

THE LANCET

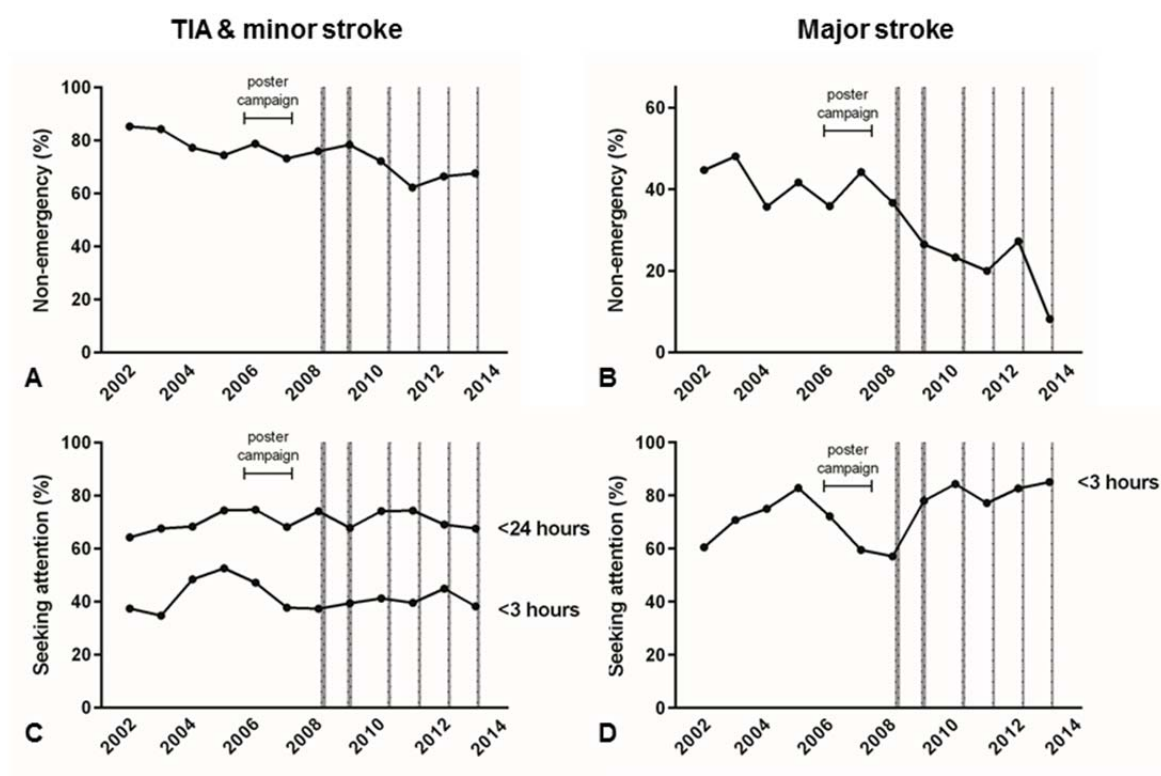
Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed.
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Supplement to: Rothwell PM, Algra A, Chen Z, Diener H-C, Norrving B, Mehta Z.
Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic
attack and ischaemic stroke: time-course analysis of randomised trials. *Lancet* 2016;
published online May 18. [http://dx.doi.org/10.1016/S0140-6736\(16\)30468-8](http://dx.doi.org/10.1016/S0140-6736(16)30468-8).

Webappendix: Pothwell PM, Algra A, Chen Z, Diener H-C, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials.

A population-based study (Oxford Vascular Study) of time-trends in patient behavior after TIA and minor stroke versus major stroke in relation to the FAST television campaigns in the UK. The shaded areas reflect the timing of the campaigns. Non-emergency presentation refers to patients making appointments to see their family doctor as opposed to presenting to the emergency department or calling for an ambulance. The lower graphs show the proportions of patients first seeking medical attention within 3 hours and within 24 hours.



