

The Efficacy and Safety of Ischemic Stroke Therapies: An Umbrella Review

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Background: Ischemic stroke is a leading cause of morbidity and mortality in neurological diseases, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). Numerous studies have evaluated the efficacy and safety of ischemic stroke therapies, but clinical data were largely inconsistent, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). Therefore, it is necessary to summarize and analyze the published clinical research data in the field, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).

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based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).

Objective: Li Y et al., based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). (Front Pharmacol, 2022 22;13:924747) aimed to perform an umbrella review to evaluate the efficacy and safety of ischemic stroke therapies, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).

Methods: Li Y et al., based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). (Front Pharmacol, 2022 22;13:924747) conducted a search for meta-analyses and systematic reviews on PubMed, the Cochrane Library, and the Web of Science to address this issue, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). Li Y et al., based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). (Front Pharmacol, 2022 22;13:924747) examined neurological function deficit and cognitive function scores, quality of life, and activities of daily living as efficacy endpoints and the incidence of adverse events as safety profiles, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).

Results: Forty-three eligible studies including 377 studies were included in the umbrella review, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). The results showed that thrombolytic therapy (tPA; alteplase, tenecteplase, and desmoteplase), mechanical thrombectomy (MTE), edaravone with tPA, stem cell-based therapies, stent retrievers, acupuncture with Western medicines, autologous bone marrow stromal cells, antiplatelet agents (aspirin, clopidogrel, and tirofiban), statins, and Western medicines with blood-activating and stasis-dispelling herbs (NaoShuanTong capsule, Ginkgo biloba, Tongqiao Huoxue Decoction, Xuesaitong injection) can improve the neurological deficits and activities of daily living, and the adverse effects were mild for the treatment of ischemic stroke, based on the Li Y et al.

INTRODUCTION

Ischemic stroke is a major cause of death and disability, so prevention and effective treatment of stroke are of utmost importance in China and the West, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). The World Health Organization has suggested that an incidence of stroke occurs once every 5 s worldwide, approximately one-third of strokes are fatal, and another third leave survivors with permanent disability (Donkor, 2018), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Moreover, surviving stroke patients impose a heavy medical burden on families and communities (Go et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2014), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). However, little is known about the efficacy and safety of treatments of ischemic stroke in the hyper-acute (0–24 h) and acute phases (1–7 days) and recovery period (>7 days) post-stroke in humans (Marzolini et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2019), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). The key challenge in the treatment of stroke is to identify the most effective way to implement the efficacious interventions currently available, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

Some evidence supports national guidelines recommending the use of recombinant tissue plasminogen activator (tPA) thrombolysis for the treatment of hyperacute ischemic stroke, which can significantly improve neurological deficits (Li et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2017; Zhou et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2020), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). In addition, the guidelines also

recommend antithrombotic (including antiplatelet and independently, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747) anticoagulant therapy), neuroprotection, traditional Chinese medicine, statins, and control of high-risk factors for articles, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). secondary prevention of ischemic stroke (Practice, 2021), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Additionally, as a bradykinin B1 and B2 receptor agonist, HUK provides functional benefits (Patel and McMullen, 2017), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Furthermore, other neuroprotective drugs are supported by comprehensive clinical reports that demonstrate their efficacy and safety in improving cognitive impairment or other major domains (Practice, 2021), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

Attempts to many systematic reviews and meta-analyses have been conducted to analyze the different stroke treatments, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). These studies, however, did not provide comprehensive appraisals of stroke therapies, and some results are still conflicting (Wu et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2007), based on

Cochrane Library until March 2022, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). The database search terms were as follows: (Ischemic stroke) and (systematic review or meta-analysis) and clinical trial, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Li Y et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747) included meta-analyses and systematic reviews that determined the efficacy and safety of treatments in patients with stroke, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Inclusion criteria were: 1) written in English; 2) published systematic review or meta-analyses; 3) including any evaluation of clinical assessment scales for stroke; 4) published in peer-reviewed journals, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Studies were excluded if 1) unpublished studies; 2) no necessary sample data; 3) patients were diagnosed with other strokes; 4) the study reported insufficient details and other outcomes; and 5) the study presented the risk of bias/study limitations, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

The AMSTAR2 tool was used to evaluate systematic reviews and meta-analyses (Shea et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2007; De Santis et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2021), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). The methodological quality of the studies was determined by the percentage of AMSTAR2 score, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). The percentage of AMSTAR2 score was classified into 0–33%, 34–66%, and 67%–100% indicating low quality, medium quality, and high quality, respectively, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

Li Y et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747) (Front Pharmacol, 2022;22:13:924747) searched for related articles using keywords and filtering

titles, and two investigators screened the literature (Front Pharmacol, 2022;22:13:924747).

Articles were downloaded and the abstracts screened using inclusion criteria, deleting any irrelevant or repetitive (Front Pharmacol, 2022;22:13:924747).

the Li Y et al. (Front Pharmacol, 2022;22:13:924747). A review of the latest literature, having removed repeated studies and research involving complications, followed by a meta-analysis to derive at pooled prevalence, was needed, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Therefore, the present study aimed to perform an umbrella review of the systematic reviews and meta-analyses of stroke therapies through a comprehensive and updated literature search and to reach a definitive conclusion by integrating all available meta-analyses to identify which of the commercially available treatments for ischemic stroke patients are efficacious and safe, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

MATERIALS AND METHODS

Our study was performed in accordance with the standard guidelines of Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) (Moher et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747), 2009), based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). The protocol for this review was prospectively registered at INPLASY PROTOCOL (INPLASY202250145), based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).

Search Strategy and Quality Assessment A

A systematic search of published peer-reviewed English language literature was conducted using PubMed, Web of Science, and the

Thereafter, Li Y et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). (Front Pharmacol, 2022 22;13:924747) manually searched the reference lists of the chosen studies for any other relevant studies not found in our initial search, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). Finally, a full-text search was performed to extract and then analyze the data from articles, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).

Data Extraction

According to the following criteria, three investigators (Yongbiao Li, Ruyi Cui, and Fangcheng Fan, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).)

independently selected those trials that met the inclusion criteria, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). The main characteristics of the selected study were extracted in a table including the year of publication, study design, number of studies, and regimens for the treatment, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). Li Y et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). (Front Pharmacol, 2022 22;13:924747) included results evaluating the efficacy of drugs in patients with at least one of the clinical assessment scales: 1) the incidence of intracranial hemorrhage (ICH); 2) the primary outcomes included: global neurological deficit scores such as the National

Institutes of Health Stroke Scale (NIHSS) score ≤ 1 and the Neurological Function Deficit Scores (NFDS); 3) all-cause mortality; 4) dependence assessed by Barthel Index (BI) scores ≥ 95 ; 5) modified Rankin Scale score of 0–1 or return to baseline (mRS); 6) clinical effect, defined according to the nationally approved criteria, is divided into essentially recovered, significant improvement, improvement, no change, deterioration, and death (the first three categories are judged to be effective); 7) the secondary outcomes included the following: cognitive function scoring; related hemorheology and lipid metabolism outcomes; quality of life; and 8) incidence of adverse events (AE), based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). The selection of assessments was extracted on study size, sample size, mean difference (Fixed, 95% CI) or odds ratio (Fixed, 95% CI), and heterogeneity (I^2), based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). A percentage of 0–25% was classified as mild, 26–50%, as moderate, and 51–75%, as significant between-study heterogeneity, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). If $I^2 > 50\%$, a random-effects model was used for the analysis, or the data were analyzed on the fixed-effects model (Wang et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2016), based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).

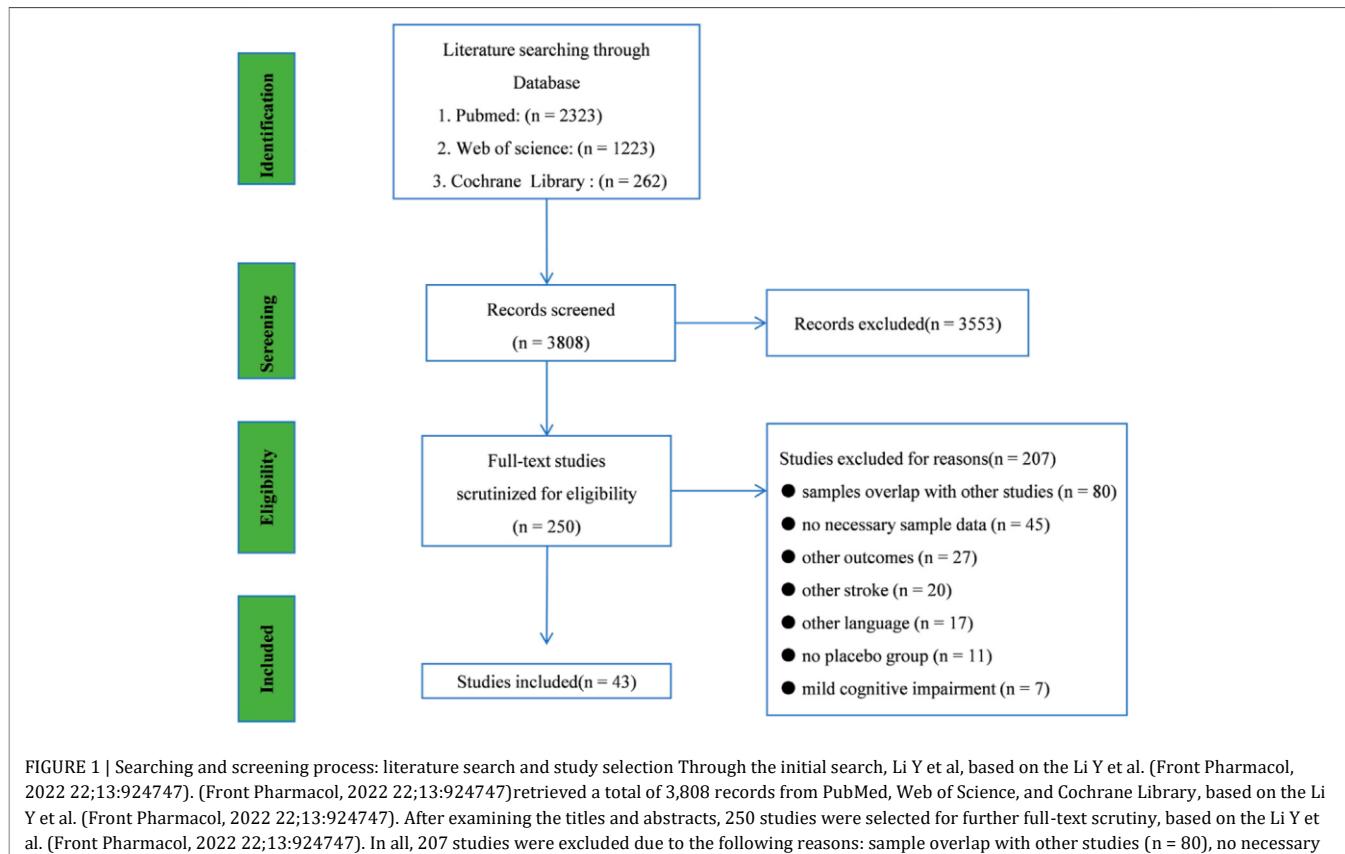


FIGURE 1 | Searching and screening process: literature search and study selection Through the initial search, Li Y et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). (Front Pharmacol, 2022;22:13:924747) retrieved a total of 3,808 records from PubMed, Web of Science, and Cochrane Library, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). After examining the titles and abstracts, 250 studies were selected for further full-text scrutiny, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). In all, 207 studies were excluded due to the following reasons: sample overlap with other studies (n = 80), no necessary sample data (n = 45), other outcomes (n = 27), other stroke (n = 20), other language (n = 17), no placebo group (n = 11), and mild cognitive impairment (n = 7), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

Statistical Analysis

The sample size and mean difference were used to calculate the four clinical assessment scales, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). NIHSS/mRS/BI scores were used to evaluate neurological status, and behavioral symptoms in patients were calculated by NFDS, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Li Y et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). (Front Pharmacol, 2022;22:13:924747) focused on the clinical effect is divided into essentially recovered, significant improvement, no change, deterioration; cognitive function scoring; quality of life as activities of daily living, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). All data analyses were performed by GraphPad Prism 5, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747) software, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). The results were expressed as OR \pm SD (standard deviation), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). The adverse events have assessed the incidence of adverse events, and the OR was calculated, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Therefore, mean difference or odds ratio with 95% CI and p values were used to assess the efficacy and safety of the study medications, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

the umbrella review: Pan et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2020; Pan et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2020; Liu et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2021; (Liu et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2011); Blann et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2015); (Blann et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2015); Emberson et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2014) (Emberson et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2014); Peng et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2014); (Peng et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2014); Zhang et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2019); Shang et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2019); Puñal-Riobó et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2015; Yuan et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2008; (Fu et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2013), Fan et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2014), Lin et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2014); Xu et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2015); Cao and Li, (2015); Marmagkiolis et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2015); Zheng et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747),

2017), Li et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2017), Zhang et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2017), Chong et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2020); (Zhao et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2021), Li et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). (2020); (Li et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2020), Gao et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2021); Huang et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2020); (Huang and Xiao, 2021), Liu et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2022), Feng et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2021), Lee et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). (2010); Zhou et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2022); Hu et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2021); Hong and Lee, 2015, Liu et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).,

RESULTS

Literature search and study selection through the initial search, Li Y et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). (Front Pharmacol, 2022 22;13:924747) retrieved a total of 3,808 records from PubMed, Web of Science, and Cochrane Library, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). After examining the titles and abstracts, 250 studies were selected for further full-text scrutiny, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). In all, 207 studies were excluded due to the following reasons: samples overlap with other studies ($n = 80$), no necessary sample data ($n = 45$), other outcomes ($n = 27$), other stroke ($n = 20$),

other language ($n = 17$), no placebo group ($n = 11$), mild impairment ($n = 7$), (Figure 1), based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). Thus, 43 studies were included in

2021); (Liu et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2021), Xin et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2020); Katsanos et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2020), Wang et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2021), Liu et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2019; (Liu et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2019), Xu et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2019); (Zhang et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2019), (Huang et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2020), Yang et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2015), Yang et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2015), (Ni et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2020); (Thelengana et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).,

2019), Shi et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., 2014) and (Siddiqui et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747)., scores of the included studies are shown in Table 1 and Supplementary material, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).

As shown in Table 1, a total of 377 clinical trials were included, with 43 drug therapies in the treatment groups, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). All studies were randomized controlled clinical trials, and the treatment duration ranged from 1 to 72 weeks, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). In total, 24 meta-analyses included were of high quality according to AMSTAR2 score, 12 meta-

analyses included were of middle quality according to AMSTAR2 score, and seven meta-analyses included were of

TABLE 1 | Description and AMSTAR2 scores of included studies, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).

Study	Condition	Studies included	Study duration (median, range)	Daily dose (median, range)	Outcome	AMSTAR2 score	Study quality
Ni et al, based on	Ligustrazine versus placebo	3	14w (2w–48w)	240 mg/day	1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747). AE	5/11	low
Xin et al, based on	Heparin versus Placebo	9	12w	<40 mg/day	1, based on the Li Y et al. SICH, 4, based on the Li Y et al. NIHSS	7/11	middle
Shang et al, based on	MTE versus placebo	7	12w	NA	1, based on the Li Y et al. NIHSS	8/11	high
Kaesmacher et al, (2019)	tPA plus MTE versus placebo	12	12w	NA	1, based on the Li Y et al. NIHSS	9/11	high
Li et al, based on	Acupuncture plus XM versus placebo	17	12W	NA	1, based on the Li Y et al. NIHSS	8/11	high
Liu et al, based on	Nimodipine versus placebo	8	18w (12w–24w)	NA	1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747). AE	10/11	high
Blann et al, based on	Aspirin plus clopidogrel versus placebo	24	12w	60 mg/day	1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747). AE	9/11	high
Emberson et al, (2014)	tPA versus placebo	12	3 h (0–6 h)	<0, based on the Li Y et al. Front Pharmacol, 2022;13:924747). AE	1, based on the Li Y et al. NIHSS	10/11	high
Peng et al, based on	XNJ versus placebo	13	4w	45 ml (30–60 ml/day)	1, based on the Li Y et al. Front Pharmacol, 2022;13:924747). AE	6/11	middle
Zhang et al, based on	NST versus placebo	13	12w	50 mg/day	1, based on the Li Y et al. and 4, based on the Li Y et al. (Front Pharmacol, 2022;13:924747). mRS	10/11	high
Yuan et al, based on	Chuanxiong versus Placebo	3	24w (1w–48w)	120 mg (80–160 mg/day)	1, based on the Li Y et al. NIHSS	10/11	high
Fu et al, based on	XXMT versus placebo	8	12w (4w–24w)	NA	1, based on the Li Y et al. (Front Effect)	5/11	low
Fan et al, based on	Safflower yellow versus placebo	7	2w	50 mg/day	1, based on the Li Y et al. (Front Effect)	5/11	low
Lu et al, based on	Rhubarb versus placebo	12	2w (1w–4w)	NA	1, based on the Li Y et al. and 4, based on the Li Y et al. (Front Pharmacol, 2022;13:924747). NIHSS, and 5, based on the Li Y et al. (Front Pharmacol, 2022;13:924747). AE	6/11	middle
Xu et al, based on	WD versus placebo	13	2w (2w–4w)	NA	1, based on the Li Y et al. (Front NFDS)	4/11	low
Cao and Li, based on	MSCs versus placebo	5	3w (1w–6w)	5 × 10 ⁷ –2, based on and 4, based on the Li Y et al. (Front Pharmacol, 2022;13:924747). AE	1, based on the Li Y et al. NIHSS	6/11	middle
Marmagkiolis et al, (2015)	stent retrievers versus placebo	5	12w	NA	1, based on the Li Y et al. and 3, based on the Li Y et al. NIHSS	8/11	high
Zheng et al, based on	Puerarin versus placebo	16	1w (1w–2w)	300 mg (100–500 mg/day)	1, based on the Li Y et al. NIHSS	6/11	middle
Li et al, based on	Alpha1 versus placebo	6	6 h (3–9 h)	90 mg/kg/day	1, based on the Li Y et al. (Front Effect)	8/11	high
Zhang et al, based on	Cerebrolysin versus placebo	7	12w (1w–12w)	50 ml/day	1, based on the Li Y et al. NIHSS	9/11	high
Chong et al, based on	Ginkgo biloba versus placebo	12	12w (1w–12w)	100 mg (40–160 mg)/day	1, based on the Li Y et al. SICH, and 4, based on the Li Y et al. NIHSS	9/11	high
Li et al, based on	Stem cell-based versus placebo	9	12w (1w–12w)	5 × 10 ⁶ –2, based on the cell	1, based on the Li Y et al. and 4, based on the Li Y et al. NIHSS	9/11	high
Zhou et al, based on	tirofiban versus placebo	6	18w (12w–24w)	(0, based on the Li Y et al. and 3, based on the Li Y et al. (Front Pharmacol, 2022;13:924747). AE)	1, based on the Li Y et al. NIHSS	5/11	low
Gao et al, based on	BHD versus placebo	11	16w (8w–24w)	NA	1, based on the Li Y et al. (Front Effect)	9/11	high
Huang and Xiao, (2021)	Albumin versus placebo	4	15w (2w–48w)	1, based on the Li Y et al. (0, based on the Li Y et al. NIHSS)	1, based on the Li Y et al. NIHSS	9/11	high
Liu et al, based on	DZSM versus placebo	28	7w (1w–13w)	NA	1, based on the Li Y et al. and 4, based on the Li Y et al. (Front Pharmacol, 2022;13:924747). NIHSS	10/11	high
Feng et al, based on	XST plus XM versus placebo	12	2w (2w–4w)	NA	1, based on the Li Y et al. (Front Effect)	5/11	middle
Lee et al, based on	Intra-A versus placebo	5	12w	NA	1, based on the Li Y et al. (Front NIHSS)	5/11	middle
Zhou et al, based on	TQHX plus XM versus placebo	12	4w	NA	1, based on the Li Y et al. (Front Effect)	9/11	high
Hu et al, based on	Edaravone plus rt-PA versus placebo	17	2w (1w–4w)	60 mg/day	1, based on the Li Y et al. (Front Effect)	5/11	middle
Hong and Lee, (2015)	Statins versus placebo	18	6w (1w–12w)	8 mg/kg/day	1, based on the Li Y et al. (Front Effect)	9/11	high

(Continued on following page)

TABLE 1 | (Continued) Description and AMSTAR2 scores of included studies, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

Study	Condition	Studies included	Study duration (median, range)	Daily dose (median, range)	Outcome	AMSTAR2 score	Study quality
Liu et al., based on	ZL versus placebo	7	2w	1, based on the Li Y (1, based on the Li Y	1, based on the Li Y et al. NIHSS	7/11	middle
Xin et al., based on	salvianolic acids versus placebo	12	2w (1w–4w)	200 mg (100–300 mg/day)	1, based on the Li Y et al. mRS, and 4, based on the Li Y	4/11	low
Katsanos et al., (2020)	Colchicine versus placebo	4	74w (4w–144w)	0, based on the Li Y	1, based on the Li Y et al.	3/11	low
Liu et al., based on	ANP versus placebo	18	2w	3 g/day	1, based on the Li Y et al.	9/11	high
Xu et al., based on	NBP versus placebo	12	6w (1w–12w)	100 mg/day	1, based on the Li Y et al. (Front	9/11	high
Wang et al., based	Pntsp versus placebo	20	6w (2w–10w)	470 mg (140–800 mg/day)	1, based on the Li Y et al. (Front and 4, based on the Li Y et al.	10/11	high
Huang et al., based	HUK versus placebo	16	3 h (0–6 h)	0, based on the Li Y	1, based on the Li Y et al.	7/11	middle
Yang et al., based	Mailuoning versus Placebo	21	12w	204 mg (8–400 mg/day)	1, based on the Li Y et al. (Front 4, based on the Li Y et al.	9/11	high
Ni et al., based on	Cinepazide maleate versus placebo	4	7w (2w–12w)	320 mg/day	1, based on the Li Y et al. (Front	7/11	middle
Thelengana et al., (2019)	TNK versus placebo	4	3 h (0–6 h)	0, based on the Li Y et (0, based on the Li Y et	1, based on the Li Y et al. 4, based on the Li Y et al.	9/12	high
Shi et al., based on	Cilostazol versus placebo	6	30w (1w–60w)	690 mg (80–1300 mg/day)	1, based on the Li Y et al.	10/11	high
Siddiqui et al., (2013)	MLC601 versus placebo	2	13w (2w–24w)	405 mg (10–800 mg/day)	1, based on the Li Y et al. (Front Pharmacol, 2022 22:13:924747). NFDs and	5/11	low

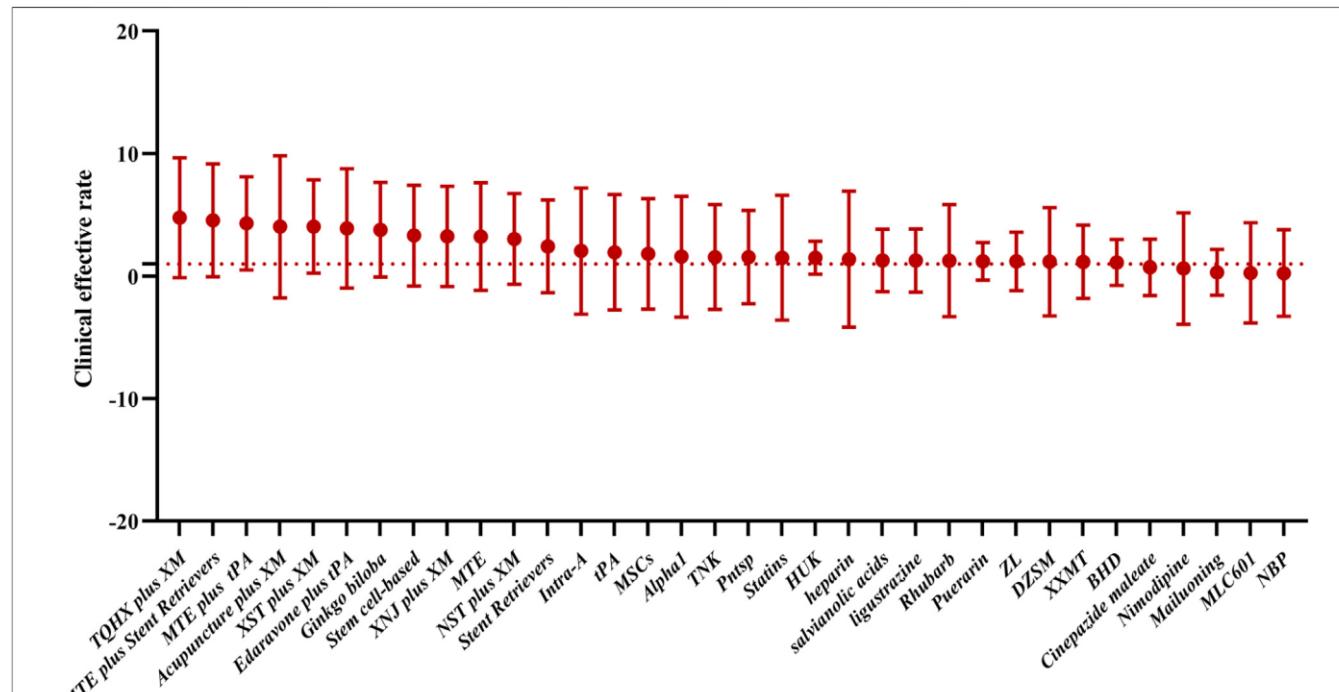


FIGURE 2 | Total clinical efficacy was used to evaluate the effect of drug therapy on ischemic stroke, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). In this study, the possible order of efficacy of the drugs was TQHX plus XM, MTE plus stent retrievers, MTE plus tPA, acupuncture plus XM, XST plus XM, edaravone plus tPA, Ginkgo biloba, stem cell-based therapy, XNJ plus XM, MTE, NST plus XM, stent retrievers, intra-A, tPA, MSCs, Alpha1, TNK, Pntsp, statins, HUK, heparin, salvianolic acids, ligustrazine, rhubarb, puerarin, ZL, DZSM, XXMT, BHD, cinepazide maleate, nimodipine, Mailuoning, MLC601, and NBP, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

TABLE 2 | Results of pairwise meta-analyses for the clinical effect, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

Comparative medication	Reference medication	Number of studies	Number of control	Number of patients	Pairwise meta-analyses	MD/OR/RR	95% CI	I ²	P
Ligustrazine	Placebo	3	321	322	1, based on	[1, based on the Li	NA	0, based	
Acupuncture	Placebo	14	643	536	4, based on	[2, based on the Li	0	0, based on	
tPA	Placebo	4	814	804	1, based on	[1, based on the Li	NA	0, based	
Nimodipine	Placebo	8	677	806	0, based on	[0, based on the Li	NA	0, based on	
Aspirin plus clopidogrel	Placebo	12	100	100	1, based on	[1, based on the Li	NA	0, based	
XNJ	Placebo	13	431	408	3, based on	[2, based on the Li	0	0, based on	
NST	Placebo	13	246	243	3, based on	[1, based on the Li	0	0, based on	
Stem cell-based therapy	Placebo	20	950	844	3, based on	[2, based on the Li	0	0, based on	
Edaravone plus rt-PA	Placebo	15	591	591	3, based on	[3, based on the Li	0	0, based on	
XXMT	Placebo	8	242	289	1, based on	[1, based on the Li	0	0, based on	
Rhubarb	Placebo	12	350	438	1, based on	[1, based on the Li	18	0, based on	
WD	Placebo	13	3,773	3,341	1, based on	[1, based on the Li	46	0, based on	
Puerarin	Placebo	16	1,427	1,540	1, based on	[1, based on the Li	47	0, based on	
Alpha1	Placebo	6	217	222	1, based on	[1, based on the Li	0	0, based	
BHD	Placebo	11	350	334	1, based on	[0, based on the Li	69	0, based	
XST plus XM	Placebo	12	879	890	4, based on	[2, based on the Li	NA	0, based	
Ginkgo biloba	Placebo	9	417	416	3, based on	[2, based on the Li	NA	0, based on	
TQHX plus XM	Placebo	12	733	755	5, based on	[3, based on the Li	NA	0, based on	
ZL	Placebo	7	293	278	1, based on	[1, based on the Li	0	0, based on	
HUK	Placebo	9	338	338	1, based on	[1, based on the Li	0	0, based on	
Statins	Placebo	18	3,013	2,988	1, based on	[1, based on the Li	0	0, based	
Salvianolic acids	Placebo	12	1884	1893	1, based on	[1, based on the Li	14	0, based on	
Pntsp	Placebo	20	48	48	1, based on	[1, based on the Li	0	0, based on	
DZSM	Placebo	5	341	340	1, based on	[1, based on the Li	85, based on the Li et al. (Front Pharmacol, 2022;22:13:924747)	0, based on the Li et al. (Front Pharmacol, 2022;22:13:924747)	

CI, confidence interval; MD, mean difference; OR, risk ratio; I², heterogeneity; NST, NaoShuanTong capsule; XNJ, Xingnaojing capsule; XXMT, Xiaoxumeng decoction; Pntsp, Panax notoginseng Saponin; XST, plus XM: Xuesaitong injection plus Western medicines; TQHX, Tongqiao Huoxue decoction; ZL, Zhilong Huoxue Tongyu capsule; BHD, Buyang Huanwu decoction; Alpaga1: Desmoteplase; WD, Wen Dan Decoction, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Western medicines (XM) (tPA, antiplatelet agents, statins, and edaravone), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

low quality according to AMSTAR2 score, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). The total clinical efficacy was used to evaluate the effect of drug therapy on ischemic stroke (Figure 2), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

Clinical Effect

Clinical effective rate was observed in 18 studies, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Detailed characteristics of included studies are listed in nimodipin (OR: 0, 95% CI: 0, based on aspirin plus clopidogrel (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).82, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).08-2, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).57), tissue plasminogen (tPA) (RR: 1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).95, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).10-2, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).56), Wen Dan Decoction (WD) (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).60, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).43-1, based on the Li Y et al. (Front

plus XM (OR: 4, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).04, 95% CI: 2, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).93-5, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).57), and DZSM (Dengzhan Shengmai capsule) (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).18, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).12 to 1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).24) was significantly better compared with placebo, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Moreover, ANP, ZL, and edaravone combined with western medicines significantly improve the total clinical effective rate compared to placebo, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

NIHSS Score

The effects of the medications on clinical change were assessed by National Institutes of Health Stroke Scale (Table Pharmacol, 2022;22:13:924747).79), Xingnaojing capsule and Western medicines (XNJ) (OR: 3, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).25, 95% CI: 2, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).30-4, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).59), NaoShuanTong capsule plus Western medicines (NST plus XM) (OR: 3, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).04, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).76-5, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).26), Xiaoxumeng decoction (XXMT) (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022;

22;13:924747).17, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).09–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).26), Rhubarb (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).27, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).18–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).37), stem cell-based (OR: 3, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).31, 95% CI: 2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).54–4, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).31), puerarin (RR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).22, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).17–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).28), Buyang Huanwu decoction (BHD) (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).12, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).99–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).27), statins (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).5, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).29–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).75), salvianolic acids (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).29, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).25–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).33), Panax notoginseng saponin (Pntsps) (RR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).55, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).37–2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).55), Xuesaitong injection plus western medicines (XST plus XM) (OR: 4, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).04, 95% CI: 2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).86–5, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).73), Tongqiao Huoxue Decoction plus Western medicines (TQHX plus XM) (OR: 5, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).43, 95% CI: 3, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).77–7, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).82), Ginkgo biloba (RR: 3, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).79, 95% CI: 2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).49–5, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).78), edaravone plus rt-PA (OR: 3, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).90, 95% CI: 3, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).02–5, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).02) Zhilong Huoxue Tongyu capsule (ZL) (RR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).2, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).12–2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).29), desmoteplase (alpha1) (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).59, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).08–2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).35), acupuncture

(20, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).0%) showed that XXMT (MD: -1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).86, 95% CI: -3, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).25–0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).48), safflower yellow (MD: -3, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).42, 95% CI: -5, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).38–2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).98), MSCs (MD: -1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).85, 95% CI: -2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).77–0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).93), ZL (MD: -2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).6, 95% CI: -3, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).41–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).79), salvianolic acids (MD: -1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).44, 95% CI: -1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).97–0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).91), heparin (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).95, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).74–5, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).11), XST (MD: -3, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).17, 95% CI: -4, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).14 to -2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).20), intra-arterial fibrinolysis (Intra-A) (OR: 2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).24, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).27–3, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).95), edaravone plus rt-PA (MD: 3, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).95, 95% CI: 2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).92–4, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).99), and human urinary kallidinogenase (HUK) (MD: -1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).65, 95% CI: -2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).12–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).71) were significantly different compared with placebo, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). In contrast, DL-3-n-butylphthalide (NBP) (OR: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).73, 95% CI: -0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).14 to 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).59, p = 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).1), BHD (MD: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).66, 95% CI: -1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).08 to 4, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).40, p = 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).1), and DZSM (MD: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).57, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).44, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).73, p = 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).11) showed no change or a deterioration,

based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).

