Effects of alteplase for acute stroke according to criteria defining the EU and US marketing authorization: individual-patient-data meta-analysis of randomised trials

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Webtable 1: Baseline characteristics of participating trials (revised EU label without an upper age restriction, and revised US label extended to 4.5 hours)

	EU label		US label		
Variable	**Yes**	**No**	**Yes**	**No**	**Total**
Number randomized	3491	2645	3326	2810	6136
Treatment delay (hours)	3.3 (0.9)	4.8 (1.1)	3.3 (0.9)	4.8 (1.1)	4.0 (1.2)
>0, ≤3	1203 (34%)	259 (10%)	1174 (35%)	288 (10%)	1462 (24%)
>3, ≤4.5	2267 (65%)	268 (10%)	2126 (64%)	409 (15%)	2535 (41%)
>4.5	-	2099 (79%)	-	2099 (75%)	2099 (34%)
Missing	21 (1%)	19 (1%)	26 (1%)	14 (<1%)	40 (1%)
Age (years)	72 (13)	71 (13)	72 (13)	72 (13)	72 (13)
≤ 80	2447 (70%)	1962 (74%)	2333 (70%)	2076 (74%)	4409 (72%)
>80	1042 (30%)	682 (26%)	991 (30%)	733 (26%)	1724 (28%)
Missing	2 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	3 (<1%)
Stroke severity (NIHSS)	12 (6)	12 (7)	13 (7)	11 (6)	12 (7)
>0, ≤4	325 (9%)	307 (12%)	286 (9%)	346 (12%)	632 (10%)
>4, ≤10	1318 (38%)	1026 (39%)	1194 (36%)	1150 (41%)	2344 (38%)
>10, ≤15	779 (22%)	526 (20%)	720 (22%)	585 (21%)	1305 (21%)
>15, ≤21	759 (22%)	428 (16%)	715 (21%)	472 (17%)	1187 (19%)
>21	265 (8%)	329 (12%)	369 (11%)	225 (8%)	594 (10%)
Missing	45 (1%)	29 (1%)	42 (1%)	32 (1%)	74 (1%)
Female	1598 (46%)	1228 (46%)	1531 (46%)	1295 (46%)	2826 (46%)
History of hypertension	2141 (61%)	1669 (63%)	2007 (60%)	1803 (64%)	3810 (62%)
History of stroke	543 (16%)	617 (23%)	619 (19%)	541 (19%)	1160 (19%)
History of diabetes mellitus	417 (12%)	580 (22%)	485 (15%)	512 (18%)	997 (16%)
History of atrial fibrillation	841 (24%)	660 (25%)	815 (25%)	686 (24%)	1501 (24%)
Aspirin use	1187 (34%)	987 (37%)	1173 (35%)	1001 (36%)	2174 (35%)
Weight (kg)	74 (16)	75 (16)	74 (16)	75 (16)	75 (16)
Systolic blood pressure (mmHg)	151 (20)	158 (25)	147 (18)	162 (25)	154 (22)
Diastolic blood pressure (mmHg)	82 (13)	84 (15)	81 (13)	85 (15)	83 (14)

Categorical data presented as n (%), continuous data presented as mean (SD).

Webtable 2: Reasons for not meeting the revised EU (no upper age restriction) and revised US (extended up to 4.5 hours) labels

	NINDS A	NINDS B	ECASS II	ATLANTIS A	ATLANTIS B	ECASS III	EPITHET	IST-3	TOTAL
Number of participants	291	333	800	142	613	821	101	3035	6136
REVISED EU label									
Number not meeting revised label	51 (18%)	62 (19%)	404 (51%)	75 (53%)	358 (58%)	42 (5%)	72 (71%)	1581 (52%)	2645 (43%)
Reason for not meeting revised EU label									
Delay >4.5 hours	0 (0%)	0 (0%)	370 (46%)	67 (47%)	321 (52%)	6 (1%)	70 (69%)	1266 (42%)	2100 (34%)
NIHSS >25	17 (6%)	30 (9%)	17 (2%)	7 (5%)	9 (1%)	0 (0%)	1 (1%)	106 (3%)	187 (3%)
SBP >185 or DBP >110 mmHg	12 (4%)	17 (5%)	13 (2%)	2 (1%)	32 (5%)	17 (2%)	0 (0%)	347 (11%)	440 (7%)
Hypo or hyperglycaemia	4 (1%)	4 (1%)	6 (1%)	1 (1%)	1 (<1%)	0 (0%)	1 (1%)	0 (0%)	17 (<1%)
Both prior diabetes and prior stroke	20 (7%)	14 (4%)	29 (4%)	7 (5%)	30 (5%)	5 (1%)	2 (2%)	97 (3%)	204 (3%)
Signs of severe stroke based on CT imaging criteria	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	15 (2%)	0 (0%)	0 (0%)	15 (<1%)
REVISED US label									
Number not meeting revised label	49 (17%)	47 (14%)	432 (54%)	72 (51%)	363 (59%)	123 (15%)	70 (69%)	1654 (54%)	2810 (46%)
Reason for not meeting revised US label									
Delay >4.5 hours	0 (0%)	0 (0%)	370 (46%)	67 (47%)	321 (52%)	6 (1%)	70 (69%)	1266 (42%)	2100 (34%)
SBP >175 or DBP>110 mmHg	49 (17%)	47 (14%)	104 (13%)	9 (6%)	94 (15%)	120 (15%)	10 (10%)	647 (21%)	1080 (18%)

Webtable 3: Baseline characteristics by randomised treatment allocation
a) Patients who would have met the current EU label

Variable	rt-PA	Control
Number randomized	1207	1242
Treatment delay (hours)	3.4 (0.9)	3.4 (0.9)
>0, ≤3	368 (30%)	377 (30%)
>3, ≤4.5	828 (69%)	856 (69%)
Missing	11 (1%)	9 (1%)
Age (years)	65.6 (11.3)	65.8 (11.0)
≤ 80	1206 (>99%)	1241 (>99%)
Missing	1 (<1%)	1 (<1%)
Stroke severity (NIHSS)	11 (6)	11 (6)
>0, ≤4	131 (11%)	112 (9%)
>4, ≤10	500 (41%)	499 (40%)
>10, ≤15	282 (23%)	278 (22%)
>15, ≤21	222 (18%)	245 (20%)
>21	54 (4%)	82 (7%)
Missing	18 (1%)	26 (2%)
Female	467 (39%)	485 (39%)
History of hypertension	702 (58%)	720 (58%)
History of stroke	145 (12%)	169 (14%)
History of diabetes mellitus	180 (15%)	175 (14%)
History of atrial fibrillation	201 (17%)	204 (16%)
Aspirin use	331 (27%)	349 (28%)
Weight (kg)	77 (15)	78 (16)
Systolic blood pressure (mmHg)	152 (20)	150 (20)
Diastolic blood pressure (mmHg)	84 (13)	83 (13)

Webtable 3: Baseline characteristics by randomised treatment allocation
b) Patients who would have met an age-revised EU label

Variable	rt-PA	Control
Number randomized	1730	1761
Treatment delay (hours)	3.3 (0.9)	3.3 (0.9)
>0, ≤3	609 (35%)	594 (34%)
>3, ≤4.5	1110 (64%)	1157 (66%)
Missing	11 (1%)	10 (1%)
Age (years)	71.7 (13.4)	71.7 (13.2)
≤ 80	1206 (70%)	1241 (70%)
>80	523 (30%)	519 (29%)
Missing	1 (<1%)	1 (<1%)
Stroke severity (NIHSS)	12 (6)	12 (6)
>0, ≤4	172 (10%)	153 (9%)
>4, ≤10	657 (38%)	661 (38%)
>10, ≤15	396 (23%)	383 (22%)
>15, ≤21	368 (21%)	391 (22%)
>21	119 (7%)	146 (8%)
Missing	18 (1%)	27 (2%)
Female	781 (45%)	817 (46%)
History of hypertension	1052 (61%)	1089 (62%)
History of stroke	261 (15%)	282 (16%)
History of diabetes mellitus	213 (12%)	204 (12%)
History of atrial fibrillation	420 (24%)	421 (24%)
Aspirin use	578 (33%)	609 (35%)
Weight (kg)	74 (15)	75 (16)
Systolic blood pressure (mmHg)	151 (19)	151 (20)
Diastolic blood pressure (mmHg)	82 (13)	82 (13)

