Supplemental Material:

Supplementary Table 1: Summary of included trials

Trial name	Population	Intervention	Comparator	Primary outcome	Training of site-investigators
CABACS	Patients with high-grade carotid stenosis (≥80%) who required coronary artery bypass grafting (n=129).	Carotid endarterectomy and coronary artery bypass grafting (n=65)	Coronary artery bypass grafting (n=64)	Stroke or death from any cause	Yes
ENGAGE AF-TIMI 48	Patients with moderate-to-high-risk atrial fibrillation (n=21,105).	High-Dose Edoxaban (n=7035) or Low-Dose Edoxaban (n=7034)	Warfarin (n=7036)	Stroke or systolic embolism.	Not reported
ESPRIT	Patients with TIA or mild stroke in the past 6 months (n=2739).	Aspirin and dipyridamole (n=1363)	Aspirin alone (n=1376)	Non-fatal stroke, non-fatal MI, major bleeding complication or death from vascular cause.	Yes
FASTEST	Patients with TIA or stroke (n=291).	Electronic decision support tool (n=172)	Usual care (n=119)	Recurrent stroke	Yes
HAEST	Patients with acute ischaemic stroke and atrial fibrillation (n=449).	Dalteparin (n=224)	Aspirin (n=225)	Recurrent ischaemic stroke	Yes
ICSS	Patients with symptomatic carotid stenosis (n=1713)	Stenting (n=855)	Carotid endarterectomy (n=858)	Fatal or disabling stroke	Not reported
J-STARS	Patients with a history of non-cardioembolic ischaemic stroke and cholesterol level between 4.65 and 6.21 mmol/L (n=1578).	Pravastatin (n=793)	No statins (n=785)	Stroke or TIA	Not reported
NASCET	Patients with non-disabling stroke and carotid stenosis of 30-99% in the internal carotid artery. There were three populations mild (<50%, n=1368), moderate (50-69%, n=858) and severe (70-99%, n=659) stenosis.	Carotid endarterectomy. In addition, patients received medical care, including antiplatelet therapy. Mild (n=678), moderate (n=430), severe (n=328).	Medical care, including antiplatelet therapy. Mild (n=690), moderate (n=428), severe (n=331)	Fatal or non-fatal ipsilateral stroke	Yes
POINT	Patients with minor ischaemic stroke or high-risk TIA (n=4881).	Clopidogrel and aspirin (n=2432)	Aspirin alone (n=2449)	Ischaemic stroke, MI or death from ischaemic vascular event	Yes
PROGRESS	Patients with a history of stroke or TIA (n=6105)	Perindopril with the addition of a diuretic at the discretion of treating physician (n=3051)	Matching placebo (n=3054)	Fatal or non-fatal stroke	Yes

REVASCAT	Patients with acute ischaemic stroke who could be treated within 8 hours (n=206)	Medical therapy (including alteplase if eligible) and thrombectomy (n=103)	Medical therapy (including alteplase if eligible) (n=103)	Functional outcome at 90 days (mRS)	Yes
SOCRATES	Patients with nonsevere ischaemic stroke or high-risk TIA (n=13199).	Ticagrelor (n=6589)	Aspirin (n=6610)	Non-fatal stroke, non-fatal MI or death.	Yes
SPS3	Patients with MRI-defined symptomatic lacunar infarctions (n=3020).	Blood pressure target <130 mmHg (n=1501)	Blood pressure target 130-149 mmHg (n=1519)	Stroke	Yes
TARDIS	Patients with acute ischaemic stroke or TIA (n=3096).	Aspirin, clopidogrel and dipyridamole (n=1556)	Aspirin and dipyridamole or clopidogrel alone (n=1540)	Recurrent stroke and TIA	Yes
VITATOPS	Patients with stroke or TIA within the past 7 months (n=8164).	B vitamins (n=4089)	Matching placebo (n=4075)	Not-fatal stroke, non-fatal MI or death from vascular cause.	Not reported

TIA refers to Transient Ischaemic Attack, MI refers to myocardial infarction, mmol/L refers to millimoles per Litre, mRS refers to modified Rankin Scale, mmHg refers to millimetres of mercury

