Neurosurgical Evidence and Randomized Trials

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Neurosurgical Evidence and Randomized Trials: The Fragility Index

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■ BACKGROUND: **Neurosurgical randomized controlled trials (RCTs) are difficult to carry out due to the low incidence of certain diseases, heterogeneous disease phenotypes, and ethical issues. This results in a weak evidence base in terms of both the number of trials and their robustness. The fragility index (FI) measures the robustness of an RCT and is the minimum number of patients in a trial whose status would have to change from a nonevent to an event to change a statistically significant result to a nonsignificant result. The smaller the FI, the more fragile the trial's outcome.**

■ METHODS: **RCTs that have influenced neurosurgical practice were included in this analysis. Simulations were run to calculate the FI. To determine associations with a high or low FI, multivariable logistic regression was used to calculate adjusted odds ratios and 95% confidence intervals adjusting for baseline confounders.**

■ RESULTS: **Of 2975 papers screened, 74 were included. The median FI was 4.5 (interquartile range: 1.5—10). RCTs included a median of 165 patients (interquartile range: 75—330), with a maximum of 10,008. A total of 38 trials had lost to follow-up patients that might have impacted the robustness of the results (51%).**

■ CONCLUSION: **Results of neurosurgical RCTs on which we base our clinical decision-making and treatment guidelines are often fragile. Improved methodologies, international collaboration, and cooperation between specialties might improve the evidence base in the future.**

INTRODUCTION

Neurosurgical practice is in need of a strong evidence base.[1] Although observational studies are informative,[2,3] they suffer from confounding by indication and are easily susceptible to other biases. Randomized controlled trials (RCTs) are the mainstay of evidence-based medicine and usually the principal design by which the effectiveness of an intervention is measured and causality is inferred. However, designing surgical RCTs is highly challenging in itself.[4-6] Neurosurgical RCTs are decidedly difficult to carry out and remain of overall low quality due to a combination of factors, including the low incidence of certain neurosurgical diseases, the heterogeneity of the study population, and the reluctance to include patients in trials.[7-10] Often, industry funding is necessary to carry out trials, leading to other potential biases.[11]

The fragility index (FI)[12] has been proposed as an intuitive measure of the certainty associated with the results of a clinical trial. It represents the number of patients who, when moved from the nonevent to the event group, would cause the result of the trial to be nonsignificant. For example, in 1983, Allen et al[13] published a trial in the *New England Journal of Medicine* comparing nimodipine with placebo for vasospasm after subarachnoid hemorrhage. In the placebo group, 8 of 60 patients had vasospasm after 21 days, compared with 1 of 56 patients in the

Key words
- Effect size measures
- Evidence
- Fragility index
- Neurosurgical trials
- Randomized clinical trials
- Study design

Abbreviations and Acronyms
CTS: Carpal tunnel syndrome
FI: Fragility index
IQR: Interquartile range
RCT: Randomized controlled trial
TBI: Traumatic brain injury

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treatment group. However, if only 1 patient were moved from the nonevent to the event group in this trial, the result would have become nonsignificant, and thus, the trial has an FI of 1.

Although there has been critique against the FI,[14] which is found to strengthen the overreliance on the P value and statistically significant findings,[15,16] its simplicity and intuitive use counterbalance the criticized aspects. At this point in time, we find the FI to be a good indicator of the state of science, and in this study, we aimed to quantify the robustness of neurosurgical trials that significantly shaped our clinical practice and evidence-based protocols using the FI.

METHODS

Together with an information specialist, we defined a Medline search from the inception of our database to March 2020 for RCTs relevant to neurosurgical practice (**Supplementary Appendix**). We also included trials investigating the role of radiotherapy or chemotherapy in neuro-oncology or stents in neurovascular practice. We cross-referenced other reviews of neurosurgical RCTs to check for missing trials.

The inclusion criteria were: 1) phase 3 or 4 RCT relevant for neurosurgical practice, 2) 2-arm parallel study arm design with 1:1 allocation, and (3) at least 1 significant primary dichotomous outcome, or mortality/functional outcome as a significant secondary outcome if the primary outcome was either nonsignificant or nondichotomous. Reports of the same RCT were included separately if they reported prespecified long-term outcomes of the same trial. Letters, systematic reviews, observational studies, post hoc analyses of RCTs, or cost-effectiveness trials were excluded.

Data Extraction and Risk-of-Bias Analysis

Two investigators (VV and VIV) extracted the data independently. Discrepancies were resolved by plenary discussion. Data were extracted in a secured database and included details about the trials, the number of patients included, the number of events, statistical analyses, funding, and conflicts of interest. Even though our report is a methodologic appraisal and simulation study and not a systematic review alone, we still decided to perform risk-of-bias analysis using the Cochrane risk-of-bias tool.[17] Two investigators (VIV and RD) performed the assessment independently, and discrepancies were resolved by plenary discussion with the first author (VV).

Statistical Analyses and Outcomes

All analyses were performed using R version 3.6.1 (The R Project for Statistical Computing, Vienna, Austria). We first ran simulations of each included study by subtracting 1 individual from the nonevent and adding it to the event group as proposed by Walsh et al.[12] This was done until the result was no longer significant when evaluated by the Fisher exact test for superiority trials or until the result was significant for noninferiority trials ("reverse" FI). If the result of the RCT was significant with the χ^2 test, but not with the Fisher exact, the FI was set at 0. We calculated all FIs for dichotomous secondary outcomes as well.

Summary measures were calculated as medians and interquartile ranges (IQR) for non-normally distributed variables. The median and IQR FI were calculated for different subgroups (various journals, subspecialty, RCT design, type of intervention, and type of outcome). The interventions were split into surgical, pharmaceutical, other types of interventions (such as endovascular therapies or hypothermia), and combinations.

Multivariable logistic regression was used with the FI both as a continuous and as a dichotomous outcome to assess which covariates were associated with having a higher or a lower FI. We dichotomized the FI by adding 1 to the median FI of all studies and splitting studies into "relatively low FI" and "relatively high FI."

We also calculated the probability of the result being overturned were all (or any) patients available from those lost to follow-up (**Supplementary Table 1**).

RESULTS

The search yielded a total of 2654 studies. An additional 321 were identified through back-tracking of references. A total of 311 full-text articles were assessed for eligibility and 74 were included in this study (**Supplementary Table 2**). One study[18] was entered twice in the database because it reported the results of 2 separate randomized cohorts.

RCTs included a median of 165 patients (IQR: 75–330), with a maximum of 10,008. Most of the trials (n = 29, 38%) evaluated a surgical intervention, whereas 10% (n = 8) evaluated a combination of interventions (**Table 1**). Less than half of the trials were multicenter (n = 31, 41%). Most RCTs (n = 37, 49%) were published in the *New England Journal of Medicine* and in *The Lancet* group journals (**Figure 1**). Most included RCTs were on vascular and trauma subspecialty topics (n = 26, 34%) (**Figure 1**).

