Slides presented to the CHM Alteplase Expert Working Group

Slides 2-27: Dr Jonathan Emberson (20.11.14)

Slides 29-67: Professor Colin Baigent (14.1.15)

Slides 69-102: Professor Colin Baigent (30.6.15)

Meta-analysis of individual patient data from the randomised trials assessing alteplase after acute ischaemic stroke

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On behalf of the Stroke Thrombolysis Trialists' Collaboration

FUNDING: UK Medical Research Council, British Heart Foundation, University of Glasgow, University of Edinburgh

STT authors' disclosures (Lancet, August 6th 2014)

CB, LB, and JE have not accepted fees, honoraria, or paid consultancies but are involved in clinical trials of lipid-modifying treatment funded by Merck to the University of Oxford, with the University the trial sponsor in all cases. KRL has received speaker fees from and has served on the data monitoring committee of trials for Boehringer Ingelheim; his department has received research grant support from Genentech. GA has received research grant support from Lundbeck, fees for consultancy and advisory board membership from Lundbeck, Covidien, Codman, and Genentech, fees for acting as an expert witness, and owns stock in iSchemaView. EB is employed by Boehringer Ingelheim. SD has received honoraria from Boehringer Ingelheim, EVER Pharma, and Sanofi and has received fees for consultancy and advisory board membership from Boehringer Ingelheim and Sanofi . GD has received research grant support from the NHMRC (Australia) and honoraria from Pfizer and Bristol-Myers Squibb. JG has received fees for consultancy and advisory board membership from Lundbeck. RvK has received speaker fees and honoraria from Penumbra and Lundbeck. RIL has received honoraria from Boehringer Ingelheim. JMO has received speaker fees from Boehringer Ingelheim. MP has received travel support from Boehringer Ingelheim. BT has received honoraria from Pfizer. DT has received speaker fees and fees for consultancy and advisory board membership from Boehringer Ingelheim and Bayer. KT has received research grant support from the Ministry of Health, Labour, and Welfare of Japan, and speaker fees from Mitsubishi Tanabe Pharma. JW has received research grant support from the UK Medical Research Council and from Boehringer Ingelheim to the University of Edinburgh for a research scanner bought more than 10 years ago. WW has received research grant support from the UK Medical Research Council. PS has received honoraria for lectures which were paid to the department from Boehringer Ingelheim. WH has received research grant support from Boehringer Ingelheim, and speaker fees and fees for consultancy and advisory board membership from Boehringer Ingelheim. PL, TB, GC, GH, MKa, MKo, ML, GM, NW, and GJdZ declare no competing interests.

The Stroke Thrombolysis Trialists' Collaboration

- Collaboration between trialists and meta-analysts, set up prior to knowledge of the results from the Third International Stroke Trial (IST-3)

- Statistical analysis plan published in *Int J Stroke 2013*

- 9 trials including 6756 randomized patients
  - ATLANTIS A/B, ECASS I/II/III, EPITHET, IST-3, NINDS A/B

Primary pre-specified aims

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

Pre-specified outcomes

- Primary efficacy
  - Modified Rankin Scale (mRS) 0/1 at 3-6 months post stroke

- Safety endpoints
  - 90-day mortality
  - Symptomatic intracranial haemorrhage (sICH)
    - Parenchymal haemorrhage of type 2 (PH2) within 7 days
    - SITS-MOST definition of PH2 type haemorrhage within 36 hrs
  - Fatal ICH within 7 days

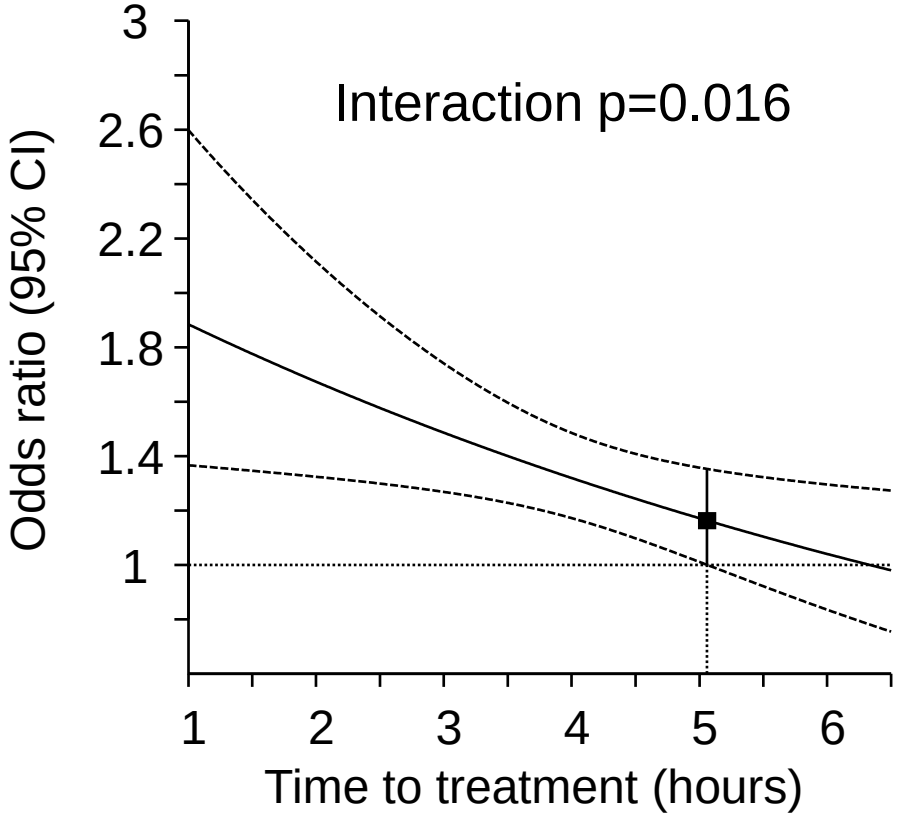
Pre-specified methods: 1-stage meta-analysis

- **Primary outcome: mRS 0-1 vs 2-6**
  - Multivariable (unconditional) logistic regression models stratified by trial and adjusted for:
    - treatment allocation
    - treatment delay, age and stroke severity
    - 2-way interactions between treatment allocation and each of the potential effect-modifiers
- **90-day mortality**
  - Equivalent Cox regression models
- **All analyses are intention-to-treat**

Baseline characteristics

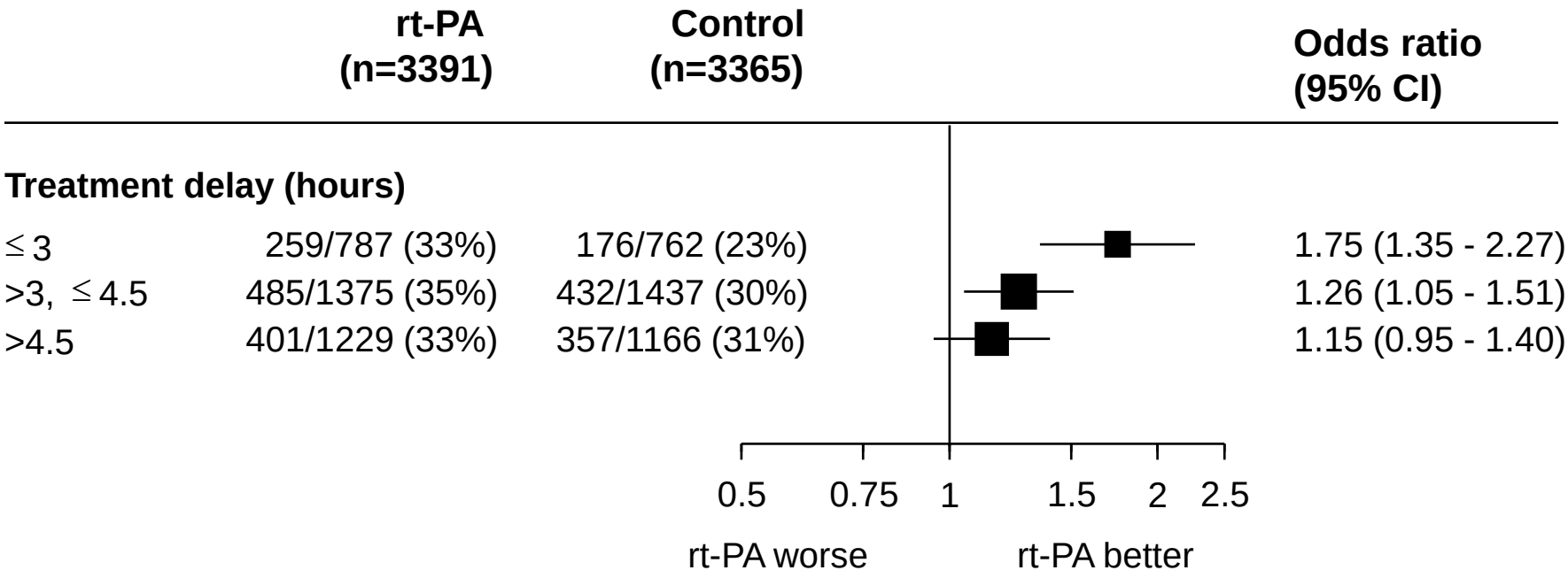
	Trial		Randomized treatment allocation	
	IST-3 (n=3035)	8 previous trials (n=3721)	rt-PA (n=3391)	Control (n=3365)
Treatment delay (hours)	4.2 (1.2)	3.9 (1.2)	4.0 (1.2)	4.0 (1.2)
≤3	20	25	23	23
>3, ≤4.5	38	44	40	42
>4.5	42	30	36	35
Age (years)	77 (12)	66 (12)	71 (13)	71 (13)
≤80	47	97	74	75
>80	53	3	26	25
Stroke severity (NIHSS)	12 (6.9)	12 (6.2)	12 (6.6)	12 (6.5)

Effect on mRS 0-1 by treatment delay



Slope not significantly altered by age or stroke severity

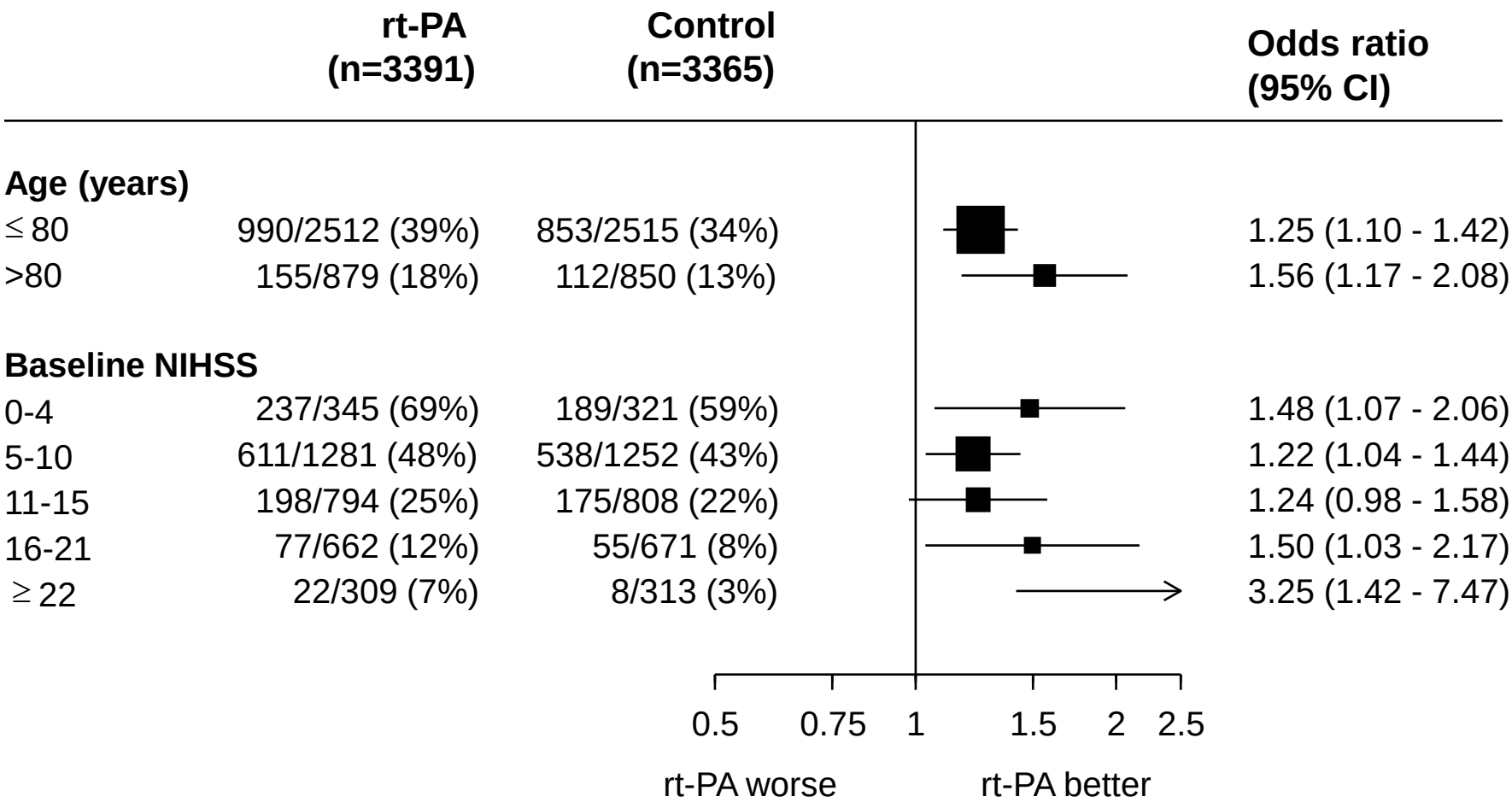
Effect on mRS 0-1 by treatment delay



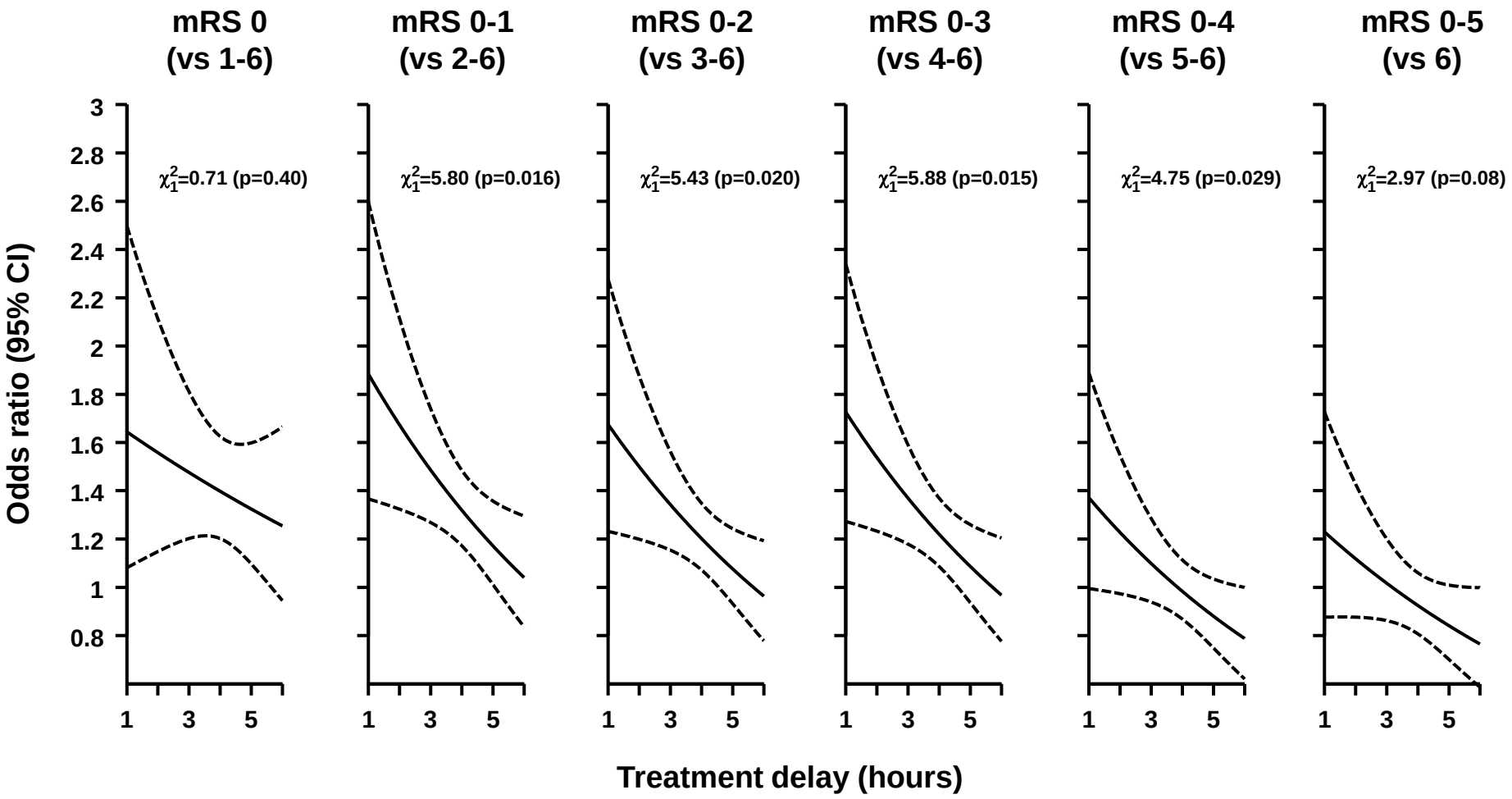
Effect on mRS 0-1 between 3 and 4.5 hrs

Trial	Allocated alteplase (n=1375)	Allocated control (n=1437)
ECASS I	42	35
ECASS II	52	40
ECASS III	218	178
ATLANTIS A	2	4
ATLANTIS B	49	52
EPITHET	3	3
IST-3	119	120
Total	**485 (35%)**	**432 (30%)**

Effect on mRS 0-1 by age and stroke severity



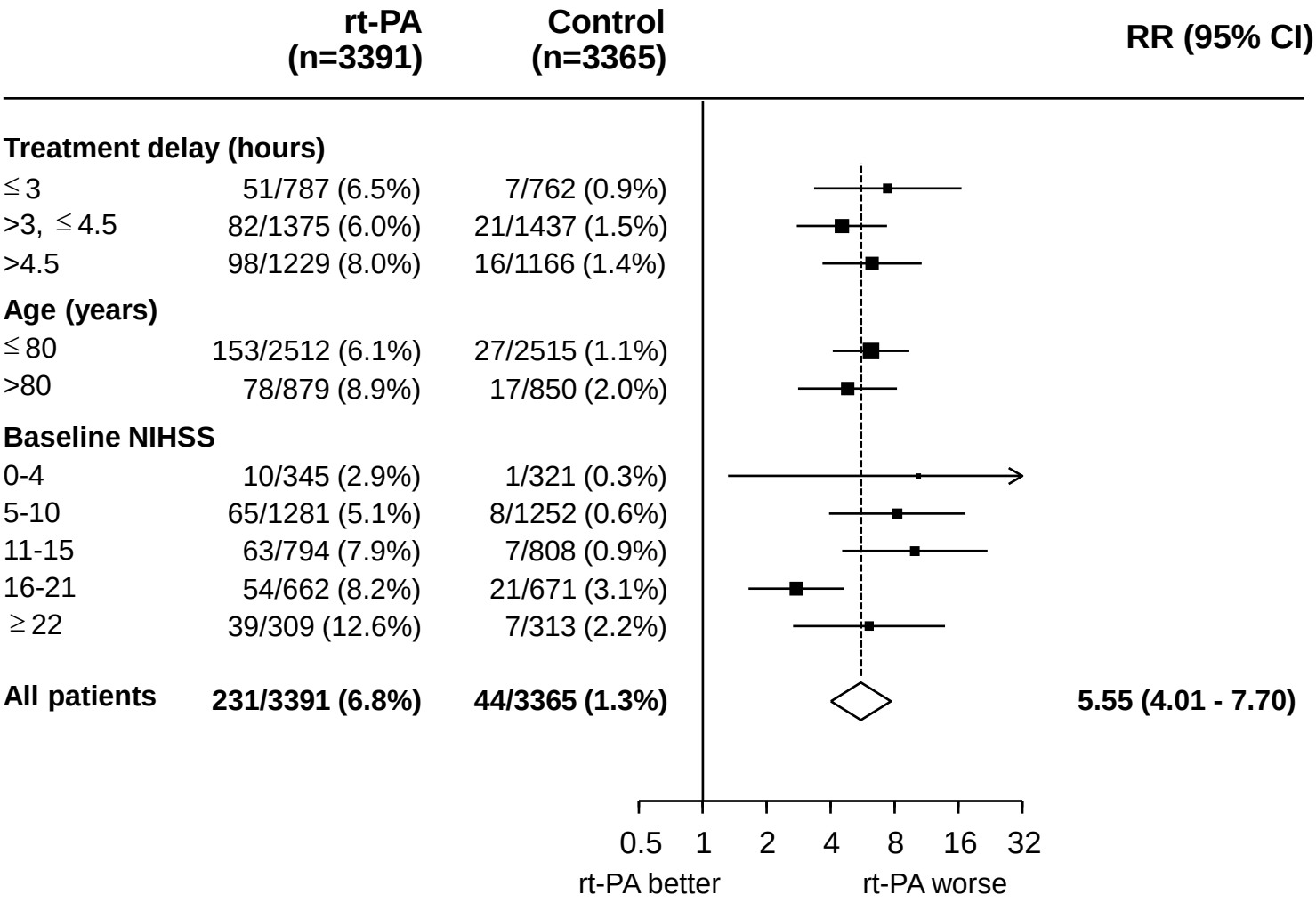
Effect on mRS by treatment delay (alternative definitions of 'good' outcome)



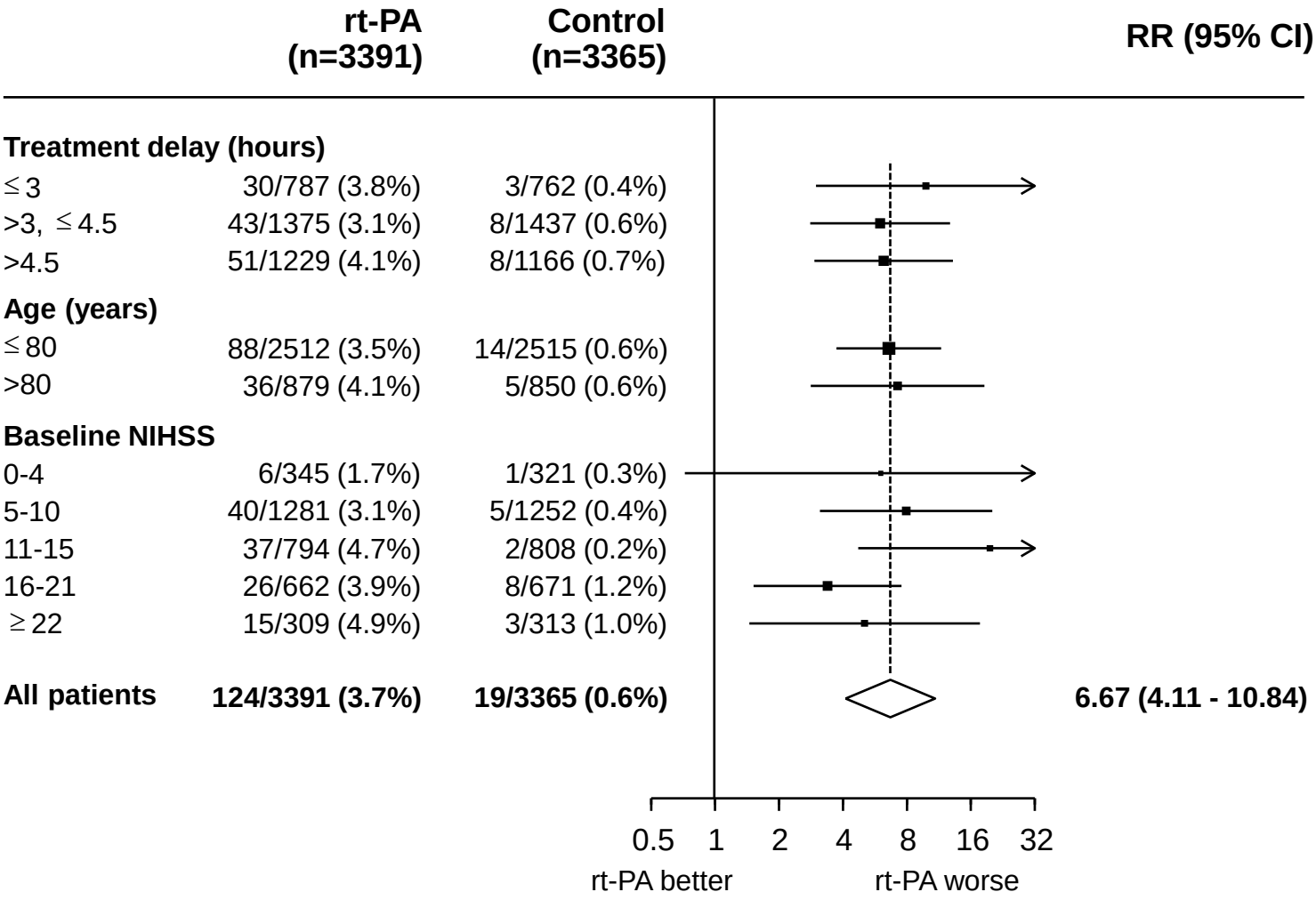
Symptomatic ICH and 90-day mortality

	rt-PA	Control	RR (95% CI)
Number randomized	3391	3365	
Intracranial haemorrhage			
- PH2 at 7 days	231 (6.8%)	44 (1.3%)	5.55 (4.01 – 7.70)
- SITS-MOST at 36 hours	124 (3.7%)	19 (0.6%)	6.67 (4.11 – 10.8)
- Fatal ICH (within 7 days)	91 (2.7%)	13 (0.4%)	7.14 (3.98 – 12.8)
Death within 90 days	608 (17.9%)	556 (16.5%)	1.11 (0.99 – 1.25)

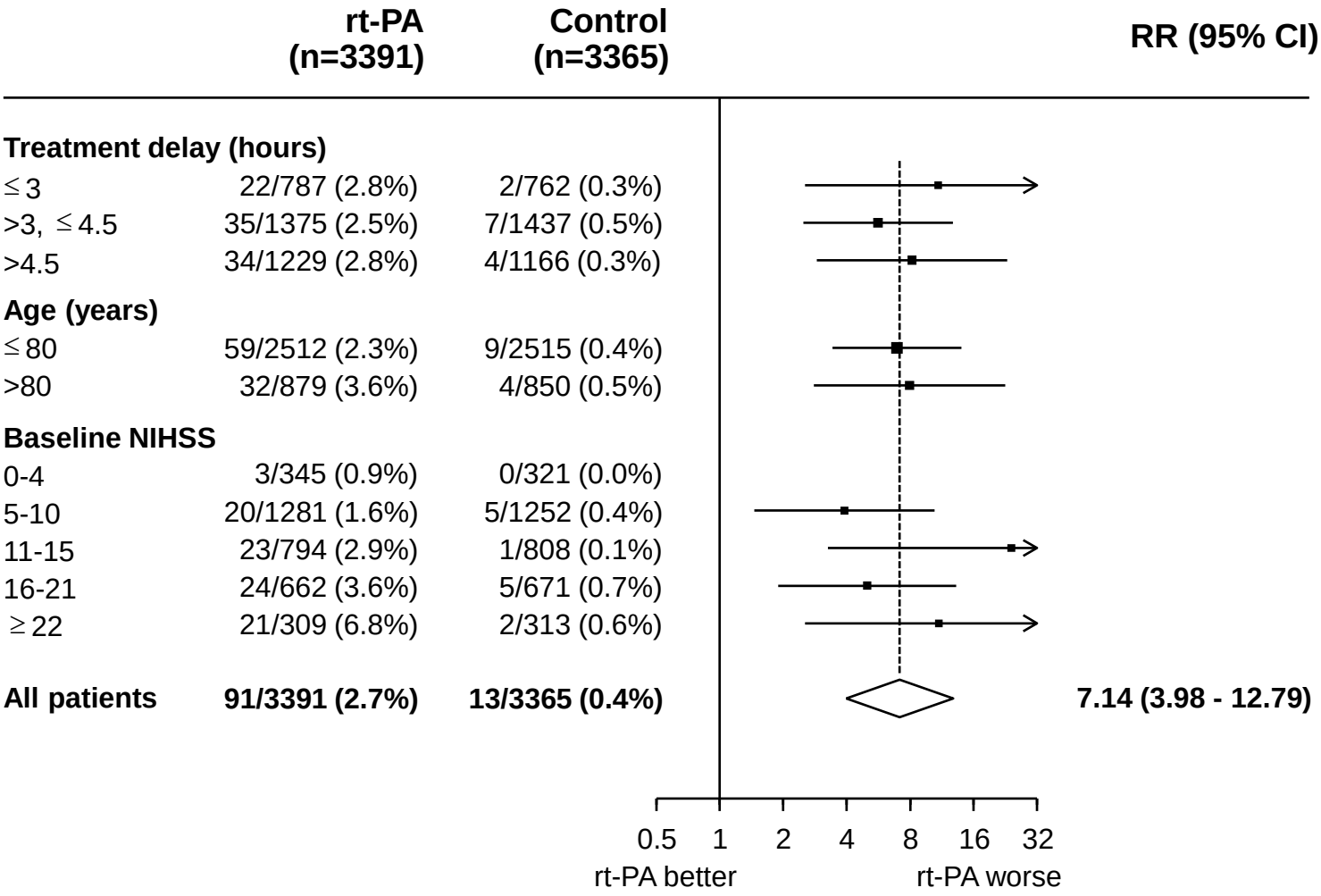
Effect on sICH (PH2 definition)