Courtesy of Dr Frank J. Wolters. Updated analysis from:

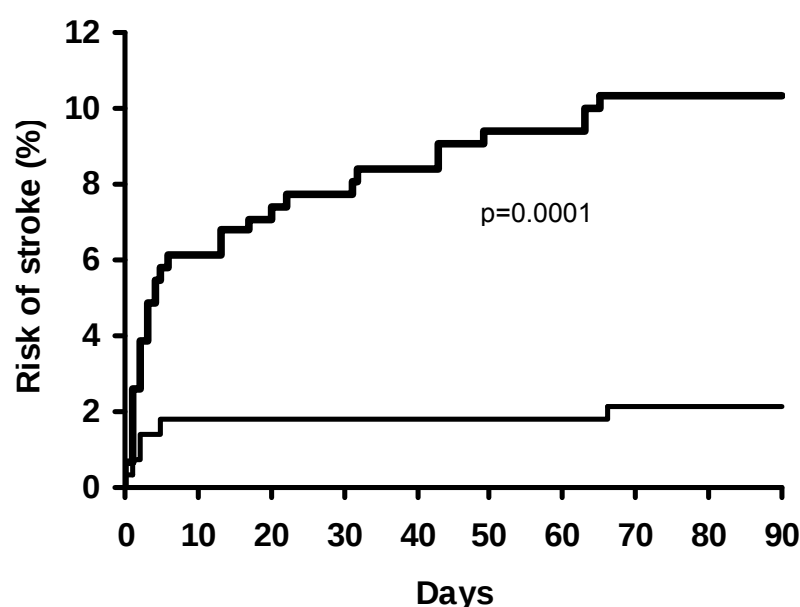
1. Wolters, FJ, Paul, NLM, Chandratheva, A et al. Contrasting impact of FAST-test public education campaign on behaviour after TIA and minor stroke versus major stroke: a population-based study. *Cerebrovascular Diseases* 2013, 35, 719-20.
2. Wolters FJ, Paul NL, Li L, Rothwell PM; Oxford Vascular Study. Sustained impact of UK FAST-test public education on response to stroke: a population-based time-series study. *Int J Stroke* 2015; 10:1108-14.

Severity of recurrent vascular events in the first 90-days after seeking medical attention in patients with TIA and minor stroke ascertained in the EXPRESS study in Phase-1 (standard treatment) versus Phase-2 (urgent treatment).^{1,2} The effect of urgent treatment increased with increasing severity of recurrent event (interaction – $p=0.002$).

	Phase-1	Phase-2
Patients	310	281
Recurrent events		
TIA	17	15
Non-disabling stroke [#]	16	5
Disabling or fatal stroke [#]	16	1

[#] Outcome is based on the modified Rankin score (mRS) at 1-3 months after the recurrent event: non-disabling stroke (mRS 0-2); Disabling or fatal stroke (mRS 3-6).

The 90-day risk of recurrent stroke after first seeking medical attention in all patients with TIA or stroke referred to the EXPRESS Study Clinic. The thick line represents phase-1 of the EXPRESS Study and the thin line represents phase-2.



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2. Luengo-Fernandez R, Gray AM, Rothwell PM. Effect of urgent treatment for transient ischaemic attack and minor stroke on disability and hospital costs (EXPRESS study): a prospective population-based sequential comparison. *Lancet Neurol.* 2009; 8:235-43.

