Outcome assessment by central adjudicators versus site investigators in randomised stroke trials: A systematic review and meta-analysis

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Abstract:

Background and Purpose: In randomised stroke trials, central adjudication of a trial's primary outcome is regularly implemented. However, recent evidence questions the importance of central adjudication in randomised trials. The aim of this review was to compare outcomes assessed by central adjudicators with outcomes assessed by site investigators.

Methods: We included randomised stroke trials where the primary outcome had undergone assessment by site investigators and central adjudicators. We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, Web of Science, PsycINFO and Google Scholar for eligible studies. We extracted information about the adjudication process as well as the treatment effect for the primary outcome, assessed both by central adjudicators and by site investigators. We calculated the ratio of these treatment effects (RTE) so that an RTE > 1 indicated that central adjudication resulted in a more beneficial treatment effect than assessment by site investigator. A random-effects meta-analysis model was fitted to estimate a pooled effect.

Results: Fifteen trials including 69,560 participants were included. The primary outcomes included were stroke (8/15, 53%), a composite event including stroke (6/15, 40%) and functional outcome after stroke measured on the modified Rankin Scale (1/15, 7%). The majority of site investigators were blind to treatment allocation (9/15, 60%). On average, there was no difference in treatment effect estimates based on data from central adjudicators and site investigators (pooled RTE=1.02, 95% C.I: [0.95, 1.09]).

Conclusions: We found no evidence that central adjudication of the primary outcome in stroke trials had any impact on trial conclusions. This suggests that potential advantages of central adjudication may not outweigh cost and time disadvantages in stroke studies if the primary purpose of adjudication is to ensure validity of trial findings.

Introduction:

Central adjudication in randomised trials refers to the evaluation of outcome data by independent experts who are typically part of an event or outcome adjudication committee[1, 2]. Events and outcomes can alternatively be assessed by local site investigators, and central adjudication is frequently seen as a marker of clinical trial quality as it is believed to ensure validity of trial results[3], such that regulatory authorities have specified the importance of adjudication in guidelines[4, 5]. The adjudication process is thought to improve the precision of treatment estimates by reducing random or systematic errors[6, 7]. Furthermore, in open-label studies, adjudication has the potential to limit detection bias as adjudicators are unaware of treatment allocation[8].

Adjudication is regularly implemented in cardiovascular trials[9], but there is inconsistent evidence as to the effect of adjudication on trial endpoints in this clinical setting[1, 2, 7, 10-15]. Central adjudication is potentially a costly and timely process[6, 10], and, given that many trials are publicly funded, it is important to assess adjudication to ensure that trials have efficient design, conduct and analysis[16], as well as sufficient but not excessive regulation and management[17]. A Cochrane review[18] found no evidence that adjudication of subjective events in randomised trials had any impact on treatment estimates, but suggested that adjudication might have most effect on outcomes when site investigators are not blinded to treatment allocation.

In stroke medicine, secondary analysis of trial data suggests that adjudication makes no meaningful difference to the endpoints of stroke[10] or functional outcome[19]. Adjudication of serious adverse events and stroke type in an acute stroke trial showed that adjudication did not alter trial conclusions[20, 21]; in contrast, a simulation study suggested that adjudicating the modified Rankin scale (mRS) in acute stroke trials could lead to sample size reductions of up to 20%[22].

The aim of this review was to investigate the effects on the primary results of stroke trials when using outcomes assessed by central adjudicators compared with outcomes assessed by site investigators. In addition, we aimed to describe which type(s) of stroke trials have adjudicated outcomes, what outcomes are adjudicated and how adjudication has been conducted.

Methods:

This systematic review and meta-analysis was performed following the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement. The review protocol can be found at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=56731. Supporting, but not individual patient, data are available from the corresponding author on reasonable request upon receipt of a data sharing and use agreement.

Eligibility Criteria:

Studies were eligible for inclusion if they (1) described a randomised trial; (2) described a stroke trial, where the participants were either being treated for stroke, or being given an intervention to prevent stroke; and (3) the primary outcome had undergone assessment by both site investigators and central adjudicators, with the trial providing data to calculate a treatment effect for the primary outcome assessed by both central adjudicators and site investigators separately. 'Site investigator' is a global term describing the persons involved in the trial who assess outcome(s) at each research site where study participants are recruited and treated. 'Adjudicator' refers to one or more assessors, independent from site investigators, who use information collected in the trial to assess the same outcome.