Rankin Scale (mRS) Score

From our search, the effects of the medications on clinical change were assessed by Rankin Score (mRS) (Table 4), based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). In total, 18 studies (42, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).5%) including tPA (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022

22;13:924747).31, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).07–3, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).59), tPA plus mechanical thrombectomy (MTE) (OR: 4, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).32, 95% CI: 2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).16–7, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).46),

TABLE 3 | Results of pairwise meta-analyses for the NIHSS score, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

Comparative medication	Reference medication	Number of studies	Number of control	Number of patients	Pairwise meta-analyses			
					MD/OR/RR	95% CI	I ₂	P
Heparin	Placebo	9	260	317	1, based on the Li Y	[0, based on the Li Y	80	0, based
XXMT	Placebo	8	91	95	-1, based on the Li	[-3, based on the Li Y	10	0, based
Safflower yellow	Placebo	7	368	394	-3, based on the Li	[-5, based on the Li Y	82	0, based
MSCs	Placebo	5	52	57	-1, based on the Li	[-2, based on the Li Y	24	0, based on
BHD	Placebo	11	96	96	1, based on the Li Y	[-1, based on the Li Y	64	0, based
XST	Placebo	12	879	890	-3, based on the Li	[-4, based on the Li Y	NA	0, based
Intra-A	Placebo	5	130	204	2, based on the Li Y	[1, based on the Li Y	0	0, based
Edaravone plus rt-PA	Placebo	17	860	859	3, based on the Li Y	[2, based on the Li Y	92	0, based on
ZL	Placebo	7	115	330	-2, based on the Li	[-3, based on the Li Y	50	0, based on
Salvianolic acids	Placebo	12	435	462	-1, based on the Li	[-1, based on the Li Y	57	0, based
NBP	Placebo	12	108	108	0, based on the Li Y	[-0, based on the Li Y	89	0, based
HUK	Placebo	16	667	659	-1, based on the Li	[-2, based on the Li Y	84	0, based on
DZSM	Placebo	5	341	340	0, based on the Li Y	[0, based on the Li Y	44, based	0, based

CI, confidence interval; MD, mean difference; OR, risk ratio; I₂, heterogeneity; rt-PA, alteplase; MSCs, autologous bone marrow stromal cells; XXMT, Xiaoxuming decoction; XST, Xuesaitong injection; NBP, DL-3-n-butylphthalide; BHD, Buyang Huanwu decoction; Intra-A, intra-arterial Fibrinolysis; HUK, human urinary kallidinogenase, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

TABLE 4 | Results of pairwise meta-analyses for the mRS score, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

Comparative medication	Reference medication	Number of studies	Number of control	Number of patients	Pairwise meta-analyses			
					MD/OR/RR	95% CI	I ₂	P
Heparin	Placebo	12	2,145	550	1, based on the Li Y	[0, based on the Li Y	83	0, based
Safflower yellow	Placebo	13	368	394	-4, based on the Li	[-5, based on the Li Y	52	0, based
Rhubarb	Placebo	13	350	438	3, based on the Li Y	[2, based on the Li Y	18	<0, based
MSCs	Placebo	7	86	86	1, based on the Li Y	[0, based on the Li Y	57	0, based
tPA	Placebo	4	814	804	1, based on the Li Y	[1, based on the Li Y	NA	0, based
MTE	Placebo	5	414	404	3, based on the Li Y	[1, based on the Li Y	NA	0, based
MTE plus stent retrievers	Placebo	5	142	143	4, based on the Li Y	[2, based on the Li Y	0	0, based on
tPA plus MTE	Placebo	17	2639	2640	4, based on the Li Y	[2, based on the Li Y	51	0, based
Stent retrievers	Placebo	5	653	634	2, based on the Li Y	[1, based on the Li Y	0	0, based on
Cerebrolysin	Placebo	5	971	808	-0, based on the Li	[-1, based on the Li Y	73, based	0, based
Intra-A	Placebo	12	171	224	2, based on the Li Y	[1, based on the Li Y	0	0, based
ZL	Placebo	9	45	60	-0, based on the Li	[-0, based on the Li Y	37	0, based on
Salvianolic acids	Placebo	7	210	242	-0, based on the Li	[-1, based on the Li Y	0	0, based
DZSM	Placebo	28	341	340	-0, based on the Li	[-1, based on the Li Y	85, based	0, based on
Cinepazide maleate	Placebo	4	236	234	0, based on the Li Y	[0, based on the Li Y	NA	0, based on

CI, confidence interval; MD, mean difference; OR, risk ratio; I₂, heterogeneity; MSCs, autologous bone marrow stromal cells; NST, NaoShuanTong capsule; tPA: tissue plasminogen XN, Xingnaojing capsule; MTE: mechanical thrombectomy, ZL, Zhilong Huoxue Tongyu capsule; Intra-A, intra-arterial fibrinolysis, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

MTE (OR: 3, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).23, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).75–7, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).33), stent retrievers (OR: 2, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).43, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).91–3, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).09), cerebrolysin (RR: -049, 95% CI: -1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).21 to 0, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).24), ZL (MD: -0, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).57, 95% CI: -0, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).84 to -0, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).30), salvianolic acids (MD: -0, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).88, 95% CI: -1, based on the Li Y et al. (Front Pharmacol, 2022;

that autologous bone marrow stromal cells (MSCs) (MD: 2, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).50, 95% CI: -4, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).69–9, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).68), TQHX plus XM (MD: 2, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).45, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).16–3, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).73), ZL (MD: 9, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).75, 95% CI: 7, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).15–12, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).36), NST (MD:

Rhubarb (OR: 3, based on the Li Y et al. (Front Pharmacol, 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).33–3, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).14), DZSM (MD: -0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).75, 95% CI: -1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).02--0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).48), and cinepazide maleate (MD: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).607, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).46–0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).801) showed better outcomes for mRS score than placebo, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). The other treatments “Safflower yellow (MD: -4, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).18, 95% CI: -5, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).38–2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).98, $p = 0$, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).1) and MSCs (RR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).81, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).37–8, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).95, $p = 0$, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).47)” indicated no significant difference in effectiveness as compared to placebo, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).

Barthel Index Score

The effects of the medications on clinical change were

assessed by

Barthel Index (BI) Score (Table 5), based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). Ten studies (25%) showed

1, based DZSM (MD: 8, 95% CI: 5, based on and cinepazide maleate (MD: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).719, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).542, 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).956), and MLC601 (MD: 2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).35, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).31, 4, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).23) were significantly different compared with placebo, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). In contrast, NBP (MD: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).65, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).25–2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).04), $p = 0$, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).08) showed no difference compared to placebo, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).

Neurological Function Deficit Score

Table 6 presents the results of the comparisons of behavioral symptoms; a total of seven studies were assessed by NFD scores, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). Patients treated with XNJ (MD: -3, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).78, 95% CI:

TABLE 5 | Results of pairwise meta-analyses for the BI score, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).

Comparative medication	Reference medication	Number of studies	Number of control	Number of patients	Pairwise meta-analyses			
					MD/OR/RR	95% CI	I ²	P
NST	Placebo	13	304	289	8, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).75	[3, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).74]	75	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
MSCs	Placebo	5	88	88	2, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).81	[-4, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).80]	74	< 0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
Intra-A	Placebo	5	139	204	1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).81	[1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).80]	0	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
TQHX plus XM	Placebo	12	225	226	2, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).81	[1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).80]	89	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
ZL	Placebo	7	115	130	9, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).67	[7, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).66]	0	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
NBP	Placebo	12	165	160	1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).67	[1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).66]	67	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
DZSM	Placebo	5	341	340	8, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).85	[5, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).80]	85	based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
Cinepazide maleate	Placebo	4	236	236	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).0	[0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).0]	0	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
MLC601	Placebo	2	237	436	2, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).0	[1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).0]	0	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).

CI, confidence interval; MD, mean difference; OR, risk ratio; I², heterogeneity; MSCs, autologous bone marrow stromal cells; NST, NaoShuanTong capsule; TQHX, Tongqiao Huoxue Decoction; ZL, Zhilong Huoxue Tongyu capsule; NBP, DL-3-n-butylphthalide; BHD, Buyang Huanwu decoction; Intra-A, intra-arterial fibrinolysis, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).

TABLE 6 | Results of pairwise meta-analyses for NFDs, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).

Comparative medication	Reference medication	Number of studies	Number of control	Number of patients	Pairwise meta-analyses			
					MD/OR/RR	95% CI	I ²	P
XNJ	Placebo	13	356	347	-3, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).54	[-4, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).95]	54	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
NST	Placebo	13	100	100	8, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).95	[10, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).95]	0	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
Chuanxiong	Placebo	3	80	81	-3, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).0	[-5, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).0]	0	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
Safflower yellow	Placebo	7	368	394	3, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).0	[2, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).0]	0	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
Rhubarb	Placebo	12	210	210	-3, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).89	[-6, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).89]	89	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
Puerarin	Placebo	16	659	699	-3, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).70	[-4, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).70]	70	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
Albumin	Placebo	4	804	807	1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).0	[0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).0]	0	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
Salvianolic acids	Placebo	12	235	235	-8, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).31	[-11, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).31]	31	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
Pntsp	Placebo	20	1464	1435	-3, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).74	[-4, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).74]	74	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
Nimodipine	Placebo	8	677	806	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).NA	[0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).NA]	NA	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
HUK	Placebo	9	338	338	1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).0	[1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).0]	0	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
DZSM	Placebo	5	341	340	-2, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).85	[-4, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).85]	85	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
Mailuoning	Placebo	15	736	755	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).0	[0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).0]	0	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
TNK	Placebo	4	656	671	1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).0	[1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).0]	0	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).
MLC601	Placebo	2	275	520	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).66	[-0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).66]	66	0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).

CI, confidence interval; MD, mean difference; OR, risk ratio; I², heterogeneity, NST, NaoShuanTong capsule; XNJ, Xingnaojing capsule; Pntsp, Panax notoginseng Saponin; TQHX, Tongqiao Huoxue decoction; TNK, tenecteplase, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).

-4, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).75 to -2, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).81), NST (MD: 8, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).15, 95% CI: 10, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).11–49, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).10), Chuanxiong (MD: -3, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).11, 95% CI: -5, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).22–1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).00), Safflower yellow (MD: 3, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).11, 95% CI: 2, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).06–4, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).68), Rhubarb (MD: -3, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).36, 95% CI: -6, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).67–2, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).71), Pntsp (MD: -3, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).20–2, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).53), HUK (MD: 1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).30, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).21 to 1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).41), and Mailuoning (OR: 0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).31, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).23–0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).42) showed better behavioral symptoms than those administered (p < 0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).05), based on the Li Y et al. (Front Pharmacol, 2022;13:924747). Moreover, Ginkgo biloba use was also associated with an improvement in activities of daily living and functional outcomes (MD: 9, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).52; 4, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).4, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).05).

the Li Y et al. (Front Pharmacol, 2022;13:924747).36, 95% CI: -4, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).20–2, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).53), HUK (MD: 1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).30, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).21 to 1, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).41), and Mailuoning (OR: 0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).31, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).23–0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).42) showed better behavioral symptoms than those administered (p < 0, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).05), based on the Li Y et al. (Front Pharmacol, 2022;13:924747). Moreover, Ginkgo biloba use was also associated with an improvement in activities of daily living and functional outcomes (MD: 9, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).52; 4, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).4, based on the Li Y et al. (Front Pharmacol, 2022;13:924747).05).

Pharmacol, 2022 22;13:924747).66 to 14, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).33, p < 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).001), based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). Subgroup analysis suggests that the impact was larger when using an injectable formulation of

Ginkgo biloba compared to the oral formulation, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). The other treatments indicated no significant difference in effectiveness as compared to placebo (p > 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).05) (Albumin (MD: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).04, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).85–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).27), based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). TNK (MD: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).56, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).0–2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).43), DZSM

(MD: -2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).81, 95% CI: 4, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).17–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).44), and MLC601 (MD: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).27, 95% CI: -0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).02–0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).55), based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).

Extracranial Hemorrhage (sICH)

The sICH events resulting from administration of other treatments were mild, and Safflower yellow (p = 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).93), stent retrievers (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).08, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).64–2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).30), Alpha1 (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).25, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).97–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).62), Ginkgo biloba (OR: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).82, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).43–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).57), tirofiban (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).14, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).72–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).82), heparin (OR: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).71, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).25–2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).05), edaravone plus rt-PA (OR: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).44, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).29–0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).66), MTE plus stent retrievers (OR: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).97), MTE (OR: 3, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).05, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).44–21, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).23), MTE plus tPA (OR: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).93, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).72–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).19), TNK (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).07, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).6–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).93), and cilostazol (OR: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).29, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).15–0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).56) had no significant difference on sICH events between these groups and placebo groups (Table 7), based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).

TABLE 7 | Results of pairwise meta-analyses for extracranial hemorrhage, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

Comparative medication	Reference medication	Number of studies	Number of control	Number of patients	Pairwise meta-analyses	95% CI	I^2	P
Heparin	Placebo	9	288	330	0, based on NA	[0, based on the Li Y NA	32	0, based
Safflower yellow	Placebo	7	368	394	1, based on 0, based on the Li Y	0, based on the Li Y	0	0, based
Stent retrievers	Placebo	5	652	634	0, based on 1, based on the Li Y	0, based on the Li Y	0	0, based
Ginkgo biloba	Placebo	12	266	281	0, based on 0, based on the Li Y	0, based on the Li Y	0	0, based
Tirofiban	Placebo	6	216	213	1, based on 0, based on the Li Y	0, based on the Li Y	0	0, based
Edaravone plus rt-PA	Placebo	8	221	221	0, based on 0, based on the Li Y	0, based on the Li Y	0	0, based
Alpha 1	Placebo	6	467	595	1, based on 0, based on the Li Y	9, based on the Li Y	9	0, based
TNK	Placebo	4	658	676	1, based on 0, based on the Li Y	0, based on the Li Y	0	0, based
MTE plus stent retrievers	Placebo	5	146	144	0, based on 0, based on the Li Y	0, based on the Li Y	0	0, based
MTE	Placebo	5	141	140	3, based on 0, based on the Li Y	0, based on the Li Y	0	0, based
tPA plus MTE	Placebo	7	2639	2640	0, based on 0, based on the Li Y	29, based on the Li Y	29	0, based
Cilostazol	Placebo	6	1728	1731	0, based on 0, based on the Li Y	0, based on the Li Y	0	0, based

CI, confidence interval; MD, mean difference; OR, risk ratio; I^2 , heterogeneity, TNK, tenecteplase, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

TABLE 8 | Results of pairwise meta-analyses for mortality, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

Comparative medication	Reference medication	Number of studies	Number of control	Number of patients	Pairwise meta-analyses	95% CI	I^2	P
Ligustrazine	Placebo	3	321	322	1, based on 1, based on the Li	95, based on the Li	<0, based	
Heparin	Placebo	9	2703	1145	0, based on [0, based on the Li	1, based on the Li	1, based	
tPA	Placebo	4	814	804	1, based on [0, based on the Li	NA, based on the Li	0, based	
Stent retrievers	Placebo	5	653	634	0, based on [0, based on the Li	29, based on the Li	0, based	
Alpha 1	Placebo	6	467	595	1, based on [0, based on the Li	0, based on the Li	0, based	
Cerebrolysin	Placebo	7	971	808	0, based on [0, based on the Li	0, based on the Li	0, based	
Ginkgo biloba	Placebo	12	213	228	1, based on [0, based on the Li	43, based on the Li	1, based	
Stem cell-based therapy	Placebo	9	218	217	0, based on [0, based on the Li	4, based on the Li	0, based	
Tirofiban	Placebo	6	218	223	0, based on [0, based on the Li	63, based on the Li	0, based	
Albumin	Placebo	4	1928	1938	1, based on [0, based on the Li	0, based on the Li	0, based	
Intra-A	Placebo	5	171	224	0, based on [0, based on the Li	0, based on the Li	0, based	
Edaravone plus rt-PA	Placebo	4	474	472	0, based on [0, based on the Li	0, based on the Li	0, based	
Statins	Placebo	18	3034	3021	0, based on [0, based on the Li	0, based on the Li	0, based	
DZSM	Placebo	5	341	340	0, based on [0, based on the Li	85, based on the Li	0, based	
TNK	Placebo	4	658	676	1, based on [0, based on the Li	0, based on the Li	0, based	
Cilostazol	Placebo	6	1728	1731	0, based on [0, based on the Li	0, based on the Li	0, based	

CI, confidence interval; MD, mean difference; OR, risk ratio; I^2 , heterogeneity; Intra-A, intra-arterial fibrinolysis; rt-PA, alteplase; TNK, tenecteplase, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

Mortality

Fifteen studies reported all-cause mortality at the end of follow-up, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Ligustrazine (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).67, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).02–2, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).67), statins (OR: 0, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).85, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).77–0, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).93) were significant different compared with placebo, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). In contrast, stent retrievers (OR: 0, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).81, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).58–1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).12), cerebrolysin (OR: 0, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).82, 95% CI: 0, based on the Li Y et al. (Front

Pharmacol, 2022;22:13:924747).55–1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).22), Ginkgo biloba (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).21, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).29–5, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).09), stem cell-based (MD: 0, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).6, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).35–1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).03), tirofiban (OR: 0, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).53, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).13–2, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).07), albumin (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).1, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).9–1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).34), Alpha1 (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).05, 95% CI: 0, based on the Li Y et al. (Front

Pharmacol, 2022 22;13:924747).7–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).59), heparin (OR: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).9, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).74–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).09), Intra-A (OR: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).83, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).48–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).39), edaravone plus rt-PA (MD: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).43, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).13–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).42), tPA (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).04, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).75–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).43), DZSM (MD: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).54, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).31–0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).95), TNK (MD: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).03, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).69–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).52), and cilostazol (MD: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).80, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).42 to 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).53, p = 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).52) had no significant differences of mortality events between these groups and placebo groups (p > 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).05) (Table 8), based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).

Adverse Events

Adverse events of the meta-analysis of participants with at least one adverse event indicated a beneficial effect in favor of placebo treatment compared with salvianolic acids (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).45, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).11–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).91, p = 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).007), Pntsp (RR: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).62, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).39–0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).97, p = 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).04), colchicine (OR: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).31, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).13–0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).71, p = 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).006), and NBP (RR: 3, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).55, 95% CI: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).19–10, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).56; p < 0.05), based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). The adverse events resulting from administration of other treatments were mild, and Chuanxiong (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).02, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).35–2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).96), MSCs (RR: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).43, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).18–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).05), Cerebrolysin (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).18, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).86–1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).64), Ginkgo biloba (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).48, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).51–2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).71), Stem cell-based (MD: 2, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).59, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).11–5, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).93), TQHX (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).78, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).51–6, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).2), HUK (RR: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).01, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).02–0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).04), Mailuoning (OR: 1, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).39, 95% CI: 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).28–6, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).76), and cinepazide maleate had no significant differences in adverse events between these groups and placebo groups (p > 0, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).05) (Table 9), based on the Li Y et al. (Front

Pharmacol, 2022;22;13:924747). Among all of the trials, in
the

TABLE 9 | Results of pairwise meta-analyses for AE, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

Comparative medication	Reference medication	Number of studies	Number of control	Number of patients	Pairwise meta-analyses			
					MD/OR/RR	95% CI	I ²	P
Chuanxiong	Placebo	3	50	49	1, based on	[0, based on the Li Y	NA	0, based
MSCs	Placebo	5	64	44	0, based on	[0, based on the Li Y	0	0, based
Cerebrolysin	Placebo	7	971	808	1, based on	[0, based on the Li Y	23	0, based
Ginkgo biloba	Placebo	12	388	406	1, based on	[0, based on the Li Y	54	0, based
Stem cell-based therapy	Placebo	9	136	139	2, based on	[0, based on the Li Y	0	0, based
TQHX plus XM	Placebo	12	180	180	1, based on	[0, based on the Li Y	0	0, based
Salvianolic acids	Placebo	12	1496	1498	1, based on	[1, based on the Li Y	0	0, based
Colchicine	Placebo	4	2764	2788	0, based on	[0, based on the Li Y	0	0, based
NBP	Placebo	4	108	108	3, based on	[1, based on the Li Y	0	< 0, based
Pntsp	Placebo	20	361	354	0, based on	[0, based on the Li Y	0	0, based
HUK	Placebo	9	387	387	0, based on	[0, based on the Li Y	0	0, based
Mailuoning	Placebo	2	64	65	1, based on	[0, based on the Li Y	0	0, based
cinepazide maleate	Placebo	NA	648	643	NA	NA	NA	0, based

CI, confidence interval; MD, mean difference; OR, risk ratio; I², heterogeneity; MSCs, Pntsp, Panax notoginseng Saponin; autologous bone marrow stromal cells; TQHX, Tongqiao Huoxue

Decoction, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

HUK groups, six cases of hypotension, four cases of fever, two cases of flushing, two cases of vomiting, one case of headache, one case of arrhythmia, and one case of pruritus were reported, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). In addition, no deaths and four serious adverse events were reported in the MLC601 group, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

DISCUSSION

Our umbrella review was conducted on the data derived from treatments for ischemic stroke patients, which was used to appraise the relative effectiveness and safety of therapies, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Li Y et al., based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). (Front Pharmacol, 2022;22:13:924747) attempted to summarize data from published systematic reviews and meta-analyses to find if there are significant beneficial treatments for ischemic stroke patients, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Our study showed that thrombolytic therapy (rt-PA, TNK, and alpha1), MTE, stem cell-based therapies, stent retrievers, acupuncture plus XM, MSCs, antiplatelet agents (aspirin, clopidogrel, and tirofiban), statins, and blood-activating and stasis-dispelling herbs can improve the neurological deficits and activities of daily living in patients with ischemic stroke, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). MTE plus Stent Retrievers or tPA, TQHX plus XM, XST plus XM, and NST plus XM show better clinical efficacy and safety, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Ligustrazine, safflower yellow, statins, Pntsp, albumin, HUK, colchicine, MLC601, salvianolic acids, and NBP have no important impact on neurological deficits or activities of daily living, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). In addition,

one study demonstrated that tPA plus MTE performed best (Kaesmacher et al., based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2019), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Our results indicated that all tPA, MTE, MTE plus tPA, MTE plus Stent Retrievers, TQHX plus XM, XST plus XM, and NST plus XM were more effective for neurological function or activities of daily living compared with placebo, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Researches have demonstrated that there was a higher effect of Stent Retrievers and MTE observed for acute ischemic stroke than that observed for the mild ischemic stroke patients (Punal-Rioboo et al., based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2015), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Similar to these studies, Stent Retrievers and MTE treatment showed statistically significant improvement in clinical effect compared to placebo in our study, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Research studies have demonstrated that Human serum albumin has shown remarkable efficacy in rodent models of ischemic stroke (Huang and Xiao, 2021), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Unfortunately, our study has demonstrated that showing no statistically significant difference between the albumin and control groups ($p > 0$, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).05), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Considering pulmonary edema and other complications are more likely to occur in such patients after albumin infusion, the administration of albumin therapy for acute ischemic stroke should be carried out with utmost caution, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

The behavioral symptoms of patients with ischemic stroke are often evaluated by NFDS/NIHSS/BI/mRS, which assesses the severity and frequency of neuropsychiatric symptoms, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). As a result, previous meta-analyses have reported that the efficacy of blood-activating and stasis-dispelling herbs may be related to the severity of ischemic

stroke, based on the Li Y et al. (Front Pharmacol, 2022 tPA, MTE, stem cell-based therapies, Stent Retrievers, Acupuncture, NST, Ginkgo biloba, TQHX, XST, and XNJ show no serious adverse events in ischemic stroke patients, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). Our results need to be interpreted with caution to determine the optimal treatment strategy for ischemic stroke patients, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).

The effects of tPA may be considerable for ischemic stroke which is incurable with current treatment paradigms, and other medications that may slow down the progression of ischemic stroke patients are worth exploring, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). Previous studies have showed that tPA or MTE has beneficial effects on hyperacute period ischemic stroke (The lengana et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747), 2019) (Liu et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747), 2016), while

22;13:924747). In addition, tPA, MTE plus tPA, MTE plus Stent Retrievers, blood-activating and stasis-dispelling herbs plus XM was reported as only a modest but significant effect found on behavior in ischemic stroke patients (Peng et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747), 2014; Punal-Rioboo et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747), 2015; Kaesmacher et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747), 2019; Shang et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747), 2019; Zhang et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747), 2019), based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). In our study, Alpha1 was more effective for neurological improvement rate compared with placebo, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). Unfortunately, the lack of placebo controls in NFDS/NIHSS/BI/mRS score studies may limit their validity, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). Interestingly, MSCs are not significant in mRS score but significant in NIHSS/BI score, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). Moreover, nimodipine can significantly improve clinical outcomes compared with

placebo, although it does not significantly reduce the incidence rate of recurrent hemorrhage and adverse reactions, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). In addition, tPA and MTE affected mRS scores and was recommended by the FDA, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Li Y et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). (Front Pharmacol, 2022;22:13:924747) considered treatment with ligustrazine,

Safflower yellow albumin, MLC601, ANP, rhubarb, and NBP to not affect neurological deficits and activities of daily living because of the lack of statistical significance of results, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

Patients with ischemic stroke deteriorate progressively with varying degrees of severity of disease, which may affect the results obtained from pooling data, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Moreover, measurement time after dosing can affect

NFDS/NIHSS/BI/mRS scoring results and cause them to be biased, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). patients has

Previous meta-analyses have demonstrated that patients treated with intra-arterial fibrinolysis provided a modest and better improvement in clinical effect change (Roaldsen et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2022), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). In addition, drug combination shows a statistically significant advantage compared to placebo the short-term and long-term analysis, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Although the effect of single blood-activating and stasis-dispelling herbs (TQHX, NST, XST, etc, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747)) use is not ideal (Erratum, 2017), they show a modest and better effect in combination with XM (Wu et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2007), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Furthermore, ischemic stroke agents are likely to have an important effect on increasing neurological function or activities of daily living in mild to moderate ischemic stroke

patients, In this study, the quality evaluated by AMSTAR2 scores of systematic reviews of ligustrazine, safflower yellow, cerebrolysin, BHD, salvianolic acids, and

ZL was low, and these may not have an important impact on neurological function or activities of daily living, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). First, ischemic stroke is a sudden disease, our review mainly selected clinical studies to demonstrate short-term efficacy on neurological function, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Although long-term clinical trials are ethically questionable, those that are high-quality are essential to uncover comparative differences between treatments of ischemic stroke, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Second, Li Y et al, based on the Li Y et al. (Front Pharmacol, 2022;

Recent studies have also found statins to be associated with atrial fibrillation, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). In addition, the promotion of collateral circulation by neuroprotective drugs may be related to the induction of NO synthesis and angiogenesis in vascular endothelium (Hu et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2021), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). In addition, the incidence of withdrawals due to adverse events tended to be higher in the salvianolic acids albumin, MLC601, and NBP treatment than in placebo groups, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Moreover, our study summarized that MTE, stem cell-based therapies, stent retrievers, acupuncture plus XM, NST, Ginkgo biloba, TQHX, XST, and XNJ show no serious adverse events in ischemic stroke patients, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

In recent years, stem cell-based therapies (MSCs, stem cell-

NFDS/NIHSS/BI/mRS scoring results and cause them to be biased, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). based) as a treatment to investigate ischemic stroke been a potential therapy (Cao and Li, 2015; Li et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2020), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). A previous study has shown that Intra-A results in a better beneficial effect for cognition and activities of daily living (Lee et al, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747), 2010), based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Similar to these studies, stem cell-based therapies may show effectiveness for neurological deficits and activities of daily living in this study, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). However, clinical trials of stem cell-based therapies for ischemic stroke are still in the early stage, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Many factors such as cell types, cell numbers, delivery routes, time windows, and medical and rehabilitation therapies affect the efficacy of stem cells, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Well-designed RCTs are necessary to explore the benefit of stem cell-based therapies as treatment in patients with ischemic stroke, and further research effects should

be carefully explored, based on the Li Y

In general, the treatment for patients with ischemic stroke is

aimed at promoting independence, clear embolism maintaining function, and treating symptoms, Previous 22:13:924747). (Front Pharmacol, 2022;22:13:924747) believe that further analyses are needed to clarify the factors associated with the increased placebo effect over time in global clinical trials, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). In the treatment of ischemic stroke, the safety of the treatments is critical since they should be taken on a long-term basis, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). The number of participants with at least one serious adverse event such as nausea, diarrhea, cardiovascular, gastrointestinal, and other disorders was extracted, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

Previous meta-analyses have demonstrated that acute and convalescent stroke patients

meta-analyses and reviews have focused on the possible effectiveness and safety of stem cell-based therapies, stent retrievers, acupuncture, MSCs, antiplatelet agents, statins, and blood-activating and stasis-dispelling herbs (Li et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747),, 2014; Cao and Li, 2015; Punal-Rioboo et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747),, 2015; Shang et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747),, 2019; Zhang et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747),, 2019; Li et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747),, 2020; Zhao et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747),, 2021; Zhou et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747),, 2022), even though patients experience modest efficacy and many adverse events with the treatment, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). As a result, Li Y et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). (Front Pharmacol, 2022 22;13:924747) need to identify an efficacious and safe treatment paradigm for ischemic stroke patients, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).

