SUPPLEMENTARY MATERIAL:

Supplementary table 1a: Functional outcome by treatment group using central adjudicator and site investigator data in REVASCAT

	Central adjudicator data		Site investigator data	
Outcome	**Treated (n=103)**	**Control (n=103)**	**Treated (n=103)**	**Control (n=103)**
mRS 0	7	6	6	3
mRS 1	18	7	23	10
mRS 2	20	16	20	16
mRS 3	19	20	15	20
mRS 4	8	17	7	15
mRS 5/6	31	37	32	39

mRS refers to modified Rankin Scale

Supplementary table 1b: Agreement on functional outcome between central adjudicators and site investigators in REVASCAT

	Central Adjudicators						
Site Investigators	mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5/6	**Total**
mRS 0	9	0	0	0	0	0	9
mRS 1	4	25	3	1	0	0	33
mRS 2	0	0	33	3	0	0	36
mRS 3	0	0	0	35	0	0	35
mRS 4	0	0	0	0	22	0	22
mRS 5/6	0	0	0	0	3	68	71
Total	13	25	36	39	25	68	206
Disagreements (%)	4 (31%)	0 (-)	3 (8%)	4 (10%)	3 (12%)	0 (-)	14 (7%)

Crude agreement = 192/206 = 93%, unweighted kappa = 0.91, weighted kappa using linear weights = 0.96. mRS refers to modified Rankin Scale

Supplementary table 1c: Functional outcome by treatment group using central adjudicator and misclassified site investigator data in REVASCAT

	Central adjudicator data		Example misclassified site investigator data	
Outcome	**Treated (n=103)**	**Control (n=103)**	**Treated (n=103)**	**Control (n=103)**
mRS 0	7	6	14	3
mRS 1	18	7	15	7
mRS 2	20	16	21	11
mRS 3	19	20	19	20
mRS 4	8	17	14	19
mRS 5/6	31	37	20	43

Misclassified site investigator data is from one of 1000 simulations (starting seed 2206). mRS refers to modified Rankin Scale

Supplementary table 1d: Agreement on functional outcome between central adjudicators and example misclassified site investigators in REVASCAT (data from one of 1000 simulations)

	Central Adjudicators						
Site Investigators	mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5/6	**Total**
mRS 0	10	7	0	0	0	0	17
mRS 1	3	15	4	1	0	0	22
mRS 2	0	3	24	5	0	0	32
mRS 3	0	0	8	26	4	1	39
mRS 4	0	0	0	8	15	10	33
mRS 5/6	0	0	0	0	6	57	63
Total	13	25	36	39	25	68	206
Disagreements (%)	3 (23%)	10 (40%)	12 (33%)	14 (36%)	10 (40%)	11 (16%)	60 (29%)

Mean crude agreement (SD) = 72.2% (2.80%), mean unweighted kappa (SD) = 0.65 (0.03), mean weighted kappa using linear weights (SD) = 0.84 (0.02). Mean crude agreement, unweighted and weighted kappa are from 1000 simulations (starting seed 2206). mRS refers to modified Rankin Scale

Supplementary table 2a: Functional outcome by treatment group using central adjudicator and site investigator data in TARDIS

	Central adjudicator data		Site investigator data	
Outcome	**Treated (n=1556)**	**Control (n=1540)**	**Treated (n=1556)**	**Control (n=1540)**
No recurrent event	1463	1435	1457	1434
TIA	32	48	34	53
Stroke: mRS 0/1	15	18	16	16
Stroke: mRS 2/3	22	23	23	22
Stroke: mRS 4/5	11	9	13	10
Fatal stroke: mRS 6	13	7	13	5

mRS refers to modified Rankin Scale

Supplementary table 2b: Agreement on incidence and severity of stroke between central adjudicators and site investigators in TARDIS

	Central Adjudicators						
Site Investigators	No recurrent event	TIA	Stroke: mRS 0/1	Stroke: mRS 2/3	Stroke: mRS 4/5	Fatal stroke: mRS 6	**Total**
No recurrent event	2881	1	3	4	0	2	2891
TIA	5	77	4	1	0	0	87
Stroke: mRS 0/1	4	2	26	0	0	0	32
Stroke: mRS 2/3	5	0	0	40	0	0	45
Stroke: mRS 4/5	3	0	0	0	20	0	23
Fatal stroke: mRS 6	0	0	0	0	0	18	18
Total	2898	80	33	45	20	20	3096
Disagreements (%)	17 (1%)	3 (4%)	7 (21%)	5 (11%)	0 (-)	2 (10%)	34 (1%)