Outcomes collected:

The primary outcome of each trial was included in this review. If the stroke trial had more than two trial arms then all comparisons were included, but for factorial trials only one comparison was selected. We accounted for the correlation between comparisons that used the same control group by calculating an adjusted weight for the trial based on this additional correlation. Continuous, binary and categorical (ordinal and nominal) outcomes were eligible, as were subjective and objective outcomes.

Search Strategy:

We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, PsycINFO and Google Scholar for relevant articles (searches from database inception until 6th November 2018, see Supplemental material). Only the first 300 articles from Google Scholar were screened, which is the amount recommended by Haddaway et al.[23] to find sufficient grey literature. There were no restrictions on the year of publication. Articles not written in English were recorded but excluded.

Selection of Studies:

Duplicate references were identified, recorded and then discarded. One review author (PJG) screened all titles and abstracts in the initial screening. A second review author (AAM) screened the title and abstract of a random sample of 100 records to check this process. If it was unclear from the title and abstract whether the record was eligible then the full text was sought. If the article clearly described a secondary analysis of a trial, then the full-text records were only obtained if the record mentioned adjudication as well as satisfying eligibility criteria 1 and 2.

Full text reports were acquired for all records where potential eligibility was unclear. Thus, studies could have multiple records (e.g. main results and protocol paper). In the full text screening, studies had to satisfy all eligibility criteria to be included in the review. Studies were assessed for inclusion by one review author (PJG), with another review author (AAM) checking the process by assessing a total of 50 random full texts.

Data Extraction:

Data from eligible studies were extracted independently by two authors (PJG, EP) using a piloted data extraction form. Disagreements were resolved by discussion between both review authors. If agreement could not be reached then one further review author (AAM) assessed the study, with the majority decision taken. We recorded whether the central adjudicators and site investigators were blind to treatment allocation, the number and profession of adjudicators, the information that was provided to the adjudicators, the process for adjudication including decision making and how disagreements between adjudicators were dealt with.

It was anticipated that outcomes assessed by site investigators would not be reported in trial publications. Therefore, if essential information was not reported, we emailed the contact author and requested unreported data[24].

Assessment of risk of bias:

For each included study, we used the Cochrane risk of bias tool[25] to assess study quality. Additionally, we assessed risk of bias associated with the process of selecting cases for adjudication, and we have termed this “adjudication risk of bias”. If central adjudicators only assess cases identified by site investigators then some bias may remain, particularly if site investigators are not blind to

treatment allocation and have a biased view of the relative effectiveness of the treatments being compared. We created four categories for adjudication risk of bias: (1) Only cases identified by site investigators not blind to treatment allocation were selected for adjudication (High risk of bias); (2) Only cases identified by site investigators blind to treatment allocation were selected for adjudication (Medium risk of bias); (3) Either all participants, or all suspected cases (e.g. using computer algorithm to identify possible cases) were selected for adjudication (Low risk of bias); (4) It is not clear how cases were selected for adjudication (Unclear risk of bias).

Statistical Analysis:

Continuous variables were summarised with mean and standard deviation, or median and interquartile range. Categorical variables were described with frequency counts and percentages. Mann-Whitney U tests, Chi-square tests and Fisher exact tests were used to assess comparability between included and potentially eligible but excluded studies.

To compare outcome assessment by central adjudicators and site investigators we calculated the ratio of treatment effects (RTE) for each trial. The RTE was determined as the treatment effect estimate using outcomes assessed by site investigators to the treatment effect estimate using outcomes assessed by central adjudicators. An RTE > 1 indicated that central adjudication resulted in a more beneficial treatment effect. Data were pooled, if appropriate, in a meta-analysis using a DerSimonian and Laird random-effects model.

To establish whether central adjudication led to a change in the number of events reported, irrespective of the RTE, we compared the number of events reported by site investigators to the number reported after central adjudication for each trial. An odds ratio (OR) > 1 indicates that central adjudication led to more events reported. For trials that used the ordinal mRS, we dichotomised so that a score of 3 and above indicated an event. As before, data were pooled in a meta-analysis using a random-effects model.

The I^2-statistic was used to quantify the level of heterogeneity between studies. Subgroup analyses and meta-regression were used to investigate heterogeneity. We tested the interaction between the RTE and the following: (1) Adjudication risk of bias (high risk/medium risk/low risk/unclear risk); (2) Blinding status of site investigators (blind to allocation/not blind to allocation); (3) Type of intervention (drug/surgery/other); (4) Sample size of trial (continuous); (5) Number of sites (continuous). A

sensitivity analysis for the meta-analysis of RTEs was carried out using a fixed-effect model. All analyses were performed in Stata version 15.1 or later.