Studies have shown that MTE plus tPA, MTE plus Stent Retrievers, TQHX plus XM, XST plus XM, NST plus XM, and acupuncture plus XM improved neurological deficits and activities of daily living, and the adverse effects were mild for the treatment of ischemic stroke (Li et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747),, 2014; Kaesmacher

et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). Due to tPA, MTE, tPA plus edaravone, blood-activating, and stasis-dispelling herbs plus XM efficacy in improving neurological deficits and activities of daily living, Li Y et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). (Front Pharmacol, 2022 22;13:924747) believe that tPA or tPA plus other drugs can be employed as first-line treatment, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).

treated with antiplatelet agents showed a modest improvement, although there is a risk of intracranial hemorrhage (Zhou et al, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747),, 2020), based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). In this review, edoxaban was likely to provide more protection from stroke and sICH than placebo, aspirin alone, or aspirin plus clopidogrel in both clinical trials and unselected community populations, Moreover, statins were found to be effective for primary

and secondary prevention of ischemic stroke in the study through the aggressive reduction of cholesterol. Some studies have found that using statins before an ischemic stroke can increase collateral circulation and improve prognosis, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). Despite an increased risk of bleeding conversion, thrombolytic use of statins resulted in overall improvement, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747).

Limitations

The limitations to this study should be acknowledged, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). our included studies was limited, based on the Li Y et al. (Front Pharmacol, 2022 22;13:924747). Second, other factors may have led to the umbrella review inconsistencies, such as the duration and

quality of studies, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). Furthermore, a considerable number of studies could not be included as they did not have the abovementioned data, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747).

CONCLUSION

In conclusion, our study suggested that tPA, tPA plus MTE, acupuncture plus XM, tPA plus edaravone, and blood-activating and stasis-dispelling herbs plus XM are the optimum cognitive and activities of daily living medication for patients with ischemic stroke, based on the Li Y et al. (Front Pharmacol, 2022;22:13:924747). In the future, the combination of well-tolerated agents and other significant beneficial treatments should be used for patients with ischemic stroke, which will contribute to better outcomes.

ID

Wang X et al.

Original research

BMJ Open Predictive role of modifiable factors in stroke: an umbrella review

Xiaotong Wang, Man Liang, Fanxin Zeng, Yue Wang, Yuetian Yang, Fangfang Nie, Mengke Shang, Na Ta, Lu Wen, Lanxin Ou, Zhibin Yang, Wanyang Liu

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► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-056680>).

XW and ML contributed equally.

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Wang X et al, based on the Wang X et al. BMJ open. 2022;12(6):e056680. BMJ open, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 2022;12(6):e056680

ABSTRACT

Background A growing number of meta-analyses reviewed the existing associations between modifiable factors and stroke, based on the Wang X et al. BMJ open. 2022;12(6):e056680. However, the methodological quality of them and quality of evidence remain to be assessed by validated tools, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Thus, this umbrella review was conducted to consolidate evidence from systematic reviews and meta-analyses of cohort studies investigating the association between modifiable factors and criteria, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Sensitivity analyses were searching, based on the Wang X et al. BMJ open. 2022;12(6):e056680. At last, 49 meta-analyses were included in the present review, based on the Wang X et al. BMJ open. 2022;12(6):e056680. The methodological quality of three meta-analyses was low, while others were critically low, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Evidence of walking pace was strong, based on the Wang X et al. BMJ open. 2022;12(6):e056680. High suggestive evidence mainly included total meat, processed meat, chocolate, sodium, obesity,

STRENGTHS AND LIMITATIONS OF THIS STUDY

® This umbrella review is the first synthesis of systematic reviews and meta-analyses of cohort studies to consider the associations between modifiable factors and stroke.

® The quality of evidence about the associations between modifiable factors and stroke was assessed and rated into five levels (strong, highly suggestive, suggestive, weak and no) using specific criteria in this review.

® The qualities of included meta-analyses were low as they did not meet the standards of assessing the methodological quality of systematic reviews 2, such as they did not establish a protocol a priori and did the report justify any significant deviations from the protocol, which can lead to potential bias in the results of meta-analyses.

® Since only evidence derived from systematic

Risk Factors Study, stroke became the second leading cause of disability-adjusted life-years

stroke increases rapidly with age, doubling every decade after 55 years of age. Patients suffering from stroke often need intensive healthcare and may experience several issues that increase their economic burden seriously.² Thus, immediate need to implement preventative strategies is of great importance to public health all over the world.

A growing number of evidences demon-

and depression turned to weak, based on the Wang X et al. BMJ open. 2022;12(6):e056680. reporting bias, based on the Wang X et al. BMJ open. 2022;12(6):e056680.

Discussion Diet with rich macronutrients and micronutrients, healthy dietary patterns and favourable physical, emotional health and environmental management should be promoted to decrease the burden of stroke, based on the between modifiable factors

INTRODUCTION

Stroke is a serious health condition that causes disability and death. According to the Global Burden of Diseases, Injuries, and

strated genetic and environmental factors may contribute to the risk of stroke.^{3,4} Among them, modifiable factors including diet and lifestyles were reported that appropriate and effective changes in them could prevent people from stroke, which are widely accepted by the public.^{5,6} Recently, meta-analyses were conducted to explore the and stroke, based on the Wang X et al. BMJ open. meta--analyses of prospective studies demonstrated higher adherence to Mediterranean and dietary approaches to stop hypertension (DASH) diet may were associated with a



decreased risk of stroke.^{7,8} Dietary factors such as dairy calcium, high dietary flavonoid intake, fish, soy, nut, tea, moderate coffee and chocolate consumption may lower the risk of stroke,^{9–13} while high salt intake, consumption of fresh red meat, processed red meat as well as total red meat and heavy alcohol intake were associated with increased risk of stroke.^{14,15} Besides, amount of evidence was observed for effects on stroke with smoking, overweight, physical activities, depression, long sleep duration and environmental management.^{16–20} However, none of these studies focused on any existing evidence between modifiable factors and stroke risk systematically. Besides, though a number of systematic reviews and meta-analyses were performed, the methodological quality of them and quality of evidence remain to be assessed by validated tools. More importantly, since the general public increasingly focus on prevention through daily self-management, a systematic umbrella review could provide scientific, instructive and meaningful guidance for them to some extent.²¹ Thus, this umbrella review of meta-analyses was conducted to gain a systematic, comprehensive overview of the existing evidence of cohort studies on modifiable factors and incidence of stroke and to assess its strength and validity.

METHODS

Umbrella reviews are systematic reviews that consider many related factors for the management of the same disease or condition, based on the Wang X et al. BMJ open. 2022;12(6):e056680. This is probably more useful for health assessments that aim to inform guidelines and clinical practice where all the management options need to be considered and weighed, based on the Wang X et al. BMJ open. 2022;12(6):e056680.²² The umbrella review followed the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and the protocol was registered in PROSPERO (registration no, based on the Wang X et al. BMJ open. 2022;12(6):e056680. CRD42021249921), based on the Wang X et al. BMJ open. 2022;12(6):e056680. In addition to the factors stated in the protocol, to make the review more comprehensive,

Patient and public involvement

Meta-analyses of prospective and retrospective cohort studies were included in this review, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Thus, in prospective cohort study, participants were general population whose age were ≥ 18 years old, while in retrospective cohort study, participants who suffered stroke were included, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Exposure levels of modifiable factors were compared, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Stroke was considered as an outcome which had been ascertained by the method of record linkage with the national and regional stroke registers, based on the Wang X et al. BMJ open. 2022;12(6):e056680.

March 2021 for meta--analyses of cohort studies investigating the association between modifiable factors and stroke risk. Wang X et al. BMJ open. 2022;12(6):e056680 included studies published from database inception through January 2021. Literature search was conducted by two authors (XW and ML). Disagreements were resolved by consensus. In the review, categories of modifiable factors including dietary factors, factors of physical health management and emotional health management were defined a priori. Detailed factors were further confirmed according to categories in the process. The search strategy including detailed factors is shown in online supplemental table S1. Subsequently, Wang X et al. BMJ open. 2022;12(6):e056680 performed a manual search of reference lists from the retrieved articles. Wang X et al. BMJ open. 2022;12(6):e056680 also screened the reference lists of relevant reviews and meta--analyses. No language restriction was performed.

Study selection

The criteria for eligibility were: (1) systematic reviews and meta--analyses of cohort studies on the associations between modifiable factors and stroke risk in humans with multivariable adjusted summary risk estimates and corresponding 95% CIs and (2) studies focusing on the subtypes of stroke. Wang X et al. BMJ open.

2022;12(6):e056680 excluded individual studies from eligible systematic reviews or meta--analyses according to the following criteria: (1) studies in which modifiable factor was not the exposure of interest and stroke incidence was not the outcome of interest; (2) publications reporting on exposure of plasma levels or biomarkers rather than dietary intake; (3) animal studies, based on the Wang X et al. BMJ open.

2022;12(6):e056680. If a systematic review or meta-analysis performed a subgroup analysis stratified by the study design (case--control and cohort studies), then the results for cohort studies were included, based on the Wang X et al. BMJ open. 2022;12(6):e056680. If more than one published meta--analysis on the same association was identified, Wang X et al, based on the Wang X et al. BMJ open. 2022;12(6):e056680. BMJ open, based on the Wang X et al. BMI open. 2022;12(6):e056680. 2022;12(6):e056680

Literature search and study selection

The systematic literature search was conducted in PubMed, Web of Science, Embase, Wanfang and China National Knowledge Infrastructure databases until

Data extraction

Data were extracted independently by two authors (XW and ML), based on the Wang X et al. BMJ open.

2022;12(6):e056680. For each published meta--analysis, Wang X et al, based on the Wang X et al. BMJ open.

2022;12(6):e056680. BMJ open, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 2022;12(6):e056680 extracted the following data: name of the first author, publication year, exposure, number of included studies, case number, study population, most adjusted risk

estimates (relative risk, OR, HR or incident risk ratio) and corresponding 95% CIs, based on the Wang X et al. BMJ open. 2022;12(6):e056680.

For each primary study included in the published meta-analysis, the first author's name, year of publication, exposure (including dose of exposure), number of total cases, number of participants and HRs that adjusted for the most confounders, 95% CIs as well as adjustment factors included in the model were extracted, based on the Wang X et al. BMJ open. 2022;12(6):e056680.

Assessment of methodological quality

Assess the methodological quality of systematic reviews 2 (AMSTAR 2), which has good inter-rater agreement, content validity and test-retest reliability, was used to evaluate the methodological quality of each included published meta-analysis, based on the Wang X et al. BMJ open. 2022;12(6):e056680. ²³ This tool has a total of 16 domains and generates an overall rating based on the weaknesses of those domains which is rated as high, moderate, low and critically low, based on the Wang X et al. BMJ open. 2022;12(6):e056680.

Statistical analysis

All calculations were conducted with Stata V, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 15, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 1, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Adjusted summary HRs and corresponding 95% CIs of the included meta-analyses were recalculated by using the random effects model by DerSimonian and Laird, based on the Wang X et al. BMJ open. 2022;12(6):e056680.

²⁴

I^2 and τ^2 were used to evaluate heterogeneity among studies, based on the Wang X et al. BMJ open.

2022;12(6):e056680. Wang X et al, based on the Wang X et al. BMJ open. 2022;12(6):e056680. BMJ open, based on the Wang X et al. BMJ open. 2022;12(6):e056680.

2022;12(6):e056680 estimated the 95% prediction interval (PI),

the range in which Wang X et al, based on the Wang X et al. BMJ open. 2022;12(6):e056680. BMJ open, based on the Wang X et al. BMJ open. 2022;12(6):e056680.

2022;12(6):e056680 expect the effect of the association will lie for 95% of future studies, based on the Wang X et al. BMJ open. 2022;12(6):e056680. The presence of small-study effects was assumed by Egger regression asymmetry test, based on the Wang X et al. BMJ open.

2022;12(6):e056680. Small-study effect was claimed when

Egger p value was <0 , based on the Wang X et al. BMJ open. 2022;12(6):e056680. 1, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Wang X et al, based on the Wang X et al. BMJ open. 2022;12(6):e056680. BMJ open, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 2022;12(6):e056680 used the excess significance test to investigate whether the observed number of studies (O) with nominally significant results ('positive'

studies, $p<0$, based on the Wang X et al. BMJ open.

2022;12(6):e056680. 05) was larger than the expected number of significant results (E), based on the Wang X et al. BMJ open. 2022;12(6):e056680. ²⁵ In each meta-analysis, E is calculated from the sum of the statistical power estimates for each component study, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Wang X et al, based on the Wang X et al. BMJ open.

2022;12(6):e056680. BMJ open, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 2022;12(6):e056680 calculated the power of each

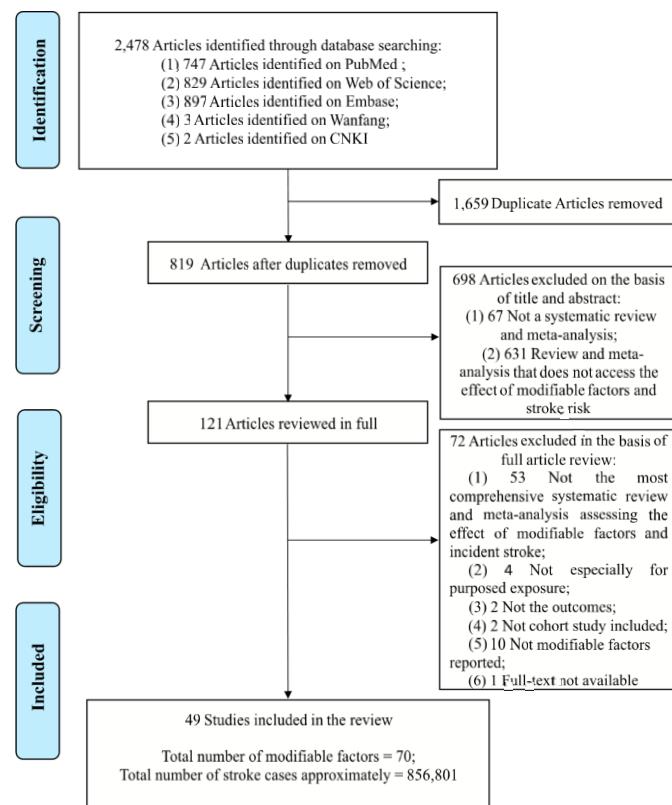


Figure 1 Flow diagram of the study search and selection process, based on the Wang X et al. BMJ open. 2022;12(6):e056680. CNKI, China National Knowledge Infrastructure, based on the Wang X et al. BMJ open. 2022;12(6):e056680.

study by using a non--central t distribution, based on the Wang X et al. BMJ open. 2022;12(6):e056680. The excess significance test was considered positive for p values <0, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 10, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Moreover, Wang X et al, based on the Wang X et al. BMJ open. 2022;12(6):e056680. BMJ open, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 2022;12(6):e056680 corrected for subgroup analyses using a Bonferroni correction that divides the p value by the number of tests (p<0, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 05/2), based on the Wang X et al. BMJ open. 2022;12(6):e056680. When the published meta--analysis presented HRs from the same cohort separately by subgroups, Wang X et al, based on the Wang X et al. BMJ open. 2022;12(6):e056680. BMJ open, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 2022;12(6):e056680 first combined

Sensitivity analyses

For each meta--analysis initially graded as showing convincing, highly suggestive or suggestive evidence, adjusted confounding factors of primary studies were re-examined, based on the Wang X et al. BMJ open. 2022;12(6):e056680. A sensitivity analysis was performed by including adjusted estimates of the most consistent potential confounders to assess the robustness of the main analysis, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Besides, sensitivity analyses including the omission of small--sized studies (<25th percentile) from those meta--analyses with evidence of small--study effects and low--quality studies were also performed, based on the Wang X et al. BMJ open. 2022;12(6):e056680.

Wang X, et al, based on the Wang X et al. BMJ open. 2022;12(6):e056680. *BMJ Open*

RESULTS

A total of 2478 records were identified through database searching; 1659 duplicate records were removed; 698 records were excluded on the basis of title and abstract and 121 records were reviewed in full, based on the Wang X et al. BMJ open. 2022;12(6):e056680. After excluding records which were not the most comprehensive systematic review and meta--analysis (n=53), not especially for purposed exposure (n=4), not the purposed outcomes (n=2), not modifiable factors reported (n=10) and whose full text was not available (n=1), 49 articles, including 70 modifiable factors and approximately 856 801 stroke cases, were included and re--analysed in the present review^{7 8 10 12 13 16–20 27–65} (figure 1, online supplemental table S3 and S4), based on the Wang X et al. BMJ open. 2022;12(6):e056680. The detailed characteristics of included studies are shown in online supplemental table S5, based on the Wang X et al. BMJ open.

total stroke are shown in figures 2–5, and online supplemental table S6, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Further subgroup analyses of ischaemic and haemorrhagic stroke are shown in online supplemental table S7 and S8, based on the Wang X et al. BMJ open. 2022;12(6):e056680.

Food factors, beverages and dietary behaviours

For total stroke, high intake levels of fruit and vegetable, olive oil, milk, high fat diary, nuts, cheese, white meat, chocolate, fish, tea (three cups/day), high levels of coffee, high adherence of Mediterranean and DASH diet were inversely and high intake levels of salt, high fat milk, total meat, red meat, processed meat and high--to--heavy

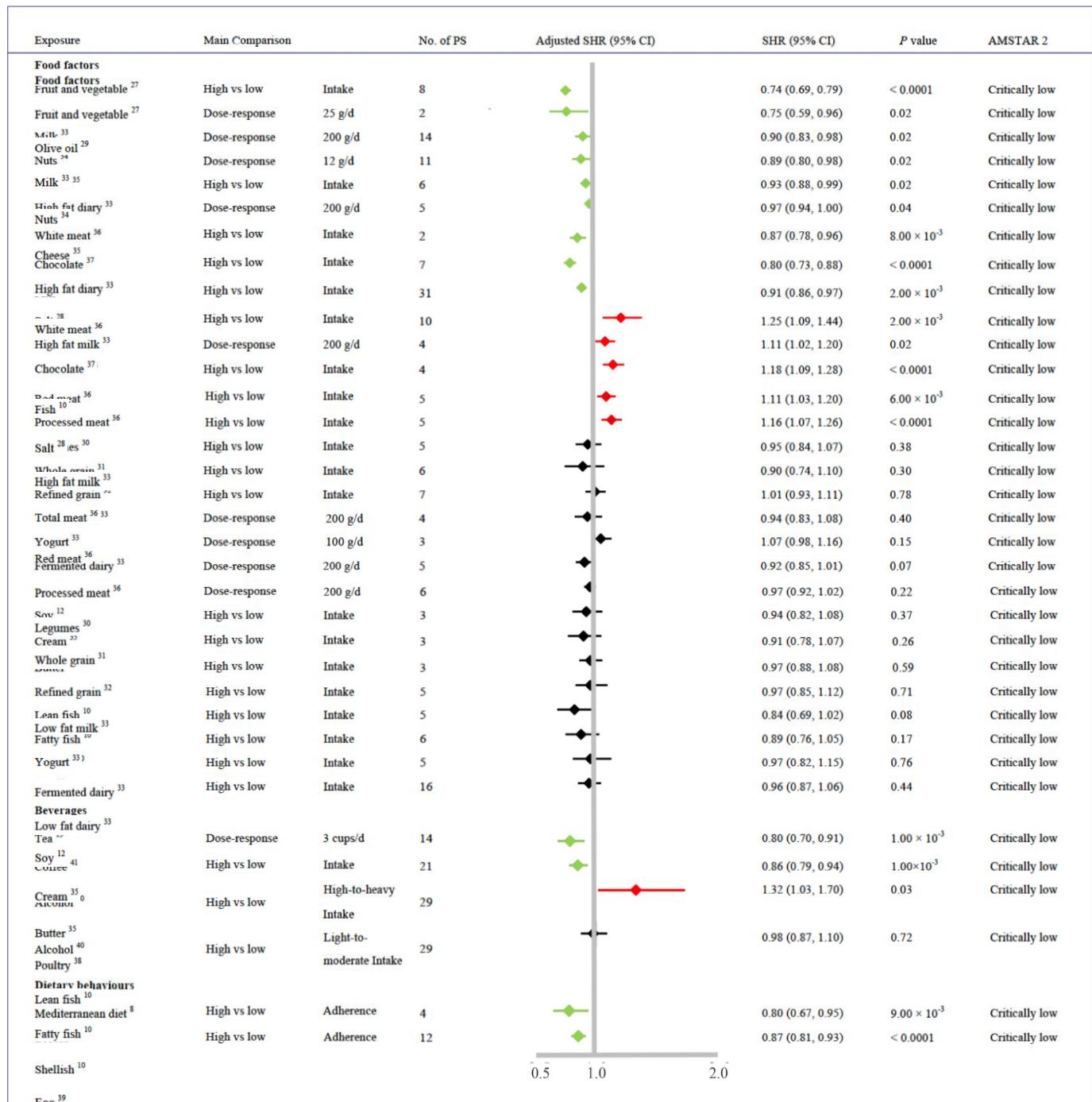
**Beverages**Tea¹³Coffee⁴¹Alcohol⁴⁰Alcohol⁴⁰

Figure 2 Adjusted summary HRs (SHR) with 95% confidence intervals and quality of evidence for association between food factors, beverages, dietary patterns and incidence of stroke, based on the Wang X et al. BMJ open. 2022;12(6):e056680.

AMSTAR = assess the methodological quality of systematic reviews; DASH = dietary approaches to stop hypertension; PS = primary studies, based on the Wang X et al. BMJ open. 2022;12(6):e056680.

levels of alcohol were positively associated with stroke (all p<0, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 05), based on the Wang X et al. BMJ open. 2022;12(6):e056680. After excluding null values of 95% PI, only inverse association of chocolate was observed (95% PI 0, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 75 to 0, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 92), based on the Wang X et al. BMJ open. 2022;12(6):e056680. For ischaemic stroke, associations for high levels of fruit and vegetable, cheese, chocolate, tea (three cups/day), light-to-moderate levels of alcohol and high adherence of DASH diet showed p<0, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 025 by the random-effects model, suggesting decreased risk, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Associations for high levels of total meat, processed meat and high-to-heavy levels of alcohol showed p<0, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 025 by the

random-effects model, suggesting increased risk, based on the Wang X et al. BMJ open. 2022;12(6):e056680. After excluding null values of 95% PI, processed meat was positively associated with ischaemic stroke (95% PI 1, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 01 to 1, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 35), based on the Wang X et al. BMJ open. 2022;12(6):e056680. For haemorrhagic stroke, high intake levels of fruit and vegetable, chocolate and fish were inversely associated with and high-to-heavy levels of alcohol were positively associated with haemorrhagic stroke (all p<0, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 025), based on the Wang X et al. BMJ open. 2022;12(6):e056680. After excluding null values of 95% PI, only inverse association of fish was observed (95% PI 0, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 79 to 0, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 99), based on the Wang X et al. BMJ open. 2022;12(6):e056680. Most studies (total stroke, 71, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 88%; ischaemic stroke, 66, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 67%;

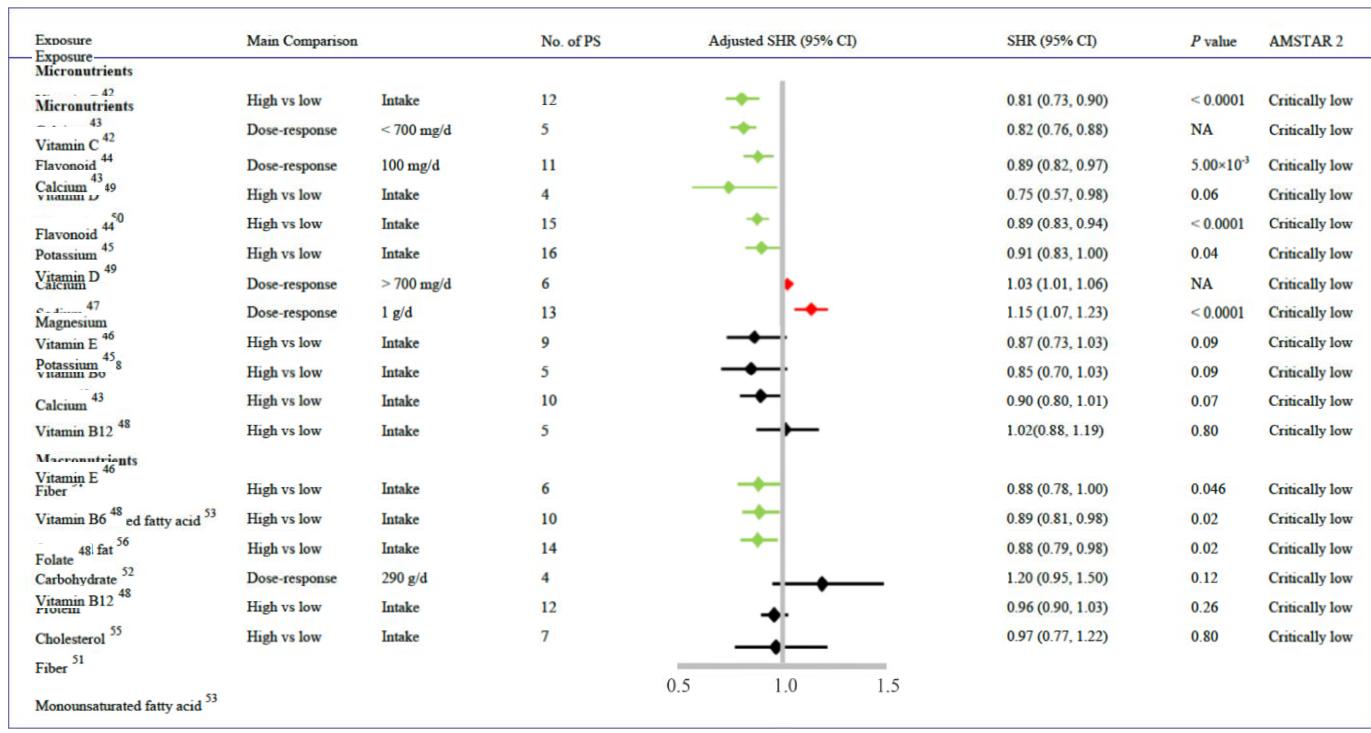
Carbohydrate⁵²

Figure 3 Adjusted summary HRs (SHR) with 95% confidence intervals and quality of evidence for association between micronutrients, macronutrients and incidence of stroke, based on the Wang X et al. BMJ open. 2022;12(6):e056680. AMSTAR = assess the methodological quality of systematic reviews; NA = not available; PS = primary studies, based on the Wang X et al. BMJ open. 2022;12(6):e056680.

haemorrhagic stroke, 70, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 83% showed low heterogeneity ($I^2 \leq 50\%$), based on the Wang X et al. BMJ open. 2022;12(6):e056680.

Factors of Physical Health Management
Macronutrients and micronutrients
 For total stroke, associations for high levels of vitamin C and D, calcium (<700 mg/day), flavonoid, potassium, magnesium fibre, monounsaturated fatty acid and saturated fat showed $p < 0$, based on the Wang X et al. BMJ open.

		No. of PS	
Factors of Physical Health Management			
Walking pace ⁵⁶	High vs low	Speed	7
Physical activity ⁵⁷	High vs low	Time	10
Obesity ⁵⁷	High vs low	Beginning weight	11
Obesity ⁵⁸	Dose-response	10 mmHg increase	8
SBP ⁵⁹	Dose-response	10 mmHg increase	6
DBP ⁵⁹	Dose-response	10 mmHg increase	6
Sleep duration ¹⁸	Dose-response	more than 7 h	12
Smoking ¹⁷	High vs low	current vs non	9
Shift-work ⁵⁸	High vs low	Time	4
Oral contraceptives ⁶⁰	High vs low	current vs non	5
Factors of Emotional Management			
Depression ⁶¹	High vs low	Scores	17
Social isolation ⁶²	High vs low	Feeling	8
Anger and hostility ⁶³	High vs low	Feeling	7

suggesting decreased risk, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Associations for high level of sodium and calcium (>700 mg/day) showed $p < 0$, based on the Wang X et al. BMJ open. 2022;12(6):e056680.05

by the random-effects model, suggesting increased risk, based on the Wang X et al. BMJ open. 2022;12(6):e056680. After excluding null values of 95% PI, associations of vitamin C, flavonoid and magnesium were observed (95% PI were based on the Wang X et al. BMJ open. 2022;12(6):e056680.71 to 0, based on the

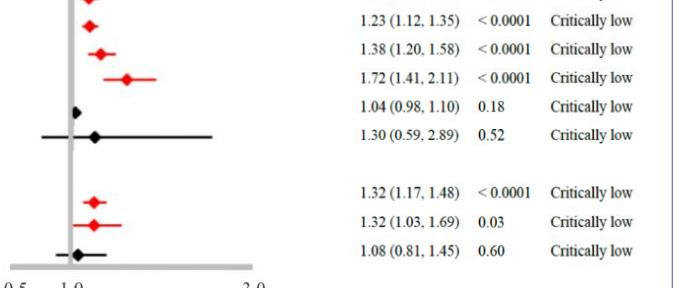


Figure 4 Adjusted summary HRs (SHR) with 95% confidence intervals and quality of evidence for association between factors of physical health and emotional management and incidence of stroke AMSTAR = assess the methodological quality of systematic reviews; DBP = diastolic blood pressure; NA = not available; PP = pulse pressure; PS = primary studies; SBP = systolic blood pressure, based on the Wang X et al. BMJ open. 2022;12(6):e056680.

