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Influence of Age on Outcome From Thrombolysis in Acute Stroke

A Controlled Comparison in Patients From the Virtual International Stroke Trials Archive (VISTA)

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Background and Purpose—Thrombolysis for acute ischemic stroke in patients aged >80 years is not approved in some countries due to limited trial data in the very elderly. We compared outcomes between thrombolysed and nonthrombolysed (control) patients from neuroprotection trials to assess any influence of age on response.

Method—Among patients with ischemic stroke of known age, pretreatment severity (baseline National Institutes of Health Scale Score), and 90-day outcome (modified Rankin Scale score; National Institutes of Health Scale score), we compared the distribution of modified Rankin score in thrombolysed patients with control subjects by Cochran-Mantel-Haenszel test and then logistic regression after adjustment for age and baseline National Institutes of Health Scale score. We examined patients ≤80 and ≥81 years separately and then each age decile.

Results—Rankin data were available for 5817 patients, 1585 thrombolysed and 4232 control subjects; 20.5% were aged >80 years (mean±SD, 85.1±3.4 years). Baseline severity was higher among thrombolysed than control subjects (median National Institutes of Health Scale score 14 versus 13, $P<0.05$). The distribution of modified Rankin Scale scores was better among thrombolysed patients ($P<0.0001$; OR, 1.39; 95% CI, 1.26 to 1.54). The association occurred independently with similar magnitude among young ($P<0.0001$; OR, 1.42; 95% CI, 1.26 to 1.59) and elderly ($P=0.002$; OR, 1.34; 95% CI, 1.05 to 1.70) patients. ORs were consistent across all age deciles >30 years; outcomes assessed by National Institutes of Health Scale score gave supporting significant findings, and dichotomized modified Rankin Scale score outcomes were also consistent.

Conclusions—Outcome after thrombolysis for acute ischemic stroke was significantly better than in control subjects. Despite the expected poorer outcomes among elderly compared with young patients that is independent of any treatment effect, the association between thrombolysis treatment and improved outcome is maintained in the very elderly. Age alone should not be a barrier to treatment. (*Stroke*. 2010;41:2840-2848.)

Key Words: elderly ■ outcome ■ thrombolysis

Thrombolysis for acute ischemic stroke has proven benefits, but randomized trial data in patients >80 years are limited.[1–5] To date, the European Medicines Evaluation Agency has not approved thrombolysis with alteplase among the very elderly.[4,6,7] Patients >80 years represent approximately 30% of acute stroke incidence.[2,4,8,9] Many experienced centers treat the elderly but others observe the terms of product approval.[7,10,11]

The National Institute of Neurological Disorders and Stroke trial initially restricted enrollment to patients aged up to 80 years.[1] The age criterion was lifted after enrolling 188 patients in Part A of the trial, but only 42 very elderly patients were enrolled.[1] All European Cooperative Acute Stroke Study (ECASS) trials applied an upper age limit of 80 years,[5] and recent studies with desmoteplase also excluded the elderly.[12] The main reasons advanced for withholding treatment from the elderly patients in clinical practice are fears that advancing age is associated with poorer prognosis with greater risk for hemorrhage and in-hospital mortality.[13,14]

Conversely, a meta-analysis of pooled thrombolysis data concluded that the risks of symptomatic intracerebral hemorrhage (ICH) did not increase among the elderly despite less favorable outcomes.[10] Less favorable outcomes are expected to occur in the elderly, mostly due to comorbidity.[4,15]

The proportion of elderly is rising in our society.[8] In the United Kingdom alone, the population aged >80 years has doubled since 1982.[16] Effective treatments should not be withheld from the elderly in the absence of compelling data suggesting unacceptable risk or proven lack of benefit. We hypothesized that clinical practice over the last decade would have been sufficiently diverse to allow analysis of existing rigorously collected clinical data[17] to construct a comparison of thrombolysis against matched control subjects with the possibility of adjusting for any imbalance in severity. We anticipated that use in the elderly would be sufficiently frequent to assess the influence of age on any association of stroke outcome with thrombolysis treatment.

Methods

Data Source and Patients

We collated the demographics, clinical data, and measures of functional outcome from neuroprotection trials conducted in the period 1998 to 2007 held within the Virtual International Stroke Trials Archive (VISTA; www.vista.gla.ac.uk).[17] All trials held necessary review board and regulatory approvals, and patients consented to participation; only anonymized data are held by VISTA. We sought data from VISTA deriving from trials in which the investigational neuroprotection agent was not vasoactive or interfered with clotting or from placebo groups. We excluded any patient who had cerebral hemorrhage or stroke of undetermined etiology. To avoid dual publication, we excluded patients who may have been enrolled in Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST)[18] determining this from their country and date of enrollment. Finally, we excluded patients lacking our chosen outcome measure, 90-day modified Rankin Score (mRS), or secondary outcome, 90-day National Institutes of Health Stroke Scale (NIHSS) score. Patients who died within 90 days were given an mRS score of 6 and categorized separately for NIHSS analysis.

Statistical Analysis

We undertook a nonrandomized, adjusted comparison of outcomes between patients who received recombinant tissue plasminogen activator (rtPA) and patients who did not receive rtPA (henceforth referred to as treated and control groups, respectively) among patients who met the age criterion for the European alteplase marketing authorization. We repeated the comparison among patients aged ≥81 years. We then examined the association of thrombolysis treatment with outcome within each age decile to illustrate the strength of evidence across the full age range. For each contrast, we compared the overall distribution of all 7 categories of Day 90 mRS scores of the 2 groups, that is, from 0 (asymptomatic) through 5 (bedbound and completely dependent), to 6 (dead). The European Medicines Evaluation Agency Points to Consider for reporting trials allows use of the full range of the Rankin scores and further suggests that this can be supported by a secondary analysis of another outcome measure such as NIHSS.[19] For analysis of our supporting end point, NIHSS, we grouped adjacent scores into categories: 0 (no measurable deficit), 1 to 4, 5 to 8, 9 to 12, 13 to 16, 17 to 20, 21 to 24, ≥25 (most severe neurological deficit), or dead. The distribution of patients across these categories was then compared between the groups as for mRS. To test for a significant association of outcome distribution with thrombolysis exposure, we used the Cochran-Mantel-Haenszel (CMH) statistic adjusting for both age and baseline NIHSS as continuous variables.[20,21] This nonparametric approach avoids invoking an assumption of propor-

tional odds in which there should be a common OR across all cut points on the ordinal outcome scale, and we consider that the CMH test provides the most conservative estimate of statistical significance. However, it does not express the extent of the association. For this, we applied logistic regression analysis, also adjusted for age and baseline NIHSS, to estimate the OR under the assumption of proportional odds and its associated 95% CI.[22] Stratification by covariates in the CMH test is limited by the sample size and precludes simultaneous adjustment for all possible variables. Hence, we prospectively planned to adjust for age and baseline NIHSS and to consider other variables only in exploratory analyses. Our choice of baseline factors for adjustment was based on 2 influences.[22] First, age and baseline severity are the 2 most powerful prognostic factors for stroke and are usually included in outcome distribution analyses.[23,24] Second, age and NIHSS data were available for our entire sample, whereas other factors of potential interest were incomplete. However, we also undertook a sensitivity analysis by considering the combined effect of the variables that differed significantly at baseline.