The primary outcome, the FI of the study, was calculated in simulations for the mortality/functional outcome as the primary outcome in 32 trials (42%), for other primary outcomes in 31 trials (41%), and for the mortality/functional outcome as the secondary outcome in 13 trials (17%). There was no difference between trials published before 2010 and more recent trials, published after 2010 (median [IQR]: 4 [1–10] and 2.5 [4.5–10], respectively).

Overall, the median FI for the included studies was 4.5 (IQR: 1.5–10) (**Figure 1**). Eight trials had an FI of 0, 6 for their primary outcomes and 3 for their secondary outcomes (mortality or functional outcome). Furthermore, 6 of these RCTs belonged to the trauma subspecialty, 1 to the vascular subspecialty (double extracranial-intracranial bypass for moyamoya disease), and 1 to the peripheral nerve subspecialty (carpal tunnel syndrome [CTS]).

Most RCTs showed low risk of bias, except for "blinding of participants and personnel" (low risk of bias: n = 9, 12%) and "blinding of outcome assessment" (low risk of bias: n = 36, 48%) (**Supplementary Figure 1**).

Multivariable logistic regression analysis results showed an association between other primary outcomes, mortality/functional outcome as a secondary outcome, and trauma subspecialty studies and a lower FI and between the log-transformed number of participants and a higher FI (**Table 2**). Multicenter studies, despite showing a strong association with a high FI, are likely collinear with other variables indicating high-quality studies, and were no longer significant in the multivariable analysis.

Table 1. Summary Measures for the Fragility Index in Various Subgroups Studies

Subgroup	Number of RCTs	Fragility Index, Median (IQR)	*P* Value (Kruskal-Wallis)
Journal			0.004
New England Journal of Medicine	18	6.5 (3–14)	
The Lancet, The Lancet Neurology and The Lancet Oncology	19	8 (3.5–13.5)	
JAMA	4	9.5 (7.25–11.25)	
BMJ	2	4–10 (range)	
Neurosurgical, Spine and Neurotrauma Journals	14	3 (2–7.75)	
Neurology and Stroke Journals	8	3 (1–7.25)	
Critical Care Journals	6	0.5 (0–1)	
Other	5	1 (1–1)	
RCT design			
Nonblinded	29	6 (1–11)	0.56
Single-blind	36	4 (1–8.25)	
Double-blind	11	5 (2.5–9)	
Subspecialty			
Oncology	8	7.5 (5–12)	0.02
Vascular	26	6.5 (2.25–12.25)	
Trauma	26	2 (1–4)	
Spine	5	8 (4–10)	
Functional	3	5–11 (range)	
Pediatric	4	10 (2.5–20.75)	
Peripheral nerve	4	3.5 (0.75–7)	
Type of intervention			
Surgery alone	29	5 (3–9)	0.61
Pharmaceutical	13	3 (1–8)	
Combinations	8	9.5 (4.25–10.25)	
Other types of interventions (e.g., endovascular)	26	3 (1.25–13.75)	
Single-center or multicenter			
Single-center	30	2 (1–5)	<0.001
Multicenter	46	8 (3–12.5)	
Industry-funded			
Funded by industry	18	7 (2–13.75)	0.26
Not funded by industry	42	4 (1–10)	
Not reported	16	5.5 (1–8)	

Continues

Table 1. Continued

Subgroup	Number of RCTs	Fragility Index, Median (IQR)	*P* Value (Kruskal-Wallis)
Outcome			
Mortality/functional outcome as primary outcome	32	4.5 (1–10)	0.12
Other primary outcome	31	6 (2.5–10.5)	
Mortality/functional outcome as secondary outcome	13	3 (1–4)	

Where subgroups included less than 4 studies, ranges were reported, as indicated in parentheses.
RCT, randomized controlled trial; IQR, interquartile range.

DISCUSSION

Summary of Findings

RCTs that inform neurosurgical practice often have low FIs. More than half of the trials had an FI under 5. The factors associated with a lower FI after multivariable logistic regression were the analysis of the FI based on a primary outcome other than the mortality or functional outcome, the analysis of the FI based on the mortality/functional outcome as a secondary outcome, and traumatic brain injury (TBI) subspecialty studies.

RCTs and Evidence in Neurosurgery

Evidence generation by means of RCTs faces considerable challenges in neurosurgery and with a median FI of 4.5; the robustness of neurosurgical RCTs is much lower than, for instance, cardiovascular RCTs (median FI, 13). Halliday et al[19] compared results between immediate versus deferred carotid endarterectomy in asymptomatic stenosis and have shown superiority of immediate surgery with an FI of 55.

The robustness of neurosurgical RCTs also falls short of the 399 trials (median FI, 8) analyzed in the original report of Walsh et al.[12] In this report, the authors analyzed RCTs published in the 5 top medical journals between 2004 and 2010, regardless of specialty, and calculated their FIs. In our analysis, 8 of the analyzed RCTs had FIs of 0, meaning that the results of these trials would be rendered nonsignificant if the more conservative Fisher exact test, rather than a χ^2 test, was used.[20] Most of these trials dealt with TBI topics, and some of them evaluated hypothermia as an intervention to prevent or treat intracranial hypertension.

Our assessment of the FI of trials with relevance to neurosurgical practice shows that TBI trials are significantly associated with a lower FI compared with other neurosurgical subspecialties. For example, despite 191 RCTs in TBI alone,[21] the evidence base is weak. This leads to "volatile" recommendations that get downgraded from one edition of the guidelines to the other on mostly methodologic grounds.[1]

Hypothermia in TBI is a good example of the difficulties of running RCTs in neurosurgical and, more specifically, in patients with TBI. It is also a cautionary tale of conclusions drawn on

