIHSS score at admission and 24 hours.

A total of 5406 patients were included in the blood pressure analysis, 2229 of whom received rt-PA treatment. Patients treated with rt-PA were found to be younger, less likely to have a history of hypertension or diabetes, and had more severe strokes.

Mean systolic blood pressure was significantly lower in the rt-PA treated patients at admission than the control subjects, and the mean fall in systolic blood pressure over 24 h was also found to be significantly greater in rt-PA treated patients (11 mmHg [95% CI: 10-12]; vs. 8.3 mmHg [95% CI: 7.5-9.2, $p < 0.001$]). A similar pattern was observed for diastolic blood pressure. After adjustment for baseline imbalances, treatment with rt-PA was still a significant predictor of greater 24 h fall in systolic and diastolic blood pressure.

The authors comment that if treatment with rt-PA was causing a greater reduction in blood pressure (and in blood glucose levels) by resolution of the acute neurological deficit, it could be expected that the greatest falls in blood pressure/blood glucose would be found in rt-PA treated patients with early neurological improvement and in control patients the greatest falls would be seen in patients with neurological improvement (spontaneously reperfused). This was not found to be the case. The authors also report that there was a statistically significant but only minor correlation between baseline NIHSS and baseline systolic and diastolic blood pressure and glucose level, and therefore it is unlikely that increases in blood pressure and glucose after stroke arose secondary to the neurological deficit, and unlikely that the greater declines at 24 h were due to rt-PA resolving the neurological deficit. There was also no correlation between 24 h changes in blood glucose with 24 h changes in systolic or diastolic blood pressure, which would be expected if they both arose from the same underlying stress response.

The limitations of this analysis include that treatment with rt-PA was not randomised and the groups were found to be highly unbalanced at baseline. Whilst the results were adjusted for baseline imbalances, residual confounding factors could remain. In addition, the blood pressure measurements for the patients in this study were made at only two time points, baseline and at 24 hours. The authors comment that it has been previously found that the biggest differences occur at 12 hours after treatment and therefore this analysis may have underestimated the differences seen.

Aggressive management (intravenous pharmacotherapy) of blood pressure on rt-PA outcome:

Aggressive management necessary to reduce blood pressure to systolic blood pressure < 185 and diastolic blood pressure < 110 mmHg is currently a contraindication to rt-PA treatment. The data available in this sub-group of patients is limited.

Martin-Schild et al (2008) conducted a review of medical records for all patients who received intravenous rt-PA within 3 hours of acute ischaemic stroke in a single centre, between January 2004 and December 2006. A total of 178 patients were treated with rt-PA, of which 50 required blood pressure lowering prior to rt-PA treatment. 26 patients (52%) required labetalol to reach the target blood pressure, and 24 (48%) patients received nicardipine either after labetalol or as first-line therapy. Monotherapy with labetalol up to 40mg was defined as "standard blood pressure lowering", whilst additional need for nicardipine or use of nicardipine alone was defined as "aggressive blood pressure lowering". Patients were excluded if they had received blood pressure lowering medication other than labetalol or nicardipine, were treated after the 3 hour window for therapy, treated with adjuvant intra-arterial therapy or enrolled in a clinical trial.

The primary end points were adverse events (including sICH, haemorrhagic transformation, neurologic deterioration NIHSS increased by >2), discharge disposition and mRS at discharge.

Patients requiring i.v. antihypertensives had higher baseline blood glucose concentrations, higher incidence of hypertension, and higher NIHSS scores, compared with patients who did not require blood pressure lowering medication. There was no difference in time from arrival to rt-PA administration and onset of stroke symptoms to rt-PA administration between the two groups.

No significant difference was observed in the rate of sICH, haemorrhagic transformation or in-hospital death, however these were numerically higher in the group of patients treated with i.v. antihypertensives than the group that did not need i.v. antihypertensives.

Table 8: Adverse events and outcomes: no blood pressure treatment vs. i.v. blood pressure treatment before rt-PA therapy (Martin-Schild et al. 2008).

Variable	No BP Treatment Before tPA Therapy (n=128)	BP Treatment Before tPA Therapy (n=50)	P Value
Any grade of hemorrhagic transformation, No. (%)	16 (12.5)	10 (20)	.30 ^a ; .32 ^b
Symptomatic intracranial hemorrhage, No. (%)	2 (1.6)	2 (4)	.32 ^a ; .09 ^b
Neurologic deterioration, No. (%)	17 (13.3)	9 (18)	.42 ^a ; .76 ^b
Good outcome, No. (%)	94 (73.4)	37 (74)	.90 ^a ; .20 ^b
In-hospital deaths, No. (%)	9 (7)	5 (10)	.50 ^a ; .90 ^b

a: univariate analysis; b: multivariate analysis controlling for age, glucose concentration at admission, and baseline NIHSS score.

After adjustment for age, baseline NIHSS score, and blood glucose concentration, administration of i.v. blood pressure lowering medication was not associated with a poor outcome (mRS ≥ 3).

The “aggressive blood pressure lowering” group were of a similar age, baseline NIHSS score and blood glucose concentration as the “standard blood pressure lowering” group, with a trend to higher initial systolic blood pressure and longer times from arrival to rt-PA administration. The rates of sICH and haemorrhagic transformation were no different in these two groups, although there was a trend to higher mortality and neurologic deterioration in the aggressively lowered group but conversely also a trend to a higher rate of good outcome, see table 9 below. The numbers of patients in these individual subgroups of patients treated with different regimens of i.v. antihypertensives were very small (n=26 and n=24).

The authors conclude that these results provide the first support for the use of aggressive blood pressure lowering prior to treatment with rt-PA, and there is a need for a prospective investigation into this subgroup of patients.

Table 9: Adverse events and outcomes: standard blood pressure treatment vs aggressive blood pressure treatment before rt-PA therapy (Martin-Schild et al. 2008)

Variable	Standard BP-Lowering Therapy (n=26)	Aggressive BP-Lowering Therapy (n=24)	P Value
Hemorrhagic transformation, all grades, No. (%)	5 (19)	5 (20.8)	.90
Symptomatic intracranial hemorrhage, No. (%)	1 (3.8)	1 (4.2)	.95
Neurologic deterioration, No. (%)	3 (11.5)	6 (25)	.20
Good outcome, No. (%)	18 (69)	19 (79)	.40
In-hospital deaths, No. (%)	2 (7.7)	3 (12.5)	.57
Length of stay, median (IQR), d	7 (4-10)	4 (2.5-5.5)	.01

IQR=interquartile range; standard BP lowering therapy = monotherapy with labetalol up to 40mg; aggressive BP lowering therapy = labetalol treatment with additional need for nicardipine or use of nicardipine alone

Comment on the data

The impact of hypertension and interventions to lower blood pressure on stroke outcomes would not necessarily be expected to be the same for non-thrombolysed as for rt-PA treated patients. Increased blood pressure could improve cerebral perfusion, but could also worsen cerebral oedema and increase the risk of haemorrhagic transformation in non-thrombolysed patients. The increased risk of ICH attributable to rt-PA may alter the optimal management of hypertension in acute ischaemic stroke patients compared with non-thrombolysed patients. Furthermore the underlying mechanism resulting in increased blood pressure in patients with acute ischaemic stroke is likely to vary from individual to individual. Potential reasons for an increase in blood pressure in this situation include the acute sympathetic response to stress of critical illness and hospitalisation, factors like pain and dehydration, the direct involvement of the ischaemic lesion and the Cushing response to increased intracranial pressure from cerebral oedema. The response to efforts to reduce blood pressure following stroke in both treated and untreated patients may therefore also differ depending upon the underlying mechanism.

Outcomes and association with blood pressure in the immediate pre/post-stroke period:

Data from clinical trials of rt-PA suggested that patients with lower mean blood pressure in the hours following acute ischaemic stroke had better outcomes, and that better outcomes occurred in patients with less variable blood pressures. There were some inconsistencies in the results, with ECASS I patients (rt-PA treated and untreated) with a higher initial baseline blood pressure having a more favourable outcome, whilst ECASS II patients (rt-PA treated patients only) demonstrating the opposite. However the patients in ECASS I with favourable outcome also had generally lower mean blood pressure profiles in the hours following admission. In ECASS II, high baseline, within-patient maximum and mean, and successive variation of systolic blood pressure were associated with increased risk of parenchymal haemorrhage within 7 days for patients treated with rt-PA, but not in placebo patients. The IST-3 trial did not find significant interactions at the $p < 0.01$ level for outcomes in subgroups of patients with increased systolic or diastolic blood pressure or pre-trial treatment for hypertension. An interaction at the $p < 0.05$ level was observed for 7 day mortality in patients with history of treatment for

hypertension, however the authors considered that this is likely related to a lower than expected death rate in control patients treated pre-trial with anti-hypertensive.

It should be noted that these analyses of clinical trial data were conducted post-hoc and in most trials, patients with systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg were excluded (as per the SmPC contraindication). The IST-3 trial excluded patients with systolic blood pressure <90 or >220 mmHg or diastolic blood pressure <40 or >130 mmHg.

Data from the SAMURAI observational study of patients treated with rt-PA showed that systolic blood pressure was higher in patients with sICH and lower in patients with favourable outcome, and variability in blood pressure profile was greater in those patients with unfavourable outcomes (sICH and death).

Analyses of rt-PA treated patients in the SITS-MOST and SITS-ISTR databases, found that increased systolic blood pressure was associated with increased frequency of sICH, and worse outcomes in terms of mortality and independence at 3 months. The data from SITS-ISTR suggested that the optimum systolic blood pressure was 141-150 mmHg.

Outcomes in patients taking antihypertensive treatment/no antihypertensive treatment in the periods before and shortly after acute ischaemic stroke:

The data available in rt-PA treatment patients in SITS-ISTR on prior treatment with antihypertensives and history of hypertension, suggested that patients with a history of hypertension who were not treated with antihypertensives in the 7 days following stroke fared the worst, whilst patients with history of hypertension who were treated with antihypertensives in the 7 days following thrombolysis had similar outcomes to patients without a history of hypertension and not treated with antihypertensives. The group of patients without a history of hypertension and treated with antihypertensives in the 7 days post thrombolysis had the best outcomes. There are, however, limitations associated with this retrospective analysis of an observational registry, in particular that the imbalances between the groups may be insufficiently accounted for, and the timing of antihypertensive treatment within the 7 days is unknown.

Effect of rt-PA on blood pressure:

The study by Kerr et al included patients in the VISTA database from studies of neuroprotectant agents, and found that rt-PA treatment was a significant predictor of greater fall in blood pressure at 24 h post-stroke. This did not appear to correlate with improvement in neurological function however.

Concluding comments:

The issue of the optimal management of high blood pressure soon after the onset of an ischaemic stroke remains controversial and the current clinical recommendations remain weak due to lack of adequate evidence from RCTs.

The data does not appear to indicate a clear association between acute moderate increases in blood pressure that are commonly observed after an ischaemic stroke and an increased risk of haemorrhagic transformation. Transient hypertension may even be beneficial in maintaining cerebral perfusion but increasing blood pressure during and soon after thrombolysis may increase the risk of haemorrhage (The NINDS rt-PA Stroke Study Group 1995 and 1997; Brott et al. 1998).

Overall, evidence suggests that patients with normal or slightly raised blood pressures have more favourable outcome than patients with high blood pressures,

although the optimum blood pressure has not been defined and may depend upon several factors including whether the patient has been treated with rt-PA or not, and the reason/mechanism for hypertension in an individual case. For example patients with moderately increased systolic blood pressure (141-150 mmHg) treated with rt-PA were found to have the best outcomes in the SITS-ISTR database. This study and others have found a U-shaped relationship between admission blood pressure and good outcomes, whilst some have reported a more linear relationship between increasing blood pressure and worse outcomes (Jauch et al, 2013).

Data from clinical trials and observational studies of rt-PA suggest that those patients with lower blood pressure and less variable blood pressure measurements may have better outcomes than those with higher and variable blood pressures. However this finding does not demonstrate whether the lower blood pressure in these patients is causal to the improved outcome, or occurs as a result of the patient faring better, and therefore these data are not sufficient to judge the appropriateness of interventions to lower blood pressure in these patients.

High baseline systolic and diastolic blood pressure increase the risk of haemorrhage after alteplase possibly by modifying the effect of infarct size (Alvarez-Sabin et al. 2013). Pre-existing chronic hypertension increases the risk of early stroke recurrence and may increase the risk of alteplase-related ICH if associated with leukoaraiosis.

Data from the observational SITS-ISTR database provide some evidence that it may be beneficial to reduce blood pressure in rt-PA treated patients in the aftermath of thrombolysis treatment, however there are limitations associated with this study, including its observational, non-randomised design and the lack of information regarding the timing of antihypertensive treatment during the 7 days after stroke. Further clinical trial data is needed to confirm or refute these findings.

Initial data from review of medical records of a small number of patients who underwent aggressive blood pressure management prior to rt-PA treatment suggested that this may be a reasonable treatment regimen for those patients whose blood pressure exceeds the contraindicated limits, however there were trends noted towards increased sICH, haemorrhagic transformation and increased mortality, compared with patients who did not require i.v. antihypertensives. Therefore further data would be required in this patient subgroup before any conclusions could be drawn about the appropriateness of this contraindication.

The European Stroke Organization guidelines (2008) note that this is a controversial area without any reliable clinical trial evidence stating that it is common practice to avoid systolic pressures above 185 mmHg during thrombolysis.

The current National clinical guideline for stroke notes that the management of blood pressure after stroke remains an area where there is little evidence to guide care and provides recommendations based on the consensus of the Intercollegiate Stroke Working Party (The Intercollegiate Working Party for Stroke 2012). Antihypertensive treatment in people with acute ischaemic stroke is recommended:

- *only if there is a hypertensive emergency or one or more of the following serious concomitant medical issues: hypertensive encephalopathy; hypertensive nephropathy; hypertensive cardiac failure/myocardial infarction; aortic dissection; pre-eclampsia/eclampsia; intracerebral haemorrhage with systolic blood pressure over 200 mmHg.*
- *blood pressure reduction to 185/110 mmHg or lower should be considered in people who are candidates for thrombolysis.*
- *parenteral drugs aimed at lowering blood pressure should only normally be given*

to people with acute stroke in the context of a clinical trial, apart from people with acute intracerebral haemorrhage and a systolic blood pressure of more than 200 mmHg who may need parenteral treatment, or people who need acute blood-pressure lowering in preparation for thrombolysis.

- *parenteral drugs aimed at raising blood pressure should only normally be used as part of a clinical trial.*

Every patient who survives should be assessed for treatable risk factors (ie hypertension and smoking), and have these treated. It is considered reasonable to start long-term antihypertensive medication after 24 h from stroke onset in most patients (Jauch et al. 2013).

Implications for the marketing authorisation

The SmPC contraindicates use of alteplase in patients with “severe uncontrolled arterial hypertension”, and in patients with “systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg, or if aggressive management (intravenous pharmacotherapy) is necessary to reduce blood pressure to these limits.”

There is also a warning in section 4.4 of the SmPC which states that “blood pressure monitoring during treatment administration and for up to 24 h seems justified; an intravenous antihypertensive therapy is also recommended if systolic blood pressure >180 mmHg or diastolic blood pressure >105 mmHg.”

From a regulatory point of view, any possibility of removing a contraindication would rely on the availability of sufficient evidence to demonstrate a positive balance of benefits and risks in the contraindicated population. Most clinical trials excluded patients with systolic blood pressure >185 mmHg, or diastolic blood pressure >110 mmHg, and therefore randomised clinical trial data available in these patients are limited. The IST-3 study exclusion criteria were less stringent, systolic blood pressure <90 mmHg or >220 mmHg or diastolic blood pressure <40 mmHg or >130 mmHg. The subgroups of patients from the IST-3 trial with systolic blood pressure ≥165 mmHg or diastolic blood pressure ≥90 mmHg had similar results for functional outcome at 6 months, mortality by 7 days, and sICH by 7 days as the other subgroups of patients (systolic blood pressure ≤143 mmHg and 144-164 mmHg; diastolic blood pressure ≤74 mmHg or 75-89 mmHg). However, the cut-offs for these subgroups are lower than the contraindicated population and these data alone would not be considered sufficient to lift the contraindication. The data from SITS-ISTR are not supportive of use in patients with very high systolic blood pressures.

There also does not appear to be substantial data to support lifting of the contraindication to use of rt-PA in patients needing aggressive management to reach these threshold blood pressures.

Given the increasing risk of sICH and potential increase in mortality/reduction of favourable outcomes with increasing blood pressure, the contraindications in patients with very high blood pressures appear rational. The current SmPC wording is also broadly consistent with current National stroke guidelines.

7.1.5. Prior stroke and concomitant diabetes

This section will consider available data on the influence of blood glucose concentrations per se on stroke outcomes, as well as possible differential effects of rt-PA compared with placebo/no treatment in subgroups with different blood glucose concentrations. It also reviews the evidence for a differential effect in diabetic patients with and without prior stroke. The MAH states that comparisons in patients with prior stroke plus diabetes give no indication of an interaction between diabetes or prior stroke on the effect of rt-PA treatment, with each showing significant benefit and no loss of benefit when these concomitant conditions co-exist (Mishra et al. 2010b; Mishra et al. 2011).

Hyperglycaemia (defined as admission blood glucose ≥ 7.2 mM) has been reported in 40% of 656 patients with acute ischaemic stroke (Williams et al. 2002). A meta-analysis of 32 studies conducted in 2001 concluded that admission glucose concentrations of >6.1 to 7 mM in nondiabetic patients with ischaemic stroke were associated with increased 30 day or in-hospital mortality (RR 3.28 [95% CI: 2.32-4.64]) and patients with glucose levels of >6.7 to 8 mM had a greater risk of poor functional recovery (RR 1.41 [95% CI: 1.16-1.73]) (Capes et al. 2001).

Blood glucose may increase as a part of the stress response (Tracey and Stout 1994) and cause neuronal damage by several potential mechanisms including:

- glycosylation of proteins, lipids and nucleic acids and production of free radicals (Giardino et al. 1994)
- intracellular acidosis and oxidative stress due to lactate accumulation (Levine et al. 1988)
- release of matrix metalloproteinases which damage the endothelial basal lamina of the blood-brain barrier and may promote haemorrhagic transformation (Enciu et al. 2013)
- promotion of neuroinflammation (Wong and Crack 2008)

Elevated blood glucose may also impact on the response to thrombolysis with rt-PA. Hafez et al. (2014) discuss the possible mechanisms by which hyperglycaemia may lead to worse functional outcome, in both patients treated with thrombolysis and untreated patients. These include a) hyperglycaemia leading to an increase in coagulation by increasing thrombin production and stimulating the tissue factor pathway b) impairment of fibrinolytic activity of rt-PA by increasing production of plasminogen activator inhibitor (PAI-1), c) hyperglycaemia may exacerbate pathologic processes involved in ischaemic brain injury and may increase the risk of cerebral haemorrhage (Hafez et al. 2014).

Complications that are associated with diabetes may also contribute to a worse outcome in patients with ischaemic stroke.

NINDS Trial

The FDA assessment

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm080832.pdf>) of NINDS and the 2004 re-analysis of the NINDS trial (O'Fallon et al. 2004) considered the sub-group of patients with diabetes mellitus included in the trial.

Diabetes mellitus in isolation is not a contraindication to treatment with rt-PA, unless the patient's blood glucose is <2.8 or >22.2 mmol/l, or the patient also has a history of previous stroke. The results for patients with both diabetes and prior stroke were not presented for the NINDS trial.

21% of patients in NINDS were diabetic, n=68 in the rt-PA treated group and n=63 in the placebo treated group. Examination of the baseline characteristics of the patients found that patients with diabetes treated with rt-PA were older, had slightly more severe strokes and slightly more pre-existing disability compared with placebo treated diabetic patients. The percentage of patients that recovered according to the dichotomised mRS definition (mRS 0-1) with and without diabetes was as follows:

Diabetes: rt-PA treated: 30.9% (n=21); placebo treated: 28.6% (n=18)
No diabetes: rt-PA treated: 46.3% (n=112); placebo treated: 26.3% (n=65)

These results correspond to a 2.3% difference in recovery rates for treatment with rt-PA versus placebo in diabetic patients compared with a 20.0% difference in non-diabetic patients. The results for the Barthel index were worse (a difference of - 4.2% for rt-PA vs. placebo in diabetic patients vs. 19.0% for the same comparison in non-diabetic patients) and slightly better for NIHSS (a difference of 7.8% for rt-PA vs. placebo for diabetic patients vs. 15.3% for the same comparison in non-diabetic patients).

Intracranial haemorrhage within 36 h of treatment was more frequent in diabetic patients treated with rt-PA than non-diabetic patients treated with rt-PA (14.3% vs. 10.3%). Meanwhile, ICH in placebo treated diabetic patients was only slightly greater than in non-diabetic patients. The difference in ICH rates was not found to be driving the observed difference in recovery rates, which remained after exclusion of patients with ICH.

Although the results from NINDS suggested that rt-PA treatment in diabetic patients was associated with a slight excess of ICH and had no benefit, a statistically significant interaction between rt-PA and diabetes was not found and therefore these results should be interpreted with caution. The size of the sub-groups of patients with diabetes was small.

The beneficial effect of rt-PA treatment in patients with prior stroke was much smaller than in patients without prior stroke. Details of the timelines of prior stroke in these patients were not given, however prior stroke within the last 3 months was an exclusion criterion in the NINDS trial (and is listed as a contraindication in the current SmPC), and therefore it is assumed that these strokes were >3 months prior to the index event. A 3.6% difference in recovery rates for mRS in patients with prior stroke treated with rt-PA versus placebo was found, compared with an 18.7% difference in patients without prior stroke. For the Barthel index the differences between treated and placebo groups were 1.5% for prior stroke compared with 15.8% for patients without prior stroke; for the NIHSS, the differences were 11.3% and 14.5% respectively. The sub-group sizes of patients with prior stroke were very small, n=45 in the rt-PA treated group and n=38 in the placebo group.

Bruno et al. (2002) analysed the relationship between admission glucose level and clinical outcome using the NINDS data. This analysis studied the effect of glucose level across both treatment groups together (rt-PA and placebo combined), and a number of confounding variables were tested: acute treatment (rt-PA/placebo), age, baseline NIHSS score, history of hypertension, history of diabetes, cigarette smoking in the 12 months prior to stroke, alcohol abuse, aspirin use, stroke subtype, time from onset of symptoms to treatment, admission blood pressure, and hypodensity on initial CT scan. The analysis found that the odds for neurologic improvement (improvement in the NIHSS by 4 or more points from baseline to 3 months or a final score of 0) decreased as admission glucose increased (OR 0.76 per 100 mg/dL [5.6 mM] glucose, 95% CI: 0.61-0.95 $p=0.01$). The percentage of subjects with diabetes mellitus increased with increasing admission glucose. Patients with neurologic improvement at 3 months had a mean admission glucose of 144 +/- 68 mg/dL

(8.0 mM), whilst those without neurologic improvement at 3 months had a mean admission glucose of 160 +/-84 mg/dL (8.9 mM). The odds for sICH also increased with glucose admission level (OR 1.75 per 100 mg/dL [5.6mM], 95% CI 1.11-2.78, $p=0.02$). An analysis of the combined ATLANTIS Trial plus Part A of the NINDS study produced similar results for relationship between admission glucose level and neurologic improvement (Bruno *et al.* 2002).

The admission glucose concentrations in both the patients with neurologic improvement and those without neurologic improvement were much lower than the upper level at which treatment with rt-PA is contraindicated – as would be expected given that >400 mg/dL/22.2 mM was an exclusion criterion in the trial. However for both groups of patients, the mean admission glucose was relatively high compared with normal fasting levels (3.6-6.0 mM), though stroke patients would not necessarily be expected to be in the fasting state and a proportion of patients may suffer stress hyperglycaemia during the acute phase of ischaemic stroke.

ECASS II

A post-hoc analysis of the ECASS II trial examined outcomes of 748 patients included in the ECASS II trial to determine the effect of hyperglycaemia on stroke outcome across rt-PA and placebo treated patients combined (Yong and Kaste, 2008b). Serum glucose was measured at baseline and at 24 h. Patients were classified as baseline hyperglycaemia, 24 h hyperglycaemia, persistent hyperglycaemia (i.e. hyperglycaemia at baseline and at 24 hours) and persistent normoglycaemia. Hyperglycaemia was defined as glucose >140 mg/dL. ECASS II excluded patients with baseline glucose levels <2.75 mM (50 mg/dL) or >22.0 mM (400 mg/dL).

Endpoints were considered at day 7 (NIHSS, haemorrhagic transformation), day 30 (BI 95-100), and day 90 (mRS 0-2, all-cause mortality).

The numbers of patients per sub-group were as follows:

Diabetics (n=161): persistent normoglycaemia n=24 (15%); baseline hyperglycaemia n=21 (13%), 24-hour hyperglycaemia n=16 (10%), persistent hyperglycaemia n=100 (62%).