Results:

Search Results:

Database searches identified 6339 records and yielded 15 trials of 69,560 participants that were eligible for inclusion[26-40] (Figure 1, see Supplementary material, Supplementary Table 1). An additional 74 trials were potentially eligible, but did not report outcomes assessed by site investigators.

Characteristics of the potentially eligible trials:

Table 1 shows the characteristics of all 15 included trials and the 74 potentially eligible studies that were excluded due to insufficient outcome data. The majority of included trials published their main results after 2010, were parallel group, secondary prevention, multicentre and compared two randomised groups. A common primary outcome for the included trials was stroke, or a composite event that included stroke (14 trials, 93%); site investigators were more likely to have assessed the primary outcome blind to treatment allocation. Studies that were potentially eligible but not included due to insufficient essential information were similar, but tended to be from older publications, were more likely to be primary prevention trials, had recruited fewer participants, used fewer trial sites and were less likely to have occurrence of stroke as the primary outcome.

Characteristics of central adjudication in included trials:

For all included trials, central adjudicators were blinded to treatment allocation (Table 2). Blinding of central adjudicators to outcome assessment made by site investigators was either not done or not reported in 9 of the 15 trials. The number of adjudicators involved in each trial ranged from 2 to 28, and in over half the studies multiple adjudicators assessed each event. Disagreements between adjudicators were dealt with in a variety of ways, with use of an additional blinded adjudication the most common.

Risk of bias:

Adjudicators commonly assessed only cases reported by site investigators, but for all ten trials where this occurred half the site investigators were not blind to treatment allocation (see Supplemental material, Supplementary Table 2). In total, five trials were assessed as low adjudication risk of bias. All studies were high quality according to the Cochrane risk of bias tool (see Supplemental material, Supplementary Table 2).

Impact of central adjudication on primary treatment effect size:

The results of the primary analysis for all included trials using both outcome assessment by site investigators and central adjudicators are displayed in Figure 2. The meta-analysis of RTEs showed no evidence that adjudication altered estimates of treatment effect size when compared to assessment by site investigators (pooled RTE=1.02, 95% C.I: [0.95, 1.09], Figure 3). We found no evidence of any interaction between impact of adjudication on treatment effect estimates and blinding of site investigators to the trial allocation, number of participants randomised, number of trial sites, type of intervention or adjudication risk of bias (see Supplemental material, Supplementary Figures 2-6). The sensitivity analysis was consistent with the random-effects pooled meta-analysis result (see Supplemental material, Supplementary Figure 1).

Impact of central adjudication on the number of events reported:

We found evidence that central adjudication reduced the number of reported events (pooled OR=0.91, 95% C.I: [0.88, 0.95], Figure 4) when compared with the number of events reported by site investigators.

Discussion:

In this meta-analysis of 15 stroke trials, including nearly 70,000 patients, we found no evidence that central adjudication of the primary outcome had any substantive impact on the primary trial result. Exploration of a number of pre-specified subgroups, including trial size, intervention type and blinding status of site investigators supported this finding. However, we found evidence that adjudicating resulted in fewer events reported for the primary outcome.

Our findings are consistent with two previous reviews. One included ten cardiovascular trials[7] and similarly found no effect of adjudication versus site reported events (ratio of odds ratios, ROR=1.00, 95% C.I: [0.97, 1.02]). Another was a Cochrane review[18] of subjective binary outcomes, across all

clinical areas, that found adjudication in 47 trials to have no impact on treatment effect estimates (ROR=1.00, 95% C.I: [0.97, 1.04]). The Cochrane review did suggest, however, that adjudication might be important when site investigators are not blinded to treatment allocation. This could be due to knowledge of the allocation influencing decisions about the primary outcome[41, 42], but we found no evidence of this in our review. This could be because the outcomes in the trials included in our review (and thus commonly adjudicated in stroke trials) are predominantly objective. Therefore, if the primary focus of adjudication is to ensure validity of trial results, this process may be redundant for trials with objective outcomes.