Effect on sICH (SITS-MOST definition)

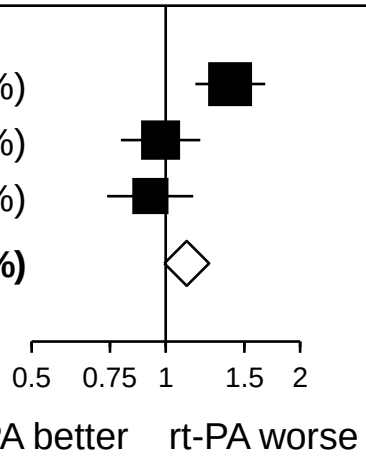


Effect on fatal ICH within 7 days



Effect on 90-day mortality by period of follow-up

Risk period	No. (%) dead within 90 days: rt-PA (n=3391)	Control (n=3365)	RR (95% CI)
Days 1-7 *	282 (8.3%)	204 (6.1%)	1.39 (1.16-1.67)
Days 8-30	178 (5.2%)	188 (5.6%)	0.97 (0.79-1.20)
Days 31-90	148 (4.4%)	164 (4.9%)	0.92 (0.74-1.15)
Subtotal: 90-day mortality	**608 (17.9%)**	**556 (16.5%)**	**1.11 (0.99-1.25)**

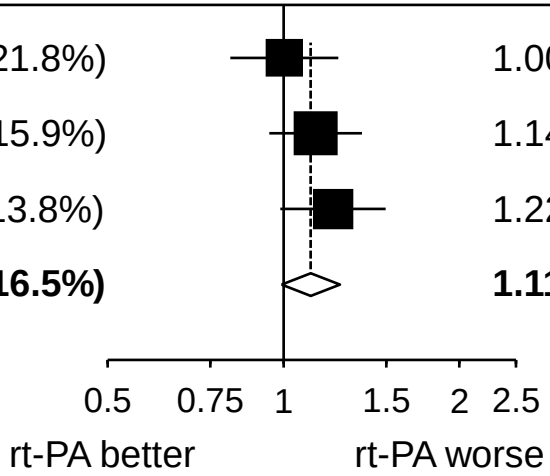


* Includes 91 vs 13 deaths from ICH and 191 vs 191 deaths from other causes

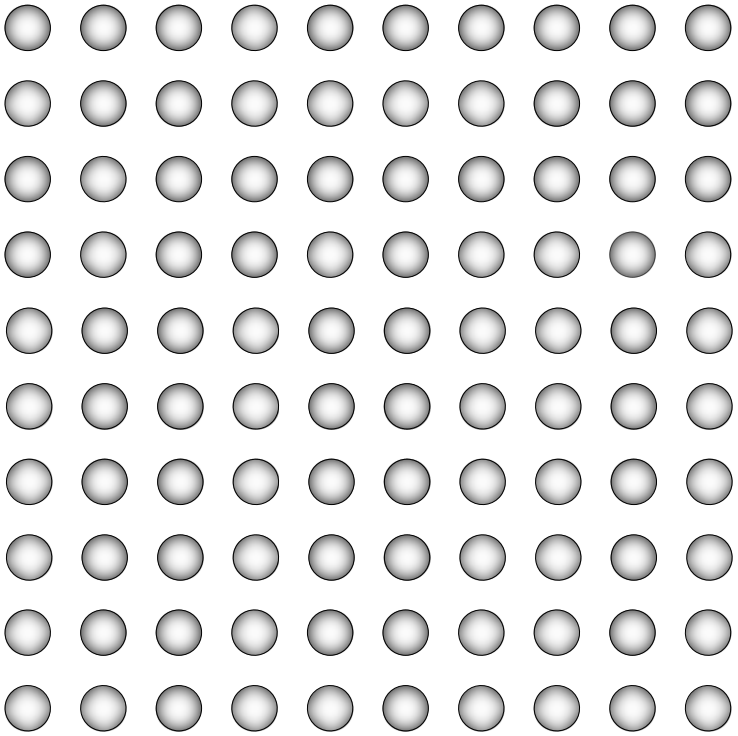
Effect on 90-day mortality by treatment delay

Treatment delay (hours)	No. (%) dead within 90 days rt-PA (n=3391)	Control (n=3365)	RR (95% CI)
≤3	175/787 (22.2%)	166/762 (21.8%)	1.00 (0.81 - 1.24)
>3, ≤4.5	232/1375 (16.9%)	229/1437 (15.9%)	1.14 (0.95 - 1.36)
>4.5	201/1229 (16.4%)	161/1166 (13.8%)	1.22 (0.99 - 1.50)
All patients	**608/3391 (17.9%)**	**556/3365 (16.5%)**	**1.11 (0.99 - 1.25)**

p-value for trend across 3 groups shown = 0.21



What does all this mean for a typical group of 100 stroke patients?



Suppose that 25 would have had a good stroke outcome (mRS 0-1) without rt-PA and 6 would have died within the first week

If they had all been given rt-PA within 3 hours…

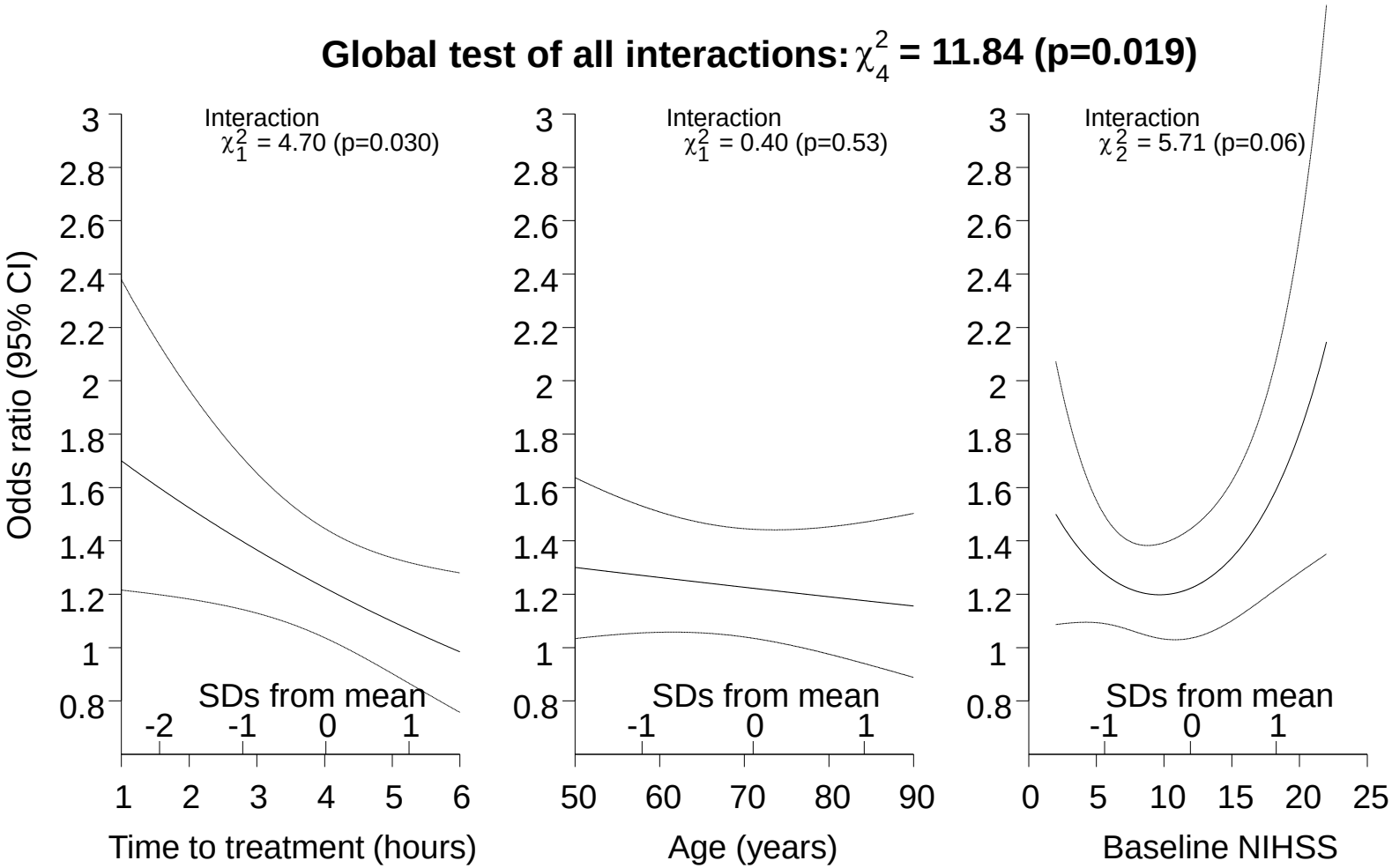
…the number recovering rises to about 35
…but 2 extra would die from ICH within 7 days

Conclusions

- rt-PA improves the odds of surviving with no significant disability when delivered within 4.5 hours of stroke onset, including among patients aged >80 years
- Earlier treatment results in bigger proportional benefits
- rt-PA increases the early risk of death from ICH, but has no significant effect on other causes of early death
- Among those treated earlier, there is a suggestion that this early hazard may be followed by later mortality benefits

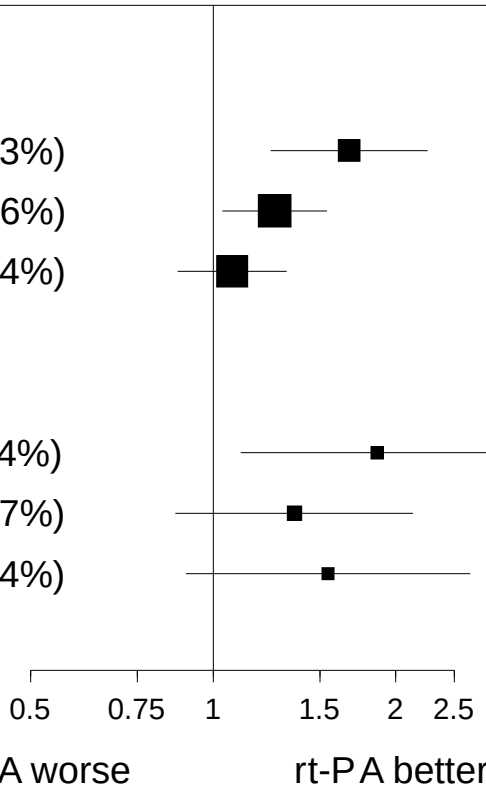
SUPPLEMENTARY SLIDES

Effect on mRS 0-1 by treatment delay, age and stroke severity



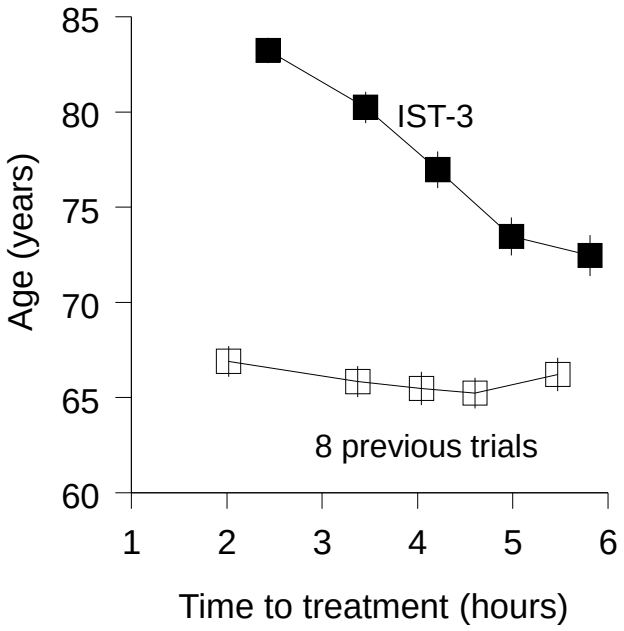
Effect on mRS 0-1 by age, at different treatment delays

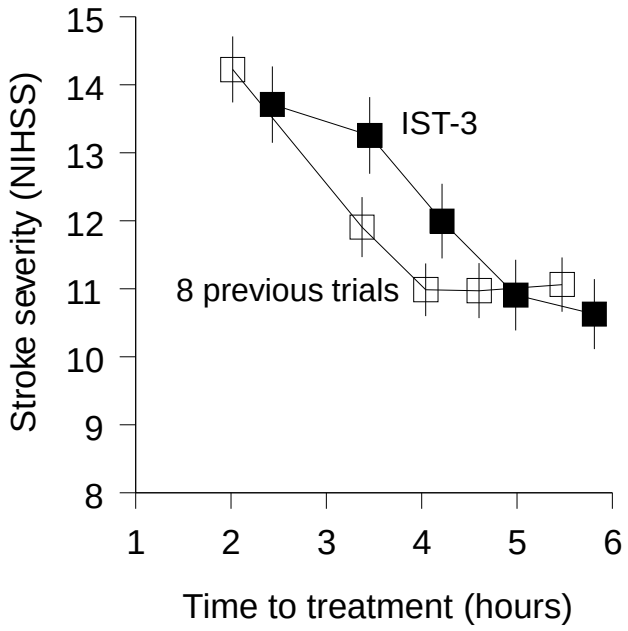
	rt-PA (n=3391)	Control (n=3365)	Odds ratio (95% CI)
≤ 80 years			
≤ 3 hours	204/485 (42.1%)	146/498 (29.3%)	1.68 (1.24-2.26)
3-4.5 hours	427/1033 (41.3%)	382/1073 (35.6%)	1.26 (1.04-1.54)
>4.5 hours	359/994 (36.1%)	325/944 (34.4%)	1.07 (0.87-1.32)
>80 years			
≤ 3 hours	55/302 (18.2%)	30/264 (11.4%)	1.86 (1.11-3.13)
3-4.5 hours	58/342 (17.0%)	50/364 (13.7%)	1.36 (0.87-2.14)
>4.5 hours	42/235 (17.9%)	32/222 (14.4%)	1.55 (0.90-2.65)



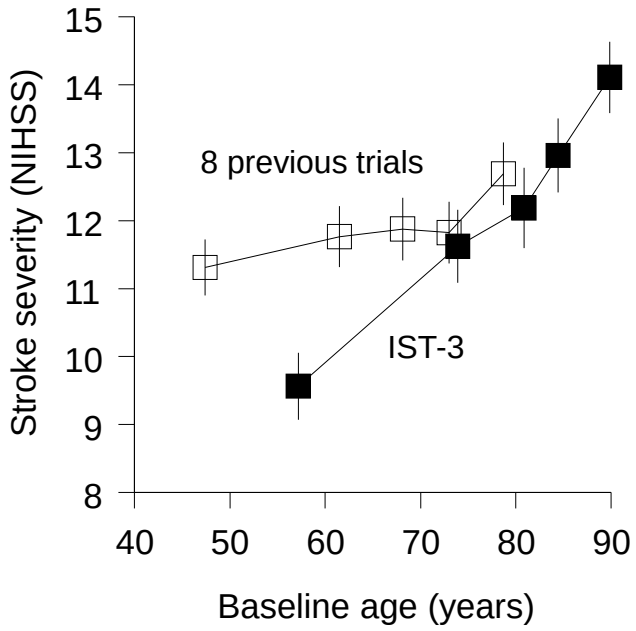
Test for whether age modifies the interaction between treatment delay and treatment effect: p-value=0.08

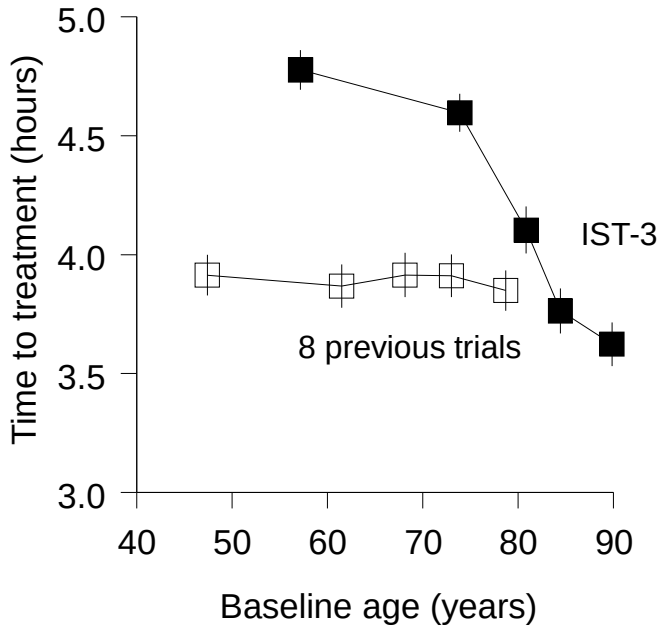
Age and stroke severity versus treatment delay



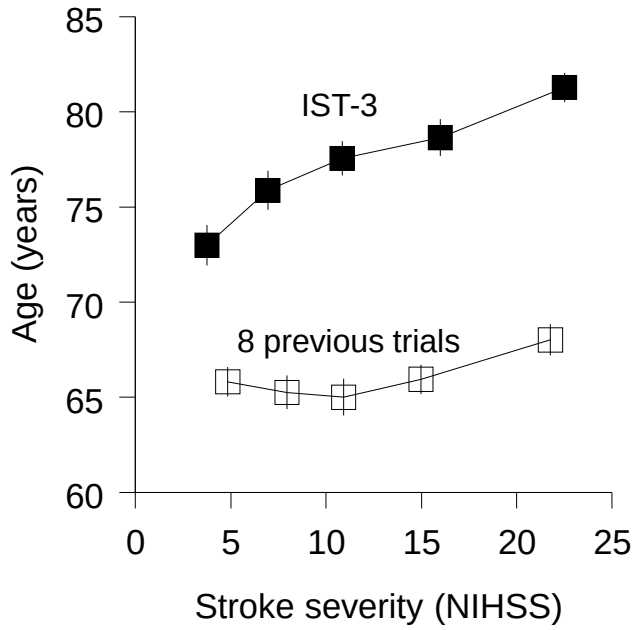


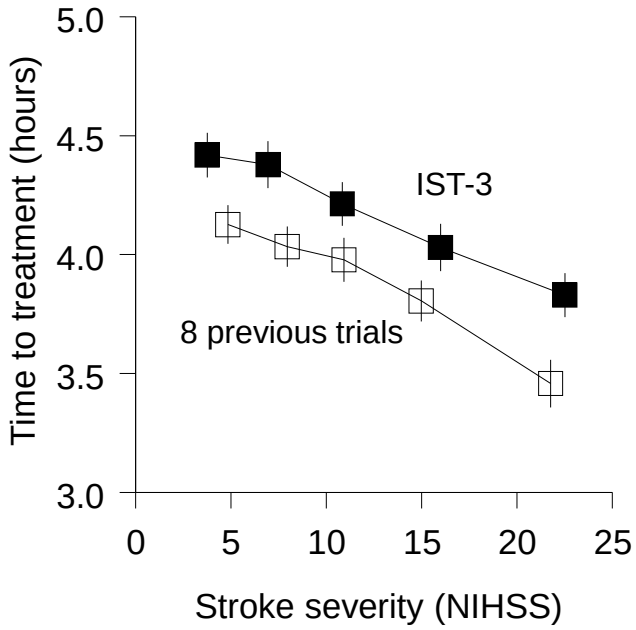
Stroke severity and treatment delay versus age





Age and treatment delay versus stroke severity





Additional analyses of the STT dataset

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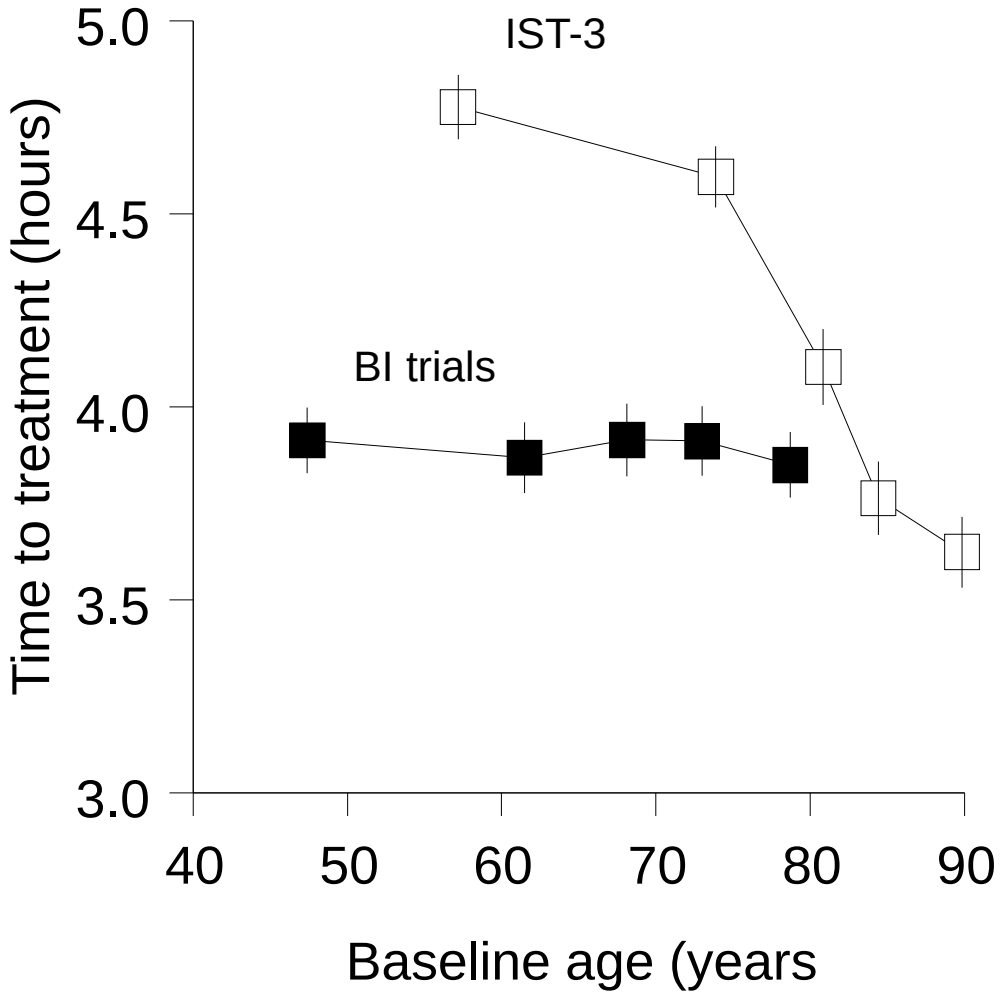
BENEFIT VS HAEMORRHAGIC STROKE RISK ACCORDING TO STROKE SEVERITY

Joint estimation of the "treatment-modifying effects" of delay, age and stroke severity

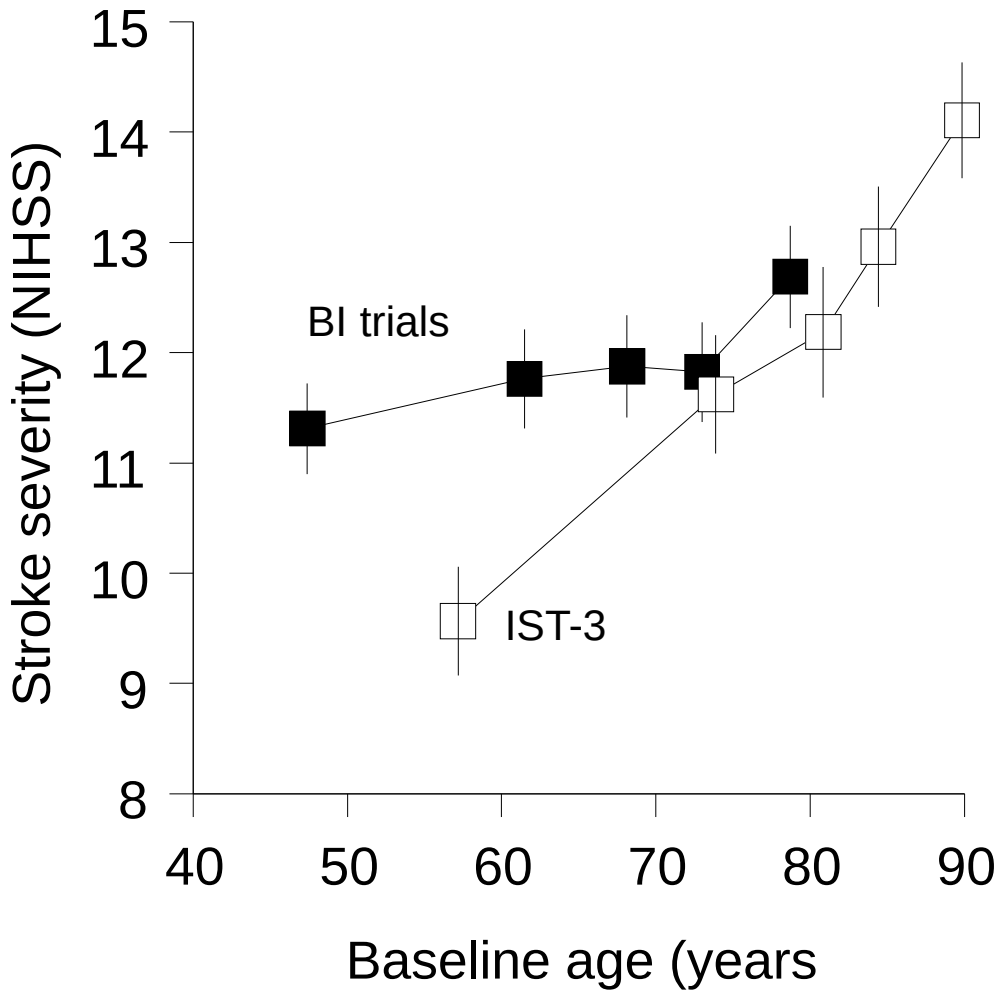
- Simple consideration of each characteristic in turn may be misleading (due to the correlation between the three characteristics)

- Multivariable (unconditional) logistic regression models stratified by trial and adjusted for:
  - treatment allocation
  - treatment delay, age and stroke severity
  - 2-way interactions between treatment allocation and each of the potential effect-modifiers
  - 2-sided p-values <0.05 considered nominally significant