Non-diabetics (n=587): persistent normoglycaemia n=408 (70%); baseline hyperglycaemia n=79 (13.5%), 24-hour hyperglycaemia n=54 (9%), persistent hyperglycaemia n=46 (8%).

Multifactorial logistic regression models were used to assess the effect of hyperglycaemia in reference to the normoglycaemia groups, and adjusted ORs were calculated to determine the effect of hyperglycaemia on outcomes, adjustments were made for age, gender, initial stroke severity (NIHSS), disease history of hypertension, history of congestive heart failure before stroke onset, and treatment with rt-PA.

Within the group of non-diabetic patients, the subgroup with persistent hyperglycaemia had the worst prognosis according to neurological outcome, functional outcome (mRS), mortality, and parenchymal haemorrhage. Non-diabetic patients with 24 h hyperglycaemia had an increased risk of poor functional outcome (mRS) mortality and 7-day parenchymal haemorrhage compared with non-diabetic patients with persistent normoglycaemia (see table). The results for non-diabetic patients with baseline hyperglycaemia were not statistically significantly different from non-diabetic patients with persistent normoglycaemia.

There were no significant differences in outcome between the sub-groups of diabetic patients when compared with diabetic normoglycaemic patients, however the sub-

group sizes were somewhat smaller. No comparison was made between diabetic and non-diabetic patients.

Table 10: Logistic regression model: adjusted ORs (95% CIs) of hyperglycaemic patterns in relation to the respective outcomes in 161 patients with and 587 patients without disease history of diabetes mellitus (Yong and Kaste, 2008b)

Outcome	Baseline Hyperglycemia	24-Hour Hyperglycemia	Persistent Hyperglycemia	Persistent Normoglycemia
Diabetics, N=161				
7-day neurological improvement ≥ 4 or 0 points on NIHSS	0.32 (0.07–1.43)	1.18 (0.29–4.79)	0.80 (0.31–2.06)	1
30-day Barthel Index 95, 100	0.38 (0.06–2.27)	0.62 (0.09–4.11)	1.42 (0.47–4.29)	1
90-day mRS 0, 1, or 2	0.21 (0.04–1.17)	0.53 (0.10–2.77)	0.93 (0.31–2.76)	1
90-day death	10.8 (0.87–134)	0.62 (0.04–8.93)	1.38 (0.26–7.43)	1
HI within 7 days	0.57 (0.09–3.46)	0.72 (0.10–4.94)	0.69 (0.22–2.17)	1
PH within 7 days	NS	NS	2.98 (0.22–39.8)	1
Nondiabetics, N=587				
7-day Neurological improvement ≥ 4 or 0 points on NIHSS	0.78 (0.47–1.29)	0.60 (0.33–1.09)	0.31 (0.16–0.60)	1
30-day Barthel Index 95, 100	1.09 (0.63–1.89)	0.65 (0.34–1.27)	0.27 (0.12–0.62)	1
90-day mRS 0, 1, or 2	1.19 (0.69–2.05)	0.40 (0.20–0.78)	0.36 (0.17–0.73)	1
90-day death	1.84 (0.74–4.58)	5.99 (2.51–14.2)	7.61 (3.23–17.90)	1
HI within 7 days	1.44 (0.83–2.48)	0.97 (0.49–1.91)	0.30 (0.13–0.71)	1
PH within 7 days	1.97 (0.64–6.10)	5.69 (2.05–15.8)	6.64 (2.63–16.78)	1

ORs are adjusted for age and gender of patients, rtPA treatment, baseline NIHSS score, and disease history of hypertension and congestive heart failure. NS indicates not significant. Estimates are not given because of too few observed events; statistically significant associations in bold.

IST-3 trial

The IST-3 trial enrolled patients using the uncertainty principle, i.e. patients for whom rt-PA was not currently licensed but where the balance of benefits and risks was not considered to be clearly negative. A paper published recently in Stroke (Lindley et al. 2015) provides the results for many subgroups of patients treated in the IST-3 trial. The analyses conducted tested the null hypothesis that across the subgroups there was no interaction with the treatment effect on six-month functional outcome, deaths or sICH within 7 days.

The analyses were chosen considering the likely power to detect clinically important interactions. Analyses with highly statistically significant results for the overall effect on the outcome were considered less likely to give false positive or false negative evidence for heterogeneity. The overall results from IST-3 for sICH within 7 days and deaths within 7 days were both highly significant (adj OR 6.94 [95% CI: 4.07–11.8, $p < 0.0001$]; and adjusted OR 1.60 [95% CI: 1.22–2.08, $p = 0.001$]) respectively), however the primary analysis – good outcome defined as OHS 0–2 at 6 months – was not significant. As a result the secondary outcome, adjusted ordinal analysis of OHS at 6 months, was used instead (adjusted OR 1.27 [95% CI: 1.10–1.47, $p = 0.001$]).

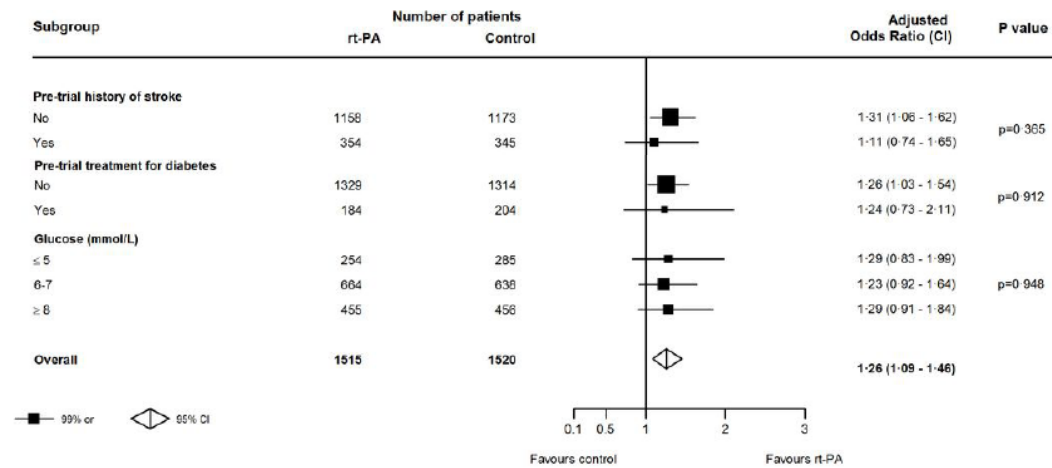
Although the overall outcome results were highly significant, the authors comment that the power to detect moderate interactions is limited. Wide confidence intervals for the subgroup result indicates likely low power, however where confidence intervals substantially overlap, this supports a conclusion of no interaction.

The trial exclusion criteria included ‘stroke within the previous 14 days’ and ‘hypo or hyperglycaemia sufficient to account for the neurological symptoms; the patient should be excluded if their blood glucose is < 3.0 or > 20.0 mM (< 54.0 or > 360.0 mg/dL). As a result, the subgroup of patients in IST-3 with prior stroke may have included some patients who would be contraindicated according to the SmPC (stroke < 3 months prior to the index event), however details of the timing of these previous events are not provided. The exclusion criterion for blood glucose was slightly more

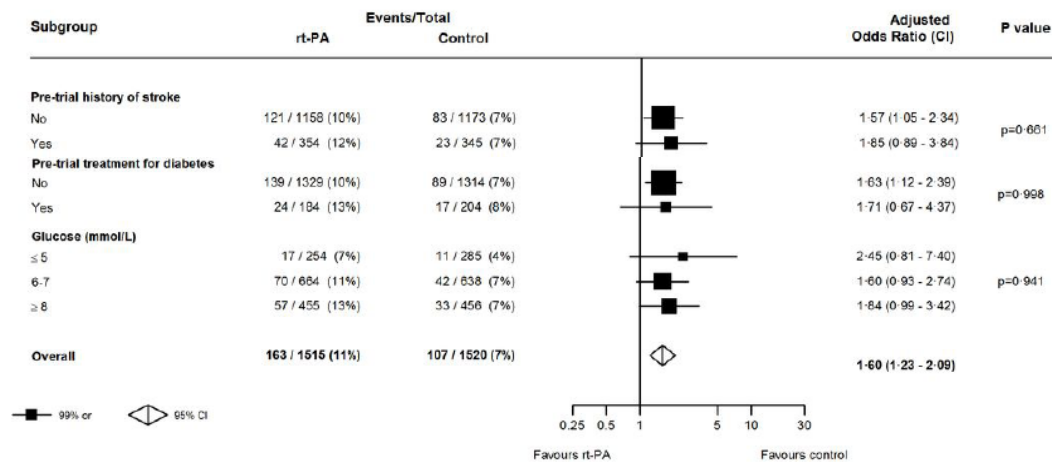
stringent than the contraindication according to the SmPC (<2.8 or >22.2 mM [<50 or >400 mg/dl]).

The analyses do not present any information in the subgroup of patients with both diabetes and prior stroke, despite the likelihood that some patients with both conditions would have been included.

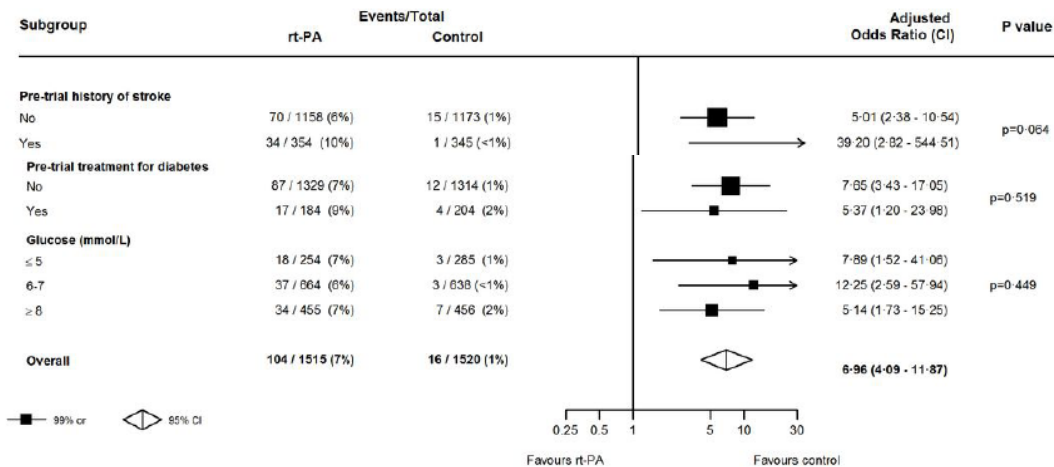
The results for functional outcome at 6 months (adjusted ordinal analysis of the OHS), for patients with prior stroke, diabetes and for different glucose levels are shown below:



The results for day 7 mortality for these subgroups are shown below:



The results for sICH within 7 days for these subgroups are shown below:



The authors conclude that the risks and benefits of rt-PA were consistent across a wide range of patient characteristics (including patients with prior history of stroke and patients with diabetes), with no clearly significant ($p < 0.01$) interactions between rt-PA and baseline clinical characteristics. The authors conclude that these results do not provide sufficient evidence to exclude any particular category of patient included in IST-3 from treatment in future, and suggest that many contraindications to treatment may not be justified. Whilst this is true, the numbers of events and subgroup sizes are quite small in some cases making it difficult to conclude with certainty that there are no differences.

Observational studies

Mishra et al. (2010b) compared data on thrombolysed and non-thrombolysed patients with or without diabetes and/or a history of prior stroke. Data were extracted from the Virtual International Stroke Trials Archive (VISTA) for 5817 patients of whom 1,585 were thrombolysed and 4,232 were not. Of these, 1334 (24%) patients had diabetes, 1898 (34%) patients had had a prior stroke and 491 (8%) patients had both. Data were sourced from neuroprotection trials (of agents that were neither vasoactive nor interfered with clotting) conducted between 1998 and 2007.

Diabetics and non-diabetics had equal baseline NIHSS scores (median 13, $p = 0.3$), patients with prior stroke had a higher baseline NIHSS score than those without prior stroke (median 13 vs. 12, $p < 0.0001$).

As seen in the paper by Frank et al (2013), discussed in section 6.1.8 of this paper, whether thrombolysed patients had better outcomes vs. non-thrombolysed patients was primarily assessed using a shift analysis of mRS at day 90 (using the Cochran-Mantel-Haenszel statistic, adjusted for age and baseline NIHSS), with an additional logistic regression analysis also adjusted for age and baseline NIHSS used to estimate the OR and associated 95% CI under the assumption of proportional odds:

Non-diabetic: OR 1.4 (95% CI: 1.3-1.6), CMH $p < 0.0001$

Diabetic: OR 1.3 (95% CI: 1.05-1.6), CMH $p = 0.1$

No prior stroke: OR 1.4 (95% CI: 1.2-1.6), CMH $p < 0.0001$

Prior stroke: OR 1.3 (95% CI: 1.04-1.6), CMH $p = 0.02$

Non-diabetic, no prior stroke: OR 1.4 (95% CI: 1.2-1.6) CMH p value not provided

Diabetic and prior stroke: OR 1.5 (95% CI: 0.98-2.3) CMH p value not provided

The authors attribute the non-significant result in the subgroup of diabetic patients with prior stroke to the small group size (n=491, 86 treated with rt-PA).

The paper also presents dichotomised analyses for mRS 0-1, as ORs adjusted for age and baseline NIHSS:

Non-diabetic: OR 1.4 (95% CI: 1.2-1.6)

Diabetic: OR 1.2 (95% CI: 0.9-1.7)

No prior stroke: OR 1.3 (95% CI: 1.1-1.5)

Prior stroke: OR 1.4 (95% CI: 1.1-2.0)

Non-diabetic, no prior stroke: OR 1.3 (95% CI: 1.07-1.6)

Diabetic and prior stroke: OR 1.4 (95% CI: 0.8-2.7)

In a proportional odds logistic regression analysis adjusting for age and baseline NIHSS, there was no interaction found between diabetes, prior stroke, and diabetes plus prior stroke with use of rt-PA.

Two of the limitations of the data obtained from this study are: 1) that onset to treatment time was not recorded – however, monitoring of protocol compliance was undertaken on behalf of trial sponsors and so administration of rt-PA should have occurred within the licensed time-window i.e. 3 hours at the time of the trials and; 2) it was not possible to study intracerebral haemorrhage, because the data were derived from neuroprotection trials which had not routinely obtained imaging information for untreated patients. It is therefore not possible to comment on the proportion of poor outcomes that were potentially related to intracerebral haemorrhage vs. a lack of treatment effect.

Furthermore, as the trials from which these data were obtained were designed to examine the effects of neuroprotection agents, thrombolysis was not a randomised treatment, and would have been based upon whether the patient was eligible for thrombolysis or not. Therefore it is unlikely that the patients who were thrombolysed were directly comparable to the patients who were not thrombolysed. The baseline characteristics of the rt-PA treated patients and those that did not receive rt-PA, for the patients with diabetes, prior stroke and patients with diabetes and prior stroke were provided in the publication, and some statistically significant differences were noted. For example a smaller proportion of patients with atrial fibrillation were treated with rt-PA than those not treated, in the diabetic group and prior stroke group. Likely related to this, there were fewer patients treated with prior anticoagulants in the rt-PA groups. A larger proportion of patients in the rt-PA treated groups had a history of myocardial infarction compared with the untreated groups.

Whilst overall these data suggest that there may be a treatment effect of rt-PA in these subpopulations of patients, the results are less convincing in these sub-groups than in patients without diabetes/prior stroke. In particular the results for patients with both diabetes and prior stroke are not significantly better for the rt-PA treated group than the non-thrombolysed group. The authors attribute this lack of significance to the smaller group size and whilst this explanation may be reasonable, these results nevertheless cannot be considered to demonstrate a positive effect in this patient subpopulation.

In 2011, Mishra et al. conducted similar analyses using data collected in the SITS-ISTR registry for patients with ischaemic stroke who had received rt-PA between 2002 and 2009, and data on non-thrombolysed patients from trials of neuroprotection agents (neither vasoactive nor interfered with clotting) conducted between 1998 and 2007 and held in the VISTA database.

Data on 23,336 patients recorded in SITS-ISTR were extracted, and 6371 control patients who did not receive thrombolysis were extracted from VISTA. Outcomes in patients who received thrombolysis were compared with those who did not receive thrombolysis, in patients with diabetes, prior stroke or both together. As before, the analysis compared the distribution of all categories of the mRS scale, using the Cochran-Mantel-Haenzel statistic and adjusting for age and baseline NIHSS. This avoids the assumption of proportional odds across all cutpoints on the outcome scale, but does not express the size of the association. Therefore the authors used a logistic regression analysis, adjusted for age and baseline NIHSS, to estimate the OR and 95% CI, under the assumption of proportional odds. A dichotomised analysis was also conducted for mRS 0-1 (adjusted for age and baseline NIHSS). Similarly to the previous study, information on sICH was not available because post-treatment imaging was not routinely applied in the neuroprotection trials.

No interaction was found between prior stroke and rt-PA treatment, diabetes and rt-PA treatment or between prior stroke and diabetes with rt-PA treatment.

The results for the ordinal regression analyses (adjusted for age and baseline NIHSS), and the CMH p values were:

Non-diabetic: OR 1.6 (95% CI: 1.5-1.7) CMH p value not stated

Diabetic: OR 1.4 (95% CI: 1.3-1.6) CMH $p < 0.0001$

No prior stroke: OR 1.5 (95% CI: 1.4-1.6) CMH p value not stated

Prior stroke: OR 1.5 (95% CI: 1.4-1.7) CMH $p < 0.0001$

Non-diabetic, no prior stroke: OR 1.5 (95% CI: 1.4-1.6) CMH $p < 0.0001$

Diabetic and prior stroke: OR 1.2 (95% CI: 0.996-1.5) CMH $p < 0.0001$

The results for the dichotomised analysis (mRS 0-1) were:

Non-diabetic: OR 1.6 (95% CI: 1.5-1.7)

Diabetic: OR 1.6 (95% CI: 1.4-1.8)

No prior stroke: OR 1.6 (95% CI: 1.4-1.7)

Prior stroke: OR 1.5 (95% CI: 1.3-1.7)

Non-diabetic, no prior stroke: OR 1.5 (95% CI: 1.4-1.7)

Diabetic and prior stroke: OR 1.3 (95% CI: 0.94-1.7)

These results are comparable to the results obtained in the Mishra et al. (2010) paper, with the confidence intervals for the results in patients with both diabetes and prior stroke crossing 1 in both cases, although when the data are dichotomised as mRS 0-2, the outcome is slightly more favourable for this subgroup: OR 1.3 [95% CI: 1.008-1.8]. The authors consider that this may be due to the smaller group size; however, whilst the Mishra et al. (2010) result for this subgroup was based upon 491 patients, the 2011 result for this subgroup was based upon 1136 patients.

This analysis has similar limitations to those conducted by the same group in 2010, in particular that treatment with thrombolysis was not randomised and it is therefore unlikely that the patients treated with thrombolysis were directly comparable with those that were not. A greater proportion of patients in the diabetic group than non-diabetics had hypertension, history of prior stroke, atrial fibrillation, heart failure and used antithrombotic medications. A greater proportion of the patients with prior stroke had hypertension, diabetes, atrial fibrillation, heart failure and use of antithrombotic medications than those without prior stroke.

The authors of both the 2010 and 2011 papers consider that although the results in the subgroup of patients with diabetes and prior stroke did not suggest a statistically significant beneficial effect of rt-PA compared with no rt-PA treatment, there is no justification to exclude these patients from receiving rt-PA because the confidence intervals were wide and there was no interaction between these two risk factors with the treatment effect of rt-PA.

Ahmed et al. (2010) investigated patients recorded in SITS-ISTR (n=16,049) between 2002 and 2007, to determine association between admission blood glucose and outcome in patients treated with thrombolysis. Outcomes considered were mortality and independence (mRS 0-2) at 3 months and sICH (defined as NIHSS deterioration ≥ 4 points within 24 hours and type 1 parenchymal haemorrhage). Admission blood glucose was divided into categories: <80 mg/dl (<4.4 mM), 80-120 mg/dl (reference range, 4.4-6.7 mM), 121-140 mg/dl (6.7-7.8 mM), 141-160 mg/dl (7.8-8.9 mM), 161-180 mg/dl (8.9-10 mM), 181-200 mg/dl (10.1-11.1 mM) and >200 mg/dl (>11.1 mM).

Blood glucose higher than 120 mg/dl (6.7 mM) was associated with significantly increased odds for mortality (OR 1.24 [95% CI: 1.07-1.44]) and lower odds for independence (OR 0.58 [95% CI: 0.48-0.70]) compared with the reference level (80-120 mg/dl [4.4-6.7 mM]). The risk of sICH was also increased after rt-PA in patients with glucose levels of 181-200 mg/dl (10.1-11.1 mM) in the SITS-ISTR compared to patients with reference glucose levels of 80-120 mg/dl (4.4-6.7 mM) (OR 2.86 [95% CI: 1.69-4.83]).

The meta-analysis by Whiteley et al. (2012) (see 6.1.1 'Stroke severity') found that higher baseline blood glucose levels were associated with a significantly higher risk of ICH after rt-PA treatment (OR 1.1 per mM) and when thresholds of 8 or 10 mM were applied.

Effect of rt-PA on blood glucose:

Kerr et al (2012) analysed data from the VISTA database on the effect of rt-PA thrombolysis on blood pressure and blood glucose compared with non-thrombolysis. Patients included were from trials of neuroprotectant agents, in many of which ~50% of subjects received rt-PA as part of normal practice. Data were collected for patients with admission and 24 h recordings of blood pressure or blood glucose, where rt-PA use (or not) was recorded and information was available on baseline prognostic variable and NIHSS score at admission and 24 h.

The blood glucose analysis included 4288 patients, of whom 1602 received rt-PA. Patients treated with rt-PA were found to be younger, less likely to have a history of hypertension or diabetes, and had more severe strokes.

The geometric mean glucose level at admission was lower in patients treated with rt-PA than in control patients. Despite this, greater falls in glucose levels at 24 h were observed in the rt-PA group than in the control group ($p < 0.001$). This finding remained after adjustment for baseline imbalances.

Considering the sub-group of patients without a history of diabetes, the geometric means of glucose level at baseline were similar in the rt-PA treated and control patients (6.5 mM [95% CI: 6.4–6.6] and 6.6 mM [95% CI: 6.5–6.6], respectively; $p = 0.173$). Glucose level did not change significantly to 24 hours in the control subjects, however the fall in the rt-PA group was significantly greater than the control group, to 6.2 mM (95% CI: 6.1-6.3).

In the sub-group of patients with a history of diabetes, the fall in glucose level from baseline to 24 hours was similar in patients treated with rt-PA and control patients. The geometric means at baseline for rt-PA and control patients were 9.7 mM (95%

CI: 9.3–10.2) and 9.9 mM (95% CI: 9.6–10.2), respectively, $p=0.560$. The geometric means at 24 h for the rt-PA and control groups were 8.5 mM (95% CI: 8.2–8.9) and 8.8 mM (95% CI: 8.6–9.1), respectively ($p=0.123$).

See section 6.1.4 for the information on effects on blood pressure and interpretation.

Comments on the data

Patients with blood glucose < 50 or > 400 mg/dl (<2.8 or >22.2 mM) are contraindicated for treatment of acute ischaemic stroke with rt-PA, as are patients with history of prior stroke and concomitant diabetes. Hyperglycaemia has been reported in 40% of patients with acute ischaemic stroke (Williams et al. 2002). Increased admission glucose levels have been associated with increased 30 day mortality and greater risk of poor function recovery.

Elevated blood glucose has been associated with poorer outcomes following ischaemic stroke in both animal and human studies, and may impact on the response to thrombolysis with rt-PA. Complications that are associated with diabetes may contribute to a worse outcome in patients with ischaemic stroke, however there is also evidence to demonstrate worse outcomes in patients with hyperglycaemia but no diagnosis of diabetes.

Effect of blood glucose concentration on stroke outcomes:

Data from NINDS suggested that increasing admission blood glucose resulted in decreasing odds for improvement in NIHSS, whilst the odds for sICH increased, across both the rt-PA and placebo groups combined.

The available data from ECASS II for both rt-PA and placebo groups combined suggested that outcomes in diabetics with hyperglycaemia (at baseline, at 24 h and at both time-points) were similar to outcomes in diabetics with persistent normoglycaemia. In contrast, in patients without a diabetes diagnosis, 24 h hyperglycaemia and hyperglycaemia at baseline as well as at 24 h (but not only at baseline) resulted in worse outcomes compared with non-diabetic patients with normoglycaemia. No comparison was made between diabetic and non-diabetic patients.

Evidence for a differential effect of rt-PA compared with placebo/no treatment at different blood glucose concentrations and in diabetic patients:

The NINDS trial found that the treatment effect of rt-PA compared with placebo was reduced in patients with diabetes compared with non-diabetics, with a 2.3% improvement in recovery rates (mRS 0-1) in patients with diabetes and a 20.0% improvement in recovery rates in patients without diabetes. ICH was also found to occur more frequently in diabetic patients treated with rt-PA than in non-diabetic patients treated with rt-PA (14.3% vs. 10.3%), meanwhile the rates of ICH in diabetic/non-diabetic patients treated with placebo were similar. The subgroup sizes in the NINDS trial were small however, and a statistically significant interaction between rt-PA and diabetes was not found.