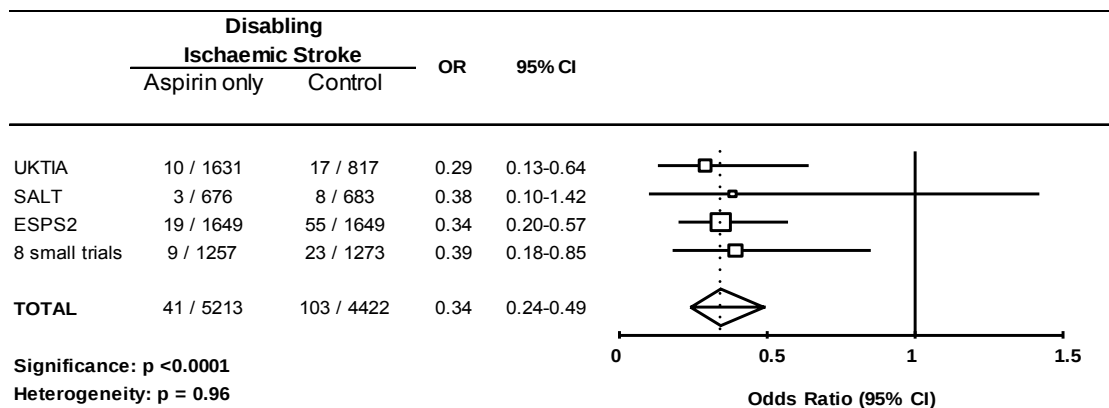
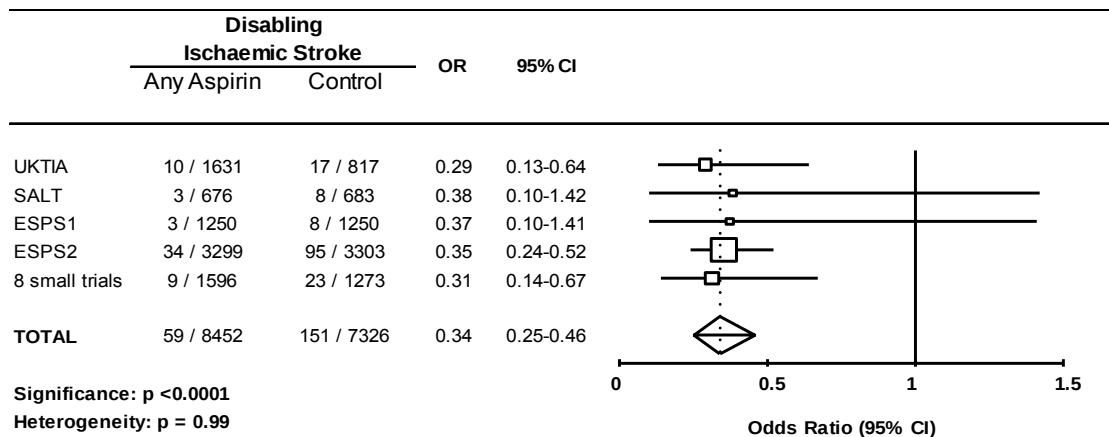
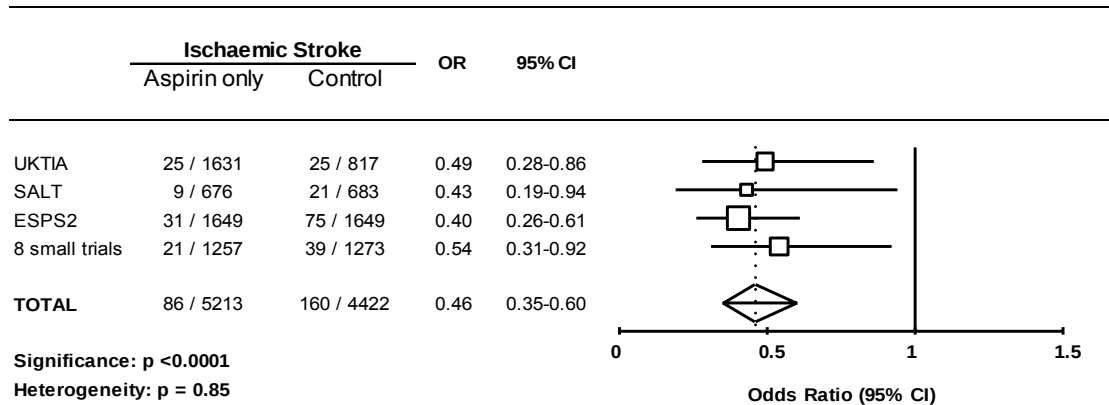
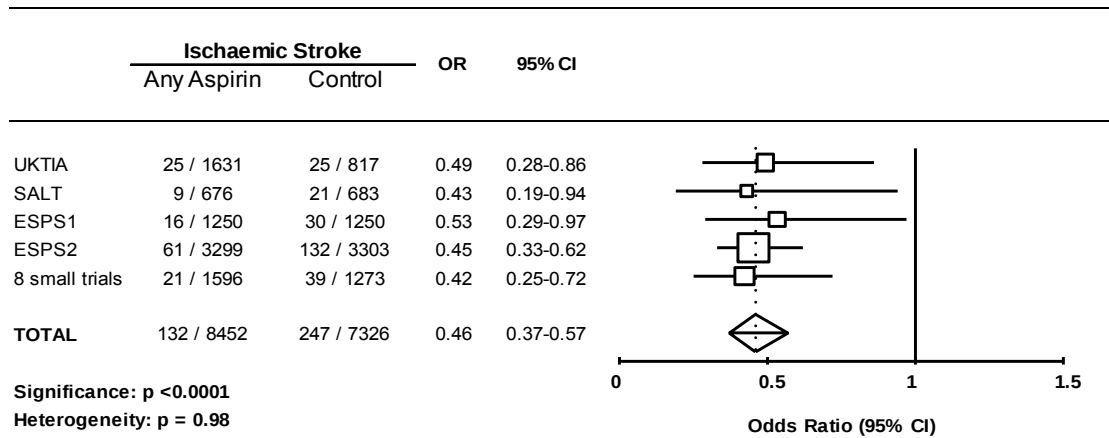
Details of the trials of aspirin and/or dipyridamole in secondary prevention after TIA and ischaemic stroke included in analyses.