For comparison with prior randomized trial and registry reports, we also present dichotomized analyses of mRS based on favorable outcome (mRS 0 to 1), independence (mRS 0 to 2), and survival; these analyses were expressed as ORs adjusted for age and baseline NIHSS, like for the primary and secondary end points.[25] ORs in our analysis express the common odds of an improved distribution of outcome in association with alteplase treatment. CMH and logistic regression analysis were undertaken using SAS 9.2 software and other analyses by StatsDirect software. Reliable information on symptomatic hemorrhage was not available because posttreatment imaging was not routinely applied in neuroprotection trials to patients who had not been treated with alteplase.

Results

Patient Sample

We collated data on 9665 patients of whom 5342 (59%) were enrolled from non-European sites. To avoid dual publication with SITS-MOST,[18] we excluded 2789 patients (28%) enrolled from European sites between 2002 and 2006 and 177 patients for whom we lacked information on nationality. Complete data were available for analysis of mRS in 5817 patients and on NIHSS in 5715 (description of data available online, see supplement; available at http://stroke.ahajournals.org).

All patients with stroke were treated as per institutional practice and stroke guidelines acceptable at the point of trial conduct. Monitoring for protocol compliance was undertaken on behalf of sponsors for these trials. This implies that when thrombolysis was administered, this was in accordance with marketing authorization for the relevant country, that is, that treatment started within 3 hours of stroke onset; however, the onset to treatment delay is not recorded for thrombolysis in these trials.

Our data derived mainly from Northern American (60%), European (16%), and Australasian (13%) centers.

Baseline characteristics are shown in the Table. Of the 5817 patients with mRS outcome data, 1585 (27.2%) received thrombolysis. Baseline severity was higher by 1 NIHSS point among the younger patients who received thrombolysis therapy compared with our control group; among patients aged ≥80 years, severity was equal between treated and control groups. The delay between stroke onset and initiation of alteplase was not recorded, but the delay to research enrollment and initiation of the investigational product was shorter in the thrombolysis group than control subjects irrespective of age (3.7 versus 5.1 hours, $P=0.0001$). Independently, baseline NIHSS accounted for 28% and age for 9.7% of the variation in 90-day outcome by mRS (both

Table. Baseline Characteristics of the Patients

	Thrombolysis		Control		P
Age, mean years (range)					
All	71 (21–98)	N=1585	72 (21–101)	N=4232	<0.05
Young age ≤80	67 (21–80)	N=1284	69 (21–80)	N=3339	<0.05
Elderly age >80	84 (81–98)	N=301	84 (75–101)	N=893	0.58
Sex, male					
All	880/1585	55.52%	2226/4232	52.6%	0.05
Young age ≤80	750/1284	58.4%	1874/3339	56.1%	0.16
Elderly age >80	130/301	34.9%	352/893	39.4%	0.25
Baseline NIHSS					
All	14 (2–32)	N=1585	13 (2–37)	N=4232	<0.05
Young age ≤80	13 (2–30)	N=1284	12 (2–32)	N=3339	<0.05
Elderly age >80	15 (4–32)	N=301	15 (2–37)	N=893	0.70
Prior antiplatelets					
All	429/1078	39.8%	446/1306	34.2%	<0.05
Young age ≤80	323/881	(36.7%)	335/1049	31.9%	0.03
Elderly age >80	106/197	53.8%	111/257	43.2	0.02
Prior anticoagulation					
All	67/1078	6.2%	198/1306	15.2%	<0.05
Young age ≤80	49/881	5.6%	151/1049	14.4%	<0.05
Elderly age >80	18/197	9.1%	47/257	18.3%	0.01
Previous stroke					
All	319/1555	20.5%	1579/4076	38.7%	<0.05
Young age ≤80	248/1255	19.8%	1178/3201	36.8%	<0.05
Elderly age >80	71/300	23.7%	401/875	45.8%	<0.05
Congestive heart failure					
All	151/1262	12%	164/1409	11.6%	0.79
Young age ≤80	100/1019	9.8%	106/1136	9.3%	0.70
Elderly age >80	51/243	21%	58/273	21.3%	0.94
Diabetes mellitus					
All	342/1548	22.1%	992/3991	24.9%	0.03
Young age ≤80	293/1250	23.4%	816/3136	26%	0.08
Elderly age >80	49/298	16.4%	176/855	20.6%	0.12
Hypertension					
All	1030/1548	66.5%	2827/3991	70.8%	<0.05
Young age ≤80	813/1250	65.04	2163/3136	69%	0.01
Elderly age >80	217/298	72.8%	664/855	77.7%	0.09
Atrial fibrillation					
All	398/1548	25.7%	1274/3991	31.3%	<0.05
Young age ≤80	268/1250	21.4%	807/3136	25.7%	<0.05
Elderly age >80	130/298	43.6%	440/855	51.5%	0.02
Myocardial infarction					
All	278/1548	18%	691/3991	17.3%	0.57
Young age ≤80	227/1250	18.2%	529/3136	16.9%	0.31
Elderly age >80	51/298	17.1%	162/855	19%	0.48

$P<0.0001$) and were included in all models, together explaining 33.5% of the variation.

Overall Outcome
Across our whole sample, the distribution of mRS scores was better among thrombolysed patients ($P<0.0001$; OR, 1.39; CI, 1.26 to 1.54).

Outcomes Among Patients Aged ≤80 Years
Among the 4623 patients with 90-day mRS data, treatment with thrombolysis was associated with a significantly more favorable distribution of mRS scores (Figure 1; CMH $P<0.0001$; adjusted OR, 1.4; 95% CI, 1.3 to 1.6). The unadjusted OR was 1.2 (95% CI, 1.1 to 1.4). Dichotomized comparisons were also significant for independence (mRS 0
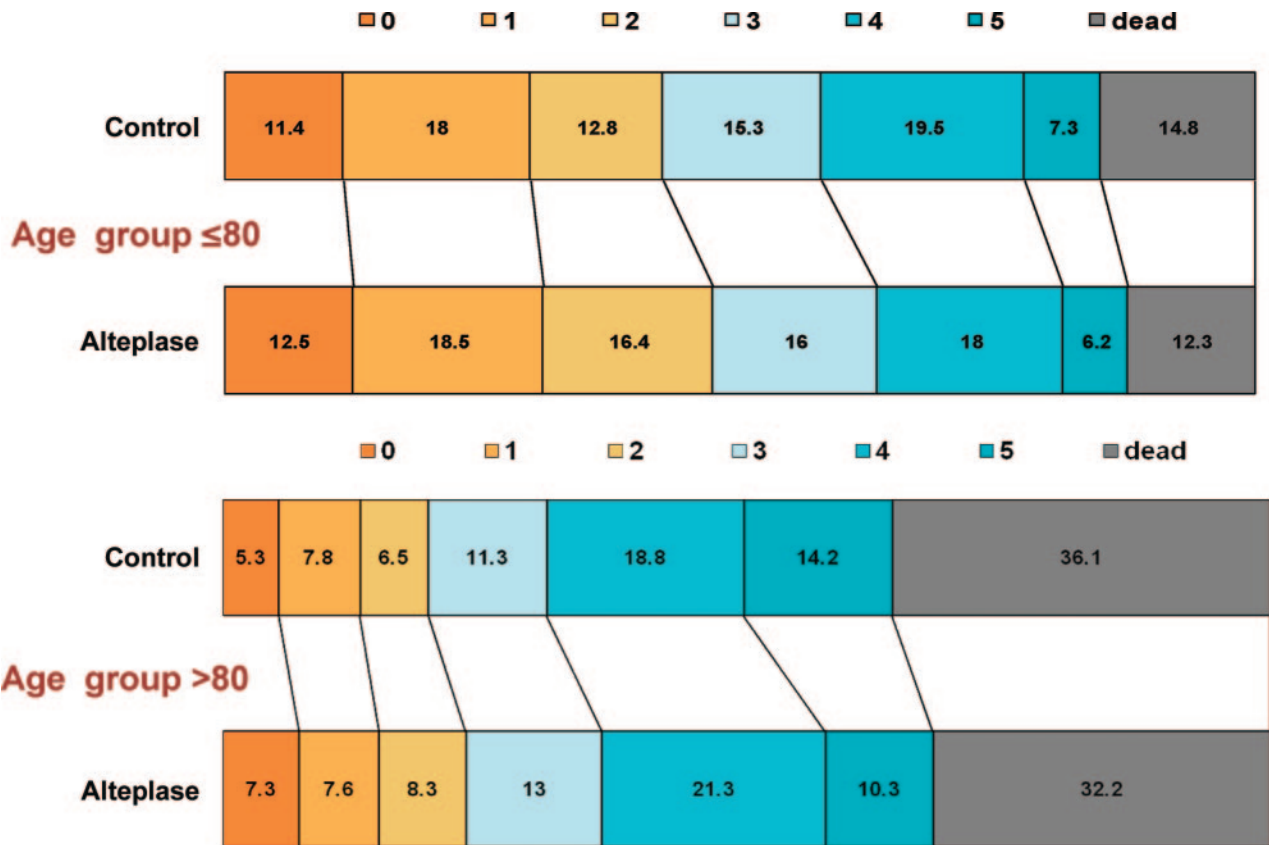
Figure 1. Diagram showing association of functional outcomes with use of rtPA in the younger patients (age ≤80 years) and elderly patients (age >80 years) having acute ischemic stroke. Each box of the horizontal bar corresponds to the mRS category specified by the color code. Upper horizontal bar belongs to control group of young and elderly patients and lower to the rtPA-treated patients in each age group. Numbers in each box denote the percent of total patients belonging to a specific treatment category (rtPA or control) and representing the mRS score corresponding to the box.