Supplementary Table 2: Risk of bias in included trials

Trial name	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Adjudication
CABACS	Sequence was generated as stratified blocks with randomly varying block size (Low risk)	Participants were allocated in a concealed way by web-based central preoperative randomisation before surgery (Low risk)	No blinding since this was an open trial but the outcome (stroke or death) was not likely to be influenced by lack of blinding (Low risk)	All primary outcome events were adjudicated by an independent blinded end point committee (Low risk)	Primary outcome data available for all participants in primary analysis (Low risk)	Protocol available and all outcomes reported in publications (Low risk)	Adjudicators reviewed events reported by unblinded site investigators (High risk).
ENGAGE AF-TIMI 48	Sequence was randomly generated with stratification for important prognostic factors (Low risk)	Participants were allocated via central, 24-hour, interactive, computerised response system (Low risk)	The subjects, investigators and staff involved in the treatment were unaware of treatment allocation (Low risk)	Staff involved in clinical evaluation were unaware of treatment allocation. In addition, an independnet clinical events committee adjudcated all efficacy endpoints in a blinded manner (Low risk)	Primary endpoint ascertained for 99.5% of the total 56,346 patient-years of potential follow-up (Low risk)	Protocol available and all outcomes reported in publications (Low risk)	Adjudicators reviewed suspected events reported by blinded site investigators as well as suspected events identified through reviewing source information and adverse event terms (Low risk).
ESPRIT	Sequence was randomly generated using computer software and stratified by hospital (Low risk)	Participants were allocated centrally by the Central Trial Coordination Centre (Low risk)	No blinding since this was an open study. However the outcome (stroke, MI, bleeding, vascular death) is unlikely to be influenced by the lack of blinding (Low risk)	Outcome cranial scans were audited by physicians who were blinded to treatment allocation (Low risk)	Primary outcome data available for 99.1% of randomised participants (Low risk)	Protocol available and all outcomes reported in publications (Low risk)	Adjudicators reviewed events reported by unblinded site investigators (High risk).
FASTEST	Sequence was randomly generated using computer software (Low risk)	General practices were allocated in clusters centrally (Low risk)	Blinding was not possible, but the outcome (stroke) was not likely to be influenced by a lack of blinding (Low risk)	All primary outcome events were adjudicated by a blinded neurologist (Low risk)	Primary outcome data available for all participants who met inclusion (Low risk)	Protocol available and all outcomes reported in publications (Low risk)	Adjudicators reviewed events reported by unblinded site investigators (High risk).
HAEST	Sequence was randomly generated using	Participants were allocated to sequential	Participants and personnel were blinded through use of	All primary outcome events were evaluated and	Primary outcome data available for all participants in	Protocol available and all outcomes	Adjudicators reviewed all events believed by blinded investigators to

	computer software (SAS, version 6.10) and was blocked with block size four (Low risk)	numbered packages containing either active drug and corresponding placebo (Low risk)	matching placebos (Low risk)	classified by a blinded independent endpoint committee (Low risk)	primary analysis (Low risk)	reported in publications (Low risk)	represent an endpoint (primary or secondary endpoint) (Medium risk).
ICSS	Sequence was randomly generated using computer software and stratified for a number of factors (Low risk)	Participants were allocated centrally and allocations were obtained by telephone or fax by staff not involved in other parts of the trial (Low risk)	Blinding was not possible, and the outcome (fatal or disabling stroke classified as mRS>3) could be influenced by a lack of blinding (High risk)	All primary outcome events were adjudicated by an independent endpoint committee that was unaware of treatment allocation (Low risk)	Primary outcome data available for all participants in primary analysis (Low risk)	Protocol available and all outcomes reported in publications (Low risk)	Adjudicators reviewed vascular events and functional status reported by unblinded site investigators (High risk).
J-STARS	Sequence was randomly generated using computer software (Low risk)	Participants were allocated centrally via a web-based registration system (Low risk)	Blinding was not possible, but the outcome (stroke or TIA) was unlikely to be influenced by a lack of blinding (Low risk)	All primary outcome events were adjudicated by the central event evaluation committee blind to treatment allocation (Low risk)	Primary outcome data available for all participants in the intention to treat analysis (Low risk)	Protocol available and all outcomes reported in publications (Low risk)	Adjudicators reviewed events reported by unblinded site investigators (High risk).
NASCET	Sequence was randomly generated using computer software and was stratified by trial centre (Low risk)	Participants were allocated centrally by the Data Management Centre (Low risk)	Blinding was not possible, but the outcome (stroke) is unlikely to be influenced by treatment allocation (Low risk)	All primary outcome events were adjudicated by blinded external adjudicators (Low risk)	Complete primary outcome data available for 99.7% of participants (Low risk)	Protocol available and all outcomes reported in publications (Low risk)	Adjudicators reviewed CT scans and details of participant's cerebrovascular history for all participants (Low risk).
POINT	Sequence was randomly generated using computer software with stratification according to trial site (Low risk)	Participants were allocated centrally using interactive web-based system (Low risk)	Participants and personnel were blinded through use of matching placebo (Low risk)	All primary outcome events were adjudicated by an independent clinical-event committee unaware of group assignments (Low risk)	Primary analysis undertaken on all randomised participants. 98% of participants were followed up for at least 7 days (Low risk)	Protocol available and all outcomes reported in publications (Low risk))	Adjudicators reviewed all suspected endpoints including those that did not meet strict definitions, identified by blinded site investigators (Low risk).
PROGRESS	Sequence was randomly generated using computer software (Low risk)	Participants were allocated centrally using a randomisation service accessed	Participants and personnel were blinded through use of matching placebos (Low risk)	An endpoint adjudication committee unaware of treatment allocation reviewed	Complete primary outcome data available for 99.9% of participants (Low risk)	Protocol available and all outcomes reported in publications (Low risk)	Adjudicators reviewed events reported by blinded site investigators (Medium risk).