Comparison / Trial	Participants	Male (%)	Mean (SD) age (years)	Diabetes (%)	Hypertension (%)	Aspirin dose (mg)	Mean duration
<i>Aspirin alone vs no antiplatelet drug</i>							
AITIA ¹	319	70%	58 (14)	-	-	1200	17
UK-TIA ²	2435	73%	60 (9)	4%	27%	300/1200	50
Reuther ³	60	65%	58 (10)	17%	50%	1500	24
CA Co-op ⁴	283	67%	61 (9)	8%	37%	1300	26
Toulouse TIA ⁵	303	86%	63 (9)	-	-	900	34
AICLA ⁶	402	68%	64 (10)	23%	64%	900	36
Danish Co-op ⁷	203	73%	59 (9)	6%	-	1000	33
Swedish Coop ⁸	505	62%	68 (10)	17%	46%	1500	24
Danish Low Dose ⁹	301	65%	59 (8)	7%	-	50	23
SALT ¹⁰	1359	66%	67 (7)	13%	47%	75	32
ESPS-2 ^{11,12}	3298	58%	67 (11)	15%	61%	50	24
<i>Aspirin + dipyridamole vs no antiplatelet drug</i>							
ESPS-1 ¹³	2500	58%	-	-	-	975	23
Toulouse TIA ⁵	293	86%	63 (9)	-	-	900	34
AICLA ⁶	406	68%	64 (10)	23%	64%	900	36
ESPS-2 ^{11,12}	3299	58%	67 (11)	15%	61%	50	24
<i>Aspirin + dipyridamole vs aspirin</i>							
ACCSG ¹⁴	890	67%	63	15%	48%	1300	25
ESPS-2 ^{11,12}	3299	58%	67 (11)	15%	61%	50	24
ESPRIT ¹⁵	2763	66%	63 (11)	19%	60%	30-325	42
EARLY ¹⁶	548	62%	68	24%	74%	50	7 days
JASAP ¹⁷	1295	72%	66 (8)	40%	88%	50/81	15
Toulouse TIA ⁵	284	86%	63 (9)	-	-	900	34
AICLA ⁶	400	68%	64 (10)	23%	64%	900	36
<i>Dipyridamole vs no antiplatelet drug</i>							
ESPS-2 ^{11,12}	3303	58%	67 (11)	15%	61%	50	24

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Meta-analyses of the effects of aspirin (any aspirin vs control and aspirin only vs control) on risk of any recurrent ischaemic stroke and any disabling ischaemic stroke within 12 weeks of randomisation.