to 2 versus 3 to 6; OR, 1.54; 95% CI, 1.33 to 1.79; $P<0.0001$); for favorable outcome (mRS 0 to 1 versus 2 to 6; OR, 1.31; 95% CI, 1.12 to 1.53; $P=0.0008$); and for survival (OR, 1.44; 95% CI, 1.18 to 1.76; $P=0.0004$).

The functional outcomes were supported by the secondary end point (Figure 2). The spectrum of NIHSS scores at 90 days was significantly better among the thrombolysed patients than control subjects (CMH $P<0.0001$; adjusted OR, 1.6; 95% CI, 1.4 to 1.8; n=4537). The unadjusted comparison yielded an OR of 1.3 (95% CI, 1.2 to 1.5).

Our sensitivity analysis, in which we adjusted for age, baseline NIHSS, previous stroke, hypertension, and atrial fibrillation, also yielded CMH $P<0.0001$.

Outcomes Among Patients Aged ≥81 Years

Among the 1194 very elderly patients with 90-day mRS data, treatment with thrombolysis was associated with a significantly more favorable distribution of mRS scores (Figure 1; CMH $P=0.002$; adjusted OR, 1.34; 95% CI, 1.05 to 1.70). The unadjusted OR was 1.26 (95% CI, 1.00 to 1.59; CMH $P<0.05$). The dichotomized comparison was significant for independence (mRS 0 to 2; OR, 1.52; 95% CI, 1.06 to 2.17; $P=0.022$). For favorable outcome (mRS 0 to 1), the OR was 1.46 (95% CI, 0.97 to 2.20, $P=0.07$); and for survival, the OR was 1.20 (95% CI, 0.90 to 1.65; $P=0.20$).

The functional outcomes were supported by the secondary end point (Figure 2). The spectrum of NIHSS scores at 90 days was significantly better among the thrombolysed patients than control subjects (CMH $P=0.0004$; adjusted OR, 1.4; 95% CI, 1.1 to 1.8; n=1178). The unadjusted comparison yielded a similar estimate (OR, 1.4; 95% CI, 1.1 to 1.7).

Our sensitivity analysis, in which we adjusted for age, baseline NIHSS, hypertension, previous stroke, and atrial fibrillation, also yielded CMH $P=0.02$.

Association of Thrombolysis With Outcome by Age Decile

Both functional outcome (Figure 3) and neurological outcome (Figure 4) were significantly better among thrombolysed patients than control subjects within each decile of age from 51 years to 90 years; and except among the small sample of 21- to 30-year-old patients, point estimates for the adjusted ORs were consistent across all age groups.

Discussion

Our analysis demonstrates that use of thrombolysis for acute stroke is associated with better functional and neurological outcomes, and probably lower mortality, in all adult patients
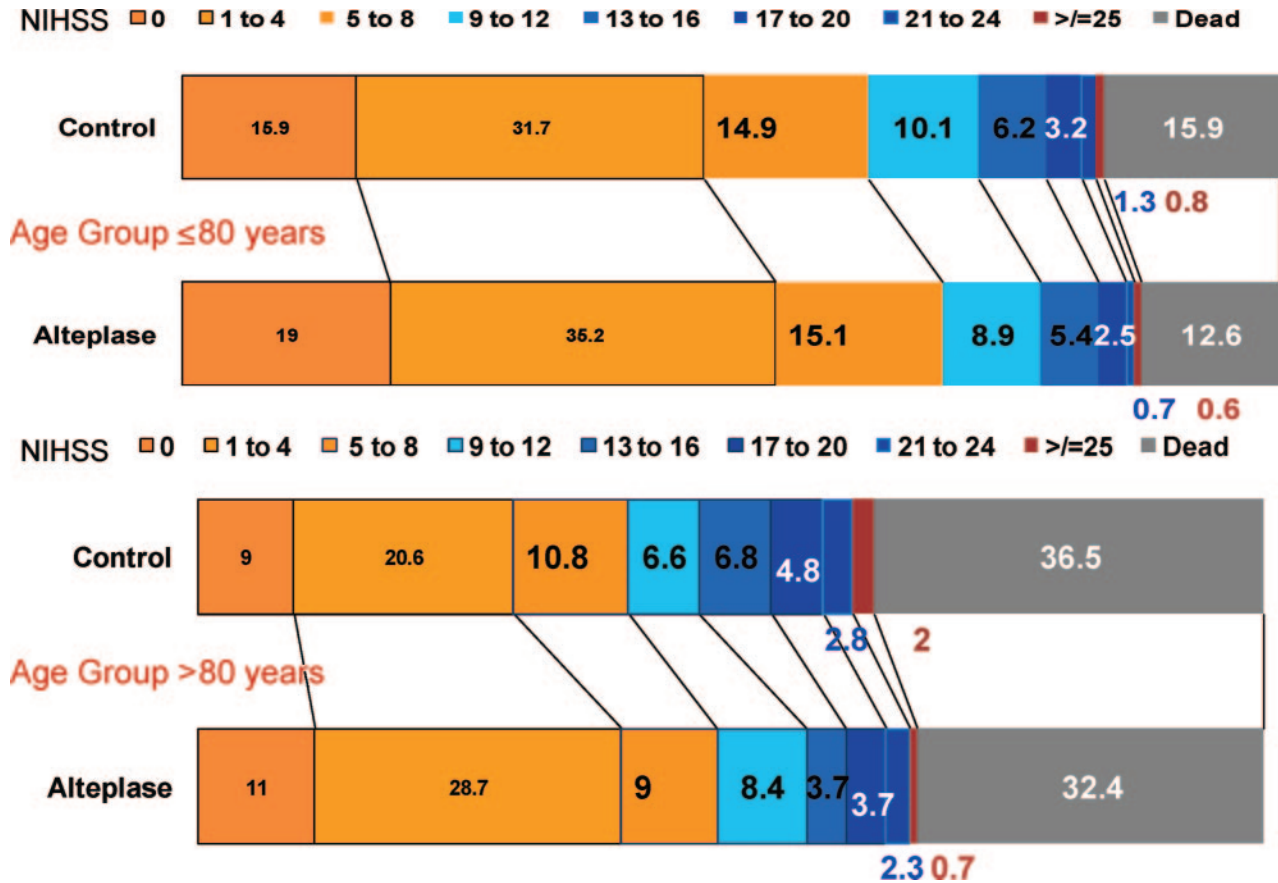
Figure 2. Diagram showing association of neurological outcomes with use of rtPA in the younger patients (age ≤80 years) and elderly patients (age >80 years) having acute ischemic stroke. Each box of the horizontal box corresponds to the mRS category specified by the color code. Upper horizontal bar belongs to control group of young and elderly patients and lower to the rtPA-treated patients in each age group. Numbers in each box denote the percent of total patients belonging to a specific treatment category (rtPA or control) and representing the mRS score corresponding to the box.