Crude agreement = 3062/3096 = 98.9%, unweighted kappa = 0.91, weighted kappa using linear weights = 0.91. TIA refers to Transient Ischaemic Attack, mRS refers to modified Rankin Scale

Supplementary table 2c: Functional outcome by treatment group using central adjudicator and misclassified site investigator data in TARDIS

	Central adjudicator data		Example misclassified site investigator data	
Outcome	**Treated (n=1556)**	**Control (n=1540)**	**Treated (n=1556)**	**Control (n=1540)**
No recurrent event	1463	1435	1472	1403
TIA	32	48	31	58
Stroke: mRS 0/1	15	18	16	26
Stroke: mRS 2/3	22	23	17	31
Stroke: mRS 4/5	11	9	10	12
Fatal stroke: mRS 6	13	7	10	10

Misclassified site investigator data is from one of 1000 simulations (starting seed 2206). mRS refers to modified Rankin Scale

Supplementary table 2d: Example agreement on incidence and severity of stroke between central adjudicators and misclassified site investigators in TARDIS (data from one of 1000 simulations)

	Central Adjudicators						
Misclassified site Investigators	No recurrent event	TIA	Stroke: mRS 0/1	Stroke: mRS 2/3	Stroke: mRS 4/5	Fatal stroke: mRS 6	**Total**
No recurrent event	2866	4	0	4	0	1	2875
TIA	10	76	2	0	0	1	89
Stroke: mRS 0/1	8	0	31	2	1	0	42
Stroke: mRS 2/3	8	0	0	39	1	0	48
Stroke: mRS 4/5	3	0	0	0	18	1	22
Fatal stroke: mRS 6	3	0	0	0	0	17	20
Total	2898	80	33	45	20	20	3096
Disagreements (%)	32 (1%)	4 (5%)	2 (6%)	6 (13%)	2 (10%)	3 (15%)	49 (2%)

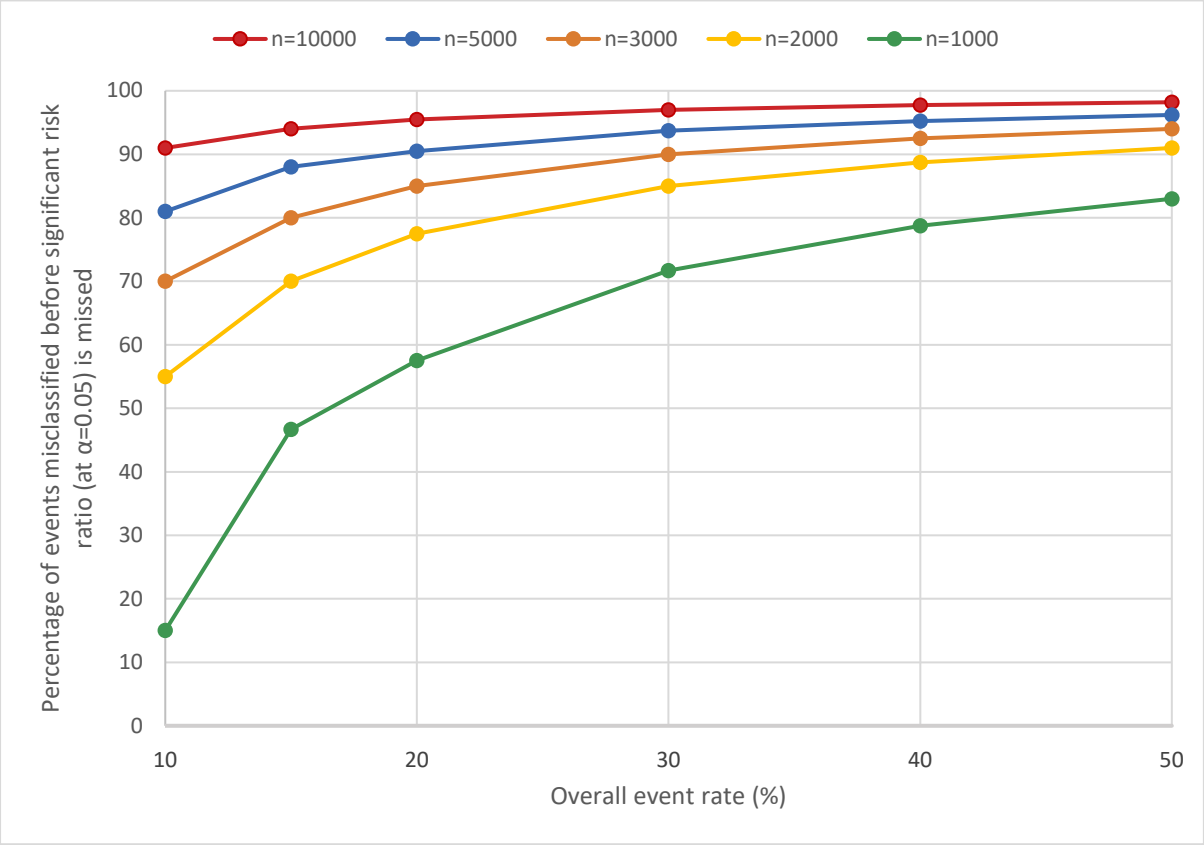
Mean crude agreement (SD) = 98.1% (0.24%), mean unweighted kappa (SD) = 0.85 (0.02), mean weighted kappa using linear weights (SD) = 0.87 (0.02). Mean crude agreement, unweighted and weighted kappa are from 1000 simulations (starting seed 2206). TIA refers to Transient Ischaemic Attack, mRS refers to modified Rankin Scale