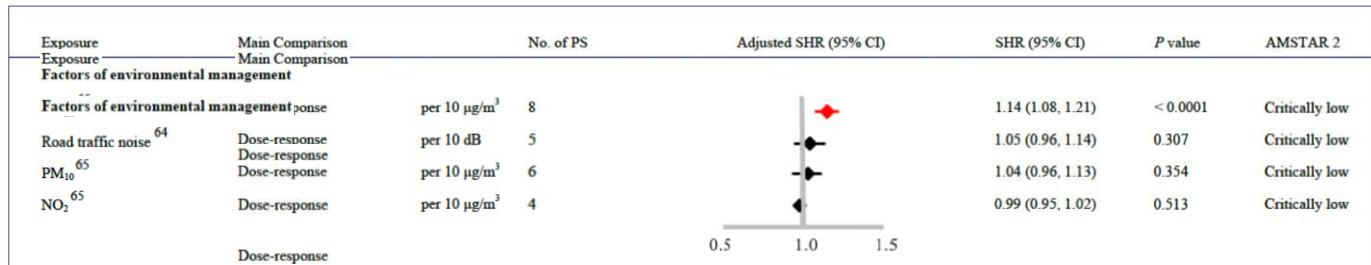


Figure 5 Adjusted summary HRs (SHR) with 95% confidence intervals and quality of evidence for association between factors of environmental management and incidence of stroke, based on the Wang X et al. BMJ open. 2022;12(6):e056680. AMSTAR = assess the methodological quality of systematic reviews; PM = particulate matter; PS = primary studies, based on the Wang X et al. BMJ open. 2022;12(6):e056680.

of vitamin C and D, potassium, folate, magnesium and saturated fat were inversely associated with the risk (all $p<0$, based on the Wang X et al. BMJ open.

2022;12(6):e056680. 025), based on the Wang X et al. BMJ open. 2022;12(6):e056680. After excluding null values of 95% PI, association of potassium was observed (95% PI 0, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 80 to 0, based on the Wang X et al. BMJ open.

2022;12(6):e056680. 97), based on the Wang X et al. BMJ open. 2022;12(6):e056680. For haemorrhagic stroke, saturated fat was inversely associated with the risk ($p=4\times 10^{-3}$), while high-to-heavy alcohol and high level of carbohydrate were positively associated with stroke (all $p<0$, based on the Wang X et al. BMJ open.

2022;12(6):e056680. 025), based on the Wang X et al. BMJ open. 2022;12(6):e056680. After excluding null values of 95% PI, no association was observed, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Most studies (total stroke, 66, based on the Wang X et al. BMJ open.

2022;12(6):e056680. 67%; ischaemic stroke, 68, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 75%; haemorrhagic stroke, 81, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 25%) showed low heterogeneity ($I_2\leq 50\%$), based on the Wang X et al. BMJ open. 2022;12(6):e056680.

Factors of physical, emotional health and environmental management

For total stroke, physical activity and high speed of walking pace were inversely associated with the risk, while overweight, obesity, 10 mm Hg increase of pulse, diastolic and systolic blood pressure (PP, DBP and SBP), >7 hours sleep duration, anti-inflammatory drugs, smoking, depression, social isolation and particulate matter 2, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 5 (PM₂, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 5) were positively associated with the

Small-study effects

According to online supplemental table S6, S7 and S8, publication bias existed in some meta-analyses (all $p<0.10$). Consequently, a trim-and-fill method was conducted to evaluate the sensitivity. The results remained after this method, except Valtorta's study which could be explained

Excess significance

For total stroke, the excess significant finding was calculated in 25 comparisons, in which 10 comparisons showed evidence of excess significant finding, based on the Wang X et al. BMJ open. 2022;12(6):e056680. For ischaemic stroke, the excess significant finding was calculated in 21 comparisons, in which 11 comparisons showed evidence of excess significant finding, based on the Wang X et al. BMJ open. 2022;12(6):e056680. For total stroke, the excess significant finding was calculated in 20 comparisons, in which 2 comparisons showed evidence of excess significant finding (online supplemental table S6, S7 and S8), based on the Wang X et al. BMJ open. 2022;12(6):e056680.

Methodological quality of studies

As shown in online supplemental table S9, the methodological quality of three meta-analyses was low,^{10 49 56} while others were critically low, based on the Wang X et al. BMJ open. 2022;12(6):e056680. 7 8 12 13 16-20 27-48 50-55 57-65 The main methodological problems found according to AMSTAR 2 were as follows: meta-analyses did not contain an explicit statement that the review methods were established prior and did not report any significant deviations from the protocol, did not provide a list of excluded studies and justify the exclusions, did not report the sources of funding for each original study and assess the impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis, based on the Wang X et al. BMJ open. 2022;12(6):e056680.

Sensitivity analyses

In the results, evidence of walking pace was strong, based on the Wang X et al. BMJ open. 2022;12(6):e056680. High suggestive evidence mainly included total meat, processed meat, chocolate, sodium, obesity, PP, SBP, DBP, sleep

DISCUSSION

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by reporting bias.⁶²

In the present umbrella review, a broad overview of the existing evidence was provided and the methodological quality of the meta--analyses and quality of evidence for all these associations were evaluated. The present review

Table 1 Summary of sensitivity analyses



suggested fruit and vegetable, olive oil, milk, nuts, cheese, meat, chocolate, poultry, fish, tea, alcohol, coffee, Mediterranean and DASH diet, vitamins, calcium, flavonoid, potassium, sodium, magnesium, fibre, monounsaturated fatty acid, saturated fat, depression, social isolation, overweight, obesity, physical activity, PP, DBP and SBP, sleep duration, anti-inflammatory drugs, smoking, walking pace and PM_{2.5} may play different roles in pathological mechanism of stroke. Among these factors, after sensitivity analyses, evidence of total meat, processed meat, chocolate, vitamin C, sodium, obesity, PP, DBP and SBP, sleep duration, smoking, walking pace and PM_{2.5} suggested strength of 'suggestive evidence' and above.

Foods having the correct balance of macronutrients and micronutrients are the key elements of a healthy diet.⁶⁶ In the present review, the protective effects of fruit and vegetable and their main nutritional ingredients including vitamin C, flavonoid, potassium and fibre were observed on stroke. Previous studies demonstrated high intake of fruit and vegetable could reduce blood pressure.⁶⁷ As raised blood pressure was a risk factor, Wang X et al. BMJ open. 2022;12(6):e056680 speculate the contributions of Mediterranean diet and food factors above to stroke risk may be explained by this.⁶⁸ In the same way, high salt, processed meat manufactured with the preservative sodium nitrate and sodium intake which are the main risk factor of hypertension and consequently exerts negative effects on the cardiovascular systems were associated with increased stroke risk in the result. The harmful effect of processed meat remained on ischaemic stroke as a suggestive evidence. Besides, highly suggestive evidence of chocolate showed as an abundant source of flavanols, chocolate has benefits for stroke.

Previous meta-analysis suggested that flavanol-rich chocolate and cocoa products caused a significant reduction in both SBP and DBP, which are risk factors of stroke, based on the Wang X et al. BMJ open. 2022;12(6):e056680.⁶⁹ Therefore, chocolate may account for the reduced risks of stroke in our review, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Based on the evidence above, it could be speculated dietary factors and behaviours which could control blood pressure may also play protective roles in stroke, based on the Wang X et al. BMJ open. nutrients (calcium, vitamin D, magnesium and monounsaturated fatty acid), dietary behaviours including Mediterranean and DASH were also observed in the present review, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Since the grade of evidence was weak, further studies are warranted to confirm these findings, based on the Wang X et al. BMJ open. 2022;12(6):e056680.

Physical and emotional health and environmental management in preventing diseases have attracted more and more attention in recent years, based on the Wang X et al. BMJ open. 2022;12(6):e056680. In the present review, highly suggestive evidence of obesity revealed it was positively associated with stroke, while more physical activity and strong evidence of high speed of walking pace were inversely associated with the risk,

which is also a highly suggestive evidence. Specifically, association between sleep durations and stroke risk was studied and the result showed long sleepers (>7 hours) had a higher predicted risk of stroke, which is a highly suggestive evidence. Although the mechanisms are not fully understood, it may be explained by increase in some inflammatory biomarkers and association with carotid artery atherosclerosis and atrial fibrillation.^{70 71} In addition, smoking has proven to be associated with mounts of cardiovascular diseases, even sudden cardiac death.⁷² The highly suggestive evidence of smoking on stroke risk reminds us it is definitely essential to stay away from smoking, which is the most critical and effective measure. As an environmental factor accompanied by people's concern commonly, the role of PM_{2.5} in stroke was explored widely. The result showed PM_{2.5} (per 10 µg/m³ increment) increased the risk of stroke. Although the accurate mechanisms remain unclear, it could be explained by the dysfunction of the autonomic system which is the major pathway that could result in air pollution-related adverse cardiovascular outcomes, such as stroke.⁷³ Besides, depression, social isolation and taking anti-inflammatory drugs also increased stroke risk according to the present result. Since the evidence of them was weak, further studies underlying the associations are needed.

Strengths and limitations

Our review systematically summarised broad evidence of modifiable factors in the prevention of stroke and its subtypes, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Moreover, our umbrella review assessed the overlapping and excess significant finding among included

meta-analyses, which provide evidence on the quality of previous reviews, based on the Wang X et al. BMJ open. 2022;12(6):e056680. However, our review also has several limitations that must be considered when interpreting the results, based on the Wang X et al. BMJ open. 2022;12(6):e056680. First, the qualities of included meta-analyses were low as they did not meet the standards of AMSTAR 2, such as they did not establish a protocol a priori and the report did not justify any significant deviations from the protocol, which can lead to suggesting the importance of exercising consistently and maintaining a healthy weight, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Besides, in the present review, PP in conjunction with SBP and DBP may be used to identify patients at high risk of stroke for improving stroke prevention,

included and excluded meta--analyses only considered the categories of modifiable factors including dietary factors, factors of physical health management and emotional health management, based on the Wang X et al. BMJ open. 2022;12(6):e056680. The detailed factors were confirmed according to the categories in the process, which may lead to flaws in the results, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Third, only evidence derived from systematic reviews and meta--analyses of cohort studies was included in our umbrella review, based on the Wang X et al. BMJ open.

2022;12(6):e056680. Evidence from original studies in other databases was beyond our scope of discussion, based on the Wang X et al. BMJ open. 2022;12(6):e056680. This condition might result in conclusion bias of association between modifiable factors and stroke, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Lastly, although subgroup analyses were conducted by subtypes of stroke, subgroup analysis by sex or geographical locations or sensitivity analysis (eg, exclusion of studies at high risk of bias) were not explored. Further studies underlying this are needed in the future.



CONCLUSION

In summary, evidence indicates that modifiable factors have an important role in the primary prevention of stroke, based on the Wang X et al. BMJ open. 2022;12(6):e056680. Diet with rich macronutrients and micronutrients, healthy dietary patterns as well as favourable physical, emotional health and environmental management significantly decrease the risk of stroke, based on the Wang X et al. BMJ open. 2022;12(6):e056680. These lifestyle modifications should be promoted in both individual and population levels to prevent and decrease the burden of stroke in the future, based on the Wang X et al. BMJ open.

2022;12(6):e056680. Although many modifiable factors were evaluated in the review, the quality of evidence was high for a small number of associations, based on the Wang X et al. BMJ open. 2022;12(6):e056680. To achieve high quality of evidence for and be able to give strong recommendation, further studies are needed regarding the following aspects: studies investigating the association between dietary factors and stroke should improve dietary measurement methods and assess changes in dietary behaviour over time; potential confounders of stroke are needed to adjust in the multivariate analysis completely and more research should focus on the physical, emotional and environmental health management the evidence of which is not enough, based on the Wang X et al. BMJ open.

2022;12(6):e056680.

Stroke is one of the major challenges for the global healthcare system, which makes it necessary to explore the relationship between various modifiable factors and stroke risk, based on the Guo Net al. BMC medicine. 2022;20(1):194. Recently, numerous meta-analyses of prospective observational studies have reported that dietary factors played a key role in the occurrence of stroke, based on the Guo Net al. BMC medicine. 2022;20(1):194. However, the conclusions of previous studies have remained controversial and unclear, based on the Guo Net al. BMC medicine. 2022;20(1):194.

Accordingly, Guo Net al, based on the Guo Net al. BMC medicine. 2022;20(1):194. BMC medicine, based on the Guo Net al. BMC medicine. 2022;20(1):194. 2022;20(1):194 conducted an umbrella review synthesizing and recalculating available evidence to assess the certainty of the associations between dietary factors and stroke, based on the Guo Net al. BMC medicine. 2022;20(1):194.

Methods

Relevant meta-analyses examining the associations between dietary factors and stroke were searched in PubMed and Embase databases up to September 1, 2021, based on the Guo Net al. BMC medicine. 2022;20(1):194. For each eligible meta-analysis, two independent reviewers appraised the methodologic quality using the AMSTAR 2 criteria and estimated the summary effect size, 95% confidence intervals, 95% prediction intervals, heterogeneity between studies, and small-study effects, based on the Guo Net al. BMC medicine. 2022;20(1):194. Moreover, Guo Net al, based on the Guo Net al. BMC medicine. 2022;20(1):194. BMC medicine, based on the Guo Net al. BMC medicine. 2022;20(1):194. 2022;20(1):194 further assessed the associations between dietary factors and ischemic stroke as well as hemorrhagic stroke, based on the Guo Net al. BMC medicine. 2022;20(1):194. Lastly, a set of pre-specified criteria was applied to qualitatively evaluate the epidemiological credibility of each dietary factor, based on the Guo Net al. BMC medicine. 2022;20(1):194.

Results

Overall, Guo Net al, based on the Guo Net al. BMC medicine. 2022;20(1):194. BMC medicine, based on the Guo Net al. BMC medicine. 2022;20(1):194. 2022;20(1):194 umbrella review included 122 qualified meta-analyses for qualitative synthesis, involving 71 dietary factors related to food groups, foods, macronutrients, and micronutrients, based on the Guo Net al. BMC medicine. 2022;20(1):194. Using the AMSTAR 2 criteria, 5 studies were assessed as high quality, 4 studies as moderate quality, and 113 studies as low or critically low quality, based on the Guo Net al. BMC medicine. 2022;20(1):194. Guo Net al, based on the Guo Net al. BMC medicine. 2022;20(1):194. BMC medicine, based on the Guo Net al. BMC medicine. 2022;20(1):194. 2022;20(1):194 identified 34 dietary factors associated with stroke occurrence, 25 dietary factors related to ischemic stroke, and 11 factors related to hemorrhagic stroke, based on the Guo Net al. BMC medicine. 2022;20(1):194. Among them, high/moderate certainty epidemiological evidence demonstrated an inverse association between intake of fruits (RR: 0, based on the Guo Net al. BMC medicine. 2022;20(1):194.90) and vegetables (RR: 0, based on the Guo Net al. BMC medicine. 2022;20(1):194.92) and stroke incidence, but a detrimental association between red meat (RR: 1, based on the Guo Net al. BMC medicine. 2022;20(1):194.12), especially processed red meat consumption (RR: 1, based on the Guo Net al. BMC medicine. 2022;20(1):194.17), and stroke incidence, based on the Guo Net al. BMC medicine. 2022;20(1):194. Besides, the evidence of high/moderate certainty suggested that the intake of processed meat, fruits, coffee, tea, magnesium, and dietary fiber was associated with ischemic stroke risk, while consumption of tea, fruits, and vegetables was relevant to hemorrhagic stroke susceptibility, based on the Guo Net al. BMC medicine. 2022;20(1):194.

Conclusions

Guo Net al, based on the Guo Net al. BMC medicine. 2022;20(1):194. BMC medicine, based on the Guo Net al. BMC medicine. 2022;20(1):194. 2022;20(1):194 study has reported that several dietary factors have a significant impact on stroke risk and offered a new insight into the relationship between dietary modification and stroke occurrence, based on the Guo Net al. BMC medicine.

2022;20(1):194. Guo Net al, based on the Guo Net al. BMC medicine. 2022;20(1):194. BMC medicine, based on the Guo Net al. BMC medicine. 2022;20(1):194. 2022;20(1):194 results may provide an effective strategy for stroke prevention, based on the Guo Net al. BMC medicine. 2022;20(1):194.

Supplementary Information

The online version contains supplementary material available at 10, based on the Guo Net al. BMC medicine. 2022;20(1):194.1186/s12916-022-02381-6, based on the Guo Net al. BMC medicine. 2022;20(1):194.

Keywords: Dietary factor, Stroke, Prospective observational study, Meta-analysis, Umbrella review

Go to:

Background

Stroke, a global health issue, is the major cause of permanent disability and death worldwide, resulting in a substantial economic burden on individuals, families, and society [1, 2]. With the aging of the global population, the American Heart Association estimates that the incidence of stroke in American adults may reach 4% by 2030, causing stroke-related medical expenses rising to \$183 billion [3]. Thus, effective prevention and management strategies of stroke are urgently needed in order to limit the prevalence and cost of stroke. To our knowledge, recent studies have found that many unmodifiable factors were associated with stroke risk, including age, gender, family history, and so on [4]. Moreover, modifiable factors also play a vital role in stroke susceptibility.

Dietary factors, an important part of modifiable factors for stroke occurrence, have attracted intense interest of researchers and clinicians. An increasing number of meta-analyses from prospective observational studies were conducted to examine the effects of dietary factors on the risk of stroke. Nevertheless, findings of previous meta-analyses (including the conclusions, strength of evidence and potential bias, etc.) investigating the association between dietary factors and stroke susceptibility were sometimes discordant and inconclusive. Therefore, it was necessary to conduct a comprehensive evaluation of all published meta-analyses to summarize and clarify the relationship between dietary factors and stroke risk.

An umbrella review, providing a systematic calculation and appraisal of meta-analyses, has been widely applied to evaluate the association between modifiable factors and disease susceptibility including dementia [5], multiple sclerosis [6], and various cancers [7, 8], thereby improving the accuracy and strength of results and revealing the breadth and robustness of associations [9]. Till now, an umbrella review investigating the association between dietary factors and stroke risk has not been conducted; hence, in order to further understand and reassess the association, we carried out a comprehensive umbrella review through collecting all available meta-analyses of prospective observational studies to explore potential strategies for stroke prevention.

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Methods

Literature retrieval strategy

The search strategy of Guo Net al. BMC medicine. 2022;20(1):194 umbrella review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10].. The following search terms Guo Net al. BMC medicine. 2022;20(1):194 re applied by searching for titles and abstracts in PubMed and Embase databases up to September 1, 2021: ("diet" OR "dietary" OR "intake" OR "consumption") AND ("stroke" OR "cerebrovascular disease" OR "ischemic stroke" OR "hemorrhagic stroke" OR "cerebral infarction" OR "brain infarction" OR "cerebral hemorrhage") AND ("meta-analysis" OR "systematic review").. Besides, the reference lists of retrieved articles Guo Net al. BMC medicine. 2022;20(1):194 re carefully screened to search for potentially eligible articles..

Inclusion and exclusion criteria

Studies that met the following criteria Guo Net al. BMC medicine. 2022;20(1):194 re included in Guo Net al. BMC medicine. 2022;20(1):194 umbrella review: (1) meta-analyses of prospective observational studies (cohort studies or nested case-control studies) investigating the relationship betGuo Net al. BMC medicine. 2022;20(1):194 en dietary factors and stroke risk; (2) eligible dietary factors consisting of two types: one is food groups, foods, and beverages (grains, vegetables, fruits, fish, meat, eggs, legumes, nut, dairy products, chocolate, coffee, tea, and sugar-sGuo Net al. BMC medicine. 2022;20(1):194 etened beverages), and the other is macronutrients (protein, fat, carbohydrates, and fiber), micronutrients (vitamin, mineral), and flavonoid; (3) considering the incidence of stroke, ischemic stroke, or hemorrhagic stroke as the outcome; (4) providing the specific data to calculate the summary effect size, 95% confidence intervals (CIs), 95% prediction intervals (PIs), heterogeneity betGuo Net al. BMC medicine. 2022;20(1):194 en studies, and small-study effects for further analysis; and (5) published in English.. In contrast, articles Guo Net al. BMC medicine. 2022;20(1):194 re excluded based on the following criteria: (1) meta-analyses of non-prospective observational studies, including randomized controlled trials, cross-sectional, or non-nested case-control studies; (2) without original data to analyze the summary risk estimate, 95%

CIs, 95% PIs, etc.. (e.g., systematic reviews without meta-analysis); (3) reviews, letters, editorials, and conference abstracts; and (4) duplicated publications..

Data extraction and methodological quality assessment

Two authors respectively collected the following data for each eligible article using a standard extraction form, including the first author's name, publication year, study design, original article retrieval time, dietary factor, outcome of interest (stroke, ischemic stroke, or hemorrhagic stroke), number of included studies, number of participants and cases, comparison of types (high versus low meta-analysis or dose-response meta-analysis), duration of follow-up, assessment tool of the original study, information of funding, and conflict of interest.. Moreover, Guo Net al. BMC medicine. 2022;20(1):194 extracted the most fully adjusted effect estimates and corresponding 95% CIs from original studies.. According to the literature, the most important adjustment factors in the investigation betGuo Net al. BMC medicine. 2022;20(1):194 en dietary factors and stroke susceptibility included age, gender, body mass index, physical activity, total energy intake, smoking, hypertension, and diabetes mellitus..

The AMSTAR (A MeaSurement Tool to Assess systematic Reviews) 2, a reliable methodological quality assessment tool, was applied to evaluate the quality of each eligible meta-analyses [11].. It was composed of 16 items, which Guo Net al. BMC medicine. 2022;20(1):194 re divided into 7 critical and 9 non-critical domains.. According to the quality of each item, including search strategy, study selection, data extraction, study limitations, risk of bias assessment, etc., Guo Net al. BMC medicine. 2022;20(1):194 further categorized each systematic review into high, moderate, low, or critical low quality..

Statistical analysis

In this umbrella review, the random and fixed effect models Guo Net al. BMC medicine. 2022;20(1):194 re applied to calculate the summary effect size and 95% CIs to assess the association betGuo Net al. BMC medicine. 2022;20(1):194 en dietary factors and stroke risk.. Guo Net al. BMC medicine. 2022;20(1):194 further computed the 95% PIs, which represented the probability range in which the effect estimates from future studies investigating the same association would lie with 95% certainty [12].. Then, the Cochran Q test and I₂ statistic Guo Net al. BMC medicine. 2022;20(1):194 re also performed to analyze the statistical heterogeneity betGuo Net al. BMC medicine. 2022;20(1):194 en original studies, and $P < 0.10$ and $I^2 > 50\%$ Guo Net al. BMC medicine. 2022;20(1):194 re deemed to be high heterogeneity.. Moreover, Egger's test and funnel plot Guo Net al. BMC medicine. 2022;20(1):194 re applied to evaluate the small-study effect and publication bias for each eligible meta-analysis by using statistical and graphical tests.. The results of P value < 0.10 Guo Net al. BMC medicine. 2022;20(1):194 re considered to be significant evidence of small-study effects.. Lastly, Guo Net al. BMC medicine. 2022;20(1):194 carried out subgroup evaluation according to stroke subtypes, namely ischemic stroke and hemorrhage stroke.. All statistical analyses Guo Net al. BMC medicine. 2022;20(1):194 re conducted using STATA software 12.0.. Apart from heterogeneity and small-study effects, all tests Guo Net al. BMC medicine. 2022;20(1):194 re considered to be significant at the level of P value < 0.05 ..

Credibility of epidemiologic evidence

In accordance with established tools applied in previous umbrella reviews, Guo Net al. BMC medicine. 2022;20(1):194 appraised the strength of epidemiologic evidence for the relationship betGuo Net al. BMC medicine. 2022;20(1):194 en each dietary factor and stroke risk by using the following criteria: (1) precision of the estimate (P value < 0.001 , a threshold with less false-positive possibility); (2) number of cases > 1000 ; (3) no significance heterogeneity ($\text{Pheterogeneity} > 0.10$ and $I^2 < 50\%$); and (4) no evidence of small-study effect ($\text{PEgger} > 0.10$).. Guo Net al. BMC medicine. 2022;20(1):194 quantified the epidemiologic evidence as high credibility (if all the above criteria Guo Net al. BMC medicine. 2022;20(1):194 re met), moderate credibility (if P value < 0.001 was found and two of the remaining three criteria Guo Net al. BMC medicine. 2022;20(1):194 re satisfied), Guo Net al. BMC medicine. 2022;20(1):194 ak credibility (all other cases with P value < 0.05), and nonsignificant association (P value > 0.05) [13]..

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Results

Study identification

Overall, 1445 related articles Guo Net al. BMC medicine. 2022;20(1):194 re initially retrieved from PubMed and Embase databases after the systematic search.. First, 448 duplicated publications and 563 irrelevant publications Guo Net al. BMC medicine. 2022;20(1):194 re removed through browsing the title and abstract.. Then, after a full-text review, Guo Net al. BMC medicine. 2022;20(1):194 excluded a total of 312 articles, including 157 conference abstracts, letters, and reviews; 61 not relevant to dietary factors; 41 not focused on stroke risk; 3 not written in English; and 50 meta-analyses involving non-prospective studies.. Moreover, all excluded full-text articles are detailed in Additional file 1: Table S1.. Finally, 122 qualified meta-analyses Guo Net al. BMC medicine. 2022;20(1):194 re enrolled in Guo Net al. BMC medicine. 2022;20(1):194 umbrella review, and the associations betGuo Net al. BMC medicine. 2022;20(1):194 en foods, food groups, and food nutrients and stroke susceptibility Guo Net al. BMC medicine. 2022;20(1):194 re extracted

and listed in Additional file 2: Table S2 and Additional file 3: Table S3 [14–135], respectively.. The flow chart of the selection process for eligible meta-analyses is presented in Fig.. Fig.11..

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Fig.. 1

Flow diagram of the literature selection process

Characteristics of included studies

A total of 228 effect estimates Guo Net al. BMC medicine. 2022;20(1):194 re reported in all eligible meta-analyses examining the relationship betGuo Net al. BMC medicine. 2022;20(1):194 en dietary consumption and stroke risk.. All eligible articles Guo Net al. BMC medicine. 2022;20(1):194 re published betGuo Net al. BMC medicine. 2022;20(1):194 en 2004 and 2021.. The median number of included meta-analyses per dietary factor was 3 (range 1–12).. Besides, the evidence of each meta-analysis was based on median 7 original studies (interquartile range 4–10, range 2–40), median 253,511 participants (interquartile range 173,274–354,718, range 20,089–4,381,604), and median 6978 stroke cases (interquartile range 4260–10,192, range 299–46,951)..

If more than one meta-analysis Guo Net al. BMC medicine. 2022;20(1):194 re available to assess the same dietary factor, the one with dose-response analysis was selected in the main analysis.. Then, when more than one published dose-response meta-analysis for the same association, the one with the largest number of participants was preferred.. Thus, the main analysis for dietary factors retained 71 risk estimates, including 40 food groups, foods, and beverages and 31 macronutrients and micronutrients.. Moreover, of the 71 dietary factors, 41 dose-response relationships Guo Net al. BMC medicine. 2022;20(1):194 re available, among which 31 provided the information of the linearity of the dose-response relationships (e.g., P for non-linearity).. Five of these 31 dose-response relationships indicated non-linearity, including vegetables, red meat, nut, vitamin E, and magnesium.. Additionally, in the main analysis based on stroke subtypes, 44 risk estimates Guo Net al. BMC medicine. 2022;20(1):194 re retained to analyze the association betGuo Net al. BMC medicine. 2022;20(1):194 en dietary factors and ischemic stroke, and 30 risk estimates focused on the influence of dietary factors on hemorrhagic stroke..

Methodological quality assessment of meta-analyses

The meta-analyses included in Guo Net al. BMC medicine. 2022;20(1):194 umbrella review Guo Net al. BMC medicine. 2022;20(1):194 re assessed for methodological quality, with 5 studies being considered as high (4..10%), 4 studies as moderate (3..28%), and 113 studies as low (43 studies, 35..25%) or critically low (70 studies, 57..38%) (see Additional file 4: Table S4).. The common critical flaws in most meta-analyses Guo Net al. BMC medicine. 2022;20(1):194 re the lack of information of registered protocols (110 studies, 90..16%).. Thus, Guo Net al. BMC medicine. 2022;20(1):194 conducted a sensitivity analysis, which did not consider the item of a registered protocol, to re-analyze the methodological quality of eligible studies.. The results of sensitivity analysis shoGuo Net al. BMC medicine. 2022;20(1):194 d that the AMSTAR 2 rating was re-determined as high in 14 studies (11..48%), moderate in 37 studies (30..33%), and low (35 studies, 28..69%) or critically low (36 studies, 29..51%) in 71 studies (see Additional file 5: Table S5)..

Quantitative analysis on 40 food groups, foods, and beverages

As shown in Fig.. Fig.2,2, the summary effect size with its corresponding 95% CI was calculated to report the associations betGuo Net al. BMC medicine. 2022;20(1):194 en food groups, foods, beverages, and stroke risk.. First of all, Guo Net al. BMC medicine. 2022;20(1):194 observed protective evidence for a dose-response relationship betGuo Net al. BMC medicine. 2022;20(1):194 en the consumption of fruits (RR: 0..90, 95% CI: 0..84–0..97) [19], vegetables (RR: 0..92, 95% CI: 0..86–0..98) [19], fish (HR: 0..94, 95% CI: 0..89–0..99) [30], and chocolate (RR: 0..90, 95% CI: 0..82–0..98) [72] and the risk of stroke.. Conversely, the consumption of red meat increased the incidence of stroke with evidence of a non-linear dose-response relationships involving 341,767 participants (RR: 1..12, 95% CI: 1..06–1..18) [19].. Besides, no clear dose-response associations Guo Net al. BMC medicine. 2022;20(1):194 re shown betGuo Net al. BMC medicine. 2022;20(1):194 en the consumption of total grain foods (RR: 0..97, 95% CI: 0..90–1..03) [16], eggs (RR: 0..99, 95% CI: 0..93–1..05) [19], legumes (RR: 0..98, 95% CI: 0..84–1..14) [48], and dairy products (RR: 0..98, 95% CI: 0..96–1..02) [19] and stroke susceptibility..