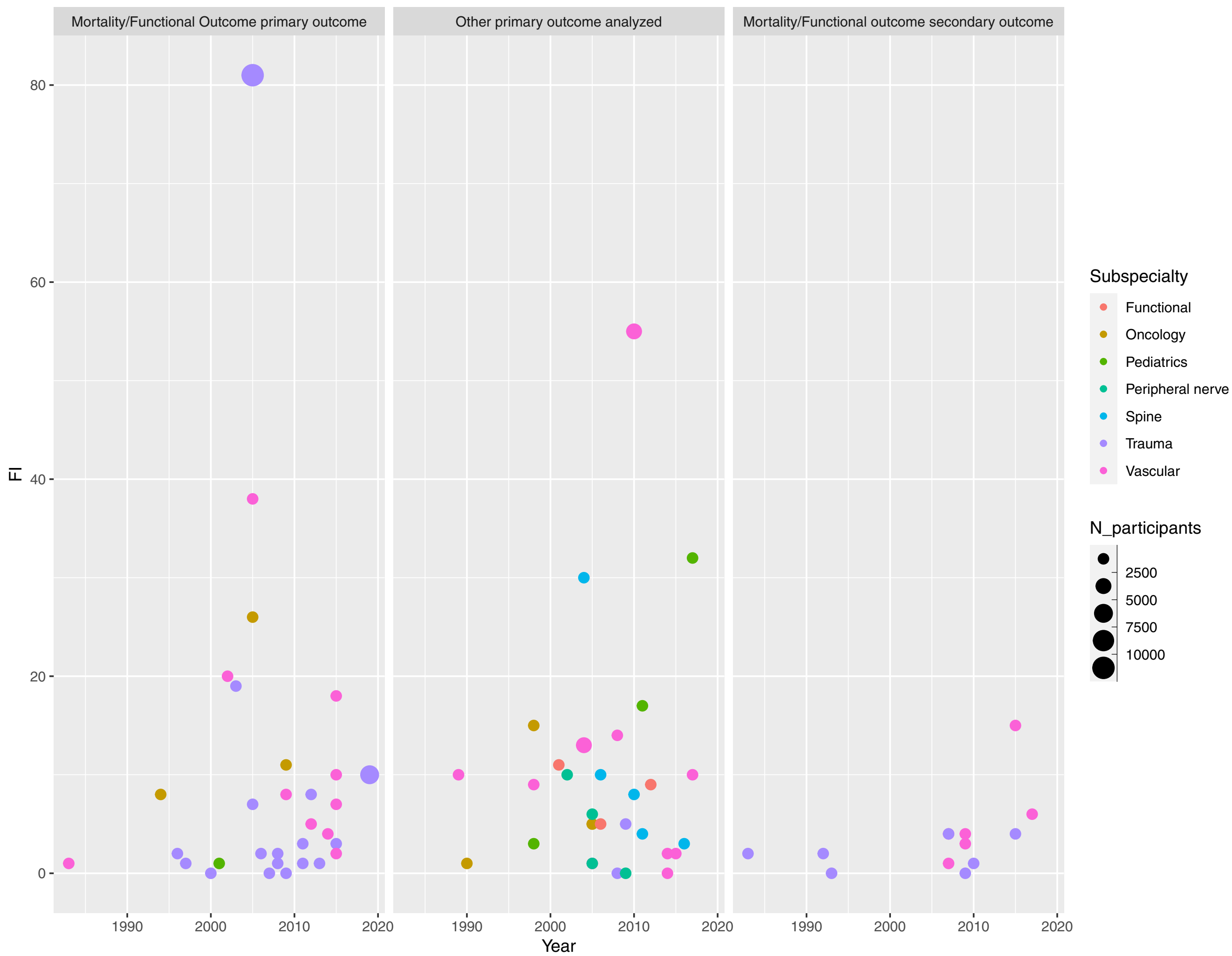

Figure 1. Size and subspecialty of RCTs, in relation to the analyzed outcomes.

poorly conducted trials: 39 RCTs[21] and 10 meta-analyses are available on hypothermia, all suggesting some form of benefit. The most recent and possibly best-conducted RCT,[22] however, was stopped early because of higher mortality in the intervention arm. Another example is a 2009 trial published in *The Lancet* on the topic of CTS, which is one of the few trials on peripheral nerve surgery.[23] Despite the high prevalence of surgical treatment of CTS, only 116 patients were included and the trial was very fragile.

Surgical RCTs[4,5] pose considerable difficulties in terms of design and methodology. Heterogeneous populations and complex interventions make standardizing the intervention challenging and require considerable sample sizes to detect an effect above the statistical "noise." Neurosurgical RCTs were prone to poor reporting in the past,[10] but some authors have suggested that there have been improvements in the last decade.[9] However, as Figure 1 demonstrates, we failed to detect a real improvement of the FI over time, regardless of the subspecialty or the outcome analyzed. This likely suggests that when considering other outcomes, factors besides sample size heavily influence the FI. We therefore propose that the focus of new guidelines, methodologies, and clinical trials should be on improving mortality and functional outcomes rather than on surrogate outcomes.[1]

Several factors can negatively (or positively) contribute to the robustness of a trial: a low sample size (especially in single-center/single-surgeon settings), a vaguely defined intervention, a power analysis based on previous data with high risk of bias, the statistical method chosen, or an early termination of a trial due to interim analyses showing harm or benefit.

The uncertainty surrounding neurosurgical RCTs should not deter clinicians from carrying out research or instill a fatalistic attitude toward the usefulness of past and future trials. Lessons can be learned from past endeavors, which in turn leads to better research. Multicenter, collaborative trials, adequately powered, are encouraged within a broader spectrum of overall good trial design.

Table 2. The Results of the Multivariable Logistic Regression of Covariates Associated with the FI Dichotomized: "Relatively Low" and "Relatively High" FI

Covariate	OR (95% CI)	*P* Value
Other primary outcome analyzed (ref: mortality/ functional outcome as a primary outcome)	0.12 (0.01—0.84)	0.048
Mortality/functional outcome as a secondary outcome analyzed (ref: mortality/ functional outcome as a primary outcome)	0.09 (0.01—0.57)	0.023
Trauma subspecialty studies (ref: oncology)	0.02 (0.01—0.26)	0.007
Number of participants	5.2 (2.3—16)	0.001

Only covariates with statistically significant associations are reported.
FI, fragility index; OR, odds ratio; CI, confidence interval.

New methods of statistical analysis, such as the proportional odds logistic regression, could be employed in order to increase statistical power.[24] Sometimes, because of difficulties regarding equipoise and the inclusion of patients in RCTs, alternative study designs[25] such as comparative effectiveness research could be employed.[26] Successful trials often require a team with various areas of expertise, neurosurgeons, methodologists, neurologists, neuroradiologists. Future collaborative projects, together with new methodologic approaches, will likely solidify the evidence base for neurosurgical practice.

Of utmost importance is not relying on P values at all, but moving toward evaluating effect sizes and effect sizes alone. A control and an intervention group might show outcomes that are "statistically significant" but that have effect sizes so small that no real benefit results from employing the intervention. This issue has led to the creation of the so-called minimal clinically important difference. The overreliance on P values should become extinct.

Limitations

The FI has been amply criticized by methodologists and clinicians alike[14] because of its overreliance on the significance of results and the P value,[15,16] the strong association with sample size, and its limitations in oncology trials and time-to-event data.[14,27] Others have considered the FI irrelevant, as evaluating the confidence interval of a trial result conveys the same information about the level of uncertainty. Nevertheless, its simplicity remains an attractive quality, as uncertainty can be summarized in a single number. Furthermore, we included only RCTs with dichotomous outcomes and 1:1 allocation, which potentially introduces a biased perspective of the evidence base by not considering other methodologies and other trials. A further expansion of the FI to estimate uncertainty when other methodologies are used would be a welcome addition.

CONCLUSION

The trials that form the basis of neurosurgical evidence-based practice are often fragile. This conclusion needs to be interpreted in the light of the difficulties associated with conducting neurosurgical RCTs. Nevertheless, more refined methodologies and more efficient use of resources could improve the evidence base in the future.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Victor Volovici: Methodology, Supervision, Investigation, Writing — original draft, Validation. **Valerie I. Vogels:** Investigation, Formal analysis. **Ruben Dammers:** Writing — review & editing. **Torstein R. Meling:** Supervision, Writing — review & editing.