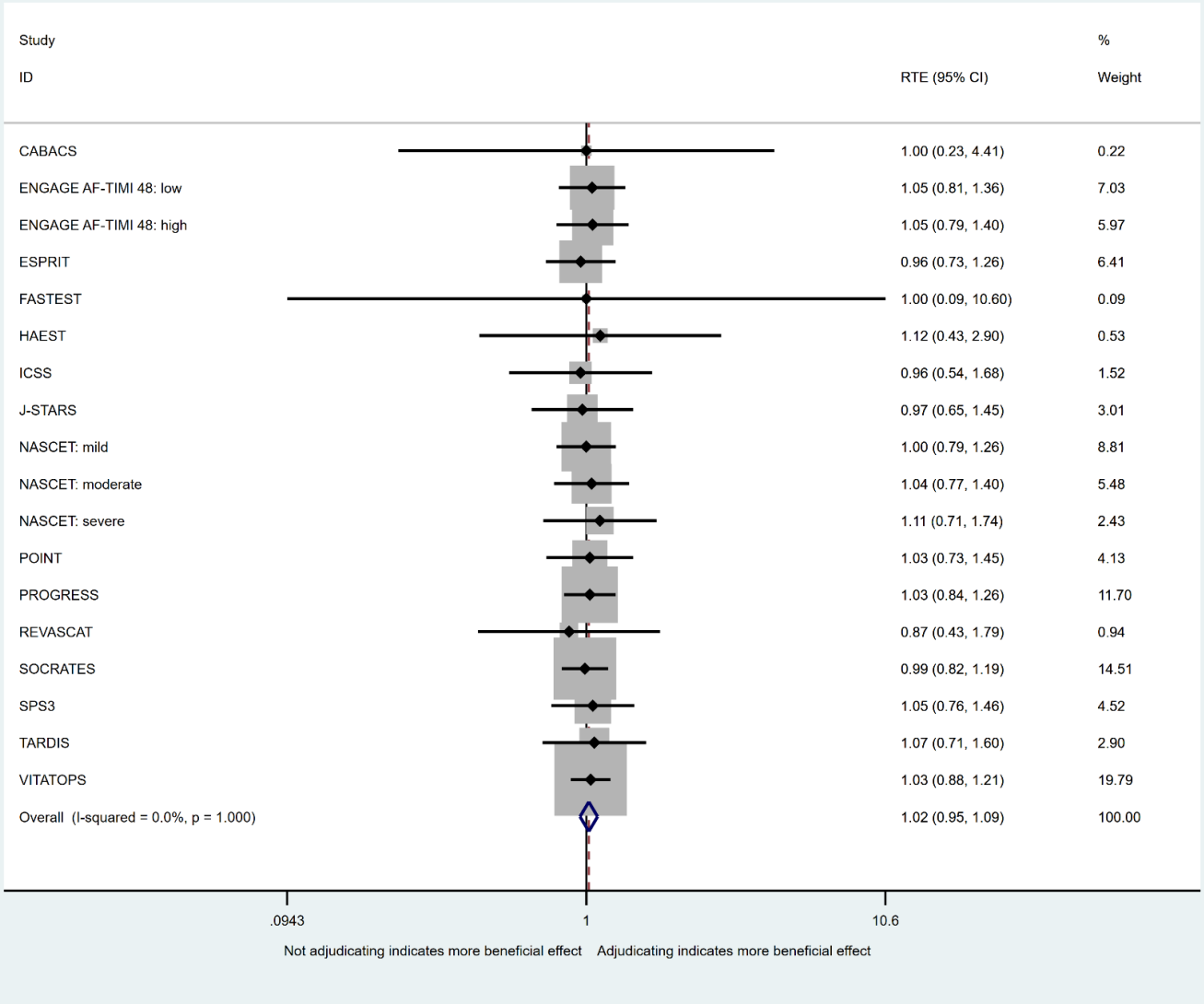
		by telephone or facsimile (Low risk)		all primary outcome events (Low risk)			
REVASCAT	Sequence was randomly generated using computer software using minimisation for age, stroke severity, therapeutic window and occlusion site (Low risk)	Participants were allocated centrally suing a web-based randomisation process (Low risk)	Participants and personnel were not blinded, as this was an open study. The outcome which was severity of disability could have been influenced by knowledge of randomisation (High risk)	All participants were adjudicated in a blinded manner (Low risk)	Complete primary outcome data was available for all participants (Low risk)	Protocol available and all outcomes reported in publications (Low risk)	All participants who reached the primary endpoint were adjudicated (Low risk).
SOCRATES	Sequence was randomly generated using computer software and generated in blocks (Low risk)	Participants were allocated using an interactive telephone and web-based system (Low risk)	Participants and personnel were blinded through use of matching placebos (Low risk	All primary outcome events were adjudicated by an independent clinical-event adjudication committee who were unaware of treatment assignment (Low risk)	All participants included in primary analysis, with 99.2% of participants in the study at the end-of-treatment visit (Low risk)	Protocol available and all outcomes reported in publications (Low risk)	Adjudicators reviewed all suspected endpoints including those that did not meet strict definitions, identified by blinded site investigators (Low risk).
SPS3	Sequence was randomly generated using computer software with a permuted block design with variable block size (Low risk)	Participants were allocated centrally by study coordinators using a web-based system (Low risk)	Participants and personnel were aware of treatment allocation (management of blood pressure) but the outcome (stroke) was unlikely to have been influenced by knowledge of this (Low risk)	All primary outcome events were adjudicated by a central adjudication committee that was unaware of treatment allocation (Low risk)	Primary outcome data available for all participants in primary analysis (Low risk)	Protocol available and all outcomes reported in publications (Low risk)	Adjudicators reviewed events reported by blinded site investigators (Medium risk).
TARDIS	Sequence was randomly generated using computer software with minimisation for prognostic factors which included a random element for 5% of	Participants were allocated centrally using a web-based system (Low risk)	Blinding was not possible as this was an open trial. The outcome (incidence and severity of stroke) could have been influenced by knowledge of treatment allocation (High risk)	All primary outcome events were validated and categorised by expert adjudicators who were masked to treatment assignment (Low risk)	Primary outcome data was available for 99.2% of participants (Low risk)	Protocol available and all outcomes reported in publications (Low risk)	Adjudicators reviewed events reported by blinded site investigators (Medium risk).