There was no clear difference between the subgroups of patients with differing glucose concentrations in the IST-3 trial in the benefit (functional outcome at 6 months), or risk (day 7 mortality and day 7 sICH) of rt-PA compared with untreated patients; however, the subgroups covered glucose ranges of ≤ 5 , 6-7 and ≥ 8 mM, which is a much lower concentration than that contraindicated in the rt-PA SmPC (>22.2 mM).

The large observational studies by Mishra et al (2010b and 2011) found fairly similar odds ratios for mRS at day 90 for rt-PA treatment vs. no rt-PA treatment for non-diabetic and diabetic patients; however the results for diabetic patients for rt-PA treatment vs. no rt-PA treatment were only consistently statistically significant in the larger study from 2011. There are limitations associated with these observational studies, for example the data were obtained from VISTA and SITS-ISTR, and therefore thrombolytic treatment was not randomised. In addition, these studies did not measure blood glucose concentration and therefore they cannot provide further information regarding pre-existing or subsequent hyperglycaemia and outcomes observed.

Evidence for a differential effect of rt-PA compared with placebo/no treatment in subgroups with prior stroke and with prior stroke and concomitant diabetes:

The NINDS trial provided data on patients with and without prior stroke (assumed to have taken place >3 months prior to the index event). Patients with prior stroke treated with rt-PA had a 3.6% improvement in recovery rate (mRS 0-1) compared with placebo patients, whilst for patients without prior stroke this difference was 18.7%.

The data available from IST-3 for the subgroup of patients with prior stroke (more than 14 days prior to the index event) did not demonstrate a significant interaction with rt-PA. The subgroup results for rt-PA treatment versus no rt-PA treatment in patients with prior stroke were in general slightly less favourable than those for patients without prior stroke, although this difference was not significant. For example for functional outcome at 6 months, the subgroup of patients without prior stroke had an OR for a favourable outcome of 1.31 (99% CI: 1.06-1.62) whilst the confidence intervals for the result for patients with prior stroke crossed 1: OR 1.11 (99% CI: 0.74-1.65). However the subgroup size for patients with prior stroke was smaller than that for patients without prior stroke.

Whilst the data available from clinical trials provides information on patients with diagnoses of diabetes or with hyperglycaemia and some information on patients with prior stroke, it does not address the subgroup of patients with both diagnoses of diabetes and prior stroke, one of the contraindications for treatment in the rt-PA SmPC. The two observational studies by Mishra et al. do analyse this subgroup, and in general whilst the ORs were favourable for rt-PA treatment vs. not treated, the results were not statistically significant.

Ongoing further work

Although the evidence suggests that patients with hyperglycaemia likely have poorer outcomes than patients with normoglycaemia following acute ischaemic stroke, it is not clear from this finding whether this is a causative factor, or only a marker for worse outcome and therefore whether intervening to correct blood glucose may be beneficial for a patient or not.

Clinical trials are needed to address this question, and a pilot study, the Treatment of Hyperglycaemia in Ischaemic Stroke (THIS) trial was published in 2008 (Bruno et al). The THIS trial included 46 patients, 31 randomised to aggressive treatment with continuous intravenous insulin and 15 randomised to usual care with s.c. insulin QID as needed. The target glucose levels were <7.2 mM (<130 mg/dl) in the aggressively treated group and <11.1 mM (<200 mg/dl) in the usual care group. Treatment was continued for 72 hours. Glucose levels were averaged at 7.4 mM (133.2 mg/dl) in the aggressively treated patients compared with 10.5 mM (189.0 mg/dl) in the usual care group and hypoglycaemia (<3.3 mM, <60 mg/dl) occurred in 11 (35%) of the aggressively treated group. Eight (26%) patients in the aggressively treated group and 2 (13%) in the usual care group received thrombolysis with rt-PA. The final

clinical outcomes at 3 months were non-significantly better in the aggressively treated group.

A second pilot study was authored by Johnston et al (2009), the Glucose Regulation in Acute Stroke Patients (GRASP) trial. This was a three-arm trial in 74 subjects, with patients randomised to tight control (70-110 mg/dl; 3.9-6.1 mM), n=24, loose control (70-200 mg/dl; 3.9-11.1 mM), n=25, or usual care (70-300 mg/dl; 3.9-16.7 mM), n=24. Of the included patients, 59% were diabetic and 35% underwent thrombolysis. The loose control and usual care groups had median glucose concentrations of 151 mg/dL (8.4 mM) and the tight control group had a median glucose concentration of 111 mg/dL (6.2 mM). The overall rate of hypoglycaemia (defined as <55 mg/dL; 3.1 mM) was 4% in the usual care group, 4% in the loose control group and 30% in the tight control group. At 3 months, the proportions of patients with mRS 0-1 were 33% (usual care), 25% (loose control), and 42% (tight control), these differences were not statistically significant. Adjustment for rt-PA treatment did not change the results.

The UK Glucose Insulin in Stroke Trial (GIST-UK) (Gray et al, 2007) was a phase III trial designed to determine whether treatment with glucose-potassium-insulin (GKI) infusions to maintain euglycaemia after acute stroke would reduce death rates at 90 days. Patients with hyperglycaemia (6.0-17.0 mM; 108.0-306.0 mg/dl) were randomised to receive variable dose insulin or saline as a 24 hour infusion. The treated group were to maintain glucose at 4-7 mM (72.0-126.0 mg/dl). The trial was stopped early due to slow recruitment, after 933 patients were enrolled. As a result the study was underpowered (original target n=2355) and there was no significant reduction in mortality at 90 days (GKI vs. control OR 1.14 [95% CI 0.86-1.51]).

Whilst some evidence is suggestive of a possible benefit to glucose control in the aftermath of stroke, the data available is insufficient to conclude on this issue. The Stroke Hyperglycaemia Insulin Network Effort (SHINE) trial is currently ongoing and should hopefully provide a more definitive answer (Bruno et al. 2014). SHINE is a blinded, randomised, phase III trial comparing insulin infusion for intensive blood glucose control (80-130 mg/dL; 4.4-7.2 mM) with standard of care glucose control using s.c. insulin (<180 mg/dL; <10.0 mM) in hyperglycaemic acute ischaemic stroke patients starting within 12 h of onset, and ongoing for up to 72 h. The primary outcome is mRS at day 90, and the enrolment target is 1400. According to clinicaltrials.gov, the trial is estimated to compete in July 2018 (<https://clinicaltrials.gov/ct2/show/NCT01369069>). As randomisation is stratified by rt-PA treatment, this trial should provide data regarding the association between blood glucose control and outcomes after thrombolysis – and the risk of sICH.

Concluding comments:

For both of these contraindicated subgroups (prior stroke and concomitant diabetes; blood glucose < 50 or > 400 mg/dl [<2.8 or >22.2 mM]), the available data is limited, with small subgroups of patients with diabetes/hyperglycaemia in clinical trials, and data from observational studies that are subject to limitations. Overall whilst there is some evidence to suggest that the overall benefit from rt-PA treatment may be reduced in these patients relative to patients without these conditions the data do not appear to conclusively indicate substantial harm or substantial benefit associated with rt-PA treatment in comparison with patients who are normoglycaemic or do not have a history of prior stroke and diabetes. It should be noted that the data available from clinical trials does not cover the more severe and contraindicated subgroup of patients with hyperglycaemia (i.e. glucose levels >22.2 mM) as these patients were excluded from trials, including the IST-3 trial.

There is currently no clinical evidence that targeting the blood glucose to a particular level during acute ischaemic stroke will improve outcomes after rt-PA. The National stroke guideline recommends that people with acute stroke should be treated to maintain a blood glucose concentration between 4 and 11 mmol/L and that optimal insulin therapy should be provided to all patients with diabetes who have stroke (The Intercollegiate Working Party for Stroke 2012). The ESO recommends treatment of serum glucose levels >180 mg/dl (>10 mM) with insulin titration (European Stroke Organization 2008).

Focal neurological deficits can appear in the presence of hypo- and hyper-glycaemic states and this is the basis for the contraindication as the required treatment would be correction of the metabolic disturbance rather than immediate thrombolysis. Numerous observational studies have noted an association between hyperglycemia around stroke onset and worse clinical outcomes including higher rates of sICH and larger infarct volumes measured by MRI (Jauch et al. 2013). Hyperglycaemia or diabetes mellitus are included in some predictive stroke models (see section 6.3.5 on predictive outcome models). However, it can not be concluded that this association is causal in the absence of interventional randomised controlled study data.

Ongoing work may provide further information on the association between stroke, blood sugar levels and rt-PA therapy.

Implications for the marketing authorisation

From a regulatory point of view, any possibility of removing a contraindication would be dependent on the availability of sufficient evidence to demonstrate a positive balance of benefits and risks in the contraindicated population. The data currently available are not considered to be sufficient to lift the contraindications in patients with blood glucose < 50 or > 400 mg/dl (<2.8 or >22.2 mM), or with prior stroke and concomitant diabetes.

In addition to the contraindications discussed, the SmPC for rt-PA also provides the following warning statement in section 4.4:

“The therapeutic benefit is reduced in patients that had a prior stroke or in those with known uncontrolled diabetes, thus the benefit/risk ratio is considered less favourable, but still positive in these patients”

This statement is considered to be a reasonable reflection of the available data, which in general suggests that benefit may be less in these subgroups of patients.

7.1.6. Concomitant medication

Anticoagulants

A meta-analysis of 7 trials involving 4624 patients assessed the efficacy and safety of anticoagulants (unfractionated or low-molecular weight heparin or heparinoids) compared to aspirin or placebo when started within 48 h of acute cardioembolic stroke (Paciaroni et al. 2007). Alteplase was not administered in any of these studies. The use of anticoagulants was associated with: a nonsignificant reduction in recurrent stroke within 7 to 14 days (3% versus 4.9%, OR 0.68 [95% CI: 0.44-1.06, $p = 0.09$]); a significant increase in sICH (2.5% versus 0.7%, OR 2.89 [95% CI: 1.19-7.01, $p = 0.02$]); and a similar rate of death or disability at final follow-up (73.5% versus 73.8%, OR 1.01 [95% CI: 0.82-1.24, $p = 0.9$]).

Patients in the International Stroke Trial were given unfractionated heparin (5000 or 12,500 iu twice daily) or a combination of heparin and aspirin for 14 days starting within 48 h of stroke onset (International Stroke Trial Collaborative Group 1997). The level of anticoagulation was not monitored or adjusted. sICH was more common in heparin-treated groups and related to the severity of stroke, dose of heparin, and a short interval between stroke onset and treatment initiation (Bath et al. 2012). If oral anticoagulation is necessary for secondary prevention of cardioembolic stroke after ischaemic stroke then it has been proposed that it should be started as soon as the patient is neurologically stable and if repeat imaging confirms the absence of a large infarct or ICH. If a large infarct or haemorrhagic transformation is present then warfarin initiation should be delayed for 2 to 3 weeks (Paciaroni et al. 2007). Although this proposal does not specifically mention how to start anticoagulation after thrombolysis, it could be applied to post-thrombolysis patients given alteplase's short half life and minimal effects on systemic coagulation factors.

A recent Cochrane review of anticoagulants for acute ischaemic stroke assessed 24 trials involving 23,748 patients (Sandercock et al. 2015). The majority of patients were anticoagulated within 48 h of stroke onset and although early anticoagulation was associated with fewer recurrent ischaemic strokes (OR 0.76 [95% CI: 0.65-0.88], it was also associated with an increased risk of sICH (OR 2.55 [95% CI: 1.96-3.33] so overall there was no net benefit. Early therapeutic heparinisation for secondary prevention of cardioembolic strokes prolonged acute hospital stays with infrequent complications in an observational study involving 229 patients with ischaemic stroke or TIAs requiring anticoagulation (Audebert et al. 2008). There is insufficient data on the safety of full anticoagulation doses of heparin with alteplase for acute ischaemic stroke as heparin is rarely indicated for long-term use (Alvarez-Sabine et al. 2013).

Prabhakaran et al. (2010) determined if warfarin treated patients with an international normalised ratio (INR) <1.7 were at increased risk of sICH after receiving alteplase for acute ischaemic stroke in 107 consecutive patients with a median baseline NIHSS score of 14 treated at a median onset-to-treatment time of 140 minutes and with a median INR of 1.04 (range 0.82-1.61). Twelve patients were receiving warfarin therapy at baseline with a median INR of only 1.21 (IQR 1.11-1.47). The overall rate of sICH using the ECASS II definition was 6.5% but it was 30.8% in those receiving warfarin vs 3.2% in those who were not ($p = 0.004$). Baseline warfarin use was still strongly associated with sICH after adjustment for covariates including age, atrial fibrillation, stroke severity and INR. The authors acknowledge that their data is hypothesis generating only due to the low number of warfarin treated patients included.

However, Nogueira and Smith (2009) reported similar major sICH rates in patients with abnormal clotting (8.6% with INR >1.7 [$n=20$] or prolonged aPTT [$n=11$] or platelets <100,000 / μ l [$n=6$] vs 8.5% with controls, $n=270$) in a trial of mechanical thrombectomy. Major sICH was defined as a 4 or more point worsening of the NIHSS score within 24 h with any blood products identified on head CT scan or any ICH in which no further NIHSS scores were available beyond baseline and the patient died. A case of procedure-related minor subarachnoid haemorrhage was not considered a major sICH. De Marchis et al. (2011) confirmed these findings in their study of 714 patients treated with intra-arterial urokinase. The rates of sICH (7.1%, $n=28$, median INR 1.79 vs 6% for those with normal INRs, $n=686$; $p = 0.8$), an unfavourable outcome (mRS 3-6, 67.9% versus 50.9%; $p = 0.11$) and mortality (17.9% versus 21.6%; $p = 0.58$) were similar in patients receiving oral anticoagulants compared to those who were not taking them. The risk of ICH but not sICH (defined using ECASS II criteria) was increased in 12 patients on oral anticoagulants with increased baseline INRs of 1.2-1.7 receiving alteplase (Aggarwal et al. 2013).

A recent meta-analysis included 6 studies describing warfarin use at baseline prior to thrombolysis (Whiteley et al. 2012). Any warfarin use was not associated with an increased risk of ICH (OR 2.46 [95% CI: 0.92-6.59, $p = 0.07$]) although no analysis of ICH risk vs reported INR values at baseline was reported. Only 1 underpowered study assessed the risks of heparin after thrombolysis (OR 19.3 [0.2-99.0]).

The risks of direct thrombin and factor Xa inhibitors with alteplase have not been defined. Animal studies using stroke models have suggested that dabigatran pre-treatment in acute ischaemic stroke is safe, even in combination with alteplase (Pfeilschifter et al. 2012).

Concluding comments:

The current US stroke guidelines recommend that patients on warfarin with an INR >1.7 or a prothrombin time >15 secs should not be given intravenous alteplase within 3 h of stroke onset and that no patient receiving an oral anticoagulant should receive alteplase (regardless of INR value) within 3 to 4.5 h (Jauch et al. 2013). Heparin received within 48 h, resulting in abnormally elevated activated partial thromboplastin time (aPTT) greater than the upper limit of normal is also a contraindication to alteplase use within 3 h of stroke onset.

The National clinical stroke guideline recommends that initiation of anticoagulation (for atrial fibrillation) should be deferred until at least 14 days after onset for a disabling stroke and aspirin 300 mg daily should be used until this time; and that it should be deferred for an interval at the discretion of the prescriber, but for no longer than 14 days from onset of a non-disabling stroke (The Intercollegiate Working Party for Stroke 2012). It does not provide any recommendations on the appropriate use of alteplase in patients receiving oral anticoagulants. The ESO guidelines do not make any specific reference to the safety of thrombolysis in anticoagulated patients (2008).

Implications for the marketing authorisation

The SmPC of Actilyse lists “*patients receiving effective oral anticoagulant treatment and administration of heparin within the previous 48 hours and a thromboplastin time exceeding the upper limit of normal for laboratory*” as contraindications.

Section 4.2 states:

The safety and efficacy of this regimen with concomitant administration of heparin and acetylsalicylic acid within the first 24 hours of onset of the symptoms have not been sufficiently investigated. Administration of acetylsalicylic acid or intravenous heparin should be avoided in the first 24 hours after treatment with Actilyse. If heparin is required for other indications (e.g. prevention of deep vein thrombosis) the dose should not exceed 10,000 IU per day, administered subcutaneously.

Section 4.4 of the SmPC for alteplase states that:

The use of Actilyse may be considered when dosing or time since the last intake of anticoagulant treatment makes residual efficacy unlikely confirmed by appropriate test(s) of anticoagulant activity for the product(s) concerned showing no clinically relevant activity on the coagulation system (e.g. INR ≤ 1.3 for vitamin K antagonists or other relevant test(s) for other oral anticoagulants are within the respective upper limit of normal).

The available evidence regarding warfarin as a risk factor for alteplase-related ICH is inconsistent and based on limited data from interventional studies or small study sub-

groups. A meta-analysis of ICH risk on warfarin was reassuring but baseline INRs were not considered. The risk of ICH is increased in patients with ischaemic stroke who are not thrombolysed. There is even less evidence for the safety of therapeutic heparin when co-administered with alteplase. The SmPC wording concerning anticoagulation is pragmatic and acceptable given the lack of data but may result in delayed thrombolysis if an INR result is required in those patients on stable doses of warfarin with recent reliable low INR results.

Section 4.5 of the SmPC warns:

The risk of haemorrhage is increased if coumarine derivatives, oral anticoagulants, platelet aggregation inhibitors, unfractionated heparin or LMWH or active substances which interfere with coagulation are administered (before, during or within the first 24 hours after treatment with Actilyse).

Anticoagulation appears to increase the risk of ICH but important potential confounders include age, atrial fibrillation and cardioembolic stroke. However, there is no clear evidence for a 'safe' INR level so the current SmPC recommendations are acceptable. The normal INR range is usually considered to be 0.9-1.1 with an accuracy of ± 0.2 (Aggarwal et al. 2013). Routinely available clotting tests (PT and aPTT) do not specifically measure the pharmacodynamic effects of low molecular weight heparins, direct thrombin and direct factor Xa inhibitors but the existing SmPC wording covers this issue.

The use of antiplatelet glycoprotein IIb/IIIa receptor antagonists, direct thrombin inhibitors or a second thrombolytic agent (eg tenecteplase) as salvage therapy if intravenous alteplase is ineffective is considered experimental and is not discussed further (Smadja 2012)..

Antiplatelet drugs

Antiplatelet agents (mainly aspirin) have not been shown to be associated with haemorrhagic transformation when started within 48 h after ischaemic stroke onset in patients that have not received alteplase (Toni et al. 1996; Paciaroni et al. 2008; Alvarez-Sabin et al. 2013).

There is conflicting evidence on the risks of thrombolysis in patients who were receiving antiplatelet drugs at stroke onset. Preceding aspirin use was not associated with asymptomatic or symptomatic ICH during the first 36 h after treatment in a subgroup analysis of the NINDS trial involving a small number of thrombolysed patients (The NINDS t-PA Study Group 1997).

However, several studies have reported increased risks of alteplase in patients pretreated with antiplatelet drugs:

- a secondary analysis of ECASS II (Larrue et al. 2001) found that aspirin use pre-stroke was associated with a higher incidence of parenchymal haemorrhage (OR 1.26 [95% CI: 0.55-2.92, $p = 0.06$]) that was not statistically significant.
- an observational study noted that prior antiplatelet drug use (aspirin in 65 patients (73.0%), aspirin and dipyridamole in 22 (24.7%), dipyridamole monotherapy in 1 (1.1%), and clopidogrel monotherapy in 1 (1.1%)) was predictive of sICH (adj OR 5.96 [95% CI: 2.0-17.1], $p = 0.001$) (Uyttenboogaart et al. 2008)
- Cucchiara et al. (2009) showed an increased risk of sICH in thrombolysed patients on baseline single (adj OR 2.04 [95% CI: 1.07-3.87, $p = 0.03$]) and dual antiplatelet drugs (aspirin and clopidogrel) (adj OR 9.29 [95% CI: 3.28-26.32,

$p = 0.001$) in the placebo arms of the SAINT-I and SAINT-II trials (neuroprotectant trials).

- the 'Antiplatelet therapy in combination with Rt-PA Thrombolysis in Ischemic Stroke' (ARTIS) RCT found that intravenous aspirin 300 mg given within 90 minutes of commencing alteplase therapy produced an excessive number of sICHs (4.3% in aspirin group [n=322] versus 1.6% in the standard treatment group [n=320]; absolute difference 2.8% [95% CI: 0.2-5.4, $p = 0.04$]) with no evidence of benefit (Zinkstok et al. 2012). The majority of sICHs were observed within 36 h and both groups started oral antiplatelet therapy 24 h after alteplase.
- Whiteley et al. (2012) showed that patients receiving any antiplatelet agent had a significantly higher risk of sICH (OR 2.08 [95% CI: 1.46-2.97, $p < 0.001$]) in their meta-analysis using data from 15 studies.
- An analysis of the data of 11,865 patients in the SITS-ISTR reported that the combination of aspirin and clopidogrel prior to stroke was associated with an increased risk of sICH (ECASS II definition) compared with no antiplatelet therapy (OR 2.11 [95% CI: 1.29-3.45, $p = 0.003$]) after alteplase but there was no effect on the functional outcome or mortality rate (Diedler et al. 2010).
- A further analysis of the data from 31,627 patients in the SITS-ISTR gave adj ORs of 1.8 (95% CI: 1.5-2.1, $p < 0.001$) for prior aspirin monotherapy and 3.2 (95% CI: 1.9-5.2, $p < 0.001$) for the combination of aspirin and clopidogrel without any effect on clinical outcomes (Mazya et al. 2012). Prior clopidogrel monotherapy increased the risk of sICH following thrombolysis (n=30/560 [5%] with sICH vs n=1087/30166 [4%] with no sICH, $p = 0.03$) in the univariate analysis.
- A secondary sub-group analysis of the IST-3 study (Lindley et al. 2015) reported that treatment with antiplatelet drugs in the 48 h before alteplase was associated with an increased risk of: death within 7 days (adj OR 2.07 [95% CI: 1.30-3.26, $p = 0.042$, n=107 on antiplatelet drug + alteplase] vs n=59 on antiplatelet drug + control); sICH within 7 days (adj OR 13.26 [95% CI: 4.38-40.14, $p = 0.019$]). Functional outcome (adjusted ordinal analysis of the OHS) at 6 months was not significantly different after treatment with antiplatelet drugs in the 48 h before alteplase (OR 1.28 [95% CI: 0.98-1.67, $p = 0.781$]).

MAH's response

The MAH has provided summaries of 2 articles that report that antiplatelet drug pre-treatment may (Dorado et al. 2010) or may not (Bravo et al. 2008) increase the risk of alteplase-induced parenchymal haematoma. Pretreatment with acetyl salicylic acid is already listed as a contraindication in the current Company Core Data Sheet of Actilyse.

Concluding comments:

The UK National clinical stroke guideline states (The Intercollegiate Working Party for Stroke 2012):

All people presenting with acute stroke who have had the diagnosis of primary intracerebral haemorrhage excluded by brain imaging should, as soon as possible but certainly within 24 hours, be given:

- *an antiplatelet orally if they are not dysphagic*
- *an antiplatelet rectally or by enteral tube if they are dysphagic.*
- *Thereafter aspirin 300 mg should be continued until 2 weeks after the onset of stroke, at which time definitive long-term antithrombotic treatment should be initiated. People being discharged before 2 weeks can be started on long-term treatments earlier.*

Any person with acute ischaemic stroke who is allergic to or genuinely intolerant of aspirin should be given an alternative antiplatelet agent (eg clopidogrel).

The combination of aspirin and clopidogrel has been compared to clopidogrel monotherapy in patients with recent TIA or stroke (Diener et al 2004). The combination was not superior to monotherapy, with some evidence of increased side-effects, particularly bleeding. Nonetheless, this combination is still widely used particularly in the acute setting and after revascularisation procedures, though the evidence to support this practice is weak. There is evidence that even in short-term use the combination carries an increased risk of bleeding complications, particularly in aspirin-naive individuals (Geraghty et al 2010).

The ESO recommends aspirin (160-325 mg loading dose) within 48 h after ischaemic stroke (European Stroke Organization 2008) but also states that aspirin or other antithrombotic therapy should not be initiated within 24 h if thrombolysis is planned or given and the use of other antiplatelet agents (single or combined) is not recommended in acute stroke.

Aspirin irreversibly acetylates a homologous serine residue at position 530 in the cyclo-oxygenase 1 enzyme (COX-1) and inhibits platelet COX-1-dependent thromboxane A₂ formation to produce its anti-platelet effects. It takes roughly 8 to 12 days (the platelet turnover time) for the anti-platelet effects to resolve after stopping aspirin (Parker et al. 2005). The half life of clopidogrel is 6 h although it varies according to polymorphisms in the cytochrome P450 2C19 gene (ultrarapid, extensive, intermediate and poor metaboliser groups identified) (Plavix SmPC, 26 Feb 2015). Dipyridamole has a dominant half life of 2-3 h (Persantin SmPC, Feb 2015).

