THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014; published online Aug 6. http://dx.doi.org/10.1016/S0140-6736(14)60584-5.

Webmaterial: Effect of treatment delay, age and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials

Webtables **Pg**

Webfigures

Webtable 1: Baseline characteristics of IST-3 and 8 previous trials, overall and separately according to time to treatment

	≤3 hours			>3, ≤4.5 hours			>4.5 hours			Total		
Baseline variable	**8 previous trials**	**IST-3**	**p value**	**8 previous trials**	**IST-3**	**p value**	**8 previous trials**	**IST-3**	**p value**	**8 previous trials**	**IST-3**	**p value**
Number randomised	929	620		1620	1148		1128	1266		3721	3035	
Treatment delay (hours)	2.2 (0.6)	2.4 (0.4)	<0.0001	3.9 (0.4)	3.8 (0.4)	<0.0001	5.2 (0.6)	5.4 (0.5)	<0.0001	3.9 (1.2)	4.2 (1.2)	<0.0001
Age (years)	67 (11)	83 (8)	<0.0001	65 (12)	79 (11)	<0.0001	66 (12)	73 (13)	<0.0001	66 (12)	77 (12)	<0.0001
≤80	869 (94%)	114 (18%)	<0.0001	1589 (98%)	474 (41%)	<0.0001	1106 (98%)	830 (66%)	<0.0001	3606 (97%)	1418 (47%)	<0.0001
>80	60 (6%)	506 (82%)		31 (2%)	674 (59%)		21 (2%)	436 (34%)		112 (3%)	1617 (53%)	
Stroke severity (NIHSS)	14 (7)	14 (7)	0.789	11 (6)	13 (7)	<0.0001	11 (6)	11 (7)	0.216	12 (6)	12 (7)	0.216
0-4	50 (5%)	54 (9%)	0.097	129 (8%)	139 (12%)	<0.0001	82 (7%)	207 (16%)	<0.0001	266 (7%)	400 (13%)	<0.0001
5-10	284 (31%)	187 (30%)		687 (42%)	370 (32%)		483 (43%)	507 (40%)		1469 (39%)	1064 (35%)	
11-15	211 (23%)	124 (20%)		394 (24%)	237 (21%)		281 (25%)	240 (19%)		887 (24%)	601 (20%)	
16-21	219 (24%)	156 (25%)		300 (19%)	244 (21%)		190 (17%)	217 (17%)		715 (19%)	618 (20%)	
≥22	135 (15%)	99 (16%)		72 (4%)	158 (14%)		52 (5%)	95 (8%)		270 (7%)	352 (12%)	
Female	373 (40%)	368 (59%)	<0.0001	637 (39%)	609 (53%)	<0.0001	462 (41%)	592 (47%)	0.004	1487 (40%)	1570 (52%)	<0.0001
History of hypertension	559 (60%)	430 (69%)	0.0002	912 (56%)	723 (63%)	0.0003	622 (55%)	800 (63%)	<0.0001	2114 (57%)	1954 (64%)	<0.0001
History of stroke	123 (13%)	142 (23%)	<0.0001	222 (14%)	291 (25%)	<0.0001	195 (17%)	266 (21%)	0.024	544 (15%)	699 (23%)	<0.0001
History of diabetes mellitus	186 (20%)	49 (8%)	<0.0001	275 (17%)	133 (12%)	<0.0001	217 (19%)	206 (16%)	0.061	690 (19%)	388 (13%)	<0.0001
History of atrial fibrillation	189 (20%)	237 (38%)	<0.0001	279 (17%)	360 (31%)	<0.0001	224 (20%)	316 (25%)	0.003	700 (19%)	914 (30%)	<0.0001
Aspirin use	262 (28%)	320 (52%)	<0.0001	411 (25%)	460 (40%)	<0.0001	276 (24%)	526 (42%)	<0.0001	955 (26%)	1306 (43%)	<0.0001
Weight (kg)	77.6 (16.5)	68.2 (13.5)	<0.0001	77.2 (15.1)	71.0 (14.5)	<0.0001	75.9 (16.5)	74.8 (15.3)	0.080	76.9 (15.9)	72.0 (14.9)	<0.0001
Systolic blood pressure (mmHg)	154 (22)	157 (24)	0.022	152 (20)	155 (24)	0.001	153 (21)	155 (24)	0.046	153 (21)	155 (24)	<0.0001
Diastolic blood pressure (mmHg)	85 (14)	81 (15)	<0.0001	84 (13)	82 (14)	0.0001	84 (13)	83 (15)	0.039	84 (13)	82 (15)	<0.0001