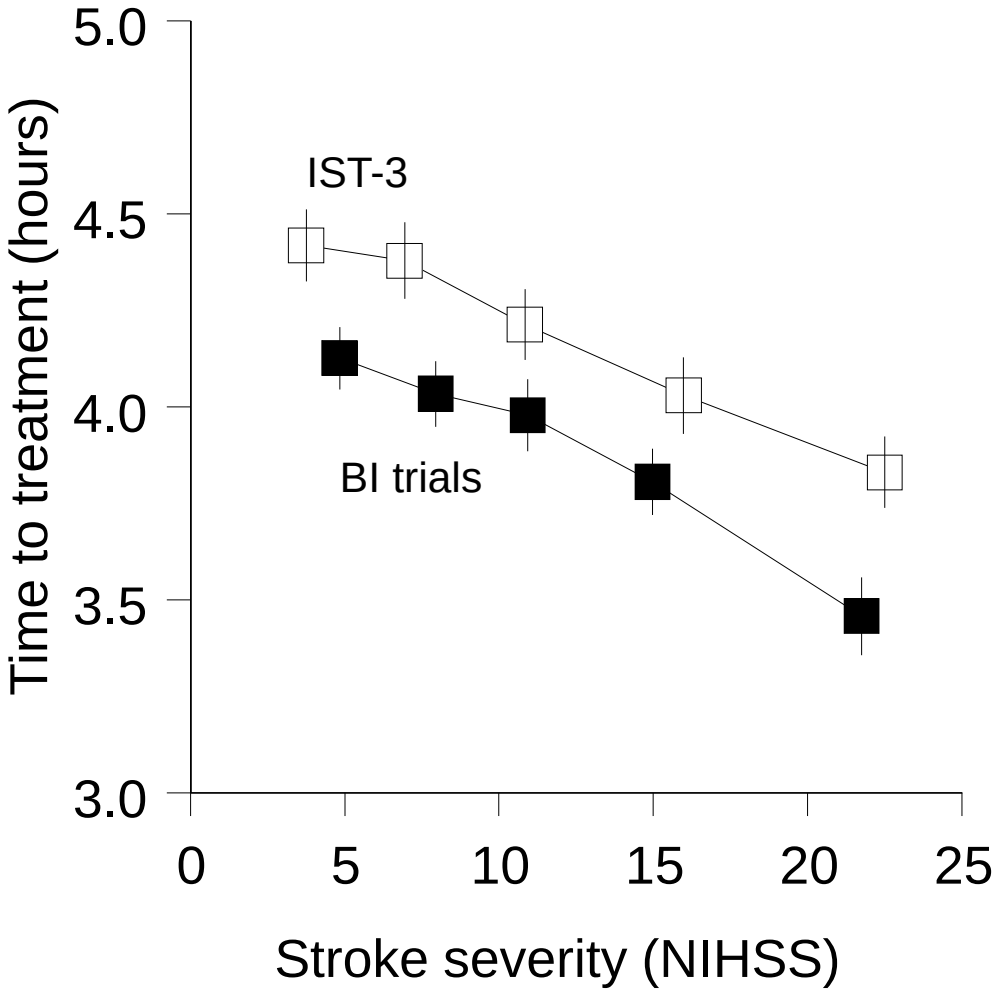
Age vs. treatment delay



Age vs. severity

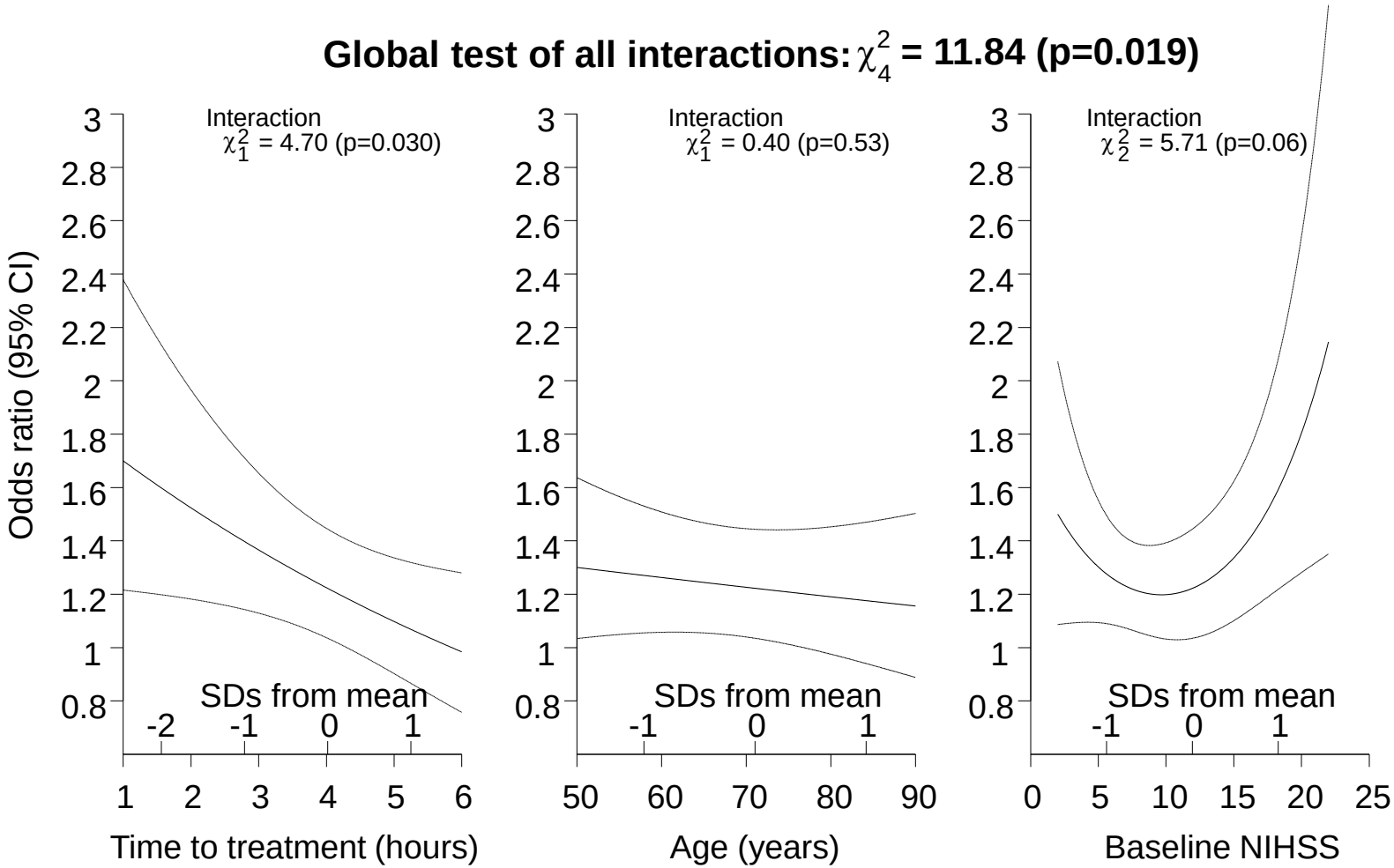


Severity vs. treatment delay

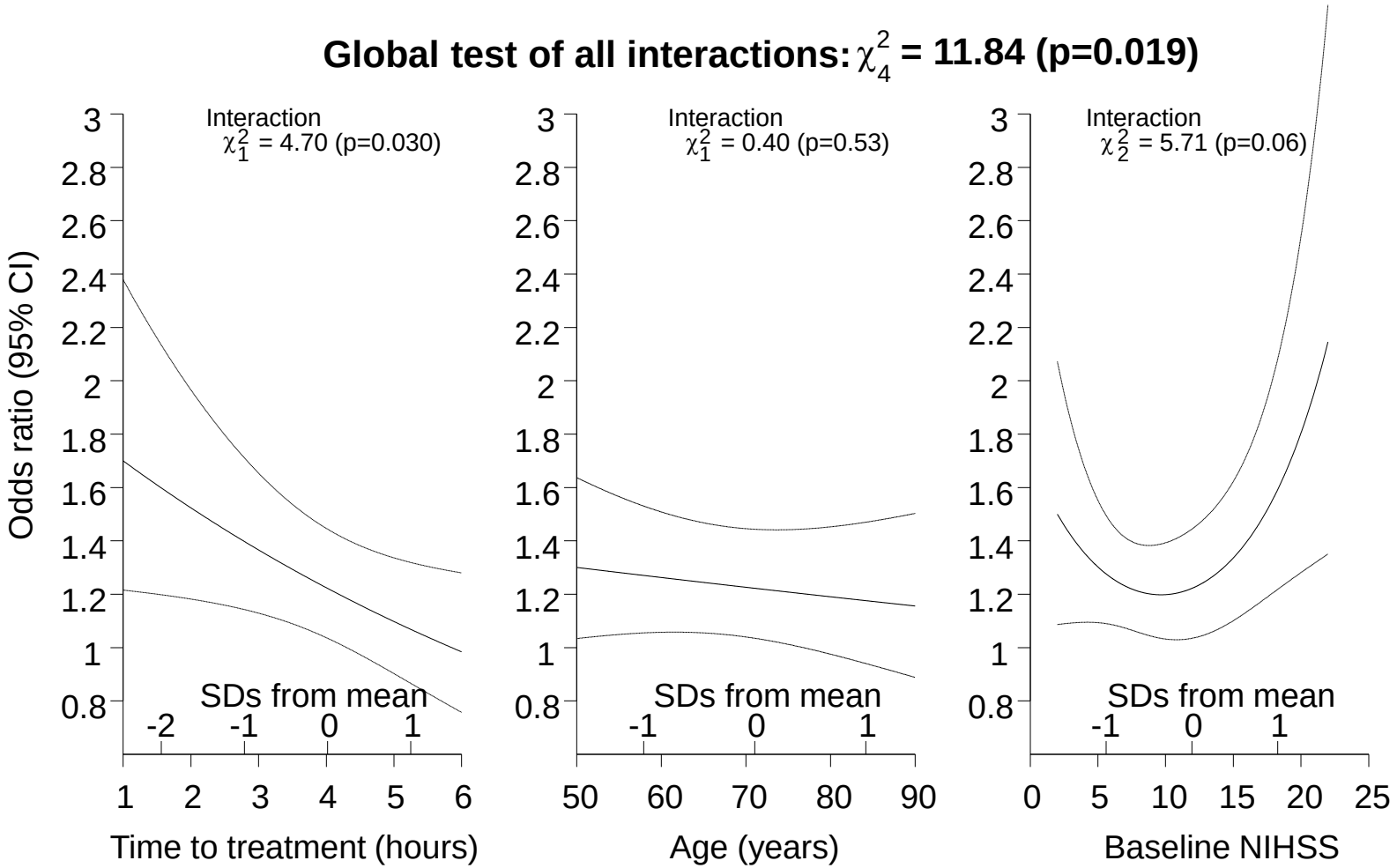


BENEFITS

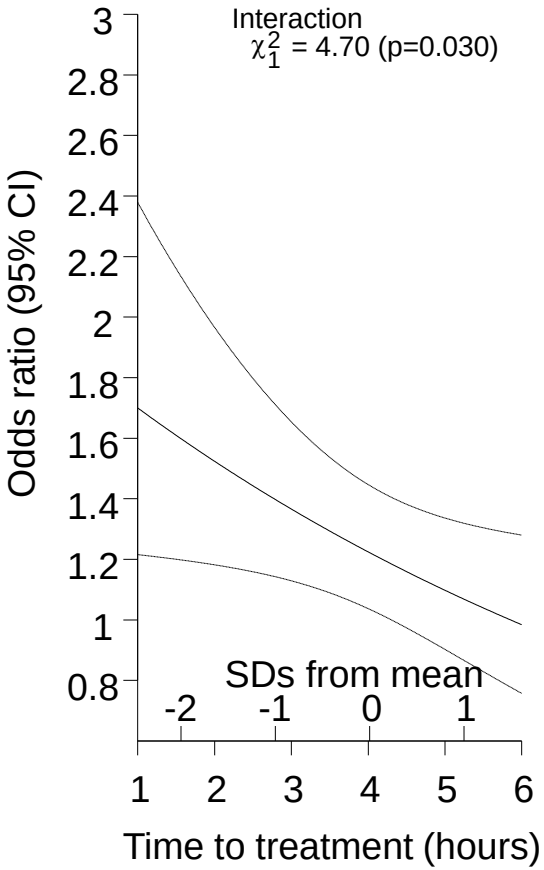
Relative odds of a good outcome (mRS 0-1) by treatment delay, age and stroke severity

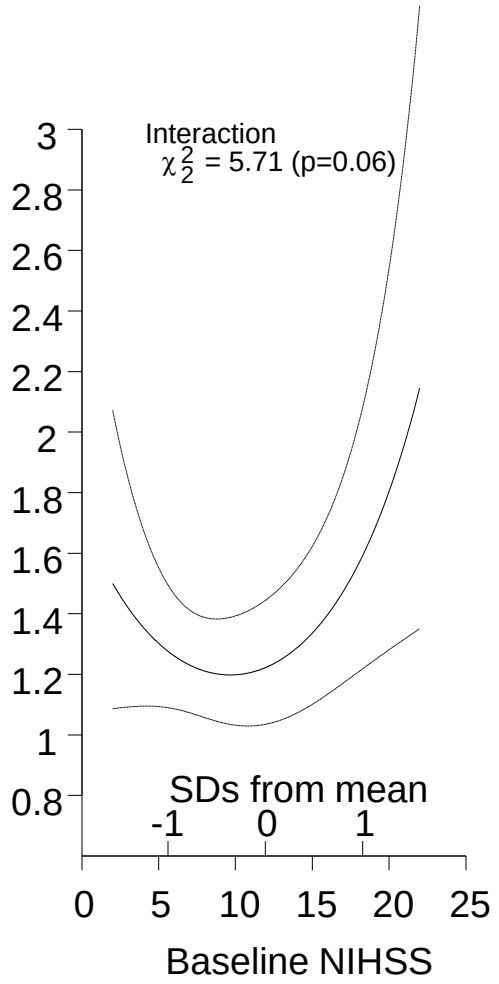


Relative odds of a good outcome (mRS 0-1) by treatment delay, age and stroke severity

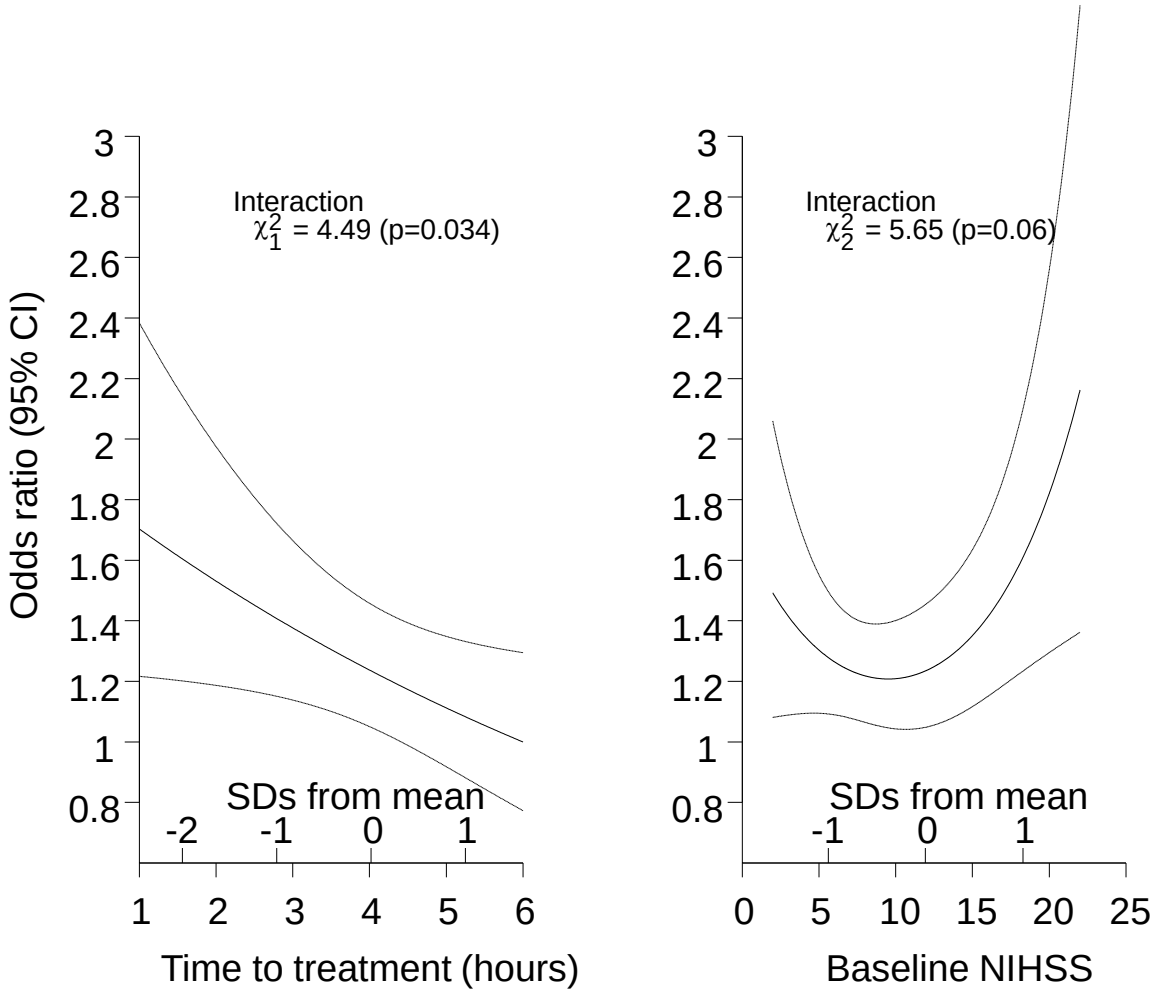


Relative odds of a good outcome (mRS 0-1) by treatment delay, age and stroke severity

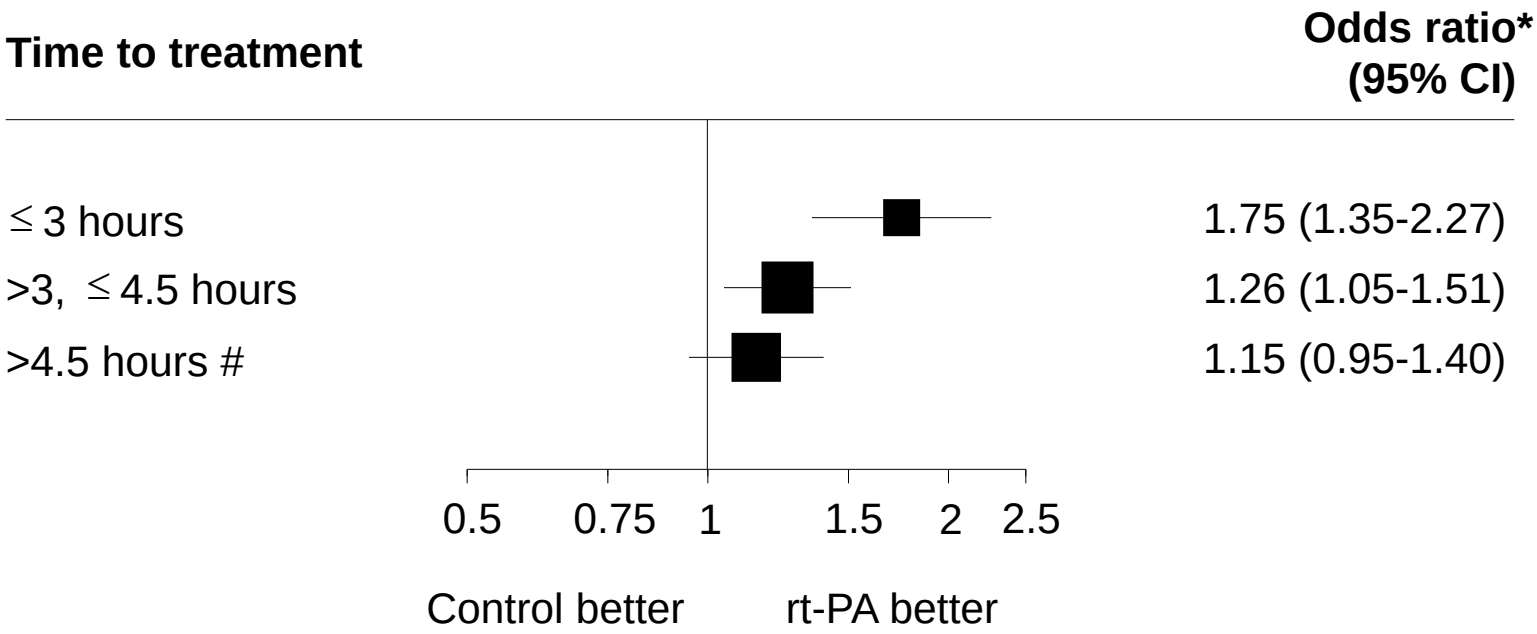




Relative odds of a good outcome (mRS 0-1) by treatment delay and stroke severity



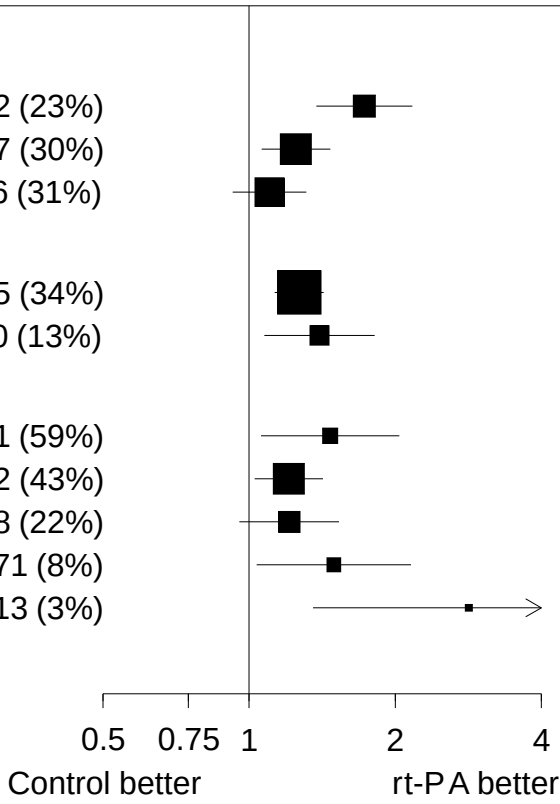
Relative odds of a good outcome (mRS 0-1) by time to treatment



* Estimates derived from a model including interactions between rt-PA and each treatment delay category
# The “conventional” subgroup result in the >4.5 hour category is 1.10 (95% CI 0.93 – 1.31)

“Conventional” meta-analysis

	rt-PA (n=3391)	Control (n=3365)	Odds ratio (95% CI)	Trend/het
Treatment delay				
≤ 3 hours	259/787 (33%)	176/762 (23%)	1.73 (1.38 - 2.17)	
>3, ≤ 4.5 hours	485/1375 (35%)	432/1437 (30%)	1.25 (1.06 - 1.47)	χ^2_1=8.80 (p=0.003)
>4.5 hours	401/1229 (33%)	357/1166 (31%)	1.10 (0.93 - 1.31)	
Age				
≤ 80 years	990/2512 (39%)	853/2515 (34%)	1.27 (1.13 - 1.42)	χ^2_1=0.43 (p=0.51)
>80 years	155/879 (18%)	112/850 (13%)	1.40 (1.07 - 1.81)	
Baseline NIHSS				
0-4	237/345 (69%)	189/321 (59%)	1.47 (1.06 - 2.04)	
5-10	611/1281 (48%)	538/1252 (43%)	1.21 (1.03 - 1.42)	χ^2_4=6.52 (p=0.16)
11-15	198/794 (25%)	175/808 (22%)	1.21 (0.95 - 1.53)	
16-21	77/662 (12%)	55/671 (8%)	1.49 (1.04 - 2.16)	
≥ 22	22/309 (7%)	8/313 (3%)	2.84 (1.35 - 5.94)	



HAZARD

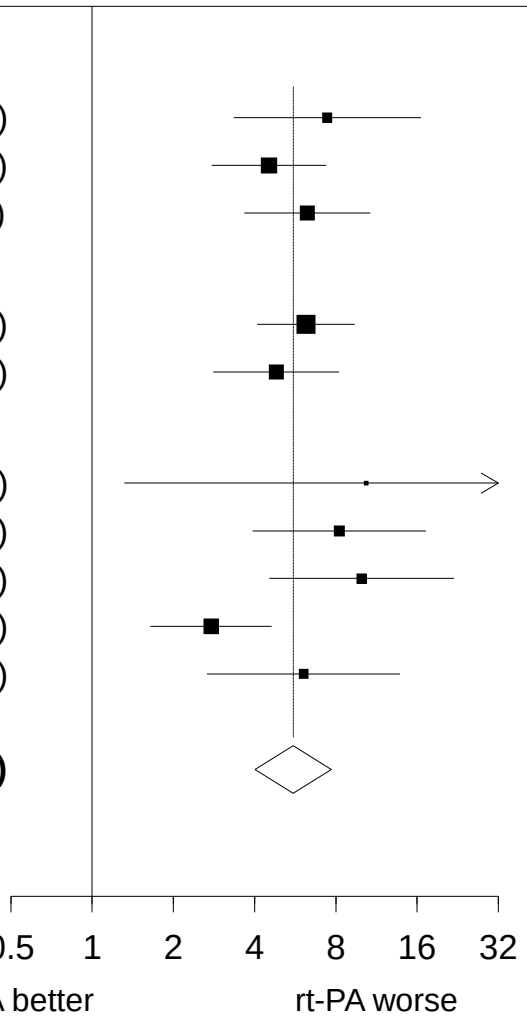
Table 1. Effect of rt-PA on symptomatic and fatal intracranial haemorrhage

	rt-PA	Control	OR (95% CI)*
Number randomized	3391	3365	
SICH (PH2 at 7 days)	231 (6.8%)	44 (1.3%)	5.55 (4.01 – 7.70)
SICH (SITS-MOST at 24-36 hours)	124 (3.7%)	19 (0.6%)	6.67 (4.11 – 10.84)
Fatal ICH (within 7 days)	91 (2.7%)	13 (0.4%)	7.14 (3.98 – 12.79)

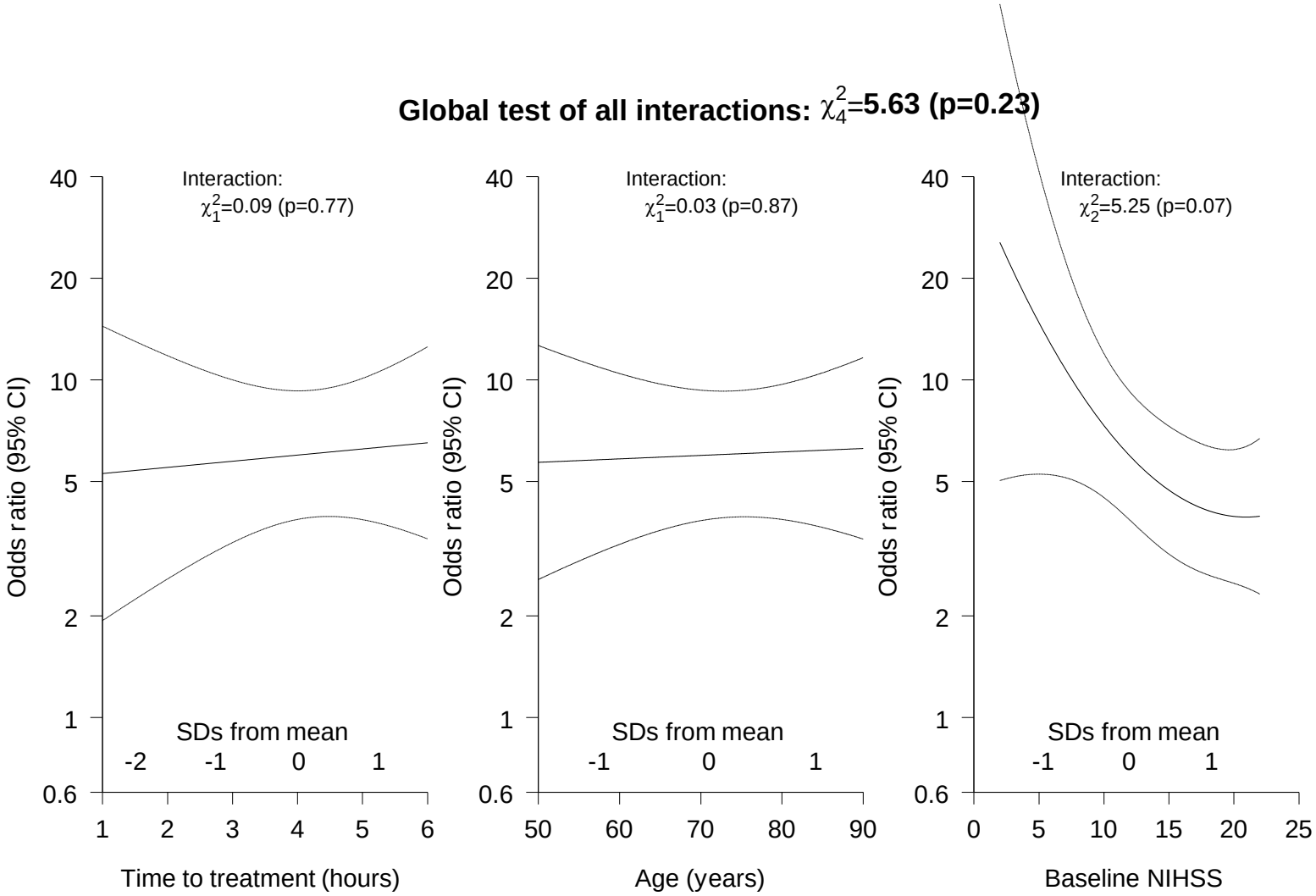
* Trial stratified odds ratio adjusted only for treatment allocation
SICH: symptomatic intracranial haemorrhage, PH2: parenchymal haemorrhage type 2;

Effect of rt-PA on SICH at 7 days (PH2) by treatment delay, age and stroke severity

	rt-PA (n=3391)	Control (n=3365)	OR (95% CI)
Treatment delay			
≤ 3 hours	51/787 (6.5%)	7/762 (0.9%)	7.43 (3.34 - 16.52)
>3, ≤ 4.5 hours	82/1375 (6.0%)	21/1437 (1.5%)	4.52 (2.77 - 7.36)
>4.5 hours	98/1229 (8.0%)	16/1166 (1.4%)	6.26 (3.66 - 10.72)
Age			
≤ 80 years	153/2512 (6.1%)	27/2515 (1.1%)	6.20 (4.09 - 9.38)
>80 years	78/879 (8.9%)	17/850 (2.0%)	4.80 (2.81 - 8.20)
Baseline NIHSS			
0-4	10/345 (2.9%)	1/321 (0.3%)	10.35 (1.32 - 81.41)
5-10	65/1281 (5.1%)	8/1252 (0.6%)	8.24 (3.94 - 17.27)
11-15	63/794 (7.9%)	7/808 (0.9%)	9.96 (4.53 - 21.92)
16-21	54/662 (8.2%)	21/671 (3.1%)	2.76 (1.64 - 4.63)
≥ 22	39/309 (12.6%)	7/313 (2.2%)	6.07 (2.66 - 13.83)
All patients	**231/3391 (6.8%)**	**44/3365 (1.3%)**	**5.55 (4.01 - 7.70)**