	participants (Low risk)						
VITATOPS	Sequence was generated using random permuted blocks stratified by hospital (Low risk)	Participants were allocated using a central 24-hour telephone service or telephone website (Low risk)	Participants and personnel were blinded through use of matching placebo (Low risk)	All primary outcome events were audited by a masked adjudication committee (Low risk)	7462 (91%) participants were followed up until the trial ended. Primary analysis based on all participants (Low risk)	Protocol available and all outcomes reported in publications (Low risk)	Adjudicators reviewed events reported by blinded site investigators (Medium risk).

mRS refers to modified Rankin Scale, TIA refers to Transient Ischaemic Attack

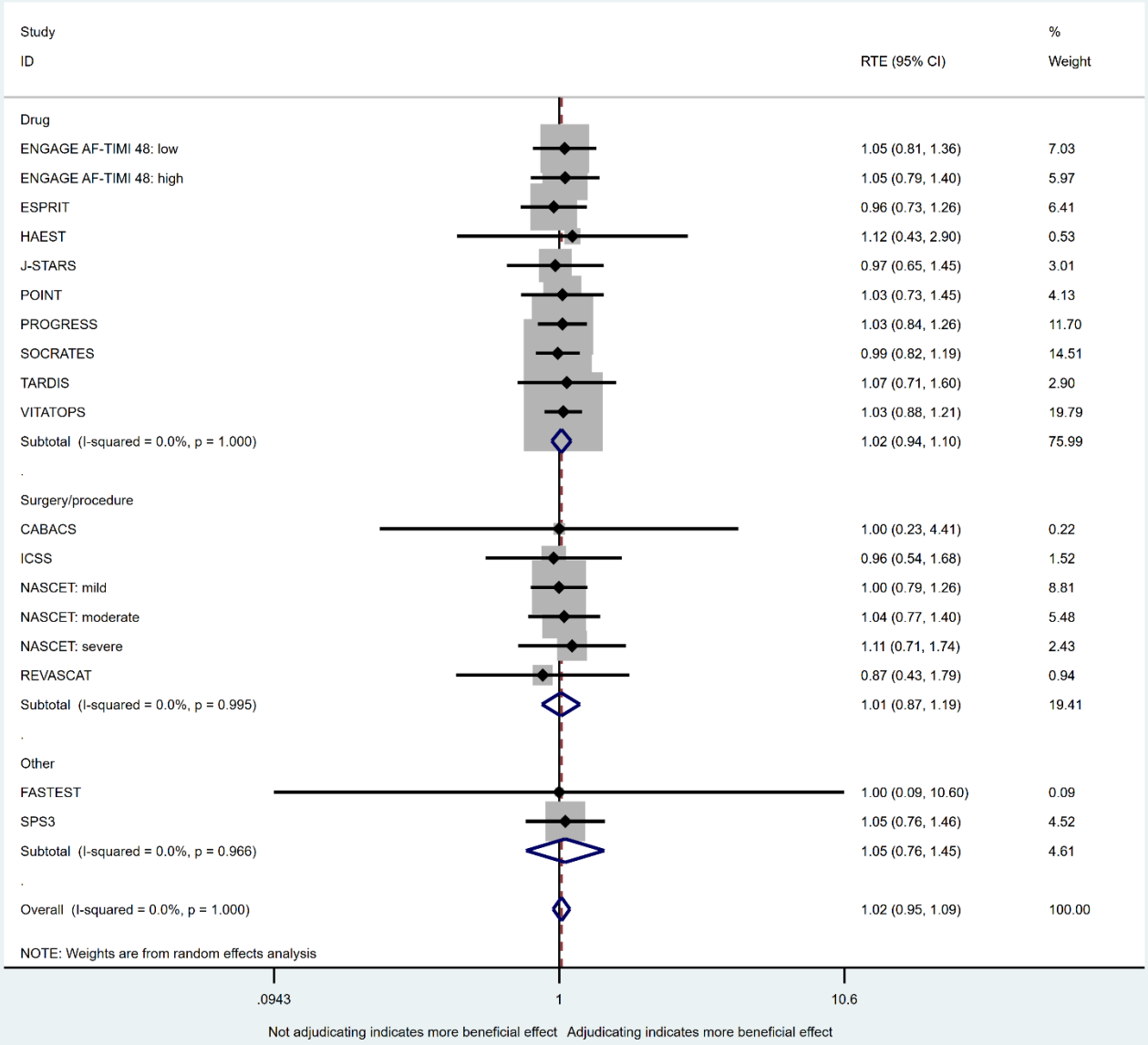
Supplemental Figures and Figure Legends:

Supplementary Figure 1: Meta-analysis of RTE, using a fixed-effect model



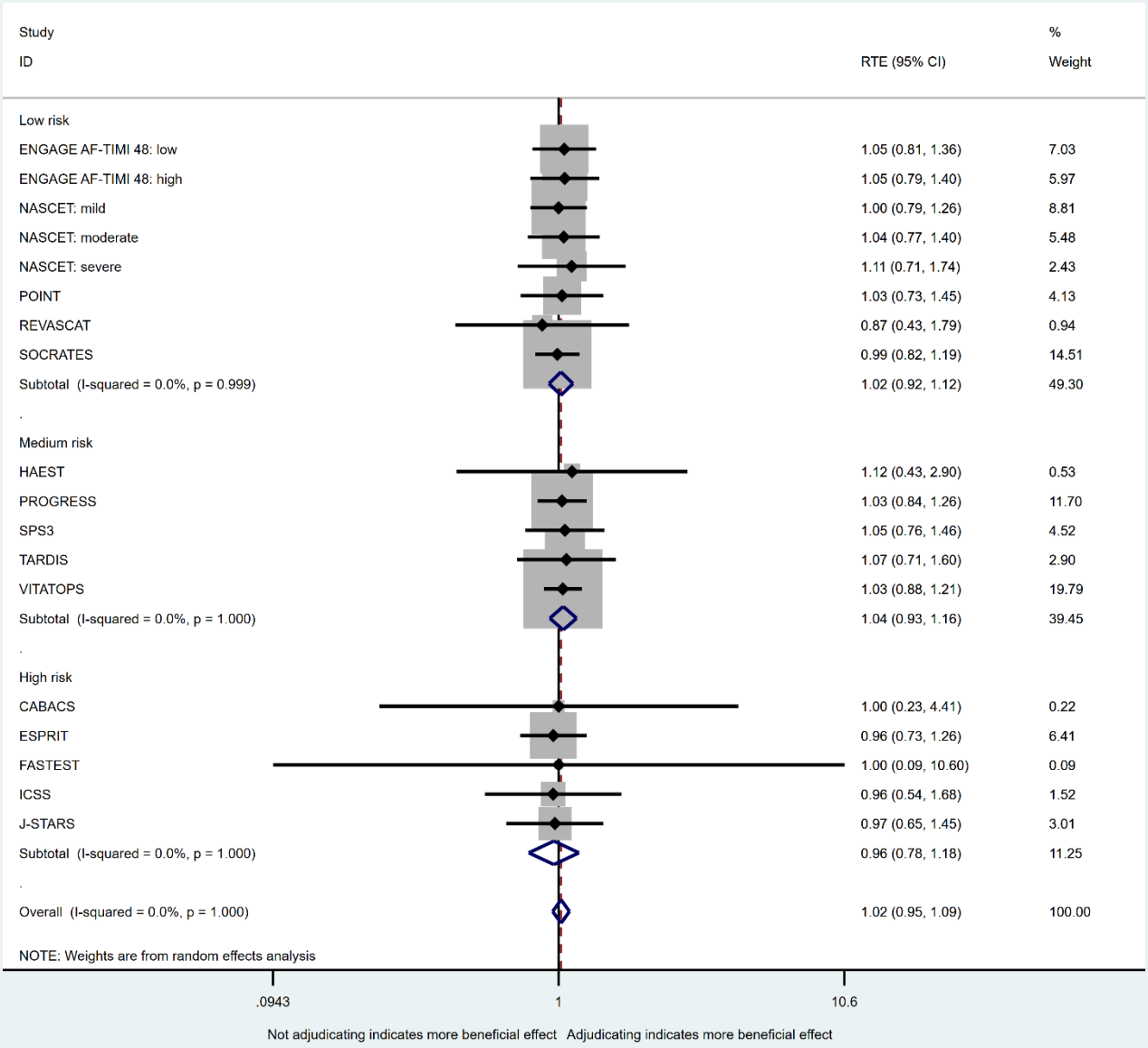
RTE refers to ratio of treatment effects