who are treated irrespective of their age. It supports the limited randomized trial data and places data on safety from stroke registries in context.

Our data draw validity from 4 origins. First, the source clinical trials of investigational medicinal products were undertaken under strict controls on reporting of concomitant treatments and outcomes, and on-site data verification procedures were in place for each trial. Second, attitudes to treatment of the very elderly vary among clinicians, some European clinicians strictly following the European Medicines Evaluation Agency marketing authorization and others in Europe and North America treating without regard to age.[26,27] Third, our estimates of control outcomes correspond closely to those from the published randomized controlled trials of thrombolysis,[3,28] our estimates of outcomes among our treated group aged ≤80 years correspond closely to those of the randomized controlled trials and of large case series such as SITS-MOST,[18] our estimate of outcomes in very elderly treated patients corresponds closely to those of Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register,[29] and our estimate of treatment ORs in the patients aged ≤80 years closely corresponds to treatment effects demonstrated in the randomized controlled trials.[5,28] Furthermore, it would be more surprising if we had

found an influence of age on the association between treatment and outcome, because there is no biological reason to expect treatment failure according to age, and there is evidence from other disease areas to support independence of treatment effects on age or even of larger absolute benefits among the elderly.[4] We acknowledge that dose-finding studies have not been undertaken in the very elderly, however. Fourth, we chose as our primary end point the mRS, which is the most prevalent outcome measure in recent stroke trials[30] and we followed an approach to analysis that is described in the European Medicines Evaluation Agency Points to Consider for interpretation of clinical trials in acute stroke.[19] There, comparison of the distribution of the full range of the mRS is proposed as acceptable with supporting evidence from a secondary end point such as NIHSS: both are positive and give similar estimates of benefit in our comparison.[31] Furthermore, although the less powerful dichotomized analyses are not all significant among the very elderly, they each give point estimates for magnitude of association that correspond to the estimates derived in the young and from the full mRS or NIHSS distributions.

Ironically, it shows that young patients <30 years may suffer harm from alteplase. This we believe could be due to other stroke mechanisms that play a role in younger age
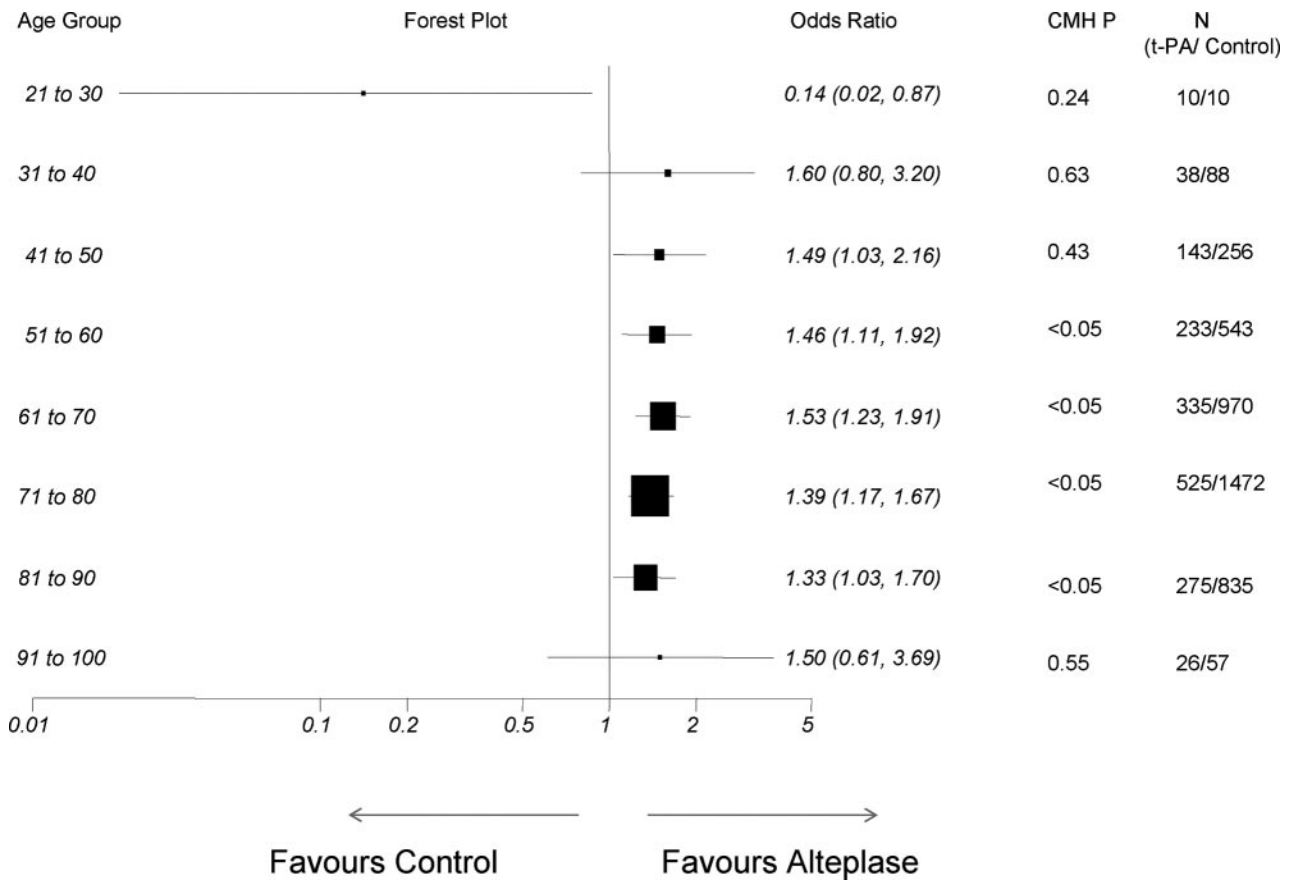
Figure 3. Forest plot showing association of functional outcomes with improved outcomes in patients who received thrombolytic therapy. Patients are shown stratified by age groups and corresponding forest plot, OR, CI, CMH *P*, and sample size are marked.

groups that are not related with thrombus that are sensitive to alteplase.