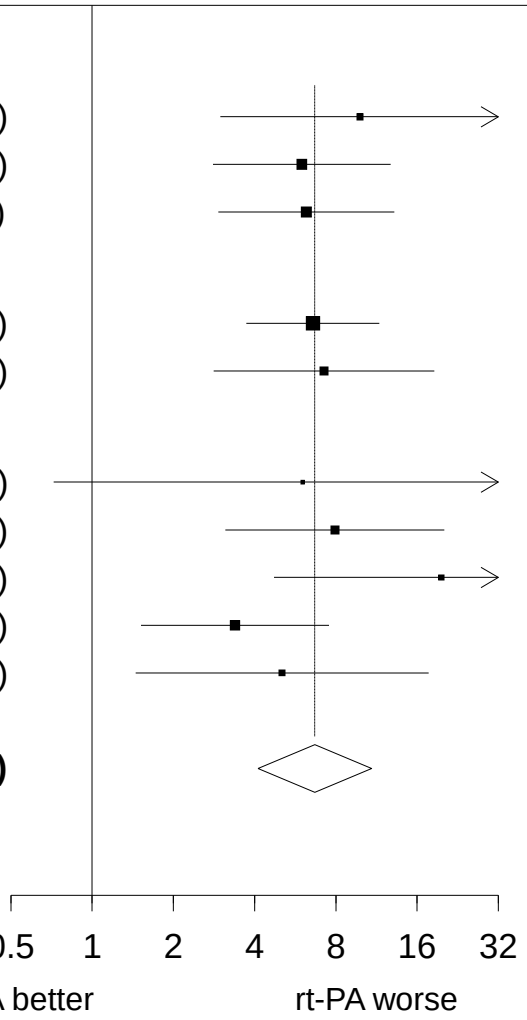


Effect of rt-PA on SICH at 7 days (PH2) by treatment delay, age and stroke severity (adjusted for all 3 treatment interactions)

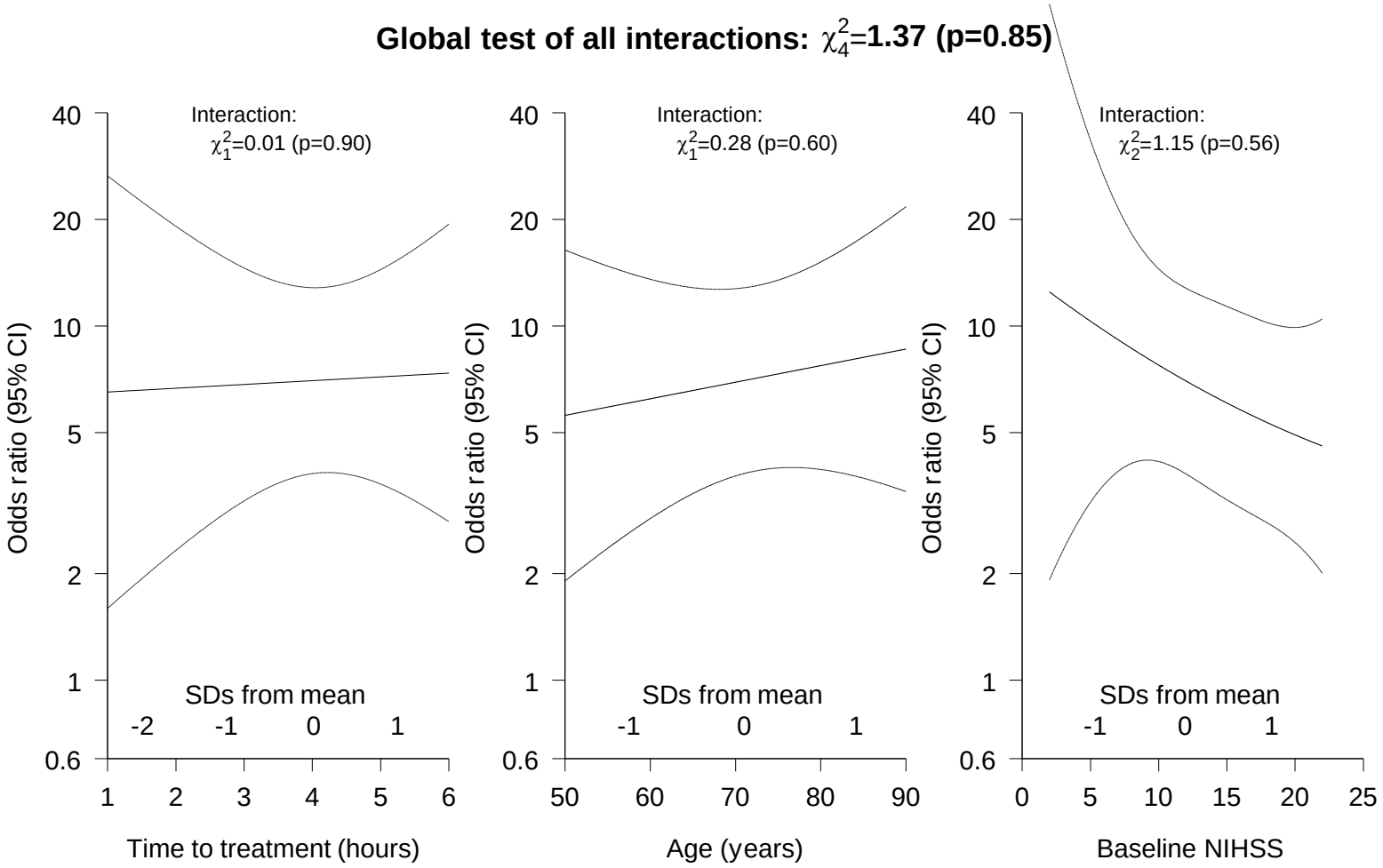


Effect of rt-PA on SICH at 24-36 hours (SITS-MOST) by treatment delay, age and stroke severity

	rt-PA (n=3391)	Control (n=3365)	OR (95% CI)
Treatment delay			
≤ 3 hours	30/787 (3.8%)	3/762 (0.4%)	9.82 (2.98 - 32.34)
>3, ≤ 4.5 hours	43/1375 (3.1%)	8/1437 (0.6%)	5.98 (2.80 - 12.78)
>4.5 hours	51/1229 (4.1%)	8/1166 (0.7%)	6.22 (2.94 - 13.17)
Age			
≤ 80 years	88/2512 (3.5%)	14/2515 (0.6%)	6.57 (3.73 - 11.59)
>80 years	36/879 (4.1%)	5/850 (0.6%)	7.22 (2.82 - 18.50)
Baseline NIHSS			
0-4	6/345 (1.7%)	1/321 (0.3%)	6.02 (0.72 - 50.30)
5-10	40/1281 (3.1%)	5/1252 (0.4%)	7.93 (3.12 - 20.17)
11-15	37/794 (4.7%)	2/808 (0.2%)	19.63 (4.71 - 81.77)
16-21	26/662 (3.9%)	8/671 (1.2%)	3.38 (1.52 - 7.53)
≥ 22	15/309 (4.9%)	3/313 (1.0%)	5.05 (1.45 - 17.66)
All patients	**124/3391 (3.7%)**	**19/3365 (0.6%)**	**6.67 (4.11 - 10.84)**

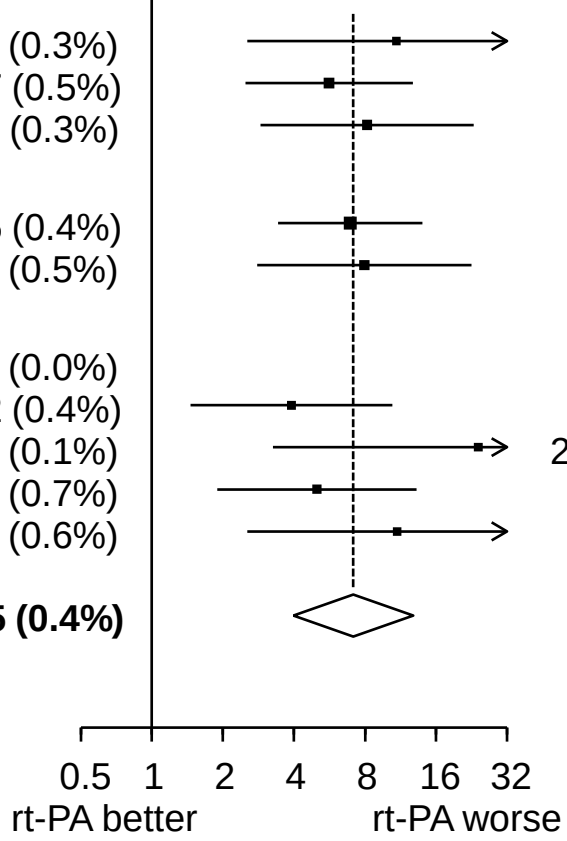


Effect of rt-PA on SICH at 24-36 hours (SITS-MOST) by treatment delay, age and stroke severity (adjusted for all 3 treatment interactions)

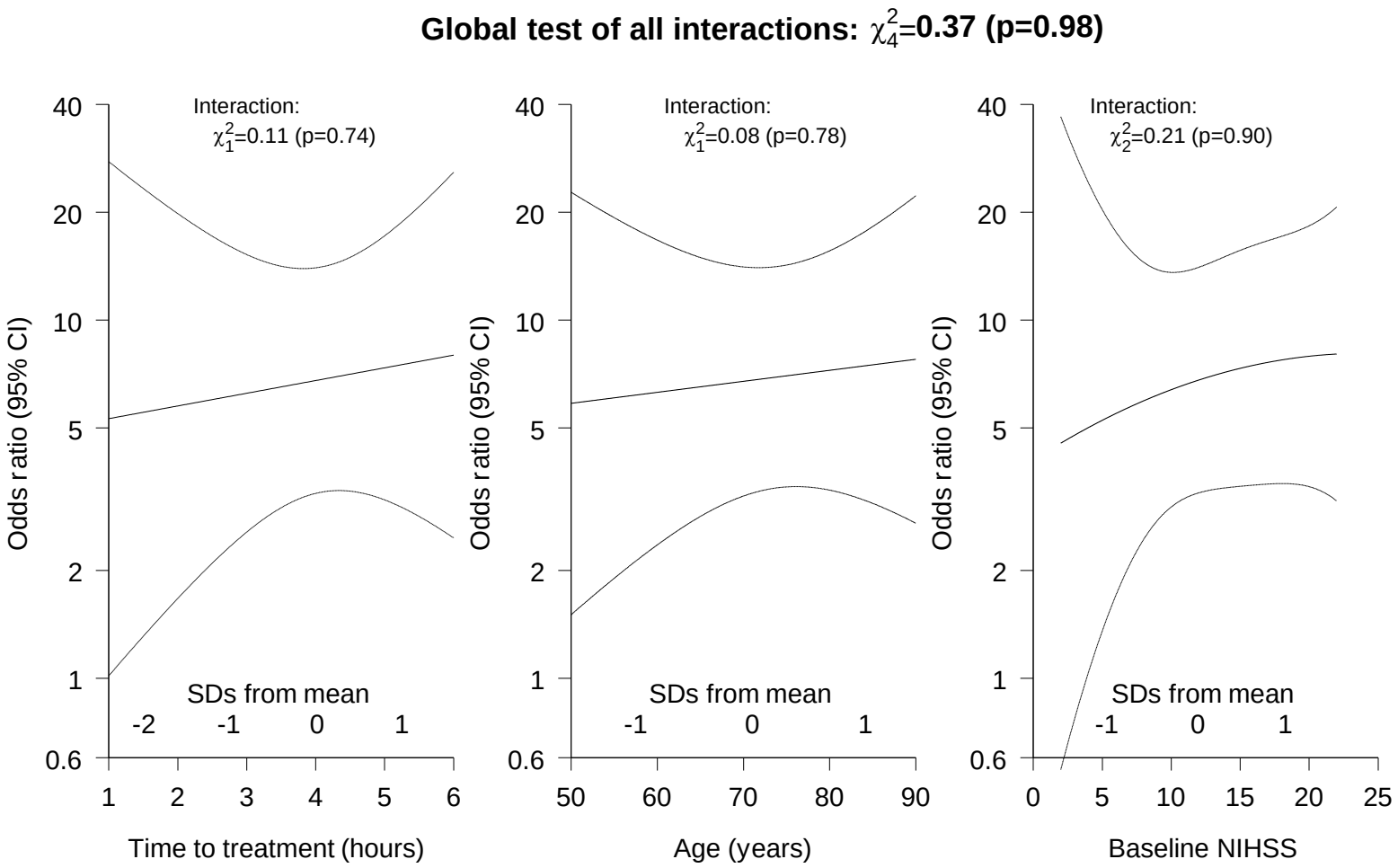


Effect of alteplase on fatal ICH at 7 days by treatment delay, age and stroke severity

	rt-PA (n=3391)	Control (n=3365)	OR (95% CI)
Treatment delay (hours)			
≤3	22/787 (2.8%)	2/762 (0.3%)	10.86 (2.54 - 46.41)
>3, ≤4.5	35/1375 (2.5%)	7/1437 (0.5%)	5.63 (2.49 - 12.76)
>4.5	34/1229 (2.8%)	4/1166 (0.3%)	8.16 (2.88 - 23.11)
Age (years)			
≤80	59/2512 (2.3%)	9/2515 (0.4%)	6.93 (3.42 - 14.02)
>80	32/879 (3.6%)	4/850 (0.5%)	7.95 (2.79 - 22.60)
Baseline NIHSS			
0-4	3/345 (0.9%)	0/321 (0.0%)	NE
5-10	20/1281 (1.6%)	5/1252 (0.4%)	3.90 (1.46 - 10.44)
11-15	23/794 (2.9%)	1/808 (0.1%)	24.14 (3.25 - 179.32)
16-21	24/662 (3.6%)	5/671 (0.7%)	5.00 (1.89 - 13.20)
≥22	21/309 (6.8%)	2/313 (0.6%)	10.94 (2.54 - 47.15)
All patients	**91/3391 (2.7%)**	**13/3365 (0.4%)**	**7.14 (3.98 - 12.79)**



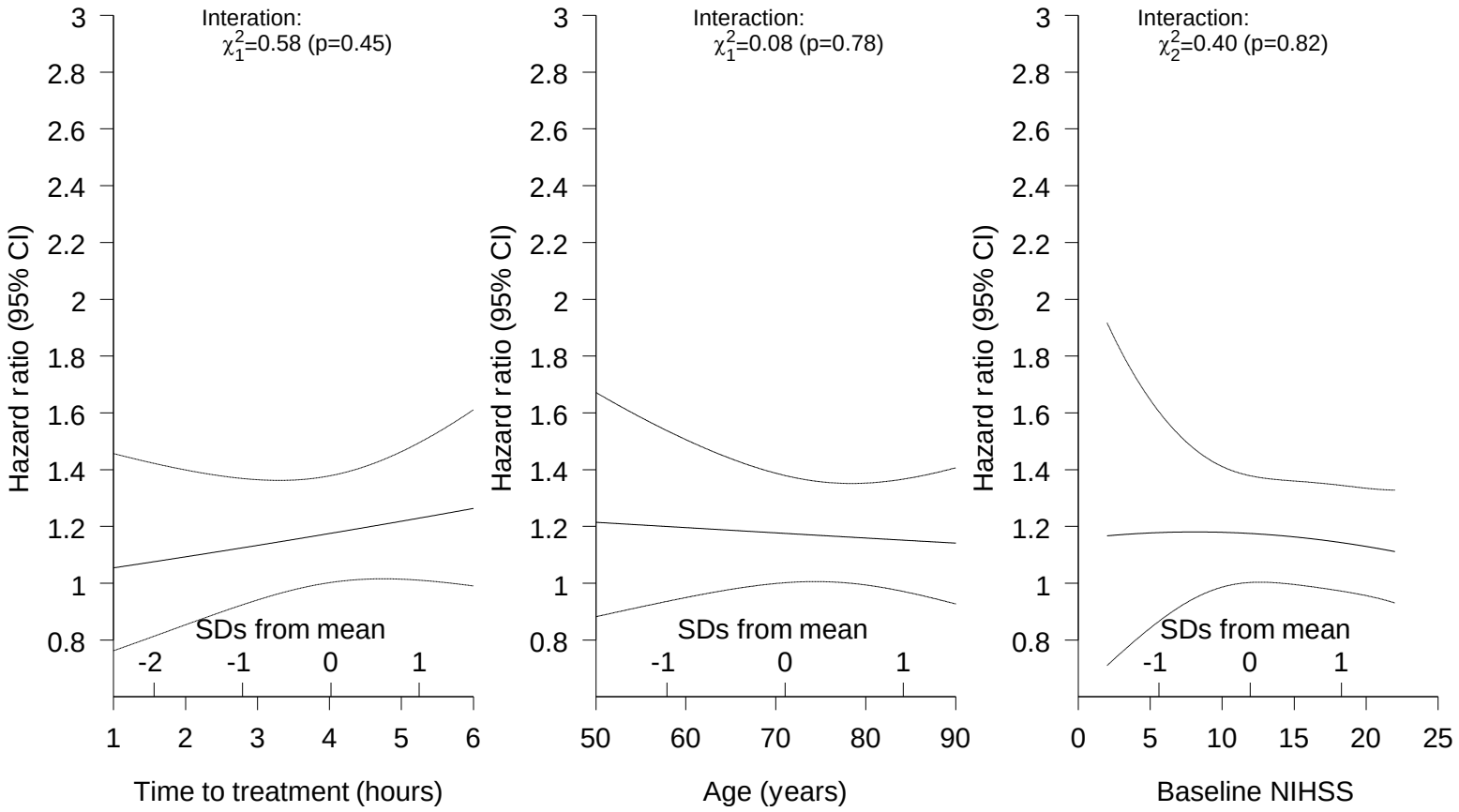
Effect of alteplase on fatal ICH at 7 days by treatment delay, age and stroke severity (adjusted for all 3 treatment interactions)



MORTALITY

90 day mortality

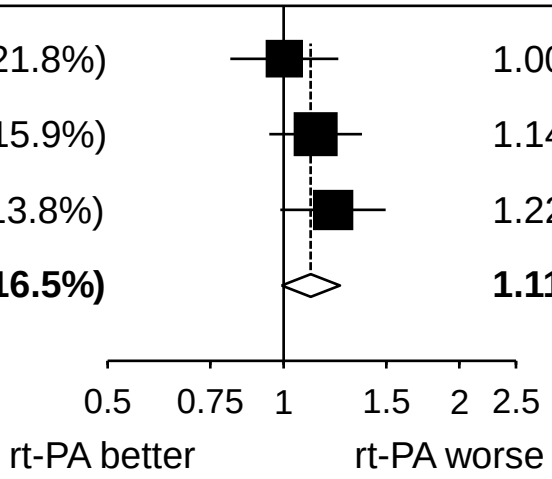
Global test of all interactions: χ^2_4=1.35 (p=0.85)



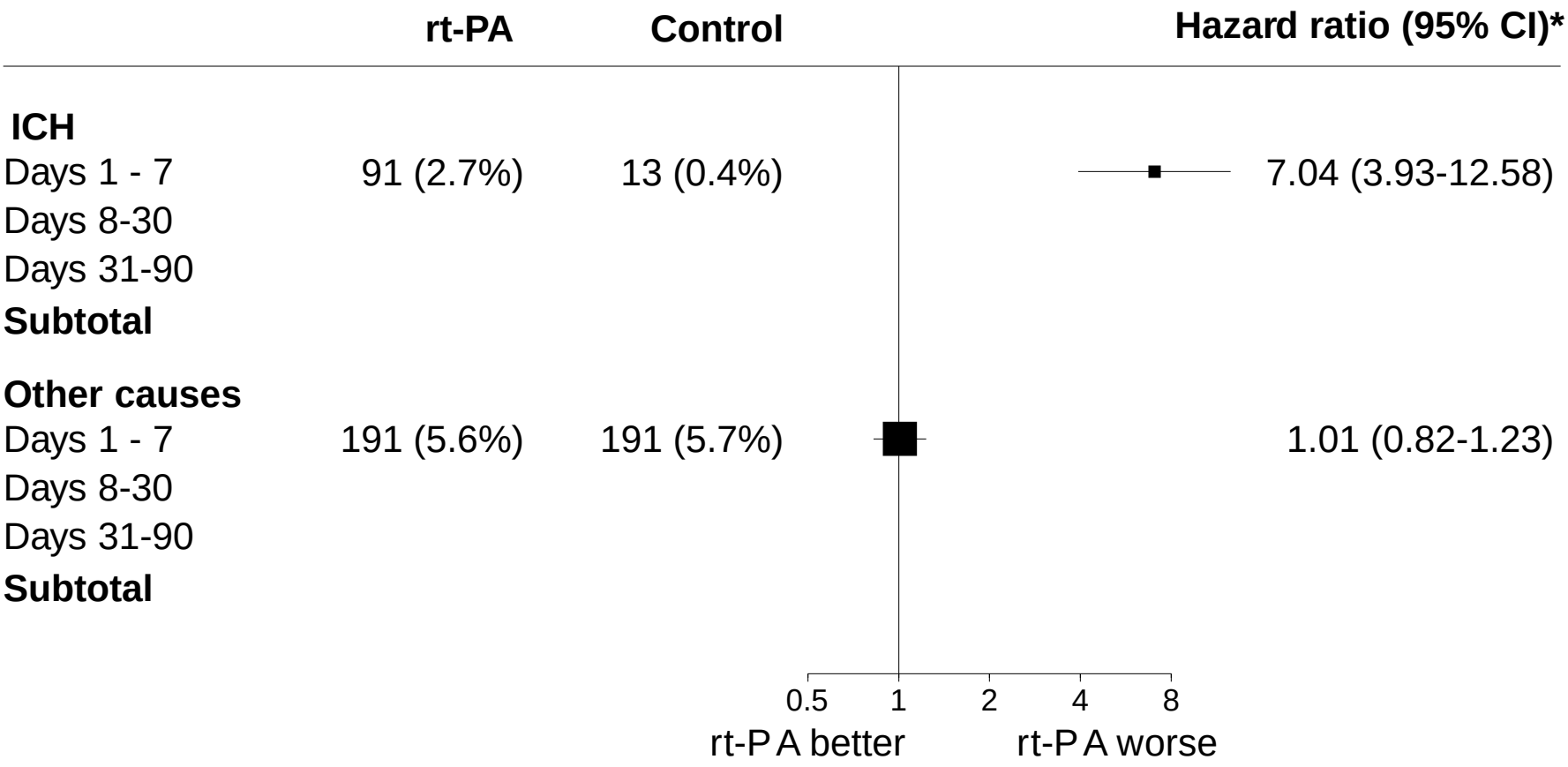
Average effect of rt-PA on 90-day mortality by treatment delay (Lancet 2014)

Treatment delay (hours)	No. (%) dead within 90 days rt-P A (n=3391)	Control (n=3365)	HR (95% CI)
≤3	175/787 (22.2%)	166/762 (21.8%)	1.00 (0.81 - 1.24)
>3, ≤4.5	232/1375 (16.9%)	229/1437 (15.9%)	1.14 (0.95 - 1.36)
>4.5	201/1229 (16.4%)	161/1166 (13.8%)	1.22 (0.99 - 1.50)
All patients	**608/3391 (17.9%)**	**556/3365 (16.5%)**	**1.11 (0.99 - 1.25)**

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

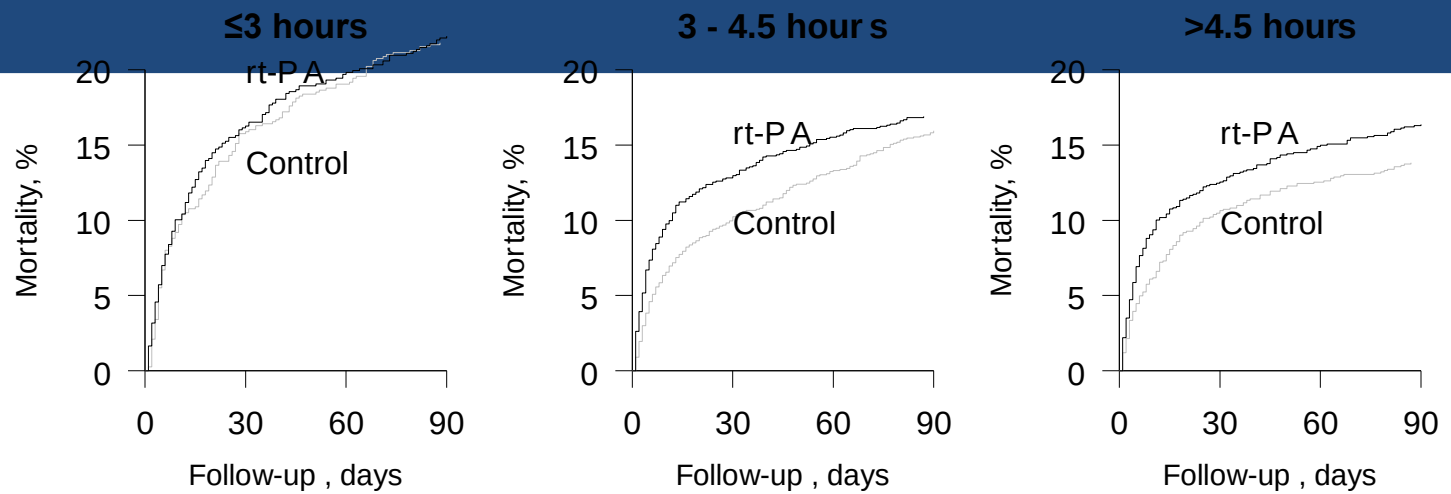


Effect of rt-PA on deaths due to ICH and deaths due to other causes within the first 90 days (would need post 1-week cause-specific mortality data to be provided)

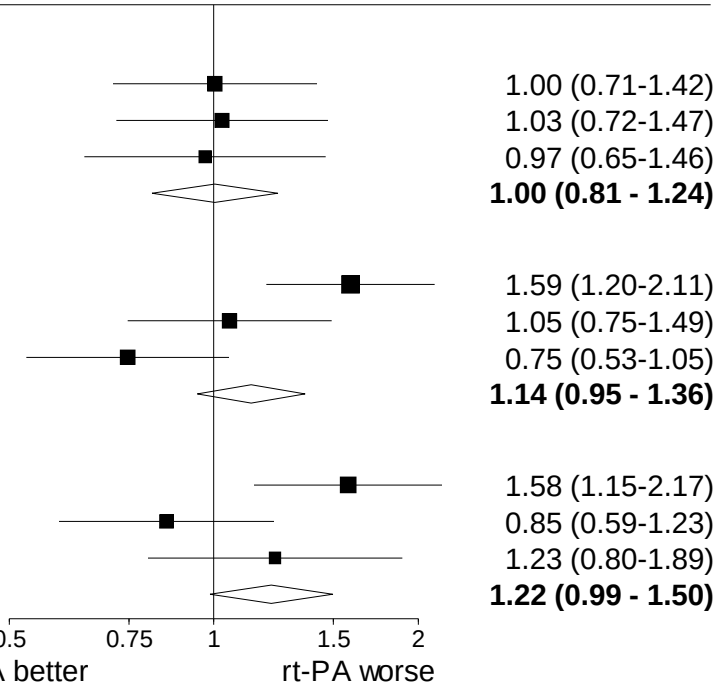


* Estimated by Cox proportional hazards regression stratified by trial (and adjusted only for Rx allocation)

Effect of rt-PA on mortality during the first 90 days by treatment delay and period of follow-up



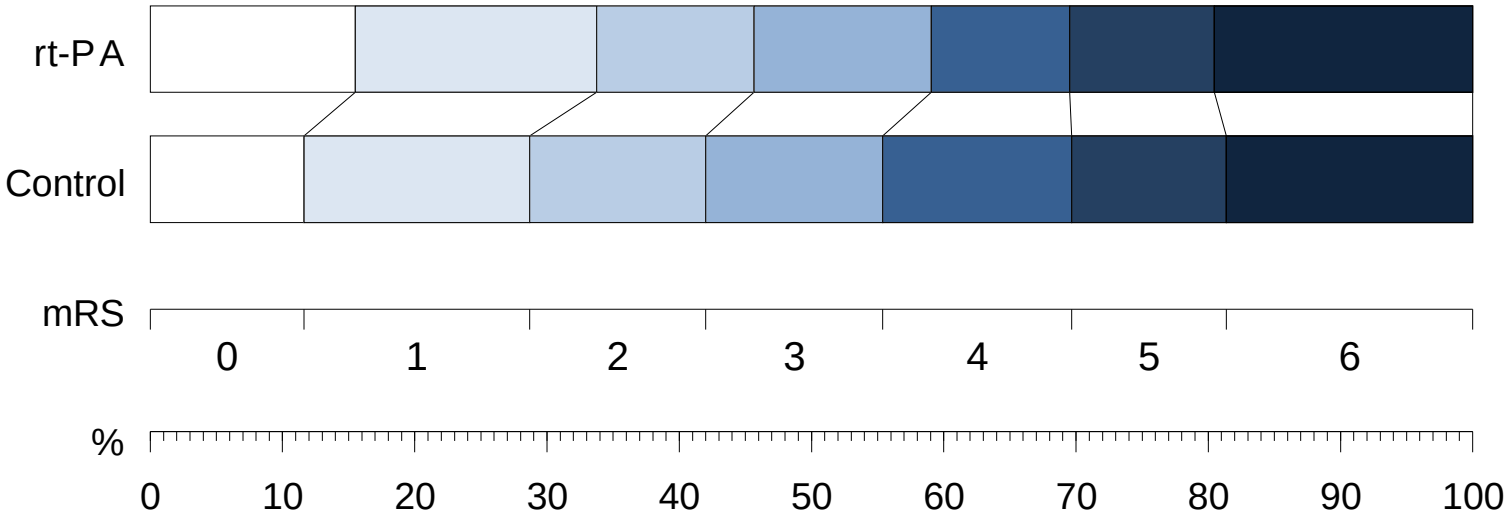
	rt-PA	Control	Hazard ratio (95% CI)*
≤3 hours			
Days 1 - 7	66 (8.4%)	63 (8.3%)	1.00 (0.71-1.42)
Days 8 - 30	62 (7.9%)	58 (7.6%)	1.03 (0.72-1.47)
Days 31 - 90	47 (6.0%)	45 (5.9%)	0.97 (0.65-1.46)
Subtotal: 90-day mortality	**175 (22.2%)**	**166 (21.8%)**	**1.00 (0.81 - 1.24)**
3-4.5 hours			
Days 1 - 7	116 (8.4%)	80 (5.6%)	1.59 (1.20-2.11)
Days 8 - 30	62 (4.5%)	67 (4.7%)	1.05 (0.75-1.49)
Days 31 - 90	54 (3.9%)	82 (5.7%)	0.75 (0.53-1.05)
Subtotal: 90-day mortality	**232 (16.9%)**	**229 (15.9%)**	**1.14 (0.95 - 1.36)**
>4.5 hours			
Days 1 - 7	100 (8.1%)	61 (5.2%)	1.58 (1.15-2.17)
Days 8 - 30	54 (4.4%)	63 (5.4%)	0.85 (0.59-1.23)
Days 31 - 90	47 (3.8%)	37 (3.2%)	1.23 (0.80-1.89)
Subtotal: 90-day mortality	**201 (16.4%)**	**161 (13.8%)**	**1.22 (0.99 - 1.50)**