Webtable 3: Baseline characteristics by randomised treatment allocation
c) Patients who would NOT have met an age-revised EU label

Variable	rt-PA	Control
Number randomized	1348	1297
Treatment delay (hours)	4.8 (1.1)	4.8 (1.1)
>0, ≤3	129 (10%)	130 (10%)
>3, ≤4.5	131 (10%)	137 (11%)
>4.5	1081 (80%)	1018 (78%)
Missing	7 (1%)	12 (1%)
Age (years)	71.9 (12.6)	71.1 (13.2)
≤ 80	993 (74%)	969 (75%)
>80	354 (26%)	328 (25%)
Missing	1 (<1%)	-
Stroke severity (NIHSS)	12 (7)	12 (7)
>0, ≤4	156 (12%)	151 (12%)
>4, ≤10	514 (38%)	512 (39%)
>10, ≤15	272 (20%)	254 (20%)
>15, ≤21	216 (16%)	212 (16%)
>21	177 (13%)	152 (12%)
Missing	13 (1%)	16 (1%)
Female	626 (46%)	602 (46%)
History of hypertension	865 (64%)	804 (62%)
History of stroke	321 (24%)	296 (23%)
History of diabetes mellitus	281 (21%)	299 (23%)
History of atrial fibrillation	352 (26%)	308 (24%)
Aspirin use	512 (38%)	475 (37%)
Weight (kg)	75 (16)	76 (16)
Systolic blood pressure (mmHg)	158 (25)	157 (25)
Diastolic blood pressure (mmHg)	84 (15)	84 (15)

Webtable 3: Baseline characteristics by randomised treatment allocation
d) Patients who would have met the current US label

Variable	rt-PA	Control
Number randomized	600	574
Treatment delay (hours)	2.2 (0.6)	2.3 (0.6)
>0, ≤3	600 (100%)	574 (100%)
Age (years)	73.9 (12.9)	72.1 (13.6)
≤ 80	365 (61%)	377 (66%)
>80	235 (39%)	197 (34%)
Stroke severity (NIHSS)	14 (7)	14 (7)
>0, ≤4	44 (7%)	25 (4%)
>4, ≤10	169 (28%)	183 (32%)
>10, ≤15	137 (23%)	117 (20%)
>15, ≤21	152 (25%)	143 (25%)
>21	90 (15%)	95 (17%)
Missing	8 (1%)	11 (2%)
Female	285 (48%)	271 (47%)
History of hypertension	377 (63%)	360 (63%)
History of stroke	111 (19%)	96 (17%)
History of diabetes mellitus	98 (16%)	83 (14%)
History of atrial fibrillation	171 (29%)	144 (25%)
Aspirin use	245 (41%)	211 (37%)
Weight (kg)	72 (15)	75 (16)
Systolic blood pressure (mmHg)	147 (17)	146 (18)
Diastolic blood pressure (mmHg)	81 (13)	81 (14)

Webtable 3: Baseline characteristics by randomised treatment allocation
e) Patients who would have met a 4.5-hour revised US label

Variable	rt-PA	Control
Number randomized	1653	1673
Treatment delay (hours)	3.3 (0.9)	3.3 (0.9)
>0, ≤3	600 (36%)	574 (34%)
>3, ≤4.5	1040 (63%)	1086 (65%)
Missing	13 (1%)	13 (1%)
Age (years)	71.7 (13.5)	71.4 (13.3)
≤ 80	1145 (69%)	1188 (71%)
>80	507 (31%)	484 (29%)
Missing	1 (<1%)	1 (<1%)
Stroke severity (NIHSS)	13 (7)	13 (7)
>0, ≤4	149 (9%)	137 (8%)
>4, ≤10	587 (36%)	607 (36%)
>10, ≤15	370 (22%)	350 (21%)
>15, ≤21	349 (21%)	366 (22%)
>21	179 (11%)	190 (11%)
Missing	19 (1%)	23 (1%)
Female	753 (46%)	778 (47%)
History of hypertension	990 (60%)	1017 (61%)
History of stroke	297 (18%)	322 (19%)
History of diabetes mellitus	242 (15%)	243 (15%)
History of atrial fibrillation	417 (25%)	398 (24%)
Aspirin use	580 (35%)	593 (35%)
Weight (kg)	74 (15)	75 (16)
Systolic blood pressure (mmHg)	147 (17)	147 (18)
Diastolic blood pressure (mmHg)	81 (13)	81 (13)

Webtable 3: Baseline characteristics by randomised treatment allocation
f) Patients who would NOT have met a 4.5-hour revised US label

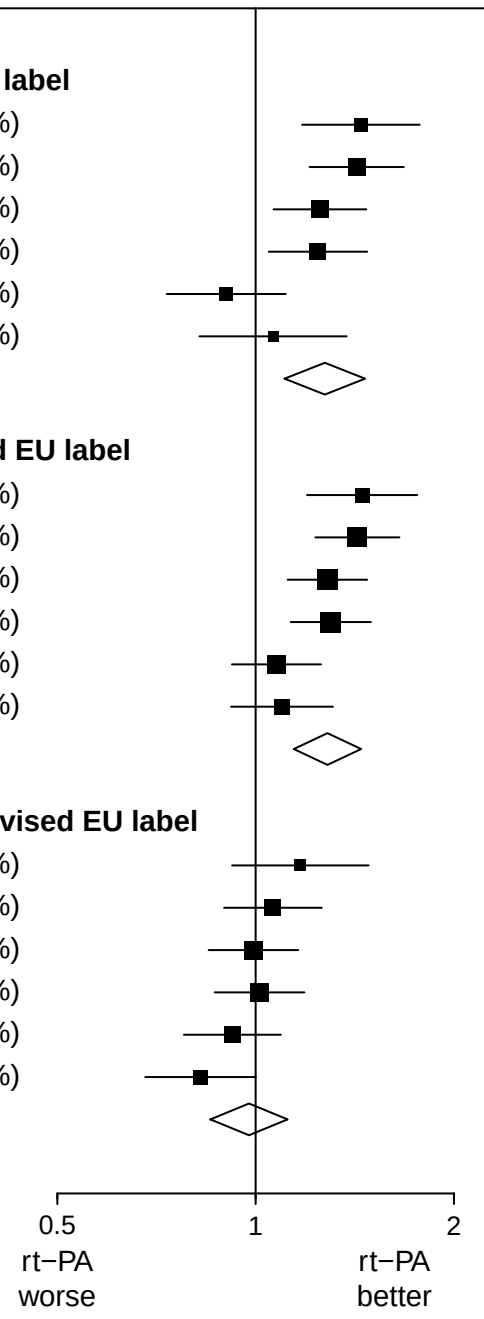
Variable	rt-PA	Control
Number randomized	1425	1385
Treatment delay (hours)	4.8 (1.1)	4.8 (1.1)
>0, ≤3	138 (10%)	150 (11%)
>3, ≤4.5	201 (14%)	208 (15%)
>4.5	1081 (76%)	1018 (74%)
Missing	5 (<1%)	9 (1%)
Age (years)	71.9 (12.5)	71.5 (13.1)
≤ 80	1054 (74%)	1022 (74%)
>80	370 (26%)	363 (26%)
Missing	1 (<1%)	-
Stroke severity (NIHSS)	11 (6)	11 (6)
>0, ≤4	179 (13%)	167 (12%)
>4, ≤10	584 (41%)	566 (41%)
>10, ≤15	298 (21%)	287 (21%)
>15, ≤21	235 (16%)	237 (17%)
>21	117 (8%)	108 (8%)
Missing	12 (1%)	20 (1%)
Female	654 (46%)	641 (46%)
History of hypertension	927 (65%)	876 (63%)
History of stroke	285 (20%)	256 (18%)
History of diabetes mellitus	252 (18%)	260 (19%)
History of atrial fibrillation	355 (25%)	331 (24%)
Aspirin use	510 (36%)	491 (35%)
Weight (kg)	75 (16)	76 (17)
Systolic blood pressure (mmHg)	162 (25)	162 (25)
Diastolic blood pressure (mmHg)	85 (15)	86 (15)