Supplementary Figure 2: Meta-analysis of RTE by intervention type, using a random effects model



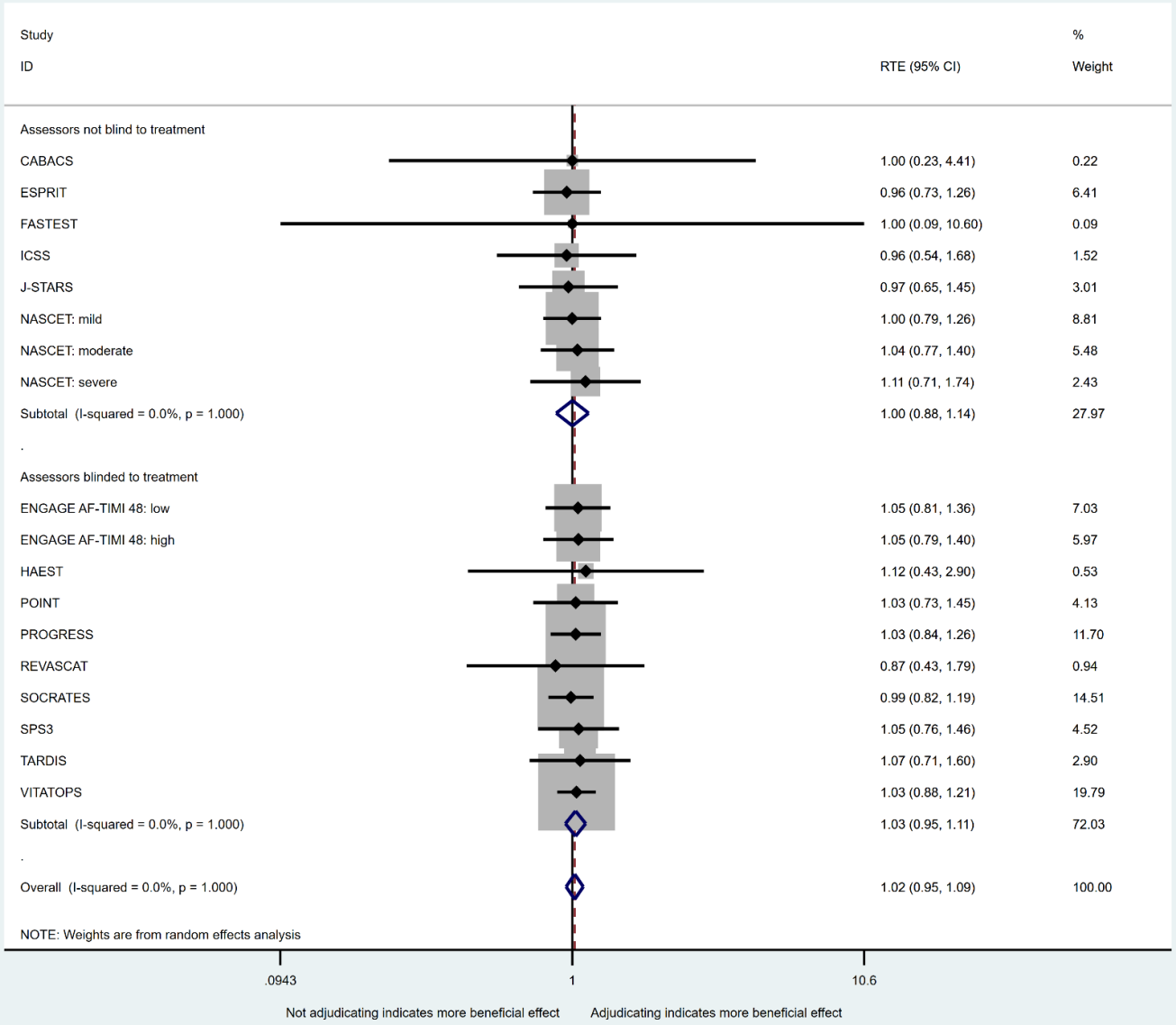
RTE refers to ratio of treatment effects

Supplementary Figure 3: Meta-analysis of RTE by adjudication risk of bias, using a random effects model