Main parameters to be incorporated into future modelling of balance of benefit and hazard

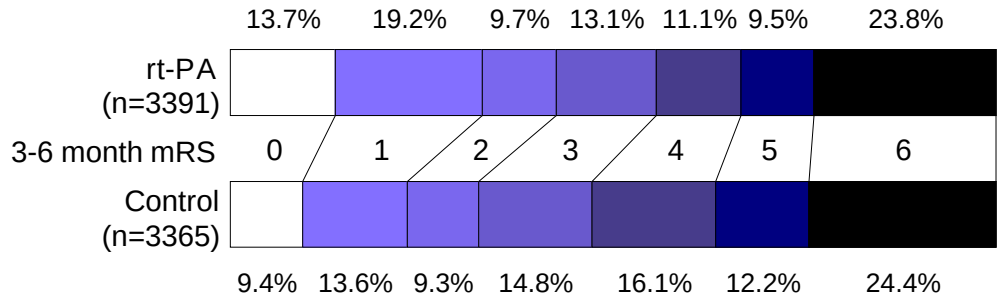
- Benefits
  - Absolute proportion achieving mRS 0-1 (without thrombolysis) correlated with severity
  - Relative odds of benefit invariant with severity
- Hazards
  - Absolute risk of haemorrhage (without thrombolysis) correlated with severity
  - Relative odds of haemorrhage invariant with severity
- Implications
  - Careful modelling required under a variety of assumptions (for discussion)

Distribution of mRS (all trials pooled together)

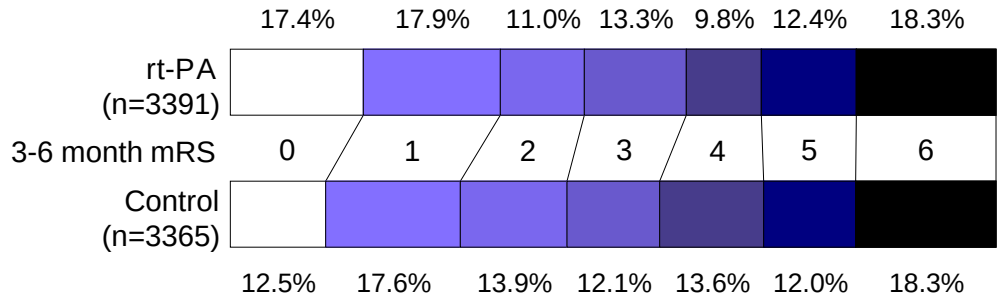


Distribution of mRS at 3-6 months by treatment delay

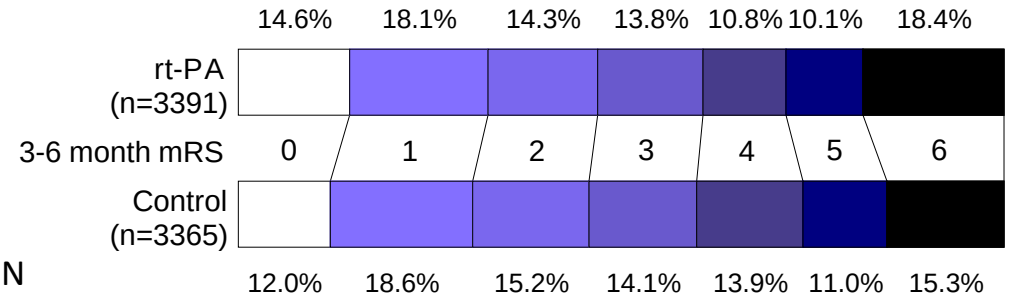
a) Treatment delay ≤3 hours (n=1549)



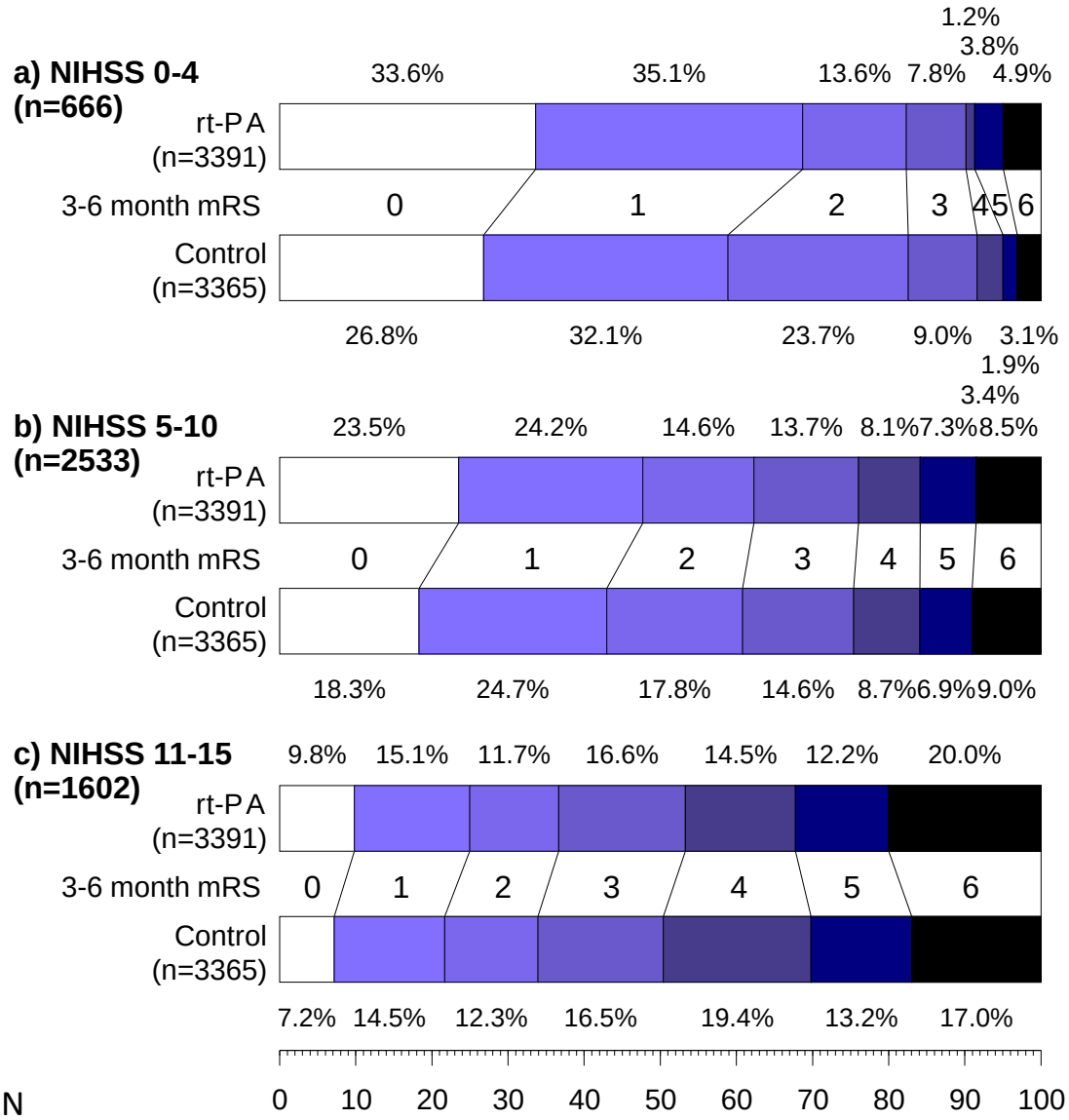
b) Treatment delay 3-4.5 hours (n=2812)



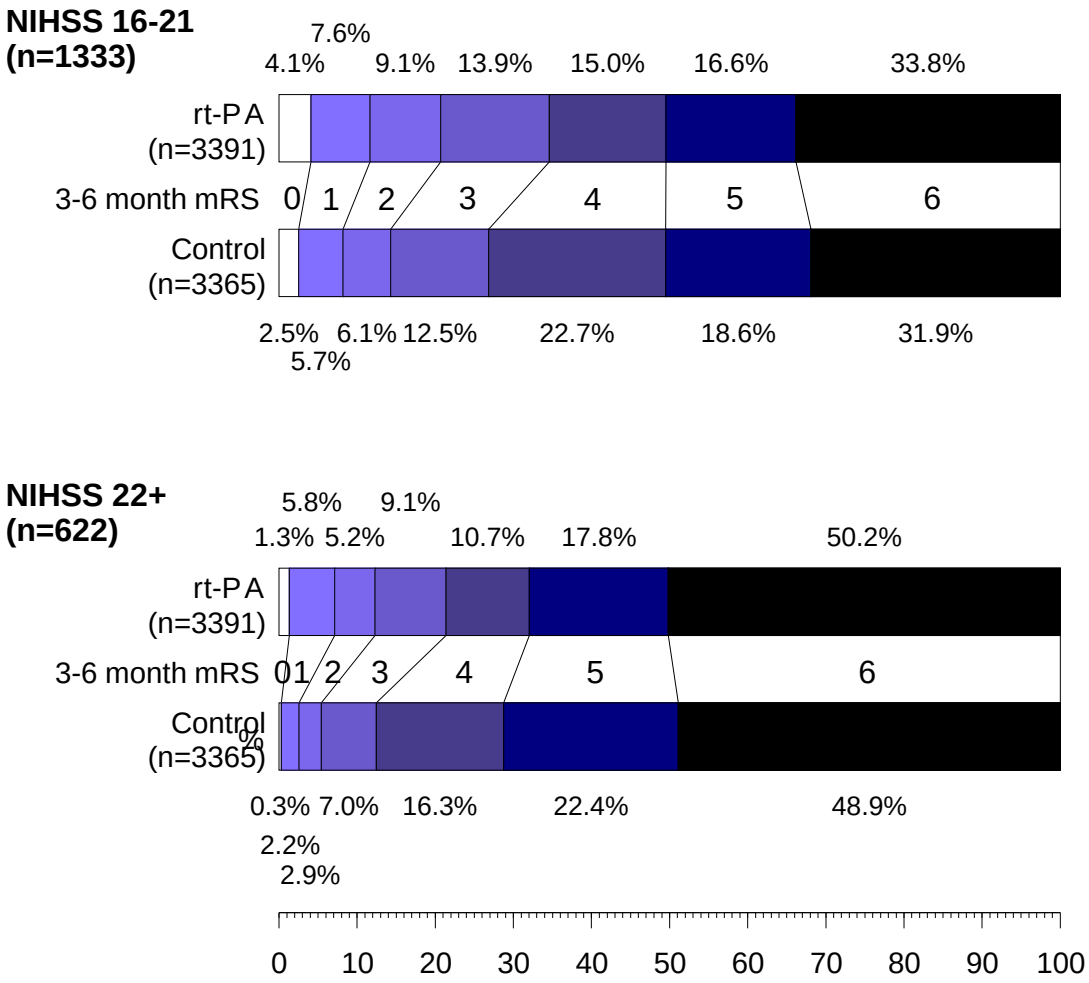
c) Treatment delay >4.5 hours (n=2812)



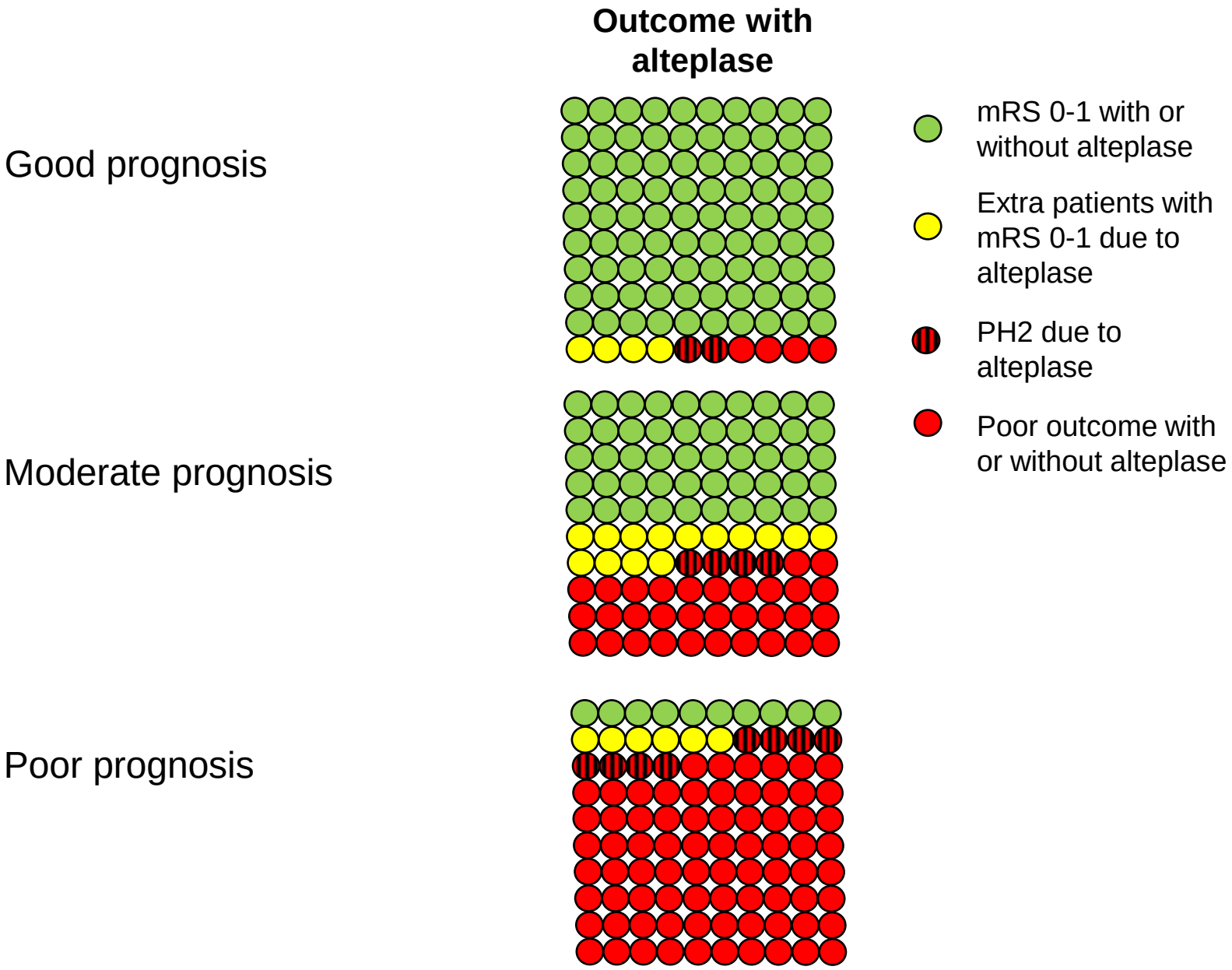
Distribution of mRS at 3-6 months by baseline NIHSS



Distribution of mRS at 3-6 months by baseline NIHSS

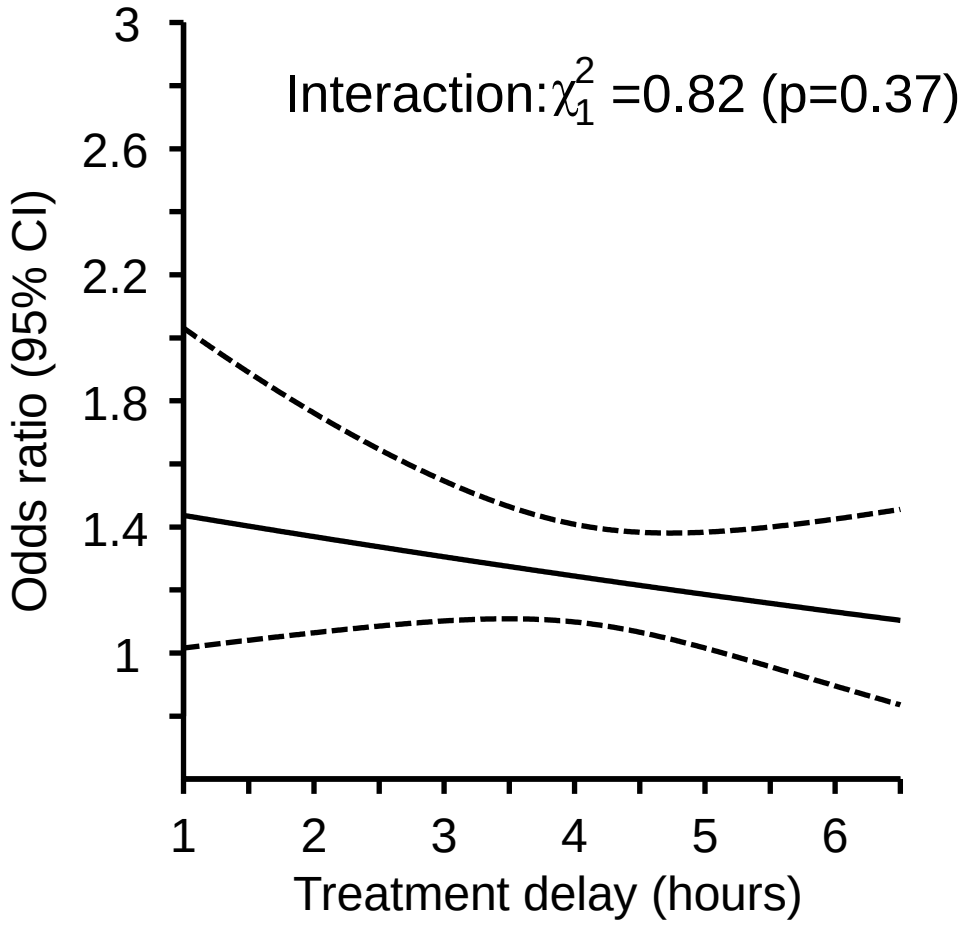


HYPOTHETICAL representation of benefits vs hazards



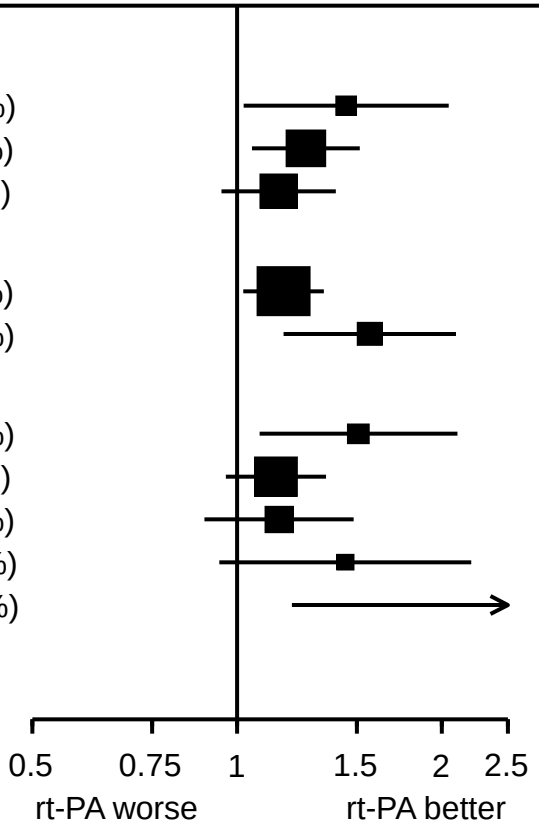
EXCLUSION OF NINDS A AND B

Effect on mRS 0-1 by treatment delay



Effect of rt–PA on a good stroke outcome (mRS 0–1), by treatment delay, age and stroke severity

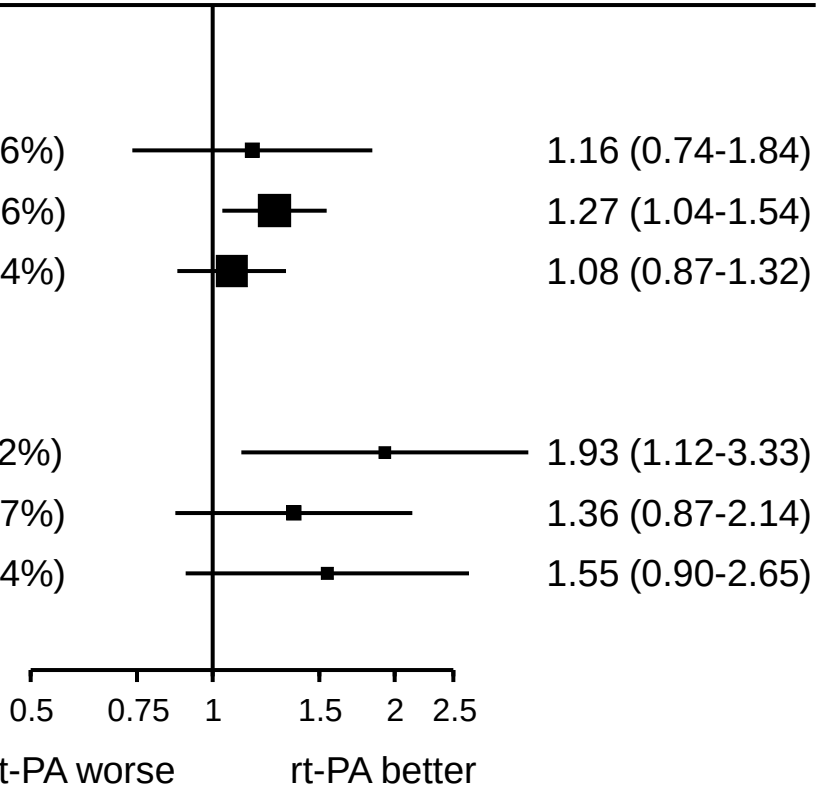
	rt-PA (n=3391)	Control (n=3365)	Odds ratio (95% CI)*
Treatment delay			
≤ 3 hours	125/476 (26.3%)	93/450 (20.7%)	1.45 (1.02 - 2.05)
>3, ≤4.5 hours	485/1374 (35.3%)	432/1437 (30.1%)	1.26 (1.05 - 1.51)
>4.5 hours	401/1229 (32.6%)	357/1166 (30.6%)	1.15 (0.95 - 1.40)
Age			
≤ 80 years	862/2233 (38.6%)	773/2226 (34.7%)	1.17 (1.02 - 1.34)
>80 years	149/846 (17.6%)	109/827 (13.2%)	1.57 (1.17 - 2.10)
Baseline NIHSS			
0-4	220/324 (67.9%)	182/313 (58.1%)	1.51 (1.08 - 2.11)
5-10	548/1194 (45.9%)	495/1163 (42.6%)	1.14 (0.96 - 1.35)
11-15	171/722 (23.7%)	159/734 (21.7%)	1.15 (0.90 - 1.48)
16-21	56/584 (9.6%)	41/595 (6.9%)	1.44 (0.94 - 2.21)
≥ 22	16/255 (6.3%)	5/248 (2.0%)	3.36 (1.20 - 9.37)



*For each of the three baseline characteristics shown, the odds ratio subgroup estimates shown are derived from a single trial−stratified logistic regression model which allows for separate estimation of the OR in each of the subgroups after adjustment for the other two baseline characteristics (but not possible interactions with those characteristics).

Effect of rt–PA on a good stroke outcome (mRS 0–1) by age, at different treatment delays

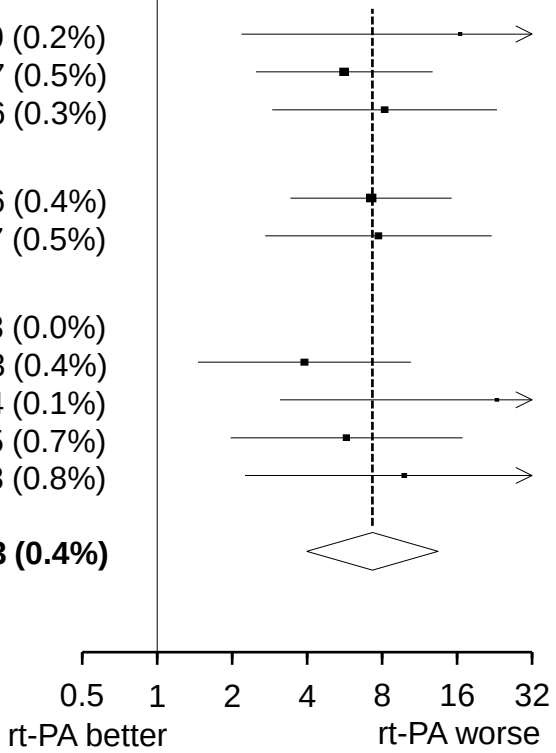
Age (years), treatment delay (hours)	rt-PA (n=3391)	Control (n=3365)	Odds ratio* (95% CI)
≤ 80 years			
≤ 3 hours	76/207 (36.7%)	66/209 (31.6%)	1.16 (0.74-1.84)
3-4.5 hours	427/1032 (41.4%)	382/1073 (35.6%)	1.27 (1.04-1.54)
>4.5 hours	359/994 (36.1%)	325/944 (34.4%)	1.08 (0.87-1.32)
>80 years			
≤ 3 hours	49/269 (18.2%)	27/241 (11.2%)	1.93 (1.12-3.33)
3-4.5 hours	58/342 (17.0%)	50/364 (13.7%)	1.36 (0.87-2.14)
>4.5 hours	42/235 (17.9%)	32/222 (14.4%)	1.55 (0.90-2.65)



*All six estimates are derived from a single stratified logistic regression model which allows the odds ratio to be estimated separately for each group (also adjusted for baseline NIHSS).