Implications for the marketing authorisation

Section 4.2 of the Actilyse SmPC states:

The safety and efficacy of this regimen with concomitant administration of heparin and acetylsalicylic acid within the first 24 hours of onset of the symptoms have not been sufficiently investigated. Administration of acetylsalicylic acid or intravenous heparin should be avoided in the first 24 hours after treatment with Actilyse.

Section 4.4 of the SmPC warns that:

- *patients pre-treated with acetyl salicylic acid (ASA) may have a greater risk of intracerebral haemorrhage, particularly if Actilyse treatment is delayed.*
- *Due to an increased haemorrhagic risk, treatment with platelet aggregation inhibitors should not be initiated within the first 24 hours following thrombolysis with alteplase*

Section 4.5 of the SmPC states:

The risk of haemorrhage is increased if coumarine derivatives, oral anticoagulants, platelet aggregation inhibitors, unfractionated heparin or LMWH or active substances

which interfere with coagulation are administered (before, during or within the first 24 hours after treatment with Actilyse) (see section 4.3).

The current SmPC wording appears to adequately describe the risk of ICH with antiplatelet drug pre-treatment and the recommendation that antiplatelet drugs should not be started within 24 h of alteplase is appropriate. However, the risk of sICH has been reported to be increased to a greater extent with combined aspirin and clopidogrel in observational studies and with dual antiplatelet therapy in a single clinical trial. The risk of sICH with combined aspirin and clopidogrel treatment appeared higher than with aspirin or clopidogrel monotherapy. Many studies have reported outcome data for a combined group of antiplatelet drugs but selective reporting of outcomes for aspirin, dipyridamole and clopidogrel mono- or dual therapy would be more useful to characterise this risk further.

Overall, this data does not suggest a need to alter the established section 4.2 and 4.4 warnings on not starting antiplatelet drugs for 24 h after alteplase therapy. The increased risk of sICH after alteplase in those receiving prior antiplatelet drug monotherapy is adequately described. However, the SmPC could be amended to warn of the risk of deleterious synergistic effects of dual antiplatelet therapy as the risks of alteplase therapy may outweigh any potential benefits in those receiving aspirin and clopidogrel if there are any additional adverse prognostic features (eg severe stroke, old age) (Diedler et al. 2010).

7.1.7. Seizure at onset of stroke

This contraindication was presumably put in place to avoid treatment in patients with stroke mimics, for example Todd paralysis. This condition may be difficult to distinguish from ischaemic stroke using CT scan and clinical examination. MR diffusion and perfusion-weighted images or angiography, perfusion CT or CT angiography can be used to confirm the diagnosis of acute ischaemic stroke.

Ischaemic stroke can also cause symptomatic seizures soon after onset (Labovitz et al. 2001).

Concluding comments:

As discussed in section 6.3.2, the available evidence suggests that treatment in patients with stroke mimics is sufficiently safe to justify rapid treatment of all patients with suspected stroke provided that haemorrhagic stroke is excluded.

7.1.8. Multiple contraindications

Frank et al. (2013) used the VISTA database to examine outcomes in sub-groups of patients with several different contraindications who were treated with rt-PA compared with those who were not treated with rt-PA. Data from trials of neuroprotectant agents carried out between 1998 and 2008 were used, excluding any trials that tested the effects of thrombolysis or any drug now known to influence outcome after stroke. A total of 9613 patients were included, of whom 8438 were enrolled in a country where treatment with rt-PA had been approved for use within 3 hours of symptom onset. 2755 out of the 8438 patients were thrombolysed according to their institutional practice. The data were searched for information on

contraindications for treatment, and where the information on a particular variable was absent the patient was excluded from the corresponding analysis. Patients could be included in more than one subgroup. The authors note that their data partially overlap with the data used by Mishra et al. 2010 and 2011 (patients with diabetes and prior stroke) and with Mishra et al. 2010 (very elderly patients).

The primary analyses were of day 90 mRS across the whole scale using the Cochran-Mantel-Haenszel (CMH) test, with adjustment for age and baseline NIHSS, followed by proportional odds logistic regression analysis to estimate the OR for a more favourable outcome. The OR and 95% CI for some of the different sub-groups, along with the corresponding CMH p values, were as follows:

Age >80 years: 1.40 [1.14-1.70], $n=1805$, CMH $p = 0.0002$

Combined history of prior stroke and diabetes: 1.50 [1.03–2.18], $n=672$, CMH $p =0.0262$

Prior single antiplatelet agent: 1.42 [1.19–1.70], $n=1626$, CMH $p =0.0001$

Oral anticoagulant and $INR \leq 1.7$: 2.20 [1.12–4.32], $n=157$, CMH $p =0.0192$

Baseline glucose >180: 1.50 [1.15–1.97], $n=879$ CMH $p =0.0019$

Baseline NIHSS >22: 1.57 [1.12–2.18], $n=620$, CMH $p =0.005$.

Other sub-groups found less favourable results, albeit with a trend to benefit for the subgroups with oral anticoagulant and for $INR >1.7$ (OR, 95%CI), for example:

Dual antiplatelets: 0.80 [0.45-1.42], $n=154$, CMH $p =0.5351$

Oral anticoagulant: 1.32 [0.83-2.10], $n=448$, CMH $p =0.2178$

$INR >1.7$: 1.21 [0.82-1.78], $n=335$, CMH $p =0.2398$

Baseline NIHSS <6: 0.97 [0.50-1.87], $n=381$, CMH $p =0.7615$

The authors also carried out dichotomised analyses using mRS 0-1 and 0-2. The results for some of the sub-groups from these analyses were less favourable than for the ordinal analyses, for example for mRS 0-1:

Age >80 years: OR 1.38 95% CI [0.99-1.93], $p =0.0576$

Combined history of prior stroke and diabetes: OR 1.38 [0.78-2.41], $p =0.2662$

Baseline NIHSS >22: OR 0.86 [0.35-2.12], $p =0.7441$

Paper 5 discussed the most appropriate endpoints and analyses of endpoints for trials in acute ischaemic stroke, and the use of ordinal/shift analyses was noted to introduce error due to the greater variability in scoring in the middle of the mRS range. Therefore the positive results in this study for rt-PA in older patients and those with a history of stroke and diabetes should be considered in the context of the non-significant results from the dichotomised analysis. However, for patients with baseline NIHSS >22, achievement of mRS 0-1 may be unfeasible and therefore an ordinal analysis in this situation may be more appropriate.

Results for frequency of sICH within 4 days after stroke were also provided for these subgroups. The overall frequency in thrombolysed patients was 4.4%, compared with 1.9% in those not treated with rt-PA. In patients >80 years of age, this number was increased to 7.5% and 2.3% respectively. In patients with prior stroke and diabetes, the frequency in thrombolysed patients was similar to the overall frequency in all thrombolysed patients (4.1%), compared with 2.2% in those not treated with rt-PA. As may be expected the frequency of sICH in patients taking single or dual

antiplatelet agents or oral anticoagulation was increased in thrombolysed patients, 6.3-8.5% versus control patients, 2.4-4.8%.

The authors acknowledge limitations of these analyses: that the data used were retrospective, observational data and therefore selection bias is inevitable, that the general standard of care may have differed in rt-PA treated patients and controls due to the average 2 year difference in time of enrolment, and duration of treatment on a stroke unit is not available. In addition, the delay between initiating rt-PA and enrolment in the VISTA trials was generally short, however some patients with contraindications who suffered complications may have been excluded from enrolment, and therefore these data may underestimate complication rate. By contrast, early improvers may also have been excluded which would have had the opposite effect.

The influence of selection bias on the results may be substantial. Treatment with rt-PA was not randomised in these trials, and therefore the treating physician has made a decision regarding whether a patient is suitable for treatment or not. The publication explains that each patient may contribute to more than one sub-group, and it is not possible to know whether patients treated with rt-PA might each have fewer characteristics constituting a contraindication than the control patients. This could be expected as a physician could be considered more likely to treat a patient with rt-PA who has only one characteristic that would be classed as a contraindication than a patient with two or three – it could therefore be expected that this would favour the results for rt-PA. Sub-group sizes are very small in many cases, this will further limit the interpretation of these results. Further to this, the paper has not corrected for the large number of multiple comparisons. Doing so would reduce the number of significant findings.

Concluding comments:

The findings from the VISTA database do not have any implications for the marketing authorisation.

7.2. Medication errors with rt-PA

The current definition of a medication error is “any unintended error in the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional (HCP), patient or consumer.” That is an error that could have been avoided through the provision of better training, clearer instructions or the introduction of additional measures to reduce the risk.

In line with this definition we have not considered thrombolysis in patients with contraindications to be “medication errors” but rather off-label use, whereby the decision to treat is a clinical one, based on a considered judgement of the individual circumstances ie it is an intentional act rather than inadvertent error.

The UK National Stroke Guidelines allow for consideration of the use of alteplase between 3 and 6 hours of known stroke symptom onset on an individual basis and also for its use in patients older than 80 years or with severe stroke - if treatment can be started within 3 hours of known symptom onset in the absence of intracerebral haemorrhage or other contraindications. The use of alteplase in such settings is therefore ‘endorsed’, even if outwith the strict terms of the marketing authorisation and for this reason will also not be considered to represent an error of prescribing or administration.

This section therefore focuses on any information provided in the alteplase licence that has been found to be responsible for unintentional errors in routine UK clinical practice.

Evidence for the occurrence of medication errors with alteplase in the UK

A number of data sources were explored to determine whether medication errors occur with the administration of alteplase in AIS and, if so, how frequently they occur and whether there is any data to suggest they are responsible for causing harm. These include information in the published literature, information from Boehringer Ingelheim, information spontaneous reports provided to the MHRA or the National Reporting and Learning System (NRLS) for NHS England and the information provided in the SmPC.

Published literature

A study on protocol adherence of rt-PA in a stroke centre in the US found that most errors related to either time to treatment or dosing (Uchino, 2010a). The safety and efficacy of time to treatment is considered extensively in papers 4, 5 and 5D. This section will therefore focus on dosing errors and, more specifically on the recommendation for weight-based dosing.

The recommended dose for rt-PA in stroke is 0.9 mg/kg. This dose is based on two dose finding studies. The first was an open label study to evaluate the safety of rt-PA given at successively higher doses in 74 patients with acute ischemic stroke (Brott 1992). In this study 7 doses of alteplase were administered within 90 minutes of onset of stroke according to the weight of the patient. Dose tiers ranged from 0.35 mg/kg to 1.08 mg/kg and the experience at each tier was reviewed before proceeding to a higher dose. The occurrence of no hematomas per group of six or more consecutive patients supported moving to a higher dose tier whilst two major bleeding complications per group of six consecutive patients supported decreasing the dose by one dose tier. The second study, an extension of the first, looked at the administration of rt-PA at doses of 0.6 mg/kg (n=8), 0.85 mg/kg (n=6), and 0.95 mg/kg (n=6) in patients whose symptoms had started 91-180 minutes before treatment (Haley, 1992). The same criteria for changing dose were applied. A total of 5 symptomatic intracerebral haemorrhages (ICH) occurred in the two studies combined, of which 4 were in patients who received a dose of 0.95 mg/kg and 1 was in a patient who received a dose of 0.85 mg/kg. No ICHs occurred at any dose <0.85 mg/kg. On the basis of these data the investigators concluded that the safety and efficacy of a 0.85mg/kg dose should undergo further testing in future randomized, placebo-controlled trials.

A dose of 0.9 mg/kg was selected by the NINDS trialists who reasoned that the dose-finding studies had shown that doses of less than 0.95 mg of rt-PA per kilogram of body weight were relatively safe and resulted in early neurologic improvement in a substantial proportion of patients.

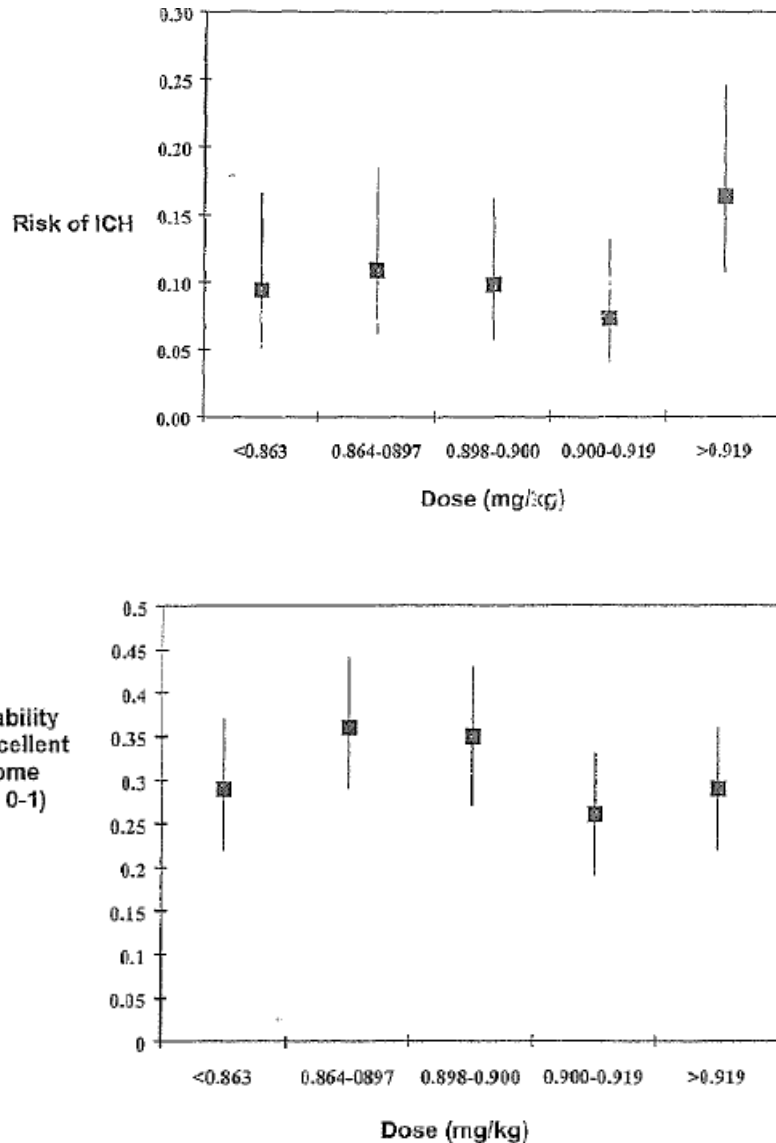
Clinical consequences of overdosing

In the dose finding study by Brott the occurrence of ICH was related significantly to the total dose of rt-PA (p=0.045) and no other clinical variable. The occurrence of major improvement at 2 hours was not related to dose (p=0.76).

In keeping with these findings the Multicentre rt-PA Acute Stroke Survey, a retrospective review of medical charts from treating hospitals in 669 patients with acute stroke from the US, Canada and Germany, identified 41 sICHs; a categorical analysis, adjusted for potential confounders for intracerebral bleeding, found the risk of ICH to be highest in patients who had received the highest quintile dose of rt-PA (>0.919mg/kg) versus the four lower quintile doses (16.5% vs 9.3%, adjusted OR

1.93, 1.08-3.44, $p=0.25$) (Messe, 2004). Conversely there was no relationship between good outcome and dose.

Figure 15: Risk for each quintile of actual rt-PA dose (mg/kg) of any ICH, adjusted for age, baseline NIHSS and major early CT changes, and probability of excellent outcome (mRS 0-1) at discharge (Messe et al. 2004).

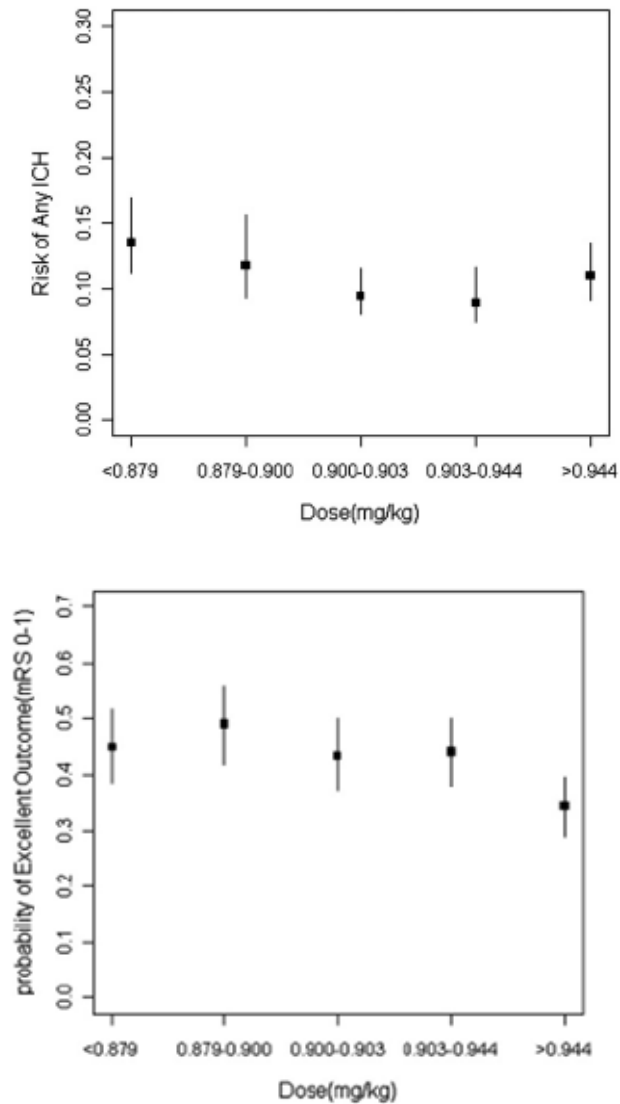


Similarly in a 4 year retrospective chart review in Canada, 4 of 13 (31%) patients treated with ≥ 1.0 mg/kg rt-PA developed ICH compared with 21 of 129 (16%) who received < 1.0 mg/kg rt-PA (difference not statistically significant); overdosed patients were less likely to experience good functional outcome (mRS score 0-2; $p=0.009$), regardless of whether they developed ICH (Sahlas 2014).

By contrast no increase in the risk of ICH was observed in a post-hoc re-analysis of NINDS (n=308). 11 patients (3.6%) received $\geq 10\%$ more than the planned dose and 33 patients experienced an ICH within 36 hours of initiation of rt-PA. The adjusted odds ratio for risk of ICH in overdosed patients vs others was not increased (OR

0.44, 0.12-1.71; $p=0.24$, Messe, 2011). Similarly there was no association between the likelihood of good outcome and actual dose.

Figure 16: Risk of any ICH for each quintile of actual rt-PA dose (mg/kg), adjusted for age, baseline NIHSS and major early CT changes and probability of excellent outcome (mRS 0-1), adjusted for age, baseline NIHSS score and time to treatment (Messe et al. 2011).



Clinical consequences of underdosing

Similarly mixed findings have been observed when patients have received less than the recommended dose of rt-PA. In the multicentre survey study in acute stroke by Messe (2004) no relationship was observed between dose and risk of ICH or the probability of a good recovery, when comparing the lowest quintile dose (<0.879mg/kg, median 0.84mg/kg) of actual dose to the 4 higher quintiles (median dose 0.90 mg/kg; OR 1.08, 0.55-2.09; $p=0.83$). See also figure XXX above. In patients who were >100kg ($n=59$, 8%) and therefore received a fixed dose of 90mg no association with ICH or good recovery was observed.

A prospective observational study in 109 patients in Germany (WAIST) found a trend towards less favourable outcome (mRS 2-6, OR 4.16, 0.78-22.23; $p=0.096$) and a significant association with death and dependency (mRS 3-6, OR 5.87, 1.26-27.34; $p=0.024$) in patients who were underdosed (Breuer 2010). The authors concluded that underestimating a patient's weight may result in insufficient or ineffective dosing; however it should be noted that the 95% confidence intervals around the relative risk estimates are very wide and reflect the very small numbers of patients.

In a post hoc analysis of the NINDS data Messe and colleagues found no association between the likelihood of good outcome (mRS 0-1 at 3 months, $n=132$) and dose, including in those who were underdosed by $>10\%$ (see figure XXX above). However, another post hoc analysis of NINDS (Lou 2009) which asked whether having a capped dose of 90mg disadvantaged patients over 100 kg ($n=20$ rt-PA treated patients), identified weight $>100\text{kg}$ as a predictor of worse outcome at 3 months relative to placebo patients ($n=32$, OR 5.76; $p = 0.017$) and neurological deterioration at 7-10 days (OR = 3.4; $p = 0.07$) after t-PA.

Comment on the data:

Since none of these studies have been powered to address the question of dose and outcome, and many have been post hoc analyses, the relationship between clinical impact of rt-PA dose, optimal neurological outcome and minimal ICH risk remains unclear.

The relationship between alteplase dose and worse clinical outcomes that has been observed in some studies was evaluated in a double-blind, double-dummy trial in which 16,949 patients with ST-segment elevation myocardial infarction (ASSENT-2 trial) and were assigned to either a bolus of tenecteplase (with alteplase placebo bolus plus infusion) or a bolus of alteplase (with tenecteplase placebo plus infusion (Mehta 2005). Thirty-day mortality was higher in patients who received an overdose (9.8%) or underdose (19.5%) of alteplase compared with those who received a correct dose (5.4%). However, the same pattern was present in patients who received an alteplase placebo (10.0% for overdose, 23.5% for underdose, and 5.4% for correct dose). Similar patterns were seen for in-hospital intracranial haemorrhage and major bleeding. The higher rates of adverse outcomes with incorrect dosing were largely accounted for by adjusting for baseline characteristics. The authors conclude that it is therefore possible that at least some of the previous observations for increased harm with higher doses of rt-PA could be explained by residual confounding and that there may be reasons relating to the health of the patient that results in their receiving more than the recommended dose of alteplase.

As weight was not measured accurately in the pivotal NINDS trial which observed an overall positive result this would suggest that some margin of error for weight-based dosing is built into the recommended authorised dose. Nevertheless, since it is entirely plausible that inaccurate dosing of rt-PA could have potentially serious clinical consequences any simple measures that can be taken to reduce the chance of dosing error and maximise the balance of benefits and risks would seem important.

Weighing acute stroke patients

It is universally acknowledged that weighing acute stroke patients who are eligible for thrombolysis is challenging for a number of reasons including the:

- narrow time window for treatment

- lack of suitable weighing instruments, particularly for supine and/or immobile patient
- inability to easily weigh patients with severe motor symptoms
- inability to obtain an estimate from patients unable to communicate

As a result, patients not weighed on admission generally tend to be those with the most severe stroke (Sahlas 2014) and patients' weight is commonly estimated. In some cases family, friends or carers are available to supply this information but in many cases the healthcare team is required to make this judgement.

Although various anthropomorphic ways of estimating weight have been devised to circumvent this problem, in many cases these have been found to be equally challenging in a hyper-acute care environment with supine and immobile patients.

Accuracy of weight estimation

The accuracy of weight estimation in the NINDS randomized trial (>10% error in 15% of patients, Messe, 2011) was similar to that observed in the Multicentre rt-PA Acute Stroke Survey (>10% error in 12% of patients Messe 2004) (table 11).

Errors in weight estimation giving rise to actual dosing errors of > 10% varied from 6% in NINDS (Messe 2011) to 35% in a study in which medical charts were reviewed in 16 acute care hospitals in Connecticut, US between 1996-1998 (Bravata, 2002).

Table 11: Errors in weight estimation and rt-PA dosing in published studies

Authors / date	Study	>10% weight error % (n)	>10% dose error % (n)
Bravata 2002	Retrospective review of medical records. 16 acute care hospitals US, n=63	-	35 (22)
Messe 2004	Post hoc analysis and retrospective chart review of the Multicentre rt-PA Acute Stroke Survey in US, Canada and Germany, n=710	12 (86)	-
Breuer 2010	Weight Approximation in Stroke before Thrombolysis (WAIST) prospective observational study in Germany n=109	-	27 (29)
Messe 2011	Re-analysis of NINDS data, n=308	15 (46)	6 (17)
Sahlas 2014	Retrospective chart review in Canada, n=140	-	21 (29)

While these studies give some indication of the degree to which weight-based dosing is subject to error, the generalizability of the findings of any individual study to the situation in the UK is doubtful due to the differences in which stroke care is organised

in the different countries, the change in practice over time as experience with using rt-PA has grown etc. Even within the UK, each centre is likely to have different ways of estimating weight and dose. Unfortunately the Sentinel Stroke National Audit Programme (SSNAP) does not include information on the accuracy of dosing or weight estimation and it could be useful to collect such data in the future.