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SUPPLEMENTARY APPENDIX

(neurosurg*[tw] OR cranial surg*[tw] OR spine surg*[tw] OR spinal surg*[tw]) AND ((randomized controlled trial[tw] OR randomized controlled study[tw] OR randomly assigned[tw] OR randomized trial[tw] OR randomized, double-blind, placebo-controlled trial[tw] OR randomized, double blind, controlled trial [tw] OR randomized, double blind[tw] OR randomized trial[tw] OR controlled clinical trial[tw] OR randomized clinical trial[tw] OR double blind[tw] OR randomised controlled trial[tw] OR randomised controlled study[tw] OR randomised trial[tw] OR randomised, double-blind, placebo-controlled trial[tw] OR randomised, double blind, controlled trial[tw] OR randomised, double blind[tw] OR randomised trial[tw] OR randomised clinical trial [tw]) OR ("Randomized controlled trial"[publication type])).

Supplementary Table 1. Every Analyzed RCT, Together with the Probabilities That a Result Would Be Overturned Were All Patients Available for Follow-Up

Study	Journal	Subspecialty	Intervention	Number of Patients with Outcome		Lost to FU		Number of Combinations of Lost to FU Patients Leading to Nonsignificant/Significant Result	Probability (%)	Number of Combinations with Overturned Result if All Patients Were Available for FU	Probability (%)	Notes
				Treatment Group	Control Group	Treatment Group	Control Group					
Allen 1983[1]	NEJM	Vascular	Nimodipine	1	8	2	3	23	39	3	50	Primary outcome
Marion 1997[2]	NEJM	Trauma	Hypothermia	24	16	1	0	1	50	1	50	Primary outcome
Barnett 1998[3]	NEJM	Vascular	Carotid endarterectomy	146	190	5	1	6	10	0	0	Primary outcome
PHVD group 1998[4]	Lancet	Pediatrics	Acetazolamide and furosemide	49	35	13	13	4493	40	71	42	Primary outcome
Gerritsen 2002[5]	JAMA	Peripheral nerve	Surgical decompression	62	46	9	3	195	36	6	22	Primary outcome
Molyneux 2002[6]	Lancet	Vascular	Endovascular coiling	190	243	12	18	3770	22	0	0	Primary outcome
Halliday 2004[7]	Lancet	Vascular	Immediate carotid endarterectomy	42	120	31	37	48,401	12	0	0	Primary outcome
Edwards 2005[8]	Lancet	Trauma	Intravenous methylprednisolone	1248	1075	153	182	143,956	21	4601	16.50	Primary outcome
Ly-Pen 2005[9]	Arthritis Rheum.	Peripheral nerve	Surgical decompression	50	75	13	3	159	15	0	0	Primary outcome
Molyneux 2005[10]	Lancet	Vascular	Endovascular coiling	250	326	10	15	291	3	0	0	Primary outcome
Van den Bent 2005[11]	Lancet	Oncology	Early radiotherapy	66	46	8	10	1287	43	28	35	Primary outcome
Dhandapani 2008[12]	IJNT	Trauma	Magnesium	22	12	5	5	165	38	9	36	Primary outcome
Jarvik 2009[13]	Lancet	Peripheral nerve	Surgical decompression	22	14	8	7	925	57	41	73	Primary outcome
Molyneux 2009[14]	Lancet Neurol	Vascular	Endovascular coiling	112	144	27	29	52,897	28	331	42	Primary outcome
Stupp 2009[15]	Lancet Oncology	Oncology	Radiotherapy plus temozolomide	33	8	3	7	57	16	0	0	Primary outcome

FU, follow-up.

Continues

Supplementary Table 1. Continued

Study	Journal	Subspecialty	Intervention	Number of Patients with Outcome		Lost to FU		Number of Combinations of Lost to FU Patients Leading to Nonsignificant/ Significant Result	Probability (%)	Number of Combinations with Overturned Result if All Patients Were Available for FU	Probability (%)	Notes
				Treatment Group	Control Group	Treatment Group	Control Group					
Yang 2009[16]	Int J Nurs Stud	Trauma	Intensive insulin (continuous infusion)	34	26	4	3	144	97	12	100	Secondary outcome
Halliday 2010[17]	Lancet	Vascular	Immediate carotid endarterectomy	56	140	34	36	56,420	14	0	0	Primary outcome
Bernard 2010[18]	Ann Surg	Trauma	Prehospital rapid sequence intubation by paramedics	80	56	3	10	359	54	18	60	Secondary outcome
Klazen 2010[19]	Lancet	Spine	Vertebroplasty	88	71	7	7	295	23	1	2	Primary outcome
Hellum 2011[20]	BMJ	Spine	Surgery with disc prosthesis	51	31	13	21	8276	31	91	33	Primary outcome
Clark 2016[21]	Lancet	Spine	Vertebroplasty	24	12	6	2	38	35	3	25	Primary outcome
van den Berg 2017[22]	NEJM	Vascular	Endovascular treatment	72	47	12	14	3849	35	21	12	Secondary outcome
CRASH-3 group 2019[23]	Lancet	Trauma	Tranexamic acid	166	207	18	17	11,321	35	45	15	Subgroup analysis

FU, follow-up.