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Fig.. 2

Summary relative risk with 95% CI, 95% PI, I₂, and quality of evidence for associations betGuo Net al. BMC medicine. 2022;20(1):194 en food groups, foods, and beverages and occurrence of stroke

Next, Guo Net al. BMC medicine. 2022;20(1):194 conducted a stratified evaluation according to the type of stroke.. For ischemic stroke, the results of meta-analyses indicated that consumption of grain foods (RR: 0..86, 95% CI: 0..74–0..99) [14], fruits and vegetables (RR: 0..94, 95% CI: 0..90–

0..98) [25], dairy products (RR: 0..79, 95% CI: 0..68–0..91) [131], and chocolate (RR: 0..87, 95% CI: 0..78–0..96) had a protective effect on ischemic stroke [73], while the consumption of meat increased the risk of ischemic stroke (RR: 1..15, 95% CI: 1..04–1..28) [35, 37, 39].. Besides, the consumption of fish (HR: 0..96, 95% CI: 0..89–1..03) [28], eggs (RR: 0..94, 95% CI: 0..88–1..00) [40], and legumes (RR: 1..06, 95% CI: 0..74–1..50) [48] was not related to the risk of ischemic stroke (Fig.. (Fig..3)..3).. Regarding hemorrhagic stroke, the reduction of hemorrhagic stroke risk was related to the consumption of fruits and vegetables (RR: 0..78, 95% CI: 0..69–0..88) [23], fish (HR: 0..88, 95% CI: 0..80–0..96) [28], dairy products (RR: 0..75, 95% CI: 0..60–0..94) [131], and chocolate (RR: 0..83, 95% CI: 0..71–0..97) [73] and the increased risk of hemorrhagic stroke was associated with meat consumption (RR: 1..41, 95% CI: 1..08–1..84) [34].. In addition, no associations Guo Net al. BMC medicine. 2022;20(1):194 re observed betGuo Net al. BMC medicine. 2022;20(1):194 en eggs (RR: 0..88, 95% CI: 0..68–1..15) [40] and legumes (RR: 1..24, 95% CI: 0..93–1..66) [48] and hemorrhagic stroke occurrence (Fig.. (Fig..44)..

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Object name is 12916_2022_2381_Fig3_HTML..jpg

Fig.. 3

Summary relative risk with 95% CI, 95% PI, I2, and quality of evidence for associations betGuo Net al. BMC medicine. 2022;20(1):194 en food groups, foods, and beverages and occurrence of ischemic stroke

An external file that holds a picture, illustration, etc..

Object name is 12916_2022_2381_Fig4_HTML..jpg

Fig.. 4

Summary relative risk with 95% CI, 95% PI, I2, and quality of evidence for associations betGuo Net al. BMC medicine. 2022;20(1):194 en food groups, foods, and beverages and occurrence of hemorrhagic stroke

Lastly, for beverages, people with high consumption of coffee Guo Net al. BMC medicine. 2022;20(1):194 re protected from subsequent stroke (RR: 0..87, 95% CI: 0..80–0..94) and ischemic stroke (RR: 0..80, 95% CI: 0..71–0..90), but not from hemorrhagic stroke (RR: 1..03, 95% CI: 0..68–1..57) [78, 79].. Additionally, dose-response evidence suggested that tea consumption (per cup per day) protected against stroke, ischemic stroke, and hemorrhagic stroke (stroke: RR: 0..96, 95% CI: 0..94–0..99; ischemic stroke: RR: 0..76, 95% CI: 0..69–0..84; hemorrhagic stroke: RR: 0..79, 95% CI: 0..72–0..87) [81–83].. Conversely, evidence from meta-analyses of prospective observational studies noted that sugar-sGuo Net al. BMC medicine. 2022;20(1):194 etened beverage consumption increased the risk of stroke (RR: 1..07, 95% CI: 1..02–1..12), but not ischemic stroke (RR: 1..16, 95% CI: 0..93–1..46) or hemorrhagic stroke (RR: 0..86, 95%CI: 0..71–1..04) [19, 85] (Figs.. (Figs..2,2, ,3,3, and and44)..

Quantitative analysis on 31 food nutrients

Macronutrients

As shown in Fig.. Fig..5,5, the associations betGuo Net al. BMC medicine. 2022;20(1):194 en macronutrients and incidence of stroke Guo Net al. BMC medicine. 2022;20(1):194 re evaluated using summary effect size with its corresponding 95% CI.. Among them, long-chain n-3 polyunsaturated fatty acid (n-3 PUFA) (RR: 0..87, 95% CI: 0..80–0..95) [93], saturated fat (SFA) (RR: 0..87, 95% CI: 0..78–0..96) [89], monounsaturated fatty acid (MUFA) (RR: 0..86, 95% CI: 0..74–1..00) [92], and dietary fiber (RR: 0..93, 95% CI: 0..88–0..98) [101] Guo Net al. BMC medicine. 2022;20(1):194 re associated with decreased incidence of stroke in meta-analyses comparing high versus low intake or dose-response meta-analyses, respectively, while a meta-analysis of 8 cohort studies involving 423,049 participants found high carbohydrate intake increased the risk of stroke (RR: 1..13, 95% CI: 1..01–1..27) [98].. Moreover, no evidence illustrated that high dietary protein and cholesterol Guo Net al. BMC medicine. 2022;20(1):194 re linked to the susceptibility of stroke (protein: RR: 0..98, 95% CI: 0..89–1..07; cholesterol: RR: 0..95, 95% CI: 0..84–1..07) [87, 95]..

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Fig.. 5

Summary relative risk with 95% CI, 95% PI, I2, and quality of evidence for associations betGuo Net al. BMC medicine. 2022;20(1):194 en food nutrients and occurrence of stroke

In further stratified evaluation based on stroke type (Figs.. (Figs..66 and and7,7), Guo Net al. BMC medicine. 2022;20(1):194 observed that n-3 PUFA and SFA intake could significantly reduce the risk of ischemic stroke (n-3 PUFA: RR: 0..87, 95% CI: 0..76–0..99; SFA: RR: 0..89, 95% CI: 0..82–0..96) and hemorrhagic stroke (n-3 PUFA: RR: 0..82, 95% CI: 0..68–0..99; SFA: RR: 0..76, 95% CI: 0..63–0..93) [90, 93].. Besides, the intake of dietary fiber had a significant protective effect on ischemic stroke (RR: 0..85, 95% CI: 0..79–0..91), while failed to reach significance in hemorrhagic stroke (RR: 0..87, 95% CI: 0..72–1..05) [99, 134].. In addition, no statistically significant evidence was found to indicate the associations betGuo Net al. BMC medicine. 2022;20(1):194 en dietary protein and

cholesterol intake and ischemic stroke (protein: RR: 0..94, 95% CI: 0..80–1..10; cholesterol: RR: 0.95, 95% CI: 0.80–1..12) and hemorrhagic stroke (protein: RR: 1..05, 95% CI: 0..97–1..14; cholesterol: RR: 1..03, 95% CI: 0..85–1..25) [87, 95].

An external file that holds a picture, illustration, etc..

Object name is 12916_2022_2381_Fig6_HTML..jpg

Fig.. 6

Summary relative risk with 95% CI, 95% PI, I2, and quality of evidence for associations betGuo Net al. BMC medicine. 2022;20(1):194 en food nutrients and occurrence of ischemic stroke

An external file that holds a picture, illustration, etc..

Object name is 12916_2022_2381_Fig7_HTML..jpg

Fig.. 7

Summary relative risk with 95% CI, 95% PI, I2, and quality of evidence for associations betGuo Net al. BMC medicine. 2022;20(1):194 en food nutrients and occurrence of hemorrhagic stroke

Micronutrients

According to the meta-analyses of prospective observational studies, several dietary micronutrients, including vitamins, minerals, and flavonoids, Guo Net al. BMC medicine.

2022;20(1):194 re associated with stroke risk.. As displayed in Fig.. Fig.5,5, dietary intake of vitamin B6 (RR: 0..94, 95% CI: 0..89–0..99) [102], folic acid (RR: 0..94, 95% CI: 0..90–0..98) [102], vitamin C (RR: 0..84, 95% CI: 0..75–0..93) [103], β-carotene (RR: 0..84, 95% CI: 0..75–0..94) [104], vitamin D (RR: 0..75, 95% CI: 0..57–0..98) [105], magnesium (RR: 0..93, 95% CI: 0..89–0..97) [112], potassium (RR: 0..89, 95% CI: 0..83–0..97) [123], and flavonoid (RR: 0..86, 95% CI: 0..77–0..96) [127] had a significant impact on decreasing the occurrence of stroke.. Conversely, sodium intake had a significant effect on increasing stroke risk (RR: 1..10, 95% CI: 1..01–1..19) with evidence of a linear dose-response relationship [125].. Additionally, no clear associations Guo Net al. BMC medicine. 2022;20(1):194 re observed betGuo Net al. BMC medicine. 2022;20(1):194 en dietary vitamin B12 (RR: 1..01, 95% CI: 0..98–1..06) [102], vitamin E (RR: 0..97, 95% CI: 0..93–1..01) [104], vitamin K (HR: 1..04, 95% CI: 0..92–1..17) [107], lycopene (RR: 0..76, 95% CI: 0..42–1..37) [104], choline (RR: 0..94, 95% CI: 0..80–1..09) [110], and calcium (RR: 0..98, 95% CI: 0..90–1..06) [115] intake and the incidence of stroke..

With regard to subgroup evaluation, Guo Net al. BMC medicine. 2022;20(1):194 observed dietary vitamin C (RR: 0..77, 95% CI: 0..64–0..92) [103], vitamin E (RR: 0..83, 95% CI: 0..69–1..00) [106], magnesium (RR: 0..91, 95% CI: 0..87–0..96) [114], and potassium (RR: 0..89, 95% CI: 0..81–0..97) [123] intake protected against ischemic stroke, but did not reach statistical significance in hemorrhagic stroke (vitamin C: RR: 1..07, 95% CI: 0..38–3..00; vitamin E: RR: 1..05, 95% CI: 0..49–2..28; magnesium: RR: 0..93, 95% CI: 0..82–1..06; potassium: RR: 0..95, 95% CI: 0..83–1..09).. Besides, flavonoid intake was not related to ischemic stroke (RR: 0..86, 95% CI: 0..71–1..04) and hemorrhagic stroke (RR: 0..90, 95% CI: 0..61–1..32) [127] (Figs.. (Figs..66 and and77)..

Heterogeneity betGuo Net al. BMC medicine. 2022;20(1):194 en primary studies, 95% prediction intervals, and small-study effects

Guo Net al. BMC medicine. 2022;20(1):194 reported the assessment of the level of heterogeneity, 95% PI, and the presence of small-study effects.. Firstly, Guo Net al. BMC medicine. 2022;20(1):194 results appraised the heterogeneity betGuo Net al. BMC medicine. 2022;20(1):194 en primary studies using the I2 value.. Most studies (57..75%, 41/71) had I2≤50..00%, implying low heterogeneity betGuo Net al. BMC medicine. 2022;20(1):194 en primary studies, while 30 associations (42..25%) shoGuo Net al. BMC medicine. 2022;20(1):194 d substantial heterogeneity (I2 >50..0%), indicating that the difference of risk estimates betGuo Net al. BMC medicine. 2022;20(1):194 en primary studies may not only be due to random error.. Next, the 95% PIs of 4 associations excluded the null value—that was the consumption of fruits and vegetables, red meat, processed red meat, and sugar-sGuo Net al. BMC medicine. 2022;20(1):194 etened beverages.. The remaining meta-analyses of dietary factors had 95% PIs which contained the null value, suggesting that, although on average some dietary factors Guo Net al. BMC medicine. 2022;20(1):194 re associated with stroke risk, this may not always be the case in certain settings.. Lastly, based on Egger's test and the funnel plot (see Additional file 6: Fig.. S1-S16), the 9 associations (14..06%) shoGuo Net al. BMC medicine. 2022;20(1):194 d the presence of small-study effects and potential publication bias ($P<0..10$).. Among them, 7 dietary factors Guo Net al. BMC medicine. 2022;20(1):194 re indicated in the dose-response meta-analyses involving legumes, nut, milk, chocolate, dietary fiber, vitamin B6, and flavonoids, and the other two factors, soy and coffee, Guo Net al. BMC medicine. 2022;20(1):194 re indicated in the meta-analyses comparing high versus low consumption..

Strength of epidemiologic evidence

Guo Net al. BMC medicine. 2022;20(1):194 study assessed the strength of epidemiologic evidence for the association betGuo Net al. BMC medicine. 2022;20(1):194 en dietary factors and stroke risk.. Among them, moderate/high certainty of evidence was found for red meat, especially processed red

meat consumption, which was associated with an increased incidence of stroke, as Guo Net al. BMC medicine. 2022;20(1):194 ll as for the intake of fruits and vegetables, which shoGuo Net al. BMC medicine. 2022;20(1):194 d an association with decreased incidence of stroke.. Additionally, 5 other risk factors and 24 protective factors Guo Net al. BMC medicine. 2022;20(1):194 re confirmed as statistically significant, but the strength of the evidence was Guo Net al. BMC medicine. 2022;20(1):194 ak.. Lastly, the included studies did not observe a significant effect of other 37 dietary factors on stroke ($P>0.05$).

With regard to stratification of stroke subtypes, 25 dietary factors Guo Net al. BMC medicine. 2022;20(1):194 re found to be significantly associated with ischemic stroke, among which the credibility of 6 dietary factors, including fruits, processed meat, coffee, tea, magnesium, and dietary fiber consumption, was moderate/high, and the other 19 dietary factors Guo Net al. BMC medicine. 2022;20(1):194 re Guo Net al. BMC medicine. 2022;20(1):194 ak.. As for hemorrhagic stroke, two protective dietary factors (fruits and vegetables, and tea consumption) shoGuo Net al. BMC medicine. 2022;20(1):194 d high/moderate strength of evidence and the remaining 9 dietary factors shoGuo Net al. BMC medicine. 2022;20(1):194 d Guo Net al. BMC medicine. 2022;20(1):194 ak evidence..

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Discussion

Principal findings

In Guo Net al. BMC medicine. 2022;20(1):194 umbrella review, a total of 122 eligible meta-analyses Guo Net al. BMC medicine. 2022;20(1):194 re included to assess the impact of 71 dietary factors on stroke, including 40 foods, food groups, and beverages and 31 macronutrients and micronutrients. After assessing the credibility of all included meta-analyses using stringent criteria, the evidence strength for fruits, vegetables, and red meat was considered as high/moderate, indicating that they may have an important impact on stroke prevention. Among them, the intake of fruits and vegetables was observed to reduce the risk of stroke, while the consumption of red meat, especially processed red meat, was considered to increase the risk.

Possible explanations

Guo Net al. BMC medicine. 2022;20(1):194 umbrella review indicated that high consumption of fruits and vegetables was beneficial to the general population for preventing stroke. This protective effect can be attributed to the various nutrients contained in fruits and vegetables, including vitamin C, potassium, dietary fiber, and flavonoids [22]. First, vitamin C, a powerful water-soluble antioxidant, has been suggested to inhibit low-density lipoprotein peroxidation and smooth muscle hyperplasia/hypertrophy, thereby retarding the formation of atherosclerosis [103, 136, 137]. Second, potassium has been found to have an impact on the development of stroke. Increased potassium levels would relax blood vessels and inhibit excessive activation of platelets. Moreover, a high-potassium diet could significantly delay the development of vascular damage by restraining the production of reactive oxygen species [122, 138]. Third, the consumption of dietary fiber can slow down gastric emptying, promote satiety, reduce absorption of food, and thus reduce body weight and blood lipid levels [101, 139, 140]. As secondary metabolites of polyphenols, flavonoids can inhibit LDL oxidation and vascular inflammation and play an important role in protecting endothelial function [141–143].

Additionally, it is also biologically reasonable that high consumption of red meat could increase the risk of stroke. First of all, high red meat intake could increase the circulating levels of LDL-C and triglycerides, which might cause atherosclerotic plaques, interrupt blood flow to the brain, and lead to stroke occurrence [34]. Then, heme iron, mainly derived from red meat, is a redox active substance that could promote the production of oxygen free radicals, leading to LDL-C peroxidation and subsequent vascular inflammation and damage [144–146]. Moreover, processed meat usually contains high levels of sodium and nitrite preservatives [124]. High sodium levels could reduce arterial compliance, cause vascular stiffness, and thus have a negative impact on subsequent high blood pressure and stroke [147, 148]. The cytotoxicity of nitrite preservatives can induce vascular endothelium damage and apoptosis, which is a critical driving factor for endothelial dysfunction [149].

Subgroup evaluation

Regarding ischemic stroke, the evidence of high/moderate certainty indicated that the intake of coffee, tea, magnesium, fruits, dietary fiber, and processed meat was associated with ischemic stroke risk. From a biological point of view, caffeine, a famous ingredient in coffee, plays a vital role in reducing oxidation stress and inflammatory response and delaying atherosclerosis progression [150]. Moreover, the chlorogenic acid contained in coffee can regulate the body's glucose and lipid metabolism and inhibit the activation of platelets [78]. As for tea, flavonoids in tea can induce vasodilation and improve cerebral blood perfusion by activating nitric oxide [151, 152]. Meanwhile, tea contains a high concentration of theanine, which can pass through the blood-brain barrier and reduce glutamate-related vascular endothelial damage [84]. Regarding micronutrients, magnesium has been shown to be associated with ischemic stroke, which could be explained by the following

reasons. As a natural calcium antagonist, magnesium could inhibit the influx of glutamate and calcium cations and eliminate the cytotoxicity of calcium cations [111]. Moreover, a previous study showed Guo Net al. BMC medicine. 2022;20(1):194 that magnesium deficiency was related to vascular dysfunction and platelet-dependent thrombosis [153]. Besides, magnesium intake also plays a vital role in Guo Net al. BMC medicine. 2022;20(1):194 on blood sugar and blood pressure levels [154].

With regard to hemorrhagic stroke, Guo Net al. BMC medicine. 2022;20(1):194 found more associations for ischemic stroke than hemorrhagic stroke. The possible reasons may be as follows: the etiology of ischemic stroke, including oxidative stress, free radical production, lipid peroxidation, and vascular inflammation and atherosclerosis, is more closely related to nutritional factors [155, 156]. More importantly, the incidence of ischemic stroke is much higher than that of hemorrhagic stroke, so it receives more attention from researchers. Thus, more original studies should be performed to investigate the relationship between dietary factors and hemorrhagic stroke.

Strengths and limitations

To the best of Guo Net al. BMC medicine. 2022;20(1):194 knowledge, Guo Net al. BMC medicine. 2022;20(1):194 umbrella review was the first to systematically collect and evaluate all published meta-analyses and summarize the evidence on the role of dietary factors in preventing stroke. Guo Net al. BMC medicine. 2022;20(1):194 have included only meta-analyses focusing on prospective observational studies, which collected exposure information before stroke diagnosis and reduced recall bias compared to retrospective studies. Meanwhile, robust criteria Guo Net al. BMC medicine. 2022;20(1):194 were adopted to assess the methodologic quality and evidence strength of eligible meta-analyses. Moreover, Guo Net al. BMC medicine. 2022;20(1):194 highlighted the dose-response relationship, subgroup evaluation, sensitivity analysis, and biological plausibility to obtain a more comprehensive and accurate conclusion for each dietary factor.

Several limitations of this umbrella review should also be recognized. First, the individual observational study may have a different definition and measurement method for exposure comparison, which makes it impossible to determine the exact comparison for the included meta-analyses. Second, within an observational design, the original studies in the meta-analysis Guo Net al. BMC medicine. 2022;20(1):194 are prone to confounding bias. Thus, some known confounders Guo Net al. BMC medicine. 2022;20(1):194 are adjusted for in most of the original studies. Moreover, Guo Net al. BMC medicine. 2022;20(1):194 extracted the fully adjusted effect estimates for further analysis. HoGuo Net al. BMC medicine. 2022;20(1):194, regarding the differences in the adjustment models in the original studies, residual confoundings cannot be completely ruled out for some summary effect estimates, thereby distorting true effect sizes. Third, for dietary factors in Guo Net al. BMC medicine. 2022;20(1):194 umbrella review, Guo Net al. BMC medicine. 2022;20(1):194 systematically selected 41 dose-response meta-analyses in the main analysis. HoGuo Net al. BMC medicine. 2022;20(1):194, information of linearity was only available for 76% (31/41) of all available dose-response meta-analyses, with 16% (5/31) showing a non-linear dose-response relationship. Thus, further investigation is required to provide the information of linearity and determine the optimal cut-off point to arrive at a recommendation. Lastly, most included meta-analyses Guo Net al. BMC medicine. 2022;20(1):194 are of low quality due to a lack of protocol. Thus, more widespread adoption of reporting guidelines, such as MOOSE (Meta-analysis Of Observational Studies in Epidemiology) and QUORUM (Quality of Reporting of Meta-analyses), may help to improve the quality of future meta-analyses [157].

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Conclusions

In conclusion, Guo Net al. BMC medicine. 2022;20(1):194 have reported the most comprehensive evaluation of the relationship between dietary factors and stroke risk and found that 34 dietary factors Guo Net al. BMC medicine. 2022;20(1):194 are associated with stroke susceptibility. After using strict criteria to assess the strength of epidemiologic evidence, a series of dietary factors shown Guo Net al. BMC medicine. 2022;20(1):194 have high/moderate-strength evidence, including red meat, especially processed red meat, fruits, and vegetables. Guo Net al. BMC medicine. 2022;20(1):194 results may provide new insights for implementing the best strategies for stroke prevention.

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Supplementary Information

Additional file 1: Table S1. List of excluded full-text articles.(50K, docx)

Additional file 2: Table S2. Characteristics of included meta-analyses evaluating associations between food groups, foods as well as beverages and stroke risk.(80K, docx)

Additional file 3: Table S3. Characteristics of included meta-analyses evaluating associations between food nutrients and stroke risk.(44K, docx)

Additional file 4: Table S4. Quality assessment of included meta-analyses using AMSTAR 2.(52K, docx)

Additional file 5: Table S5. Quality assessment of included meta-analyses using AMSTAR 2, without considering item 2 (sensitivity analysis).(50K, docx)

Additional file 6: Fig. S1 Funnel plots for the association between A) total grains, B) whole grain, C) refined grain, D) whole grain bread, E) whole grain breakfast cereals, F) rice, G) oat and incidence of stroke. Fig. S2 Funnel plots for the association between A) fruits and vegetables, B) fruits, C) vegetables, D) potato and incidence of stroke. Fig. S3 Funnel plots for the association between A) fish, B) fatty fish, C) lean fish and incidence of stroke. Fig. S4 Funnel plots for the association between A) meat, B) red meat, C) processed meat, D) processed red meat, E) fresh red meat, F) white meat (poultry) and incidence of stroke. Fig. S5 Funnel plots for the association between eggs and incidence of stroke. Fig. S6 Funnel plots for the association between A) legumes, B) soy, C) nut, D) peanuts, E) tree nuts, F) walnuts, G) peanut butter, H) nut plus peanut butter and incidence of stroke. Fig. S7 Funnel plots for the association between A) dairy products, B) milk, C) cheese, D) cream, E) butter, F) yogurt and incidence of stroke. Fig. S8 Funnel plots for the association between chocolate and incidence of stroke. Fig. S9 Funnel plots for the association between A) coffee, B) tea, C) sugar-sweetened beverages, D) artificially sweetened beverage and incidence of stroke. Fig. S10 Funnel plots for the association between A) protein, B) animal protein, C) plant protein and incidence of stroke. Fig. S11 Funnel plots for the association between A) saturated fat, B) MUFA, C) n-3 PUFA, D) cholesterol, E) α-linolenic acid and incidence of stroke. Fig. S12 Funnel plots for the association between carbohydrate and incidence of stroke. Fig. S13 Funnel plots for the association between A) total fiber, B) soluble dietary fiber, C) insoluble dietary fiber, D) cereal fiber, E) fruit fiber, F) vegetable fiber and incidence of stroke. Fig. S14 Funnel plots for the association between A) vitamin B6, B) vitamin B12, C) vitamin C, D) vitamin D, E) vitamin E, F) vitamin K, G) folate acid, H) β-carotene, I) lycopene, J) dietary choline and incidence of stroke. Fig. S15 Funnel plots for the association between A) magnesium, B) calcium, C) potassium, D) sodium and incidence of stroke. Fig. S16 Funnel plots for the association between A) flavonoid, B) anthocyanins and incidence of stroke.(709K, pdf)

Go to:

Baratloo A, Mohamadi M, Mohammadi M, Toloui A, Neishaboori AM, Alavi SN, Nahiye A, Yousefifard M. The value of predictive instruments in the screening of acute stroke: an umbrella review on previous systematic reviews. *Frontiers in Emergency Medicine*. 2022 May 8.

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FRONTIERS IN EMERGENCY MEDICINE. 2022; 6(3):e38

Baratloo et al.

REVIEW ARTICLE

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The value of predictive instruments in the screening of acute stroke: an umbrella review on previous systematic reviews

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Abstract: **Objective:** Although various predictive instruments have been introduced for early stroke diagnosis, there is no consensus on their performance, based on the Baratloo A et al. *Front Emer Med*. 2022. Therefore, Baratloo A et al., based on the Baratloo A et al. *Front Emer Med*. 2022. *Front Emer Med*, based on the Baratloo A et al. *Front Emer Med*.

2022. 2022 decided to assess the value of predictive instruments in the de-tention of stroke by conducting an umbrella review, based on the Baratloo A et al. Front Emer Med. 2022.

Method: A search was performed in the Medline, Embase, Scopus and Web of Science databases by the end of August 2021 for systematic reviews and meta-analyses, based on the Baratloo A et al. Front Emer Med. 2022. Original articles included in the systematic reviews were retrieved, summarized and pooled sensitivity, specificity and diagnostic odds ratio were calculated, based on the Baratloo A et al. Front Emer Med. 2022. The level of evidence was divided into five groups: convincing (class I), highly suggestive (class II), suggestive (class III), weak (class IV) and non-significant, based on the Baratloo A et al. Front Emer Med. 2022.

Results: The value of 33 predictive instruments was evaluated, based on the Baratloo A et al. Front Emer Med. 2022. The sample size included in these scoring sys-tems' assessments varied between 182 and 47072 patients, based on the Baratloo A et al. Front Emer Med. 2022. The level of evidence was class I in one tool, class II in 18 tools, class III in 2 tools, class IV in 11 tools, and non-significant in one tool, based on the Baratloo A et al. Front Emer Med. 2022. Apart from Med PACS, which had a low diagnostic value, other tools appeared to be able to detect a stroke, based on the Baratloo A et al. Front Emer Med. 2022. The optimum performance for diagnosis of stroke was for ROSIER, NIHSS, PASS, FAST, LAMS, RACE and CPSS, based on the Baratloo A et al. Front Emer Med. 2022.

Conclusion: Convincing to suggestive evidence shows that ROSIER, NIHSS, PASS, FAST, LAMS, RACE and CPSS have the optimum performance in identifying stroke, based on the Baratloo A et al. Front Emer Med. 2022. Since ROSIER's calculation is simple and has the high-est sensitivity and specificity among those predictive instruments, it is recommended for stroke diagnosis in pre-hospital and in-hospital settings, based on the Baratloo A et al. Front Emer Med. 2022.

Keywords: Decision Support Techniques; Diagnosis; Emergency Medical Service; Stroke

Cite this article as: Baratloo A, Mohamadi M, Mohammadi M, Toloui A, Madani Neishaboori A and et al. The value of predictive instruments in the screening of acute stroke: an umbrella review on previous systematic reviews. Front Emerg Med. 2022;6(3):e38.

1. Introduction

Stroke is one of the main causes of mortality and morbidity with an annual incidence rate of 25 million cases (1). Stroke is one of the top 10 causes of death worldwide (1, 2) and is the cause of 5 to 10 percent of acute deaths. Based on the responsible pathophysiological processes, stroke is di-vided into two types: hemorrhagic and ischemic. The preva-lence of ischemic stroke is much higher than the hemor-rhagic type; However, mortality due to hemorrhagic stroke is much higher than the ischemic type (1).

The most well-known treatment for ischemic stroke is the use of intravenous thrombolytics such as tissue plasminogen activator (tPA), which should be administrated in 3.5 to 4 hours after the onset of stroke symptoms (3). Another treatment mentioned in recent studies is thrombectomy. Endovascu-

lar thrombectomy in great vessels is one of the most effec-tive treatments for ischemic stroke (4-6). While surgery and endovascular embolization are used to treat strokes, the ef-fectiveness of these treatments could be reduced in many cases due to delayed diagnosis. If the response team is able to quickly diagnose cerebrovascular accidents, the onset-to-door time could be substantially decreased.

Computed tomography scan (CT scan) and magnetic reso-nance imaging (MRI) are reliable modalities to detect strokes (7), but the lack of access to these imaging techniques in pre-hospital settings and even in some hospitals has led re-searchers to look for other alternatives.

One of these al-ternative methods is using clinical screening tools. Vari-ous predictive instruments have been introduced to detect stroke, such as the Cincinnati Prehospital Stroke Severity Scale (CPSS); Los Angeles Motor Scale (LAMS); National In-

stitutes of Health Stroke Scale (NIHSS); Rapid Arterial Occlusion Evaluation; the Stroke Vision, Aphasia, Neglect assessment (VAN); Melbourne Ambulance Stroke Screen (MASS); Medic Prehospital Assessment for Code Stroke (Med PACS); Ontario Prehospital Stroke Screening Tool (OPSS); Recognition of Stroke in the Emergency Room (ROSIER) and Face Arm Speech Test (FAST) (8-11). Several systematic reviews have evaluated the value of these tools in stroke diagnosis, but there are substantial differences in their conclusions. Some believe that the value of these predictive instruments is equivalent in the diagnosis of stroke, but others do not have such an opinion (8, 10). Therefore, Baratloo A et al. Front Emer Med. 2022 decided to assess the value of predictive instruments in stroke detection by conducting an umbrella review to find the optimum diagnostic tools for early stroke detection.