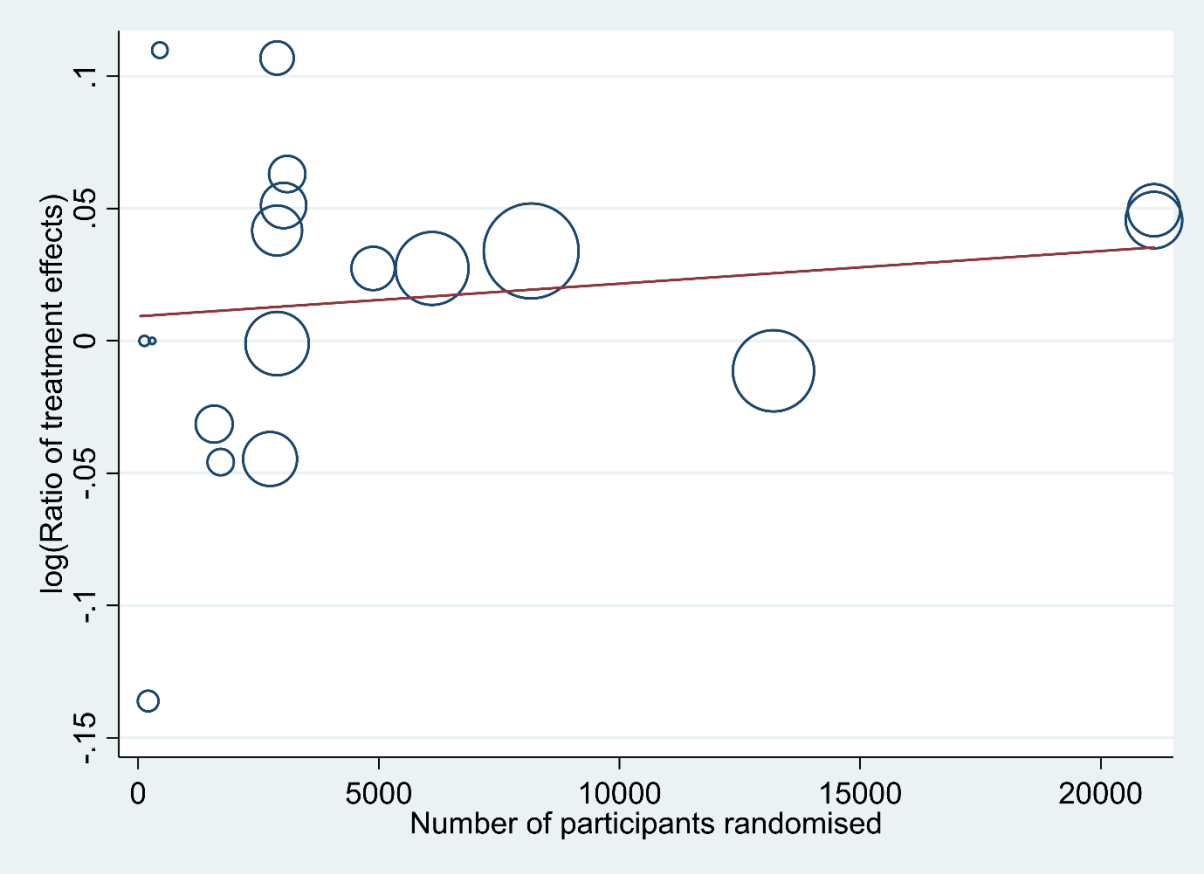
RTE refers to ratio of treatment effects

Supplementary Figure 4: Meta-analysis of RTE by blinding status of site investigators, using a random effects model