Supplementary Table 2. Characteristics of Included RCTs

Name	Year	Journal	Design	Subspecialty	Population	Number of Participants	Number of Interventions	Number of Controls	Intervention	Control	Subgroup Analysis	Protocol Published	Funder
Primary outcome analyzed													
Mortality/functional outcome													
Allen 1983[1]	1983	New England Journal of Medicine	Double-blind, multicenter	Vascular	Subarachnoid hemorrhage	121	56	60	Nimodipine	Placebo	—	No	Miles Pharmaceuticals (west Haven, Conn.)
Vecht 1994[24]	1994	Neurology	Noninferiority, double-blind	Oncology	Metastatic brain tumor	47	20	22	Low-dose dexamethasone 8 mg	High-dose dexamethasone 16 mg	—	No	Not reported
Vecht 1994[24]	1994	Neurology	Noninferiority, double-blind	Oncology	Metastatic brain tumor	49	24	23	Low-dose dexamethasone 4 mg	High-dose dexamethasone 16 mg	—	No	Not reported
Harders 1996[25]	1996	Journal of Neurosurgery	Double-blind, multicenter	Trauma	Traumatic subarachnoid hemorrhage	123	60	61	Nimodipine	Placebo	CGS >12 at entry	No	Bayer AG, Leverkusen, Germany
Marion 1997[2]	1997	New England Journal of Medicine	Single-blind	Trauma	Severe traumatic brain injury (TBI)	82	40	42	Hypothermia	Normothermia	GSC of 5—7 at entry	No	National Institute of Neurological Disorders and Stroke
Jiang 2000[26]	2000	Journal of Neurosurgery	Single-blind	Trauma	Severe TBI	87	43	44	Hypothermia	Normothermia	—	No	Not reported
Taylor 2001[27]	2001	Child's Nervous System	Nonblind	Pediatrics	Children with TBI	27	13	14	Very early decompressive craniectomy	Conventional medical treatment	—	No	Not reported
Molyneux 2002[6]	2002	Lancet	Nonblind, multicenter	Vascular	Ruptured intracranial aneurysm	2143	801	793	Endovascular coiling	Neurosurgical clipping	WFNS grade at randomization, age groups by decade, amount of blood on CT scan (Fisher grade), and lumen size of aneurysm and its site	Yes	Medical Research Council, UK; Programme Hospitalier de Recherche Clinique 1998 of the French Ministry of Health. Assistance Publique, Hôpitaux de Paris (AP-HP); the Canadian Institutes of Health Research; the Stroke Association of the UK for the Neuropsychological assessments
Zhi 2003[28]	2003	Surgical Neurology	Nonblind	Trauma	Severe TBI	396	198	198	Hypothermia	Normothermia	—	No	Not reported
Edwards 2005[8]	2005	Lancet	Double-blind, multicenter	Trauma	TBI	10008	4854	4819	Intravenous corticosteroid (methylprednisolone)	Placebo	Time from injury to randomization (<1 h, >1 to <3 h, or >3 to 8 h); GCS at randomization (severe 3—8, moderate 9—12, mild 13—14)	Yes	UK Medical Research Council, and Pharmacia & Upjohn
Stupp 2005[29]	2005	New England Journal of Medicine	Nonblind, multicenter	Oncology	Glioblastoma in adults	573	287	286	Radiotherapy plus temozolomide	Radiotherapy alone	Age, gender, prior surgery, WHO performance status, baseline steroids	No	National Cancer Institute and Schering-Plough, Kenilworth, NJ
Molyneux 2005[10]	2005	Lancet	Nonblind, multicenter	Vascular	Ruptured intracranial aneurysm	2143	1063	1055	Endovascular coiling	Neurosurgical clipping	WFNS grade at randomization, age groups by decade, amount of blood on CT scan (Fisher grade), and lumen size of aneurysm and its site	Yes	Medical Research Council, UK; Programme Hospitalier de Recherche Clinique 1998 of the French Ministry of Health. Assistance Publique, Hôpitaux de Paris (AP-HP); the Canadian Institutes of Health Research; the Stroke Association of the UK for the Neuropsychological assessments
Jiang 2005[30]	2005	Journal of Neurotrauma	Single-blind, multicenter	Trauma	Severe TBI with refractory intracranial hypertension	486	241	245	Standard trauma craniectomy (frontotemporoparietal bone flap)	Limited craniectomy (temporoparietal bone flap)	—	No	Not reported

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Supplementary Table 2. Continued

Name	Year	Journal	Design	Subspecialty	Population	Number of Participants	Number of Interventions	Number of Controls	Intervention	Control	Subgroup Analysis	Protocol Published	Funder
Jiang 2006[31]	2006	Journal of Cerebral Blood Flow and Metabolism	Single-blind, multicenter	Trauma	Severe TBI	215	108	107	Long-term hypothermia	Short-term hypothermia	—	No	Medical Research Council, UK; Programme Hospitalier de Recherche Clinique 1998 of the French Ministry of Health. Assistance Publique, Hôpitaux de Paris (AP-HP); the Canadian Institutes of Health Research; the Stroke Association of the UK for the Neuropsychological assessments
Qiu 2007[32]	2007	J Crit Care	Nonblind	Trauma	Severe TBI	80	40	40	Hypothermia	Normothermia	—	No	Health Bureau of Hangzhou, Zheijang Province
Xiao 2008[33]	2008	Crit Care	Double-blind	Trauma	Severe TBI	159	82	77	Progesterone	Placebo	Sex, GCS of 6–8 at entry	Yes	Scientific Research Fund of Zhejiang Provincial Education Department, China
Dhandapani 2008[12]	2008	The Indian Journal of Neurotrauma	Nonblind	Trauma	Severe TBI	70	30	30	Magnesium	Placebo	—	No	Not reported
Stupp 2009[15]	2009	Lancet Oncology	Nonblind, multicenter	Oncology	Glioblastoma in adults	573	287	286	Radiotherapy plus temozolomide	Radiotherapy alone	Age, methylation of MGMT promotor gene	Yes	EORTC, NCIC, Nélia and Amadeo Barletta Foundation, Schering-Plough
Wang 2009[34]	2009	International Journal of Stroke	Single-blind, multicenter	Vascular	Intracerebral hemorrhage	377	181	165	Invasive craniopuncture therapy	Conservative treatment	—	No	Not reported
Qiu 2009[35]	2009	Crit Care	Single-blind	Trauma	TBI	74	37	37	Unilateral decompressive craniectomy	Unilateral routine temporoparietal craniotomy	—	Yes	Scientific Research Fund of Zhejiang Health Department, the Scientific Research Fund of Hangzhou Health Department and the Scientific Research Fund of Science and Technology Department of Zhejiang, China
Cooper 2011[36]	2011	New England Journal of Medicine	Single-blind, multicenter	Trauma	Severe TBI with refractory intracranial hypertension	155	73	82	Bifrontotemporoparietal decompressive craniectomy	Standard care	—	Yes	National Health and Medical Research Council of Australia; the Transport Accident Commission of Victoria, Australia; the Intensive Care Foundation of the Australian and New Zealand Intensive Care Society; and the Western Australian Institute for Medical Research
Zhao 2011[37]	2011	J Crit Care	Nonblind	Trauma	Severe TBI	81	40	41	Hypothermia	Normothermia	Mean intracranial pressure, blood glucose, and lactic acid before and after hypothermia therapy	No	Not reported
Li 2012[38]	2012	Neurosurgery Quarterly	Nonblind	Trauma	TBI with transtentorial herniation	182	92	90	Decompressive craniotomy plus cerebellar tentorium incision	Decompressive craniotomy	—	No	Not reported
Zhao 2012[39]	2012	Neurocritical Care	Single-blind, multicenter	Vascular	Middle cerebral artery infarction	47	24	23	Decompressive hemicraniectomy	Conservative treatment	Age 60–80 years	No	Not reported