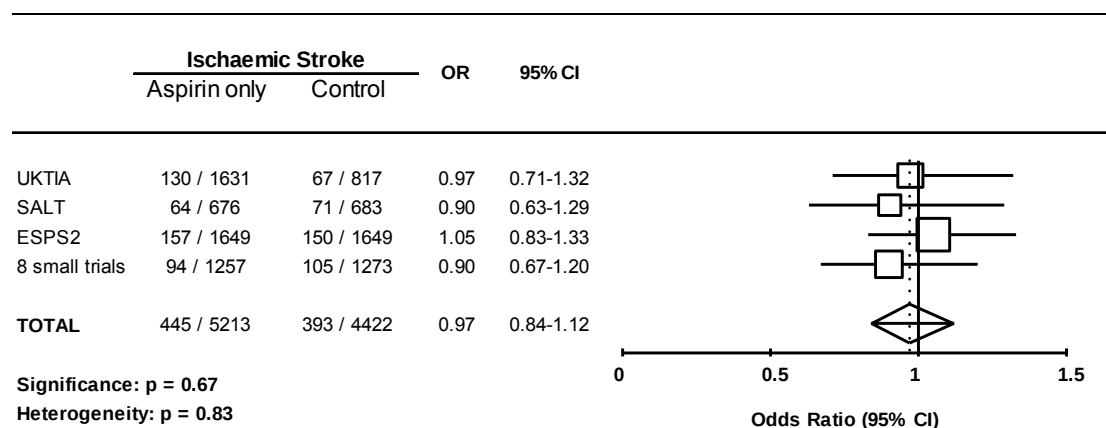


Pooled analysis of the effect of any aspirin vs control in secondary prevention after TIA and ischaemic stroke on the early risk of any recurrent ischaemic stroke and on disabling or fatal ischaemic stroke stratified by baseline clinical characteristics. Complete baseline data available on only the 10,409 participants in UKTIA, SALT and ESPS-2.

	HR	LL	UL	p	p(interaction)
All ischaemic stroke					
Age					0.95
<65	0.50	0.33	0.74	0.0006	
65-74	0.39	0.26	0.57	<0.0001	
≥75	0.54	0.36	0.83	0.0049	
Sex					0.84
Female	0.45	0.30	0.67	<0.0001	
Male	0.48	0.36	0.64	<0.0001	
Hypertension					0.12
No	0.66	0.42	1.05	0.079	
Yes	0.40	0.30	0.53	<0.0001	
Current smoking					0.57
No	0.49	0.35	0.68	<0.0001	
Yes	0.42	0.28	0.63	<0.0001	
Diabetes					0.92
No	0.47	0.35	0.62	<0.0001	
Yes	0.43	0.24	0.77	0.0045	
Aspirin Dose					0.53
Low (≤100mg)	0.51	0.37	0.71	<0.0001	
High (≥300mg)	0.44	0.33	0.59	<0.0001	
Disabling or fatal ischaemic stroke					
Age					0.44
<65	0.33	0.17	0.66	0.0017	
65-74	0.27	0.16	0.45	<0.0001	
≥75	0.48	0.29	0.81	0.0056	
Sex					0.84
Female	0.34	0.20	0.57	<0.0001	
Male	0.36	0.24	0.54	<0.0001	
Hypertension					0.20
No	0.52	0.29	0.95	0.033	
Yes	0.29	0.19	0.43	<0.0001	
Current smoking					0.45
No	0.39	0.25	0.60	<0.0001	
Yes	0.30	0.18	0.51	<0.0001	
Diabetes					0.77
No	0.36	0.25	0.52	<0.0001	
Yes	0.30	0.14	0.67	0.0034	
Aspirin dose					0.82
Low (≤100mg)	0.33	0.20	0.55	<0.0001	
High (≥300mg)	0.36	0.24	0.52	<0.0001	

Meta-analysis of the effect aspirin only vs. control on the risk of recurrent ischaemic stroke more than 12 weeks after randomisation in trials of aspirin in secondary prevention after TIA and ischaemic stroke.

This preliminary analysis includes strokes known to be ischaemic and strokes of unknown type and the UK-TIA trial outcomes are confined to the 'major stroke; primary outcome (i.e. events with symptoms lasting longer than 7 days). The denominators are the numbers of patients at randomisation rather than at 12 weeks. The analysis is by intention-to-treat and so no account is taken of compliance with randomised treatment allocation. More detailed analyses are ongoing.



Details of the trials aspirin vs control in treatment of acute ischaemic stroke that were included in analyses.