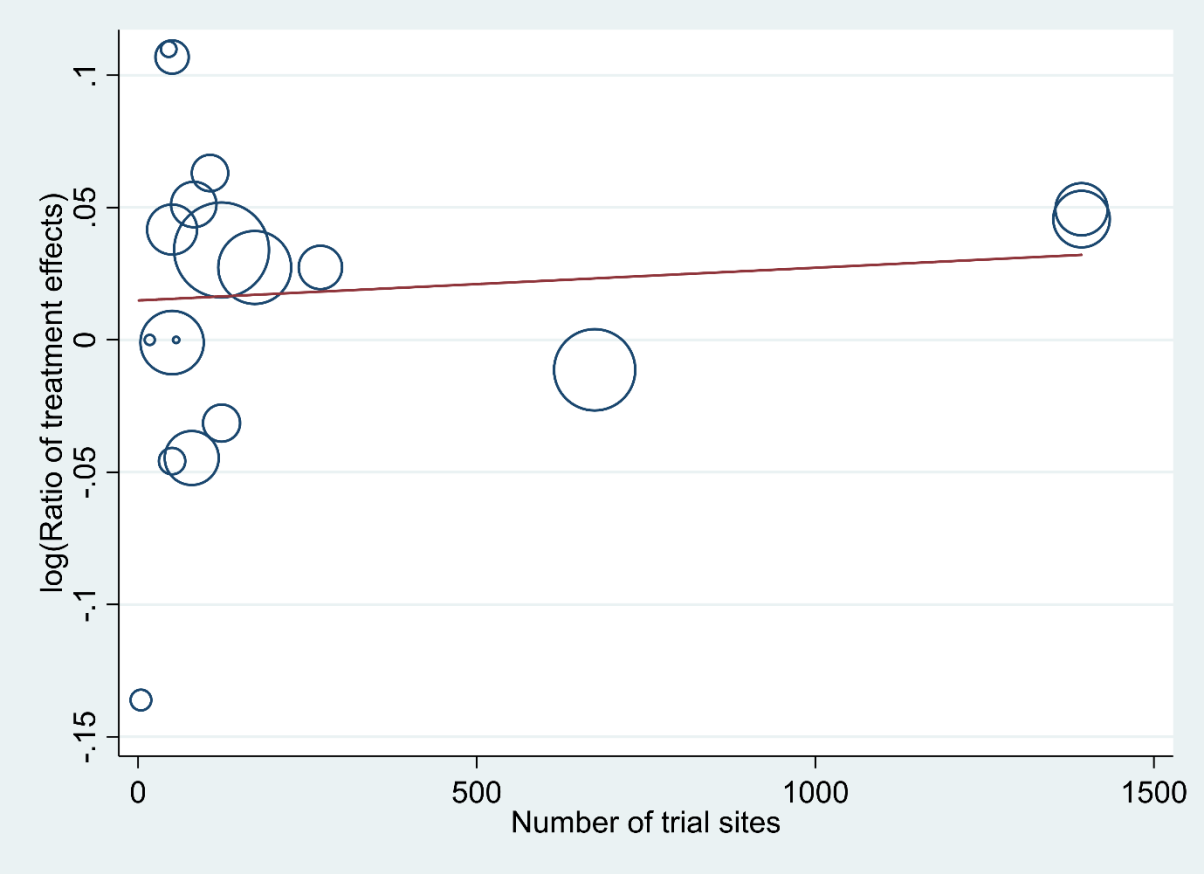
RTE refers to ratio of treatment effects

Supplementary Figure 5: Meta-regression with number of participants randomised fitted as a covariate



Number of comparisons included = 18, estimate for covariate = 1.00 (95% C.I:[1.00, 1.00], p=0.83)

Supplementary Figure 6: Meta-regression with number of trial sites fitted as a covariate



Number of comparisons included = 18, estimate for covariate = 1.00 (95% C.I:[1.00, 1.00], p=0.88)

Search Strategy (06 November 2018):

EMBASE (1669):

1. exp randomised controlled trial/
2. exp animal/ not human/
3. exp stroke/
4. ((adjudicat* or endpoint or outcome or review or classification or central or event)adj2(adjudicat* or committee or panel or review)).mp.
5. 1 not 2
6. 3 and 4 and 5

MEDLINE (249):

1. exp Randomized controlled trial/
2. exp animals/ not exp humans/
3. exp Stroke/
4. ((adjudicat* or endpoint or outcome or review or classification or central or event)adj2(adjudicat* or committee or panel or review)).mp.
5. 1 not 2
6. 3 and 4 and 5

PsycINFO (249):

1. exp *Clinical Trials/
2. exp *Drug Therapy/
3. exp *Evidenced Based Practice/
4. exp *Treatment Effectiveness Evaluation/
5. exp *cerebrovascular accidents/
6. ((adjudicat* or endpoint or outcome or review or classification or central or event)adj2(adjudicat* or committee or panel or review)).mp.
7. 1 or 2 or 3 or 4
8. 5 and 6 and 7

CENTRAL (2395):

"stroke" AND (adjudicat* OR "advisory committee" OR "outcome assessment" OR "endpoint committee" OR "endpoint review" OR "outcome committee" OR "outcome panel" OR "outcome review" OR "review committee" OR "review panel" OR "classification committee" OR " classification panel" OR "central committee" OR "central panel" OR "central review" OR "event committee" OR "event panel" OR “end point committee” OR “end-point committee”)

Web of Science (1477):

"stroke" AND (adjudicat* OR "advisory committee" OR "outcome assessment" OR "adjudication committee" OR "adjudication panel" OR "endpoint committee" OR "endpoint review" OR "endpoint adjudication" OR "outcome adjudication" OR "outcome committee" OR "outcome panel" OR "outcome review" OR "review committee" OR "review panel" OR "classification committee" OR " classification panel" OR "central adjudication" OR "central committee" OR "central panel" OR "central review" OR "event adjudication" OR "event committee" OR "event panel")

Google Scholar (300 (only first 300 selected)):

(“randomised” OR “randomized”) AND "stroke" AND ("adjudication" OR "outcome assessment" OR "event panel" OR "endpoint committee" OR "review committee" OR "central review” OR “event committee”)