Rockswold 2013[40]	2013	Journal of Neurosurgery	Single-blind	Trauma	Severe TBI	42	19	21	Hyperbaric oxygen therapy + normobaric hyperoxia	Standard care	ICP at enrollment	Yes	National Institute of Neurological Disorders and Stroke Hyperbaric and Normobaric Oxygen in Severe Brain Injury
Juttler 2014[41]	2014	The New England Journal of Medicine	Nonblind, multicenter	Vascular	Middle cerebral artery infarction	112	49	63	Hemicraniectomy	Conservative treatment	—	Yes	Deutsche Forschungsgemeinschaft
Andrews 2015[42]	2015	New England Journal of Medicine	Single-blind, multicenter	Trauma	TBI	387	195	192	Hypothermia	Normothermia	Age, postresuscitation GCS score, time from injury, pupillary response	Yes	National Institute for Health Research Health Technology Assessment program
Campbell 2015[43]	2015	New England Journal of Medicine	Single-blind, multicenter	Vascular	Acute ischemic stroke	70	35	35	Endovascular thrombectomy	Alteplase alone	—	Yes	Australian National Health and Medical Research Council of Australia, Royal Australasian College of Physicians, Royal Melbourne Hospital Foundation, the National Heart Foundation of Australia, and the National Stroke Foundation of Australia
Goyal 2015[44]	2015	New England Journal of Medicine	Single-blind, multicenter	Vascular	Acute ischemic stroke	315	164	147	Rapid endovascular thrombectomy	Standard care	Age, sex, baseline NIHSS score, baseline ASPECTS, location of occlusion, status of intravenous alteplase treatment	Yes	Covidien
Jovin 2015[45]	2015	New England Journal of Medicine	Single-blind, multicenter	Vascular	Acute ischemic stroke	206	103	103	Endovascular thrombectomy	Medical therapy (alteplase)	Age, baseline NIHSS, site of occlusion, time to randomization, alteplase, ASPECTS score	Yes	Covidien, Spanish Ministry of Health cofinanced by Fondo Europeo de Desarrollo Regional, Generalitat de Catalunya
Saver 2015[46]	2015	New England Journal of Medicine	Single-blind, multicenter	Vascular	Acute ischemic stroke	196	98	98	Endovascular thrombectomy + t-PA	Tissue plasminogen activator (t-PA)	Sex, age, NIHSS score, occlusion location, geographic location, ASPECTS, site of initial administration of t-PA, time from onset to randomization	Yes	Covidien
CRASH-3 group 2019[23]	2019	Lancet	Double-blind, multicenter	Trauma	TBI	5650	2846	2769	Tranexamic acid	Placebo	GCS of 9—15	Yes	The JP Moulton Charitable Trust, National Institute for Health Research Health Technology Assessment, Joint Global Health Trials, Medical Research Council, Department for International Development, Global Challenges Research Fund, and the Wellcome Trust
Other primary outcome													
Pickard 1989[47]	1989	BMJ	Double-blind, multicenter	Vascular	Subarachnoid hemorrhage	554	278	276	Nimodipine	Placebo	Age, sex, loss of consciousness at ictus, time from ictus to entry, GCS score on entry; limb weakness, neck stiffness, and headache; hypertension; angiographic findings; computed tomographic findings	No	Bayer UK
Patchell 1990[48]	1990	New England Journal of Medicine	Nonblind	Oncology	Single brain metastasis	48	25	23	Surgical resection plus radiotherapy	Needle biopsy and radiotherapy	Age, sex, location of brain metastasis, type of primary tumor (lung vs. all other types), extent of disease, initial Karnofsky score (70% vs. >80%), length of time between diagnosis of primary tumor and brain metastasis.	No	Not reported

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Supplementary Table 2. Continued

Name	Year	Journal	Design	Subspecialty	Population	Number of Participants	Number of Interventions	Number of Controls	Intervention	Control	Subgroup Analysis	Protocol Published	Funder
Barnett 1998[3]	1998	The New England Journal of Medicine	Single-blind, multicenter	Vascular	Symptomatic moderate carotid artery stenosis	2226	1108	1118	Carotic endarterectomy (CEA)	Medical care	Moderate stenosis (50%—69%) versus low-moderate stenosis (<50%)	No	National Institute of Neurological Disorders and Stroke
Patchell 1998[49]	1998	JAMA	Nonblind, multicenter	Oncology	Single brain metastasis	95	49	46	Surgery plus postoperative whole-brain radiotherapy	Only surgery	Location of metastasis, primary tumor type, extent of disease, initial Karnofsky score, time between diagnosis of primary and development of brain metastases	No	Not reported
PHVD group 1998[4]	1998	Lancet	Single-blind, multicenter	Pediatrics	Infants with posthemorrhagic ventricular dilatation	177	75	76	Acetazolamide and furosemide plus standard therapy	Standard therapy	Birthweight, gestational age, postnatal age, ventricular index, and head circumference at entry	No	Action Research. The National Perinatal Epidemiology Unit is funded by the Department of Health
Wiebe 2001[50]	2001	New England Journal of Medicine	Nonblind	Functional	Temporal-lobe epilepsie	80	40	40	Surgery	Antiepileptic drug for 1 year	—	No	Grant from Physicians' Services Incorporated Foundation
Gerritsen 2002[5]	2002	JAMA	Nonblind, multicenter	Peripheral nerve	Carpal tunnel syndrome	176	87	89	Surgical decompression	Splinting during the night	Patient's preference before randomization	Yes	Health Care Insurance Council of the Netherlands
Halliday 2004[7]	2004	Lancet	Single-blind, multicenter	Vascular	Asymptomatic carotid artery stenosis	3120	1529	1523	Immediate carotid endarterectomy	Deferred CEA	Age, sex, extent of stenosis, prerandomization cholesterol, blood pressure, comorbidity, medications	Yes	UK Medical Research Council and The Stroke Association
Zucherman 2004[51]	2004	Eur Spine J	Nonblind, multicenter	Spine	Lumbar stenosis	191	100	91	X-STOP Interspinous Process Distraction System	No surgery	—	No	St. Francis Medical Technologies
Ballotta 2005[52]	2005	Journal of Vascular Surgery	Nonblind	Vascular	Internal carotid artery elongation with coiling or kinking	182	92	90	Surgical correction	Medical treatment	Coiled versus kinked artery	No	Not reported
Ly-Pen 2005[9]	2005	Arthritis and Rheumatism	Nonblind	Peripheral nerve	Carpal tunnel syndrome	163	67	80	Surgical decompression	local steroid injection	Unilateral wrist and most symptomatic wrist in patients with bilateral CTS	No	Not reported
Patchell 2005[53]	2005	Lancet	Nonblind, multicenter	Oncology	Metastatic spinal cord compression	101	50	51	Surgery plus radiotherapy	radiotherapy alone	Patients entering the study unable to walk	No	Grants from National Cancer Institute and the National Institute for Neurological Disorders and Stroke
Robert 2005[54]	2005	European Urology	Nonblind	Peripheral nerve	Pudendal neuralgia	32	16	16	Surgical decompression	No surgery	—	No	CHU of Nantes
Van den Bent 2005[55]	2005	Lancet	Nonblind, multicenter	Oncology	Low-grade astrocytoma or oligodendroglioma	314	157	157	Early radiotherapy	Deferred radiotherapy	Low-grade tumors only (high-grade excluded)	Yes	Grants from Foundation Cancer (Belgium) and the National Cancer Institute (Bethesda, Maryland, USA)
Anderson 2006[56]	2006	Journal of Neurosurgery. Spine	Nonblind, multicenter	Spine	Lumbar degenerative spondylolisthesis	75	42	33	X-STOP	No surgery	—	No	St. Francis Medical Technologies
Kupsch 2006[57]	2006	New England Journal of Medicine	Double-blind, multicenter	Functional	Primary generalized or segmental dystonia	40	20	18	Neurostimulation of internal globus pallidus	Sham therapy	—	Yes	Medtronic, German Ministry of Research and Technology
Eckstein 2008[58]	2008	The Lancet Neurology	Noninferiority, nonblind, multicenter	Vascular	Symptomatic severe carotid artery stenosis	1214	607	589	Carotid artery stenting	Carotid endarterectomy	Sex, age, indicator event, side of treated stenosis, grade of treated stenosis, contralateral status	No	Federal Ministry of Education and Research; German Research Foundation; The German Society of Neurology; The German Society of Neuroradiology; The German Radiological Society; Boston Scientifi c; Guidant; Sanofi -Aventis