Categorical data presented as n (%), continuous data presented as mean (SD). The p-values can be used to identify the statistically, but not necessarily clinically, significant differences between patients in IST-3 and patients in the 8 earlier trials.

Webtable 2: Baseline characteristics by randomised treatment allocation

	Randomised treatment allocation	
Baseline variable	**Alteplase**	**Control**
Number randomised	3391	3365
Treatment delay (hours)	4.0 (1.2)	4.0 (1.2)
≤3	787 (23%)	762 (23%)
>3, ≤4.5	1354 (40%)	1414 (42%)
>4.5	1229 (36%)	1165 (35%)
Age (years)	71 (13)	71 (13)
≤80	2510 (74%)	2514 (75%)
>80	879 (26%)	850 (25%)
Stroke severity (NIHSS)	12 (7)	12 (6)
0-4	345 (10%)	321 (10%)
5-10	1281 (38%)	1252 (37%)
11-15	747 (22%)	741 (22%)
16-21	662 (20%)	671 (20%)
≥22	309 (9%)	313 (9%)
Female	1532 (45%)	1525 (45%)
History of hypertension	2041 (60%)	2027 (60%)
History of stroke	619 (18%)	624 (19%)
History of diabetes mellitus	531 (16%)	547 (16%)
History of atrial fibrillation	827 (24%)	787 (23%)
Aspirin use	1125 (33%)	1136 (34%)
Weight (kg)	74.4 (15.3)	75.0 (15.9)
Systolic blood pressure (mmHg)	154 (22)	154 (23)
Diastolic blood pressure (mmHg)	83 (14)	83 (14)

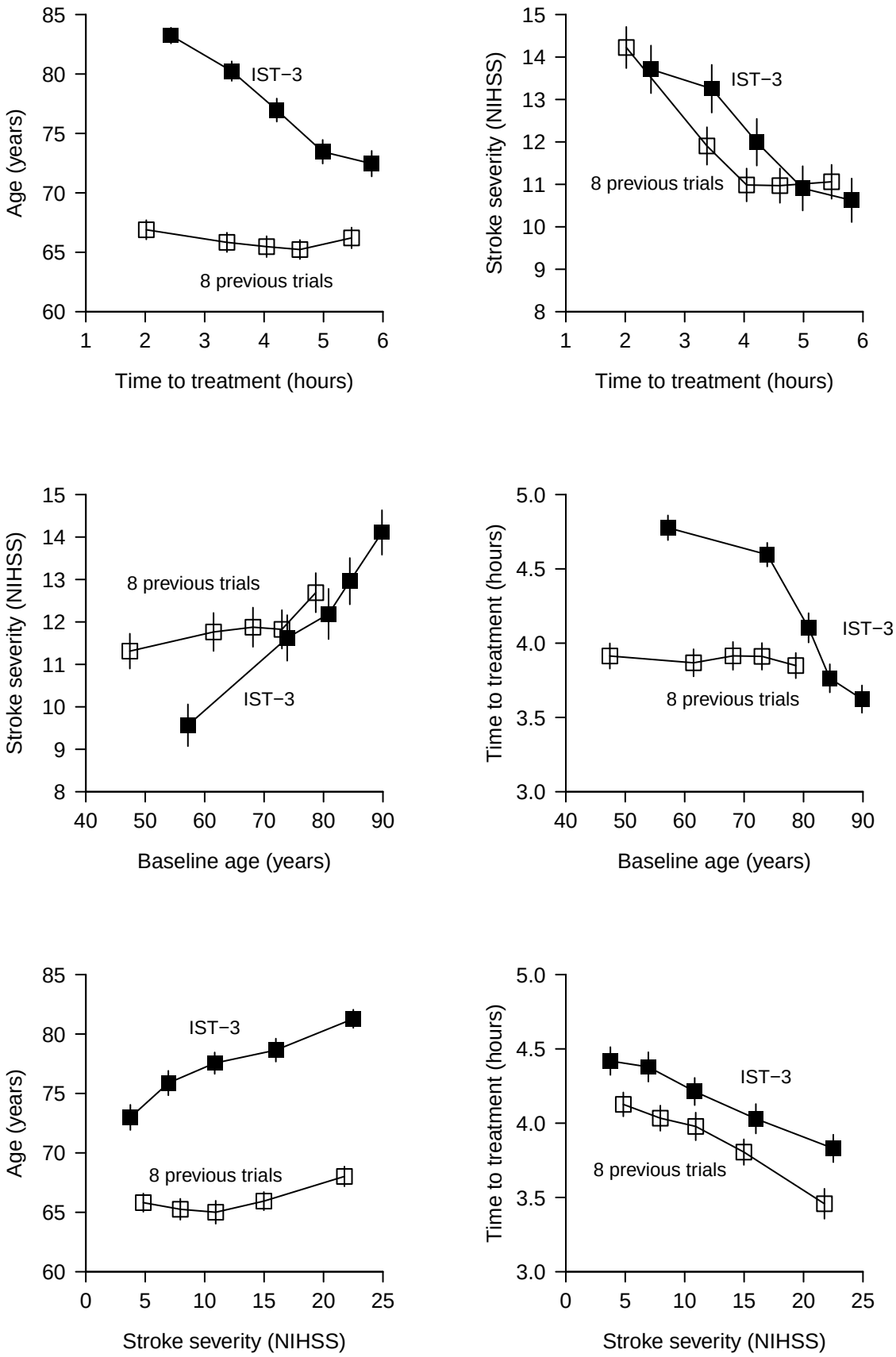
Note. No imputation of missing values.
Categorical data presented as n (%), continuous data presented as mean (SD).