CAST¹

Double blind

21,106 participants

63% male

28% were more than 70 years old

87% had CT before entry

Ischaemic stroke less than 48 hours since stroke onset

Interventions Rx: aspirin 160 mg once daily orally or via nasogastric tube

Control: placebo

Duration: 4 weeks, or until death or earlier discharge

FU: 4 weeks

IST²

Unblinded

19,435 participants

54% male

61% more than 70 years

67% CT prior to randomisation, 29% CT after randomisation

Ischaemic stroke less than 48 hours since stroke onset

Interventions Rx: subcutaneous heparin (5000 IU or 12 500 IU 12 hourly), aspirin 300 mg, both, or neither (factorial design)

Duration: 14 days or until discharge from hospital

Interventions Rx: Aspirin by mouth if able to swallow, if not then by rectal suppository or by injection of 100 mg of the lysine salt of aspirin

FU: 6 months

Rödén-Jülig³

Double blind

441 participants

226 (51%) male

100% CT before entry

Ischaemic stroke less than 72 hours since stroke onset

Interventions Rx: aspirin 325 mg orally once daily

Control: placebo

Duration: 5 days

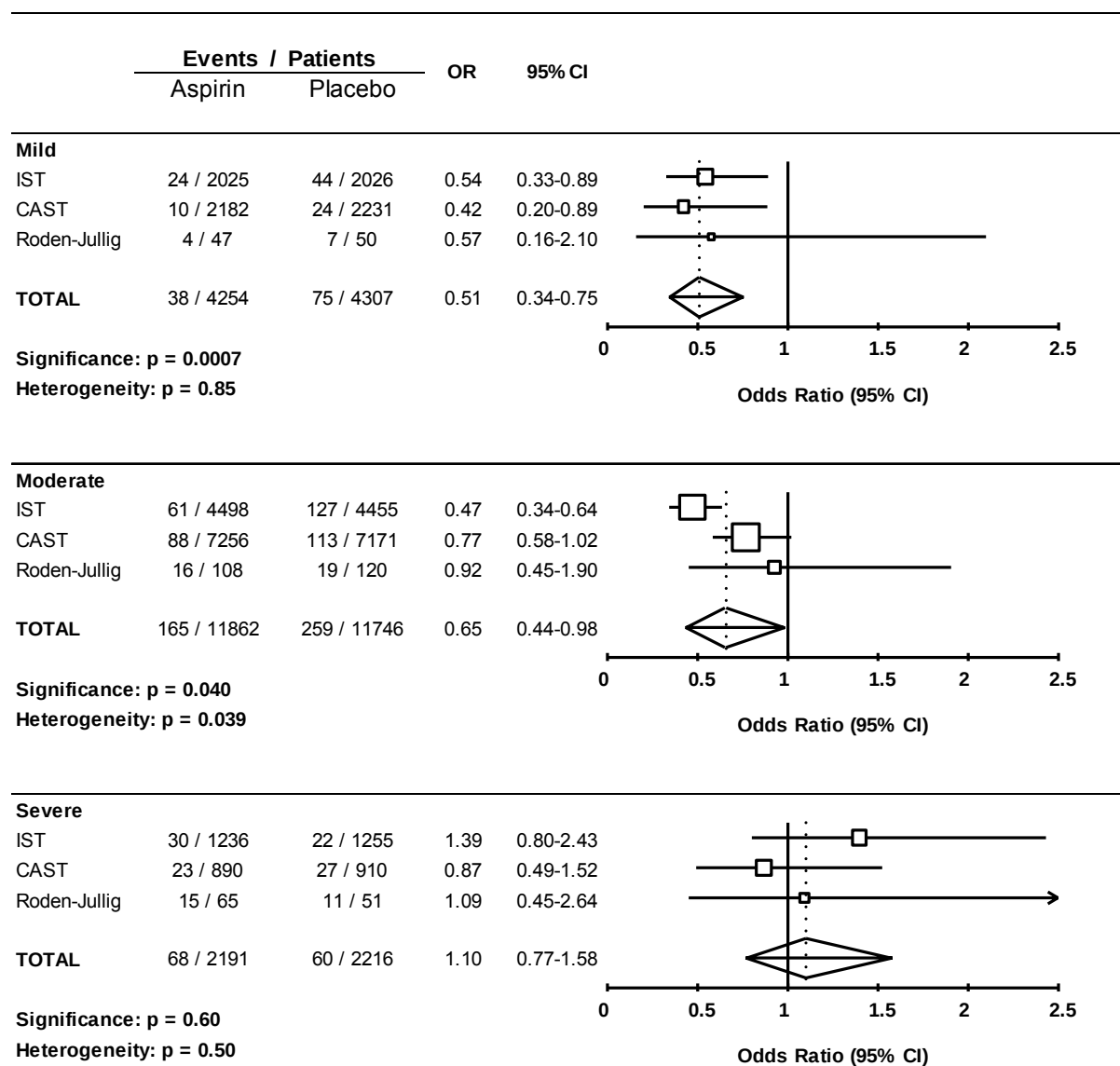
FU: 3 months

References