Webtable 4: Sensitivity analyses of the effect of alteplase on particular outcomes after additional adjustment for treatment delay, age and stroke severity

	EU label: Patients who would...			US label: Patients who would...		
Endpoint	**have met the current label**	**have met an age-revised label**	**not have met an age-revised label**	**have met the current label**	**have met an 4.5 hour revised label**	**not have met a 4.5 hours revised label**
mRS 0-1	1.40 (1.16-1.69)	1.45 (1.23-1.71)	1.12 (0.93-1.36)	1.69 (1.26-2.28)	1.45 (1.22-1.72)	1.15 (0.96-1.37)
90-day mortality	1.05 (0.82-1.34)	1.03 (0.88-1.22)	1.13 (0.95-1.36)	0.94 (0.74-1.20)	1.00 (0.85-1.17)	1.21 (1.01-1.46)
PH-2	5.39 (2.79-10.42)	5.35 (3.24-8.83)	7.41 (4.42-12.43)	6.53 (2.52-16.91)	5.70 (3.41-9.51)	7.13 (4.30-11.82)
SITS-MOST	5.97 (2.49-14.34)	6.93 (3.28-14.64)	7.77 (3.70-16.33)	9.75 (2.26-41.98)	7.35 (3.32-16.29)	7.36 (3.64-14.87)
Fatal ICH within 7 days	8.45 (2.52-28.33)	8.93 (3.51-22.70)	8.72 (3.44-22.10)	15.26 (2.01-115.64)	9.24 (3.64-23.43)	8.51 (3.35-21.61)
Any upwards shift in mRS	1.20 (1.04-1.38)	1.27 (1.12-1.43)	1.05 (0.91-1.20)	1.42 (1.15-1.76)	1.29 (1.14-1.46)	1.04 (0.91-1.18)

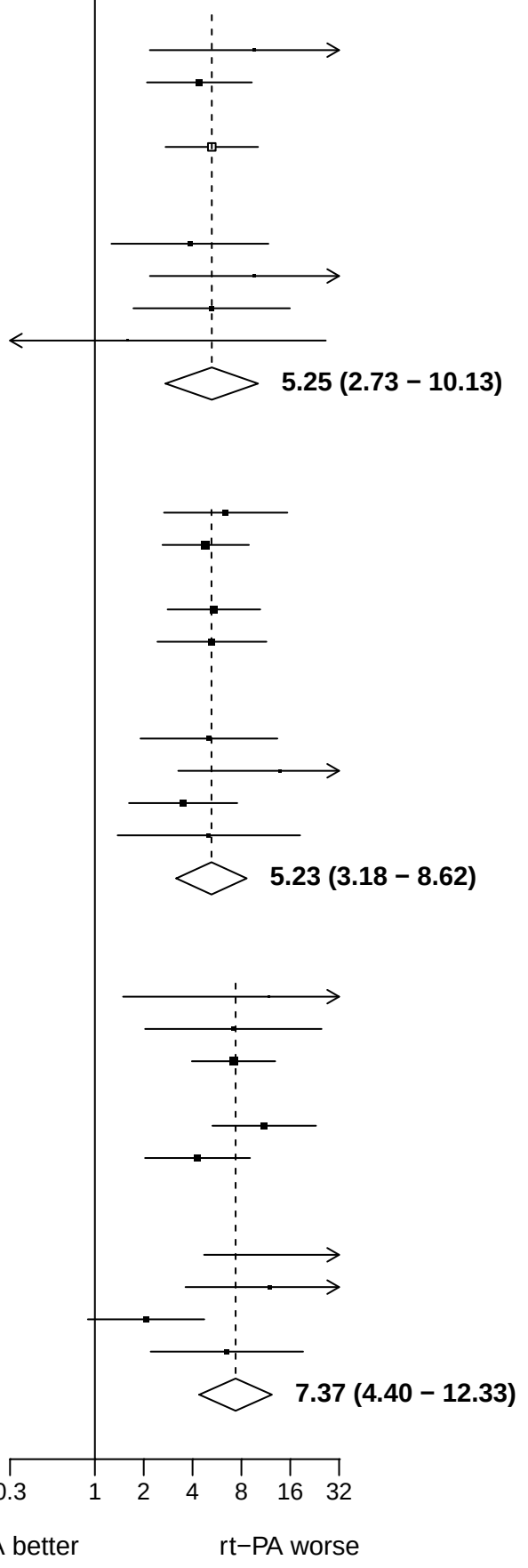
Webfigure 1: Relative odds of a good stroke outcome with rt−PA, for each definition of good outcome in groups defined by the current EU label as well as an EU label without an upper age restriction

mRS comparison ('good' vs 'bad')	No. patients with 'good' outcome: rt−PA	Control	Odds ratio (95% CI)
a) Patients who would have met the current EU label			
0 vs 1−6	264 (21.9%)	199 (16.0%)	1.44 (1.18−1.77)
0−1 vs 2−6	535 (44.3%)	444 (35.7%)	1.42 (1.21−1.68)
0−2 vs 3−6	677 (56.1%)	626 (50.4%)	1.25 (1.06−1.47)
0−3 vs 4−6	838 (69.4%)	801 (64.5%)	1.24 (1.05−1.48)
0−4 vs 5−6	966 (80.0%)	1009 (81.2%)	0.90 (0.73−1.11)
0−5 vs 6	1081 (89.6%)	1104 (88.9%)	1.06 (0.82−1.37)
Any upwards shift			**1.27 (1.11 − 1.47)**
b) Patients who would have met an age−revised EU label			
0 vs 1−6	297 (17.2%)	219 (12.4%)	1.45 (1.20−1.76)
0−1 vs 2−6	635 (36.7%)	512 (29.1%)	1.43 (1.23−1.65)
0−2 vs 3−6	834 (48.2%)	742 (42.1%)	1.29 (1.12−1.48)
0−3 vs 4−6	1068 (61.7%)	977 (55.5%)	1.30 (1.13−1.50)
0−4 vs 5−6	1239 (71.6%)	1232 (70.0%)	1.08 (0.92−1.26)
0−5 vs 6	1427 (82.5%)	1427 (81.0%)	1.10 (0.92−1.31)
Any upwards shift			**1.29 (1.14 − 1.45)**
c) Patients who would NOT have met an age−revised EU label			
0 vs 1−6	172 (12.8%)	144 (11.1%)	1.17 (0.92−1.48)
0−1 vs 2−6	399 (29.6%)	367 (28.3%)	1.06 (0.90−1.26)
0−2 vs 3−6	573 (42.5%)	553 (42.6%)	0.99 (0.85−1.16)
0−3 vs 4−6	758 (56.2%)	723 (55.7%)	1.01 (0.87−1.19)
0−4 vs 5−6	899 (66.7%)	882 (68.0%)	0.92 (0.78−1.09)
0−5 vs 6	1056 (78.3%)	1052 (81.1%)	0.82 (0.68−1.00)
Any upwards shift			**0.98 (0.85 − 1.12)**



Webfigure 2: Effect of rt−PA on type 2 parenchymal haemorrhage within 7 days in groups defined by the current EU label as well as an EU label without an upper age restriction