Assessment of weight by HCPs, family/carers and patients

One study of weight estimation by 11 physicians, 26 nurses and 117 patients in emergency departments in Canada identified an error of 3% by patients and 8% by both nurses and physicians (Fernandes 1999). Estimates were out by more than 15% by 11% of nurses, 16% of physicians and 3% of patients. However, it is possible that older patients are worse at estimating their own weight, with 20% misreporting their weight by at least 10lbs in another study (Vailas 1998).

In a similar large prospective observational study conducted in Australia the weight of 1137 supine patients was estimated by physicians, nurses and patients in an emergency room setting. Broadly consistent with Fernandes, the average error was 4% for patients, 8% for nurses and 11% for physicians (Menon 2005). Estimates were inaccurate by >10% for 9% of patients, 22% of nurses and 41% of physicians.

In the German observation study (WAIST) the body weight of 109 patients was estimated by 2 physicians, 2 emergency nurses, a neuroradiological technician, the patient and, where possible, their relatives (Breuer 2010). Patients were then weighed within 24 hours of rt-PA. Around 50% of patients were able to provide an estimate of their weight and where this was not possible relatives provided the information in a further 20% of cases. Estimation errors ranged from 21% for patients, to 38% for treating physicians and 42% for emergency nurses. Actual dosing was based on a consensus view or according to a known body weight and gave rise to dosing errors of >10% in 29 patients (29%) of which the majority (17%) were overdoses.

In a UK study to compare weight estimation of 30 different stroke patients by 30 doctors, 33 nurses and 33 medical students half of the 898 weight estimations were within 10% of the actual weight (Pintilie et al. 2012). Although the difference in weight estimation between the three groups of HCP was not statistically significant, amongst HCPs nurses were the best estimators of weight followed by medical students then doctors. In general weight was more commonly overestimated in lighter patients and underestimated in heavier patients. This study also found that patients provided the most accurate estimates.

Conclusion on weight based dosing

Dosing recommendations are based on limited data which suggest that rt-PA has a relatively narrow therapeutic window (Brott 1992, Haley 1993). Although the NINDS pivotal trial used weight estimation rather than actual weight to calculate rt-PA dose, indicating that some margin of error is already built into the dosing recommendations, the plausibility for a dose effect and the presence of confirmatory findings albeit from a few small studies, suggests that it is nevertheless important to try and minimise the potential for inaccurate dosing.

Thrombolytic medicines may be particularly susceptible to dosing errors given that they often involve multistep regimens under substantial time pressure and patients who have suffered a stroke are often physically difficult to weigh or unable to communicate their weight.

Determining the weight of a stroke patient in the emergency setting is a challenging and unavoidable part of administering rt-PA. Results from arguably one of the most complete and accurate datasets (NINDS) suggests that weight estimation is an acceptable practice that does not have a major impact on the benefit or risk of thrombolysis. Nevertheless it is possible that the degree of variation in weight and dosing estimates observed in this randomized study under controlled conditions underestimates the degree to which dosing errors occur during routine clinical practice.

The clinical consequences of using estimated as opposed to actual weight for calculating rt-PA dose remain unclear but it is important to consider that overdosing may lead to an increased risk of ICH and underdosing may potentially lead to a reduction in effectiveness. Although the accuracy of dosing could in theory be improved by weighing patients prior to calculation of the required dose, in an acute medical emergency it is unclear how feasible any recommendation to mandate weighing would be and, perhaps in recognition of this, the national guidelines are silent.

The limited data that are available in the acute stroke setting suggest that best practice would be to ensure that:

- stroke facilities have access to functioning weighing equipment that are suitable for supine patients and provide a rapid assessment of weight
- in the event that weighing the patient is not possible those who are not aphasic or obtunded should be asked their weight; where the patient is not capable of providing their weight, estimations should ideally be sought from family or carers; where this is not possible the consensus view of more than one healthcare professional should be used.
- all weights should be recorded in kg

Boehringer Ingelheim response document September 2014

The MAH was asked for evidence relating to harm in clinical practice including the impact on outcome of reconstitution mistakes and other medication errors. The MAH states that it screened the available published literature in their company literature database (which is maintained on a continuous basis for all their products) up to 10th September 2014.

The MAH identified 8 publications relating to administration error. These have been reviewed in section 6.2.1.1 above. On this basis the MAH concludes that:

“The reliability of different methods of body weight determination is investigated. The risk associated with incorrect dosing remains controversial, dosing errors did not have a major impact on the risk of intracerebral haemorrhage.”

Although the MAH has provided a limited and uncritical review of the published literature their conclusion is supported by the assessor’s own review. Nevertheless, it does not mean that further measures cannot be taken to try and minimise errors.

Reports to the MHRA or the National Reporting and Learning System (NRLS), NHS England (24 February 2015)

MHRA

The MHRA has received only one Yellow Card report of medication error in association with alteplase. This concerned a [redacted] year old [redacted] patient, who was reported to have presented with signs and symptoms compatible with diagnosis of stroke (NIHSS 24). [redacted] was at 1hr 50mins at time of presentation and was treated with rt-PA for stroke thrombolysis. The patient weighs 68kg but rt-PA dose was calculated on a weight estimation of 87.8kg and so [redacted] actually received 1.16mg/kg. The patient initially improved after infusion and after 6 hours was able to talk. However, at 12 hours after treatment [redacted] developed intracerebral bleed with oedema and died 4 days later. [redacted] was also reported to have had "haemorrhagic convulsion" after the infusion. The overdose was judged to be medically significant. Patient had a past history of AF, myocardial infarction, type II diabetes but concomitant medications were not reported. The reporter's causality assessment between administration of Actilyse and the event "haemorrhagic convulsion" was reported as related but they assessed that there was no causal relationship between administration of Actilyse and the intracerebral bleed with oedema and midline shift and that the patient was high risk prior to the Actilyse treatment.

National Reporting and Learning System (NRLS)

The NRLS is a voluntary reporting tool that captures, analyses and feeds back patient safety incident reports to the NHS, providing an opportunity to reduce the risk of future incidents through learning.

We asked NHS England to query the NRLS database to identify any reports of medication error relating to the prescribing, dispensing, dilution, administration (dose/route/timing/speed) of rt-PA. The NRLS database was searched for the period 1st January 2014 to 31st January 2015 using the following strategy:

% alteplase % OR

% actilyse % OR

% rt-pa % OR

% rtpa %

It was not possible to identify only those reports relating to the use of rt-PA in acute stroke as many did not provide details of the indication; however, many of the issues reported were general and could be thought to apply to all indications.

A total of 64 reports documenting a variety of errors were identified for the last year. In 6 of these, the error related to a different drug (and alteplase was simply mentioned in the text) and in a number of others a breach of hospital procedures was reported that was not alteplase-specific. Many of the remaining cases described a lack of supply within the hospital and delays in treating patients, errors in storage conditions, infusion pump failures and errors in infusion rates, and unclear labelling of vials and dilution bags.

However, a number of reports describe a complete lack of knowledge by the ancillary staff of the treatment and/or confusion caused by its various names ie. Alteplase, rt-PA, TPA, Actilyse etc. Furthermore, very few, if any, of the staff mentioned in the reports had any knowledge of the correct dose or infusion rate of rt-PA to use in the various indications, with the subsequent errors resulting in the patient receiving the wrong dose or in treatment being delayed. Although these reports relate to a self-

selecting and therefore skewed sample they make it clear that many of the centres had no written guidance on alteplase dosing and no idea where to find such details. None refer to the BNF, which includes all rt-PA infusion details, and none refer to the SmPC.

Severe harm to the patient as a result of the error was considered in only one case in which a patient received rt-PA for PE post hernia repair with bowel resection, despite rt-PA being contraindicated for three weeks following surgery. The patient went on to develop a significant liver haematoma with retroperitoneal extension.

It is not clear if the documented confusion surrounding alteplase thrombolysis is typical of stroke units or even most hospitals, where it would be hoped that protocols for the administration of rt-PA would be in place and staff would have a far greater level of experience.

No reports concerning the treatment of stroke mention weighing or estimating the weight of the patient and none describe errors relating to underdosing or overdosing but, given the general lack of clarity over the administration of rt-PA dosing, it is possible that AIS patients treated in non-specialist units could receive a dose that is not appropriate and may not be based on weight.

Concluding comment

The provision of clear instructions for dilution and administration for thrombolysis is advisable within all hospitals that could potentially treat acute ischaemic stroke with rt-PA

7.3. Potential impact of emerging data on stroke diagnosis and treatment on the alteplase marketing authorisation

In recognition of the advances being made in stroke diagnosis and treatment we have also looked to see whether any new data provide sufficient evidence to support an update to the SmPC. In particular we have reviewed evidence relating to stroke subtype, stroke mimics, body temperature and radiological signs. We also provide a high level overview of prognostic stroke models.

7.3.1. Stroke subtype

Stroke is a heterogeneous disease with more than 150 known causes. Most stroke registries have failed to identify a definite cause in 25-39% of patients ('cryptogenic strokes'), depending on the quality, completeness, and rapidity of the workup (Amarenco et al. 2009a). Subtyping ischaemic stroke can have different purposes such as characterising patients in a clinical trial; selecting appropriate treatments in clinical practice and predicting outcomes. The effectiveness and safety of alteplase in small vessel disease, including lacunar stroke, is controversial as thrombolysis may not be clearly demonstrated, lacunar strokes are considered the most benign of ischaemic stroke subtypes and small vessel disease may be a risk factor for thrombolysis-related ICH (Pantoni et al. 2014).

A precise classification scheme requires the integration of clinical features with the results of diagnostic investigations by an experienced stroke physician. It should

identify the most likely cause(s) and incorporate mixed phenotypes such as co-existing small and large-vessel ischaemic disease.

The National stroke clinical guidelines do not specify the use of stroke classification schemes for the acute management of ischaemic stroke (The Intercollegiate Working Party for Stroke 2012) and the Sentinel Stroke National Audit Programme (SSNAP) does not present outcome data according to ischaemic stroke subtypes. However, a number of stroke classification schemes have been used in prognostic and therapeutic outcome studies so the current stroke classification systems will be briefly described along with relevant data from studies involving alteplase.

Stroke Classification Systems

Oxfordshire Community Stroke Project Subtype Classification (OCSP)

The OCSP classification was originally developed to characterise patients in a population-based epidemiological study using clinical findings alone or in combination with computed tomography (CT) imaging results (table 12; Bamford et al. 1991).

Table 12: The Oxfordshire Community Stroke Project (OCSP) classification (Bamford et al. 1991)

Type of infarct	Diagnosis
Cerebral infarction	Patients had a definite cerebral infarct if: a) a CT scan performed within 28 days of symptom onset shows an area of low attenuation, no relevant abnormality, or an area of irregular high attenuation within a larger area of low attenuation (i.e. an area of haemorrhagic infarction) <i>or</i> b) a necropsy examination shows an area of cerebral infarction (pale or haemorrhagic) in a region compatible with the clinical signs and symptoms.
Lacunar infarct (LACI)	One of the 4 classic clinical lacunar syndromes*. Patients with faciobrachial or brachiorocral deficits are included, but more restricted deficits are not.
Total anterior circulation infarct (TACI)	Combination of new higher cerebral dysfunction (eg dysphasia, dyscalculia, visuospatial disorders), homonymous visual field defect, and ipsilateral motor and/or sensory deficit of at least 2 areas of the face, arm, and leg. If the conscious level is impaired and formal testing of higher cerebral function or the visual fields is not possible, a deficit is assumed.
Partial anterior circulation infarct (PACI)	Only 2 of the 3 components of the TACI syndrome, with higher dysfunction alone, or with a motor/sensory deficit more restricted than those classified as LACI (e.g. confined to 1 limb, or to the face and hand but not the whole arm).
Posterior circulation infarct (POCI)	Any of the following: ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit, bilateral motor and/or sensory deficit, disorder of conjugate eye movement, cerebellar dysfunction without ipsilateral long-tract deficit (i.e. ataxic hemiparesis), or isolated homonymous visual field defect.

Key: *=pure motor or sensory stroke, sensorimotor stroke or ataxic hemiparesis.

It can predict the size and site of cerebral infarction on computed tomography (CT) with positive predictive values ranging from 0.63 for small subcortical infarcts to 0.94 for large cortical infarcts (Wardlaw et al. 1996). The baseline clinical findings and CT

results for the first 510 patients in the Third International Stroke Trial (IST-3) were assessed within 6 h of stroke onset and the site and size of ischaemic change on the CT scan was consistent with the clinical syndrome in 79% of patients with total anterior circulation infarcts, 37% with partial anterior circulation infarcts, 2% with lacunar infarcts and 14% with posterior circulation infarcts. The OCSF correlated well with the pattern of ischaemic change on hyperacute CT imaging for all stroke subtypes except lacunar syndromes (Kobayashi et al. 2009). Advances in neuroradiological techniques and neuropathology have resulted in many stroke classifications describing aetiological subtypes. The most important schemes used in clinical trials are the following: Trial Org 10172 in Acute Stroke (TOAST) and its modification, the Causative Classification System (CCS); Atherosclerosis, Small-vessel disease, Cardiac source, Other cause (ASCO); and the Chinese Ischaemic Stroke Classification (CISS) (table 13).

Other classification schemes

Many other classification schemes have been proposed but not widely adopted such as: the Lausanne Stroke Registry which includes patients with intracranial arterial stenosis <50% or plaques with at least 2 risk factors in the atherosclerosis with stenosis group (Bogousslavsky et al. 1988); the Génétique de l'Infarctus Cérébral (GENIC) classification which included patients with carotid stenosis >30% in their atherothrombotic group (Touboul et al. 2000); the Subtypes of Ischemic Stroke Classification Scheme (SPARKLE) that assesses carotid plaque burden rather than stenosis to reduce the proportion of patients with undetermined causes of stroke (Bogiatzi et al. 2014); and schemes or variants proposed for Asian populations (Kim and Kim 2014).

Stroke subtyping in clinical trials of alteplase

The recent Cochrane review of thrombolysis for acute ischaemic stroke reported that 7 clinical trials of alteplase randomised all types of ischaemic stroke (cortical, lacunar and posterior circulation) (Clark et al. 1999 and 2000; Hacke et al. 2008; Haley et al. 1993; The IST-3 Collaborative Group 2012; The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995; Wang et al. 2003 [in Chinese]) and that three trials included only participants with symptoms of hemispheric cortical ischaemia (Hacke et al. 1995 and 1998; Davis et al. 2008). Patients were selected on clinical criteria and baseline CT findings (Wardlaw et al. 2014).

The relevant inclusion and exclusion criteria and relevant reported outcome data for these studies are listed in table 14.

Table 13: Characteristics of major aetiological classification schemes for ischaemic stroke (taken and modified from Chen et al. 2012).

	TOAST (Adams et al. 1993)	CCS (Ay et al. 2007)	ASCO (Amarenco et al. 2009b)	CISS (Gao et al. 2011)
Type of system	Causal	Causal and phenotypic	Phenotypic	Causal and phenotypic
Major subtypes	<ul style="list-style-type: none"> • Large artery atherosclerosis • Cardioembolism • Small vessel occlusion (lacune) • Other determined aetiology • Undetermined aetiology 	<ul style="list-style-type: none"> • Supra-aortic large artery atherosclerosis • Cardio-aortic embolism • Small artery occlusion • Other causes • Undetermined causes 	<ul style="list-style-type: none"> • Atherosclerosis • Small vessel disease • Cardioembolism • Other causes • (D – for dissection Amarenco et al. 2013) 	<ul style="list-style-type: none"> • Large artery atherosclerosis • Cardiogenic stroke • Penetrating artery disease • Other aetiologies • Undetermined aetiology
Advantages	<p>Simple and convenient to use</p> <p>Validated by independent groups</p> <p>Predicts prognosis and risk of stroke recurrence</p> <p>Widely accepted</p>	<p>Cardioembolism stratified into high- and low-risk groups</p> <p>Excellent reliability</p> <p>Rules and criteria are evidence-based</p> <p>Fewer 'undetermined' cases</p>	<p>Levels of certainty defined by investigation results</p> <p>Clear criteria to exclude a stroke aetiology</p> <p>Noncausative factors incorporated into definitions</p>	<p>Includes aetiology and mechanisms</p> <p>Includes penetrating artery disease</p> <p>Large artery atherosclerosis contains 4 subtypes</p>
Disadvantages	<p>Moderate inter-rater reliability</p> <p>High prevalence of 'undetermined' aetiology</p> <p>Does not incorporate advances in imaging</p> <p>Aortic atherosclerosis not included</p>	<p>Incorporates results of modern diagnostic techniques</p> <p>Aortic arch atherosclerosis classified as cardioembolic</p> <p>Numerous phenotypic subtypes (n=96)</p> <p>Based on evidence from diverse studies</p>	<p>Reliability and validity not established</p> <p>Restrictive definitions for atherosclerosis and small vessel disease</p> <p>Excessive number of phenotypic subtypes</p> <p>Incorporates results of modern diagnostic techniques</p>	<p>Reliability and validity not established</p> <p>Incorporates results of modern diagnostic techniques</p> <p>Identification of penetrating artery disease may require high resolution MRA</p>

Key: ASCO=Atherosclerosis, Small vessel disease, Cardiac causes, Other uncommon causes; CCS=Causative Classification of Stroke System; CISS= Chinese Ischaemic Stroke Subclassification; MRA=Magnetic Resonance Angiography; TOAST=Trial of Org 10172 in Acute Stroke Treatment.

Table 15 shows outcomes at 3 months for the NINDS study according to the classification of the stroke subtype at baseline (The NINDS rt-PA Stroke Study Group 1995). However, this study was inadequately powered to detect clinically important subgroup or treatment interaction effects (Ingall et al. 2004).

Table 15: Outcomes at 3 months according to the classification of the stroke subtype at baseline (The NINDS rt-PA Stroke Study Group 1995).

Stroke subtype*	Alteplase	Placebo
	% with favourable outcome [†]	% with favourable outcome [†]
Small-vessel occlusive	n =51	n =30
BI	75	50
mRS	63	40
GOS	63	43
NIHSS	47	33
Large-vessel occlusive	n =117	n =135
BI	49	36
mRS	40	22
GOS	45	28
NIHSS	33	18
Cardioembolic	n =136	n =137
BI	46	37
mRS	38	28
GOS	39	31
NIHSS	29	20

Key: BI=Barthel Index; GOS=Glasgow Outcome Scale; mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale score *Eighteen patients (2.9 percent) with other stroke subtypes were excluded from the analysis; † Scores of 95 or 100 on the Barthel index, ≤1 on the NIHSS and modified Rankin scale, and 1 on the Glasgow outcome scale were considered to indicate a favourable outcome.

Table 14: Relevant inclusion and exclusion criteria and outcome data from RCTs of alteplase according to stroke subtypes

Clinical Trial	Relevant inclusion/exclusion criteria	Results
<i>All stroke subtypes included</i>		
Haley et al. 1993	<p>Ischemic stroke subtype classified at 7 to 10 days using clinical features and CT scan results:</p> <ul style="list-style-type: none"> • Large-vessel atherosclerotic and atheroembolic infarcts distinguished angiographically and by CT topography; • Cardioembolic strokes associated with known cardiac sources • Lacunar strokes diagnosed using classic clinical criteria plus small deep infarct on follow-up CT scanning. <p>Patients with pure sensory loss or ataxia were excluded</p>	<p>Stroke subtypes included:</p> <ul style="list-style-type: none"> • Large-vessel atheroembolic infarct (alteplase, n=4; placebo, n= 5) • Large-vessel atherothrombotic infarct (alteplase, n=3; placebo, n= 1) • Cardioembolic infarct (alteplase, n=5; placebo, n= 4) • Lacunar infarct (alteplase, n=2; placebo, n= 2) • Mechanism uncertain (placebo, n= 1) <p>26 carotid territory and 1 posterior cerebral artery infarcts.</p> <p>No analysis of outcome data by stroke subtype due to small numbers, baseline differences in stroke severity and use of heparin.</p>
NINDS 1995	<p>Ischaemic stroke subtype classified at baseline using clinical features and CT scan findings.</p> <p>Patients with isolated dysarthria, ataxia, facial weakness or sensory loss were excluded.</p>	<p>Stroke subtypes included:</p> <ul style="list-style-type: none"> • Small-vessel occlusive infarcts (alteplase, n=33; placebo, n= 20) • Cardioembolic infarcts (alteplase, n=87; placebo, n= 88) • Large-vessel occlusive infarcts (alteplase, n=74; placebo, n= 87) • Other infarcts (alteplase, n=5; placebo, n= 6). <p>Equal efficacy for alteplase for all stroke subtypes across all outcome measures at three months (table 15).</p>

Clinical Trial	Relevant inclusion/exclusion criteria	Results
ATLANTIS A (Clark et al. 2000) ATLANTIS B (Clark et al. 1999)	Ischaemic stroke diagnosed at baseline using clinical features and CT scan findings. Included: clinical diagnosis of stroke causing a measurable neurological deficit (defined as impairment of language, motor function, cognition, gaze, or vision or as neglect). Excluded: <ul style="list-style-type: none"> • coma, fixed eye deviation or complete hemiplegia • CT scan showing: <ul style="list-style-type: none"> ○ evidence of significant mass effect with midline shift ○ signs of cerebral ischaemia in more than a third of the MCA territory (ATLANTIS B only) 	No outcome data based on stroke subtypes was presented.
Wang et al. 2003	NIHSS not defined. Patients with low-density lesions on CT scan were excluded (Wardlaw et al. 2014)	No outcome data based on stroke subtypes was presented (Wardlaw et al. 2014)
ECASS III (Hacke et al. 2008)	Ischaemic stroke diagnosed at baseline using clinical features and imaging. Excluded: signs of major ischaemic infarction involving more than a third of the MCA territory on a CT or MR scan.	No outcome data based on stroke subtypes was presented.
IST-3 (The IST-3 Collaborative Group 2012)	This study included patients with symptoms and signs of clinically definite acute stroke of mild, moderate or severe severity who satisfied the uncertainty principle (Sandercock et al. 2008).	See primary outcome results at 6 months by stroke subtype in table 16. Analyses of the effect of treatment at six months among all those allocated alteplase versus those allocated control subdivided by the clinical stroke syndrome defined by the OCSP classification was a pre-planned subgroup assessment (table 16). The primary outcome measure was not statistically different between the various stroke subtypes. Risks of alteplase according to stroke subtypes not presented but the clinical

Clinical Trial	Relevant inclusion/exclusion criteria	Results
IST-3 (IST-3 Collaborative Group 2012)		utility of 5 prognostic models to predict ICH following alteplase has been presented in abstract form. None of the prognostic models assessed incorporated stroke subtype data (Whiteley et al. 2013).
<i>Only patients with hemispheric infarcts included</i>		
ECASS (Hacke et al. 1995)	<p>Patients with a moderate to severe hemispheric stroke syndrome (defined as moderate to high-grade hemiparesis, sensory disturbance, dysarthria or nonfluent dysphasia, and occasionally hemianopia) were included if there were none or minor ischaemic changes on the baseline CT scan.</p> <p>Those with hemiplegia and impaired consciousness and/or forced head and eye deviation were excluded. Patients with major early infarct signs such as diffuse swelling of the affected hemisphere, parenchymal hypodensity and/or effacement of the cerebral sulci in > 33% of the MCA territory were also excluded.</p>	No outcome data based on stroke subtypes was presented.
ECASS II (Hacke et al. 1998)	<p>ECASS II included patients with a clinical diagnosis of moderate to severe ischaemic hemispheric stroke who showed no or only minor early signs of infarction on the baseline CT scan.</p> <p>The exclusion criteria included those with: brain swelling or parenchymal hypoattenuation exceeding a third of the MCA territory on CT; coma; and hemiplegia plus fixed eye deviation.</p>	No outcome data based on stroke subtypes was presented.
EPITHET (Davis et al. 2008)	Patients with acute hemispheric ischaemic stroke were included and those with ischaemia of more than a third of the MCA territory on the baseline CT scan were excluded.	No outcome data based on stroke subtypes was presented.

Table 16 shows the primary efficacy outcome results at 6 months for the IST-3 study by stroke subtype (The IST-3 collaborative group 2012). This study was also under-powered so subgroup analyses should be interpreted with caution (The IST-3 collaborative group 2013).

It is not possible to draw any firm conclusions on whether a particular stroke subtype alters the risk-benefit profile of alteplase in acute ischaemic stroke from randomised clinical trial data as none of them have used aetiological classification schemes and the 2 studies that have presented outcome data for various stroke subtypes were under-powered (The NINDS rt-PA Stroke Study Group 1995; The IST-3 collaborative group 2012). Also it may not be possible to accurately classify stroke subtypes on the basis of baseline clinical features and CT findings (Toni et al. 2000).

Clinical outcomes according to stroke subtype with alteplase in clinical practice

In general, most of the published observational studies have assessed whether the benefit-risk profile of alteplase for small-vessel strokes differs to that for large-vessel disease.

Some small studies have shown nonsignificant trends towards better outcomes in lacunar (Hsia et al. 2003 [n=90]; Pashapour et al. 2013 [n=40]) and nonlacunar stroke (Cocho et al. 2006 [n=44]). This assessment will only cover the largest studies of outcomes according to stroke subtypes.