Effect on fatal ICH within 7 days

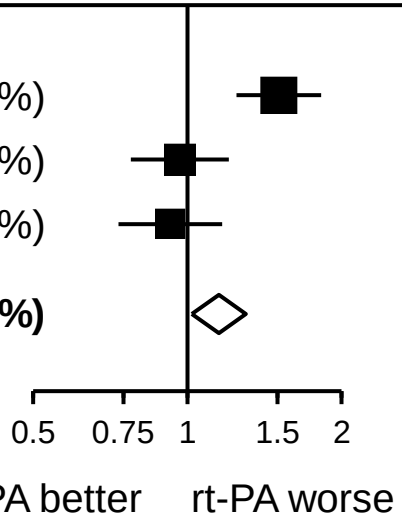
	rt-PA (n=3391)	Control (n=3365)	Odds ratio (95% CI)*
Treatment delay			
≤ 3 hours	17/476 (3.6%)	1/450 (0.2%)	16.46 (2.18 - 124.34)
>3, ≤ 4.5 hours	35/1374 (2.5%)	7/1437 (0.5%)	5.63 (2.49 - 12.75)
>4.5 hours	34/1229 (2.8%)	4/1166 (0.3%)	8.18 (2.89 - 23.16)
Age			
≤ 80 years	55/2233 (2.5%)	8/2226 (0.4%)	7.23 (3.43 - 15.23)
>80 years	31/846 (3.7%)	4/827 (0.5%)	7.74 (2.72 - 22.05)
Baseline NIHSS			
0-4	3/324 (0.9%)	0/313 (0.0%)	NE
5-10	20/1194 (1.7%)	5/1163 (0.4%)	3.90 (1.46 - 10.44)
11-15	22/722 (3.0%)	1/734 (0.1%)	23.12 (3.11 - 172.07)
16-21	22/584 (3.8%)	4/595 (0.7%)	5.75 (1.97 - 16.82)
≥ 22	19/255 (7.5%)	2/248 (0.8%)	9.80 (2.25 - 42.62)
All patients	**86/3079 (2.8%)**	**12/3053 (0.4%)**	**7.31 (3.99 - 13.41)**



NE - Not estimable

Effect of rt-PA on 90-day mortality, overall and by period of follow-up

	rt-PA (n=3391)	Control (n=3365)	Hazard ratio* (95% CI)
Days 1-7**	266 (8.6%)	178 (5.8%)	1.51 (1.25-1.82)
Days 8-30	154 (5.0%)	165 (5.4%)	0.97 (0.78-1.20)
Days 31-90	134 (4.4%)	149 (4.9%)	0.93 (0.73-1.17)
Total: 90-day mortality	**554 (18.0%)**	**492 (16.1%)**	**1.15 (1.02 - 1.30)**



Test for varying log HR with increasing duration of follow-up (p<0.0001)

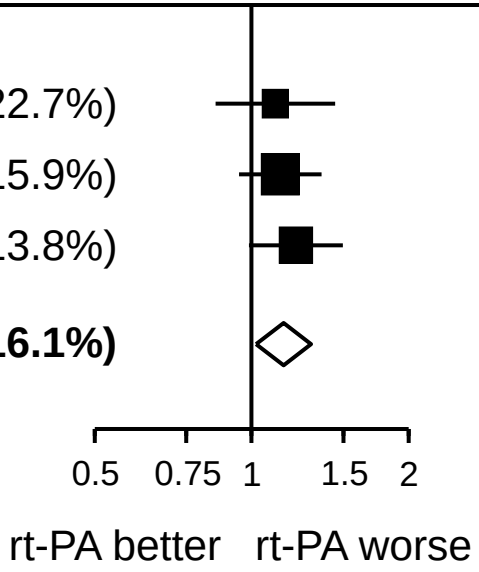
Patients can only contribute to a particular risk period if they have already survived any preceding risk periods

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

** Includes 86 vs. 12 deaths due to ICH (with PH2 evidence; Figure 4) and 180 vs. 166 deaths from other causes.

Average effect of rt-PA on 90-day mortality by treatment delay

	rt-PA (n=3391)	Control (n=3365)	Hazard ratio* (95% CI)
≤3 hours	121 (25.4%)	102 (22.7%)	1.11 (0.85 - 1.45)
>3, ≤ 4.5 hours	232 (16.9%)	229 (15.9%)	1.14 (0.95 - 1.36)
>4.5 hours	201 (16.4%)	161 (13.8%)	1.22 (0.99 - 1.50)
Total: 90-day mortality	**554 (18.0%)**	**492 (16.1%)**	**1.15 (1.02 - 1.30)**



Test for linear trend in the log HR with increasing treatment delay (p=0.55)

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

Update on the Stroke Thrombolysis Treatment (STT) Trialists' Collaboration

Colin Baigent
STT Co-chair
Professor of Epidemiology and Deputy Director, CTSU, University of Oxford

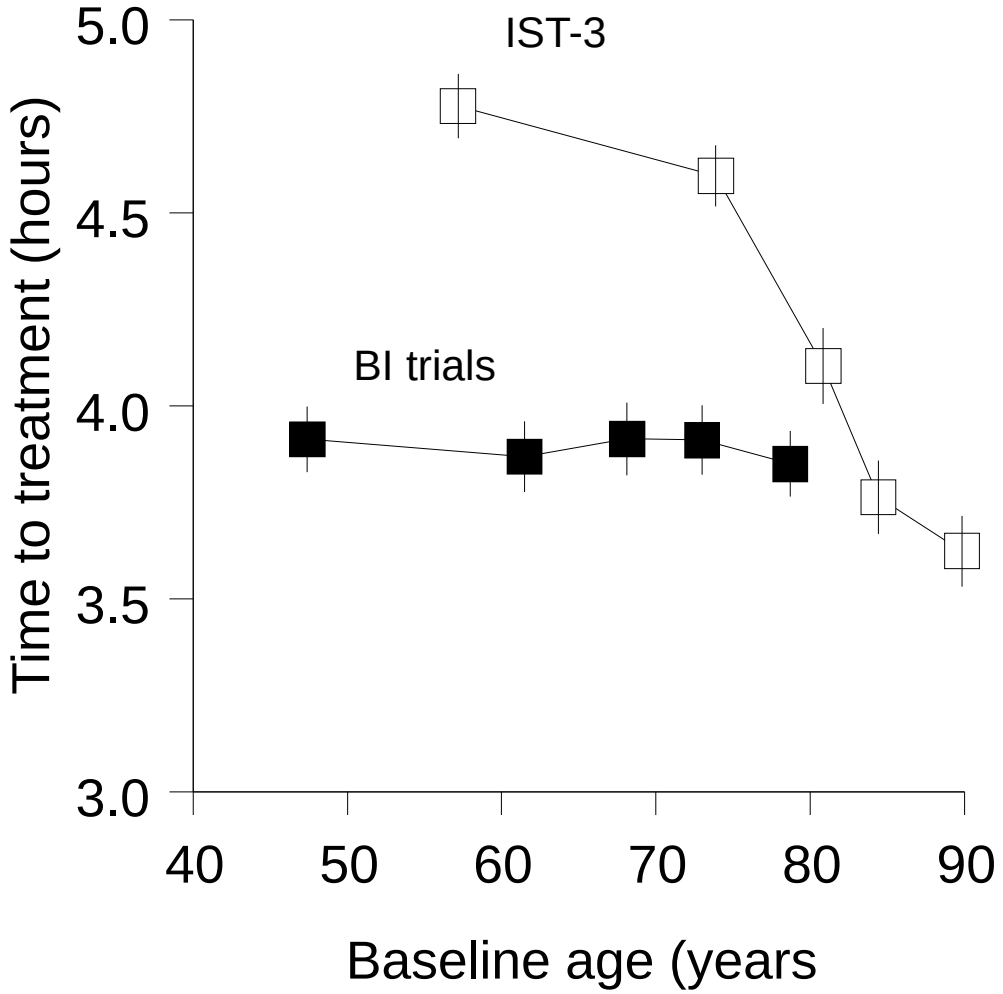
Baseline characteristics

	Trial		Randomized treatment allocation	
	IST-3 (n=3035)	**8 previous trials (n=3721)**	**rt-PA (n=3391)**	**Control (n=3365)**
Treatment delay (hours)	4.2 (1.2)	3.9 (1.2)	4.0 (1.2)	4.0 (1.2)
≤3	20%	25%	23%	23%
>3, ≤4.5	38%	44%	40%	42%
>4.5	42%	30%	36%	35%
Age (years)	77 (12)	66 (12)	71 (13)	71 (13)
≤80	47%	97%	74%	75%
>80	53%	3%	26%	25%
Stroke severity (NIHSS)	12 (6.9)	12 (6.2)	12 (6.6)	12 (6.5)

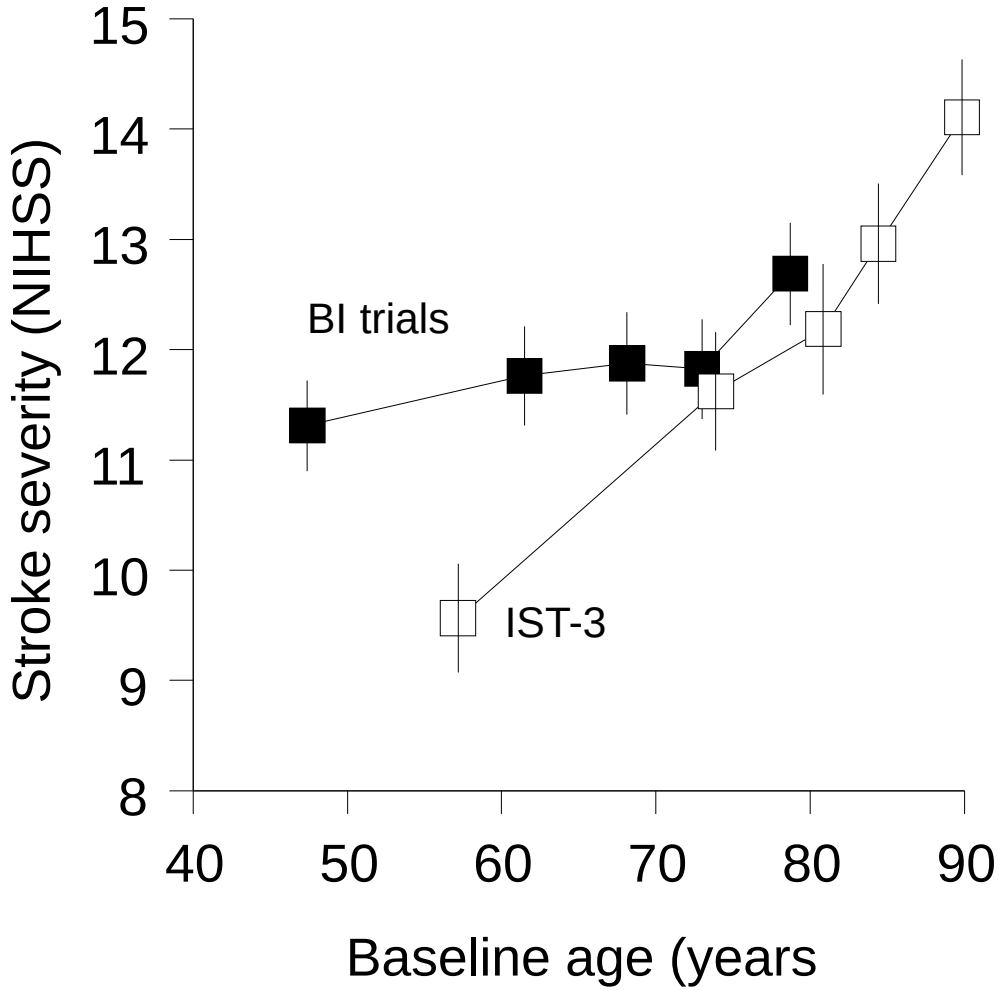
Baseline characteristics

	Trial		Randomized treatment allocation	
	IST-3 (n=3035)	**8 previous trials (n=3721)**	**rt-PA (n=3391)**	**Control (n=3365)**
Female	52%	40%	45%	45%
Systolic pressure	155 (24)	153 (21)	154 (22)	154 (22)
Diastolic pressure	82 (15)	84 (13)	83 (14)	83 (14)
History of:				
Hypertension	64%	57%	60%	60%
Stroke	23%	15%	18.3%	18.5%
Diabetes mellitus	13%	19%	16%	16%
Atrial fibrillation	30%	19%	24%	23%

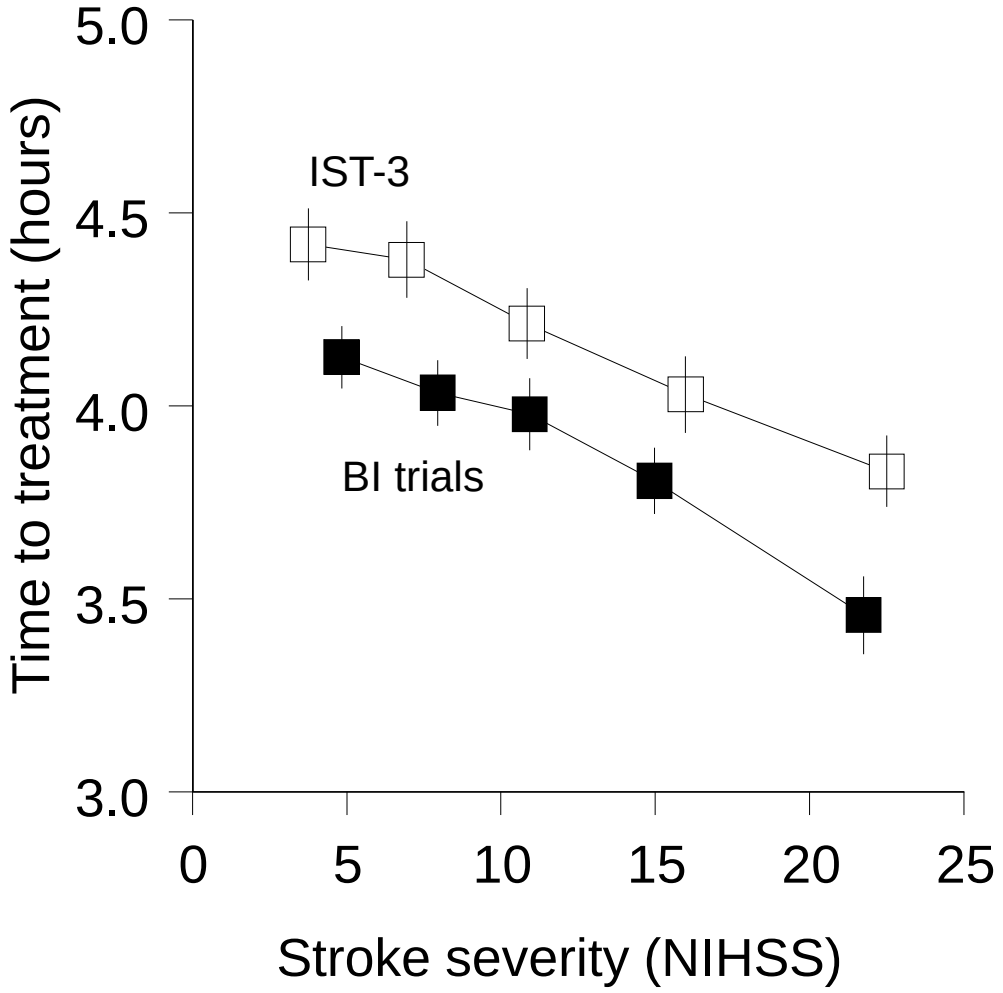
Age vs. treatment delay



Age vs. severity



Severity vs. treatment delay

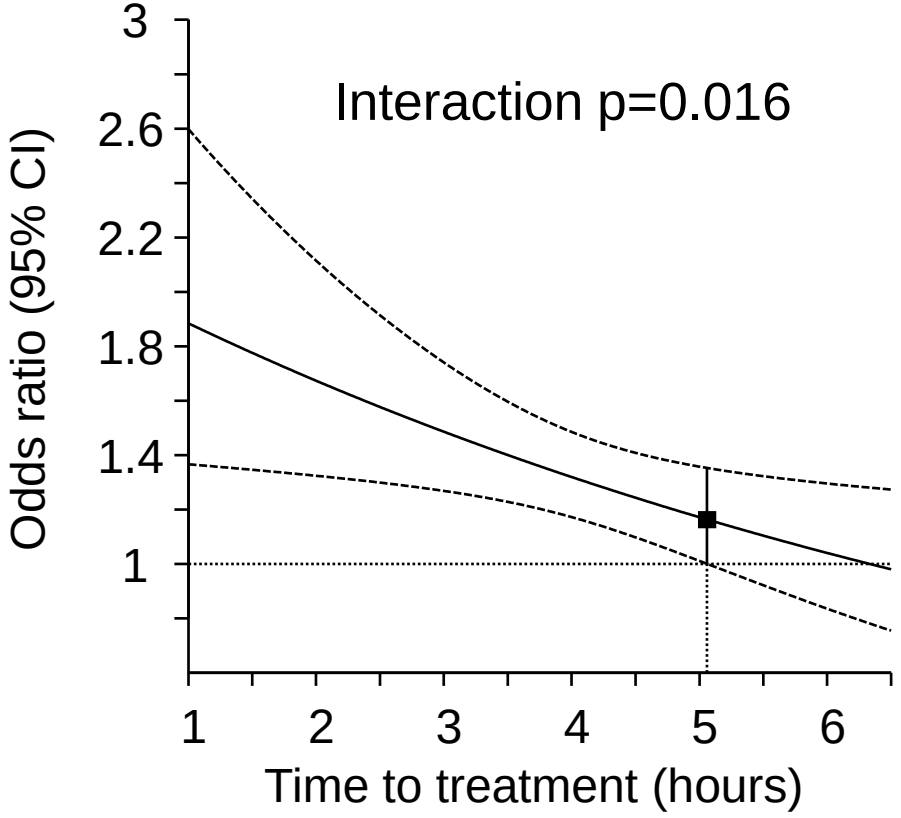


Joint estimation of the "treatment-modifying effects" of delay, age and stroke severity

- Simple consideration of each characteristic in turn may be misleading (due to the correlation between the three characteristics)

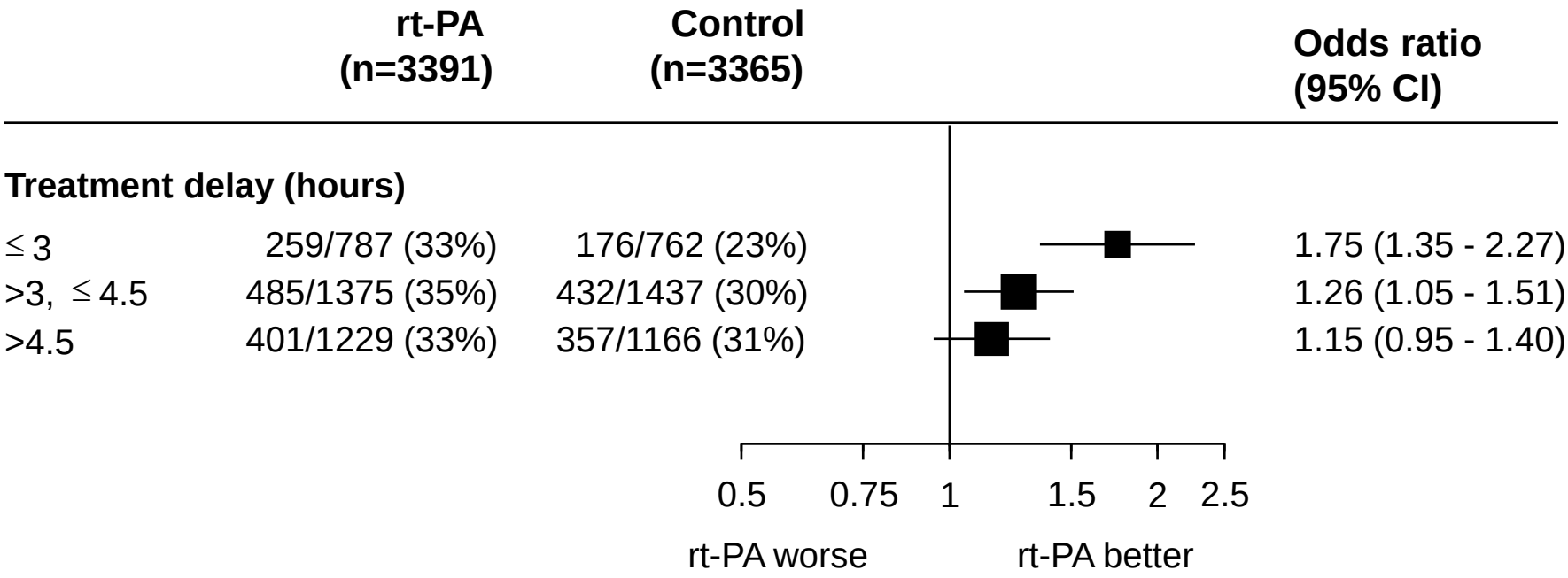
- Multivariable (unconditional) logistic regression models stratified by trial and adjusted for:
  - treatment allocation
  - treatment delay, age and stroke severity
  - 2-way interactions between treatment allocation and each of the potential effect-modifiers
  - 2-sided p-values <0.05 considered nominally significant

Effect of alteplase of a good outcome (mRS 0-1) by treatment delay

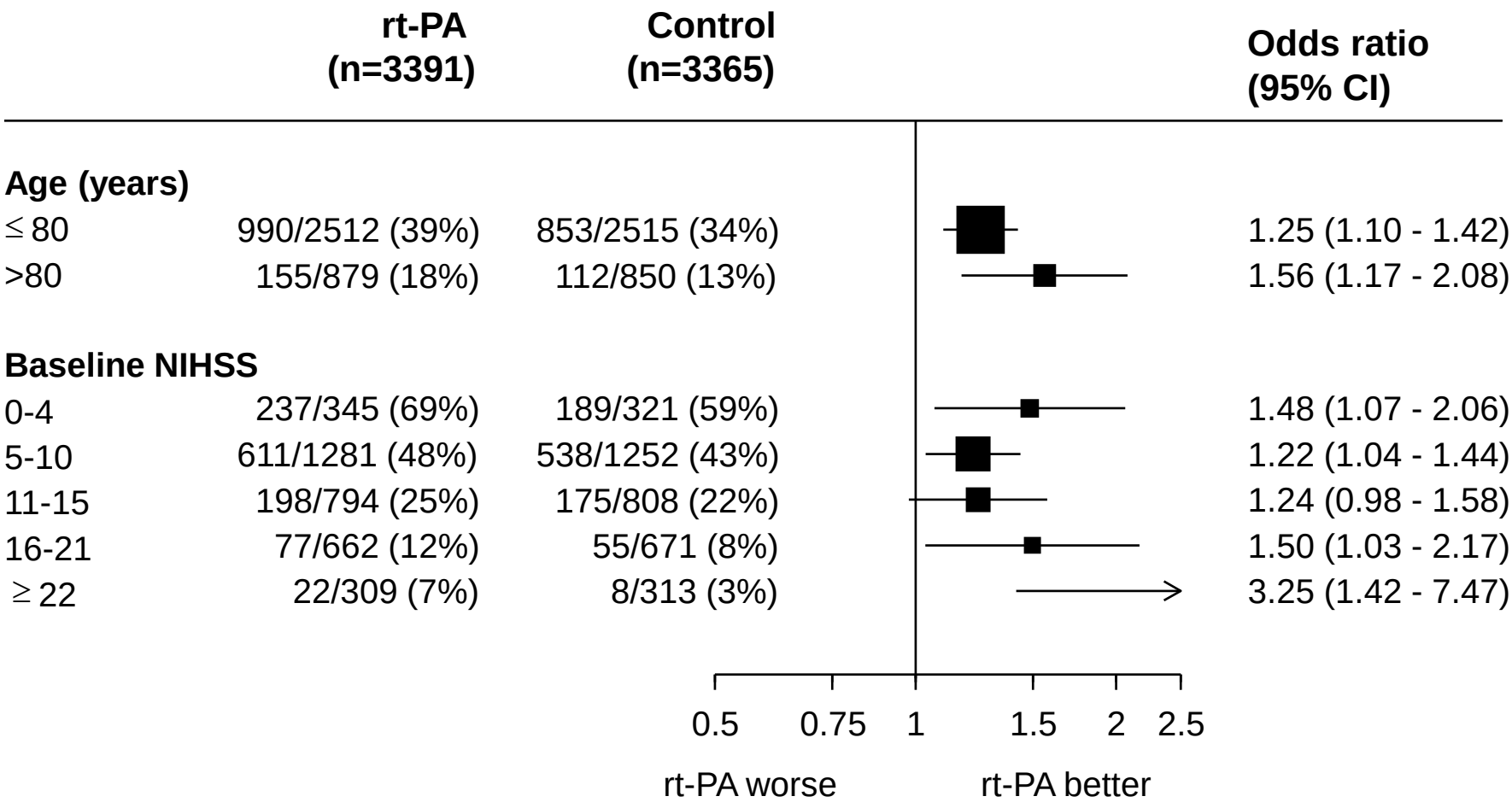


Slope not significantly altered by age or stroke severity

Effect of alteplase of a good outcome (mRS 0-1) by treatment delay



Effect on mRS 0-1 by age and stroke severity (at the mean treatment delay of 4 hours)



Haemorrhage definitions

Parenchymal haemorrhage type 2 within 7 days

Approximated in IST-3: "significant brain PH local or remote from the infarct, or significant haemorrhagic transformation of an infarct within 7 days"

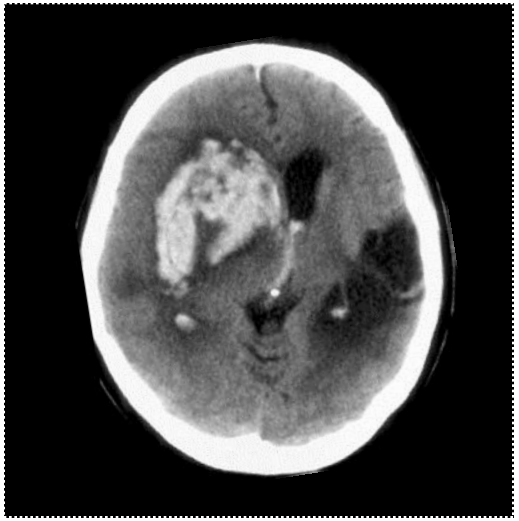
SITS-MOST at 24-36 hours

PH2 +>4 NIHSS points

*Approximated in IST-3: "*clinically significant deterioration/death together with evidence of either significant brain PH local or remote from the infarct or significant haemorrhagic transformation of an infarct on brain imaging which, in the judgement of the adjudication panel, was likely to have worsened mass effect or contributed to the burden of brain damage <24 hrs"

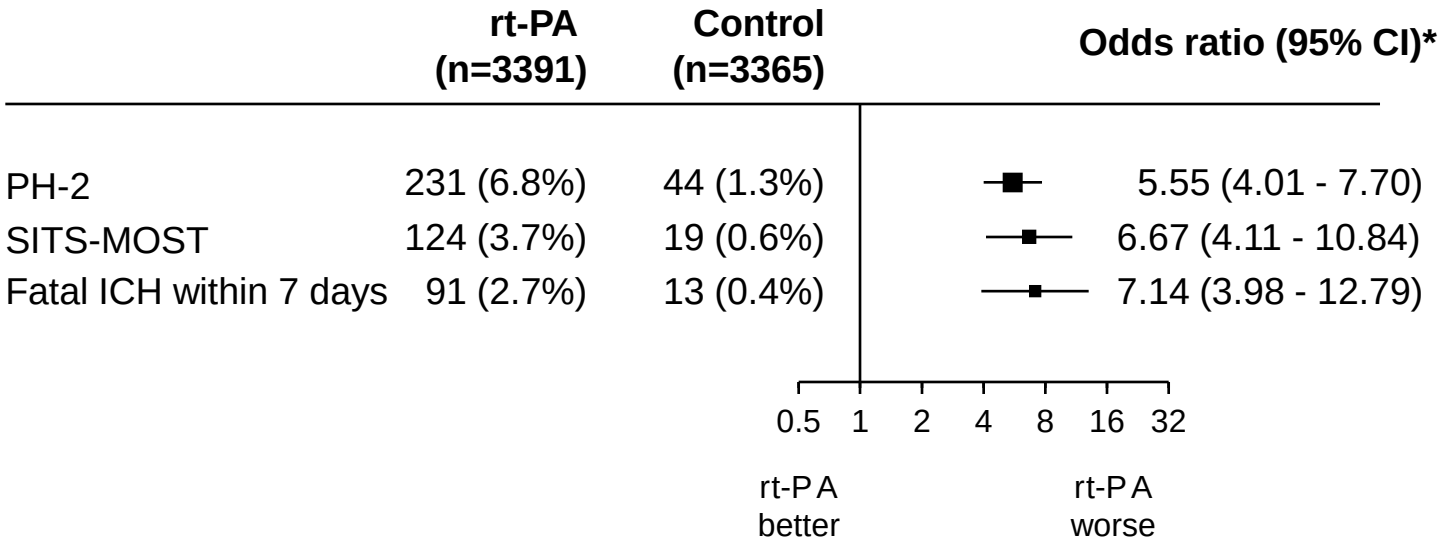
Fatal ICH within 7 days

PH2 and death within 7 days



CT of PH2 haemorrhage

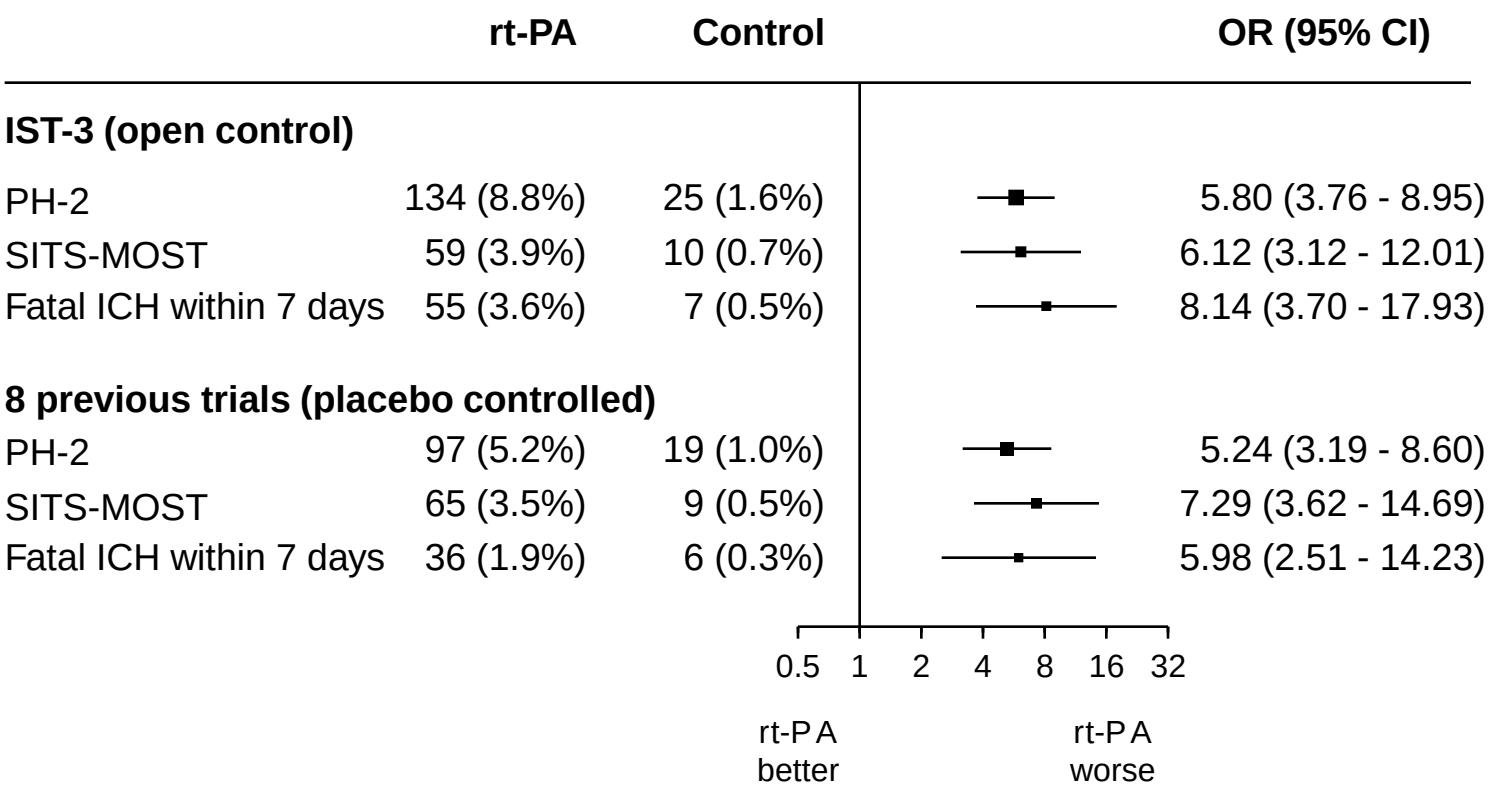
Effect of rt-PA on symptomatic and fatal intracranial haemorrhage