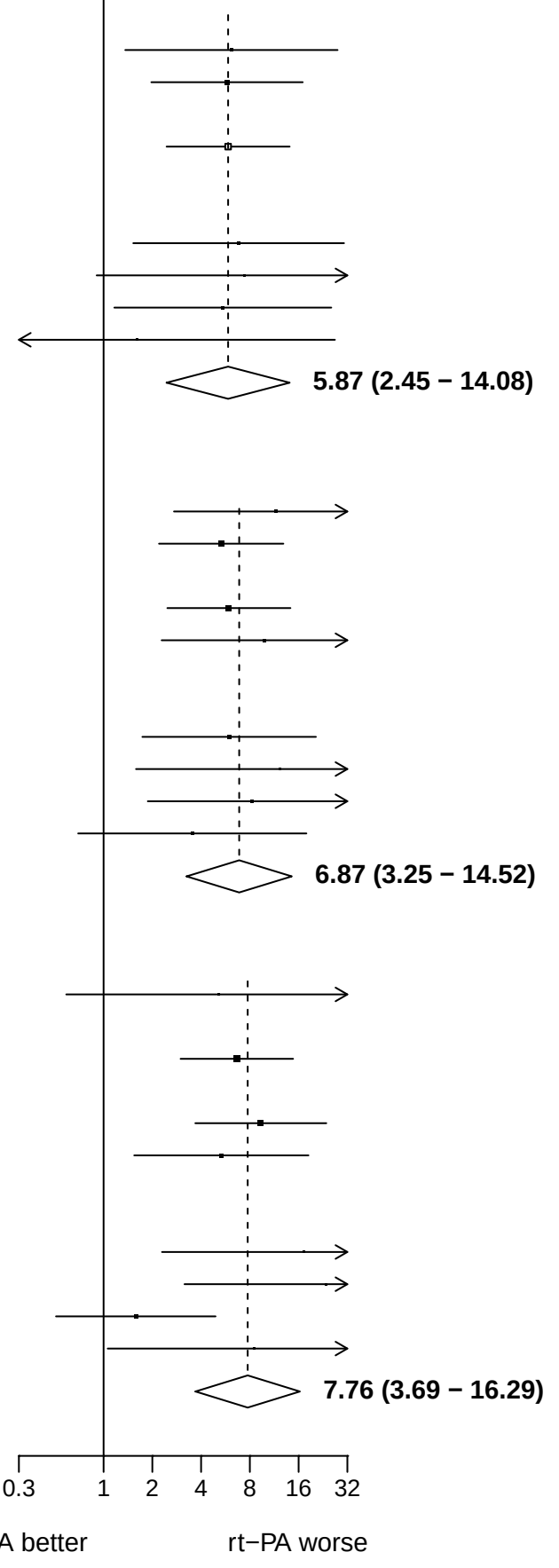
	rt−PA	Control	Odds ratio (95% CI)
a) Patients who would have met the current EU label			
Treatment delay			
≤ 3 hours	18/368 (4.9%)	2/377 (0.5%)	
>3, ≤ 4.5 hours	35/839 (4.2%)	9/865 (1.0%)	
Age			
≤ 80 years	53/1207 (4.4%)	11/1242 (0.9%)	
Baseline NIHSS			
0−4	2/131 (1.5%)	0/112 (0.0%)	
5−10	15/500 (3.0%)	4/499 (0.8%)	
11−15	17/300 (5.7%)	2/304 (0.7%)	
16−21	18/222 (8.1%)	4/245 (1.6%)	
≥ 22	1/54 (1.9%)	1/82 (1.2%)	
Subtotal	**53/1207 (4.4%)**	**11/1242 (0.9%)**	**5.25 (2.73 − 10.13)**
b) Patients who would have met an age−revised EU label			
Treatment delay			
≤ 3 hours	37/609 (6.1%)	6/594 (1.0%)	
>3, ≤ 4.5 hours	55/1121 (4.9%)	13/1167 (1.1%)	
Age			
≤ 80 years	53/1207 (4.4%)	11/1242 (0.9%)	
>80 years	39/523 (7.5%)	8/519 (1.5%)	
Baseline NIHSS			
0−4	2/172 (1.2%)	0/153 (0.0%)	
5−10	24/657 (3.7%)	5/661 (0.8%)	
11−15	26/414 (6.3%)	2/410 (0.5%)	
16−21	28/368 (7.6%)	9/391 (2.3%)	
≥ 22	12/119 (10.1%)	3/146 (2.1%)	
Subtotal	**92/1730 (5.3%)**	**19/1761 (1.1%)**	**5.23 (3.18 − 8.62)**
c) Patients who would NOT have met an age−revised EU label			
Treatment delay			
≤ 3 hours	11/129 (8.5%)	1/130 (0.8%)	
>3, ≤ 4.5 hours	18/138 (13.0%)	3/148 (2.0%)	
>4.5 hours	90/1081 (8.3%)	13/1019 (1.3%)	
Age			
≤ 80 years	80/994 (8.0%)	8/969 (0.8%)	
>80 years	39/354 (11.0%)	9/328 (2.7%)	
Baseline NIHSS			
0−4	8/156 (5.1%)	0/151 (0.0%)	
5−10	33/514 (6.4%)	1/512 (0.2%)	
11−15	34/285 (11.9%)	3/270 (1.1%)	
16−21	18/216 (8.3%)	9/212 (4.2%)	
≥ 22	26/177 (14.7%)	4/152 (2.6%)	
Subtotal	**119/1348 (8.8%)**	**17/1297 (1.3%)**	**7.37 (4.40 − 12.33)**



Analyses done as for Figure 1 of the main manuscript

Webfigure 3: Effect of rt−PA on SITS−MOST intracerebral haemorrhage at 24−36 hours in groups defined by the current EU label as well as an EU label without an upper age restriction