There are also limitations to our study that must be considered. Our data are based on a nonrandomized comparison, and there is a high potential for selection bias for thrombolytic treatment. Although many of the usual descriptors of baseline prognosis are reasonably matched between our groups, and although we have adjusted our analyses for the most important of these, age and baseline severity,[24] which together account for 33.5% of the variation in outcome, we could not adjust for every factor. Atrial fibrillation, use of warfarin, and prior diabetes were all less prevalent among our treated group. However, the magnitude of these differences was small, the absolute differences were equal for young versus very elderly, and our sensitivity analyses with adjustment for these additional factors also yielded significantly positive findings. This implies that although our estimate of the association of treatment with outcome may be imprecise, our estimates of trends in this measure across the age range are robust. Some of the patients in our study received an investigational neuroprotective agent and we must consider that these could interact with thrombolysis; however, each contributing trial has already tested for, and excluded, a significant interaction. VISTA data handling procedures preclude further testing for effects of the original investigational agent or identification of source trials.

We do not know the delay between stroke onset and treatment initiation in our thrombolysis group, but the time of

baseline NIHSS assessment is earlier in the thrombolysed than nonthrombolysed patients. Presentation delay is associated with outcome, but this is mediated through earlier presentation of more severe stroke, a factor that favored our control group in the young only. Last is the possibility of systematic bias in other aspects of care and thus outcome between centers that used thrombolysis routinely versus those that did not or that restricted use in the elderly. We cannot counter criticism on this point, except to indicate that the contributing trials sought to minimize such effects through site selection, training of investigators, and monitoring of care and of outcomes; and to point again to the correspondence of outcomes in each of our treatment groups with those from randomized controlled trials and registry data.

Trials and registries of thrombolysis generally report 3 outcomes: functional attainment, mortality, and symptomatic or serious ICH.[15,18,29] We lack data on the last of these, because patients who are not treated with thrombolysis generally do not undergo follow-up cerebral imaging for routine detection of hemorrhagic transformation. Fortunately, information on this aspect can be inferred from other sources: the rate of serious or symptomatic bleeding is very low among patients who do not receive thrombolysis, approximately 1%,[5,28,32–34] and registry data such as Safe Implementation of Thrombolysis in Stroke (SITS) inform us on the rate among treated patients and have found no significant increase in the very elderly compared with the young.[35] A more
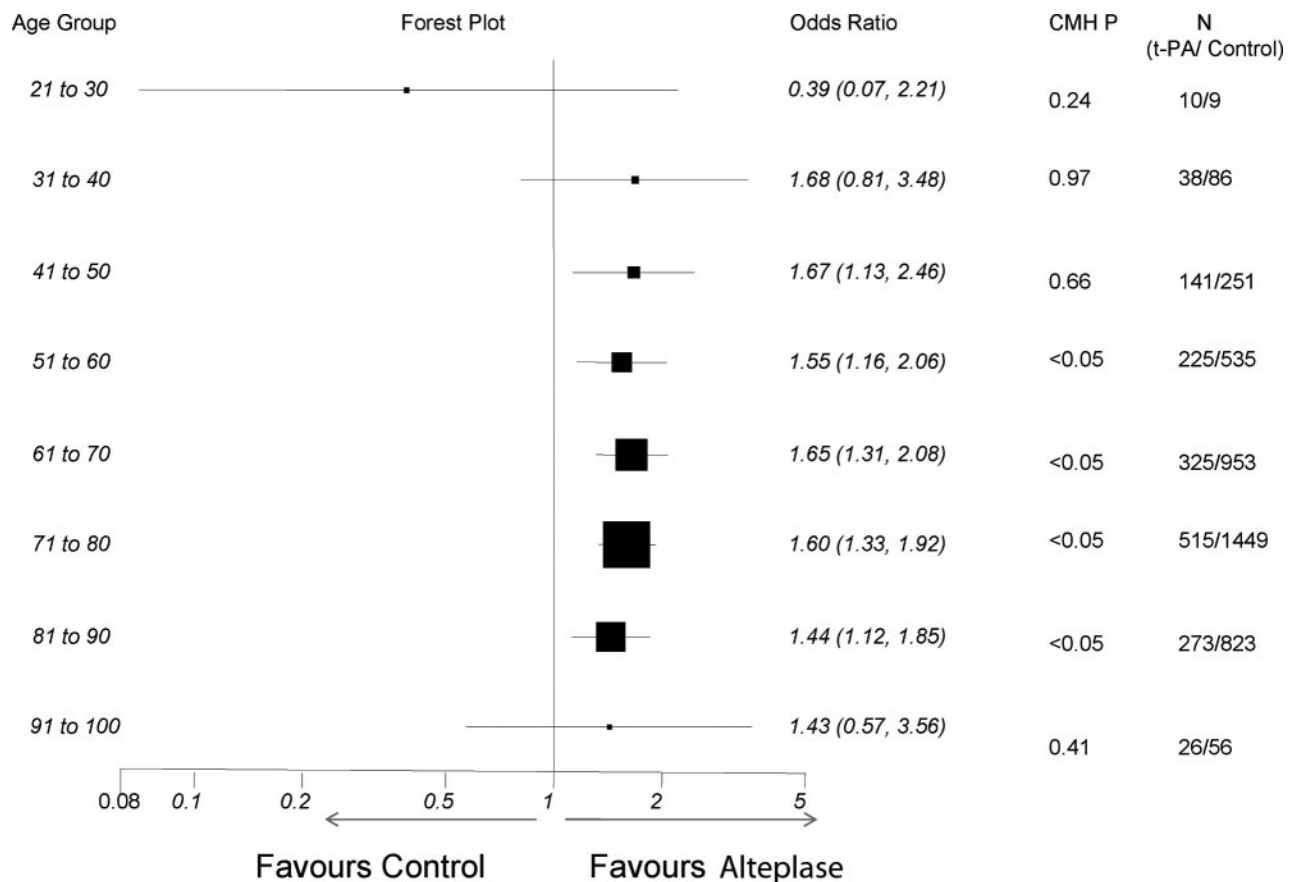
Figure 4. Forest plot showing association of neurological outcomes with improved outcomes in patients who received thrombolytic therapy. Patients are shown stratified by age groups and corresponding forest plot, OR, CI, CMH *P*, and sample size are marked.

important response on the issue of serious bleeding comes from our use of the full mRS distribution as our outcome measure. Bleeding is relevant only if it affects eventual functional outcome. Dichotomization of mRS outcomes into 0 to 1 versus 2 to 6 or 0 to 2 versus 3 to 6 could conceal harmful results of serious bleeding reflected by higher proportions of severely disabled patients within the unfavorable outcome group (for example, more mRS 5 among patients with mRS 3 to 5). Our data and analysis approach exclude this possibility; even if hemorrhage were more common in the very elderly than young, which has been discounted,[35,36] this does not translate into poorer functional outcomes after adjustment for age and stroke severity.