Perez-Barcena 2008[59]	2008	Crit Care	Single-blind	Trauma	Severe TBI with refractory intracranial hypertension	44	22	22	Pentobarbitol	Thiopentone	—	Yes	Spanish government's Fondo de Investigación Sanitaria
Santarius 2009[60]	2009	Lancet	Single-blind	Trauma	Chronic subdural hematoma	215	108	107	Drain inserted into subdural space	No drain after evacuation	—	Yes	Academy of Medical Sciences, Health Foundation, and NIHR Biomedical Research Centre (Neurosciences Theme)
Jarvik 2009[13]	2009	Lancet	Single-blind, multicenter	Peripheral nerve	Carpal tunnel syndrome	116	49	52	Surgical decompression	No surgery (hand therapy)	Open versus endoscopic surgery, electrodiagnostic tests, MRI baseline variables	Yes	NIH/NIAMS and the Intramural Research Program of the NIH Clinical Center
Halliday 2010[17]	2010	Lancet	Single-blind, multicenter	Vascular	Asymptomatic carotid artery stenosis	3120	1526	1524	Immediate carotid endarterectomy	Deferral of any carotid procedure	Age, sex, extent of stenosis, perandomization cholesterol, blood pressure, comorbidity, medications	Yes	UK Medical Research Council, Stroke Association, and BUPA Foundation
Klazen 2010[19]	2010	Lancet	Nonblind, multicenter	Spine	Osteoporotic vertebral fracture	202	94	94	Vertebroplasty	Conservative treatment	—	Yes	ZonMw, COOK Medical
Adzick 2011[61]	2011	New England Journal of Medicine	Single-blind, multicenter	Pediatrics	Prenatal myelomeningocele	183	78	80	Prenatal surgery	Standard postnatal repair	—	Yes	Eunice Kennedy Shriver National Institute of Child Health and Human Development, the Clinical and Translational Science Awards, National Institutes of Health
Hellum 2011[20]	2011	BMJ	Single-blind, multicenter	Spine	Low back pain and degenerative disc	179	73	66	Surgery with disc prosthesis	Rehabilitation	—	Yes	South Eastern Norway Regional Health Authority and EXTRA funds from the Norwegian Foundation for Health and Rehabilitation
Engel 2012[62]	2012	JAMA	Single-blind, multicenter	Functional	Drug-resistant epilepsy	38	15	23	Anteromesial temporal resection + antiepileptic drug (AED) treatment	AED treatment	—	Yes	National Institutes of Health
Miyamoto 2014[63]	2014	Stroke	Nonblind, multicenter	Vascular	Hemorrhagic moyamoya disease	70	42	38	Bilateral extracranial-intracranial bypass	Conservative treatment	—	Yes	Japanese Ministry of Health, Labour and Welfare
Derdeyn 2014[64]	2014	Lancet	Single-blind, multicenter	Vascular	Acute ischemic stroke	451	224	227	Stent with aggressive medical treatment	Aggressive medical treatment alone	Age, gender, symptomatic artery, qualifying event, days to enrolment, old infarct in territory of symptomatic artery, antithrombotic, old infarct while on antithrombotic treatment	Yes	US Public Health Service National Institute of Neurological Disorders and Stroke (NINDS). Clinical and Translational Science Awards, National Institutes of Health, Medical University of South Carolina, University of Florida, University of Cincinnati, and University of California, San Francisco. Stryker Neurovascular
Zaidat 2015[65]	2015	JAMA	Single-blind, multicenter	Vascular	Symptomatic intracranial stenosis	112	59	53	Balloon-expandable intracranial stent	Medical therapy	—	Yes	Micrus Endovascular
Clark 2016[21]	2016	Lancet	Double-blind, multicenter	Spine	Osteoporotic vertebral fracture	120	61	59	Vertebroplasty	Placebo simulated vertebroplasty	Fracture position by spinal segment and fracture age (<3 weeks or >3 weeks)	Yes	CareFusion Corporation
Mohr 2017[66]	2017	Lancet	Nonblind, multicenter	Vascular	Unruptured brain arteriovenous malformations	226	114	109	Interventional therapy with or without medical management	Medical management alone	Spetzler-Martin grade, location of AVM, venous drainage pattern, age, time from discovery of AVM	Yes	National Institute of Neurological Disorders and Stroke of the US National Institutes of Health
Dwivedi 2017[67]	2017	New England Journal of Medicine	Single-blind	Pediatrics	Children with drug-resistant epilepsy	116	57	59	Surgery	Medical therapy	—	Yes	Indian Council of Medical Research
Secondary Outcome Analyzed													
Mortality/Functional Outcome													