2. Methods

2.1. Study design

The protocol of the present study has been registered and approved by Tehran University of Medical Sciences. The university ethics committee oversaw the study process. In the present study, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations (12) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (13) were used. All steps of searching, screening and summarizing the articles were performed by at least two independent researchers and any disagreements were resolved by discussion with a third researcher.

2.2. Search strategy

The purpose of this umbrella review is to compare the value of scoring systems in identifying stroke. For this purpose, an extensive search was initially conducted in the electronic resources of Medline, Embase, Scopus, and Web of Science by the end of August 2021. Then, with the appropriate combination of keywords related to stroke and predictive instruments, systematic reviews and meta-analyses were searched. The full search strategies for these databases have been reported in Appendix 1. PICO definition of the present study is as follows: diagnostic value of clinical decision rules (I) in stroke diagnosis (P). Comparisons (C) were done with a gold standard modality (CT scan and/or MRI) and the outcome (O) was considered the diagnostic value of these tools in detection of stroke. In addition to the systematic search, a manual search was also performed on Google search engine, and Google scholar.

Articles were screened based on title and abstract and systematic reviews and meta-analyses were studied in full text subsequently. Inclusion criteria were systematic reviews and meta-analysis that were conducted to assess the diagnostic value of scoring systems in identifying strokes. Exclusion criteria included studies with a pediatric population, narrative reviews, non-stroke studies, radiology-based decision tools and non-diagnostic reviews.

2.3. Data extraction

Data collection and summarization were performed by at least two independent researchers. Following the acquisition of the full text of systematic review and meta-analysis articles, information related to the name of the first author, year of publication, number of articles included in the systematic review/meta-analysis, samples' size and setting of study (in-hospital or pre-hospital) were recorded. Since in some cases, systematic reviews and meta-analyses included identical articles and some eligible reviews did not report pooled results, it was decided to obtain the full text of included original articles and extract the required data from them. FBaratloo A et al. Front Emer Med. 2022 independent researchers attained the papers and extracted the required data. If a study stratified the analysis by different subgroups, Baratloo A et al. Front Emer Med. 2022 also recorded the findings sepa-

rately. In some studies, the diagnostic value of several predictive instruments was examined and therefore, the data were recorded separately for each tool. The quality of the methodology of systematic reviews and meta-analyses was assessed using AMSTAR (A Measurement Tool to Assess systematic Reviews) version 2 (14).

2.4. Data synthesis, certainty of evidence and statistical analyses

In the present umbrella review, True Positive (TP), True Negative (TN), False Positive (FP) and False Negative (FN) values were extracted from the articles. If the values of TP, TN, FP and FN were not reported, these values were calculated based on sensitivity, specificity and sample size. Since most of the review articles reported only sensitivity and specificity, all the original studies included in these review articles were investigated and data were extracted as required. Data were entered only once if a study was reported in two or more systematic reviews.

For each tool a sensitivity, specificity, Diagnostic Odds Ratio (DOR), Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio (NLR) were calculated. The "metandi" package in STATA 17.0 statistical software was used to calculate Since this

package is only able to perform analy-values. ses in cases where there are at least 4 articles, in cases that the number of imported original articles was less than 4, the "meta" package was used to report pooled effect size. For this purpose, the values of sensitivity, specificity, DOR, PLR and NLR and its 95% confidence interval (95% CI) were calculated and then the analyses were pooled with the meta command. Heterogeneity between studies was assessed using the I²statistics and I²above 50% was considered as heterogeneity. Deek's asymmetry plot was used to examine the publication bias and small-study effect. Excess significance bias was also investigated using the method proposed by Ioannidis and Trikalinos (15) and p <0.05 indicated excess significant bias.

Level of evidence was assessed based on the method proposed in the previous article (16). Since DOR is a representative value for sensitivity and specificity, it was used for as-

essment of certainty of evidence. The level of evidence was divided into fBaratloo A et al. Front Emer Med. 2022 groups: convincing (class I), highly suggestive (class II), suggestive (class III), weak (class IV) and non-significant. Convincing level of evidence was in cases where the sample size was more than 1000 patients, p value obtained for pooled DOR in random effect model was less than 10-6, no evidence of heterogeneity was present ($I^2 < 50\%$), prediction interval did not cross the null and no evidence of small-study effect and excess significance was present. Highly suggestive level was in cases where the sample size was more than 1000 patients, random effect p value for effect size was lower than 10-6, the largest included study had a significant effect whilst class I criteria were not met. The level of evidence was suggestive when the sample size was more than 1000 patients, p value of random effect model was lower than 10-3, the largest included study had a significant effect whilst class I-II criteria were not met. The level of evidence was poor when the p value was < 0.05 and no Class I-III criteria were met. Finally, non-significant was reported when the p value of effect size was higher than 0.05. This approach has been done based on the previous umbrella review (16).

3. Results

3.1. Search results

The search eventually resulted in 4,936 records. After removing duplicates, the abstract and title of 3496 articles were evaluated. Finally, 22 full-text articles were studied and 11 systematic reviews/meta-analyses were included in the present study (8-10, 17-24) (Figure 1).

3.2. Summary of data

Table 1 shows a summary of the included articles. 8 systematic reviews and 3 meta-analyses were included. The risk of bias assessment according to AMSTAR-2 showed that the quality of evidence from all 11 studies was critically low (Table 2). In these 11 articles, the diagnostic value of a total of 33 predictive instruments was examined. The number of articles included in the review articles ranged from 6 to 25. The list of scoring systems is reported in tables 3 and 4. CPSS (in 5. 32 original articles), NIHSS (in 32 original articles), ROSIER (in 18 original articles) and 3-item stroke scale (3I-SS; in 15 original articles) were the most studied tools, respectively. Based on the number of articles included in each clinical as-

sessment tool, the analyses were performed in two parts. A) predictive instruments that at least 4 articles have examined their diagnostic value in identifying stroke (Table 3) and B) predictive instruments that less than 4 studies have examined their diagnostic value (Table 4).

The number of people included in the diagnostic value of scoring systems varied between 182 and 47072 patients. The largest sample sizes were related to NIHSS, CPSS, Rapid Arterial Occlusion Evaluation (RACE), 3I-SS, FAST, Postural Assessment Scale for Stroke (PASS), and Los Angeles Pre-Hospital Stroke Screen (LAPSS) systems. The sample size in

the evaluation of 9 tools was less than 1000 patients. Except for the Vision, Aphasia, Neglect (VAN) scale and Med PACS, significant DOR for stroke was observed in studied predictive instruments. Out of 33 analyses, the p-value for 28 tools (82.86%) was less than 10-6. Significant heterogeneity was observed in 51.51% of the analyses. Prediction interval in 24.24% of the analyses included null. In three scoring systems (9.09%) evidence of small study effect and 5 analyses (15.15%) evidence of excess significant bias was observed (Tables 5 and 6). In general, the level of evidence was class I in 1 tool, class II in 18 tools, class III in 2 tools, class IV in 11 tools and non-significant in 1 tool. All tools reported in at least 4 studies were class I-III (Tables 5 and 6).

3.3. Diagnostic performance of clinical instruments that have been reported in at least 4 studies

The level of evidence of predictive instruments reported in at least 4 studies was between classes I-III. There was no class IV in this group. Therefore, the evidence obtained is between convincing to suggestive. Level of evidence of Balance, Eyes, Face, Arm, Speech, Time (BE-FAST) tools was also in class I and the sensitivity and specificity of this clinical tool were

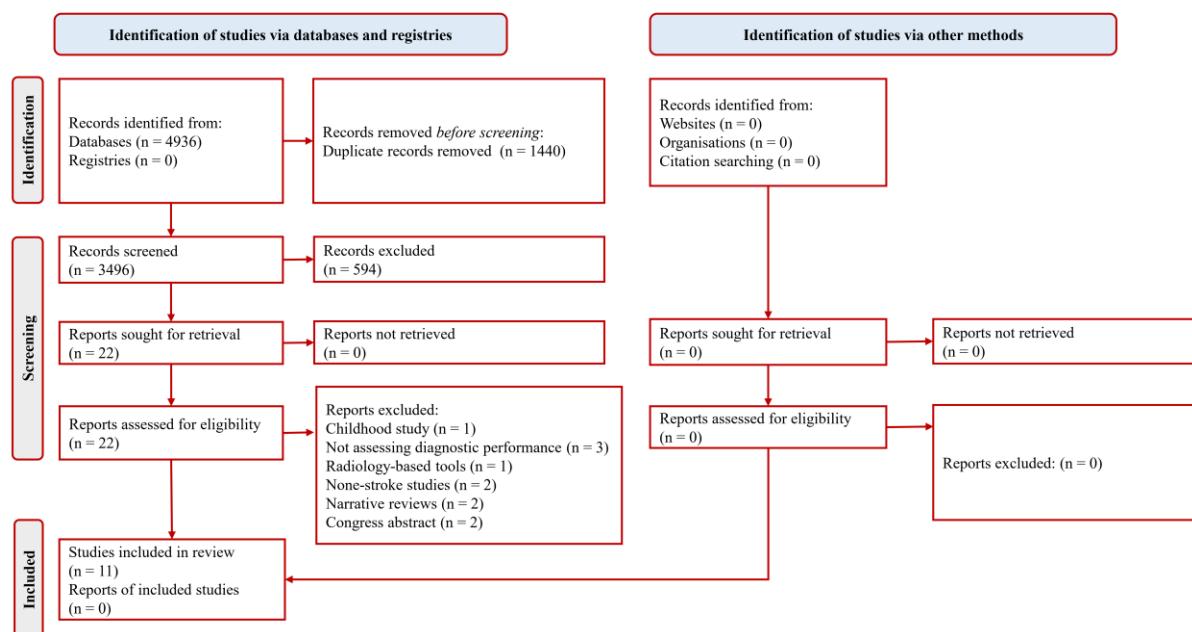
0.62 (95% CI: 0.38, 0.86) and 0.79 (95% CI: 0.62, 0.96), respectively. As can be seen, the diagnostic performance of BE-FAST is not very high.

Among class II evidence, the highest sensitivity and specificity were for ROSIER (sensitivity = 0.88, specificity = 0.67), NIHSS (sensitivity = 0.83, specificity = 0.69), PASS (sensitivity = 0.80, specificity = 0.72), FAST (sensitivity = 0.80, specificity = 0.62), LAMS (sensitivity = 0.76, specificity = 0.87), shortened NIHSS-8 (sNIHSS8) (sensitivity = 0.75, specificity = 0.77), Rapid Arterial Occlusion Evaluation (RACE) (sensitivity = 0.73, specificity = 0.80), CPSS (sensitivity = 0.75, specificity = 0.75) and Bernese score (sensitivity = 0.71, specificity = 0.82). The sensitivity of other tools was less than 0.70. In class III evidence, there were three tools of Cincinnati Stroke Triage Assessment Tool (C-STAT) and LAPSS, which LAPSS had the best performance (sensitivity = 0.79, specificity = 0.91) (Table

3.4. Diagnostic performance of predictive instruments that have been reported in less than 4

FBaratloo A et al. Front Emer Med. 2022 predictive instruments of Aphasia/ Neglect/ Gaze Deviation (ANGD), shortened NIHSS-5 (sNIHSS-5), Ambulance Clinical Triage for Acute Stroke Treatment (ACT-FAST), modified NIHSS (mNIHSS) and shortened NIHSS-1 (sNIHSS-1) were in class II level of evidence.

The optimum performance in stroke diagnosis was for ACT-FAST (sensitivity = 0.91, specificity = 0.89), ANGD (sensitivity = 0.94, specificity = 0.58) and sNIHSS-5 (sensitivity = 0.73, specificity = 0.79) (Table 6).

**Figure 1** Flow diagram of current umbrella review.**Table 1** Summary of included studies

First author	Year	Type of review	Number of included studies	Number of included instruments	Setting of studies	Type of stroke	Reference
Antipova	2019	Systematic	25	33	Hospital & pre-hospital	Ischemic; TIA	(17)
Bandler	2014	Systematic	8	7	Pre-hospital	Ischemic; hemorrhagic; TIA	(8)
De Luca	2019	Meta-analysis	11	1	Hospital & pre-hospital	Ischemic; hemorrhagic; TIA	(18)
Han	2020	Meta-analysis	14	1	Pre-hospital	Ischemic; hemorrhagic; TIA	(19)
Krebs	2017	Systematic	8	6	Pre-hospital	Ischemic	(20)
Loudon	2019	Systematic	6	11	Pre-hospital	Ischemic	(21)
Meyran	2020	Meta-analysis	24	10	Pre-hospital	Ischemic; hemorrhagic; TIA	(22)
Oostema	2016	Systematic	7	3	Pre-hospital	Ischemic; TIA	(23)
Rudd	2015	Systematic	21	7	Hospital & pre-hospital	Ischemic; TIA	(24)
Smith	2018	Systematic	36	5	Hospital & pre-hospital	Ischemic; hemorrhagic; TIA	(9)
Vidale	2018	Systematic	13	19	Pre-hospital	Ischemic	(10)

TIA: Transient ischemic stroke

4. Discussion

Based on Baratloo A et al. Front Emerg Med. 2022 knowledge, this study is the first umbrella re-review performed on the value of predictive instruments in stroke diagnosis. In the present study, 33 scoring systems were examined and the evidence obtained for 21 tools were in class I-III. Apart from Med PACS, whose DOR was non-significant for stroke diagnosis, other tools appear to be able to detect a stroke. Among these tools, the optimum per-

formance was seen for ROSIER, NIHSS, PASS, FAST, LAMS, RACE and CPSS. Although the highest sensitivity and specificity in stroke diagnosis belonged to ACT-FAST, the number of studies included in the assessment of this clinical tool was two (sample size 1130), pointing to a need for further comprehensive studies.

ROSIER tool consists of 7 variables including the level of consciousness, seizure activity, asymmetric weakness (facial,

Table 2 AMSTAR risk of bias assessment of included studies

Item	Antipova, 2019	Bandler 2014	De Luca, 2019	Han, 2020	Krebs, 2017	Loudon, 2019	Meyran, 2020	Oostema, 2016	Rudd, 2015	Smith, 2018	Vidale, 2018
1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No	No
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	No	No	No	No	No	No	Yes	No	No	No	No
8	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	P/Y	Yes	Yes
10	No	No	No	No	No	No	No	No	No	No	No
11	No meta	No meta	Yes	Yes	No meta	No meta	Yes	No meta	No meta	No meta	No meta
12	No meta	No meta	No	Yes	No meta	No meta	No	No meta	No meta	No meta	No meta
13	No	No	No	No	No	No	No	No	No	No	No
14	No	No	Yes	Yes	No	No	No	No	No	No	No
15	No meta	No meta	No	Yes	No meta	No meta	No	No meta	No meta	No meta	No meta
16	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low	Critically low

P/Y: Partial yes; No meta: No meta-analysis conducted

Table 3 Diagnostic performance of scoring systems in detection of stroke in analyses with a minimum 4 included studies

Score	Number of studies	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	PLR (95% CI)	NLR (95% CI)
CPSS	32	22996	0.75 (0.68, 0.81)	0.75 (0.68, 0.82)	9.27 (6.56, 13.09)	3.05 (2.38, 3.90)	0.33 (0.26, 0.41)
NIHSS	32	47072	0.82 (0.75, 0.86)	0.69 (0.63, 0.75)	10.0 (7.66, 13.10)	2.66 (2.26, 3.13)	0.26 (0.21, 0.34)
ROSIER	18	7223	0.88 (0.84, 0.91)	0.67 (0.55, 0.77)	15.24 (9.07, 25.60)	2.69 (1.93, 3.75)	0.18 (0.13, 0.24)
3I-SS	15	16421	0.59 (0.43, 0.73)	0.87 (0.77, 0.93)	9.71 (6.89, 13.68)	4.57 (3.06, 6.84)	0.47 (0.35, 0.64)
FAST	12	14965	0.80 (0.66, 0.90)	0.62 (0.39, 0.81)	6.77 (5.16, 8.91)	2.12 (1.36, 3.32)	0.31 (0.24, 0.41)
RACE	12	16535	0.73 (0.65, 0.81)	0.80 (0.72, 0.85)	10.73 (7.24, 15.91)	3.58 (2.68, 4.78)	0.33 (0.26, 0.44)
PASS	9	14075	0.80 (0.68, 0.88)	0.72 (0.53, 0.85)	10.27 (6.78, 15.55)	2.83 (1.77, 4.52)	0.28 (0.20, 0.39)
C-STAT	7	10660	0.71 (0.59, 0.81)	0.77 (0.60, 0.87)	8.64 (3.78, 19.71)	3.18 (1.74, 5.80)	0.37 (0.25, 0.54)
FAST-ED	7	5716	0.61 (0.54, 0.67)	0.86 (0.82, 0.89)	9.48 (6.50, 13.82)	4.32 (3.40, 5.50)	0.46 (0.38, 0.54)
aNIHSS	7	7433	0.75 (0.62, 0.85)	0.64 (0.53, 0.73)	5.37 (3.86, 7.45)	2.07 (1.74, 2.46)	0.39 (1.74, 2.46)
LAMS	6	5587	0.76 (0.65, 0.84)	0.87 (0.81, 0.91)	21.16 (9.04, 49.51)	5.81 (3.68, 9.18)	0.27 (0.18, 0.43)
LAPSS	6	13988	0.79 (0.76, 0.83)	0.91 (0.74, 0.97)	40.03 (9.28, 172.66)	8.92 (2.70, 29.47)	0.22 (0.17, 0.29)
Bernese score	5	5425	0.71 (0.68, 0.74)	0.82 (0.80, 0.84)	11.38 (9.58, 13.5)	3.99 (3.57, 4.48)	0.35 (0.32, 0.39)
sNIHSS-8	5	4237	0.75 (0.73, 0.77)	0.83 (0.81, 0.84)	12.0 (10.05, 14.02)	3.53 (3.22, 3.84)	0.32 (0.29, 0.35)
BE-FAST	4	1436	0.62 (0.38, 0.86)	0.79 (0.62, 0.96)	8.38 (5.78, 10.97)	3.19 (1.71, 4.67)	0.44 (0.22, 0.67)
MPDS	4	12925	0.58 (0.40, 0.75)	0.95 (0.79, 0.99)	28.10 (11.0, 71.32)	12.0 (3.40, 43.20)	0.44 (0.31, 0.62)

3I-SS: 3-item stroke scale; aNIHSS: Abbreviated National Institutes of Health Stroke Scale, or NIH Stroke Scale; BE-FAST: BE-FAST: Balance, Eyes, Face, Arm, Speech, Time; C-STAT: Cincinnati Stroke Triage Assessment Tool; CPSS: Cincinnati Pre-Hospital Stroke Scale; FAST: Face Arm Speech Test; FAST-ED: Field Assessment Stroke Triage for Emergency Destination; LAMS: Los Angeles Motor Scale; LAPSS: Los Angeles Pre-Hospital Stroke Screen; MPDS: Medical Priority Dispatch Software; NIHSS: National Institutes of Health Stroke Scale; PASS: Postural Assessment Scale for Stroke; RACE: Rapid Arterial Occlusion Evaluation; ROSIER: Recognition of Stroke in the Emergency Room; sNIHSS: Shortening National Institutes of Health Stroke Scale.

arm, leg), speech disturbance and visual field defect, which are much easier to calculate than NIHSS. The NIHSS is an 11-domain tool that is time-consuming to evaluate. The current umbrella review demonstrates that ROSIER performance is better than all NIHSS versions (full and abbreviated version) and may be used as an effective tool in emergency settings to diagnose stroke. That caution should be exercised on the use of the Ioannidis

In the present study, there was no evidence of excess significance bias present. Since in all included tools, the largest studies demonstrated significant findings, therefore, it was expected that there would be no excess significance bias in

the studies. Since in Ioannidis and Trikalinos method (15), the power is calculated based on the effect size of the largest study and regarding the fact that the sample size was very high in these studies, the expected number of significant studies was very similar to the observed number of significant studies. Nevertheless, the Cochrane guideline states

and Trikalinos method, considering that its accuracy has not yet been properly evaluated.

There was significant heterogeneity among the included studies in the assessment of the value of predictive instru-

Table 4 Diagnostic performance of scoring systems in detection of stroke in analyses less than 4 included studies

Score	Number of studies	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	PLR (95% CI)	NLR (95% CI)
ANGD	3	1841	0.94 (0.91, 0.97)	0.58 (0.39, 0.76)	21.93 (11.29, 32.57)	2.39 (1.53, 3.24)	0.11 (0.06, 0.15)
MASS	3	981	0.85 (0.83, 0.87)	0.82 (0.78, 0.86)	27.19 (20.62, 35.87)	4.85 (3.86, 6.10)	0.17 (0.15, 0.20)
sNIHSS-5	3	2830	0.73 (0.71, 0.76)	0.79 (0.77, 0.82)	10.15 (8.30,	3.50 (3.13, 3.87)	0.34 (0.30, 0.37)
ACT-FAST	2	1130	0.91 (0.81, 1.0)	0.89 (0.83, 0.96)	80.87 (8.0,	9.24 (4.14, 14.35)	0.10 (0.01, 0.20)
VAN	2	838	0.96 (0.91, 1.00)	0.73 (0.39, 1.00)	22.69 (1.0, 46.40)	4.22 (1.68, 10.14)	0.08 (0.00, 0.17)
mNIHSS	2	2089	0.78 (0.75, 0.80)	0.77 (0.74, 0.79)	11.23 (8.80,	3.31 (2.93, 3.68)	0.29 (0.26, 0.33)
sNIHSS-1	2	2089	0.64 (0.61, 0.67)	0.81 (0.78, 0.83)	7.34 (5.80, 8.88)	3.31 (2.88, 3.75)	0.44 (0.40, 0.48)
M-	1	327	0.74 (0.65, 0.83)	0.92 (0.88, 0.96)	33.0 (9.7, 56.34)	9.33 (4.90, 13.76)	0.28 (0.18, 0.38)
DIRECT							
EMSA	1	1663	0.74 (0.67, 0.81)	0.50 (0.48, 0.52)	2.92 (1.86, 3.98)	1.49 (1.34, 1.64)	0.51 (0.37, 0.64)
FAST	1	435	0.93 (0.88, 0.98)	0.47 (0.41, 0.53)	11.31 (2.54, 20.08)	1.75 (1.55, 1.95)	0.15 (0.04, 0.26)
PLUS							
FPSS	1	856	0.54 (0.40, 0.64)	0.91 (0.89, 0.93)	12.25 (6.46, 18.04)	6.15 (4.35, 7.95)	0.50 (0.40, 0.60)
LEGS	1	182	0.86 (0.77, 0.95)	0.96 (0.92, 1.00)	127.44 (41.6, 390.36)	19.32 (9.60, 30.13)	0.15 (0.06, 0.24)
MPSS	1	1004	0.84 (0.80, 0.88)	0.65 (0.61, 0.69)	9.83 (6.47, 13.19)	2.40 (2.12, 2.68)	0.24 (0.18, 0.30)
Med PACS	1	416	0.74 (0.68, 0.80)	0.33 (0.26, 0.40)	1.42 (0.79, 2.05)	1.11 (1.00, 1.24)	0.78 (0.54, 1.0)
OPSS	1	554	0.87 (0.82, 0.92)	0.59 (0.54, 0.64)	9.61 (5.12, 14.01)	2.13 (1.84, 2.42)	0.22 (0.14, 0.30)
rNIHSS	1	1004	0.73 (0.68, 0.78)	0.39 (0.35, 0.43)	1.72 (1.22, 2.22)	1.2 (1.09, 1.31)	0.69 (0.55, 0.83)
sNIHSS-	1	741	0.70 (0.65, 0.75)	0.81 (0.77, 0.85)	9.90 (6.57, 13.34)	3.37 (2.89, 4.55)	0.37 (0.30, 0.44)
EMS							

CI: Confidence Interval; DOR: Diagnostic Odds Ratio; PLR: Positive Likelihood Ratio; NLR: Negative Likelihood Ratio. FAST PLUS: ACT-FAST: Ambulance Clinical Triage for Acute Stroke Treatment; ANGD: Aphasia; Neglect/gaze deviation; The first part is the FAST test and the second part evaluates only the presence of severe arm or leg motor deficit; FPSS: Finnish Prehospital Stroke Scale; LEGS: Lower extremity strength, Eyes/visual fields, Gaze deviation, Speech difficulty; M-DIRECT: Madrid-Direct Referral to Endovascular Center; MASS: Melbourne Ambulance Stroke Screen; Med PACS: Medic Prehospital Assessment for Code Stroke; mNIHSS: Modified National Institutes of Health Stroke Scale; MPSS: Maria Prehospital Stroke Scale; OPSS: Ontario Prehospital Stroke Screening Tool; rNIHSS: Revised National Institutes of Health Stroke Scale; sNIHSS: Shortening National Institutes of Health Stroke Scale; sNIHSS-EMS: Shortening National Institutes of Health Stroke Scale for Emergency Medical Services; VAN: Vision, Aphasia, Neglect

Table 5 Level of evidence among included scoring systems in detection of stroke in analyses with a minimum 4 included studies

Score	Number of studies	Sample size	DOR (95% CI)	P value for random effect	Prediction interval	I ₂	LS	Small study effect	Excess significance bias	Level of evidence
CPSS	32	22996	9.27 (6.56, 13.09)	<1.0 × 10 ⁻⁵⁰	1.26, 67.61	95.45	Yes	0.133	No	II
NIHSS	32	47072	10.0 (7.66, 13.10)	<1.0 × 10 ⁻⁵⁰	2.49, 35.24	95.85	Yes	0.337	No	II
ROSIER	18	7223	15.24 (9.07, 25.60)	<1.0 × 10 ⁻⁵⁰	1.52, 162.25	93.15	Yes	0.110	No	II
3I-SS	15	16421	9.71 (6.89, 13.68)	<1.0 × 10 ⁻⁵⁰	2.70, 32.73	88.49	Yes	0.713	No	II
FAST	12	14965	6.77 (5.16, 8.91)	<1.0 × 10 ⁻⁵⁰	2.85, 17.69	77.17	Yes	0.126	No	II
RACE	12	16535	10.73 (7.24, 15.91)	<1.0 × 10 ⁻⁵⁰	2.27, 49.43	95.45	Yes	0.993	No	II
PASS	9	14075	10.27 (6.78, 15.55)	<1.0 × 10 ⁻⁵⁰	2.47, 41.30	91.19	Yes	0.342	No	II
C-STAT	7	10660	8.64 (3.78, 19.71)	2.1 × 10 ⁻⁶	0.35, 208.40	97.82	Yes	0.600	No	III
FAST-ED	7	5716	9.48 (6.50, 13.82)	<1.0 × 10 ⁻⁵⁰	2.29, 39.81	86.08	Yes	0.872	No	II
aNIHSS	7	7433	5.37 (3.86, 7.45)	<1.0 × 10 ⁻⁵⁰	1.57, 17.97	90.03	Yes	0.190	No	II
LAMS	6	5587	21.16 (9.04, 49.51)	3.0 × 10 ⁻¹¹	0.95, 513.86	94.74	Yes	0.151	No	II
LAPSS	6	13988	40.03 (9.28, 172.66)	1.6 × 10 ⁻⁵	0.09, 2000	98.04	Yes	0.785	No	III
Bernese score	5	5425	11.38 (9.58, 13.5)	<1.0 × 10 ⁻⁵⁰	6.37, 20.38	50.25	Yes	<0.001	No	II
sNIHSS-8	5	4237	12.0 (10.05, 14.02)	<1.0 × 10 ⁻⁵⁰	9.34, 15.77	0.00	Yes	0.418	No	II
BE-FAST	4	1436	8.38 (5.78, 10.97)	<1.0 × 10 ⁻⁵⁰	4.16, 20.76	10.82	Yes	0.458	No	I
MPDS	4	12925	28.10 (11.0, 71.32)	8.5 × 10 ⁻⁸	0.08, 7400.9	97.37	Yes	0.044	No	II

CI: Confidence Interval; DOR: Diagnostic Odds Ratio; LS: Largest study with significant effect.

3I-SS: 3-item stroke scale; aNIHSS: Abbreviated National Institutes of Health Stroke Scale, or NIH Stroke Scale; BE-FAST: Balance, Eyes, Face, Arm, Speech, Time; C-STAT: Cincinnati Stroke Triage Assessment Tool; CPSS: Cincinnati Pre-Hospital Stroke Scale; FAST: Face Arm Speech Test; FAST-ED: Field Assessment Stroke Triage for Emergency Destination; LAMS: Los Angeles Motor Scale; LAPSS: Los Angeles Pre-Hospital Stroke Screen; MPDS: Medical Priority Dispatch Software; NIHSS: National Institutes of Health Stroke Scale; PASS: Postural Assessment Scale for Stroke; RACE: Rapid Arterial Occlusion Evaluation; ROSIER: Recognition of Stroke in the Emergency Room; sNIHSS: Shortening National Institutes of Health Stroke Scale.

Table 6 Level of evidence among included scoring systems in detection of stroke in analyses less than 4 included studies

Score	Number of studies	Sample size	DOR (95% CI)	P value for random effect	Prediction interval	I ₂	LS	Small study effect	Excess significance bias	Level of evidence
ANGD	3	1841	21.93 (11.29, 32.57)	<1.0 × 10-50	1.42, 388.29	0.00	Yes	0.737	No	II
MASS	3	981	27.19 (20.62, 35.87)	2.3 × 10-14	0.006, 7100,0	48.3	Yes	0.431	No	IV
sNIHSS-5	3	2830	10.15 (8.30, 11.99)	<1.0 × 10-50	3.20, 32.36	0.00	Yes	0.030	No	II
ACT-FAST	2	1130	80.87 (8.0, 153.74)	<1.0 × 10-50	NA	0.00	Yes	NA	No	II
VAN	2	838	22.69 (1.0, 46.40)	3.3 × 10-4	NA	53.5	Yes	NA	No	IV
mNIHSS	2	2089	11.23 (8.80, 13.65)	<1.0 × 10-50	NA	0.00	Yes	NA	No	II
sNIHSS-1	2	2089	7.34 (5.80, 8.88)	<1.0 × 10-50	NA	0.00	Yes	NA	No	II
M-DIRECT	1	327	33.0 (9.7, 56.34)	<1.0 × 10-50	NA	NA	NA	NA	NA	IV
EMSA	1	1663	2.92 (1.86, 3.98)	4.4 × 10-9	NA	NA	NA	NA	NA	IV
FAST PLUS	1	435	11.31 (2.54, 20.08)	2.8 × 10-11	NA	NA	NA	NA	NA	IV
FPSS	1	856	12.25 (6.46, 18.04)	<1.0 × 10-50	NA	NA	NA	NA	NA	IV
LEGS	1	182	127.44 (41.60, 390.36)	<1.0 × 10-50	NA	NA	NA	NA	NA	IV
MPSS	1	1004	9.83 (6.47, 13.19)	<1.0 × 10-50	NA	NA	NA	NA	NA	IV
Med PACS	1	416	1.42 (0.79, 2.05)	0.11	NA	NA	NA	NA	NA	NS
OPSS	1	554	9.61 (5.12, 14.01)	<1.0 × 10-50	NA	NA	NA	NA	NA	IV
rNIHSS	1	1004	1.72 (1.22, 2.22)	2.2 × 10-4	NA	NA	NA	NA	NA	IV
sNIHSS-EMS	1	741	9.90 (6.57, 13.34)	<1.0 × 10-50	NA	NA	NA	NA	NA	IV
EMS										

CI: Confidence Interval; DOR: Diagnostic Odds Ratio; LS: Largest study with significant effect.