Data on stroke outcomes associated with thrombolysis use in the elderly come from 3 other sources. A meta-analysis of cohort studies by Ringleb and colleagues in 2007 found that the elderly experienced similar rates of symptomatic hemorrhage as the young (6.1% versus 5.1%) but higher mortality (32% versus 14%) with fewer attaining favorable outcome by 90 days (mRS 0 to 1: 26% versus 41%).[36] However, within 1 of the largest studies in this analysis, the baseline severity of stroke was much higher in elderly than young patients (NIHSS 16 versus 13.9, respectively).[37] Outcomes of very elderly patients described by the SITS registry reinforce these findings; stroke severity was higher in the 643 elderly versus 6749 younger patients, NIHSS 15 versus 13. Symptomatic ICH was no more common in the very elderly (2.0% [95% CI,

1.1 to 3.5] versus 1.5% [1.2 to 1.8]), but 90-day mortality was higher (31% [27 to 36] versus 15% [14 to 16]); and independence (mRS 0 to 2) was achieved less frequently (30% [26 to 34] versus 52% [51 to 53]).[35] Interpretation of these uncontrolled registry findings is compromised by the known influence of age and stroke severity on outcome in the absence of thrombolysis treatment. Only 164 patients aged ≥80 years were included among the large randomized trials combined.[1,5,28,34,38,39] The elderly group was again more severely affected at baseline than the younger patients, but there was also a severity imbalance among the elderly that favored the control subjects. A pooled analysis of these data in the elderly (0 to 4.5 hours subgroup: N=137 of 2199) estimated ORs for independence (mRS 0 to 2 at Day 90) and mortality under alteplase versus placebo of 1.09 and 1.28, respectively, based on unadjusted data. However, after adjustment for the demonstrable imbalance in baseline NIHSS, the ORs, respectively, improved to 1.77 and 0.96 (Boehringer Ingelheim, data on file, see online supplement). The sample size was small and none of these outcomes reached statistical significance. Thus, our present findings are entirely consistent with the randomized trial data not only in terms of the estimated extent of benefit from treatment, but also with regard to the influence of baseline severity on the interpretation of outcomes.

Treatment allocation in our study was not randomized, and a randomized controlled trial would more conclusively in-

form the influence of rtPA on outcomes among elderly. Two trials currently aim to examine this topic.[40,41] There is an Italian trial that has so far enrolled approximately 10% of the planned 600 patients over a 2-year period.[40] The International Stroke Trial-3 aims to examine outcomes among all patients who receive thrombolytic therapy and has prescribed no upper age limit.[41,42] Over 12 years, the trial has enrolled approximately 2000 patients from the originally planned 6000.[42] Approximately one third of these patients are very elderly and being treated within the time window of interest.[2,41,42] Although our analysis is not a randomized controlled trial, it is the only current source of evidence to support the registry and randomized controlled trial data that are currently available.[2,10,37,43–45]

In summary, outcome among patients treated with thrombolysis as standard of care within clinical research trials is more favorable than among patients who are not offered thrombolysis, and this apparent advantage to patients who are treated extends to patients aged ≥81 years. We not only fail to find evidence to support the present restriction of the European marketing authorization for alteplase use in the elderly; we find positive evidence that alteplase is beneficial among patients aged 81 to 90 years and that this is likely to extend even to patients aged 91 to 100 years. Our data support and extend the extensive uncontrolled data on outcomes from registries and the limited randomized controlled trial data. Age is not a relevant factor when considering whether to use alteplase for acute stroke.

## Sources of Funding

Disclosures

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The following document contains supplemental material published online with "Influence of age on outcome from thrombolysis in acute stroke: a controlled comparison in patients from the Virtual International Stroke Trials Archive (VISTA)" by Mishra NK et al. This material comprise a flow chart showing description of VISTA data used in the main analysis of paper (page 2 and3) and a supplementary appendix "Overview of efficacy and safety in the randomized controlled clinical trials" (page 4 to 13). The appendix is based on data extracted and text edited by KR Lees from a regulatory submission document prepared by Dr T Machnig, based on analyses conducted by Dr E Bluhmki.

Figure: A flow diagram describing selection of data from VISTA

neuroprotection trials (1998-2007) for the analyses reported.

Figure 1
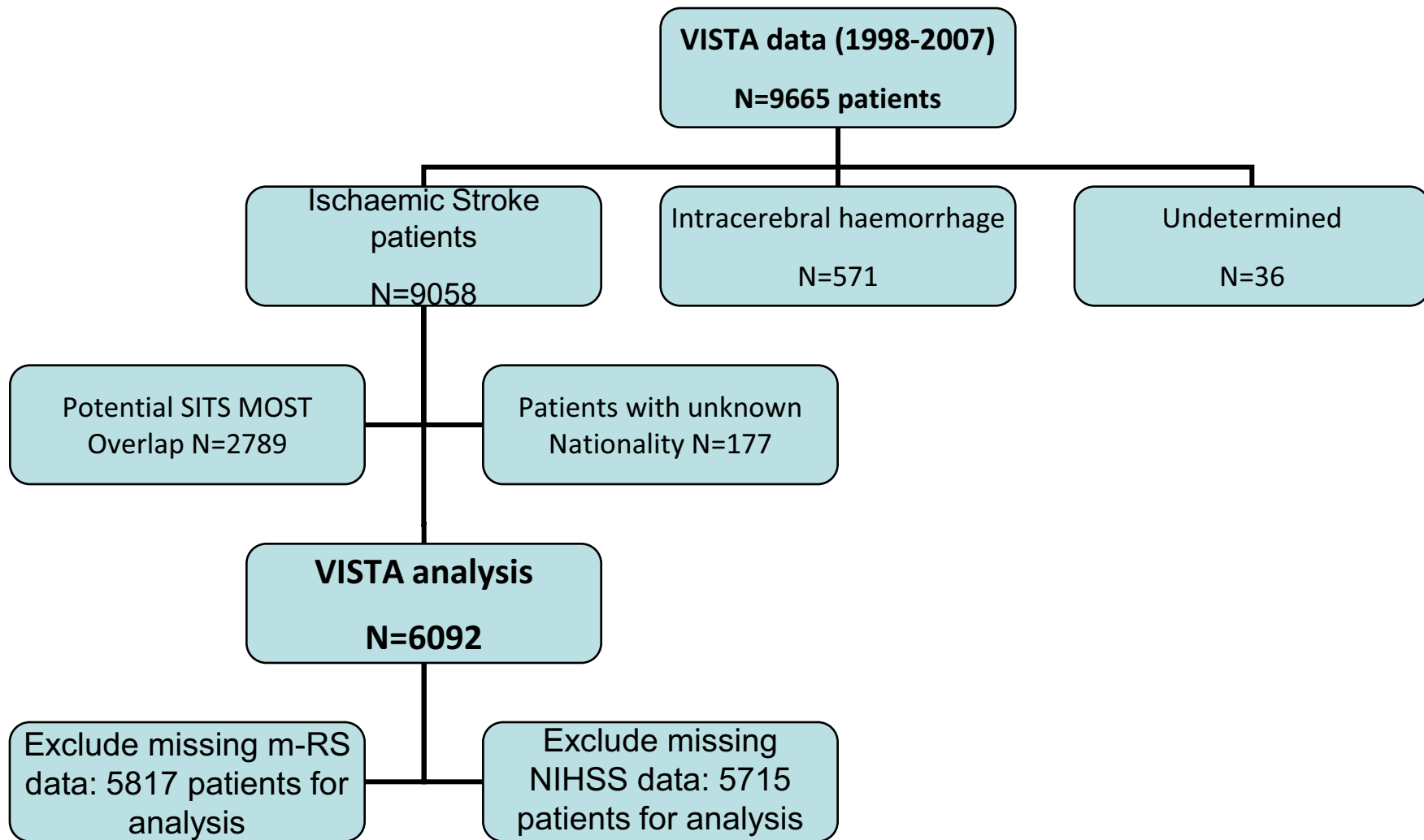
Appendix: Overview of efficacy and safety in the randomized controlled clinical trials.