Continues

Supplementary Table 2. Continued

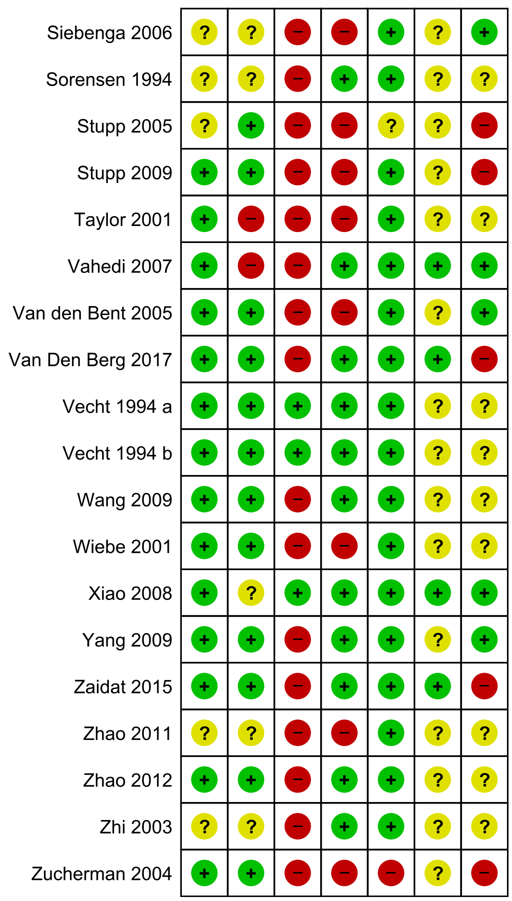
Name	Year	Journal	Design	Subspecialty	Population	Number of Participants	Number of Interventions	Number of Controls	Intervention	Control	Subgroup Analysis	Protocol Published	Funder
Rapp 1983[68]	1983	Journal of Neurosurgery	Single-blind	Trauma	TBI	38	20	18	Total parenteral nutrition	Standard enteral nutrition	—	No	Baxter Travenol Laboratories, Deerfield, Illinois
Rockswold 1992[69]	1992	Journal of Neurosurgery	Single-blind	Trauma	Severe TBI	168	84	82	Hyperbaric oxygen therapy	Control	Initial GCS score, peak ICP >29 mm Hg	No	Minneapolis Medical Research Foundation
Shiozaki 1993[70]	1993	Journal of Neurosurgery	Nonblind	Trauma	Severe TBI	33	16	17	Hypothermia	Normothermia	—	No	Not reported
Vahedi 2007[71]	2007	Stroke	Single-blind, multicenter	Vascular	Middle cerebral artery infarction	38	20	18	Early decompressive craniectomy	Conservative therapy	Age, infarction volume	Yes	Programme Hospitalier de Recherche Clinique of the French Ministry of Health. Departement de la Recherche Clinique et du Developpement of Assistance Publique-Ho-pitaux de Paris
Juttler 2007[72]	2007	Stroke	Nonblind, multicenter	Vascular	Middle cerebral artery infarction	32	17	15	Decompressive hemicraniectomy	Conservative therapy	—	Yes	University of Heidelberg
Etemadrezaie 2007[73]	2007	Clinical Neurology and Neurosurgery	Double-blind	Trauma	Severe TBI	90	44	46	Fresh frozen plasma	Placebo	—	No	The Research Counselor of Mashhad University of Medical Sciences
Yang 2009[16]	2009	International Journal of Nursing Studies	Single-blind	Trauma	Severe TBI	240	121	119	Intensive insulin (continuous infusion)	Conventional insulin therapy (only when glucose levels >11.1 mmol/L)	GCS of 3–5 versus 6–8 at entry	No	Nature Science Foundation of Heilongjiang Province
Hofmeijer 2009[74]	2009	Lancet Neurology	Single-blind, multicenter	Vascular	Acute ischemic stroke	64	32	32	Early decompressive surgery	Conservative therapy	Age, time of randomization	Yes	Grant from the Netherlands Heart Foundation
Molyneux 2009[14]	2009	Lancet Neurology	Nonblind, multicenter	Vascular	Ruptured intracranial aneurysm	2143	1046	1041	Endovascular coiling	Neurosurgical clipping	WFNS grade at randomization, age groups by decade, amount of blood on CT scan (Fisher grade), and lumen size of aneurysm and its site	Yes	UK Medical Research Council
Bernard 2010[18]	2010	Ann Surg	Single-blind, multicenter	Trauma	Severe TBI	312	157	142	Prehospital rapid sequence intubation by paramedics	Transport to a hospital emergency department for intubation by physicians	Initial GCS $\geq$ 5, patients aged $\leq$60 years, patients with EMS transport time >20 minutes	No	The National Health and Medical Research Council of Australia and the Victorian Transport Accident Commission
Mendelow 2015[75]	2015	Journal of Neurotrauma	Single-blind, multicenter	Trauma	Traumatic intracerebral hemorrhage	170	82	85	Early decompressive surgery	Initial conservative treatment	Age, volume of hematoma, GCS	Yes	National Institute of Health Research (NIHR) Health Technology Assessment program
Berkhemer 2015[76]	2015	New England Journal of Medicine	Single-blind, multicenter	Vascular	Acute ischemic stroke	500	233	267	Endovascular treatment	Conventional treatment	NIHSS score, age, occlusion of internal-carotid artery terminus, additional occlusion, time to randomization, ASPECTS	Yes	Dutch Heart Foundation and AngioCare Covidien/ev3, Medac/Lamepro, and Penumbra
Van den Berg 2017[22]	2017	New England Journal of Medicine	Single-blind, multicenter	Vascular	Acute ischemic stroke	417	194	197	Endovascular treatment	Conventional treatment	NIHSS score, age, occlusion of internal-carotid artery terminus, additional occlusion, time to randomization, ASPECTS	Yes	Dutch Heart Foundation and AngioCare Covidien/ev3, Medac/Lamepro, Stryker and Penumbra

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Adzick 2011	+	+	−	+	+	+	+
Allen 1983	?	?	+	+	+	?	−
Anderson 2006	+	+	−	−	+	?	−
Andrews 2015	+	+	−	+	+	+	+
Ballotta 2005	+	+	−	−	+	?	?
Barnett 1998	+	+	−	+	+	?	?
Berkhemer 2015	+	+	−	+	+	+	−
Bernard 2010	+	+	−	+	−	?	?
Campbell 2015	+	+	−	+	?	+	+
Clark 2016	+	+	+	+	−	+	+
Cooper 2011	+	+	−	+	+	+	+
CRASH-3 group 2019	+	+	+	+	+	+	+
Derdeyn 2014	+	+	−	+	+	+	−
Dhandapani 2008	+	+	−	−	+	?	?
Dwivedi 2017	+	+	−	+	+	+	+
Eckstein 2008	+	+	−	−	+	?	−
Edwards 2005	+	+	+	+	+	+	+
Engel 2012	+	+	−	+	−	+	−
Etemadrezaie 2007	+	+	+	+	+	?	?
Gerritsen 2002	+	+	−	−	+	+	?
Goyal 2015	+	+	−	+	+	+	?
Halliday 2004	+	+	−	+	+	+	+
Halliday 2010	+	+	−	+	+	−	+
Harders 1996	?	?	+	+	+	?	−

Supplementary Figure 1. Risk of bias analysis results.

Hellum 2011	+	+	−	+	−	+	+
Hofmeijer 2009	+	+	−	+	+	+	+
Jarvik 2009	+	+	−	+	+	−	+
Jiang 2000	?	?	−	+	+	?	?
Jiang 2005	+	+	−	+	+	?	?
Jiang 2006	+	−	−	+	+	?	?
Jovin 2015	+	+	−	+	+	+	−
Jüttler 2007	+	+	−	−	+	+	+
Jüttler 2014	+	+	−	−	+	+	+
Klazen 2010	+	+	−	−	+	+	+
Kupsch 2006	+	+	+	+	+	−	+
Li 2012	?	?	−	−	+	?	?
Ly-Pen 2005	+	+	−	−	−	?	?
Marion 1997	+	+	−	+	+	?	?
Mendelow 2015	+	+	−	+	+	+	+
Miyamoto 2014	+	+	−	−	+	?	+
Mohr 2017	+	+	−	−	+	+	+
Molyneux 2002	+	+	−	−	−	+	−
Molyneux 2005	+	+	−	−	+	+	−
Molyneux 2009	+	+	−	−	+	+	−
Patchell 1990	+	+	−	−	+	?	?
Patchell 1998	+	+	−	−	+	?	?
Patchell 2005	+	+	−	−	+	?	+
Perez-Barcena 2008	+	?	−	+	+	−	+
PHVD trial group 1998	+	+	−	?	+	?	?
Pickard 1989	+	−	+	+	+	?	−
Qiu 2007	+	+	−	−	?	?	?
Qiu 2009	+	+	−	+	+	+	+
Rapp 1983	?	?	−	+	+	?	−
Robert 2005	?	+	−	−	+	?	?
Rockswold 1992	?	?	−	+	+	?	?
Rockswold 2013	?	?	−	+	+	−	?
Santarius 2009	+	+	−	+	+	+	+
Saver 2015	+	?	−	+	+	+	−
Shiozaki 1993	?	?	−	−	+	?	?

Supplementary Figure 1. (Continued).



Supplementary Figure 1. (Continued).

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