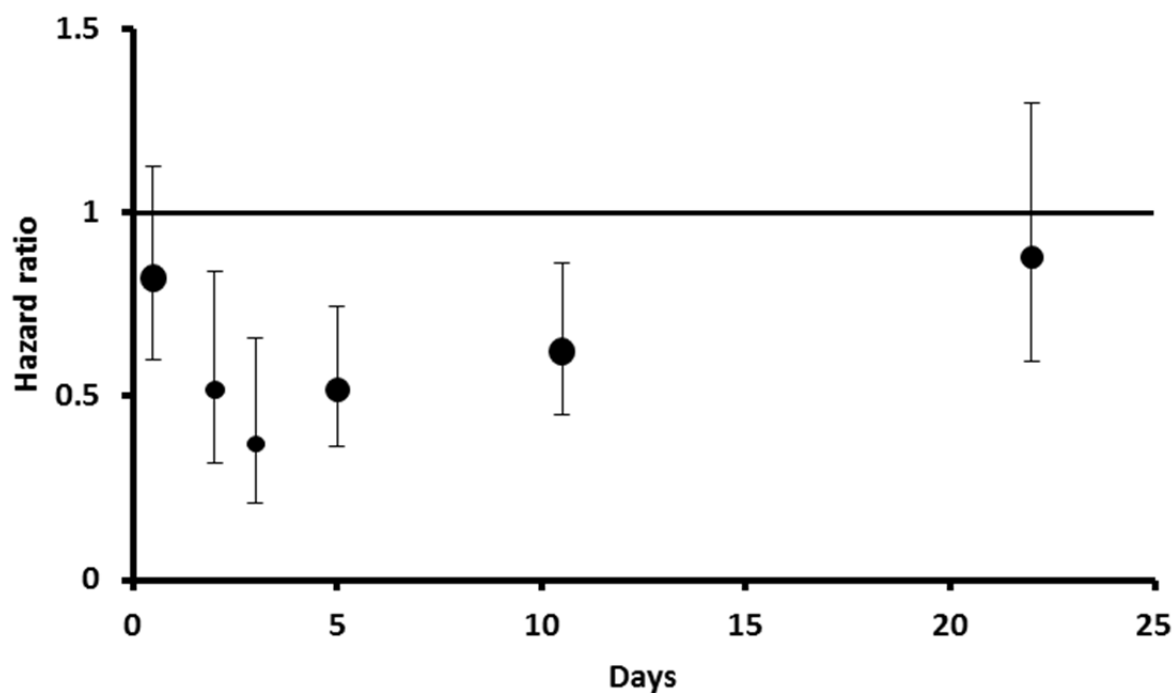
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Meta-analysis of the effect of aspirin vs control on the 14-day risk of recurrent ischaemic stroke in trials of aspirin in treatment of acute stroke stratified by the extent of the initial neurological (mild, moderate or severe).

Heterogeneity between 3 severity groups: $p=0.014$



Pooled hazard ratios for the effect of aspirin vs control on risk of recurrent ischaemic stroke in patients with mild and moderately severe initial neurological deficits during early follow-up (days 0-1; 2-3,4-6; 7-14; >15) in two large trials of aspirin in treatment of acute stroke. This analysis is equivalent to figure 3 in the main body of the paper except that it includes 3292 (21.3%) patients with mild or moderately severe stroke in the International Stroke trial who had received aspirin during the days prior to randomisation.



Meta-analysis of the effect dipyridamole plus aspirin versus aspirin alone on the risk of recurrent ischaemic stroke within 12 weeks after randomisation in trials in secondary prevention after TIA and ischaemic stroke.