* Trial stratified odds ratio adjusted only for treatment allocation

SICH: symptomatic intracranial haemorrhage, PH2: parenchymal haemorrhage type 2

Effect of rt-PA on symptomatic and fatal intracranial haemorrhage

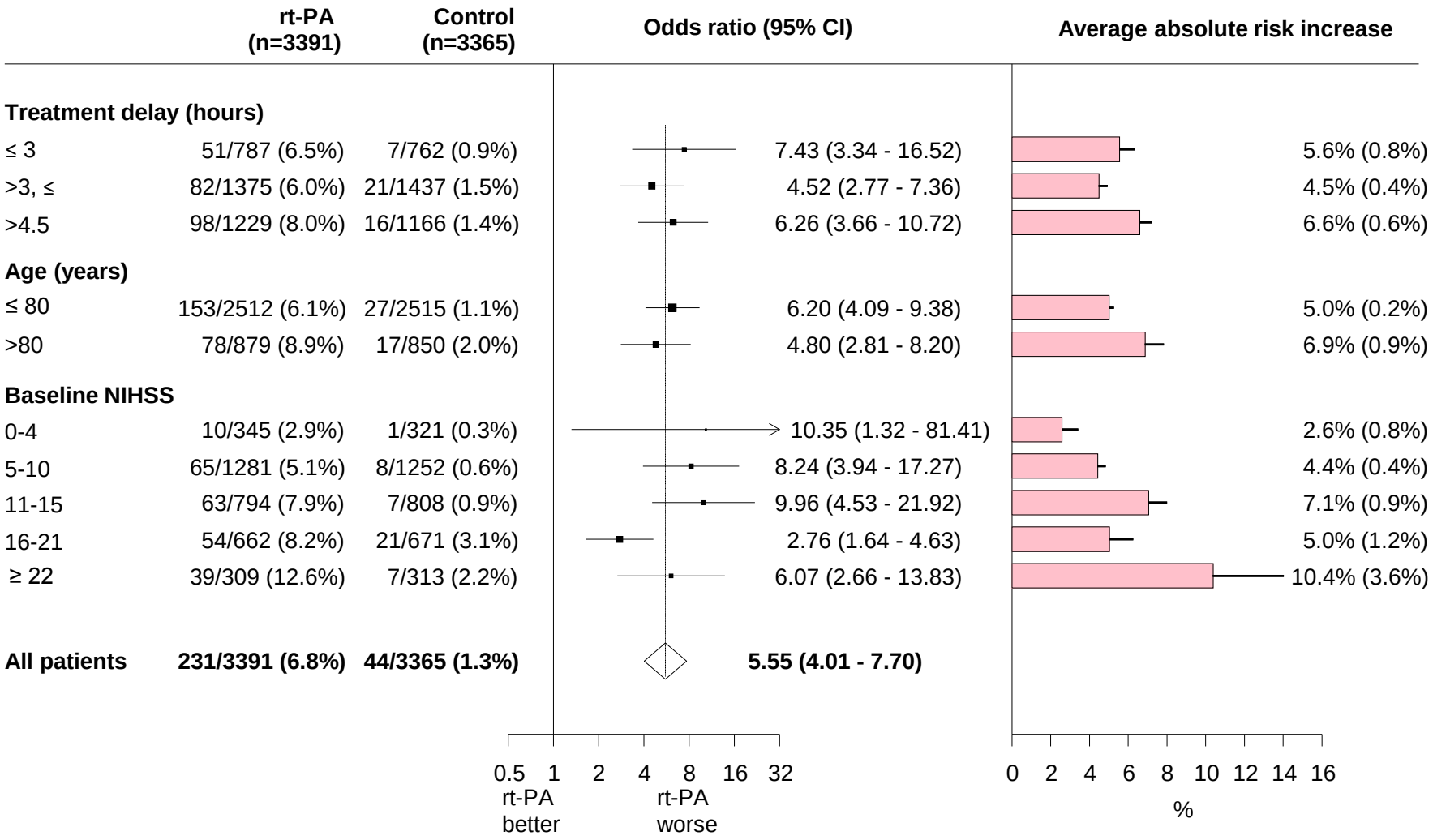


Interaction between IST-3 and other trials for PH2: $\chi^2_1 = 0.09$ (p=0.76)

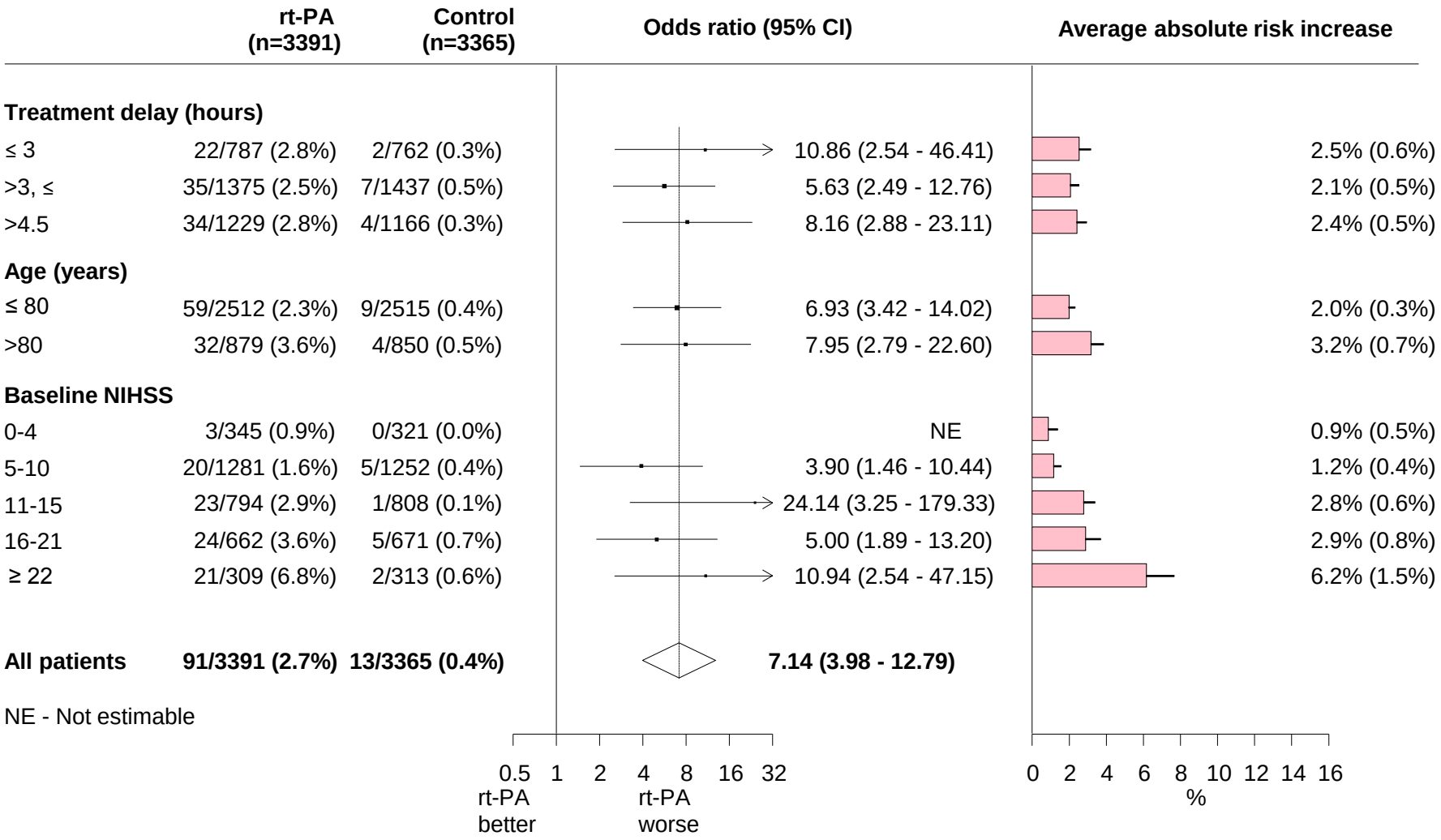
Interaction between IST-3 and other trials for SITS-MOST: $\chi^2_1 = 0.13$ (p=0.72)

Interaction between IST-3 and other trials for fatal ICH: $\chi^2_1 = 0.27$ (p=0.61)

Effect of rt-PA on SICH at 7 days (PH2) by treatment delay, age and stroke severity

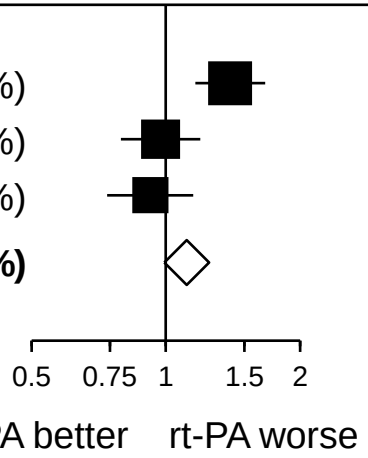


Effect of alteplase on fatal ICH at 7 days by treatment delay, age and stroke severity



Effect of rt-PA on 90-day mortality, overall and by period of follow-up

Risk period	No. (%) dead within 90 days rt-PA (n=3391)	Control (n=3365)	RR (95% CI)
Days 1-7 *	282 (8.3%)	204 (6.1%)	1.39 (1.16-1.67)
Days 8-30	178 (5.2%)	188 (5.6%)	0.97 (0.79-1.20)
Days 31-90	148 (4.4%)	164 (4.9%)	0.92 (0.74-1.15)
Subtotal: 90-day mortality	**608 (17.9%)**	**556 (16.5%)**	**1.11 (0.99-1.25)**



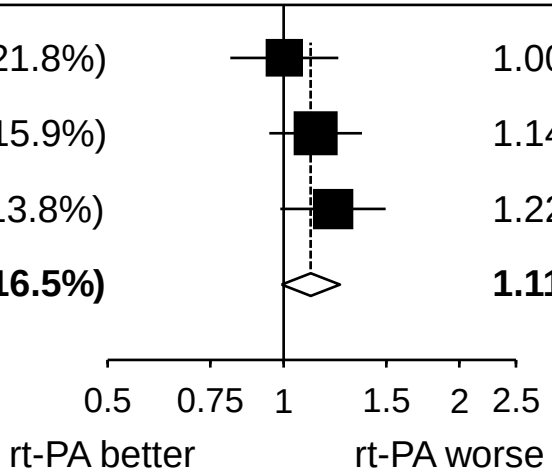
* Includes 91 vs 13 deaths from ICH and 191 vs 191 deaths from other causes

P-value for non-proportionality <0.0001

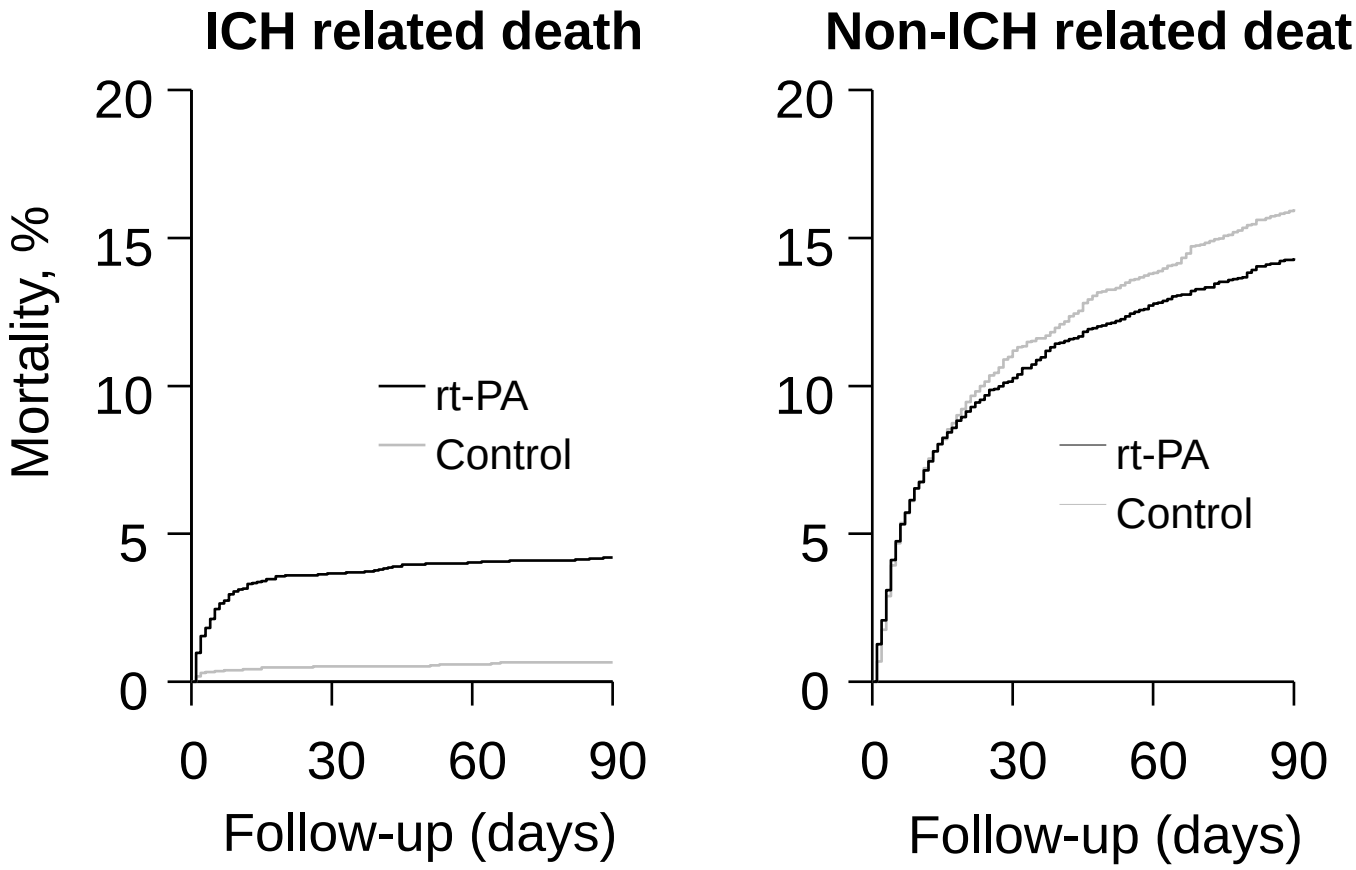
Average effect of rt-PA on 90-day mortality by treatment delay

Treatment delay (hours)	No. (%) dead within 90 days rt-P A (n=3391)	Control (n=3365)	RR (95% CI)
≤3	175/787 (22.2%)	166/762 (21.8%)	1.00 (0.81 - 1.24)
>3, ≤4.5	232/1375 (16.9%)	229/1437 (15.9%)	1.14 (0.95 - 1.36)
>4.5	201/1229 (16.4%)	161/1166 (13.8%)	1.22 (0.99 - 1.50)
All patients	**608/3391 (17.9%)**	**556/3365 (16.5%)**	**1.11 (0.99 - 1.25)**

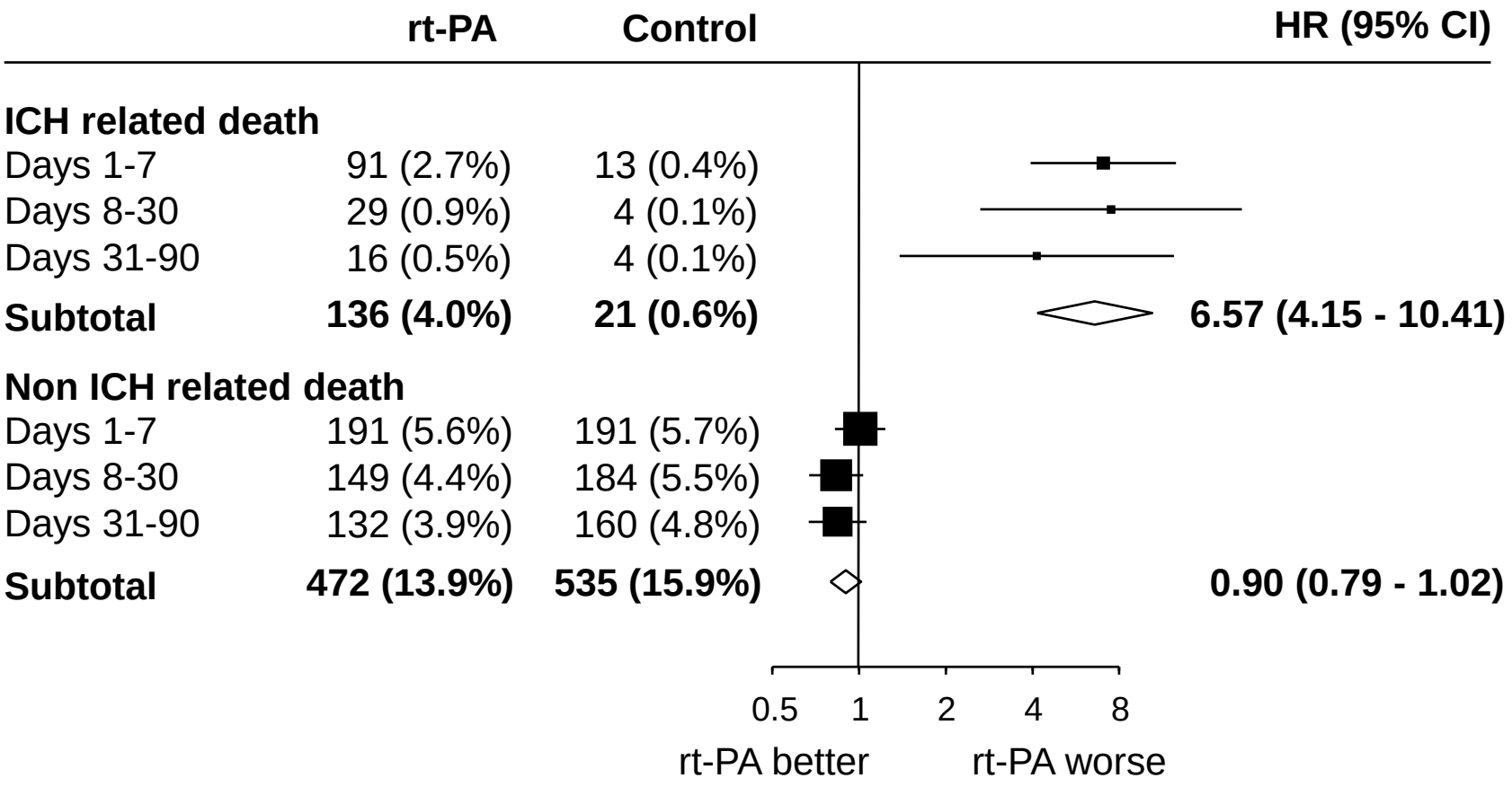
p-value for trend across 3 groups shown = 0.21



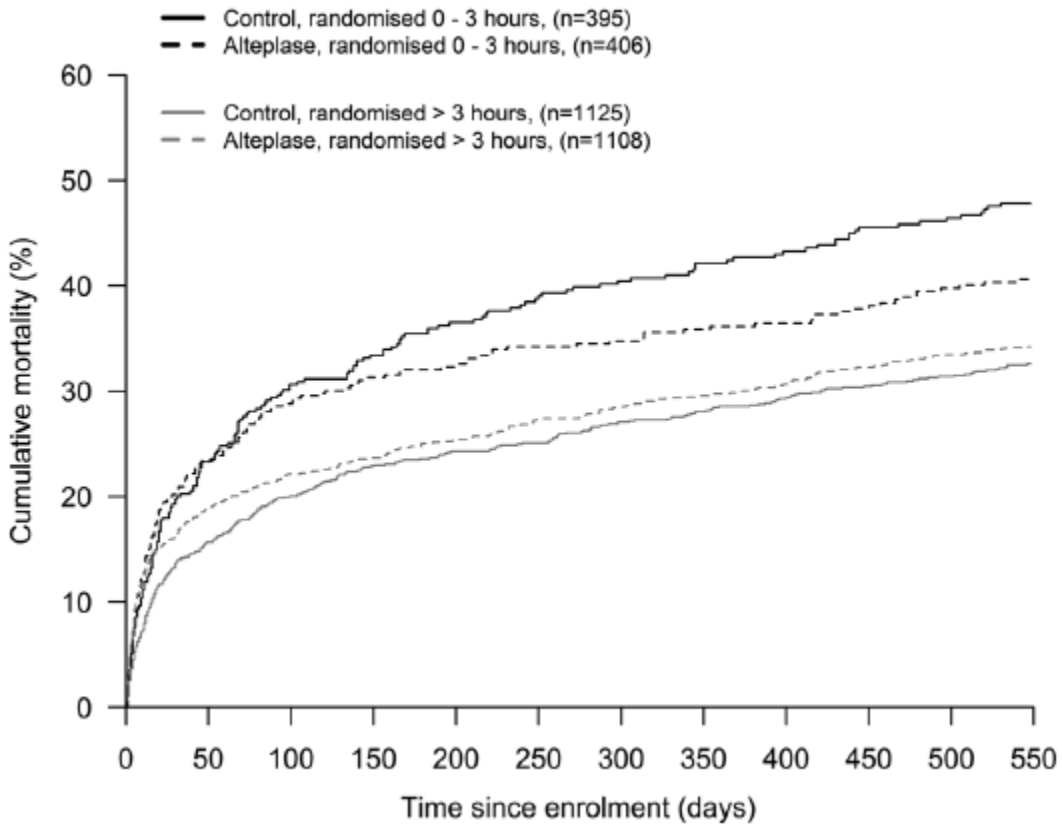
Effect of rt-PA on ICH and non-ICH related death during the first 90 days



Effect of rt-PA on ICH and non-ICH related death during the first 90 days

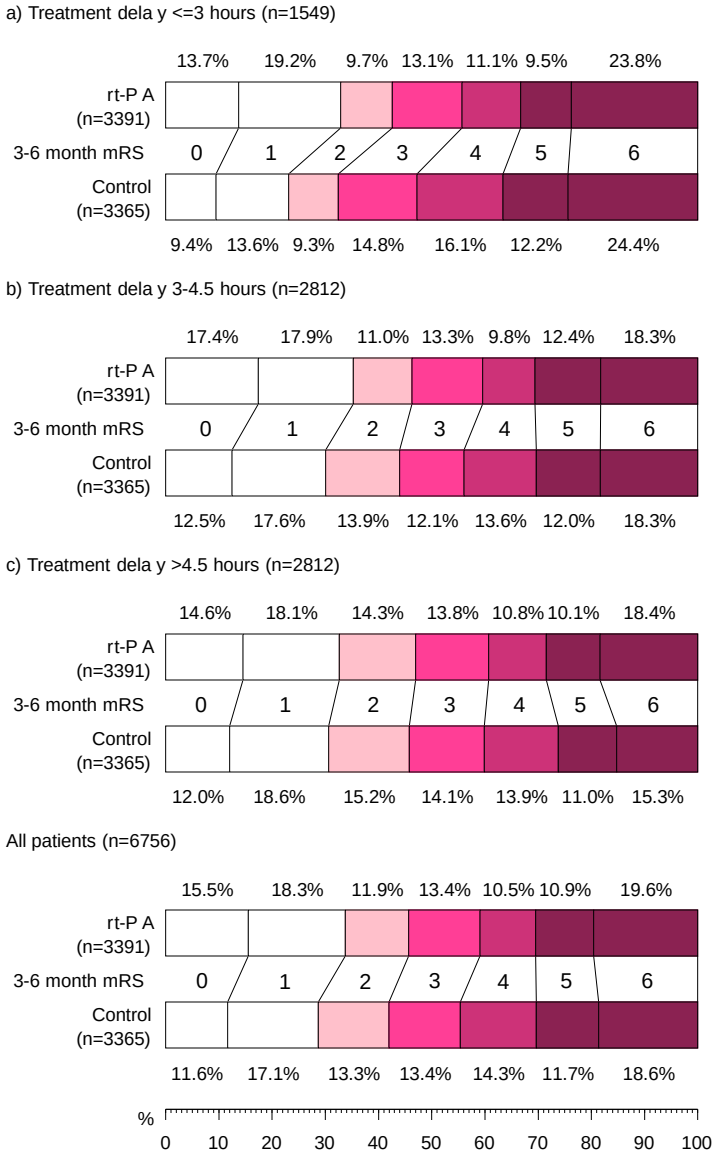


IST3: 18-month follow up for all-cause mortality



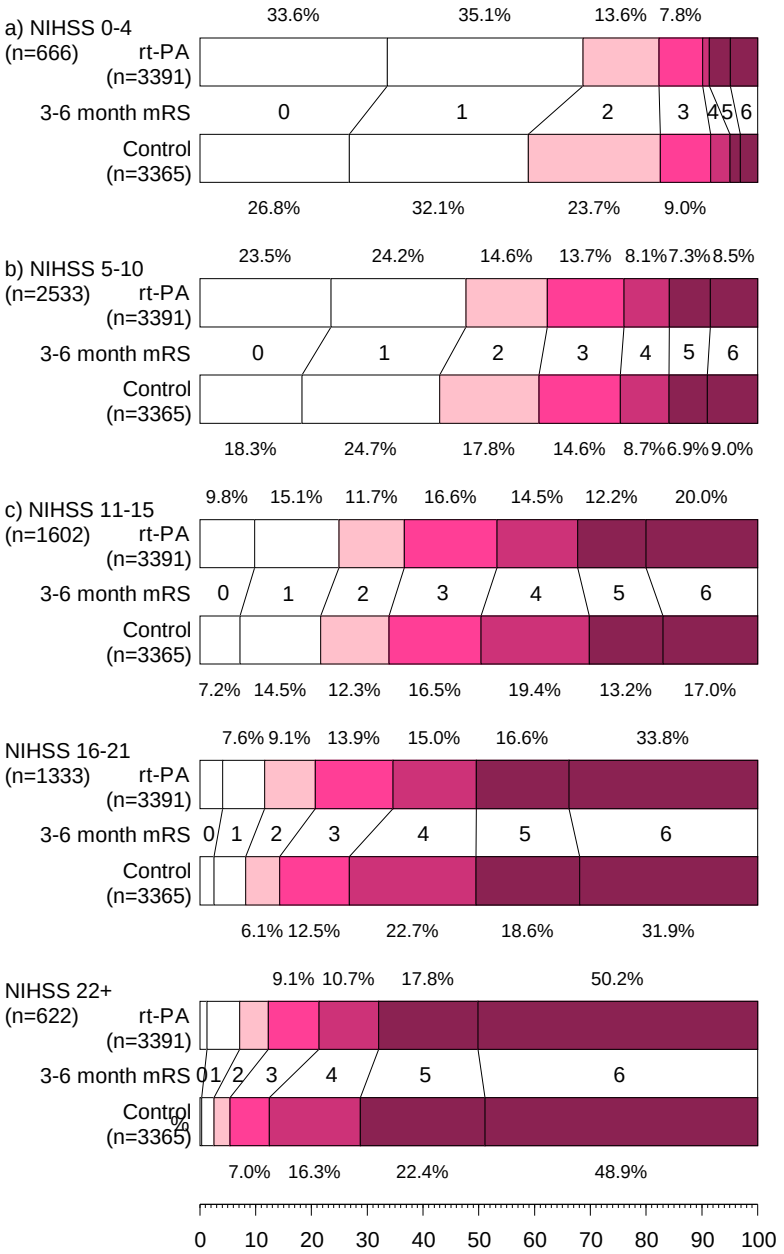
Whiteley W et al. Stroke 2014; 45: 3612-7