Shoba et al. (2013) compared the clinical outcomes of 11,503 patients according to stroke subtypes using a case-control design. Data from the Registry of the Canadian Stroke Network was analysed from Jul 2003 to Mar 2008 and 1630 patients received alteplase.

Stroke severity was measured using the Canadian Neurological Scale (CNS) score. The OCSF criteria were used to define stroke subtypes on the basis of follow-up clinical information and cerebral imaging results. Lacunar stroke was defined as a lacunar clinical syndrome supported by a CT scan showing a subcortical hypodense lesion with a diameter <20 mm.

The frequency of the various ischaemic stroke subtypes was: PACI (44%), POCI (25%); LACI (19%) and TACI (12%). Those patients thrombolysed had more severe strokes (median CNS score for alteplase was 5.5 [interquartile range, IQR, 3.5] vs 9 [4] for control). Patients with lacunar strokes who were thrombolysed had milder strokes (n=195; median CNS score 7.5 [2.5]) than other subtypes given alteplase (TACI, n=511, median CNS score 4.5 [3]; PACI, n=733, median CNS score 6.5 [3.5]; POCI, n=191, median CNS score 5.5 [4.5]). The adjusted relative risks (RR) for mortality at 90 days, a mRS score of 0-2 at discharge and discharge home were not significantly different for lacunar strokes compared to TACI and PACI subtypes (table 17). ICH occurred in 12.5% of those thrombolysed and sICH, defined according to ECASS criteria, was observed in 6.8%. ICH (2.1%) and sICH (1.5%) were least common in the lacunar stroke subgroup. Although no clear benefit for thrombolysis was seen in the POCI group it was concluded that these results were similar to those seen in clinical trials and that lacunar syndromes do benefit from thrombolysis. However, there appeared to be intergroup differences in baseline demographic variables that were not adjusted for and treatment times from stroke onset were not reported.

Table 16: IST-3 study primary outcome results by stroke subtype at 6 months (The IST-3 collaborative group 2012)

Oxford Community Stroke Project Stroke Syndrome†	Baseline variables collected before treatment allocation		Adjusted effect of treatment on the primary outcome at 6 months (Alive and Independent, Oxford Handicap Score 0, 1, or 2)			
	Alteplase (n=1515)	Control (n=1520)	Events/number of patients		Adjusted Odds ratio (99% CI)	Adjusted p value
			Alteplase	Control		
TACI	639 (42%)	666 (44%)	106/639 (16.6%)	96/665 (14.4%)	1.36 (0.89-2.08)	0.465
PACI	596 (39%)	551 (36%)	281/596 (47.1%)	254/550 (46.2%)	1.07 (0.76-1.51)	
LACI	168 (11%)	164 (11%)	100/168 (59.5%)	103/164 (62.8%)	0.91 (0.48-1.72)	
POCI	110 (7%)	136 (9%)	66/110 (60.0%)	79/136 (58.1%)	1.04 (0.49-2.22)	
Other	2 (<1%)	3 (<1%)	-	-	-	

† Stroke clinical syndrome derived from baseline features assigned by an algorithm; - = insufficient numbers for analysis

Key: LACI=lacunar infarct; PACI=partial anterior circulation infarct; POCI=posterior circulation infarct; TACI=total anterior circulation infarct

Table 17: Effect of thrombolysis on outcome stratified by stroke type (Shoba et al. 2013)

Outcome	RR CI ₉₅ (Unadjusted)	RR CI ₉₅ (Adjusted)*
mRS 0-2		
All	0.72 (0.66-0.78)	1.49 (1.38-1.61)
LACS	1.25 (1.08-1.44)	1.84 (1.59-2.13)
PACS	0.79 (0.71-0.87)	1.48 (1.33-1.64)
TACS	1.97 (1.45-2.67)	2.10 (1.56-2.83)
POCS	0.53 (0.41-0.68)	1.12 (0.87-1.42)
Discharge home		
All	0.74 (0.69-0.80)	1.29 (1.20-1.40)
LACS	1.07 (0.92-1.24)	1.38 (1.19-1.60)
PACS	0.79 (0.71-0.88)	1.27 (1.14-1.41)
TACS	1.77 (1.33-2.33)	1.91 (1.43-2.55)
POCS	0.63 (0.50-0.79)	1.14 (0.92-1.41)
Death		
All	1.33 (1.20-1.48)	0.99 (0.90-1.10)
LACS	1.03 (0.62-1.71)	0.89 (0.54-1.47)
PACS	1.19 (1.01-1.40)	0.98 (0.84-1.15)
TACS	0.67 (0.58-0.78)	0.81 (0.70-0.92)
POCS	1.66 (1.26-2.19)	1.03 (0.79-1.34)

*Adjusted for age, gender, baseline stroke severity, baseline serum glucose, stroke unit care, mRS score, modified Rankin Scale score; LACS, lacunar strokes; PACS, partial anterior circulation strokes; TACS, total anterior circulation strokes; POCS, posterior circulation strokes; CI₉₅, 95% confidence interval.

Fuentes et al. (2012) used the TOAST classification scheme to categorise 1489 consecutive patients treated with alteplase and compare its effectiveness in stroke subtypes. Ten patients were excluded as their final diagnosis was not ischaemic stroke or they had incomplete data, 178 patients (12%) had large vessel disease with carotid stenosis $\geq 50\%$; 175 (11.8%) had other large vessel disease; 638 (43%) had cardioembolism; 60 (4.1%) had lacunar infarction; 72 (4.9%) had other/unusual causes; and 356 (24.1%) had unknown/multiple causes. The extent of clinical investigation for each patient was determined by their physician and was not pre-specified. Patients were classified at discharge on the basis of the results of all clinical investigations. Stroke severity was highest in the cardioembolic subgroup (median NIHSS score=14) and lowest in the lacunar subtype at presentation (median NIHSS score=6, $p < 0.001$). There were no differences between the stroke subtypes in the improvement in NIHSS scores at 24 h. The large vessel with carotid stenosis subgroup was less likely to have improved at 7 days than the other subtypes (OR 0.544 [95% CI: 0.383-0.772, $p = 0.001$]) after adjustment for age, gender, risk factors, and stroke severity but stroke aetiological subtypes did not influence functional outcome measured by the mRS at 3 months. Mortality and ICH data were not presented. The authors concluded that all stroke subtypes benefit from intravenous thrombolysis at 3 months although they noted that lacunar stroke may have been underrepresented in their study possibly due to selection bias as lacunar syndromes can cause minor neurological deficits with low scores on the NIHSS. No statements on the comparative efficacy of alteplase could be made without a control arm.

The clinical outcomes of 957 patients with ischaemic stroke treated with alteplase in the Helsinki Stroke Thrombolysis Registry from 1995 to 2008 have also been reported (Mustanoja et al. 2011). Patients were categorised using the TOAST criteria: 389 (41%) had cardioembolism; 217 (23%) large-artery atherosclerosis; 101 (11%) small-vessel disease; 27 (2.8%) had other determined aetiology; 28 (2.9%) had multiple aetiologies; 130 (14%) had undetermined aetiology with extensive investigations; and 65 (6.8%) had undetermined aetiology with incomplete evaluation (table 18). The median baseline NIHSS scores (IQR) was lower at baseline in the small-vessel disease subtype at 7 (4.5-10) and the median NIHSS scores for the other subtypes varied from 9 to 11. There was no significant difference in the ICH,

Table 18: Patient outcomes, mortality, and ICH Rates (using NINDS and ECASS Criteria) in different aetiological subgroups (Mustanoja et al. 2011).

Stroke Etiology (TOAST)	LAA	CE	SVD	Other Determined Etiology	Multiple Etiologies	Undetermined Etiology With Extensive Workup	Undetermined Etiology but Incomplete Evaluation	Total
Etiologic subtypes	217 (23)	389 (41)	101 (11)	27 (2.8)	28 (2.9)	130 (14)	65 (6.8)	957 (100)
sICH (NINDS criteria)	23 (11)	40 (10)	0 (0)	2 (7.4)	3 (11)	9 (6.9)	15 (23)	92 (9.6)
sICH (ECASS criteria)	16 (7.4)	27 (6.9)	0 (0)	2 (7.4)	2 (7.1)	8 (6.2)	13 (20)	68 (7.1)
Any ICH	36 (17)	102 (26)	2 (2.0)	3 (11)	4 (14)	25 (19)	22 (34)	194 (20)
mRS 3 months, median (IQR)	2 (1–4)	2 (1–4)	1 (10–2)	2 (2–3)	3 (1–4)	2 (0–3)	3 (1–6)	2 (1–4)
Mortality by 3 months	18 (8.5)	47 (12)	1 (1.0)	1 (4.0)	5 (18)	9 (7.1)	16 (26)	97 (10)
Excellent outcome	64 (31)	128 (34)	56 (57)	4 (16)	8 (29)	63 (50)	19 (31)	342 (37)
OR	0.69	0.80	2.48	0.32	0.68	1.85	0.77	
95% CI	0.50–0.96	0.61–1.06	1.63–3.79	0.11–0.94	0.30–1.56	1.27–2.70	0.44–1.34	
Good outcome	115 (55)	196 (52)	81 (82)	18 (72)	13 (46)	91 (72)	29 (48)	543 (58)
OR	0.81	0.63	3.59	1.86	0.61	1.96	0.63	
95% CI	0.60–1.11	0.48–0.82	2.12–6.10	0.77–4.50	0.29–1.29	1.30–2.96	0.37–1.05	
Good outcome, adjusted for baseline NIHSS, age, sex								
OR	0.78	1.00	1.81	0.66	0.88	1.23	0.84	
95% CI	0.54–1.11	0.73–1.39	1.01–3.23	0.22–1.99	0.36–2.19	0.75–2.02	0.44–1.61	

mRS and mortality at 3 months in numbers and percentages. Excellent outcome equals to mRS 0 to 1 and good outcome mRS 0 to 2. Any ICH may have no increase in NIHSS score including both asymptomatic and symptomatic hemorrhages. sICH has a decline in neurologic status with an increase in the NIHSS score by ≥ 1 (NINDS) or ≥ 4 (ECASS). Data are no. (%) unless otherwise stated. IQR indicates interquartile range.

Key: LAA=large-artery atherosclerosis; CE=cardioembolism; SVD=small-vessel disease; OR=Odds ratio; CI=confidence intervals.

sICH and mortality rates in the cardioembolism and large-vessel disease subtypes when compared with overall rates. However, the patients with small-vessel disease had significantly lower NIHSS scores at all timepoints after thrombolysis at 2 h, 24 h and 7 days and there were no sICHs (using NINDS and ECASS criteria) and the ICH rate was also significantly lower when compared to those without small-vessel disease (2.2% versus 22%; OR, 0.07 [95% CI: 0.02–0.29, $p < 0.001$]). The median mRS at 3 months and mortality rate (1% versus 11.6%; OR 0.08 [95% CI: 0.01–0.57, $p = 0.001$]) were also significantly lower in the small-vessel disease group even after adjusting for baseline NIHSS score, glucose level, age and hyperdense artery signs. This study suggests that small-vessel stroke has a better prognosis regardless of initial stroke severity with low risk of alteplase-related complications. However a large proportion of the study population had an undetermined aetiology and absolute numbers in each TOAST category were relatively small.

Fluri et al. (2010) analysed data from the Swiss thrombolysis registry and reported that 1 of their 65 patients with ischaemic stroke due to small artery occlusion died following thrombolysis compared to 11.2% (110/983) in the non-small artery occlusion group ($p = 0.014$). The functional outcome (mRS score ≤ 2 at 3 mo) was not significantly different in the small artery occlusion group after adjustment for age, gender and stroke severity (adj OR 1.41 [95% CI: 0.71–2.79, $p = 0.32$]). Fatal ICH occurred in 3.3% of the non-small artery occlusion group but in none of the small artery occlusion group. The risk of sICH was similar in the small (4.6%) and non-small artery occlusion groups (5.3%, $p > 0.8$).

Sarikaya et al. (2011) reported the outcomes of intravenous alteplase in posterior and anterior circulation stroke subtypes using data from 883 consecutive patients treated between 1998 and 2008. A posterior circulation stroke was defined as a symptomatic infarct in the territory of the vertebral, cerebellar, posterior cerebral or basilar arteries. An anterior circulation stroke was defined as a symptomatic infarct in the territory of the middle or anterior cerebral artery or both. Patient classification was performed by experienced stroke physicians using clinical and radiological findings.

The data from 9 patients was excluded as the stroke subtype was unclear, 788 (89%) had an anterior circulation stroke and 95 had a posterior circulation stroke. Patients with posterior circulation strokes were significantly younger, had significantly lower mean NIHSS scores although stroke aetiologies were similar:

Table 19: baseline characteristics of patients with anterior and posterior circulation strokes (Sarıkaya et al. 2011).

	Posterior Circulation Stroke (n=95)	Anterior Circulation Stroke (n=788)	P
Male sex, %	62.1	62.8	0.892
Mean age±SD, y	62.9±15.1	66.9±14.3	0.012*
Hypertension, %	62.1	63.1	0.854
Current smoking, %	25.3	24.8	0.918
Diabetes mellitus, %	16.0	13.6	0.528
Hypercholesterolemia, %	46.4	38.7	0.171
Antiplatelet medication at stroke onset, %	38.9	36.1	0.584
Anticoagulation at stroke onset, %	1.1	2.4	0.714†
Coronary artery disease, %	19.1	18.0	0.793
Atrial fibrillation, %	17.0	24.6	0.102
Mean NIHSS score±SD	9.3±7.9	12.2±5.9	<0.001*
Time to treatment±SD	169.0±54.5	160.0±40.0	0.243*
Mean systolic blood pressure±SD, mm Hg	152.8±24.7	155.6±24.9	0.211*
Mean diastolic blood pressure±SD, mm Hg	85.9±14.7	88.1±16.4	0.210*
Mean blood glucose±SD, mmol/L	6.9±2.6	6.9±2.4	0.890*
Cause of stroke			
Large artery atherosclerosis, %	15.2	12.9	
Cardiac embolism, %	43.5	47.8	0.331
Small artery disease, %	8.7	4.3	
Other determined etiology, %	6.5	9.2	
Undetermined etiology, %	26.1	25.9	

P values apply to χ^2 tests unless otherwise indicated.

NIHSS indicates National Institutes of Health Stroke Scale; SD, standard deviation.

*Mann-Whitney U test.

†Fisher exact test.

The clinical outcomes are shown:

Table 20: Clinical outcomes in patients with anterior and posterior circulation strokes treated with alteplase (Sarıkaya et al. 2011).

	Symptomatic ICH			Mortality			Favorable Outcome		
	(n/N [%])	P Unadjusted	P Adjusted	(n/N [%])	P Unadjusted	P Adjusted	(n/N [%])	P Unadjusted	P Adjusted
Posterior circulation stroke	0/93 (0)	0.026*	0.001†	8/94 (9)	0.243	0.251‡	62/94 (66)	<0.001	0.177§
Anterior circulation stroke	36/784 (5)			100/784 (13)			364/784 (46)		

Symptomatic intracranial hemorrhage (ICH) refers to National Institute of Neurological Disorders and Stroke criteria. P-values apply to χ^2 tests unless otherwise indicated.

ICH indicates intracranial hemorrhage; NIHSS, National Institutes of Health Stroke Scale.

*Fisher exact test.

†Adjusted for atrial fibrillation, antiplatelet medication, and diastolic blood pressure in logistic regression analysis (bootstrap method).

‡Adjusted for age, NIHSS score and blood glucose in logistic regression analysis.

§Adjusted for NIHSS score, blood glucose, age, antiplatelet medication, and anticoagulation in logistic regression analysis.

SICH (using NINDS criteria) occurred in 5% of patients with anterior circulation strokes but was not observed in posterior circulation stroke patients. There was a strong association between stroke territory and sICH independent of atrial fibrillation, antiplatelet medication and diastolic blood pressure. Mortality did not differ significantly between anterior and posterior strokes (but was numerically higher in anterior strokes) although a favourable outcome (mRS 0 or 1) occurred more frequently in those patients with posterior circulation strokes (66% versus 46%, $p < 0.001$). There are a number of limitations of this study: the NIHSS is weighted towards anterior circulation neurological deficits; possible selection bias as patients with severe basilar artery occlusion may have received primary endovascular treatment and infarct volumes were not assessed. Patient numbers in each subgroup were also relatively small. Another study of 237 patients treated with alteplase found higher rates of small vessel disease in posterior circulation strokes but similar clinical outcomes with anterior and posterior strokes (Forster et al. 2011).

MAH's response

The MAH has provided summaries for a selection of articles that address the benefits and harms of alteplase for various stroke subtypes (Miedema et al. 2010; Forster et al. 2011; Pashapour et al. 2013; Erabi et al. 2014).

The MAH concludes that *it is already known, that the occlusion of relatively large arteries, like internal carotid artery provide less chance for successful treatment than the occlusion of smaller arteries. No difference is found with respect to the location of stroke. The findings presented in this section to not trigger any change of the reference safety information.*

Concluding comments:

The MAH has referenced 4 small studies, one in Japanese, that fail to adequately address this issue as the presented papers do not adequately reflect the available scientific data.

Miedema et al. (2010) assessed the impact of selective serotonin re-uptake inhibitors (SSRIs) on the functional outcomes of 476 acute ischaemic stroke patients treated with alteplase. The MAH concluded that further evidence of the potentially deleterious effects of SSRIs on functional outcome is needed. Forster et al. (2011) report on their single centre experience (n=237) of thrombolysis within 3 h of stroke onset. Pashapour et al. (2013) report a small case series of only 40 patients with only 18 patients in the largest stroke sub-type (cardio-embolic). The MAH has provided the following abstract summary of the Erabi et al. (2014) paper *internal carotid artery occlusion is a factor associated with unfavourable outcome*.

The aim of intravenous alteplase treatment is to achieve recanalization of an occluded artery. Early recanalization rates assessed by transcranial Doppler at 2 h after the start of alteplase are lower for proximal large arteries: 44.5% for the distal MCA but no more than 30% for the proximal MCA segment and only 5.9% for the carotid T segment (Saqqur et al. 2007).

Implications for the marketing authorisation

The SmPC does not contain any specific wording relating the benefit-risk profile of alteplase to stroke sub-type or underlying pathophysiological cause. The limited conflicting evidence that stroke sub-type may be important in determining clinical outcomes is largely derived from observational studies and not from the RCTs that have assessed it. The available data is considered insufficient to warrant any changes to the current SmPC.

The MAH's conclusion that the effects of alteplase are not dependent on the location of stroke is considered valid.

7.3.2. Stroke mimics

Patients with acute neurological symptoms consistent with an ischaemic stroke may be misdiagnosed and treated with alteplase if a CT scan of their head excludes an intracranial haemorrhage. The benefit-risk profile of alteplase for 'stroke mimics' is expected to be negative. Numerous retrospective studies have reported on the safety of alteplase for stroke mimics. The proportion of patients with stroke mimics in alteplase-treated cohorts varies from 1.2% to 31% in hospital-based studies (Artto et al. 2012; Zinkstok et al. 2013; Hand et al. 2006) and was 7% (10/151) for emergency departments without a stroke team evaluation (Scott and Silbergleit 2003).

The variability in reported incidence rates reflects the lack of a standardised definition of stroke mimics. Despite the small numbers of stroke mimics reported in most series and the variety of misdiagnosed disorders, there have been a few attempts to define the clinical characteristics that support a diagnosis of stroke mimic. A study reporting the clinical features of 350 suspected acute stroke presentations by 336 patients to a British academic unit proposed that cognitive impairment and abnormal signs in other body systems independently predicted the diagnosis of a stroke mimic. An exact time of onset, definite focal symptoms, abnormal vascular findings, presence of neurological signs, being able to lateralize the signs to the left or right side of the brain, and being able to determine a clinical stroke sub-classification suggested the diagnosis of a stroke (Hand et al. 2006). However, most of their clinical assessments were not done within the existing time window for thrombolysis (3 h), approximately half of the patients with stroke mimics had a history of cerebrovascular disease and only 4% of their patients had MR imaging.

Libman et al. (1995) reported the clinical features of 78 patients with a stroke mimic presenting to an emergency department and found that female gender, abnormal visual fields, diastolic hypertension and atrial fibrillation increased the odds of a stroke. Normal eye movements and an abnormal baseline neurological examination increased the odds of a stroke mimic.

The commonest stroke mimics include: migraine; partial epilepsy; structural lesions such as cerebral tumours; and conversion disorders. Stroke mimics are a very heterogeneous group and attempts to describe clinical features that can accurately distinguish stroke from non-stroke in the hyperacute setting are ultimately unlikely to prove successful due to referral bias and variations in the clinical expertise of physicians or nurses involved in the initial assessment. Stroke remains a clinical diagnosis and few studies of stroke mimic report the frequency of possible strokes. Diffusion-weighted MR sequences are most sensitive at detecting acute ischaemia but false-positives and negatives can occur and abnormalities may reverse with successful treatment so there is no gold standard investigation to confirm stroke at presentation.

There seems little point in listing all of the findings in the available stroke mimic series but the results of the 2 largest studies will be described as they are representative.

Zinkstok et al. (2013) reported the safety of thrombolysis in 100 patients with stroke mimics (1.8%) identified from 5581 consecutive patients from 12 experienced European stroke centres. Stroke mimics were defined as patients in whom clinical details did not suggest a vascular aetiology but who had an alternate final diagnosis

convincingly explaining their symptoms. In case additional diagnostic tests failed to establish an alternate diagnosis but the physician was convinced that, on clinical grounds, the symptoms were not caused by cerebral ischemia, a stroke mimic was diagnosed as well. An ischaemic stroke was assumed in all patients with history, examination, and disease course typical for involvement of an intracerebral vascular territory with supportive or non-contradictory brain imaging. If clinical signs were suggestive of stroke or transient ischemic attack, ischemic lesions had to be absent on MRI with diffusion-weighted sequences. Patients with a stroke mimic were younger, more often female, and had fewer risk factors except smoking and previous stroke or transient ischemic attack. The commonest stroke mimics were: seizure disorders in 41%; psychogenic disorders in 28%; migraine in 12%; demyelination in 5%; and encephalitis in 3%. The sICH rate (using ECASS II criteria) in stroke mimics was 1.0% (95% CI: 0.0–5.0) compared with 5.5% (95% CI: 4.9–6.1) in ischaemic strokes. Two deaths occurred in the stroke mimic group but none were related to ICH (86 year old with epilepsy and sudden death; 75 year old with a cerebral tumour).

Chernyshev et al. (2010) reported the safety of alteplase in 69 patients with stroke mimics. The diagnosis of a stroke mimic was based on the absence of acute ischaemia/infarction on pre- and post-alteplase treatment neuroimaging performed less than 24 h from onset and >24 h afterwards in addition to an alternate diagnosis at discharge. The most common stroke mimics were: seizure disorders in 38%; complicated migraine in 37%; and conversion disorder in 21%. The median NIHSS score at admission was 7 (IQR 4-11), falling over the median length of stay of 3 days to 0 at discharge. There were no sICHs reported (although a single patient bled into an epidural spinal mass and required surgical decompression).

The available evidence suggests that alteplase treatment of stroke mimics is sufficiently safe to justify rapid treatment of all patients with suspected ischaemic stroke if haemorrhage is excluded. Acceptable misdiagnosis rates of $\leq 3\%$ for centres using noncontrast CT and $\leq 1\%$ for centres using multimodal imaging have been proposed (Saver and Barsan 2010). It seems logical that stroke misdiagnosis rates should decrease with increasing experience at centralised hyperacute stroke centres and the development of stroke medicine as a sub-speciality in the UK, although there is little data on British misdiagnosis rates (10% incidence of stroke mimics reported in a London stroke unit offering alteplase, Moynihan et al 2010) and conflicting evidence that experienced stroke centres produce better outcomes in ischaemic stroke (Lees et al. 2008; Morris et al. 2014). Some authors have proposed large prospective studies to assess the clinical, imaging and biomarker characteristics of ischaemic stroke patients versus those with stroke mimics to avoid unnecessary alteplase treatment (Guerrero and Savitz 2013).

MAH's response

The MAH has provided summaries for a selection of articles that address the harms of alteplase in misdiagnosed patients (Kluenemann et al. 2003; Mouradian et al. 2004; Chua et al. 2005; Uchino et al. 2005; Cook et al. 2007; Grimm et al. 2007; Sung et al. 2010; Uchino et al. 2010b; Artto et al. 2012; Chang et al. 2012; Demaerschalk et al. 2012; Guillan et al. 2012; Okada et al. 2012; Sarikaya et al. 2012; Son et al. 2012; Yaghi et al. 2012; Brunser et al. 2013; Papavasileiou et al. 2013; Yokoyama et al. 2013; Spokoynny et al. 2014; Yamashiro et al. 2014).