In addition, we found that site investigators over-reported the number of events for the primary outcome, which is consistent with a review of ten cardiovascular trials[7] that showed that adjudication reduced the number of reported events. However, this reduction of events had no effect on the primary analysis in both ours and the previous review, indicating that site investigators over-report events in a similar proportion in both treatment arms. Whilst this non-differential misclassification by site investigators will not affect the primary trial analysis, it could affect the comparison of the rate of the primary outcome relative to other events (e.g. bleeding with a new anticoagulant). This would influence the risk-benefit calculation of bleeding versus prevention of the primary event, which is important for both clinicians and regulators. However, it is important to note that the process of adjudication in many trials does not enable central adjudication to add events as adjudicators only assess events reported by site investigators. Thus, the extent that sites over-report events may not be as high as we found. Additionally, there may be other reasons to adjudicate in randomised trials, which can have benefits that are more difficult to quantify. Central adjudication could identify poorly performing sites or even act as a policing effect that strengthens local assessment as investigators assess outcomes that are to be adjudicated more thoroughly.

Before the inclusion of central adjudication in a clinical trial, the costs should also be considered. In one cardiovascular trial[43], the total cost of the adjudication process was estimated at $125,000 or $72 per adjudicated case. If regulators and academic reviewers continue to advocate adjudication for the purpose of ensuring validity of results, then trialists will have no choice but to include potentially redundant adjudication committees, which in turn will lead to excessive research waste[16, 17, 44]. In this review we have not attempted to estimate the cost of adjudication, but this appears to be the next challenge to establish the role of adjudication in clinical trials. If the cost can be accurately predicted,

then trialists can decide during the study design stage of a trial what they (and the funder and their reviewers) will be prepared to fund for adjudication and its potential, unmeasurable benefit.

One limitation of our review is that whilst we identified a total of 89 trials that were potentially eligible, we only managed to receive data from 15 of these, even after three reminders[24]. A large proportion of studies that did not provide data mentioned that the unadjudicated data were not available, and it is possible that our review may have found different results had more trials provided data. However, the characteristics of the excluded studies were similar to those that were included, and the individual results from all 15 included trials agreed with the overall pooled estimate. Another limitation of our small sample size is that the included studies are high quality trials in respect to the usual components of risk of bias, and higher quality studies could have less need for adjudication than lower quality trials. Furthermore, our review largely included prevention stroke trials and studies with binary primary outcomes. A larger sample of trials that had greater variation in quality, type and outcome could potentially have different findings. In our protocol, we stated that we would investigate the impact of adjudication on RTE by subjectivity of the outcome, but we did not undertake this analysis. This was because all the included outcomes are common in stroke trials and are sufficiently objective to change clinical practice.

Of further interest, would be to identify the number of events that need to be misclassified before the RTE differs from one. This would give an estimate for the magnitude of disagreement between central adjudicators and site investigators before central adjudication would alter the treatment effect estimate. In addition, an RTE close to one does not rule out the possibility of missing real treatment effects if central adjudication truly is the gold standard and is not implemented. For borderline cases, even a small amount of misclassification could give this unwelcome situation. However, understanding which clinical trials are at greatest risk of this is challenging, due to it relying on trialists knowing treatment efficacy at the design stage of their trial. This research is out of the scope of this study and warrants simulation.

In summary, this review found no evidence that central adjudication of the primary outcome in stroke trials had any impact on estimated treatment effect size. However, central adjudication did control non-differential misclassification and limit over-reporting of events by site investigators. If the primary purpose of central adjudication is to ensure validity of trial conclusions, then these results suggest that

the potential advantages of central adjudication may not outweigh cost and time disadvantages in stroke studies.

Collaborative group:

AOST Collaborative group: PJ Godolphin, PM Bath, L Duley, AA Montgomery (University of Nottingham); E Patsko (University of Leicester); C Weimar, SC Knipp (CABACS, 129 participants); RP Giugliano, (ENGAGE AF-TIMI 48, 21105 participants); A Algra, JP Greving (ESPRIT, 2739 participants); A Ranta (FASTEST, 291 participants); E Berge, PM Sandset (HAEST, 449 participants); MM Brown, LH Bonati, J Gregson (ICSS, 1713 participants); N Hosomi, Y Nagai, M Matsumoto (J-STARS, 1578 participants); HJM Barnett, AJ Fox, M Eliasziw (NASCET, 2885 participants); M Farrant, JD Easton, JJ Elm (POINT, 4881 participants); J Chalmers, B Neal, H Arima (PROGRESS, 6105 participants); J Serena, A Dávalos (REVASCAT, 206 participants); SC Johnston, P Amarenco, S Evans (SOCRATES, 13199 participants); PM Bath, N Sprigg, R Dineen (TARDIS, 3096 participants); GJ Hankey, JW Eikelboom, C Chen (VITATOPS, 8164 participants).