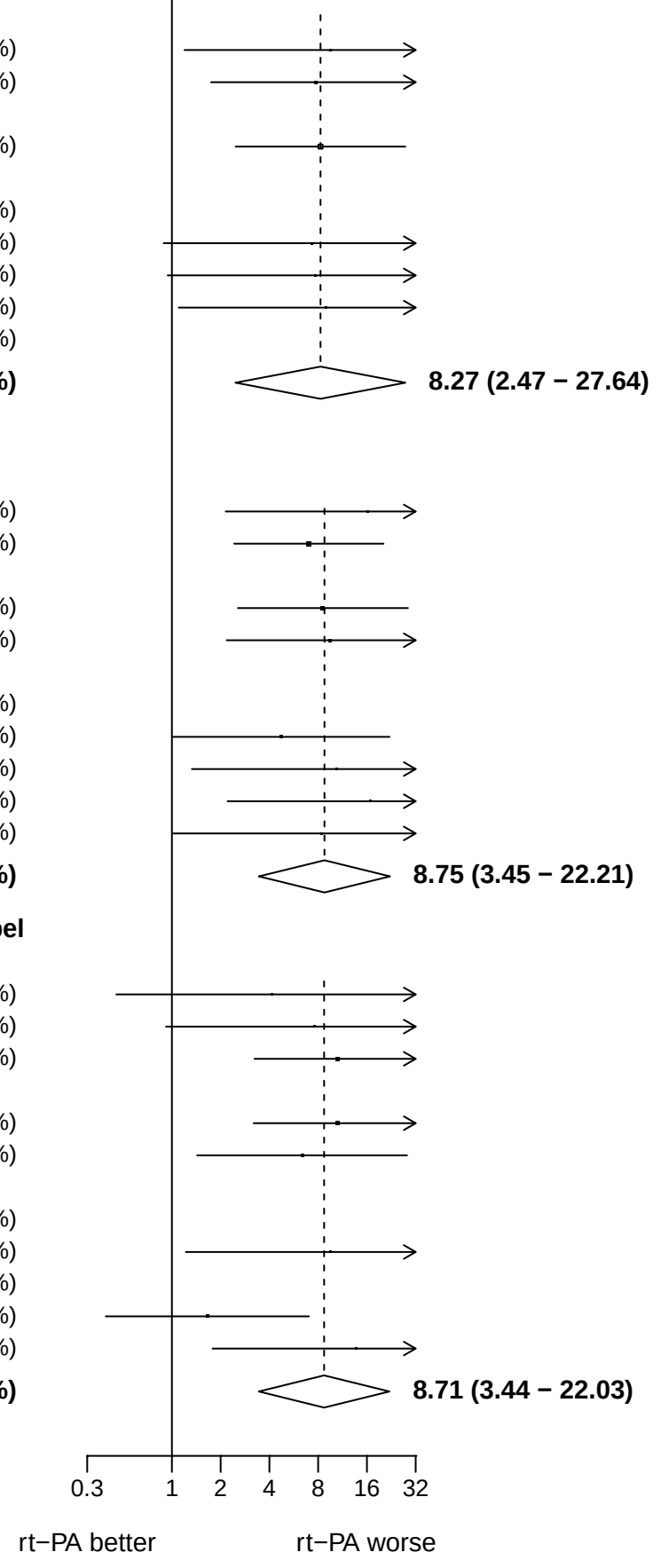
	rt−PA	Control	Odds ratio (95% CI)
a) Patients who would have met the current EU label			
Treatment delay			
≤ 3 hours	12/368 (3.3%)	2/377 (0.5%)	
>3, ≤ 4.5 hours	21/839 (2.5%)	4/865 (0.5%)	
Age			
≤ 80 years	33/1207 (2.7%)	6/1242 (0.5%)	
Baseline NIHSS			
0−4	2/131 (1.5%)	0/112 (0.0%)	
5−10	13/500 (2.6%)	2/499 (0.4%)	
11−15	7/300 (2.3%)	1/304 (0.3%)	
16−21	10/222 (4.5%)	2/245 (0.8%)	
≥ 22	1/54 (1.9%)	1/82 (1.2%)	
Subtotal	**33/1207 (2.7%)**	**6/1242 (0.5%)**	**5.87 (2.45 − 14.08)**
b) Patients who would have met an age−revised EU label			
Treatment delay			
≤ 3 hours	23/609 (3.8%)	2/594 (0.3%)	
>3, ≤ 4.5 hours	29/1121 (2.6%)	6/1167 (0.5%)	
Age			
≤ 80 years	33/1207 (2.7%)	6/1242 (0.5%)	
>80 years	19/523 (3.6%)	2/519 (0.4%)	
Baseline NIHSS			
0−4	2/172 (1.2%)	0/153 (0.0%)	
5−10	17/657 (2.6%)	3/661 (0.5%)	
11−15	12/414 (2.9%)	1/410 (0.2%)	
16−21	15/368 (4.1%)	2/391 (0.5%)	
≥ 22	6/119 (5.0%)	2/146 (1.4%)	
Subtotal	**52/1730 (3.0%)**	**8/1761 (0.5%)**	**6.87 (3.25 − 14.52)**
c) Patients who would NOT have met an age−revised EU label			
Treatment delay			
≤ 3 hours	5/129 (3.9%)	1/130 (0.8%)	
>3, ≤ 4.5 hours	9/138 (6.5%)	0/148 (0.0%)	
>4.5 hours	47/1081 (4.3%)	7/1019 (0.7%)	
Age			
≤ 80 years	44/994 (4.4%)	5/969 (0.5%)	
>80 years	17/354 (4.8%)	3/328 (0.9%)	
Baseline NIHSS			
0−4	4/156 (2.6%)	0/151 (0.0%)	
5−10	17/514 (3.3%)	1/512 (0.2%)	
11−15	23/285 (8.1%)	1/270 (0.4%)	
16−21	8/216 (3.7%)	5/212 (2.4%)	
≥ 22	9/177 (5.1%)	1/152 (0.7%)	
Subtotal	**61/1348 (4.5%)**	**8/1297 (0.6%)**	**7.76 (3.69 − 16.29)**



Analyses done as for Figure 1 of the main manuscript

Webfigure 4: Effect of rt−PA on fatal intracerebral haemorrhage within 7 days in groups defined by the current EU label as well as an EU label without an upper age restriction

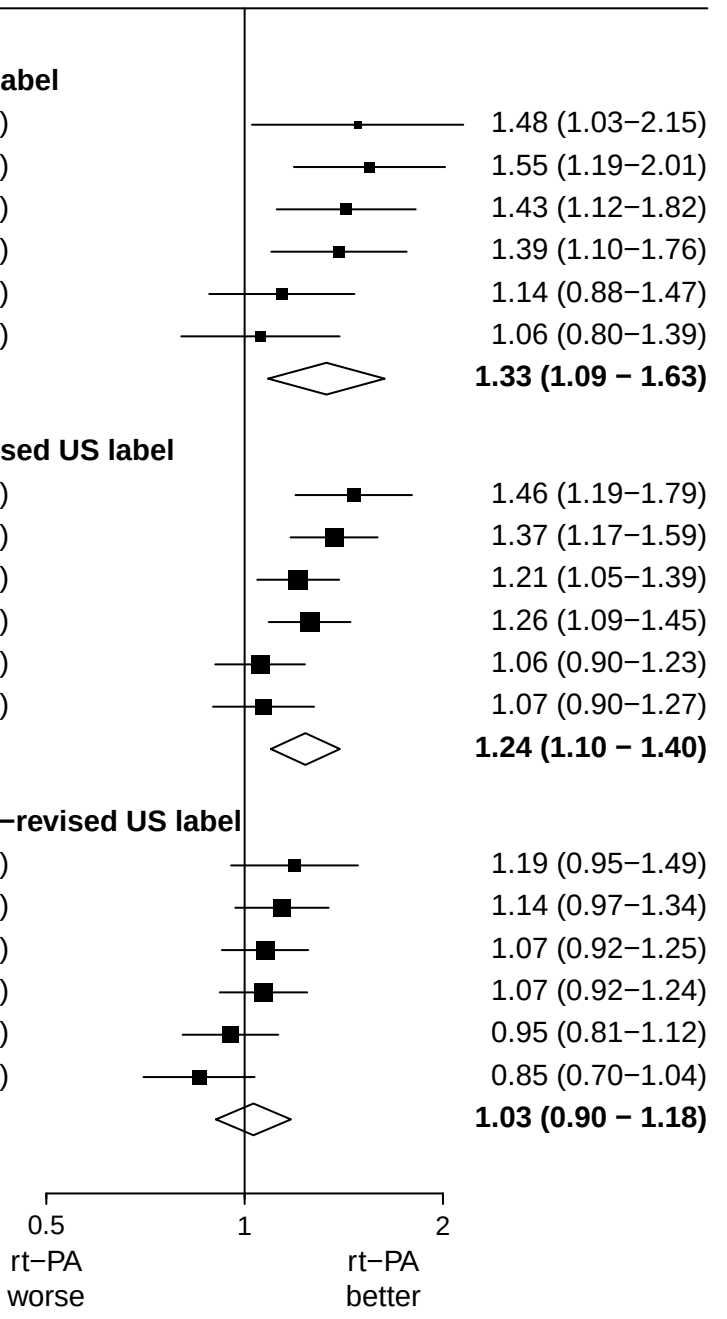
	rt−PA	Control	Odds ratio (95% CI)
a) Patients who would have met the current EU label			
Treatment delay			
≤ 3 hours	9/368 (2.4%)	1/377 (0.3%)	
>3, ≤ 4.5 hours	14/839 (1.7%)	2/865 (0.2%)	
Age			
≤ 80 years	23/1207 (1.9%)	3/1242 (0.2%)	
Baseline NIHSS			
0−4	0/131 (0.0%)	0/112 (0.0%)	
5−10	7/500 (1.4%)	1/499 (0.2%)	
11−15	7/300 (2.3%)	1/304 (0.3%)	
16−21	8/222 (3.6%)	1/245 (0.4%)	
≥ 22	1/54 (1.9%)	0/82 (0.0%)	
Subtotal	**23/1207 (1.9%)**	**3/1242 (0.2%)**	**8.27 (2.47 − 27.64)**
b) Patients who would have met an age−revised EU label			
Treatment delay			
≤ 3 hours	16/609 (2.6%)	1/594 (0.2%)	
>3, ≤ 4.5 hours	25/1121 (2.2%)	4/1167 (0.3%)	
Age			
≤ 80 years	23/1207 (1.9%)	3/1242 (0.2%)	
>80 years	18/523 (3.4%)	2/519 (0.4%)	
Baseline NIHSS			
0−4	0/172 (0.0%)	0/153 (0.0%)	
5−10	9/657 (1.4%)	2/661 (0.3%)	
11−15	10/414 (2.4%)	1/410 (0.2%)	
16−21	15/368 (4.1%)	1/391 (0.3%)	
≥ 22	7/119 (5.9%)	1/146 (0.7%)	
Subtotal	**41/1730 (2.4%)**	**5/1761 (0.3%)**	**8.75 (3.45 − 22.21)**
c) Patients who would NOT have met an age−revised EU label			
Treatment delay			
≤ 3 hours	4/129 (3.1%)	1/130 (0.8%)	
>3, ≤ 4.5 hours	7/138 (5.1%)	1/148 (0.7%)	
>4.5 hours	33/1081 (3.1%)	3/1019 (0.3%)	
Age			
≤ 80 years	30/994 (3.0%)	3/969 (0.3%)	
>80 years	14/354 (4.0%)	2/328 (0.6%)	
Baseline NIHSS			
0−4	3/156 (1.9%)	0/151 (0.0%)	
5−10	10/514 (1.9%)	1/512 (0.2%)	
11−15	12/285 (4.2%)	0/270 (0.0%)	
16−21	5/216 (2.3%)	3/212 (1.4%)	
≥ 22	14/177 (7.9%)	1/152 (0.7%)	
Subtotal	**44/1348 (3.3%)**	**5/1297 (0.4%)**	**8.71 (3.44 − 22.03)**