The MAH considers that the following topics were addressed:

- administration of intravenous rtPA to all patients in whom acute ischemic stroke is clinically suspected remains safe
- intravenous fibrinolysis has low complication rates in stroke mimics

- risks associated with the use of Telemedicine are not prominent.
- the risk of missing the diagnosis of relevant somatoform disorders is addressed; glioblastoma multiforme, aortic dissection and meningoencephalitis are examples identified in this context.

Most of the cited published literature addresses a basic challenge in intravenous lysis with alteplase: the narrow time to treatment window does sometimes not allow further diagnostic investigations to be applied. Glioblastoma is obviously one of the bigger challenges in pre diagnostic investigations before lysis is started. This may be addressed in specific guidelines and is a topic beyond prescribing information.

Concluding comments:

The SmPC for Actilyse does not specifically refer to the benefit-risk profile of alteplase in stroke mimics. However, Section 4.4 of the SmPC states that *no sustained antibody formation to the recombinant human tissue-type plasminogen activator molecule has been observed after treatment. There is no systemic experience of the risk of hypersensitivity with re-administration of Actilyse.*

It is possible that patients who receive alteplase after being mistakenly diagnosed as acute ischaemic stroke may later require thrombolysis for this condition (or indeed those with recurrent ischaemic events who are correctly diagnosed). A recent systematic review of the limited data related to the safety of repeat doses of alteplase for recurrent ischaemic stroke did not reveal any concerns if standard exclusion criteria are used (Qureshi et al. 2015).

A number of areas in Europe, including parts of the UK, have set-up telemedicine services to assess the clinical characteristics and radiological data of acute stroke patients who present in remote areas that lack specialist care (Muller-Barna et al. 2014; Sairanen et al. 2011). The NHS has invested in telemedicine to improve access and minimise delay in delivering thrombolysis (Chowdhury et al. 2012). The clinical outcomes after thrombolysis appear similar to standard care although there are potential medicolegal issues and the cost-effectiveness for short and long term outcomes in the UK is not yet established (Chowdhury et al. 2012; Amadi-Obi et al. 2014).

The MAH has provided data from small observational and case studies to outline the harms of alteplase when given to stroke mimics and highlighted the difficulty in correctly diagnosing all patients in the setting of hyperacute stroke. Many of the larger observational studies were not referenced. However, the MAH's conclusions are considered valid.

Implications for the marketing authorisation

The currently available evidence has no implications for the SmPC.

7.3.3. Co-morbidities

Biomarkers

Animal and human studies of ischaemic stroke have correlated serum levels of various biomarkers related to vascular injury, blood-brain-barrier integrity or the coagulation system with the frequency and severity of HT. Potential biomarkers for

ICH severity include: matrix metalloproteinases 2 and 9; cellular fibronectin; vascular adhesion protein-1/semicarbazide-sensitive amine oxidase activity; ferritin; plasminogen activator inhibitor-1/thrombin-activatable fibrinolysis inhibitor; fibrin degradation products; activated protein C; and the coagulation factor XIII Val34Leu polymorphism (Alvarez-Sabin et al. 2013). However, the clinical utility of these potential prognostic biomarkers has not been determined.

Body temperature

Animal models of ischaemic stroke have shown that body temperature is related to functional outcome and infarct size (Fukuda et al. 1999). Clinical studies have reported that hyperthermia is associated with increased initial stroke severity, infarct size, worse functional outcome and death (Reith et al. 1996; Hajat et al. 2000). Poor neurological outcome may result from increased metabolic demands, excitotoxicity from neurotransmitter release, increased free radical production or elevated plasma levels of inflammatory mediators (Azzimondi G et al. 1995; Leira et al. 2012). The rate of alteplase induced fibrinolysis is temperature dependent in vitro (Tamura et al. 1996).

Leira et al. (2012) reported that hyperthermia within the first 24 h was independently associated with haemorrhagic transformation in 229 patients with ischaemic stroke who did not receive alteplase (OR 7.3 [95% CI: 2.4-22.6]). Outcome results of 985 stroke patients treated with alteplase from the Helsinki Stroke Registry showed that clinical improvement was unlikely (OR 0.66 per °C [95% CI: 0.45-0.95, $p = 0.03$]) with poorer outcomes (OR 1.63 per °C [95% CI: 1.24-2.14, $p < 0.001$]) if body temperature increased over the first day from stroke onset (Tiainen et al. 2013). However, baseline temperature of 5586 patients did not influence stroke outcomes at 3 months after thrombolysis in the Virtual International Stroke Trials Archive (Lees et al. 2011).

Concluding comments:

Numerous interventional studies using pharmacological or mechanical methods to lower temperature after ischaemic stroke have reported inconclusive outcomes (Jauch et al. 2013; European Stroke Organization (ESO) 2008).

The National clinical stroke guidelines recommend that a patient's temperature should be closely monitored after an ischaemic stroke but do not provide any guidance on treatment (The Intercollegiate Working Party for Stroke 2012). The ESO guidelines recommend that the presence of pyrexia (temperature $>37.5^{\circ}\text{C}$) should prompt a search for concurrent infection. Treatment of pyrexia (temperature $>37.5^{\circ}\text{C}$) with paracetamol and fanning is recommended (European Stroke Organization 2008).

Implications for the marketing authorisation

The SmPC for Actilyse lists increased body temperature as a common adverse drug reaction but does not provide any clinical guidance on temperature control.

The current SmPC wording is considered acceptable given the limited observational data.

7.3.4. Effect of radiological signs

Early ischaemic changes on CT imaging

Early focal hypodensity on a CT scan performed within 5 h of stroke onset was the only independent predictor of HT in 150 patients with anterior circulation strokes who were not thrombolysed (Toni et al. 1996). The presence of focal hypodensity was associated with HT in 77% (95% CI: 68-86%) of cases and its absence predicted no HT in 94% (95% CI: 89-99%) of cases.

The presence of brain oedema (defined as acute hypodensity) or mass effect on the baseline CT scan was an independent predictor of an increased risk of sICH (OR 7.8 [95% CI: 2.2-27.1]) in the 312 alteplase-treated patients in the NINDS trial (The NINDS Study Group 1997). A secondary analysis of the ECASS II study also showed that the extent of parenchymal hypoattenuation on the baseline CT scan (categorised as none, $\leq 33\%$ or $> 33\%$ of the middle cerebral artery (MCA) territory) was an independent predictor of sICH (Larrue et al. 2001).

The ASPECTS score is derived by dividing the territory of the MCA into 10 parts based on two axial CT cuts (one at the level of the thalamus/basal ganglia and another rostral to these structures) and deducts 1 point for each part that shows early ischaemic change. A normal scan has an ASPECT score of 10 and a score > 7 corresponds well with early ischaemic changes in less than one third of the MCA territory (Demchuk and Coutts 2005). A multivariable logistic regression analysis of the ECASS II data showed that low ASPECT scores (≤ 7) were associated with a significantly increased risk of parenchymal haematoma after alteplase treatment (Dzialowski et al. 2006). ECASS II excluded patients with hypoattenuation or swelling on CT exceeding more than one third of the MCA territory. However, a post hoc multivariable logistic regression analysis of the NINDS study reported that the median ASPECT score in the patients showing ischaemic changes in greater than one third of the MCA territory was 5 (IQR 3-8) compared with 9 (IQR 7-10) in patients with ischemia in less than one third of the MCA territory and that there was no evidence that a lower ASPECT score increased the risk of sICH when the ASPECT score was trichotomised using cut-off values of 3 and 7 (Demchuk et al. 2005). The meta-analysis of Whiteley et al. (2012) indicated that the presence of a visible brain lesion was predictive of an increased risk of ICH (OR 2.39 [95% CI: 1.59-3.58, $p < 0.001$]) if assessed vs no lesion or if its size was dichotomised using an ASPECTS score at 5, 7 or 8 (OR, 3.46 [95% CI: 1.92-6.21, $p < 0.001$]). Early ischaemic changes exceeding one third of the MCA territory were also reported as a marker of an increased risk of ICH in a series of 1205 patients treated with alteplase within 3 h of stroke onset (Tanne et al. 2002).

The IST-3 collaborative group (2015) recently reported a pre-planned secondary analysis that examined the relationship between ischaemic signs on baseline CT or MR scans taken up to 6 h after stroke onset and outcomes after alteplase. The IST-3 study included patients with cortical, lacunar, and posterior circulation ischaemic strokes of all severities and those with early ischaemic or pre-existing radiological signs on baseline imaging but excluded patients with signs of established infarction.

The IST-3 protocol specified minimum standards for brain imaging, all patients had either a CT or MR brain scan at baseline which was repeated 24-48 h after stroke and again if neurological deterioration occurred in the first week after treatment. All scans were reviewed at the IST-3 coordinating centre to assess the accuracy of reported findings and their technical quality. Adjudicators (neuroradiologists or stroke neurologists with radiological expertise) rated 60 scans from the ACCESS study and 25 scans from IST-3 that were randomly selected to ensure adequate inter-rater

reliability (defined as Cohen's Kappa Coefficient, $\kappa > 0.70$) for the detection of early ischaemic signs (tissue hypoattenuation, lesion size, swelling, and hyperattenuated artery) and no more than one category difference for pre-existing signs (old infarcts, leukoaraiosis, and atrophy). All signs were classified using validated scales. The adjudicators were blinded to treatment allocation and completed their analyses before database lock. Any discrepancies between the interpretations of the adjudicator and clinical data were resolved by a single neuroradiologist who assigned the final rating.

The presence and degree of hypoattenuated tissue was graded as either mild (grey matter attenuation equal to normal white matter) or severe (grey and white matter attenuation slightly less than normal white matter but still consistent with onset of stroke within 6 h). The extent of acute ischaemic changes were classified in 3 ways using: the one third MCA territory method; the IST-3 method which assesses all arterial territories and was used as the primary measure of infarct size; and the ASPECTS score.

Small infarcts were defined as lacunar, small cortical, small cerebellar, less than half of brainstem, or less than half of the anterior cerebral (ACA) or posterior cerebral (PCA) territory (equivalent to an ASPECTS score of 8-10). Medium infarcts were classified as striatocapsular, the anterior or posterior half of the peripheral MCA territory, or more than half of the ACA or PCA territory (equivalent to an ASPECTS score of 5-7 and less than a third of the MCA territory). Large infarcts involved the whole peripheral MAC territory or all of the MCA territory and very large infarcts affected the whole MCA and PCA territory, all of the MCA and ACA territory or all three territories (large and very large infarcts are equivalent to an ASPECTS score of 0-4 and involvement of more than a third of the MCA territory).

Ischaemic lesion swelling was graded on a 7-point scale (0 indicates no swelling; 1, effacement of cortical sulci; 2, grade 1 plus minor effacement of the ipsilateral lateral ventricle; 3, grade 1 plus complete effacement of the ipsilateral lateral ventricle; 4, grade 3 plus effacement of the third ventricle; 5, shift of the midline away from the side of the infarction; and 6, grade 5 plus effacement of basal cisterns [Wardlaw and Sellar 1994]). The presence and severity of leukoaraiosis was noted on CT imaging and the Fazekas scale was used to grade it on MRI. Atrophy was graded as none, moderate or severe against standard images.

Logistic regression was done to find associations between radiological signs and:

(a) age, stroke severity and time to randomisation.

(b) outcomes at 7 days (sICH) and at 6 months (Oxford Handicap Scale scores (OHS) of 0-2 and 0-1).

Multivariate logistic regression was then conducted to identify whether any combinations of imaging variables were associated with sICH or an OHS score of 0-2, adjusting for the linear effects of age, stroke severity and time to randomisation.

Interactions of imaging signs and response to alteplase were then assessed for sICH, death within 7 days and OHS score of 0-2 at 6 months. A prespecified meta-analysis of data from IST-3 with imaging results from other RCTs involving alteplase was also done.

Baseline brain scans were available for 3017 patients (1507 allocated alteplase and 1510 controls, 18 scans were not available) (98% CT scans and 2% MRI scans). Table 21 summarises the baseline variables and radiological signs. Only 9% of scans were completely normal; 41% had early ischaemic signs and 51% had pre-existing signs without early ischaemic changes. Hypoattenuation was observed in 40% of

Table 21: Baseline clinical and imaging variables (The IST-3 collaborative group 2015).

	Alteplase (n=1507)	Control (n=1510)
Age (years)		
≤80	693 (46%)	715 (47%)
>80	814 (54%)	795 (53%)
18–50	58 (4%)	68 (5%)
51–60	98 (7%)	102 (7%)
61–70	187 (12%)	175 (12%)
71–80	350 (23%)	370 (25%)
81–90	703 (47%)	697 (46%)
>90	111 (7%)	98 (6%)
NIHSS score*		
0–5	303 (20%)	304 (20%)
6–10	419 (28%)	428 (28%)
11–15	304 (20%)	295 (20%)
16–20	268 (18%)	271 (18%)
>20	213 (14%)	212 (14%)
Time to randomisation (h)		
0 to ≤3	431 (29%)	415 (27%)
>3 to ≤4.5	575 (38%)	596 (39%)
>4.5 to ≤6	501 (33%)	497 (33%)
>6	0	2 (<1%)
Randomising clinician's assessment of acute ischaemic change on prandomisation imaging		
No change	890 (59%)	892 (59%)
Possibly change	359 (24%)	339 (22%)
Definitely change	258 (17%)	279 (18%)
Expert reader's assessment of acute ischaemic change on prandomisation imaging		
Scan completely normal	140 (9%)	129 (9%)
Scan not normal but no sign of any early ischaemic change	743 (49%)	781 (52%)
Signs of any early ischaemic change	624 (41%)	600 (40%)
Early ischaemic lesion territory		
Indeterminate	885 (59%)	914 (61%)
MCA or ACA or border zone	589 (39%)	555 (37%)
Posterior	22 (1%)	36 (2%)
Lacunar	11 (1%)	5 (<1%)
Early ischaemic lesion changes in MCA territory		
None	925 (61%)	960 (64%)
One-third or less	357 (24%)	354 (23%)
More than one-third	225 (15%)	196 (13%)

(Table 1 continues in next column)

	Alteplase (n=1507)	Control (n=1510)
(Continued from previous column)		
Early ischaemic lesion size†		
None visible	885 (59%)	914 (61%)
Small	110 (7%)	97 (6%)
Medium	250 (17%)	250 (17%)
Large	124 (8%)	137 (9%)
Very large	138 (9%)	112 (7%)
ASPECTS score‡		
0–4	162 (11%)	138 (9%)
5–7	201 (13%)	228 (15%)
8–10	1144 (76%)	1144 (76%)
Early ischaemic lesion depth of tissue hypoattenuation§		
None	892 (59%)	922 (61%)
Mild	503 (33%)	492 (33%)
Severe	112 (7%)	96 (6%)
Early ischaemic lesion degree of swelling		
None	1152 (76%)	1171 (78%)
Mild sulcal effacement	283 (19%)	265 (18%)
Mild ventricular effacement	71 (5%)	73 (5%)
Moderate effacement	1 (<1%)	0
Severe effacement	0	1 (<1%)
Location of hyperattenuated arteries		
None	1131 (75%)	1151 (76%)
Anterior circulation	360 (24%)	342 (23%)
Posterior circulation	16 (1%)	17 (1%)
ICA, or BA, or MCA and ACA	42 (3%)	33 (2%)
MCA, or ACA, or PCA main	334 (22%)	326 (22%)
Pre-existing brain changes		
Evidence of atrophy	1161 (77%)	1166 (77%)
Evidence of leukoaraiosis	765 (51%)	782 (52%)
Evidence of old infarcts	685 (45%)	651 (43%)
Evidence of non-stroke lesions	73 (5%)	77 (5%)

Data are number of patients (%). ACA=anterior cerebral artery. ASPECTS=Alberta Stroke Program Early CT Stroke. BA=basilar artery. ICA=internal carotid artery. IST-3=third International Stroke Trial. MCA=middle cerebral artery. NIHSS=National Institutes of Health Stroke Scale. PCA=posterior cerebral artery. *Assesses neurological deficit in stroke. †Refers to IST-3 image reading categorisation of lesion extent (all vascular territories). ‡Assesses the extent of infarct affecting the MCA territory by subtracting a point for each of ten regions that are involved in the acute ischaemic lesion. §Classed as mild (ie, grey matter attenuation had become the same as normal white matter) or severe (ie, grey and white matter attenuation less than normal white matter).

Table 1: Baseline clinical and imaging variables

scans and pre-existing abnormalities were common (old infarct in 44%; leukoaraiosis in 51% and atrophy in 77%).

Each point increase in the NIHSS score was associated with a ~10% increase in the odds of tissue hypoattenuation, swelling, large lesion or hyperdense artery. Each increase in age by 1 year decreased the odds of tissue hypoattenuation, large lesion, swelling or hyperdense artery sign by approximately 2% but odds of pre-existing signs increased in the logistic linear regression analysis (table 22).

The full multivariate logistic regression models showed that hyperattenuated arteries (OR 0.70 [95% CI: 0.54-0.91, $p = 0.007$]), large lesions (vs small, medium, or no lesion: OR 0.69 [95% CI: 0.49-0.99, $p = 0.043$]), and severe leukoaraiosis (vs none: OR 0.64 [95% CI: 0.48-0.85, $p = 0.002$]) each reduced the chance of a good outcome (defined as an OHS score 0-2 vs OHS score 3-6). Old infarcts (vs none: OR 1.75

Table 22: Logistic regression analysis of associations between imaging signs and age, stroke severity and time to randomisation (The IST-3 collaborative group 2015).

	Age, adjusted for NIHSS score		NIHSS score, adjusted for age		Delay, adjusted for age and NIHSS score	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Early ischaemic signs						
Visible infarct	0.98 (0.97-0.98)	<0.0001	1.11 (1.09-1.12)	<0.0001	1.08 (1.01-1.16)	0.019
Hypoattenuation	0.98 (0.97-0.98)	<0.0001	1.10 (1.09-1.12)	<0.0001	1.10 (1.03-1.18)	0.006
Large lesion*	0.98 (0.97-0.99)	<0.0001	1.11 (1.09-1.13)	<0.0001	1.03 (0.94-1.12)	0.561
Swelling	0.98 (0.97-0.99)	<0.0001	1.09 (1.08-1.11)	<0.0001	1.04 (0.96-1.13)	0.302
Hyperattenuated artery	0.98 (0.97-0.98)	<0.0001	1.10 (1.09-1.12)	<0.0001	1.02 (0.94-1.10)	0.664
Pre-existing signs						
Atrophy	1.11 (1.10-1.12)	<0.0001	0.99 (0.98-1.00)	0.179	0.98 (0.89-1.07)	0.621
Leukoaraiosis	1.09 (1.08-1.09)	<0.0001	0.99 (0.98-1.00)	0.221	0.99 (0.93-1.06)	0.843
Old infarct	1.03 (1.03-1.04)	<0.0001	0.99 (0.98-1.00)	0.017	0.98 (0.92-1.05)	0.566

Associations for visible infarct (the summary variable) are provided for completeness. Odds ratios and 95% CIs indicate the increased or decreased odds of the imaging sign being present for a 1 point change in NIHSS score, a 1 year change in age, or a 1 h increase in time to randomisation. Each of the eight imaging variables was used separately in two logistic regressions: first on age and NIHSS score (both linear) to give the values in the first two pairs of columns; and second on age, NIHSS score, and time to randomisation (all linear) to give the values in the last pair of columns. IST-3=third International Stroke Trial. NIHSS=National Institutes of Health Stroke Scale. *Large lesion defined as a combination of large and very large on IST-3 score.

[95% CI: 1.17-2.63, $p=0.007$]), use of antiplatelet treatment at stroke onset (vs none: OR 1.60 [95% CI: 1.07-2.38, $p=0.021$]) and alteplase use (vs control: OR 6.65 [95% CI: 3.89-11.35, $p<0.0001$]) were significant predictors of sICH at 7 days. However, with standard stepwise model selection methods, the retention of age, stroke severity, time to randomisation and treatment group, both old infarcts and hyperattenuated arteries were significant predictors of sICH:

Table 23: Multivariate logistic regression models selected by stepwise logistic regression for sICH and functional outcome at 6 months (The IST-3 collaborative group 2015).

	OHS score 0-2 versus OHS score 3-6		Symptomatic intracranial haemorrhage	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Age (years)	0.96 (0.95-0.97)	<0.0001	0.99 (0.98-1.01)	0.556
NIHSS score	0.83 (0.82-0.85)	<0.0001	1.07 (1.04-1.10)	0.0001
Time to randomisation (h)	1.04 (0.96-1.13)	0.288	0.98 (0.83-1.15)	0.798
Alteplase versus control	1.12 (0.94-1.34)	0.196	6.71 (3.93-11.46)	<0.0001
Antiplatelets at the time of stroke versus none	1.60 (1.07-2.38)	0.021
Small or medium lesion versus no lesion	0.85 (0.67-1.07)	0.173
Large or very large lesion versus no lesion	0.54 (0.39-0.74)	0.0001
Hyperattenuated artery versus none	0.71 (0.55-0.92)	0.009	1.61 (1.07-2.42)	0.023
Old infarct versus none	1.67 (1.13-2.46)	0.009
Mild leukoaraiosis versus none	0.76 (0.62-0.93)	0.009
Severe leukoaraiosis versus none	0.59 (0.45-0.79)	0.0003

Odds ratios indicate the increased or decreased odds of the clinical factor being present for a 1 year increase in age, a 1 point increase in NIHSS score, or a 1 h increase in time to randomisation. Models were selected by stepwise logistic regression from full models. The first four variables were forced into all models. We used $p\leq 0.05$ as criteria for both forward and backward steps. Blank cells represent variables that were dropped as non-significant during stepwise selection. The final nominal p values take no account of model selection. Age, NIHSS score, and time to randomisation were entered into the model as continuous variables; thus the odds ratio for age represents the estimated change in odds of the outcome for a 1 year increase in age, with all other variables unchanged. The units for NIHSS score are points on a scale from 0 to 37 (maximum observed in this trial). Factors with three levels were either retained or excluded at each step; the method did not permit separate consideration of the individual 1 of contrasts comprising the three-level factors. NIHSS=National Institutes of Health Stroke Scale. OHS=Oxford Handicap Scale.

There was no interaction between alteplase use and any individual or combined imaging sign for sICH or functional outcome (OHS score 0-2) even when time to randomisation was considered. However, the absolute increase in sICH after alteplase with combined imaging signs was large (OR 2.98 [95% CI: 1.71-5.15 for combination of old infarct and hyperattenuated artery vs neither sign; absolute excess of events with alteplase 13.8%, 95% CI: 6.9-20.7]). No difference in absolute effects was observed for functional outcome at 6 months (OHS score 0-2) for all patients and by separate time windows.

In conclusion, the authors state that there was no unequivocal evidence that any radiological sign modified the response to alteplase in the study population, even extensive early ischaemic signs that are listed as contraindications. Some combinations of radiological signs increased the absolute risk of sICH (table 23).

Magnetic Resonance imaging

The results of multimodal magnetic resonance imaging using diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) sequences may predict the risk of HT. Singer et al. (2008) reported the sICH risk according to DWI lesion size using data from 645 patients with anterior circulation infarcts treated with intravenous (n=536) or intra-arterial alteplase within 6 h of stroke onset. SICH defined using NINDS criteria and pretreatment DWI lesion size was categorised into 3 prespecified groups: small (≤ 10 ml; n=218); moderate (10-100 ml; n=371); and large (>100 ml; n=56). The sICH rate increased with DWI lesion size (2.8% for small; 7.8% for moderate; and 16.1% for large lesion sizes, $p<0.05$). Similar findings were seen when lesion size was assessed using the ASPECT score in 217 patients with anterior circulation stroke (Singer et al. 2009). The DEFUSE Trial performed MR imaging immediately before and at 3 to 6 h after treatment with intravenous alteplase given at 3 to 6 h after stroke onset in 72 patients (Albers et al. 2006). A malignant mismatch pattern, defined as a large (>100 ml) baseline DWI lesion or a PWI lesion with a delayed time to maximum concentration, was associated with an unfavourable outcome and a 50% risk of fatal haemorrhage. A post hoc multivariate analysis of the DEFUSE data noted that DWI lesion volume was the single independent baseline predictor of sICH (OR 1.42 [95% CI: 1.13-1.78 per 10 ml increase in DWI lesion volume]) (Lansberg et al. 2007). Studies using CT perfusion have reported similar findings but this technique requires further validation (Bivard et al. 2011; Souza et al. 2012).

Small vessel changes

White matter lesions (leukoaraiosis)

The term leukoaraiosis was introduced to describe areas of white matter hypoattenuation seen on early CT scans (Hachinski et al. 1987). MRI is a more sensitive method than CT at detecting white matter lesions, which appear as hyperintense areas on T2 and FLAIR sequences often located around the ventricular system and the intermediate subcortical white matter. Population-based studies have shown strong associations between hypertension and age with leukoaraiosis and genome-wide association studies have identified 6 novel single-nucleotide polymorphisms that may be linked to white matter lesions (Fornage et al. 2011). White matter lesions are seen in more than 80% of subjects aged over 60 years and are more common in women (Rincon and Wright 2014). Pathological examination of leukoaraiosis has shown marked arteriosclerosis, loss of myelin, gliosis, axonal loss, venous collagenosis and multiple small cavitations consistent with ischaemia. Severe lesions may show loss of endothelium with disruption of the blood-brain barrier which may pre-dispose to ICH (Young et al. 2008). Leukoaraiosis was historically considered an incidental finding but recent epidemiological studies have

associated white matter lesions with cognitive decline and a large meta-analysis of 46 observational studies has linked leukoaraiosis with a greater risk of future stroke, dementia and death (Debette and Markus 2010).