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PJG, AAM and PMB conceived the study; PJG, AAM and PMB applied for funding; PJG wrote the study protocol; PMB, CW, RPG, AA, AR, EB, MMB, JG, NH, ME, MF, JJE, AD, SCJ and GJH provided the data for the study; PJG and EP collected the data; PJG analysed the data; All authors interpreted the data; PJG wrote the first draft of the manuscript; all authors commented critically on the manuscript for important intellectual content; All authors read and approved the final manuscript.

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Disclosures:

None

References:

1. Mahaffey, K.W., et al., *Disagreements between central clinical events committee and site investigator assessments of myocardial infarction endpoints in an international clinical trial: review of the PURSUIT study.* Current Controlled Trials in Cardiovascular Medicine, 2001. **2**(4): p. 187-194.
2. Hata, J., et al., *Effects of the Endpoint Adjudication Process on the Results of a Randomised Controlled Trial: The ADVANCE Trial.* PLoS ONE, 2013. **8**(2): p. e55807.
3. Kahan, B.C., B. Feagan, and V. Jairath, *A comparison of approaches for adjudicating outcomes in clinical trials.* Trials, 2017. **18**(1): p. 266.
4. European Medicines Agency, *Committee for Medicinal Products for Human Use: Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus*. 2012.
5. Food and Drug Administration, *Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees*. 2006.
6. Granger, C.B., et al., *Do we need to adjudicate major clinical events?* Clin Trials, 2008. **5**(1): p. 56-60.
7. Pogue, J., S.D. Walter, and S. Yusuf, *Evaluating the benefit of event adjudication of cardiovascular outcomes in large simple RCTs.* Clin Trials, 2009. **6**(3): p. 239-51.
8. Walter, S.D., et al., *Outcome assessment for clinical trials: how many adjudicators do we need? Canadian Lung Oncology Group.* Control Clin Trials, 1997. **18**(1): p. 27-42.
9. Stuck, A.K., et al., *Adjudication-related processes are underreported and lack standardization in clinical trials of venous thromboembolism: a systematic review.* J Clin Epidemiol, 2014. **67**(3): p. 278-84.
10. Ninomiya, T., et al., *Effects of the end point adjudication process on the results of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS).* Stroke, 2009. **40**(6): p. 2111-5.
11. Mahaffey, K.W., et al., *Systematic adjudication of myocardial infarction end-points in an international clinical trial.* Curr Control Trials Cardiovasc Med, 2001. **2**(4): p. 180-186.
12. Mahaffey, K.W., et al., *Ticagrelor effects on myocardial infarction and the impact of event adjudication in the PLATO (Platelet Inhibition and Patient Outcomes) trial.* J Am Coll Cardiol, 2014. **63**(15): p. 1493-9.
13. Mahaffey, K.W., et al., *Strategic lessons from the clinical event classification process for the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial.* Contemp Clin Trials, 2011. **32**(2): p. 178-87.
14. Petersen, J.L., et al., *Comparing classifications of death in the Mode Selection Trial: agreement and disagreement among site investigators and a clinical events committee.* Contemp Clin Trials, 2006. **27**(3): p. 260-8.
15. Sepehrvand, N., et al., *Alignment of site versus adjudication committee-based diagnosis with patient outcomes: Insights from the Providing Rapid Out of Hospital Acute Cardiovascular Treatment 3 trial.* Clin Trials, 2016. **13**(2): p. 140-8.
16. Ioannidis, J.P., et al., *Increasing value and reducing waste in research design, conduct, and analysis.* Lancet, 2014. **383**(9912): p. 166-75.
17. Al-Shahi Salman, R., et al., *Increasing value and reducing waste in biomedical research regulation and management.* Lancet, 2014. **383**(9912): p. 176-85.
18. Ndounga Diakou, L.A., et al., *Comparison of central adjudication of outcomes and onsite outcome assessment on treatment effect estimates.* Cochrane Database of Systematic Reviews, 2016(3).