Analyses done as for Figure 1 of the main manuscript

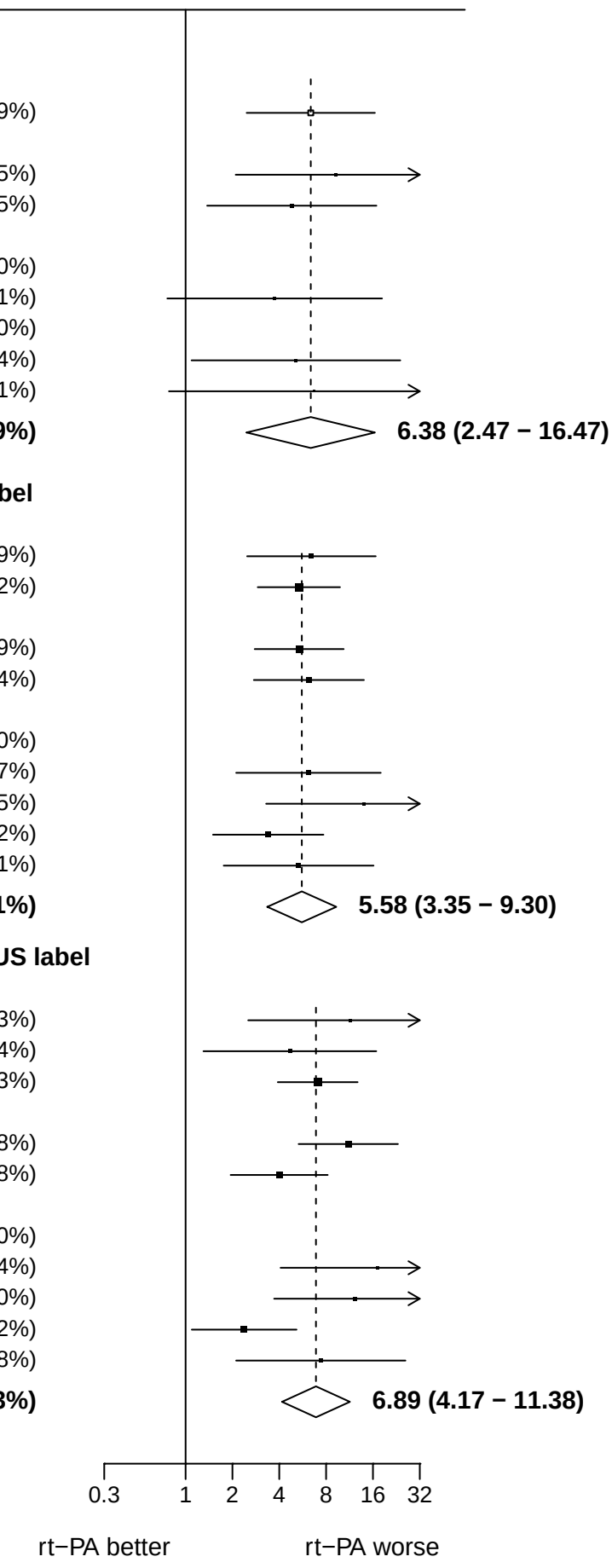
Webfigure 5: Relative odds of a good stroke outcome with rt−PA, for each definition of good outcome in groups defined by the current US label as well as a US label extended to 4.5 hours

mRS comparison ('good' vs 'bad')	No. patients with 'good' outcome: rt−PA	Control	Odds ratio (95% CI)
a) Patients who would have met the current US label			
0 vs 1−6	80 (13.3%)	58 (10.1%)	1.48 (1.03−2.15)
0−1 vs 2−6	193 (32.2%)	142 (24.7%)	1.55 (1.19−2.01)
0−2 vs 3−6	249 (41.5%)	198 (34.5%)	1.43 (1.12−1.82)
0−3 vs 4−6	330 (55.0%)	277 (48.3%)	1.39 (1.10−1.76)
0−4 vs 5−6	400 (66.7%)	374 (65.2%)	1.14 (0.88−1.47)
0−5 vs 6	459 (76.5%)	438 (76.3%)	1.06 (0.80−1.39)
Any upwards shift			**1.33 (1.09 − 1.63)**
b) Patients who would have met a 4.5−hour−revised US label			
0 vs 1−6	268 (16.2%)	194 (11.6%)	1.46 (1.19−1.79)
0−1 vs 2−6	580 (35.1%)	475 (28.4%)	1.37 (1.17−1.59)
0−2 vs 3−6	761 (46.0%)	692 (41.4%)	1.21 (1.05−1.39)
0−3 vs 4−6	981 (59.3%)	901 (53.9%)	1.26 (1.09−1.45)
0−4 vs 5−6	1151 (69.6%)	1143 (68.3%)	1.06 (0.90−1.23)
0−5 vs 6	1336 (80.8%)	1332 (79.6%)	1.07 (0.90−1.27)
Any upwards shift			**1.24 (1.10 − 1.40)**
c) Patients who would NOT have met a 4.5−hour−revised US label			
0 vs 1−6	201 (14.1%)	169 (12.2%)	1.19 (0.95−1.49)
0−1 vs 2−6	454 (31.9%)	404 (29.2%)	1.14 (0.97−1.34)
0−2 vs 3−6	646 (45.3%)	603 (43.5%)	1.07 (0.92−1.25)
0−3 vs 4−6	845 (59.3%)	799 (57.7%)	1.07 (0.92−1.24)
0−4 vs 5−6	987 (69.3%)	971 (70.1%)	0.95 (0.81−1.12)
0−5 vs 6	1147 (80.5%)	1147 (82.8%)	0.85 (0.70−1.04)
Any upwards shift			**1.03 (0.90 − 1.18)**



Webfigure 6: Effect of rt−PA on type 2 parenchymal haemorrhage within 7 days in groups defined by the current US label as well a US label extended to 4.5 hours