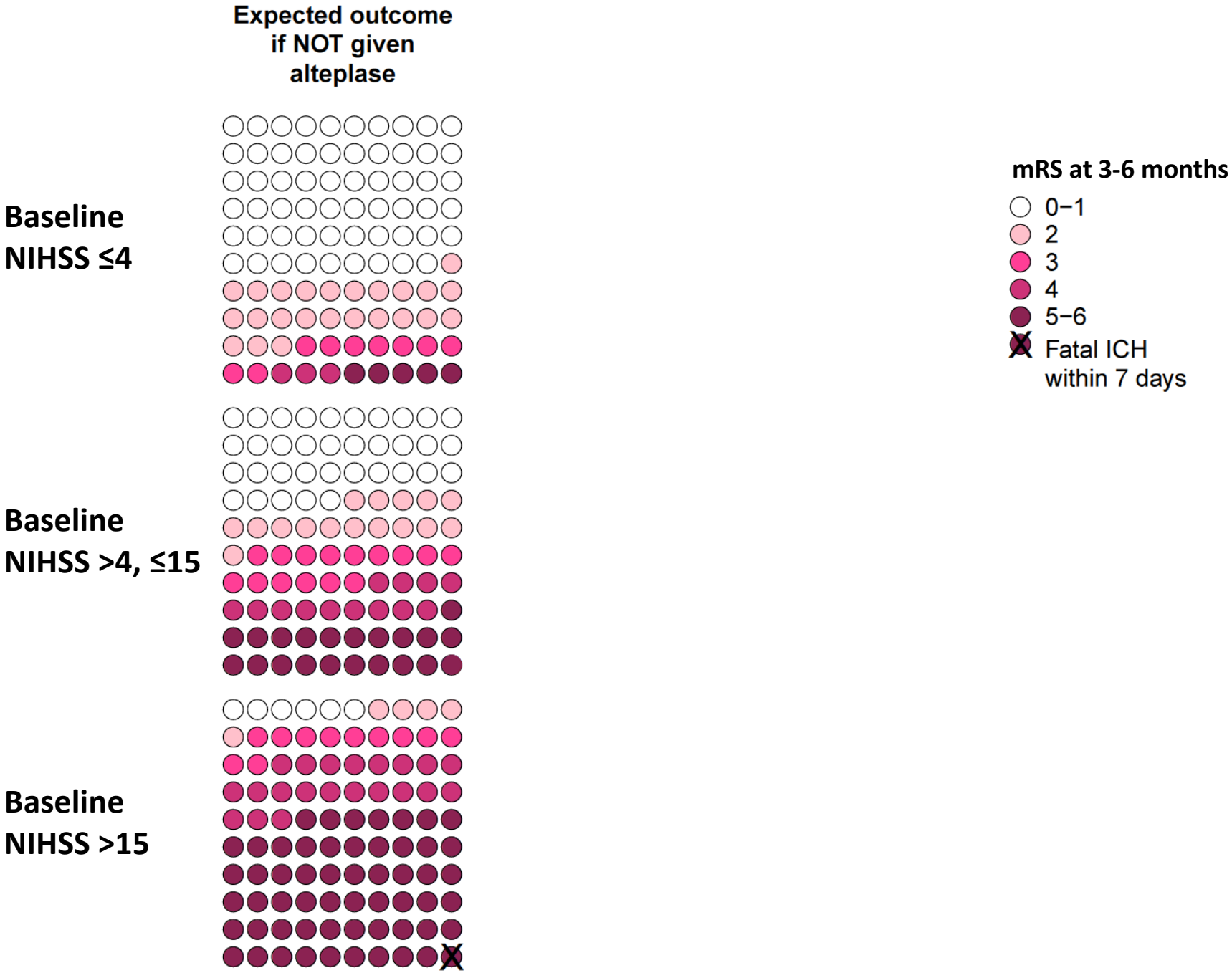
mRS at 3-6 months, overall and by treatment delay

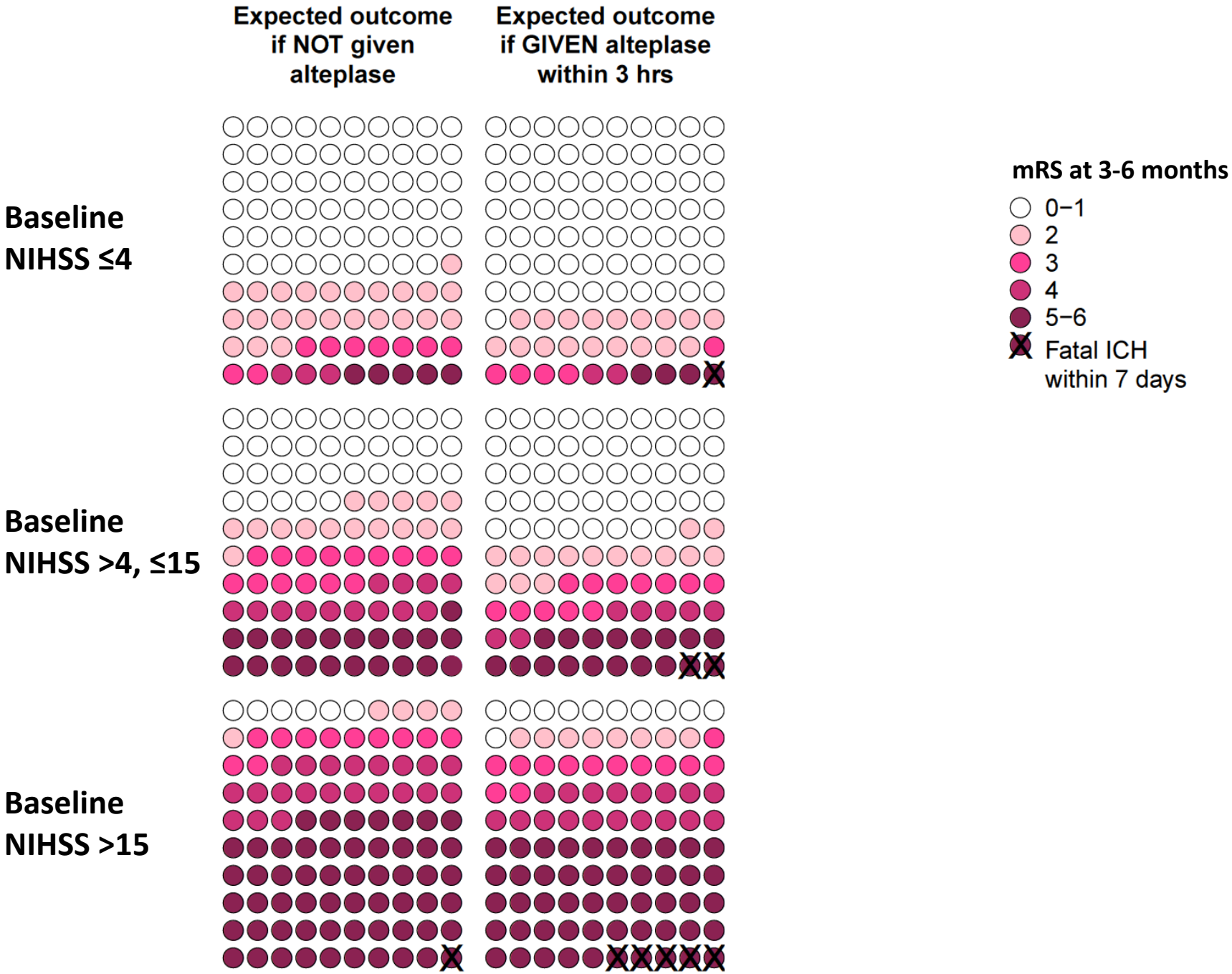


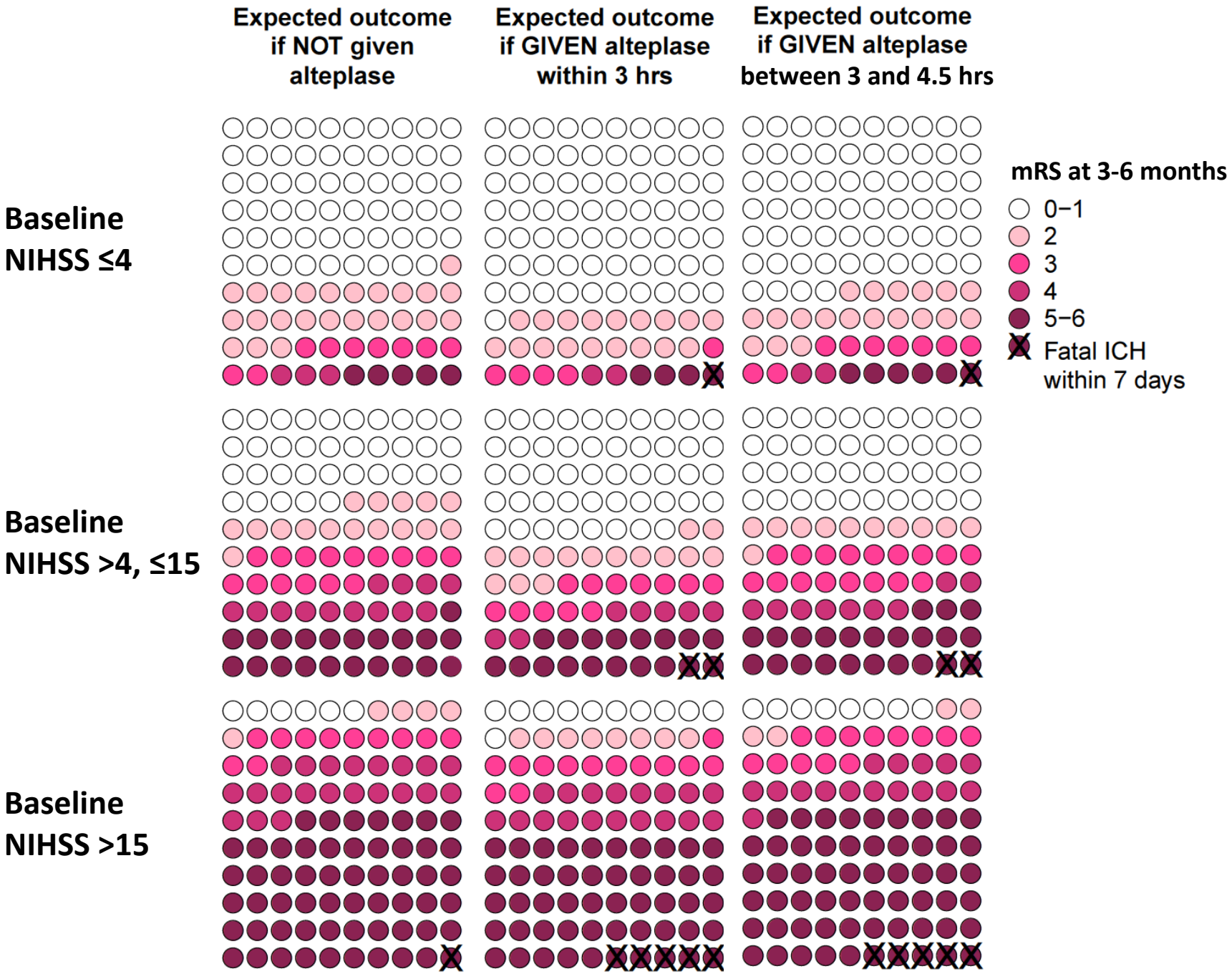
* mRS score ascer tained at 6 months f or IST-3 and 3 months f or other tr ials.

mRS at 3-6 months, overall and by stroke severity




Expected outcome if NOT given alteplase
Baseline NIHSS ≤4
Baseline NIHSS >4, ≤15
Baseline NIHSS >15
mRS at 3-6 months
0–1
2
3
4
5–6
Fatal ICH within 7 days


Expected outcome if NOT given alteplase
Expected outcome if GIVEN alteplase within 3 hrs
Baseline NIHSS ≤4
Baseline NIHSS >4, ≤15
Baseline NIHSS >15
mRS at 3-6 months
0–1
2
3
4
5–6
Fatal ICH within 7 days


Expected outcome if NOT given alteplase
Expected outcome if GIVEN alteplase within 3 hrs
Expected outcome if GIVEN alteplase between 3 and 4.5 hrs
Baseline NIHSS ≤4
Baseline NIHSS >4, ≤15
Baseline NIHSS >15
mRS at 3-6 months
0–1
2
3
4
5–6
Fatal ICH within 7 days

RESERVE

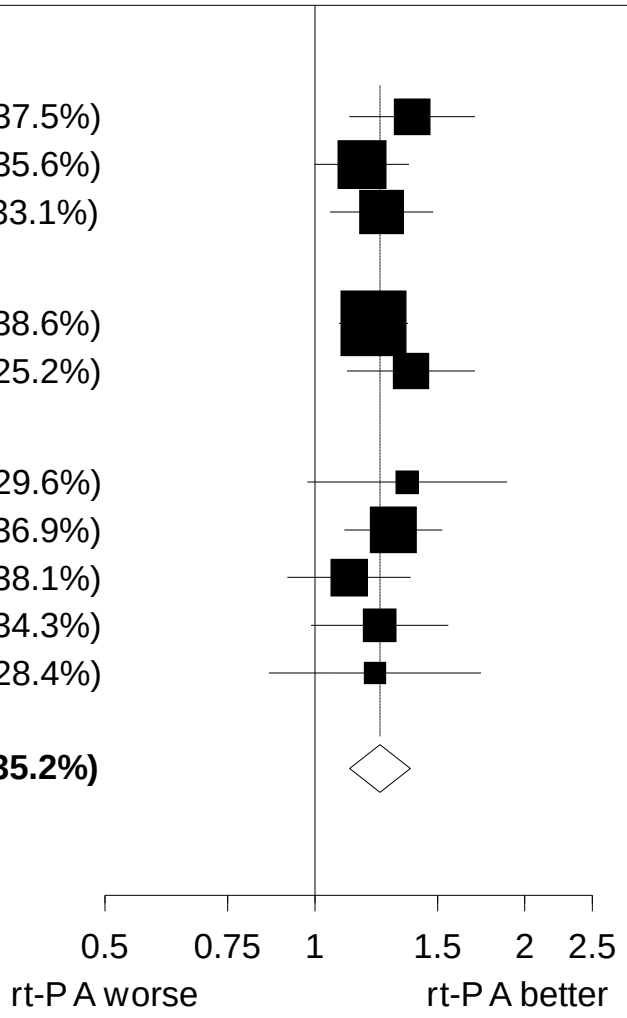
Classification of 'better than expected' mRS

Probability of good functional outcome *	Modified Rankin Score at 3-6 months							
	0	**1**	**2**	**3**	**4**	**5**	**6**	**Total**
<6%	**21**	**48**	**66**	**119**	**180**	287	628	1349
7 – 22%	**59**	**127**	**120**	**201**	300	200	330	1337
23 – 45%	**150**	**254**	**196**	245	184	133	197	1359
46 – 67%	**272**	**317**	225	209	124	96	96	1339
>67%	**415**	447	244	132	47	48	39	1372
Total	917	1193	851	906	835	764	1290	6756

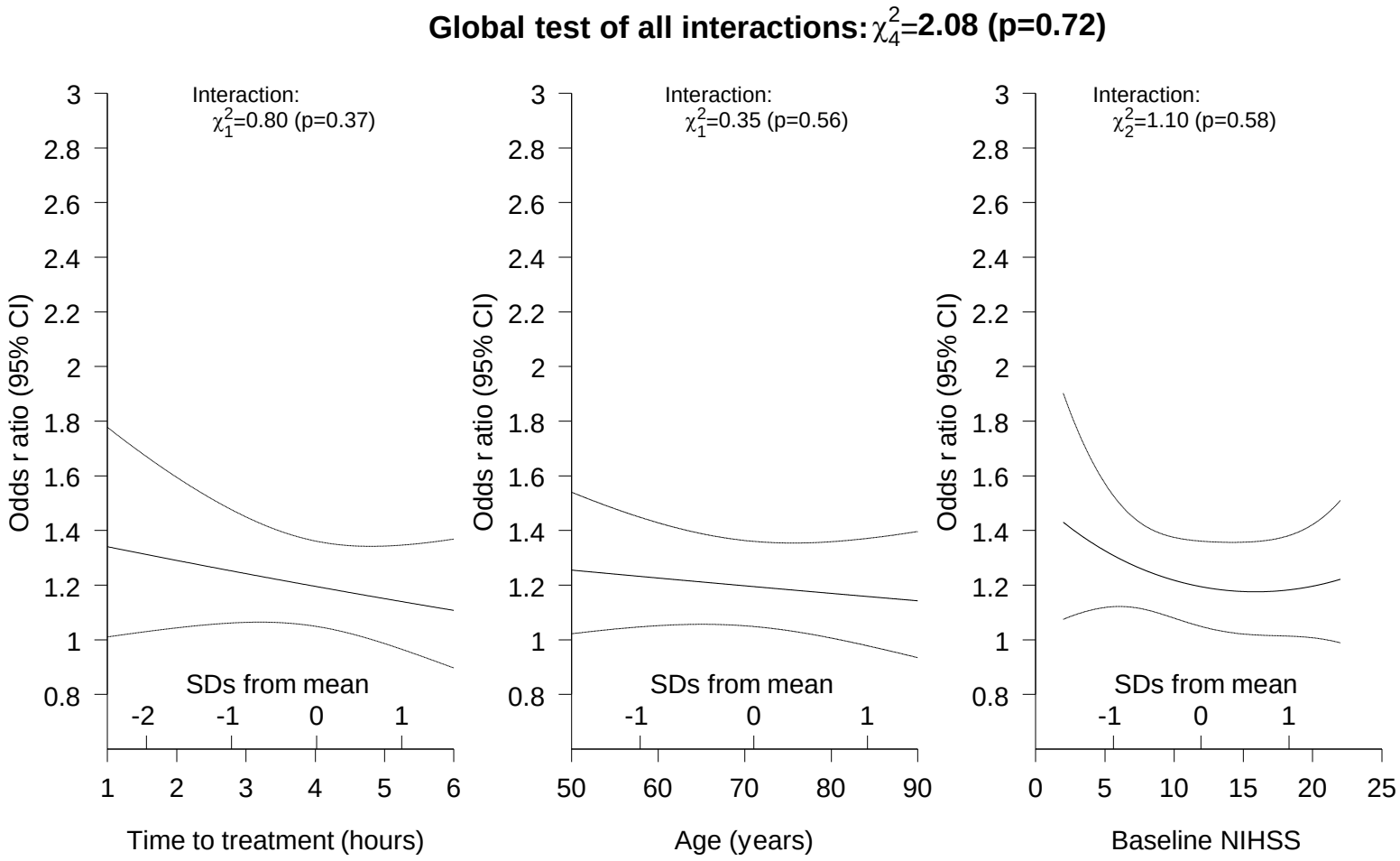
* Based on the "original functional recovery model" in Konig *et al.* Stroke 2008; 39: 1821-26

Effect of rt-PA on a better than expected mRS outcome by treatment delay, age and stroke severity

	rt-PA (n=3391)	Control (n=3365)	Odds ratio (95% CI)*
Treatment delay			
≤ 3 hours	352/787 (44.7%)	286/762 (37.5%)	1.38 (1.12 - 1.70)
>3, ≤ 4.5 hours	543/1375 (39.5%)	512/1437 (35.6%)	1.17 (1.00 - 1.36)
>4.5 hours	466/1229 (37.9%)	386/1166 (33.1%)	1.25 (1.05 - 1.48)
Age			
≤ 80 years	1083/2512 (43.1%)	970/2515 (38.6%)	1.21 (1.08 - 1.36)
>80 years	278/879 (31.6%)	214/850 (25.2%)	1.37 (1.11 - 1.70)
Baseline NIHSS			
0-4	127/345 (36.8%)	95/321 (29.6%)	1.36 (0.98 - 1.89)
5-10	552/1281 (43.1%)	462/1252 (36.9%)	1.30 (1.10 - 1.52)
11-15	325/794 (40.9%)	308/808 (38.1%)	1.12 (0.91 - 1.37)
16-21	259/662 (39.1%)	230/671 (34.3%)	1.24 (0.99 - 1.55)
≥ 22	98/309 (31.7%)	89/313 (28.4%)	1.22 (0.86 - 1.73)
All patients	**1361/3391 (40.1%)**	**1184/3365 (35.2%)**	**1.24 (1.12 - 1.37)**



Effect of rt-PA on a better than expected mRS outcome by treatment delay, age and stroke severity (adjusted for all 3 treatment interactions)



Analyses of mRS across the whole spectrum by treatment delay (Howard et al. 2012)

≤3 hours (mean 2hrs 20 min)

mRS in rt-PA group	mRS in control group					
	0	1	2	3	4	5/6
0	1449	2243	1578	2349	2702	5573
1	2006	3554	2475	3929	4075	10650
2	853	2017	1381	2385	2122	7800
3	1268	2472	1695	2848	2744	8449
4	1120	2204	1526	2428	2470	7023
5-6	2751	6897	4778	8250	7196	27969

Interpretation:

For each 1000 patients treated with rt-PA rather than control

- 431 would be expected to have a better stroke outcome with rt-PA
- 259 would be expected to have the same outcome
- 310 would be expected to have a worse outcome

Absolute benefit:

122 per 1000
(95% CI 61 to 171); p<0.001

Analyses of mRS across the whole spectrum by treatment delay (Howard et al. 2012)

>3, ≤4.5 hours (mean ~4 hrs)

mRS in rt-PA group	mRS in control group					
	0	1	2	3	4	5/6
0	13137	15829	12551	9587	11003	21105
1	13416	16817	14271	10488	11645	27665
2	7955	10027	8586	6356	7066	17164
3	8477	11856	11501	8405	8809	30088
4	5916	7823	6527	5176	5829	13771
5-6	17899	26348	26877	19235	19456	76046

Interpretation:

For each 1000 patients treated with rt-PA rather than control

- 399 would be expected to have a better stroke outcome with rt-PA
- 236 would be expected to have the same outcome
- 364 would be expected to have a worse outcome

Absolute benefit:

35 per 1000
(95% CI -14 to 77); p=0.14

Analyses of mRS across the whole spectrum by treatment delay (Howard et al. 2012)

≤4.5 hours (mean 3 hrs 20 min)

mRS in rt-PA group	mRS in control group					
	0	1	2	3	4	5/6
0	16975	22129	17294	16260	17691	40614
1	19144	27170	22849	21341	21910	64080
2	11704	17134	14865	13767	13625	44714
3	13227	21275	19240	18633	17880	66508
4	9580	14211	11927	11824	12141	36398
5-6	30677	53635	50846	48065	44158	188894

Interpretation:

For each 1000 patients treated with rt-PA rather than control

- 400 would be expected to have a better stroke outcome with rt-PA
- 255 would be expected to have the same outcome
- 345 would be expected to have a worse outcome

Absolute benefit:

55 per 1000
(95% CI 13 to 91); p=0.004

Analyses of mRS across the whole spectrum by treatment delay (Howard et al. 2012)

>4.5 hours (mean 5 hrs 20 min)

mRS in rt-PA group	mRS in control group					
	0	1	2	3	4	5/6
0	7319	10790	10047	9241	7075	17756
1	9398	14216	13684	12326	9162	24872
2	8263	12581	12421	11265	7764	23202
3	7898	12039	11930	10699	7415	22249
4	5088	7490	6818	6291	5098	11818
5-6	15566	24360	24511	21816	14795	47184

Interpretation:

For each 1000 patients treated with rt-PA rather than control

- 410 would be expected to have a better stroke outcome with rt-PA
- 200 would be expected to have the same outcome
- 390 would be expected to have a worse outcome

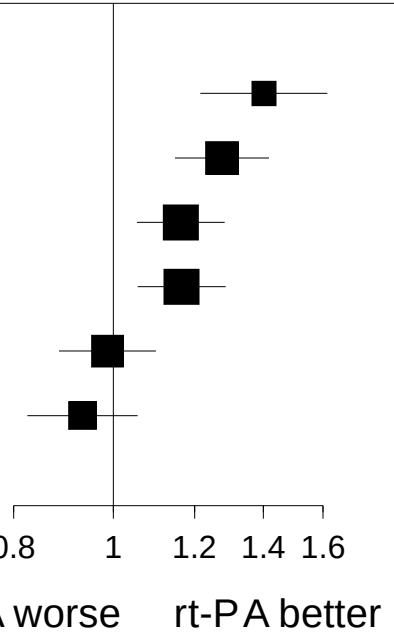
Absolute benefit:

20 per 1000

(95% CI -31 to 75); p=0.45

Relative odds of a good stroke outcome for each alternative definition of ‘good outcome’

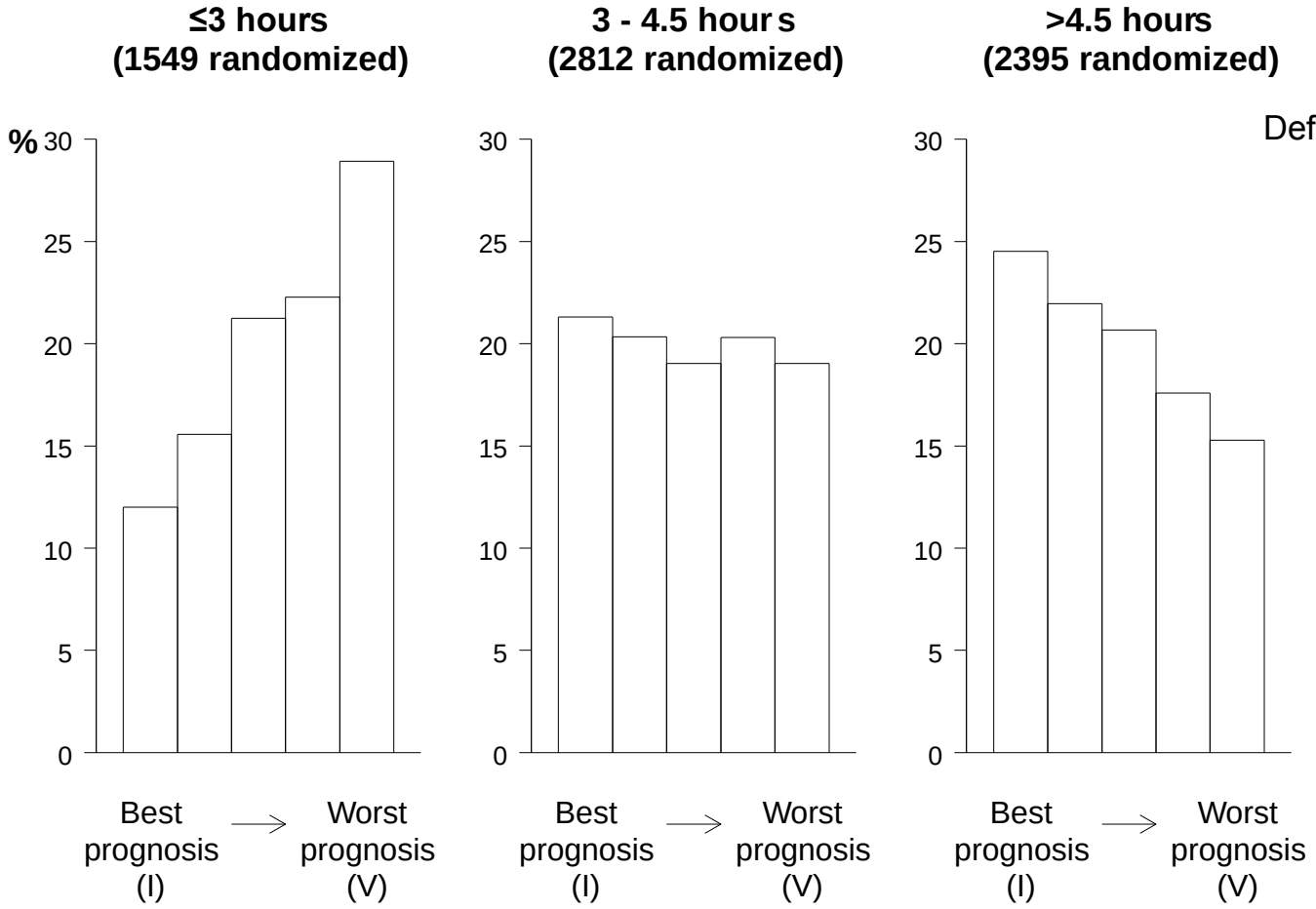
mRS comparison ('good' vs 'bad')	No. patients with 'good' outcome: rt-PA (n=3391)	Control (n=3365)	Odds ratio* (95% CI)
0 vs 1-6	526 (15.5%)	391 (11.6%)	1.40 (1.22-1.62)
0-1 vs 2-6**	1145 (33.8%)	965 (28.7%)	1.28 (1.15-1.42)
0-2 vs 3-6	1548 (45.7%)	1413 (42.0%)	1.16 (1.05-1.28)
0-3 vs 4-6	2003 (59.1%)	1864 (55.4%)	1.17 (1.06-1.29)
0-4 vs 5-6	2358 (69.5%)	2344 (69.7%)	0.99 (0.89-1.10)
0-5 vs 6	2358 (69.5%)	2344 (69.7%)	0.93 (0.82-1.06)



* Estimated from a logistic regression model stratified by trial and adjusted only for Rx allocation

** Primary prespecified mRS comparison

Distribution of stroke prognosis* by treatment delay



Definition of 'better than expected'

Prognosis	mRS:
I (best)	0
II	0 or 1
III	0, 1 or 2
IV	0, 1, 2 or 3
V (worst)	0, 1, 2, 3 or 4

* Based on each patient's age and stroke severity