19. Lopez-Cancio, E., et al., *Phone and Video-Based Modalities of Central Blinded Adjudication of Modified Rankin Scores in an Endovascular Stroke Trial.* Stroke, 2015. **46**(12): p. 3405-10.
20. Godolphin, P.J., et al., *Central adjudication of serious adverse events did not affect trial's safety results: Data from the Efficacy of Nitric Oxide in Stroke (ENOS) trial.* PLoS One, 2018. **13**(11): p. e0208142.
21. Godolphin, P.J., et al., *Central masked adjudication of stroke diagnosis at trial entry offered no advantage over diagnosis by local clinicians: Secondary analysis and simulation.* Contemporary Clinical Trials Communications, 2018. **12**: p. 176-181.
22. McArthur, K.S., et al., *Improving the efficiency of stroke trials: feasibility and efficacy of group adjudication of functional end points.* Stroke, 2013. **44**(12): p. 3422-8.
23. Haddaway, N.R., et al., *The Role of Google Scholar in Evidence Reviews and Its Applicability to Grey Literature Searching.* PLOS ONE, 2015. **10**(9): p. e0138237.
24. Godolphin, P.J., P.M. Bath, and A.A. Montgomery, *Short email with attachment versus long email without attachment when contacting authors to request unpublished data for a systematic review: a nested randomised trial.* BMJ Open, 2018.
25. Higgins, J. and S. Green, *Chapter 8: Assessing risk of bias in included studies. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011].* The Cochrane Collaboration, 2011.
26. Barnett, H.J.M., et al., *Benefit of Carotid Endarterectomy in Patients with Symptomatic Moderate or Severe Stenosis.* New England Journal of Medicine, 1998. **339**(20): p. 1415-1425.
27. *B vitamins in patients with recent transient ischaemic attack or stroke in the VITAmins TO Prevent Stroke (VITATOPS) trial: a randomised, double-blind, parallel, placebo-controlled trial.* Lancet Neurol, 2010. **9**(9): p. 855-65.
28. ESPRIT, et al., *Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial.* Lancet, 2006. **367**(9523): p. 1665-73.
29. *Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack.* Lancet, 2001. **358**(9287): p. 1033-41.
30. Bath, P.M., et al., *Antiplatelet therapy with aspirin, clopidogrel, and dipyridamole versus clopidogrel alone or aspirin and dipyridamole in patients with acute cerebral ischaemia (TARDIS): a randomised, open-label, phase 3 superiority trial.* The Lancet, 2018. **391**(10123): p. 850-859.
31. *Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial.* The Lancet, 2013. **382**(9891): p. 507-515.
32. Berge, E., et al., *Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. HAEST Study Group. Heparin in Acute Embolic Stroke Trial.* Lancet, 2000. **355**(9211): p. 1205-10.
33. Bonati, L.H., et al., *Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial.* The Lancet, 2015. **385**(9967): p. 529-538.
34. Giugliano, R.P., et al., *Edoxaban versus Warfarin in Patients with Atrial Fibrillation.* New England Journal of Medicine, 2013. **369**(22): p. 2093-2104.
35. Hosomi, N., et al., *The Japan Statin Treatment Against Recurrent Stroke (J-STARS): A Multicenter, Randomized, Open-label, Parallel-group Study.* EBioMedicine, 2015. **2**(9): p. 1071-8.
36. Johnston, S.C., et al., *Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack.* New England Journal of Medicine, 2016. **375**(1): p. 35-43.
37. Jovin, T.G., et al., *Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke.* New England Journal of Medicine, 2015. **372**(24): p. 2296-2306.

38. Weimar, C., et al., *Safety of Simultaneous Coronary Artery Bypass Grafting and Carotid Endarterectomy Versus Isolated Coronary Artery Bypass Grafting: A Randomized Clinical Trial.* Stroke, 2017. **48**(10): p. 2769-2775.
39. Ranta, A., et al., *Cluster randomized controlled trial of TIA electronic decision support in primary care.* Neurology, 2015. **84**(15): p. 1545.
40. Johnston, S.C., et al., *Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA.* New England Journal of Medicine, 2018. **379**(3): p. 215-225.
41. Hrobjartsson, A., et al., *Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors.* Bmj, 2012. **344**: p. e1119.
42. Hrobjartsson, A., et al., *Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors.* Cmaj, 2013. **185**(4): p. E201-11.
43. Heels-Ansdell, D., et al., *Methods Center Adjudication Costs For 5 Morbidity Outcomes In A Thromboprophylaxis Trial*, in *A48. CLINICAL RESEARCH*. 2011, American Thoracic Society. p. A1678-A1678.
44. Berge, E., et al., *Increasing value and reducing waste in stroke research.* Lancet Neurol, 2017. **16**(5): p. 399-408.