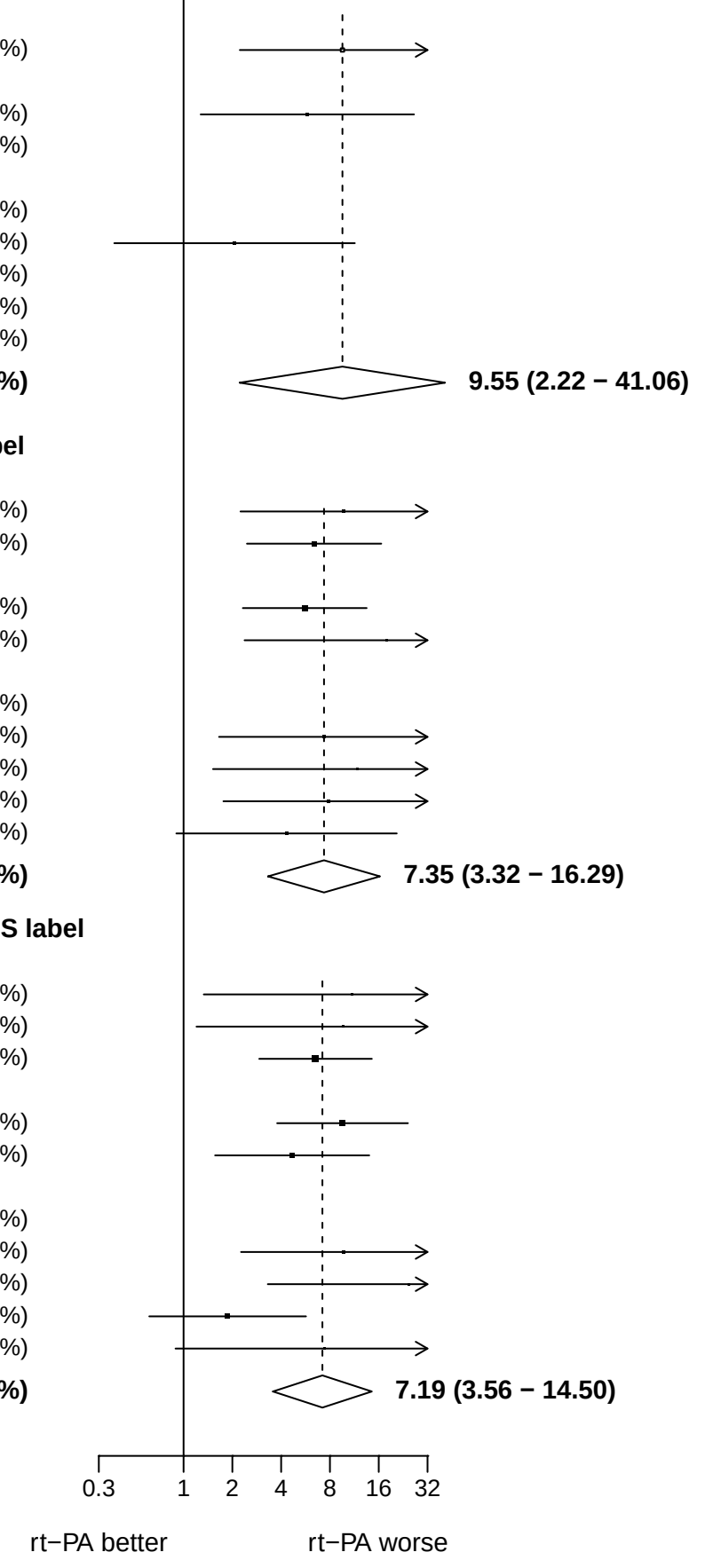
	rt−PA	Control	Odds ratio (95% CI)
a) Patients who would have met the current US label			
Treatment delay			
≤ 3 hours	33/600 (5.5%)	5/574 (0.9%)	
Age			
≤ 80 years	17/365 (4.7%)	2/377 (0.5%)	
>80 years	16/235 (6.8%)	3/197 (1.5%)	
Baseline NIHSS			
0−4	1/44 (2.3%)	0/25 (0.0%)	
5−10	7/169 (4.1%)	2/183 (1.1%)	
11−15	9/145 (6.2%)	0/128 (0.0%)	
16−21	10/152 (6.6%)	2/143 (1.4%)	
≥ 22	6/90 (6.7%)	1/95 (1.1%)	
Subtotal	**33/600 (5.5%)**	**5/574 (0.9%)**	**6.38 (2.47 − 16.47)**
b) Patients who would have met a 4.5−hour−revised US label			
Treatment delay			
≤ 3 hours	33/600 (5.5%)	5/574 (0.9%)	
>3, ≤ 4.5 hours	60/1053 (5.7%)	13/1099 (1.2%)	
Age			
≤ 80 years	52/1146 (4.5%)	11/1189 (0.9%)	
>80 years	41/507 (8.1%)	7/484 (1.4%)	
Baseline NIHSS			
0−4	1/149 (0.7%)	0/137 (0.0%)	
5−10	23/587 (3.9%)	4/607 (0.7%)	
11−15	27/389 (6.9%)	2/373 (0.5%)	
16−21	24/349 (6.9%)	8/366 (2.2%)	
≥ 22	18/179 (10.1%)	4/190 (2.1%)	
Subtotal	**93/1653 (5.6%)**	**18/1673 (1.1%)**	**5.58 (3.35 − 9.30)**
c) Patients who would NOT have met a 4.5−hour−revised US label			
Treatment delay			
≤ 3 hours	15/138 (10.9%)	2/150 (1.3%)	
>3, ≤ 4.5 hours	13/206 (6.3%)	3/216 (1.4%)	
>4.5 hours	90/1081 (8.3%)	13/1019 (1.3%)	
Age			
≤ 80 years	81/1055 (7.7%)	8/1022 (0.8%)	
>80 years	37/370 (10.0%)	10/363 (2.8%)	
Baseline NIHSS			
0−4	9/179 (5.0%)	0/167 (0.0%)	
5−10	34/584 (5.8%)	2/566 (0.4%)	
11−15	33/310 (10.6%)	3/307 (1.0%)	
16−21	22/235 (9.4%)	10/237 (4.2%)	
≥ 22	20/117 (17.1%)	3/108 (2.8%)	
Subtotal	**118/1425 (8.3%)**	**18/1385 (1.3%)**	**6.89 (4.17 − 11.38)**



Analyses done as for Figure 1 of the main manuscript

Webfigure 7: Effect of rt−PA on SITS−MOST intracerebral haemorrhage at 24−36 hours in groups defined by the current US label as well a US label extended to 4.5 hours