Overview of efficacy and safety in the randomized controlled clinical trials

There has been no formal clinical trial programme for very elderly patients aged ≥80 years. So far, in randomized trials of alteplase for acute stroke treatment, few patients aged ≥80 years were included and randomized. The majority of these patients derive from part 2 of the NINDS trial, in which age >80 years was not an exclusion criterion. In contrast, an age of ≥80 years was an exclusion criterion in NINDS part 1, ECASS II, ECASS III, ATLANTIS A and ATLANTIS B.[1-4] Nevertheless, some patients aged ≥80 years were still included in these trials.

Methods

To gain insight into the efficacy and safety of treatment with alteplase under randomized controlled trial (RCT) conditions in this group, the available data on patients aged ≥80 years from trials using 0.9 mg/kg of alteplase were pooled. Overall, 164 very elderly patients (age ≥80 years) were enrolled and treated in the six randomized trials. Of those very elderly patients, 137 were treated in the 0–4.5 hour time window. The NINDS trial contributed most of the patients (22 from part 1 and 56 from part 2), with 15 from ECASS-II, 34 from ECASS-III and 2 and 8 from ATLANTIS parts A and B respectively. [1-4]

The main efficacy outcome measures in the pooled analysis were excellent outcome (mRS 0 or 1) and favourable outcome (mRS 0–2) at day 90. The main safety endpoints analyzed in the pooled data set of the very elderly were incidence of any intracranial haemorrhage (ICH), the incidence of symptomatic ICH (sICH) as defined by the SITS-MOST definition,[5] and mortality.

For both safety and efficacy, odds ratios (OR) given in the paragraphs that follow are adjusted for NIHSS at baseline and are also presented as unadjusted ORs.

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Due to imbalances between treatment arms regarding the severity of stroke at baseline in this cohort (figure A-1), two subgroups were defined according to their NIHSS score at baseline:

• 48 very elderly patients with severe stroke at baseline (NIHSS ≥20)

• 89 very elderly patients (NIHSS <20), excluding patients with severe stroke.

These subgroups were viewed alongside comparable subgroups from a cohort of younger patients (<80 years old) pooled from the same RCTs.

Results

Baseline demographics

Very elderly patient cohort – overall

Amongst the patients at and above (≥) 80 years of age, most were marginally over 80: median 81 years, range 80-101. A striking imbalance of the mean /median NIHSS at baseline between the very elderly cohort and the younger cohort was apparent. Very elderly patients receiving alteplase had a clinically relevant 5 point higher median NIHSS at baseline than younger patients (Table A-1). Within the very elderly cohort there was a 3 point difference in the median NIHSS to the detriment of the alteplase group. *Post hoc* categorisation of the stroke severity at baseline by three NIHSS severity categories (0–9, 10–19 and ≥20) demonstrated that this imbalance in baseline stroke severity in the very elderly group was driven mainly by a disproportionately higher number of alteplase-treated patients (n=31) compared with placebo-treated patients (n=17) in the most severe category of baseline stroke (NIHSS score ≥20):   19 vs 20; 26 vs 24; 31 vs 17 respectively.

Other risk factors known to be associated with poor outcomes after stroke, independent of treatment, were also more prevalent within the very elderly compared to the younger patients, including hypertension, atrial fibrillation and the use of concomitant aspirin at baseline. A history of smoking was less common among the very elderly and the

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proportion of females was increased. However, within the very elderly group, prognostic factors such as diabetes, atrial fibrillation, prior stroke and aspirin use were well matched.

Subgroup of very elderly patients excluding those with severe stroke

The median NIHSS score in this subgroup of very elderly patients excluding those with severe stroke at baseline did not differ from that in the subgroup of younger patients (median score 11.0). The mean and median NIHSS scores in the very elderly subgroup were also balanced between treatment arms (alteplase group: median 11.0; mean 11.2; placebo group: median 10.5; mean 11.0). With respect to other risk factors (e.g. hypertension, atrial fibrillation and prior aspirin) the findings in this subgroup mirrored those in the overall cohort of the very elderly patients.

Subgroup of very elderly patient with severe stroke

In this subgroup of the very elderly with severe stroke at baseline (NIHSS ≥20) the median NIHSS score was 1.5 points higher compared with their younger counterparts. The median NIHSS scores in the alteplase-treated arm (23.0) versus the placebo-treated arm (25.0) were balanced in this subgroup of the very elderly.

Regarding other risk factors, such as hypertension, atrial fibrillation and prior aspirin use, the findings in this subgroup of patients with severe stroke at baseline reflected the findings in the overall patient cohort of the very elderly patients.

Functional neurological outcome at day 90

Very elderly patient cohort – overall (n=137)

The efficacy results for the 0–4.5 hour cohort of very elderly patients (n=137) are shown in tables A-1 and A-2.

In the very elderly patient group there was no significant clinical benefit with alteplase treatment before adjustment for baseline imbalance in severity. In terms of excellent outcome (mRS 0 - 1) the absolute benefit was 1.4% in favour of alteplase over placebo; in terms of favourable outcome (mRS 0–2) the absolute benefit was 2.1% in favour of

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alteplase over placebo. After adjustment for baseline NIHSS the point estimates for excellent outcome (OR 1.72; 95 % CI 0.67–4.41) and favourable outcome (OR 1.77; 95 % CI 0.73–4.25) were consistent with a higher chance for good outcome in the very elderly treated with alteplase compared with placebo, but the confidence intervals were not sufficiently narrow to exclude the possibility of harm with treatment.

The treatment effect observed in the very elderly cohort was also not as pronounced as that observed in the younger cohort. In the patients aged <80 years old a significant treatment effect was observed in terms of excellent outcome (absolute benefit with alteplase 9.7%; OR 1.43; 95 % CI 1.18–1.75) and favourable outcome (absolute benefit with alteplase 8.6%; OR 1.35; 95% CI 1.11–1.64).

Subgroup of very elderly patients excluding those with severe stroke

In this subgroup excluding patients with severe stroke, a clinically meaningful absolute difference of 8.1% in favour of alteplase was observed for the endpoint mRS 0-1 and of 10.1% for the endpoint mRS 0–2. However, the confidence intervals for the adjusted ORs were wide for both excellent (mRS 0 or 1: OR 1.63; 95% CI 0.63–4.21) and favourable outcome (mRS 0–2: OR 1.87; 95% CI 0.71–4.91).

Subgroup of very elderly patients with severe stroke

In the small subgroup of very elderly patients with severe stroke at baseline (48 patients) the functional outcome at 3 months was very poor. None of the patients in the placebo arm achieved excellent outcome (mRS 0 or 1), though one patient in the alteplase arm did. One patient in the placebo arm and 3 patients in the alteplase arm had favourable outcome (mRS 0–2) at day 90.

Safety outcomes

Very elderly patient cohort – overall

In the very elderly patient cohort mortality at 90 days was more than twice the level seen in the younger patient cohort, both in the alteplase arm and the placebo arm. Among the very elderly there was an absolute excess of mortality of 4.7% in the alteplase arm

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compared with the placebo arm (27.6% versus 23.0%), whereas the level of mortality among patients aged <80 years was comparable between treatment arms (10.2% vs. 11.5%, respectively). The adjusted OR for mortality in the younger patients (<80 years) was 0.92 (95% CI 0.69–1.23) and for the patients ≥80 years 0.96 (95% CI 0.36–2.59).