Webtable 3: Number of outcomes by participating trial

				Symptomatic intracranial haemorrhage			mRS 3-6 months					
STT trial	**Number randomized**	**mRS 0-1 at 3-6 months**	**Death within 90 days**	**SITS-MOST at 24-36 hours**	**PH2 at 7 days**	**Fatal ICH at 7 days**	**0**	**1**	**2**	**3**	**4**	**5/6***
NINDS A	291	109	55	4	5	3	48	61	25	42	45	70
NINDS B	333	108	63	5	7	3	44	64	35	43	60	87
ECASS I	620	197	117	14	28	9	85	112	62	82	109	170
ECASS II	800	308	84	26	36	16	159	149	94	133	143	122
ATLANTIS A	142	22	21	3	6	3	9	13	4	3	7	106
ATLANTIS B	613	252	55	9	15	4	106	146	88	77	105	91
ECASS III	821	401	60	9	15	2	203	198	125	85	94	116
EPITHET	101	30	20	4	4	2	9	21	13	13	17	28
IST-3	3035	683	689	69	159	62	254	429	405	428	255	1264
Total	**6756**	**2110**	**1164**	**143**	**275**	**104**	**917**	**1193**	**851**	**906**	**835**	**2054**

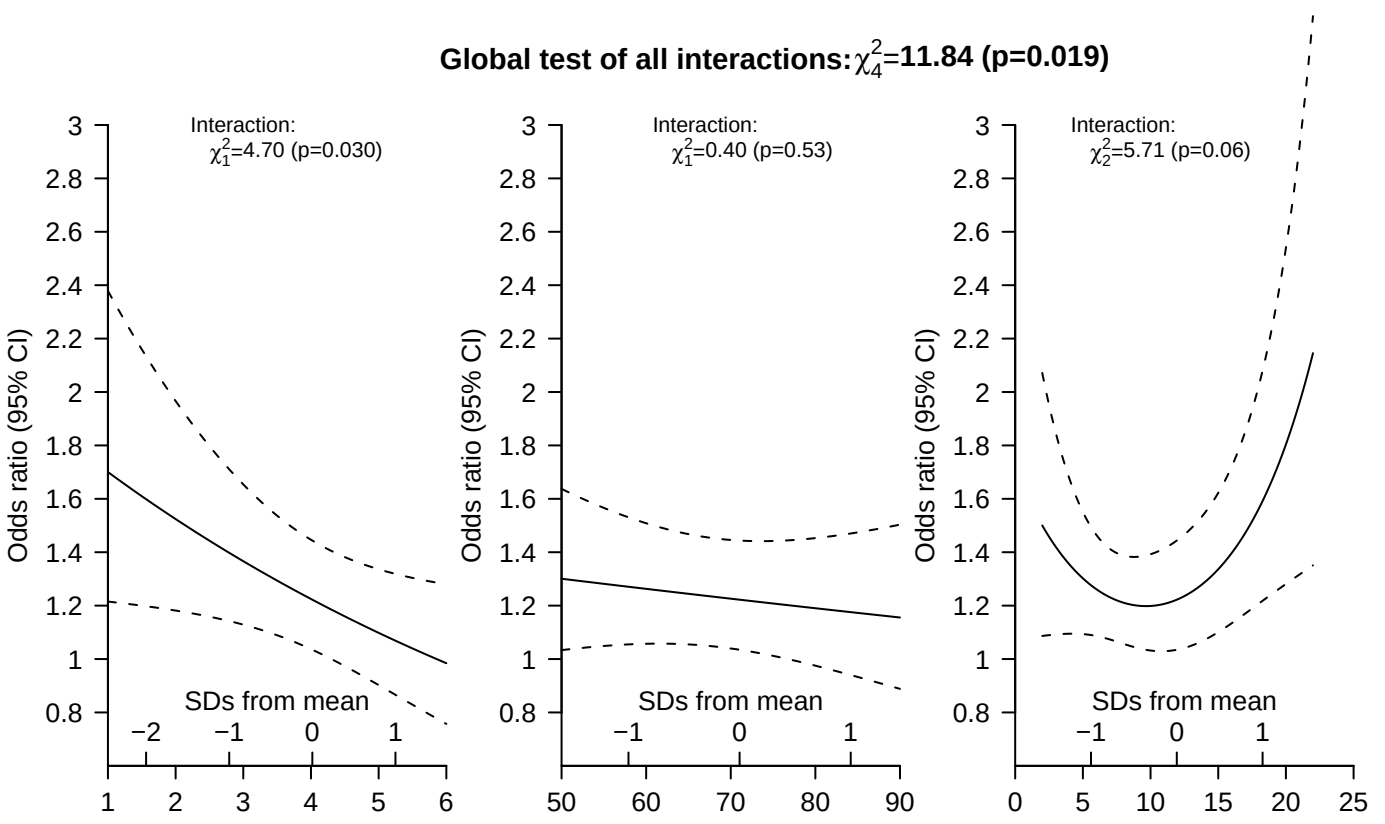
* mRS group 6 is not directly comparable between IST-3 and the 8 previous trials because it is based on vital status at 6 rather than 3 months (see Methods). However mRS groups 5 and 6 grouped together are likely to be broadly comparable across all the trials.

Webfigure 1: Pairwise relationships between baseline age, stroke severity and time to treatment in two groups of trials



Means and 95% confidence intervals shown. Plotted y values are shown against the mean x value within each fifth of the respective distribution.

Webfigure 2: Effect of alteplase on a good stroke outcome (mRS 0−1) by treatment delay, age and stroke severity



The solid line on each plot represents the interaction between alteplase with one of time, age or baseline NIHSS. Each is adjusted for treatment delay (linear), age (linear) and baseline NIHSS (quadratic), and interactions between alteplase with the other main effects (i.e. two of age, time and baseline NIHSS).

The estimated odds ratio is plotted for patients with AVERAGE levels of the other 2 baseline characteristics. The OR for alteplase was 1.22 at the mean values of age (71 years), NIHSS (12 points) and time to treatment (4 hours). The significance of each interaction is tested by comparing the change in deviance between two nested models that differ only by the interaction term(s) (ie, the likelihood ratio test).