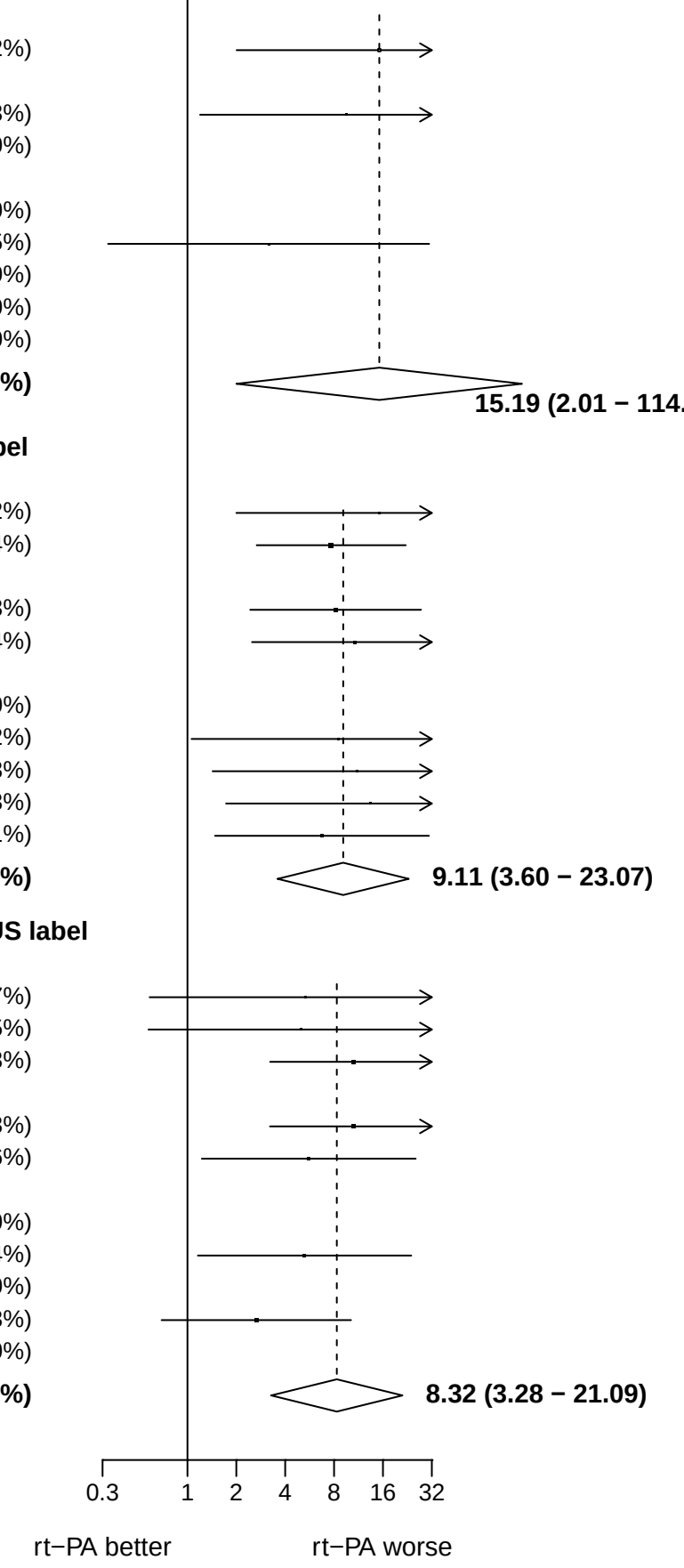
	rt−PA	Control	Odds ratio (95% CI)
a) Patients who would have met the current US label			
Treatment delay			
≤ 3 hours	20/600 (3.3%)	2/574 (0.3%)	
Age			
≤ 80 years	11/365 (3.0%)	2/377 (0.5%)	
>80 years	9/235 (3.8%)	0/197 (0.0%)	
Baseline NIHSS			
0−4	1/44 (2.3%)	0/25 (0.0%)	
5−10	4/169 (2.4%)	2/183 (1.1%)	
11−15	4/145 (2.8%)	0/128 (0.0%)	
16−21	8/152 (5.3%)	0/143 (0.0%)	
≥ 22	3/90 (3.3%)	0/95 (0.0%)	
Subtotal	**20/600 (3.3%)**	**2/574 (0.3%)**	**9.55 (2.22 − 41.06)**
b) Patients who would have met a 4.5−hour−revised US label			
Treatment delay			
≤ 3 hours	20/600 (3.3%)	2/574 (0.3%)	
>3, ≤ 4.5 hours	29/1053 (2.8%)	5/1099 (0.5%)	
Age			
≤ 80 years	31/1146 (2.7%)	6/1189 (0.5%)	
>80 years	18/507 (3.6%)	1/484 (0.2%)	
Baseline NIHSS			
0−4	1/149 (0.7%)	0/137 (0.0%)	
5−10	14/587 (2.4%)	2/607 (0.3%)	
11−15	12/389 (3.1%)	1/373 (0.3%)	
16−21	14/349 (4.0%)	2/366 (0.5%)	
≥ 22	8/179 (4.5%)	2/190 (1.1%)	
Subtotal	**49/1653 (3.0%)**	**7/1673 (0.4%)**	**7.35 (3.32 − 16.29)**
c) Patients who would NOT have met a 4.5−hour−revised US label			
Treatment delay			
≤ 3 hours	8/138 (5.8%)	1/150 (0.7%)	
>3, ≤ 4.5 hours	9/206 (4.4%)	1/216 (0.5%)	
>4.5 hours	47/1081 (4.3%)	7/1019 (0.7%)	
Age			
≤ 80 years	46/1055 (4.4%)	5/1022 (0.5%)	
>80 years	18/370 (4.9%)	4/363 (1.1%)	
Baseline NIHSS			
0−4	5/179 (2.8%)	0/167 (0.0%)	
5−10	20/584 (3.4%)	2/566 (0.4%)	
11−15	23/310 (7.4%)	1/307 (0.3%)	
16−21	9/235 (3.8%)	5/237 (2.1%)	
≥ 22	7/117 (6.0%)	1/108 (0.9%)	
Subtotal	**64/1425 (4.5%)**	**9/1385 (0.6%)**	**7.19 (3.56 − 14.50)**



Analyses done as for Figure 1 of the main manuscript

Webfigure 8: Effect of rt−PA on fatal intracerebral haemorrhage within 7 days in groups defined by the current US label as well a US label extended to 4.5 hours

	rt−PA	Control	Odds ratio (95% CI)
a) Patients who would have met the current US label			
Treatment delay			
≤ 3 hours	16/600 (2.7%)	1/574 (0.2%)	
Age			
≤ 80 years	9/365 (2.5%)	1/377 (0.3%)	
>80 years	7/235 (3.0%)	0/197 (0.0%)	
Baseline NIHSS			
0−4	0/44 (0.0%)	0/25 (0.0%)	
5−10	3/169 (1.8%)	1/183 (0.5%)	
11−15	3/145 (2.1%)	0/128 (0.0%)	
16−21	5/152 (3.3%)	0/143 (0.0%)	
≥ 22	5/90 (5.6%)	0/95 (0.0%)	
Subtotal	**16/600 (2.7%)**	**1/574 (0.2%)**	**15.19 (2.01 − 114.90)**
b) Patients who would have met a 4.5−hour−revised US label			
Treatment delay			
≤ 3 hours	16/600 (2.7%)	1/574 (0.2%)	
>3, ≤ 4.5 hours	27/1053 (2.6%)	4/1099 (0.4%)	
Age			
≤ 80 years	22/1146 (1.9%)	3/1189 (0.3%)	
>80 years	21/507 (4.1%)	2/484 (0.4%)	
Baseline NIHSS			
0−4	0/149 (0.0%)	0/137 (0.0%)	
5−10	8/587 (1.4%)	1/607 (0.2%)	
11−15	11/389 (2.8%)	1/373 (0.3%)	
16−21	12/349 (3.4%)	1/366 (0.3%)	
≥ 22	12/179 (6.7%)	2/190 (1.1%)	
Subtotal	**43/1653 (2.6%)**	**5/1673 (0.3%)**	**9.11 (3.60 − 23.07)**
c) Patients who would NOT have met a 4.5−hour−revised US label			
Treatment delay			
≤ 3 hours	4/138 (2.9%)	1/150 (0.7%)	
>3, ≤ 4.5 hours	5/206 (2.4%)	1/216 (0.5%)	
>4.5 hours	33/1081 (3.1%)	3/1019 (0.3%)	
Age			
≤ 80 years	31/1055 (2.9%)	3/1022 (0.3%)	
>80 years	11/370 (3.0%)	2/363 (0.6%)	
Baseline NIHSS			
0−4	3/179 (1.7%)	0/167 (0.0%)	
5−10	11/584 (1.9%)	2/566 (0.4%)	
11−15	11/310 (3.5%)	0/307 (0.0%)	
16−21	8/235 (3.4%)	3/237 (1.3%)	
≥ 22	9/117 (7.7%)	0/108 (0.0%)	
Subtotal	**42/1425 (2.9%)**	**5/1385 (0.4%)**	**8.32 (3.28 − 21.09)**



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