A recent review evaluated the risk of ICH in patients with neuroimaging evidence of leukoaraiosis who are treated with alteplase for ischaemic stroke (Pantoni et al. 2014):

Table 24: Clinical studies investigating the risk of ICH in patients with leukoaraiosis treated with thrombolysis (Pantoni et al. 2014).

Study and year	Study design	Patient number	Extent definition of leukoaraiosis	Treatment	Major outcome measures	Results
Neumann-Haefelin et al., 2006 [24]	Retrospective multicenter	449 (74.6)	By Fazekas and Schmidt visual rating scale	IV rt-PA ± IA rt-PA or urokinase	PH with any neurological deterioration	Higher rate of symptomatic ICH in patients with moderate-to-severe leukoaraiosis
Palumbo et al., 2007 [25]	Retrospective multicenter	936 (-)	By van Swieten scale	IV rt-PA	ICH with any neurological deterioration	Higher rate of symptomatic ICH in patients with severe leukoaraiosis
Demchuk et al., 2008 [6]	Retrospective multicenter	299 (33.1) ¹ 304 (33.2) ²	By van Swieten scale	IV rt-PA; placebo	ICH with any neurological deterioration	Nonsignificant trend for higher rate of symptomatic ICH in patients with leukoaraiosis receiving thrombolysis compared with placebo
Ariès et al., 2010 [27]	Retrospective single center	400 (24.3)	By van Swieten scale	IV rt-PA	PH2 with worsening by ≥4 points on NIHSS or death	Nonsignificant trend for higher rate of symptomatic ICH in patients with leukoaraiosis
Shi et al., 2012 [30]	Retrospective single center	105 (-)	By Fazekas and Schmidt visual rating scale	Mechanical thrombectomy ± IA rt-PA ± IV rt-PA	Any hemorrhagic transformation	Higher rate of any hemorrhagic transformation in patients with moderate-to-severe leukoaraiosis

Values in parentheses denote % leukoaraiosis. IV = Intravenous; IA = intraarterial; PH = parenchymal hematoma; PH2 = PH type 2.

¹ rt-PA arm.

² Placebo arm.

Standard scales for the visual grading of white matter changes on CT and MRI have been developed (Fazekas et al. 1987; van Swieten et al. 1990).

Neumann-Haefelin et al. (2006) reported a significantly higher rate of sICH (n=12 of 114; 10.5%) in patients with moderate-to-severe leukoaraiosis (defined as early confluent foci and confluent changes) on MRI in deep white matter vs those with none or mild leukoaraiosis (punctate foci; n=13 of 335; 3.8%). The OR was 2.9 (95% CI: 1.29-6.59, $p=0.015$). Leukoaraiosis remained an independent risk factor after a logistic-regression analysis (including age, stroke severity and type of thrombolytic treatment) with an OR 2.9 ($p=0.03$). This study included 363 patients treated with intravenous alteplase within 3 h of stroke onset and 86 treated with intra-arterial or combined intravenous/intra-arterial treatment with alteplase or urokinase within 3 h although the mean thrombolysis times exceeded 180 mins in all groups. We are not told how many patients received urokinase.

Palumbo et al. (2007) measured the presence and extent of leukoaraiosis on the CT scans of 820 patients using the van Swieten scale (the anterior and posterior regions of the axial CT are rated using a three-point scale ranging from 0 (no white matter hypodensity) to 2 (confluent white matter hypodensity from the ventricles to the grey matter). The total score is calculated by adding the scores from anterior and posterior regions giving a maximum score of 4). In this study, each cerebral hemisphere was scored separately and added to give a total score of 0-8 for the whole brain, the van Swieten score was then dichotomised with a total score >4 (10th percentile) denoting severe white matter disease. A significant association was observed between ICH risk and either severe leukoaraiosis (RR 2.7 [95% CI 1.1-6.5]) or multiple lacunes (RR 3.4 [95% CI 1.5-7.6]). Patients with multiple lacunes, but not leukoaraiosis, had higher mortality at 90 days compared to those with one or no lacunes (OR 2.9 [95%

CI: 1.3-6.2, $p = 0.008$). No difference was observed in the good outcome (defined as mRS score 0-1) rate among patients with and without small vessel disease. 8.4% of the patients with severe white matter disease developed sICH compared to 3% of patients with none or moderate leukoaraiosis (RR 2.75 [95% CI 1.15-6.53, $p = 0.03$]). SICH occurred in 10% of patients with multiple lacunes, and in 2.9% of patients with one lacune or less (RR 3.40 [95% CI: 1.50-7.68, $p = 0.008$]). These relative risk ratios did not alter significantly after multivariable analysis.

A systematic review concluded that the risk of clinically important ICH was increased in the presence of leukoaraiosis at baseline (OR 2.45 [95% CI: 1.64-3.66, $p < 0.001$]) using data from 6 studies (Whiteley et al. 2012).

Cerebral microbleeds

Cerebral microbleeds are small deep or superficial haemorrhages of 2-10 mm diameter seen on MRI (Rincon and Wright 2014). These abnormalities represent collections of hemosiderin-laden macrophages around small perforating vessels. Cerebral microbleeds occurring in a lobar distribution are considered to be related to cerebral amyloid angiopathy (Yates et al. 2014). The prevalence of cerebral microbleeds in the general population is around 5% but it rises to 23% in patients that have had a first ischaemic stroke and up to 52-80% in those that have experienced an ICH (Cordonnier et al. 2007).

The clinical studies reporting the risk of ICH in patients with cerebral microbleeds treated with thrombolysis are shown:

Table 25: Clinical studies reporting the risk of ICH in patients with cerebral microbleeds treated with thrombolysis (Pantoni et al. 2014).

Study and year	Study design	Patient number	Age, years	NIHSS score at onset	MRI sequences	Treatment	Major outcome measures
Kidwell et al., 2002 [31]	Nonrandomized prospective single center	41 (12.2)	-	-	Conventional GRE and susceptibility-weighted imaging	IV rt-PA + IA rt-PA ± mechanical thrombectomy; IA rt-PA or urokinase ± mechanical thrombectomy	ICH with worsening by ≥4 points on NIHSS or ≥1 point on NIHSS LOC
Dereix et al., 2004 [32]	Retrospective single center	44 (18.2)	63 ¹	14 ¹	Conventional GRE	IV rt-PA	ICH with worsening by ≥4 points on NIHSS or ≥1 point on NIHSS LOC
Kakuda et al., 2005 [33]	Prospective multicenter	70 (15.7)	71 ¹	13 ¹	Conventional GRE	IV rt-PA	ICH with worsening by ≥2 points on NIHSS
Kim et al., 2006 [34]	Retrospective single center	65 (38.5)	67 ¹	-	Conventional GRE	IV rt-PA; IA urokinase	ICH with any neurological deterioration
Fiehler et al., 2007 [35]	Nonrandomized prospective-retrospective multicenter	570 (15.1)	69 ²	13 ²	Conventional GRE	IV rt-PA	Space-occupying PH2 with worsening by ≥4 points on NIHSS

Values in parentheses denote % cerebral microbleeds. GRE = Gradient-echo imaging; IV = intravenous; IA = intraarterial; LOC = level of consciousness; PH2 = parenchymal hematoma type 2.

¹ Mean value.

² Median value.

The largest study included 570 patients treated with intravenous alteplase with magnetic resonance imaging data (including T2*-weighted sequences) acquired within 6 h of stroke onset (Fiehler et al. 2007). The number of cerebral microbleeds ranged from 1 to 77 per patient. SICH was defined using ECASS criteria. There was no significant absolute increase in the risk of sICH in those with cerebral microbleeds (5.8% vs 2.7% in those without, $p = 0.17$).

A meta-analysis of the 5 studies included in table 25 reported that the overall prevalence of cerebral microbleeds was 135/790 (17.1%) and that 10/135 (7.4%) of those with microbleeds had a sICH after thrombolysis compared to 29/655 (4.4%) of patients with none (Charidimou et al. 2013). The pooled RR of ICH was 1.90 (95% CI: 0.92-3.93; $p = 0.08$). Another meta-analysis of the same data reported an OR of

1.98 (95% CI: 0.90-4.35, $p = 0.09$) for the risk of sICH after thrombolysis in those with cerebral microbleeds (Shoamanesh et al. 2013).

Concluding comments:

The SmPC for Actilyse lists *severe stroke as assessed clinically (eg NIHSS >25) and/or by appropriate imaging techniques and prior stroke within the last 3 months* as a contra-indication and states that *patients with extensive infarctions are at greater risk of poor outcome including severe haemorrhage and death* in section 4.4.

The National clinical stroke guideline recommends that patients with severe stroke and those with early signs of infarction on the initial scan also benefit from treatment (as long as these early radiological signs are subtle and consistent with the stated time of onset and do not suggest a lesion older than 6 h) (The Intercollegiate Working Party for Stroke 2012). Severe stroke is not defined but the guidelines note that IST-3 only recruited patients with no significant restriction of their activities of daily living (defined as Oxford Handicap Score <3).

The European Stroke Organization guidelines (2008) note that patients with a hypoattenuating ischaemic lesion which exceeds one third of the middle cerebral artery territory may benefit less from thrombolysis and the American Heart Association Guidelines (Jauch et al. 2013) consider this finding to be a relative contra-indication to alteplase treatment.

Implications for the marketing authorisation

On the basis of the available data, the existing SmPC wording is considered adequate at describing the increased risks of alteplase associated with large or established areas of infarction.

There is conflicting data from observational studies on an increased risk of ICH after alteplase in patients with long-standing abnormalities on the baseline imaging scans such as previous infarction, leukoaraiosis and cerebral microbleeds. The IST-3 study reported that some combinations of pre-existing radiological signs increased some absolute risks. However, severe leukoaraiosis does appear to increase the risk of sICH after thrombolysis.

The SmPC could be amended to reflect this risk as this degree of leukoaraiosis is usually apparent on a baseline CT scan.

7.3.5. Predictive outcome models

A number of scoring systems based on logistic regression models incorporating clinical features, neuroradiological and laboratory findings have attempted to estimate the effectiveness of alteplase and risk of ICH after thrombolysis. The potential uses of predictive models include: estimation of the benefits and risks of alteplase therapy to provide accurate prognostic information when counselling patients and their relatives; identifying patients who are likely to have a poor outcome despite thrombolysis and plan additional interventions such as endovascular procedures or neurosurgery; balancing baseline risks of comparator groups in future clinical studies of treatments for acute ischaemic stroke, diagnostic techniques or stroke biomarkers (Echouffo-Tcheugui et al. 2013).

Age, stroke severity and hyperglycaemia or diabetes mellitus are the most frequently included factors and some include radiological features derived from CT scans (table 26).

Table 26: Selected scores that predict ICH after alteplase

Score	Demographic factors	Clinical factors	Neuroimaging factors
Haemorrhage After Thrombolysis (HAT) (Lou 2008)	Diabetes mellitus	Hyperglycaemia NIHSS score	Hypodensity on initial CT
Cucchiara 2008	Age	NIHSS score Hyperglycaemia Platelet count	None
DRAGON* (Strbian 2012a)	Age Onset-to-treatment time	Baseline mRS Glucose NIHSS score	Dense MCA sign or early infarct on CT head
Glucose Race Age Sex blood Pressure Severity (GRASPS) (Menon 2012)	Age Gender Ethnicity	NIHSS score Blood pressure Hyperglycaemia	None
iSCORE (Saposnik 2012)	Age Disability Gender Vascular risk factors (AF, CHF) Co-morbidity (cancer or renal dialysis)	Canadian Neurological Scale Stroke subtype Hyperglycaemia	None
Sugar Early infarct (hyper)Dense cerebral artery Age NIHSS (SEDAN) (Strbian et al. 2012b)	Age	Hyperglycaemia NIHSS score	Hyperdense artery sign Early infarct changes on initial CT
Stroke Prognostication using Age and NIHSS (SPAN)-100 (Saposnik 2013b)	Age	NIHSS score	None
SITS-sICH Risk Score (Mazya 2012)	Age Aspirin or combined Aspirin and clopidogrel Onset-to-treatment time Hypertension	NIHSS score Hyperglycaemia Systolic blood pressure Body weight	None
Stroke-Thrombolytic Predictive Instrument (Kent 2006)	Age Sex Onset-to-treatment time Prior stroke Diabetes mellitus	NIHSS score Glucose Systolic blood pressure	None
Totaled Health Risks In Vascular Events (THRIVE) (Flint 2013)	Age Hypertension Diabetes mellitus Atrial fibrillation	NIHSS score	None

Key: AF=atrial fibrillation; CCF=congestive heart failure; DRAGON=Dense middle cerebral artery sign or early infarct on CT, baseline modified Rankin Scale, **A**ge, **G**lucose, **O**nset-to-treatment time, **NIH** Stroke scale score; MCA=middle cerebral artery; mRS=modified Rankin Scale score.

The Stroke-Thrombolytic Predictive Instrument (Stroke-TPI) predicts a good outcome defined as a mRS of 0-1, the DRAGON (dense middle cerebral artery sign or early infarct on CT, baseline modified Rankin Scale, age, glucose, onset-to-treatment time, NIHSS) model uses a mRS of 0-2 and the HAT predicts mRS scores of 0-1 or 0-2 at day 90 (Kent et al. 2006; Strbian et al. 2012a; Lou et al. 2008). The following predictive models were developed to assess risk of ICH: HAT (haemorrhage after thrombolysis); SEDAN (sugar, early infarct sign, hyperdense middle cerebral artery, age, neurological deficit); and the GRASPS (glucose at presentation, race, age, sex, systolic blood pressure at presentation, and severity of stroke at presentation) score. The iScore was originally developed to predict mortality after stroke but also predicts outcome and sICH after alteplase (Rempé 2014).

A recent systematic review of 13 risk models to predict ICH after thrombolysis concluded that they possessed modest to acceptable discriminative abilities but calibration, external validity and applicability issues limited their current use (Echouffo-Tcheugui et al. 2013). The predictive qualities of the Cucchiara et al. (2008) score, Haemorrhage After Thrombolysis (HAT), SITS-sICH, Glucose Race Age Sex blood Pressure Severity (GRASPS) and Stroke Prognostication using Age and NIHSS (SPAN)-100 risk scores were assessed prospectively in 548 Taiwanese patients using the area under the receiver operating characteristic curve (ROC; C statistic) (Sung et al. 2013). The Cucchiara, HAT, and the SITS-sICH risk scores predicted sICH reasonably well but only the HAT score had acceptable discriminatory ability. The Total Health Risk in Vascular Events (THRIVE) score has been validated as a predictor of ICH risk with endovascular treatment (Flint et al. 2010; Flint et al. 2014a) and after thrombolysis (Kamel et al. 2013; Flint et al. 2013; Flint et al. 2014b). The predictive value of the THRIVE score was also equivalent to the HAT score and superior to the SPAN-100 score using ROC analysis (Flint et al. 2013).

The NINDS study data was re-analysed to calculate iScores (Saposnik et al. 2013c). Logistic regression analysis adjusting for alteplase showed that an iScore ≥ 200 was associated with a 3-fold greater risk of sICH (OR 3.08 [95% CI: 1.41-6.74; C statistic 0.75; 95.4% correctly classified) and no benefit (mRS score 0-2 at 3 months) after alteplase.

The IST-3 collaborative group have recently compared the discrimination and calibration properties of the following scales: HAT; SEDAN; GRASPS; Stroke Thrombolytic Predictive Instrument; Dense Artery, Rankin score, Age, Glucose, Onset to treatment time and NIHSS (DRAGON); THRIVE, with a new model and a simple model comprising NIHSS and age (Whiteley et al. 2014). All of these models were modest predictors of sICH with similar areas under receiver operator characteristic curves (AUROCC, 0.56-0.68). The simplest model (age and NIHSS co-variables) predicted both sICH (AUROCC 0.63 [95% CI: 0.58-0.68]) and poor functional outcome (AUROCC 0.8 [95% CI: 0.77-0.82]) with similar accuracy to more complex models. Alteplase appeared to be as effective in patients at high predicted risk of sICH as in those at lower risk and it was concluded that predictive models of sICH should not be used to select patients for thrombolysis in routine clinical practice.

Concluding comments:

Although the idea of an objective prognostic model is attractive, the profusion of instruments described would indicate that none are universally accepted. The accuracy of prediction models in validation cohorts is variable and lower than in their derivation studies so their current clinical utility is limited. Nevertheless, the widespread availability of bed-side electronic devices that can conduct complex

calculations may lead to the development of more accurate predictive tools to guide acute management and inform patients and their relatives (see paper 8).

7.4. Overall conclusions

The benefit-risk balance of alteplase for the indication of acute ischaemic stroke has been extensively reviewed at the national and EU level since initial licensing of the indication in 2002.

Outcome data from the placebo arms of the randomised clinical trials of thrombolytic therapy have led to a better understanding of the independent prognostic factors of acute ischaemic stroke which include age, stroke severity and co-morbidities such as diabetes mellitus, hypertension and vascular disease. Unsurprisingly, many of the same factors modify the positive and negative outcomes after thrombolysis and time-to-treatment is also important. Many of these factors interact so multivariable regression analyses are often needed to define the relative importance of each variable.

This paper evaluates evidence on the benefits and harms of alteplase when used in clinical practice, including in different patient sub-groups contra-indicated patient populations and off-label use and considers whether there are any implications for the alteplase marketing authorisation. Medication errors in association with routine use of alteplase have also been reviewed.

Use in patient sub-groups

Time to treatment

The benefit-risk balance of alteplase changes with increasing time-to-treatment from onset. There is robust evidence that treatment within the 0-3 h window is effective with an acceptable risk of ICH and mortality. The benefits of alteplase therapy appear to reduce with time up to 4.5 h after onset with similar risks. Overall the data available for the 3-4.5 hour time-window are supportive of a positive balance of benefits and risks when used within the conditions of the licence. The benefit-risk balance of alteplase beyond 4.5 h appears to be negative on the basis of available evidence

The SmPC for alteplase includes much clear information on the importance of time to treatment and the authorised stroke indication states that:

“Treatment must be started as early as possible within 4.5 h after onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques (e.g. cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage). The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.”

The information and recommendations provided in the SmPC remain appropriate on the basis of the current evidence.

Stroke severity

The available evidence indicates that stroke severity, as measured using the National Institutes of Health Stroke Scale (NIHSS), is an independent predictor of the risk of symptomatic and fatal intracerebral haemorrhage following alteplase treatment given within the 4.5 h window from stroke onset. The effectiveness of alteplase within the 4.5 h therapeutic window does not appear to vary according to stroke severity although

there is little data concerning patients with severe (NIHSS scores >22) or mild (NIHSS < 5) strokes.

Severe stroke (e.g. NIHSS >25) and mild neurological deficits or symptoms that are rapidly improving before the start of infusion are contraindications for alteplase. These remain appropriate.

Age

The benefits of alteplase are not age-related particularly when patients are treated early, and although the absolute risks of fatal and symptomatic ICH may be increased in those aged over 80 years their prognosis is also worse and so there is reason to believe that elderly patients should not be denied thrombolysis on the basis of age alone.

The benefit-risk balance of alteplase in children has not been established but is likely differ on a case-by-case basis as paediatric stroke can have different causes.

Hypertension

The association between blood pressure and stroke outcome, with and without rt-PA therapy, is complex. The management of blood pressure in early ischaemic stroke remains controversial and current clinical recommendations are based on limited and inconsistent data. Blood pressure lowering drugs are indicated to treat hypertensive emergencies and to reduce the risk of ICH associated with alteplase. Given the increasing risk of sICH and potential increase in mortality/reduction of favourable outcomes with increasing blood pressure, the contraindications in patients with very high blood pressures appear rational.

Blood glucose

There is currently no clinical evidence that controlling blood glucose during an ischaemic stroke improves outcomes after alteplase although appropriate interventional studies are underway.

Concomitant medication

Concomitant anticoagulant therapy appears to increase the risk of ICH but any assessment is confounded by indication (eg AF), age and possibly by stroke mechanism (eg cardioembolism). The risks of ICH may be increased in patients receiving aspirin and clopidogrel when thrombolysed and in those with leukoaraiosis or other established brain lesions at stroke onset.

Stroke mimics

The safety of alteplase in patients with stroke mimics was also reviewed and was considered acceptable. There is limited information on the risks of repeat alteplase treatment and we found little evidence that medication errors occur frequently although it could be useful to collect and report more data in the Sentinel Stroke Audit Programme to characterise and reduce any identified risks.

Predictive outcome models

A number of predictive outcome models for acute ischaemic stroke have been developed but none are universally accepted due to issues around validation and generalisability. Many are designed to be simple to use but the widespread availability of bed-side electronic devices that can perform complex calculations may lead to the introduction of more accurate predictive tools to guide patient management.

Medication errors

Determining the weight of a stroke patient in the emergency setting is a challenging and unavoidable part of administering rt-PA. The clinical consequences of using estimated as opposed to actual weight for calculating rt-PA dose remain unclear but it is important to consider that overdosing may lead to an increased risk of ICH and underdosing may potentially lead to a reduction in effectiveness. Although the accuracy of dosing could in theory be improved by weighing patients prior to calculation of the required dose, in an acute medical emergency it is unclear how feasible any recommendation to mandate weighing would be.

The limited data that are available in the acute stroke setting would support recommendations on best practice in national guidelines with respect to access to functioning weighing equipment for supine patients, provision of an estimate by patients then family/carers and then healthcare professionals and recording of all weights in kg. In addition the provision of clear instructions for dilution and administration for thrombolysis is advisable within all hospitals that could potentially treat acute ischaemic stroke with rt-PA.

In light of the evidence reviewed in this paper the balance of benefits and risks of alteplase in the indication of acute ischaemic stroke remains positive when used in accordance with the current restrictions in the marketing authorisation. However, minor updates to the product information could be considered at the next regulatory opportunity in order to reflect recent data on the risk of ICH in patients with leukoaraiosis and concomitant dual antiplatelet therapy.

7.5. List of recommendations for the EWG

1. The Summary of Product Characteristics (SmPC) is considered to adequately describe the benefit-risk balance for alteplase therapy according to: stroke severity; time to onset of treatment; age; concomitant anticoagulant medication; and co-morbidities of high blood pressure and previous stroke with or without high blood glucose.
2. The current contraindications for alteplase treatment for acute ischaemic stroke contained in the SmPC are considered acceptable and in line with current evidence.
3. A small number of observational studies have reported that the risk of alteplase-induced intracerebral haemorrhage may be increased in the presence of severe leukoaraiosis. This degree of leukoaraiosis should be visible on a baseline CT scan of the brain. Section 4.4 of the SmPC should be amended (*in italic*) as follows:

Other special warnings:

Data from a small number of observational studies indicates that the presence of severe leukoaraiosis on a baseline CT brain scan may increase the risk of intracerebral haemorrhage.

4. A small number of observational studies involving a large number of patients have observed that the combination of aspirin and clopidogrel increases the risk of alteplase-induced intracerebral haemorrhage over that associated with aspirin and clopidogrel monotherapy at stroke onset. The EWG recommends that Section 4.4 of the SmPC should be amended (*in italic*) as follows:
 - patients pre-treated with acetyl salicylic acid (ASA) may have a greater risk of intracerebral haemorrhage, particularly if Actilyse treatment is delayed. *This*

risk may be further increased in patients treated with the combination of aspirin and clopidogrel.

5. There is evidence to suggest that errors are made due to the weight-based dosing requirement for alteplase. The national guidelines could include the following recommendations:
 - All stroke facilities should have access to functioning weighing equipment that are suitable for supine patients and provide a rapid assessment of body weight in. If this is not possible then patients should be asked to state their body weight. If this is not possible then relatives should be consulted, where this is not possible the consensus view of more than one healthcare professional should be used. All body weights should be recorded in kilograms.
 - The provision of clear instructions for dilution and administration for thrombolysis is advisable within all hospitals that could potentially treat acute ischaemic stroke with alteplase
 - Data on medication errors and specifically dosing errors should be routinely recorded and reported in the Sentinel Stroke National Audit Programme.

7.6. Key points for discussion by the EWG.

- Does the EWG agree with the conclusions and recommendations?
- Is any further regulatory action required to more accurately reflect current evidence and to optimise the balance of benefits and risks of alteplase in acute ischaemic stroke?
- Does the EWG have any comments on the level of data available to demonstrate a positive (or otherwise) balance of benefits and risks in patients aged >80 years?
- Are medication errors, in particular relating to dosing, a significant issue in routine clinical practice?
- Is misdiagnosis of acute ischaemic stroke a significant concern that is under-reported in the literature?

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