Figures Legends:

Figure 1: Flow diagram

Figure 2: Analysis of 18 comparisons from 15 included trials, comparing the effect size for the primary outcome based on whether assessment was by central adjudicators or not

Figure 3: Meta-analysis of RTE in included studies, using a random-effects model

Figure 4: Meta-analysis of change in number of reported events in included studies, using a random-effects model

Tables:

Table 1: Characteristics of included trials and potentially eligible trials

	Included (n=15)	Potentially eligible, but data not received (n=74)	p
Year of main trial publication			
1990-2000	2 (13%)	5 (7%)	0.13*
2001-2005	1 (7%)	9 (12%)	
2006-2010	2 (13%)	20 (27%)	
2011-2015	6 (40%)	35 (47%)	
2016-2018	4 (27%)	5 (7%)	
Study design			
Parallel	13 (87%)	70 (95%)	0.27*
Factorial	2 (13%)	4 (5%)	
Type of trial			
Primary prevention	3 (20%)	34 (46%)	0.16*
Secondary prevention	9 (60%)	30 (41%)	
Acute stroke	3 (20%)	10 (14%)	
Number of randomised groups			
2	12 (80%)	61 (82%)	0.86*
3	1 (7%)	7 (9%)	
≥4	2 (13%)	6 (8%)	
Participants randomised			
Mean (SD)	4637 (5764)	3717 (5246)	0.33†
Median [25th, 75th centile]	2885 [449, 6105]	1633 [439, 4576]	
Min, Max	129, 21105	48, 20702	
No. of sites			
Mean (SD)	216 (365)	185 (269)	0.59†
Median [25th, 75th centile]	82 [50, 172]	85 [27, 179]	
Min, Max	4, 1393	1, 1178	
Not reported	0 (-)	5 (7%)	
Intervention			
Drug	9 (60%)	52 (70%)	0.39*
Surgery/procedure	4 (27%)	18 (24%)	
Other	2 (13%)	4 (5%)	
Comparator			
Placebo	2 (13%)	14 (19%)	0.069*
Standard care	10 (67%)	41 (55%)	
Active treatment	0 (-)	14 (19%)	
Surgery/procedure	2 (13%)	5 (7%)	
Other	1 (7%)	0 (-)	
Primary outcome			
Stroke	8 (53%)	20 (27%)	0.18*
Composite including stroke	6 (40%)	39 (53%)	
Functional outcome after stroke	1 (7%)	6 (8%)	
Other	0 (-)	9 (12%)	
Blinding status of site investigators			
Blind to treatment allocation	9 (60%)	37 (50%)	0.48‡

Not blind to treatment allocation	6 (40%)	37 (50%)	

Data are n(%) unless otherwise stated
*p-value from Fisher exact test
†p-value from Mann-Whitney U test
‡p-value from Chi-square test

Table 2: Characteristics of central adjudication in included trials

	Total (n=15)
Adjudicators blind to treatment allocation	
Yes	15 (100%)
Adjudicators blind to assessment of the site investigators	
Yes	6 (40%)
No	4 (27%)
Not reported	5 (33%)
Number of adjudicators	
2-4	9 (60%)
5-9	2 (13%)
≥10	4 (27%)
Adjudicators profession*	
Neurologist	14 (93%)
Cardiologist	3 (20%)
Other health professional	5 (33%)
Not a health professional	2 (13%)
Not reported	1 (7%)
Information provided to adjudicators*	
Medical notes	10 (67%)
Original case report forms	11 (73%)
Cranial scans	7 (47%)
Audio recording	1 (7%)
Video footage	1 (7%)
Not reported	3 (20%)
Number of adjudicators per case	
1	5 (33%)
>1	9 (60%)
Not reported	1 (7%)
Method used to deal with disagreements	
Each event assessed by single adjudicator, so no disagreements	4 (27%)
Further adjudication	5 (33%)
Consensus decision between adjudicators/committee	4 (27%)
Not reported	2 (13%)
How cases were selected for adjudication	
Only those identified by *unblinded* site investigators	6 (67%)
Only those identified by *blinded* site investigators	5 (27%)
All participants, or all suspected cases identified by *blinded* site investigators	4 (7%)

Data are n(%)
*Categories are not mutually exclusive