Supplementary Table 3: Number and proportion of non-differentially misclassified events required such that treatment effect is no longer significant at 5% level

		Overall event rate					
Proportion of events: Treatment vs Control		**10%**	**15%**	**20%**	**30%**	**40%**	**50%**
N=10000	**60% vs 40%**	910/1000 (91%)	1410/2000 (94%)	1910/2000 (95.5%)	2910/3000 (97%)	3910/4000 (97.75%)	4910/5000 (98.2%)
	55% vs 45%	629/1000 (62.9%)	1129/1500 (75.27%)	1629/2000 (81.45%)	2629/3000 (87.63%)	3629/4000 (90.73%)	4629/5000 (92.58%)
	52.5% vs 47.5%	NA	169/1500 (11.27%)	680/2000 (34%)	1680/3000 (56%)	2680/4000 (67%)	3690/5000 (73.8%)
N=5000	**60% vs 40%**	405/500 (81%)	660/750 (88%)	905/1000 (90.5%)	1405/1500 (93.63%)	1905/2000 (95.25%)	2405/2500 (96.2%)
	55% vs 45%	149/500 (29.8%)	400/750 (53.33%)	649/1000 (64.9%)	1149/1500 (76.6%)	1649/2000 (82.45%)	2149/2500 (85.96%)
	52.5% vs 47.5%	NA	NA	NA	329/1500 (21.93%)	829/2000 (41.45%)	1329/2500 (53.16%)
N=3000	**60% vs 40%**	210/300 (70%)	360/450 (80%)	510/600 (85%)	810/900 (90%)	1110/1200 (92.5%)	1410/1500 (94%)
	55% vs 45%	NA	109/450 (24.22%)	260/600 (43%)	560/900 (62%)	860/1200 (71.63%)	1160/1500 (77.33%)
	52.5% vs 47.5%	NA	NA	NA	NA	200/1200 (17%)	499/1200 (41.6%)
N=2000	**60% vs 40%**	110/200 (55%)	210/300 (70%)	310/400 (77.5%)	510/600 (85%)	710/800 (88.75%)	910/1000 (91%)
	55% vs 45%	NA	NA	80/400 (20%)	280/600 (46.67%)	480/800 (60%)	680/1000 (68%)
	52.5% vs 47.5%	NA	NA	NA	NA	NA	129/1000 (12.9%)
N=1000	**60% vs 40%**	15/100 (15%)	70/150 (46.67%)	115/200 (57.5%)	215/300 (71.63%)	315/400 (78.75%)	415/500 (83%)
	55% vs 45%	NA	NA	NA	29/300 (9.67%)	129/400 (32.25%)	229/500 (45.8%)
	52.5% vs 47.5%	NA	NA	NA	NA	NA	NA