ACT-FAST: Ambulance Clinical Triage for Acute Stroke Treatment; ANGD: Aphasia; Neglect/gaze deviation; FAST PLUS: The first part is the FAST test and the second part evaluates only the presence of severe arm or leg motor deficit; FPSS: Finnish Prehospital Stroke Scale; LEGS: Lower extremity strength, Eyes/visual fields, Gaze deviation, Speech difficulty; M-DIRECT: Madrid-Direct Referral to Endovascular Center; MASS: Melbourne Ambulance Stroke Screen; Med PACS: Medic Prehospital Assessment for Code Stroke; mNIHSS: Modified National Institutes of Health Stroke Scale; MPSS: Maria Prehospital Stroke Scale; OPSS: Ontario Prehospital Stroke Screening Tool; rNIHSS: Revised National Institutes of Health Stroke Scale; sNIHSS: Shortening National Institutes of Health Stroke Scale; sNIHSS-EMS: Shortening National Institutes of Health Stroke Scale for Emergency Medical Services; VAN: Vision, Aphasia, Neglec

ments in stroke diagnosis. It is worth mentioning that the diagnostic value studies are often heterogeneous due to significant differences in the methodology, different gold standards and variation in the expertise of operators conducting the index test. Therefore, as a resort, it is suggested that random effect models be used in all meta-analyses of diagnostic value studies, even if heterogeneity is not observed.

Finally, it should be noted that the study of heterogeneity in studies of diagnostic values is difficult and is associated with

numerous pitfalls (25). Inspecting Table 6, it becomes clear that the reason behind most studies being in class II of ev-

idence is due to high heterogeneity among them. Accordingly, if Baratloo A et al. Front Emer Med. 2022 ignore the existence of heterogeneity in the evaluation of certainty of the evidence, the evidence obtained in most predictive instruments is classified as convincing (class I). Therefore, it may be necessary to omit heterogeneity as a criterion in the certainty of evidence assessment of diagnostic accuracy studies, or at least not consider it for class I of evidence, regarding that the power of analysis for assessment of heterogeneity among diagnostic accuracy studies is low (25). In the present umbrella review, it was found that 17 predictive instruments were only evaluated in less than 4 studies. In other words, the available systematic reviews and meta-analyses evaluating these tools included a maximum of 3

5. Limitations

The risk of bias assessment of included systematic reviews/meta-analyses was critically low. Although this is a possible limitation of the current umbrella review, since Baratloo A et al. Front Emer Med. 2022 pooled data of original studies, therefore, the low quality of systematic reviews/meta-analyses did not consider as a significant limitation. In addition, Baratloo A et al. Front Emer Med. 2022 assessed the level of evidence for each tool, separately.

6. Conclusion

Convincing to suggestive evidence shows that ROSIER, NIHSS, PASS, FAST, LAMS, RACE and CPSS have the optimum performance in identifying stroke, based on the Baratloo A et al. Front Emer Med. 2022. Since ROSIER's calculation is simple and has the highest sensitivity and specificity, it is recommended as an effective tool in identifying strokes in pre-hospital and in-hospital settings, based on the Baratloo A et al. Front Emer Med. 2022. Moreover, it was found that the diagnostic value of 17 scoring systems was examined in less than 4 studies, pointing to the need for more comprehensive systematic reviews on these scoring systems, based on the Baratloo A et al. Front Emer Med. 2022.

7, based on the Baratloo A et al. Front Emer Med. 2022. Declarations

7.1. Acknowledgment

7.2. Authors' contribution

Study design and conception: AB and MY; Data gathering:

studies. Although new studies have been performed on these None. predictive instruments in recent years, (26-30) the need for more comprehensive systematic reviews and probable meta-analyses is felt for the clinical decision rules presented in Ta-

Overview of systematic reviews comparing endovascular to best medical treatment for large-vessel occlusion acute ischaemic stroke: an umbrella review

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Safouris A et al. Therap Advanc Neurol Disord. 2024:17562864241246938.

Abstract

Background: The literature on endovascular treatment (EVT) for large-vessel occlusion (LVO) acute ischaemic stroke (AIS) has been rapidly increasing after the publication of positive randomized-controlled clinical trials (RCTs) and a plethora of systematic reviews (SRs) showing benefit compared to best medical therapy (BMT) for LVO.

Objectives: An overview of SRs (umbrella review) and meta-analysis of primary RCTs were performed to summarize the literature and present efficacy and safety of EVT.

Design and methods: MEDLINE via Pubmed, Embase and Epistemonikos databases were searched from January 2015 until 15 October 2023. All SRs of RCTs comparing EVT to BMT were included. Quality was assessed using Risk of Bias in Systematic Reviews scores and the RoB 2 Cochrane Collaboration tool, as appropriate. GRADE approach was used to evaluate the strength of evidence. Data were presented according to the Preferred Reporting Items for Overviews of Reviews statement. The primary outcome was 3-month good functional outcome [modified Rankin scale (mRS) score 0–2].

Results: Three eligible SRs and 4 additional RCTs were included in the overview, comprising a total of 24 RCTs, corresponding to 5968 AIS patients with LVO (3044 randomized to EVT *versus* 2924 patients randomized to BMT). High-quality evidence shows that EVT is associated with an increased likelihood of good functional outcome [risk ratio (RR) 1.78 (95% confidence interval (CI): 1.54–2.06); 166 more per 1000 patients], independent ambulation [mRS-scores 0–3; RR 1.50 (95% CI: 1.37–1.64); 174 more per 1000 patients], excellent functional outcome [mRS-scores 0–1; RR 1.90 (95% CI: 1.62–2.22); 118 more per 1000 patients] at 3 months. EVT was associated with reduced 3-month mortality [RR 0.81 (95% CI: 0.74–0.88); 61 less per 1000 patients] despite an increase in symptomatic intracranial haemorrhage [sICH; RR 1.65 (95% CI: 1.23–2.21); 22 more per 1000 patients].

Conclusion: In patients with AIS due to LVO in the anterior or posterior circulation, within 24 h from symptom onset, EVT improves functional outcomes and increases the chance of survival despite increased sICH risk.

Registration: PROSPERO Registration Number CRD42023461138.

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Introduction

The first positive randomized-controlled clinical trials (RCTs) of endovascular treatment (EVT) in acute ischaemic stroke (AIS) patients treated in the early time window with a large-vessel occlusion (LVO) of the anterior circulation were published in 2015 and provided high-quality evidence for EVT safety and efficacy in AIS due to anterior circulation LVO.¹ Current American Heart Association/American Stroke Association and European Stroke Organization guidelines strongly recommend EVT for AIS patients presenting with anterior circulation LVO and National Institutes of Health Stroke Scale (NIHSS) score ≥ 6 , Alberta Stroke Program Early CT Score (ASPECTS) ≤ 6 , up to 6 h from symptom onset based on high-quality data (Class IA) derived from multiple RCTs.^{2,3} After publication of these guidelines, multiple RCTs and numerous systematic reviews (SRs) have demonstrated EVT efficacy and safety in LVO subgroups. In particular, published SRs on EVT refer to either anterior or posterior circulation, to early or late-time windows, to large or moderate infarct size and to standard or advanced neuroimaging.⁴⁻⁷

However, even a flawless single SR and meta-analysis may offer a shortsighted view of the evidence.⁸ Overviews of SRs ('umbrella reviews') aim to provide intuitive summaries of the breadth of research to decision makers without demanding from them to assimilate the results of multiple SRs themselves.⁹ Overviews, by synthesizing the results of multiple SRs, are broader in scope and may examine the same intervention for different subgroups of patients.¹⁰

These LVO subgroups have different characteristics, but all gain significant benefits from EVT; if risks and benefits remain similar throughout, the idea of continuing using these subgroups may be redundant for any practical or clinical purpose. Overall benefit is also an important piece of information for health policymakers, as both high- and low-income countries strive to develop EVT networks.¹¹ Cost-benefit analyses have also been published referring mostly to the anterior circulation and specifically to early or late-time windows.¹² It is time to combine all high-quality information available through a rigorous scientific

approach rather than extrapolating the results from a subgroup to all patients with AIS and LVO. Safouris Aet al. Therap Advanc Neurol Disord. 2024;17562864241246938 have thus performed an overview of SRs and meta-analysis to evaluate the safety and

efficacy of EVT in LVO patients. This overview is restricted to primary RCTs published after 2015.

Methods

Standard protocol approvals and registrations

The pre-specified protocol of the present overview of SRs and meta-analysis has been registered in the International Prospective Register of Ongoing Systematic Reviews PROSPERO (Registration Number: CRD42023461138). No amendments were made to the registered protocol. Results are reported according to the Preferred Reporting Items for Overviews of Reviews statement.¹³

Data sources, searches and study selection

Following the PICOS format, a systematic literature search was conducted to identify available studies evaluating adult patients with AIS due to LVO (intracranial internal carotid, proximal middle cerebral artery, basilar artery occlusion; P: population) that were treated with EVT (mechanical thrombectomy and/or thromboaspiration) together with best medical treatment [BMT, conservative treatment with or without intravenous thrombolysis (IVT)] (I: intervention) versus BMT alone (C: comparator). Reporting of functional outcome at 3 months, as assessed by modified Rankin scale (mRS; 0: outcome) scores, was required for studies to be considered for inclusion. The primary outcome of interest was good functional outcome at 3 months, as defined by mRS-scores 0–2, among patients treated with EVT and BMT versus BMT alone.^{14,15} Secondary outcomes of interest comprised the following: (i) independent ambulation at 3 months as defined by a mRS-scores 0–3; (ii) excellent functional outcome at 3 months as defined by a mRS-scores 0–1; (iii) symptomatic intracranial haemorrhage (sICH); (iv) all-cause mortality at 3 months and (v) reduced disability as assessed by 1-point reduction across all mRS-scores at 3 months (shift analysis).^{14,15} Included studies (S: Study design) were SRs of RCTs and primary RCTs. Included SRs provided pre-specified criteria for including and excluding studies and results were reported according to specific guidance for SRs and meta-analyses.

The literature search was performed independently by fSafouris Aet al. Therap Advanc Neurol Disord. 2024;17562864241246938 reviewers (AS, LP, AHK, KP). Safouris Aet al. Therap Advanc Neurol Disord. 2024;17562864241246938

searched MEDLINE, Embase and Epistemonikos databases, using search strings that included the following terms: 'stroke', 'endovascular treatment', 'randomized-controlled trial', 'LVO', 'intracranial occlusion', 'trial', 'meta-analysis', 'review', and 'systematic review'. The complete search algorithms used in MEDLINE, Embase and Epistemonikos and the complete inclusion and exclusion criteria are provided in Supplemental Table S1.¹⁶⁻²⁰ Safouris Aet al. Therap Advanc Neurol Disord. 2024;17562864241246938 have limited Safouris Aet al. Therap Advanc Neurol Disord. 2024;17562864241246938 search in SRs comprising only studies published in 2015 onwards. No language or other restrictions were applied. Safouris Aet al. Therap Advanc Neurol Disord. 2024;17562864241246938 search spanned from 1 January 2015 to 10 October 2023, for each electronic database.²¹ Safouris Aet al. Therap Advanc Neurol Disord. 2024;17562864241246938 also manually searched reference lists of published articles manually to ensure the bibliography's comprehensiveness. SRs that included non-controlled studies, case series and case reports were excluded.

Commentaries, editorials and narrative reviews were also discarded. Among the studies presenting duplicate data, the ones with the largest data-set were retained, while the others were excluded.

For overlapping reviews, the Jadad algorithm has been adapted and was used independently by two reviewers (OK, KIB); disagreements were settled by consensus after discussion with the corresponding author (GT) (Supplemental Table S2).^{22,23} Among equivalent SRs, Safouris Aet al. Therap Advanc Neurol Disord. 2024;17562864241246938 opted for studies with pooled demographic data that were

available to Safouris Aet al. Therap Advanc Neurol Disord. 2024;17562864241246938 search for primary RCTs published after the publication of each SR has been performed. Safouris Aet al. Therap Advanc Neurol Disord. 2024;17562864241246938 applied the respective search string for the same databases used in each selected SR, starting on the date the search was performed in each review and ending on 15 October 2023 (Supplemental

Table S3).

Risk of bias assessment and data extraction

Eligible SRs were assessed for bias using the Risk of Bias in Systematic Reviews (ROBIS) tool.²⁴ For supplemental RCTs, quality assessment has been performed with the Cochrane Collaboration tool (RoB 2).²⁵ The risk of bias assessment was conducted independently by two reviewers not

in structured forms, including author names, publication date, study design, country, number of included patients, patient characteristics (age, NIHSS, ASPECTS, sex, stroke onset-to-randomization time, IVT rates, posterior versus anterior circulation) and outcome events independently by two reviewers (AS, LP).

Statistical analysis. Statistical analysis was performed using the Cochrane Collaboration's Review Manager (RevMan 5.3) Software Package (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and Open Meta Analyst.²⁶ mRS shift analysis has been performed using an online tool available at: <https://www.thembc.com.au/tournament-methods>.²⁷ Hundred-person icon arrays (HPIAs) have been previously published to quantify the magnitude of

benefit of EVT and IVT versus non-reperfusion in AIS patients with LVO²⁸; Safouris Aet al. Therap Advanc Neurol Disord. 2024;17562864241246938 provide updated HPIAs (<https://www.iconarray.com>) by summation of mRS-scores from each study.

For each dichotomous outcome of interest, the corresponding risk ratio (RR) with 95% confidence interval [95% confidence interval (CI)] was calculated using the random-effects model (DerSimonian and Laird).¹⁶ Subgroup differences were assessed by the *Q* test for sub-groups.¹⁷ For the analysis of the baseline characteristics (age, sex, admission NIHSS,

IVT pretreatment, onset-to-recanalization times) of the patients in each arm, Safouris Aet al. Therap Advanc Neurol Disord. 2024;17562864241246938 calculated the pooled proportion of each dichotomous variable and the overall mean for each continuous variable. For studies reporting continuous outcomes in median values and corresponding interquartile ranges, Safouris Aet al. Therap Advanc Neurol Disord. 2024;17562864241246938 estimated the sample mean and standard deviation using the quantile estimation method.¹⁶ Comparison of the base-

included in the author lists of the eligible studies (OK, KIB) and disagreements were settled by consensus after discussion with the corresponding author (GT). Data extraction was performed

line characteristics between the two arms was performed using odds ratio (OR) and mean difference for dichotomous and continuous variables, respectively.

Heterogeneity was assessed with the I^2 and Cochran Q statistics. For

the qualitative interpretation of heterogeneity, I^2 values $>50\%$ and values $>75\%$ were considered to represent substantial and considerable heterogeneity, respectively. The significance level for the Q statistic was set at 0.1. Publication bias across individual studies was assessed using funnel plot inspection and the use of Egger's test.

Results

Literature search and included studies

The systematic database search yielded a total of 637, 620 and 594 records from the MEDLINE, Embase and Epistemonikos databases, respectively (Figure 1). After initial screening, Safouris Aet al. Therap Advanc Neurol Disord.

2024:17562864241246938 retrieved the full text of 114 records that were considered potentially eligible for inclusion. After reading the full-text articles, 111 were further excluded (Supplemental Table S4). Finally, Safouris Aet al. Therap Advanc Neurol Disord. 2024:17562864241246938 identified three eligible SRs for inclusion (Table 1),^{29–31} that included 20 RCTs.^{32–51} Besides using different statistical approaches (Bayesian mixed-effects model in 1 SR²⁹ and Random-effects model in 2 SRs^{30,31}), different outcomes and different summary statistics were reported (Supplemental Table S5). To overcome this source of heterogeneity and to present an overall comparison of the two treatment methods, a meta-analysis of RCTs has also been performed.

Anterior circulation LVO with moderate infarct. The SR by Rajkumar et al.²⁹ included RCTs on anterior circulation LVO published from 2015 up to July 2020. In total, 12 RCTs were included, reporting a median NIHSS between 16 and 20 (Table 2).

Patients were randomized from <4.5 up to 24 h after symptom onset (1 trial <4.5 h; 1 trial <5 h; 4 trials <6 h; 2 trials <8 h; 1 trial <12 h; 1 trial 6–16 h; 1 trial 6–24 h; 1 trial unspecified). Safouris Aet al. Therap Advanc Neurol Disord. 2024:17562864241246938 considered only two trials investigating EVT in late-time windows since the trial randomizing patients up to 12 h reported onset-to-randomization times like that of the early time window trials (Supplemental Table S6). IVT rates ranged from 5% to 100% of included patients. All RCTs included patients with internal carotid artery (ICA) and middle cerebral artery segment 1 (M1) occlusions. Seven out of 12 studies included a substantial proportion of patients with segment 2 of the middle cerebral artery (M2) occlusion, whereas other sites of occlusion (anterior cerebral artery, basilar artery) were rare (Table 2). No data on ASPECTS and onset-to-randomization times were provided within the main text and Supplemental Files, Safouris Aet al. Therap Advanc Neurol Disord. 2024:17562864241246938 therefore searched primary studies. Mean ASPECTS was found to be 7–9 and mean onset-to-randomization was 169–810 min (Supplemental Table S6).

results from 2022 to 30 May 2023. In total, fSafouris Aet al. Therap

RCTs were included, reporting a median NIHSS of 29 and an IVT pretreatment rate of 23%. Patients were randomized within 24 h of onset in three RCTs and up to 6 h of onset in one RCT, except if there were no FLAIR magnetic resonance imaging early changes, which extended the therapeutic time window up to 24 h. As a result, onset-to-randomization times were low in the latter trial (214–229 min) compared to the rest of the trials (453–587 min). Safouris Aet al. Therap Advanc Neurol Disord. 2024:17562864241246938 considered the former trial an early time window trial and the rest both early and late-time window trials (Table 2). All primary RCTs used ASPECTS limits as eligibility criteria (three trials ASPECTS 3–5 and one trial ASPECTS 2–5) and two trials also permitted inclusion based on ischaemic core volume (70–

Anterior circulation LVO with large infarct. The SR by Palaiodimou et al.,³⁰ included RCTs on anterior circulation large-core LVO that reported their

100 ml or at least 50 without upper limit). All included patients had anterior circulation strokes and most had ICA and M1 occlusions. IVT rates ranged from 17% to 29%.

Basilar artery occlusion. The SR by Palaiodimou *et al.*³¹ included RCTs on basilar artery LVO published from 2020 to 29 November 2022. In total, 10 RCTs were included, reporting a median NIHSS of 24 and an IVT pretreatment rate of 39%. One trial randomized patients <6 h from symptom onset, 1 trial <8 h, 1 trial <12 h and 1 trial 6–24 h. Safouris *et al.* Therap Advanc Neurol Disord. 2024:17562864241246938 considered the latter trial as a late-time window trial, whereas the rest as early time window trials since median onset-to-randomization time of the trial randomizing up to 12 h from symptom onset was 4.9 h (Table 2). There was no overlap of primary studies among included SRs (Table 2).

Supplemental search for RCTs that have reported their results since the publication of each SR has been performed (Supplemental Table S3). Only 1 RCT was identified.

RCTs (MR CLEAN-LATE, POSITIVE, TENSION, LASTE), not previously included in the SRs, were added to the analysis^{52–55} (Supplemental Table S7).

Safouris *et al.* Therap Advanc Neurol Disord. 2024:17562864241246938 therefore included 3 SRs and 4 additional RCTs, 24 RCTs in total, comprising a total of 5968 AIS patients with LVO (mean age: 67.9 years; 56% men; mean NIHSS-score: 18.4; 50% received IVT; mean onset-to-randomization time: 388 min; Supplemental Figures S1–S5). A total of 3044 patients were randomized to EVT and 2924 patients were randomized to BMT. There were no significant differences

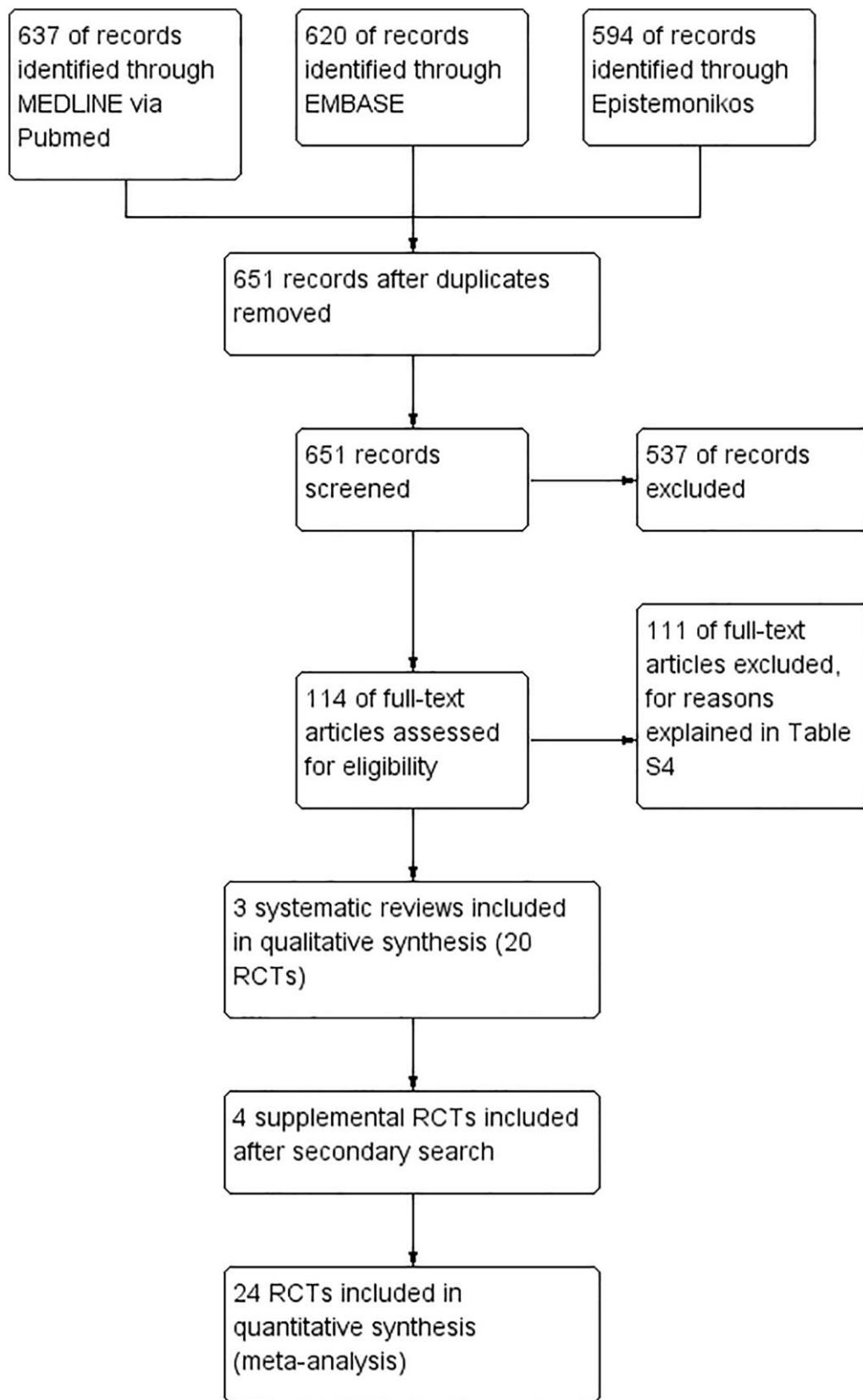


Figure 1. Flow chart presenting the selection of eligible studies.

Table 1. Main characteristics of SRs included in the overview ($n = 3$).

	Publication date	Databases	Setting	Participants	Objectives	Citation, date range of searched year	Number of studies searching included	Types of studies	Country of origin of studies	Risk of bias	Publication bias	Outcomes reported	Method of synthesis / analysis	Comments
Rajkumar <i>et al.</i> , 2022 ²⁹	EVT using stent retriever or aspiration catheter	AIS patients with anterior circulation LVO treated up to 24 h from symptom onset	Stroke centres	Pubmed	January 2010 to 2 July 2020	2015–2020	12	RCTs	Worldwide	Cochrane Rob; some concerns ^a	No evidence in funnel plot inspection and Egger statistical test	90-Day mRS, all-cause mortality and sICH	Bayesian mixed-effects model	Low IIT percentage in both late-window trials (DAWN and DEFUSE3)
Palaiodimou <i>et al.</i> , 2023 ³⁰	EVT for large-core AIS defined by ASPECTS 2–5 or volumetric methods	AIS patients with anterior circulation LVO	Stroke centres	MEDLINE and SCOPUS	To 30 May 2023	2022–2023, one trial pending publication	4	RCTs	China, Japan, USA, international	RoB 2; some concerns ^b	Impossible to assess due to the small number of RCTs	90-Day mRS 0–2, all-cause mortality and sICH	Random-effects model	
Palaiodimou <i>et al.</i> , 2023 ³¹	EVT for BAO	AIS patients with BAO	Stroke centres	MEDLINE and SCOPUS	To 29 November 2022	2020–2022	4	RCTs	3 China, one international	RoB 2; some concerns ^c	Impossible to assess due to the small number of RCTs	90-Day mRS 0–2, all-cause mortality and sICH	Random-effects model	

^aPatients were aware of treatment allocation. Two trials did not blind the outcome assessor to treatment allocation.^bPatients were aware of treatment allocation. Minor deviations from intended interventions in three trials. In one trial minor concerns of the randomization process due to inclusion of more patients with diabetes mellitus in the EVT arm compared to control.^cPatients were aware of treatment allocation. Some concerns about bias arising in the randomization process in one trial and due to missing outcome data in one study.

AIS, acute ischaemic stroke; Anterior circulation LVO, large-vessel occlusion in the internal carotid artery, middle cerebral artery or anterior cerebral artery; BAO, basilar artery occlusion; mRS, modified Rankin scale; NA, not applicable; NR, not reported; RoB, risk of bias; SD, standard deviation; sICH, symptomatic intracerebral haemorrhage.

Table 2. Table mapping the primary studies contained within included systematic reviews.

RCTs	Year	Circulation	Extent of infarct	Time window	LVOs (vessel occlusions <5%)	Rajkumar et al.	Palaiodimou et al.	Palaiodimou et al.
MR CLEAN ³²	2015	Anterior	Moderate	Early	ICA, M1, M2 (A1, A2)	+		
ESCAPE ³³	2015	Anterior	Moderate	Early	ICA, M1 (M2)	+		
EXTEND-IA ³⁴	2015	Anterior	Moderate	Early	ICA, M1, M2	+		
SWIFT PRIME ³⁵	2015	Anterior	Moderate	Early	ICA, M1, M2	+		
REVASCAT ³⁶	2015	Anterior	Moderate	Early	ICA, M1, M2	+		
THRACE ³⁷	2016	Anterior ^a	Moderate	Early	ICA, M1 (M2, basilar)	+		
THERAPY ³⁸	2016	Anterior	Moderate	Early	ICA, M1, M2	+		
PISTE ³⁹	2017	Anterior	Moderate ^b	Early	ICA, M1, M2	+		
EASI ⁴⁰	2017	Anterior ^a	Moderate ^b	Early	ICA, M1, M2, basilar	+		
RESILIENT ⁴¹	2020	Anterior	Moderate	Early	ICA, M1 (M2)	+		
DAWN ⁴²	2017	Anterior	Moderate	Late	ICA, M1 (M2)	+		
DEFUSE 3 ⁴³	2018	Anterior	Moderate	Late	ICA, M1	+		
RESCUE Japan Limit ⁴⁴	2022	Anterior	Large	Early	ICA, M1 (M2)		+	
SELECT 2 ⁴⁵	2023	Anterior	Large	Early and late	ICA, M1 (M2)		+	
ANGEL ASPECT ⁴⁶	2023	Anterior	Large	Early and late	ICA, M1 (M2)		+	
TESLA ⁴⁷	2023	Anterior	Large	Early and late	ICA, M1 ^c		+	
BEST ⁴⁸	2020	Posterior		Early	Basilar, V4			+
BASICS ⁴⁹	2021	Posterior		Early	Basilar			+
ATTENTION ⁵⁰	2022	Posterior		Early	Basilar, V4			+
BAOCHE ⁵¹	2022	Posterior		Late	Basilar			+

Early window studies randomized most patients <12 h from symptom onset. Large infarct trials included patients with anterior circulation infarcts with ASPECTS lower than 6. Sites of occlusion are presented according to the published results; sites of occlusion representing less than 5% of each treatment arm are shown in parentheses.

^aMost patients had anterior circulation LVO; 87% in EASI and 99% in THRACE.

^bDespite trial protocols allowing lower ASPECTS for inclusion, most patients had moderate extent of infarction; 94% in PISTE and 86% of patients in EASI had ASPECTS 5 or higher.

^cAccording to published protocol, final publication of the results is pending.

ASPECTS, Alberta stroke program early CT score; ICA, internal carotid artery; M1, first branch of middle cerebral artery; M2, second branch of middle cerebral artery; V4, intracranial segment of vertebral artery.

between the two arms regarding age, sex and onset-to-randomization times (Supplemental Figures S6–S8). Safouris Aet al. Therap Advanc Neurol Disord. 2024:17562864241246938 documented marginally higher NIHSS-scores in the EVT arm at randomization (mean difference 0.39; 95% CI: 0.03–0.74, 20 studies, $I^2 = 5\%$, p for Cochran $Q = 0.39$; Supplemental Figure S9). IVT rates

were significantly lower in the EVT arm (OR: 0.86; 95% CI: 0.74–0.99, 18 studies, $I^2 = 0\%$, p for Cochran $Q = 0.69$; Supplemental Figure S10) after removing studies that have not included patients receiving IVT or studies in which all or almost all included patients received

IVT.