The incidence of any ICH was increased for both the very elderly and the younger patients in the alteplase arm compared with the placebo arm. This increased risk in the alteplase arm was more pronounced in patients aged ≥80 years (OR 4.01; 95% CI 1.76–9.13) than in patients aged <80 years (OR 1.44; 95% CI 1.17–1.77). Similar findings were made for sICH (as per SITS-MOST definition[5]), with a higher OR for sICH in the alteplase arm in the very elderly cohort than in the younger cohort.

Subgroup of very elderly patients excluding those with severe stroke

In this subgroup of the very elderly excluding those with severe stroke the rate of mortality at 90 days was comparable between treatment arms. Overall mortality in the alteplase arm was 8.9% versus 11.4% in the placebo arm. The adjusted OR for mortality was 0.61 (95% CI 0.13–2.88) in the patients aged ≥80 years and 0.88 (95% CI 0.61–1.27) in patients <80 years. These point estimates again indicate that alteplase treatment in the very elderly may not necessarily be associated with excess mortality.

The incidence of any ICH was increased for both the very elderly and the younger patients in the alteplase arm compared with the placebo arm. Again, this increased risk in the alteplase arm was more pronounced in the very elderly (OR 4.82; 95% CI 1.55–14.94) compared with younger patients (OR 1.53; 95% CI 1.20–1.95). Similar observations were made for sICH (as per SITS-MOST definition[5]), with a higher OR for sICH in the alteplase arm in patients aged ≥80 years compared with patients aged <80 years.

Subgroup of very elderly patients with severe stroke

In the subgroup of very elderly patients with severe stroke at baseline, mortality at 90 days was very high, regardless of treatment arm (54.8% with alteplase versus 52.9% with placebo). Overall mortality at 90 days was more than twice as high in the very elderly

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compared with their younger counterparts, and was observed equally in the placebo arm (52.9% vs 23.3%, respectively) and the alteplase arm (54.8% vs 25.6%, respectively). The adjusted OR for mortality was 1.36 (95% CI 0.37–4.98) for patients aged ≥80 years and 0.99 (95% CI 0.61–1.62) for patients aged <80 years. Again the point estimates indicate that alteplase treatment in the very elderly may not necessarily be associated with excess mortality.

The incidence of any ICH was increased for both the very elderly and the younger patients in the alteplase arm compared with the placebo arm. Again, this increased risk in the alteplase arm was more pronounced in the very elderly patients (OR 3.03; 95% CI 0.88–10.47) compared with the younger patients (OR 1.37; 95% CI 0.91–2.06). Similar observations were again made for sICH (as per SITS-MOST definition[5]), with a higher OR for sICH in the alteplase arm in the very elderly than in the younger age group.

Conclusions

Only 137 very elderly patients aged ≥80 years were included in the 0–4.5 hour time window in all of the RCTs of alteplase used at the standard dose of 0.9 mg/kg bodyweight. This small number of patients provides low power to assess treatment effects. Although there appeared to be a minimal absolute benefit with alteplase treatment in the total cohort of the very elderly, this contrasted with the absolute benefit of 9.7% for excellent outcome observed in the cohort of patients younger than 80 years. Looking at the baseline data it became obvious that the most important prognostic baseline parameter, namely stroke severity, was heavily skewed to the disadvantage of the alteplase arm. Excluding patients with severe stroke at baseline (NIHSS ≥20) left a subgroup of 89 very elderly patients in whom the NIHSS scores at baseline were balanced between treatment arms. In this subgroup of very elderly patients with a baseline NIHSS score of <20, the absolute treatment benefit of alteplase over placebo for excellent outcome was found to be in the same range (8.1%) as that in younger patients with a baseline NIHSS score of <20 (8.8%). Differences between the treatment arms were not statistically significant. Except in a subgroup of patients with very advanced age and severe stroke in whom outcomes are poor, adverse safety outcomes show no excess amongst alteplase treated patients in the very elderly group.

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Table A-1

Baseline demography and 90-day outcome.

		Younger <= 80 years		Very elderly >= 80 years	
		Alteplase	**Placebo**	**alteplase**	**placebo**
N		1021	1041	76	61
Age	Mean	64.6	64.9	82.4	82.5
	Median, range	67 (20-79)	67 (23-79)	81 (80-98)	81 (80-101)
Diabetes	N, %	196 (19%)	184 (18%)	14 (18%)	12 (20%)
Atrial fibrillation	N, %	158 (16%)	171 (16%)	34 (45%)	25 (41%)
Prior stroke	N, %	132 (13%)	155 (15%)	10 (13%)	8 (13%)
Prior aspirin or other antiplatelet	N, %	317 (31%)	315 (30%)	35 (46%)	24 (39%)
Baseline NIHSS	Mean	13.0	13.7	16.5	15.0
	Median, range	12.0 (1-46)	13.0 (1-37)	17.0 (4-32)	14.0 (2-34)
mRS 0-1	N, %	470 (46%)	378 (36%)	21 (28%)	16 (26%)
mRS 0-2	N, %	592 (58%)	514 (49%)	29 (38%)	22 (36%)
Mortality	N, %	104 (10%)	120 (12%)	21 (28%)	14 (23%)
Post treatment ICH	N, %	295 (29%)	245 (24%)	39 (51%)	13 (21%)
Post treatment sICH	N, %	25 (2.4%)	5 (0.5%)	5 (6.6%)	0 (0.0%)

ICH: intracerebral haemorrhage
SICH: symptomatic intracerebral haemorrhage, as defined for the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST). [5]

Table A-2

90 day outcomes, expressed as odds ratios and 95% confidence intervals

90-day outcomes		Younger <= 80 years			Very elderly >= 80 years		
		OR	95% CI	P	OR	95% CI	p
mRS 0-1	Unadjusted	1.50	1.25-1.78	<0.0001	1.07	0.50-2.30	0.85
	Adjusted*	1.43	1.18-1.75	0.0003	1.72	0.67-4.41	0.26
mRS 0-2	Unadjusted	1.41	1.19-1.68	<0.0001	1.09	0.54-2.20	0.80
	Adjusted*	1.35	1.11-1.64	0.003	1.77	0.73-4.25	0.20
Mortality	Unadjusted	0.87	0.66-1.15	0.33	1.28	0.59-2.80	0.53
	Adjusted*	0.92	0.69-1.23	0.57	0.96	0.36-2.59	0.94
Any ICH		1.32	1.08-1.61	0.006	3.89	1.82-8.32	0.0005
		1.44	1.17-1.77	0.0005	4.01	1.76-9.13	0.0009
SICH	Unadjusted	5.20	1.98-13.6	0.0008	8.52@	0.46-159.0	0.15
	Adjusted*	5.24	2.00-13.8	0.0008	#		

Adjusted for NIHSS at baseline
@imputation of incidence of 0.5 in case of no event
#an adjusted analysis was not possible due to the limited incidence of events
ICH: intracerebral haemorrhage
SICH: symptomatic intracerebral haemorrhage, as defined for the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST)[5]

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Correction

The article entitled "Influence of Age on Outcome From Thrombolysis in Acute Stroke: A Controlled Comparison in Patients From the Virtual International Stroke Trials Archive (VISTA)" by Mishra et al that published online ahead of print on October 28, 2010 included data that needs to be updated in Figures 1 and 2 and the Table. The alterations are as follows: "<81" should be replaced by "≤80." This will be corrected for the print and final online versions. The authors regret this error.