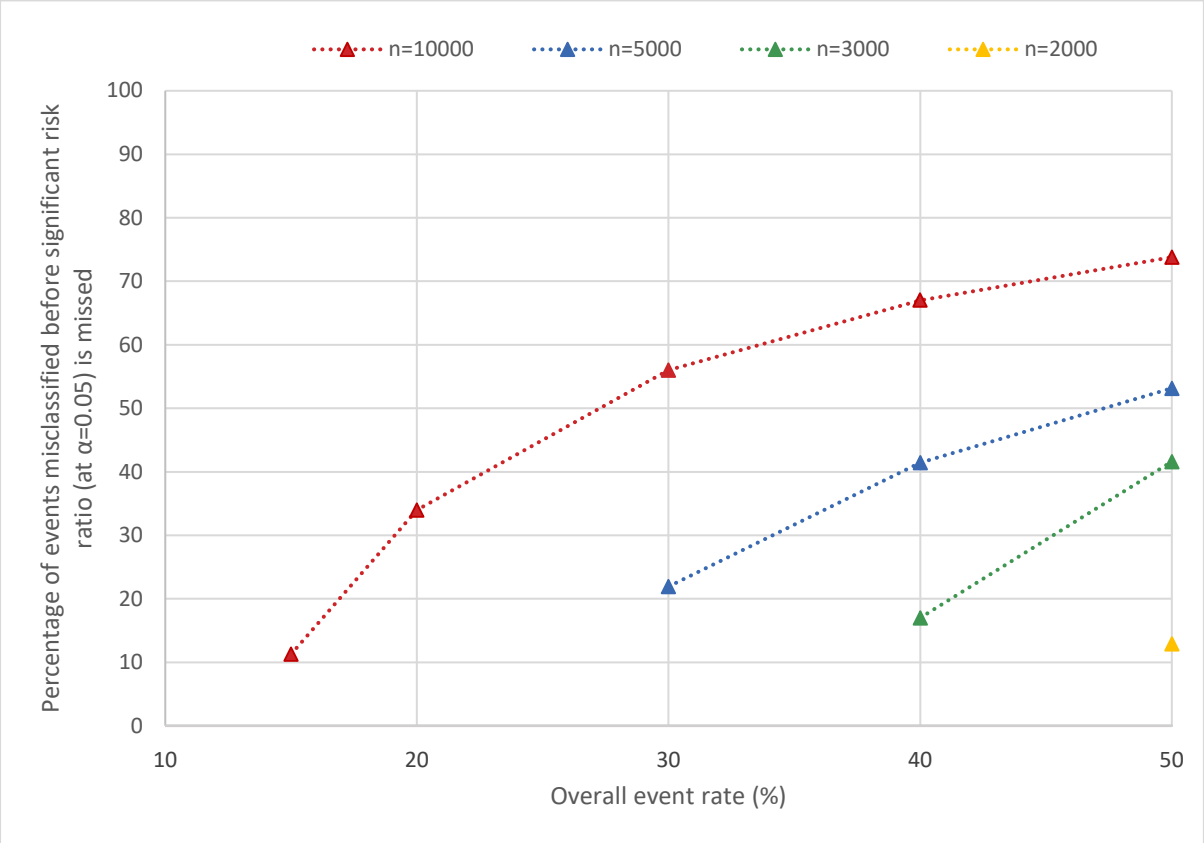
Data are number of events misclassified/total number of events (%)
Significant treatment effect is set at α=0.05 and is from a risk ratio
Proportion of events 60% vs 40% corresponds to a treatment effect of 0.67, a proportion of events 55% to 45% corresponds to a treatment effect of 0.82, and a proportion of events 52.5% to 47.5% corresponds to a treatment effect of 0.90. A treatment effect less than one indicates treatment is beneficial.
NA refers to scenarios where the initial treatment effect before misclassification was non-significant ($p>0.05$)

Supplemental figure 1: Amount of non-differential misclassification required such that treatment effect (relative risk=0.67) is no longer significant at 5% level for various sample sizes and overall event rates



n refers to hypothetical trial sample size

Supplemental figure 2: Amount of non-differential misclassification required such that treatment effect (relative risk=0.90) is no longer significant at 5% level for various sample sizes and overall event rates



Missing scenarios are due to the initial treatment effect before misclassification being non-significant (p>0.05). n refers to hypothetical trial sample size