Quality control of included studies

The risk of bias in the included SRs was assessed by the ROBIS tool²⁴ and is presented in Supplemental Table S8. Two studies presented a low overall risk of bias^{30,31}; the SR by Rajkumar *et al.*²⁹ searched a single database. Supplemental RCTs were examined using the Risk of Bias 2 (RoB2) Cochrane assessment tool. The major concern of the additional RCTs^{52–55} was the fact that randomized participants and treating physicians were aware of the intervention, also some deviations from intended interventions were noted. Overall, the RCTs were considered of high quality despite the existence of performance bias (Supplemental Figure S11).

Quantitative analyses

Study-level meta-analysis was performed in the 24 included RCTs. An overview of all primary and secondary outcomes, as reported in the included SRs and as estimated in Safouris *Aet al.* Therap Advanc Neurol Disord. 2024;17562864241246938 meta-analy-sis, is summarized in Table 3. Regarding the pri-mary outcome, EVT was associated with a higher likelihood of achieving good functional outcomes at 3 months compared to BMT (RR: 1.78; 95% CI: 1.54–2.06; 24 studies; $I_2 = 62\%$; p for Cochran $Q < 0.0001$; Figure 2). Regarding secondary out-comes, EVT was associated with independent ambulation at 3 months compared to BMT (RR: 1.50; 95% CI: 1.37–1.64; 24 studies; $I_2 = 54\%$; p for Cochran $Q = 0.001$; Supplemental Figure S12) and with excellent functional outcome at 3 months compared to BMT (RR: 1.90; 95% CI: 1.62–2.22; 24 studies; $I_2 = 27\%$; p for Cochran

$Q = 0.11$; Supplemental Figure S13). Regarding safety outcomes, sICH was more common in the patients receiving EVT *versus* BMT (RR: 1.65; 95% CI: 1.23–2.21; 23 studies; $I_2 = 0\%$; p for Cochran $Q = 0.52$; Supplemental Figure S14).

EVT was associated with reduced risk of all-cause mortality at 3 months compared to BMT (RR: 0.81; 95% CI: 0.74–0.88; 24 studies; $I_2 = 11\%$; p for Cochran $Q = 0.31$; Supplemental Figure S15). The odds of reduction of disability (mRS shift) were significantly in favSafouris *Aet al.* Therap Advanc Neurol Disord. 2024;17562864241246938 of EVT (unadjusted generalized OR: 1.64; 95% CI: 1.64–1.81; 24 studies; $I_2 = 39\%$; p for Cochran $Q = 0.03$; Supplemental Figure S16). Safouris *Aet al.* Therap Advanc Neurol Disord. 2024;17562864241246938 have performed leave-one-out analysis in all outcomes. For the primary outcome RRs ranged from 1.72 (95% CI:

RRs ranged from 1.75 (95% CI: 1.54–1.99) to 1.86 (95% CI: 1.63–2.12). For sICH RRs ranged from 1.53 (95% CI: 1.13–2.08) to 1.72 (95% CI: 1.27–2.34). For mortality RRs ranged from 0.83 (95% CI: 0.76–0.90) to 0.79 (95% CI: 0.73–0.87). Consequently, the treatment effects for all outcomes did not change direction or lose statisti-cal significance in the leave-one-out analysis, con-firming the robustness of all documented associations.

The pooled proportions of efficacy and safety outcomes, as reported in the included SRs and as estimated in Safouris *Aet al.* Therap Advanc Neurol Disord. 2024;17562864241246938 meta-analysis of the 24 included RCTs, are presented in Table 2. Regarding the primary outcome, 38% of patients after EVT (95% CI: 35–46%; 24 studies; $I_2 = 93\%$; p for Cochran $Q < 0.001$; Supplemental Figure S17) and 22% of patients after BMT (95% CI: 17–27%; 24 studies; $I_2 = 93\%$; p for Cochran $Q < 0.001$; Supplemental Figure S18) achieved good functional outcome (mRS-scores 0–2) at 3 months. Regarding secondary outcomes, 53% of patients after EVT (95% CI: 47–59%; 24 stud-ies; $I_2 = 91\%$; p for Cochran $Q < 0.001$; Supplemental Figure S19) and 35% of patients after BMT (95% CI: 30–41%; 24 studies; $I_2 = 91\%$; p for Cochran $Q < 0.001$; Supplemental Figure S20) retained independent ambulation at 3 months; 23% of patients after EVT (95% CI: 18–27%; 24 studies; $I_2 = 92\%$; p for Cochran $Q < 0.001$; Supplemental Figure S21) and 11% of patients after BMT (95% CI: 8–14%; 24 stud-ies; $I_2 = 88\%$; p for Cochran $Q < 0.001$; Supplemental Figure S22) had excellent func-

tional outcome at 3 months. Regarding safety outcomes, 4.3% of patients after EVT (95% CI: 3.1–5.6%; 24 studies; $I_2 = 68\%$; p for Cochran $Q < 0.001$; Supplemental Figure S23) and 2.1% of patients after BMT (95% CI: 1.4–2.8%; 24 studies; $I_2 = 32\%$; p for Cochran $Q = 0.07$; Supplemental Figure S24) were complicated with sICH. Finally, 23% of patients after EVT (95%

1.50–1.98) to 1.83 (95% CI: 1.57–2.12). For mRS 0–3, RRs ranged from 1.47 (95% CI: 1.34–

CI: 19–27%; 24 studies; $I^2 = 88\%$; p for Cochran $Q < 0.001$; Supplemental Figure S25) and 29% of patients after BMT (95% CI: 24–34%; 23 studies; $I^2 = 91\%$; p for Cochran $Q < 0.001$; Supplemental Figure S26) were dead at 3 months.

1.61) to 1.52 (95% CI: 1.38–1.67). For mRS 0–1

Publication bias. Publication bias was evaluated using funnel plots for every outcome of the analysis. Visual inspection of the funnel plots did not reveal evidence of publication bias (Supplemental Figures S27–S32). Egger's test revealed

Table 3. Overview of analyses for primary and secondary outcomes.

EVT compared to BMT for large-vessel occlusion AIS.

Population: AIS patients with large-vessel occlusion

Setting: stroke centre

Intervention: EVT

Comparison: BMT

Outcomes	Anticipated absolute effects ^a (95% CI)		Summary measure (95% CI)	Number of patients (studies)	I^2 (<i>p</i> for Cochran)	Certainty of the evidence (GRADE)
	Events per 1000 with BMT	Events per 1000 with EVT				
Rajkumar <i>et al.</i>, 2022²⁹						
Disability reduction (mRS shift) at 90 days			OR 1.92 (1.64–2.17)	1276 (12 RCTs)	48%	HIGH
Good functional outcome (mRS 0–2) at 90 days	280	465	OR 2.27 (1.92–2.7)		–	
sICH	40	42	OR 1.12 (1.24–2.62)		0%	
Death at 90 days	192	161	OR 0.81 (0.66–0.99)		0%	
Palaiodimou <i>et al.</i>, 2023³⁰						
Disability reduction (mRS shift) at 90 days			OR 1.70 (1.39–2.07)	1311 (4 RCTs)	0%	⊕⊕⊕⊕ HIGH
Independent ambulation (mRS 0–3) at 90 days	210 (130–300)	370 (290–450)	RR 1.69 (1.33–2.14)		39%	
Good functional outcome (mRS 0–2) at 90 days	90 (70–110)	200 (130–280)	RR 2.33 (1.76–3.1)		0%	
Excellent functional outcome (mRS 0–1)	50 (10–100)	80 (50–120)	RR 1.46 (0.91–2.33)		39%	
sICH	20 (10–40)	40 (10–90)	RR 1.98 (1.07–3.68)		0%	
Death at 90 days	290 (200–400)	280 (190–380)	RR 0.98 (0.83–1.15)		0%	
Palaiodimou <i>et al.</i>, 2023³¹						
Disability reduction (mRS shift) at 90 days			cOR 1.96 (1.26–3.05)	988 (4 RCTs)	59% (0.06)	HIGH
Independent ambulation (mRS 0–3) at 90 days	–	–	RR 1.54 (1.16–2.05)		60% (0.06)	
Good functional outcome (mRS 0–2) at 90 days	–	–	RR 1.83 (1.08–3.08)		79% (0.02)	
sICH	–	54 (36–74)	RR 7.78 (2.36–25.61)		0% (0.97)	
Death at 3 months	–	–	RR 0.76 (0.65–0.89)		0% (0.42)	
Total						
Good functional outcome (mRS 0–2) at 90 days	216 (168–265)	382 (320–443)	RR 1.78 (1.54–2.06)	5920 (24 RCTs)	62% (<i>p</i> <0.0001)	⊕⊕⊕⊕ HIGH**
Independent ambulation (mRS 0–3) at 90 days	354 (295–413)	528 (469–587)	RR 1.50 (1.37–1.64)	5920 (24 RCTs)	54% (<i>p</i> =0.001)	
Excellent functional outcome (mRS 0–1) at 90 days	108 (82–135)	226 (180–271)	RR 1.90 (1.62–2.22)	5920 (24 RCTs)	27% (<i>p</i> =0.11)	
sICH	21 (14–28)	43 (31–56)	RR 1.65 (1.23–2.21)	5427 (23 RCTs)	0% (<i>p</i> =0.52)	
Death at 90 days	290 (236–344)	229 (186–271)	RR 0.81 (0.74–0.88)	5920 (24 RCTs)	11% (<i>p</i> =0.31)	
Disability reduction (mRS shift) at 90 days			genOR 1.64 (1.49–1.81)	5920 (24 RCTs)	39% (<i>p</i> =0.03)	

AIS, acute ischaemic stroke; BMT, best medical treatment; CI, confidence interval; cOR, common odds ratio; EVT, endovascular treatment; genOR, generalized odds ratio; mRS, modified Rankin scale; OR, odds ratio; RR, risk ratio; RCT, randomized-controlled clinical trials; sICH, symptomatic intracranial haemorrhage.

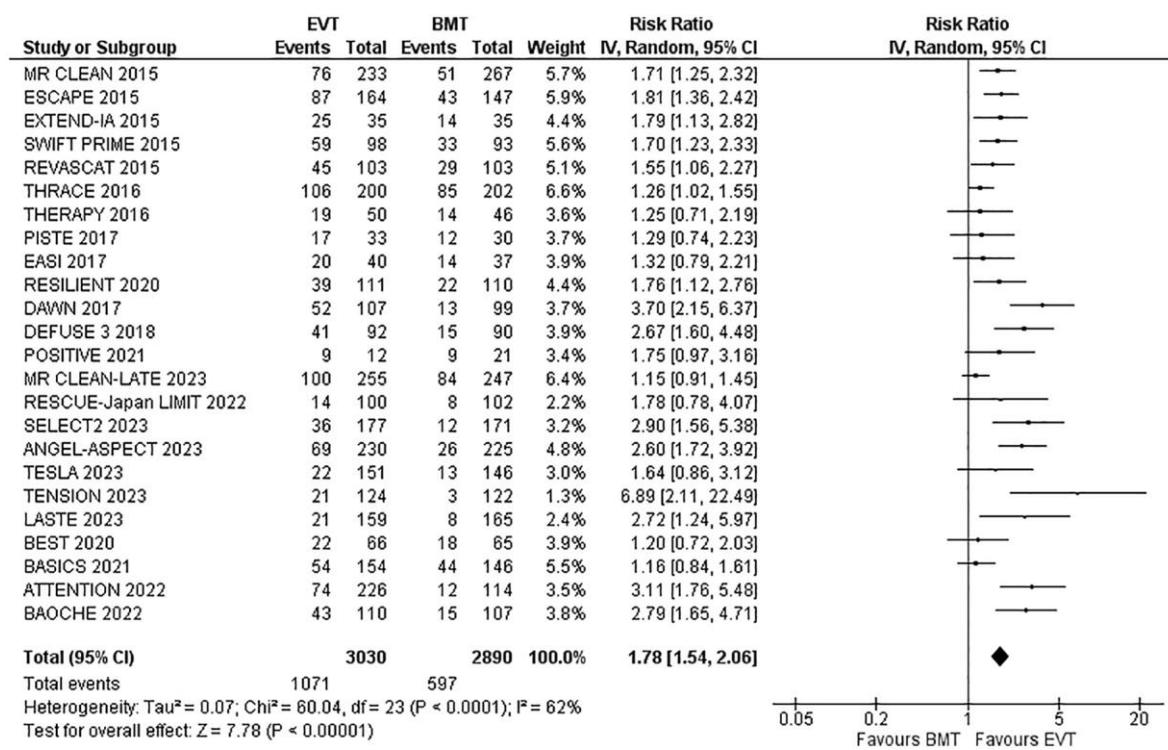


Figure 2. Forest plot presenting the risk ratio of achieving mRS 0–2 at 3 months among EVT- versus BMT-treated patients.

BMT, best medical therapy; EVT, endovascular treatment; mRS, modified Rankin scale.

asymmetry in the outcomes of 3-month mRS 0–1 (p -value = 0.0027), mRS 0–2 (p Value = 0.0014) and mRS 0–3 (p value = 0.01) but not for sICH, 3-month mortality and 3-month disability reduction (p values = 0.99, 0.93 and 0.078, respectively). The rates of IVT pretreatment significantly differed between the two arms and meta-regression analysis was pursued for all examined outcomes. Nevertheless, no significant interaction between IVT pretreatment and achieved mRS-scores 0–2 (omnibus p value = 0.786, Supplemental Figure S33), mRS-scores 0–3 (omnibus p value = 0.671, Supplemental Figure S34) and mRS-scores 0–1 (omnibus p value = 0.214, Supplemental Figure S35) at 3 months was detected.

Similarly, there was no significant interaction between IVT pretreatment and sICH (omnibus p value = 0.127, Supplemental Figure S36) or mor-

relevant data used different summary statistics (ORs, common ORs, rate ratio, RRs) on different outcomes (mRS shift, mRS 0–3).

To visually present the beneficial effects of EVT for LVO, Safouris Aet al. Therap Advanc Neurol Disord. 2024:17562864241246938 calculated the pooled proportions of the scores for mRS 0–2, mRS 0–3 and mortality and Safouris Aet al. Therap Advanc Neurol Disord. 2024:17562864241246938 supply HPIA representing the clinical benefit of EVT by encompassing the full spec-trum of LVO treatment including extended time windows of treatment, large established infarcts and posterior circulation infarctions (Figure 3).

Heterogeneity. Substantial heterogeneity of treatment effect was noted for the primary outcome (good functional outcome; $I_2 = 62\%$; p for Cochran $Q < 0.0001$; Figure 2) and independent ambulation at 3 months ($I_2 = 54\%$; p for Cochran $Q = 0.001$; Supplemental Figure S12). Such discrepancies in treatment effect have already been highlighted in RCTs evaluating EVT efficacy for LVO in the anterior circulation and have been attributed to different study protocols, with more

tality at 3 months (omnibus p -value = 0.985, Supplemental Figure S37). Safouris Aet al. Therap Advanc Neurol Disord. 2024:17562864241246938 were unable to perform a sensitivity analysis since many studies have not reported odds of favourable outcomes depending on IVT pretreatment, and those that provided

EVT for LVO



- 38 out of 100 patients will have good functional outcome at 3 months
- 15 out of 100 patients will ambulate independently at 3 months
- 24 out of 100 patients will have moderately severe and severe disability at 3 months
- 23 out of 100 patients will be dead at 3 months

BMT for LVO



- 22 out of 100 patients will have good functional outcome at 3 months
- 13 out of 100 patients will ambulate independently at 3 months
- 36 out of 100 patients will have moderately severe and severe disability at 3 months
- 29 out of 100 patients will be dead at 3 months

Figure 3. Hundred-person icon array demonstrating outcomes after EVT and BMT for LVO.
BMT, best medical treatment; EVT, endovascular treatment; LVO, large-vessel occlusion.

selective studies reporting higher odds of benefit from EVT per patient but excluding more patients that could still derive benefit from treatment.⁵⁶

Concerning the posterior circulation, subgroup analysis in the SR by Palaiodimou *et al.*³¹ has suggested that there are statistically significant differences between studies that were conducted in

China compared to international studies that were conducted in Europe and North America, while the overall EVT benefit is derived by the RCTs recruiting patients in China.

Subgroup analyses. To further assess for potential reasons of the heterogeneity noted in this analysis, pre-specified subgroup analyses were conducted by stratifying the effect of treatment into

three subgroups: anterior circulation *versus* posterior circulation, early time window *versus* late-time window, moderate infarct *versus* large infarct (Supplemental Figures S38–S55). The following subgroup differences were disclosed: sICH risk with EVT compared to BMT was higher in the posterior (RR: 7.48; 95% CI: 2.27–24.62;

fSafouris Aet al. Therap Advanc Neurol Disord. 2024:17562864241246938 anterior (RR: 1.50; 95% CI: 1.11–2.02; 17 studies; $I_2 = 0\%$) circulation (p for subgroup differences 0.01; Supple-

mental Figure S42), as already shown in the current overview of SRs (Supplemental Figure S5). The RR for good functional outcome with EVT compared to BMT was higher in the late (RR: 2.31; 95% CI: 1.24–4.31; fSafouris Aet al. Therap Advanc Neurol Disord. 2024:17562864241246938 studies;

$I_2 = 88\%$) and early and late (RR: 2.41; 95% CI: 1.78–3.26; three studies; $I_2 = 0\%$) than in the early (RR: 1.60; 95% CI: 1.40–1.83; 17 studies; $I_2 = 38\%$) time window trials (p for subgroup differences 0.03; Supplemental Figure S44); Safouris Aet al. Therap Advanc Neurol Disord.

2024:17562864241246938 therefore confirm previous observations known as ‘the late-window paradox’.⁵⁷ The RR for mortality was neutral in the early and late treatment group (RR: 1.00; 95% CI: 0.84–1.19; three stud-

ies; $I_2 = 0\%$) whereas it was lower in the early (RR: 0.77; 95% CI: 0.70–0.85; 17 studies; $I_2 = 0\%$) and the late (RR: 0.78; 95% CI: 0.64–0.95; fSafouris Aet al. Therap Advanc Neurol Disord. 2024:17562864241246938 studies; $I_2 = 0\%$) treatment groups (p for subgroup differences 0.04; Supplemental Figure S49); this variation could either be fortuitous or due to the fact that the early and late studies are all more recent, more inclusive studies, excluding patients presenting with better profile and, thus, potentially deriving

was higher with large (RR: 2.49; 95% CI: 1.89–3.29; six studies; $I_2 = 7\%$) than moderate (RR: 1.62; 95% CI: 1.39–1.88; 14 studies; $I_2 = 54\%$) volume infarcts of the anterior circulation (p for subgroup differences 0.00006; Supplemental Figure S50); the RR for independent ambulation with EVT compared to BMT was higher with large (RR: 1.90; 95% CI: 1.50–2.40; six studies; $I_2 = 51\%$) than moderate (RR: 1.39; 95% CI: 1.26–1.53; 14 studies; $I_2 = 45\%$) volume infarcts of the anterior circulation (p for subgroup differences 0.02; Supplemental Figure S51).

Discussion

The main findings of Safouris Aet al. Therap Advanc Neurol Disord. 2024:17562864241246938 meta-analysis indicate that high-quality data converge into a clear benefit of EVT for a wide variety of indications in AIS patients with LVO: intracranial internal carotid, proximal middle cerebral artery, basilar artery occlusion. Proximal middle cerebral artery consists of the M1 segment in all included studies and, in most included studies of moderate

occlusions. Safouris Aet al. Therap Advanc Neurol Disord. 2024:17562864241246938 have limited information about the primary intention recanalization

treatment, had low recanalization rates and sub-

optimal treatment pathways resulting in time

delays.⁵⁸ The low to moderate heterogeneity

found in Safouris Aet al. Therap Advanc Neurol

Disord. 2024:17562864241246938 supports that, despite

Safouris Aet al. Therap Advanc Neurol Disord.

2024:17562864241246938 tendency to consider different subgroups of AIS patients, the benefit from

EVT is consistent and invariable. Relative risks

remained statistically significant for different

locations of occlusion, time windows and size of

infarcts. It is of note that the absence of heterogeneity regarding

reduction of disability (mRS shift analysis) and

mortality at 3 months in LVO patients treated

with EVT. Despite differences in prognosis in the

more benefit from

treatment; those are

eligible for EVT according

to criteria with older,

more selective studies.

included subgroups, treatment effect seems to be steadily in favSafouris Aet al. Therap Advanc Neurol Disord. 2024:17562864241246938 of EVT for all examined sub-groups. Distinguishing treatment approaches to early *versus* late-time window, to moderate *versus* large infarct size or to anterior *versus* posterior cir-culation LVOs used to be necessary since differ-ent imaging or clinical criteria have been followed in each respective RCT. However, current knowl-edge, as presented in this overview, crosses these

boundaries, as the treatment effect remains robust across LVO subgroups. The recently published MR CLEAN-LATE trials⁵² exemplifies this approach by being a late-time window RCT that randomized patients with both moderate and large infarcts, providing a more pragmatic approach to late-window anterior LVO patient selection for EVT through simple rather than advanced neuroimaging.

During the last decade, Safouris *Aet al.* Therap Advanc Neurol Disord. 2024;17562864241246938 have continuously witnessed reports of improvement in the rates of good functional outcomes after EVT for ever-expanding indications.⁵⁹ Novel approaches of post-recanalization intra-arterial thrombolysis have also shown promising results.⁶⁰ Hopefully, ongoing trials will succeed in crossing the next frontier, namely the distal artery occlusions.⁶¹ However, from a global health care perspective, focus should be on translating the available data into clinical practice and funnelling funds to provide EVT to as many stroke victims as possible. Despite the improvement in treatment rates in recent years, there are persistent inequalities between countries in access to EVT for acute stroke patients, with most low and middle-income countries lagging.¹¹ The results of the current overview of SRs may be used to convey the import-

tance of EVT to health policymakers. Epidemiologic data on the prevalence of LVO may be used in conjunction with the RRs reported herein to improve the accuracy of cost-effectiveness and future burden of stroke projection models.^{62,63}

Safouris *Aet al.* Therap Advanc Neurol Disord. 2024;17562864241246938 umbrella review provides overwhelming evidence that EVT compared to BMT reduces the risk of death at 3 months by 19% (95% CI: 12–26%) with low (11%) heterogeneity across all 24 RCTs. This translates into 61 fewer deaths for every 1000 patients treated with EVT. This finding is in line with a previous meta-analysis from Safouris *Aet al.* Therap Advanc Neurol Disord. 2024;17562864241246938 collaborative group that, after pooling data from 11 RCTs, documented a 17% risk reduction with a number needed to treat of 31 (32 fewer deaths for every 1000 patients treated) with EVT compared to BMT.⁶⁰ Given the fact that EVT was associated with reduced disability across all ranks of mRS (ordinal shift analysis), the reduction in mortality with EVT is not associated with increased likelihood of

3-month mortality.^{7,64} In other words, wider implementation of EVT will result in fewer deaths in addition to lower disability rates.

Standard umbrella review methodology extracts statistical results intact and presents them. However, when the literature is as extensive and rapidly evolving as it is in the field of EVT, meta-analyses include different studies and no SR could be viewed as definitive.⁶⁵ The fact that there was no overlapping of primary studies among the included SRs permitted us to perform meta-analysis of all primary studies. Safouris *Aet al.* Therap Advanc Neurol Disord.

2024;17562864241246938 also included additional studies published in the last 2 years that would have otherwise been missed. As a result, the strength of Safouris *Aet al.* Therap Advanc Neurol Disord. 2024;17562864241246938 study is the incorporation of 24 RCTs comprising 5968 patients. Safouris *Aet al.* Therap Advanc Neurol Disord. 2024;17562864241246938 subgroup analyses further solidify the role of EVT as one of the most effective advances in medicine in recent years for all tested LVO sub-groups. The selection of subgroups was according to Safouris *Aet al.* Therap Advanc Neurol Disord. 2024;17562864241246938 registered research protocol, and it was based on the stages of clinical research on EVT during the last decade. It may seem counterintuitive that the RR of mortality is 1 (neutral) in the early and late-time window trials but significantly lower in both the early window and the late-window trials in the EVT arm (RR: 0.77 and 0.78,

respectively; Supplemental Figure S49) but the main characteristic of the three early and late-window trials is the inclusion of stroke patients with large established infarctions (large-core RCTs).

The absence of reduction in mortality risk with EVT in this subgroup confirms the findings of the relevant SR by Palaiodimou *et al.*³⁰ severe disability (mRS-scores of 4–5). This is an important additional benefit of EVT compared to BMT, given the fact that IVT compared to BMT does not reduce

However, reduction of disability remains highly significant and primary outcome is significantly higher in the large-core subgroup compared to moderate core of the anterior circulation (Supplemental Figure S50). Safouris Aet al. Therap Advanc Neurol Disord. 2024:17562864241246938 therefore conclude that most outcomes of efficacy and safety remain important, irrespective on how Safouris Aet al. Therap Advanc Neurol

Disord. 2024:17562864241246938 define subgroups: the net benefit of EVT remains robust. Regarding publication bias, no asymmetry was unravelled through funnel plot inspection, but evidence of publication bias was detected for the 3-month functional outcomes using Egger's test. Furthermore, substantial heterogeneity was present only for the primary outcome but was not significant for all secondary outcomes, despite the differences among treated subgroups of LVO patients. Age, sex and onset-to-randomization times were similar between the two arms in the meta-analysis. The mean NIHSS-scores were

slightly higher in the EVT than in the BMT group.

IVT pretreatment rates significantly differed between the two arms, but meta-regression analysis for all examined outcomes failed to identify any interaction between IVT pretreatment rates and the comparative efficacy of EVT versus BMT with regard to primary and secondary outcomes. A very recent SR that included 10 RCTs showed significantly increased odds of functional independence with bridging therapy at the expense of an increase in mortality and sICH as compared to direct EVT.⁶⁶ An individual-patient meta-analysis of six RCTs has failed to show non-inferiority of direct EVT to bridging therapy or superiority of bridging therapy in anterior circulation LVO in the context of mothership paradigm (excluding drip-and-ship studies) and in centres with rapid door-to-groin puncture times (median less than 30 min).⁶⁷ As far as the posterior circulation is concerned, Palaiodimou *et al.* performed subgroup analysis after stratification for IVT and found no significant subgroup differences in patients with and without IVT pretreatment.³¹ Notably, in the sub-

group of patients pretreated with IVT, the effect size of EVT compared to BMT regarding mRS 0–3 was substantially attenuated (data available from two RCTs). The role of IVT before EVT remains established by recent head-to-head RCTs (comparing bridging therapy to direct EVT) and current international recommendations that advocate that all EVT-eligible LVO patients should be

pretreated with IVT (if they fulfil the relevant inclusion criteria), especially in the drip-and-ship treatment paradigm.^{68,69} It remains to be seen if there is reason to omit IVT in patients admitted directly to thrombectomy centres that have proven records of very short groin to recanalization times.⁶⁸ Direct EVT versus bridging therapy for BAO will be investigated in the BEST-BAO trial (Direct Endovascular Treatment Versus Bridging Treatment In Basilar Artery Occlusive Stroke; <https://www.clinicaltrials.gov>; Unique identifier:

NCT05631847).

The current overview aims to present the best available evidence to date on EVT benefit for patient-oriented outcomes that were predefined

previously in other SRs.⁶⁶ The current review further solidifies the important clinical benefit regarding reduction of dependency and mortality after LVO stroke and Safouris *Aet al.* Therap Advanc Neurol Disord. 2024:17562864241246938 conclusions may be communicated from stroke physicians to policy-makers to increase global access to EVT.

A comprehensive approach to improve outcomes for stroke patients will also need to consider that the outcome of a stroke is contingent upon numerous variables, encompassing factors such as age, comorbidities like hypertension, diabetes and asthma, as well as additional elements like smoking and hyperlipidaemia.^{71–73} Despite advancements in stroke treatment, especially ischaemic stroke, various pre- and postoperative conditions, such as blood pressure control, gastrointestinal motility, malnutrition linked to stroke and pneumonia associated with stroke, persist as reported predictors affecting outcomes.⁷⁴ Additionally, determining the optimal blood pressure threshold after intervention for achieving the best outcome remains an ongoing challenge.⁷⁵

The main limitation of Safouris *Aet al.* Therap Advanc Neurol Disord. 2024:17562864241246938 study is that it is a study-level meta-analysis, lacking individual patient data. In addition, Safouris *Aet al.* Therap Advanc Neurol Disord. 2024:17562864241246938 documented unadjusted associations that may be prone to residual confounding. Also, the substantial heterogeneity across different studies for the primary outcome of good functional outcomes needs to be taken into account when interpreting Safouris *Aet al.* Therap Advanc Neurol Disord. 2024:17562864241246938 study findings.

Conclusion

The current overview of SRs (umbrella review) of data from randomized-controlled trials strongly supports EVT for AIS patients with LVO. Despite an increase in sICH rates, EVT appears superior to BMT in the anterior circulation even for large infarcts and for posterior circulation LVOs; beneficial effects persist in extended time windows. However, it should be acknowledged that Safouris *Aet al.* Therap Advanc Neurol Disord. 2024:17562864241246938 did not evaluate systematically peri-procedural complications of EVT and that there was substantial heterogeneity across RCTs and SR for the primary Safouris *Aet al.* Therap Advanc Neurol Disord.

2024:17562864241246938 study protocol and were used as primary or secondary endpoints in all included RCTs. Safouris Aet al. Therap Advanc Neurol Disord. 2024:17562864241246938 have not examined periprocedural complications, recanalization rates, asymptomatic ICH or other surrogate outcomes ⁷⁰ that have been addressed

mary outcome (mRS score 0–2) of Safouris Aet al. Therap Advanc Neurol Disord. 2024:17562864241246938 umbrella review. The beneficial effects of EVT are related to improved efficacy outcomes in terms of excellent or good functional outcomes, independent ambulation and survival. The consistency of the magnitude of benefit dictates rapid implementation of this lifesaving and disability-sparing treatment modality across the globe.

