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META-ANALYSIS

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Salvianolic Acids for Injection Combined with Conventional Treatment for Patients with Acute Cerebral Infarction: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: This meta-analysis was conducted to evaluate the clinical effectiveness and safety of Salvianolic acids for injection (SAFI) plus conventional treatment (CT) for patients with acute cerebral infarction (ACI) and to assess the evidence to guide clinical practice.

Material/Methods: PubMed, EMBASE, Cochrane Library, Web of Science, and 4 Chinese electronic databases were searched to identify relevant randomized controlled trials (RCTs). The methodological quality of eligible studies was evaluated using the Cochrane risk of bias tool. The reporting quality of eligible studies was evaluated by Consolidated Standards of Reporting Trials (CONSORT) for traditional Chinese medicine. Meta-analysis and evidence quality were performed using RevMan 5.3 and Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

Results: A total of 14 RCTs involving 1309 patients were included. Meta-analysis showed that SAFI plus CT was better than CT alone in improving the total effective rate (RR=1.35, 95% CI 1.25 to 1.44, $P<0.00001$), reducing the National Institutes of Health Stroke Scale (NIHSS) score (130 mg: WMD=−3.31, 95% CI −3.80 to −2.47, $P<0.00001$; 100 mg: WMD=−1.91, 95% CI −2.28 to −1.54, $P<0.00001$), improving the activity of daily living and cognitive function of ACI, and improving the hemorheology (HBV: high shear rate blood viscosity, LBV: low shear rate blood viscosity, PV: plasma viscosity) and C-reactive protein (CRP).

Conclusions: SAFI plus CT in the treatment of ACI can improve the total effective rate, neurological deficit, and ability to perform activities of daily living, and there is no serious adverse reaction. Based on the GRADE system, the evidence quality is low. More large-scale, well-designed, and high-quality RCTs are required to confirm the positive results.

MeSH Keywords: **Medicine, Chinese Traditional • Meta-Analysis • Randomized Controlled Trial • Stroke**

Abbreviations: **ACI** – acute cerebral infarction; **SAFI** – salvianolic acids for injection; **HBV** – high shear rate blood viscosity; **LBV** – low shear rate blood viscosity; **PV** – plasma viscosity; **PRISMA** – Preferred Reporting Items for Systematic Review and Meta-Analyses; **RCTs** – randomized controlled trials; **CI** – confidence interval; **RR** – risk ratio; **MD** – mean difference; **NIHSS** – National Institutes of Health Stroke Scale; **ADL** – activity of daily living; **BI** – Barthel Index; **MRS** – Modified Rankin Scale; **MMSE** – mini-mental state examination; **MoCA** – Montreal Cognitive Assessment; **CRP** – C-reactive protein; **ADEs** – adverse events; **ADRs** – adverse reactions; **GRADE** – Working Group grades of evidence; **VEGF** – vinyl ester glass flake mortar; **BDNF** – brain derived neurotrophic factor; **GDNF** – glial cell line-derived neurotrophic factor

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Background

Acute cerebral infarction (ACI), also known as stroke, is a neurological deficit syndrome caused by circulatory dysfunction [1]. Cerebral infarction has high rates of morbidity, disability, and mortality. In 2005, there were about 62 million people suffering from stroke worldwide, and it is predicted that by 2030 there will be 77 million such people [2]. The incidence of stroke in China exceeded that of cardiovascular, cancer, and other diseases in 2014 [3]. Thrombolytic therapy is the most important method to restore blood flow. Recombinant tissue plasminogen activator (rt-PA) and urokinase (UK) are the main thrombolytic agents used in China [4]. However, the success or failure of thrombolytic therapy depends on a strict time window. The time between onset and arrival at the hospital of stroke patients in China often exceeds this time window, which causes some patients to lose the chance to benefit from thrombolytic therapy [5].

The Guidelines for the Diagnosis and Treatment of Cerebral Infarction Using Integrated Traditional Chinese Medicine and Western Medicine (2017), formulated by the Committee of Neurology of the Chinese Society of Integrated Chinese and Western Medicine in China recommended the following: in the acute phase of cerebral infarction, the root of red-rooted Salvia injection for promoting blood circulation and removing blood stasis can be administered by intravenous drip, and the combination of traditional Chinese and Western Medicine can be synergistic [6].

Salvianolic acids for injection (SAFI) is a traditional Chinese medicinal preparation composed of multiple salvianolic acids from the aqueous extracts of the plant *Salvia miltiorrhiza*. The main chemical components are salvianolic acid B, rosmarinic acid, lithospermic acid, salvianolic acid D, salvianolic acid Y, mannitol, and other aqueous phenolic acids [7,8]. Modern pharmacological research shows that SAFI has pharmacological effects of anti-inflammatory, antioxidative stress, neurotrophic, regeneration, and protective effects on ACI [9]. The specific chemical composition and pharmacological effects are shown in Table 1.

We systematically searched Cochrane Library, PubMed, EMBASE, Web of Science, and 4 electronic Chinese databases, finding only 1 systematic review and meta-analysis of SAFI [24]. That review had certain limitations: incomplete search, few included studies (only 7), incomplete outcomes, excessive publication time, and not being updated in time to be included in the latest research. Therefore, a meta-analysis of RCTs was needed to evaluate the clinical effectiveness and safety of SAFI plus CT for ACI.

Objectives

To establish the best current treatment evidence, we conducted a systematic review to evaluate the clinical effectiveness and safety of SAFI plus CT for ACI, and to provide clear evidence to guide clinical practice.

Material and Methods

This meta-analysis was conducted and reported according the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [25] and a measurement tool to Assess the Methodological Quality of Systematic Reviews (AMSTAR) [26]. Also, all included studies was assessed by CONSORT for TCM [27].

Search strategy

The electronic databases Cochrane Library, PubMed, EMBASE, Web of Science, China Biological Medicine Database (CBM), China National Knowledge Infrastructure (CNKI), Chinese Wan Fang Database (Wan Fang), and VIP Chinese Sci-tech periodical

Table 1. Chemical composition and pharmacological effects of SAFI.

Chemical composition	Amount (%)	Pharmacological effects (Animal model: cerebral ischemia or infarction)
Salvianolic acid B	63.2	a. anti-cerebral ischemic injury, improve neurobehavioral score, reduce cerebral infarction volume, reduce IL-1β, IL-6, increase IL-10, inhibit TLR4/NF-κB signaling pathway [10,11]; b. increase oxidative stress molecules SOD, GSH levels and ATP content, reduce MDA and lactic acid content; enhance mitochondrial ATPase activity, resist lipid peroxidation, effectively scavenge oxygen free radicals and enhance energy metabolism [10,12–14]; c. promotes the secretion of neurotrophic factors VEGF, BDNF and GDNF, activates VEGF and BDNF-TrkB-CREB pathway [15–18]; d. promote the proliferation of nerve cells in hippocampus and improve the learning and memory ability of cerebral ischemic injury [19–23].
Mannitol	22.5	
Lithospermic acid	4.12	
Salvianolic acid Y	3.85	
Rosmarinic acid	2.74	
Salvianolic acid D	2.38	
Other aqueous phenolic acids	1.21	

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Database (VIP) were systematically searched for relevant studies between the journal establishment date and December 2018. The following search terms were used separately or combined: 'salvianolic acid' or 'salvianolic injection' AND 'acute cerebral infarction', 'cerebral infarction', or 'acute ischemic stroke'.

Selection criteria

The studies were selected according to these inclusion criteria: (1) Participants diagnosed as ACI or Acute Ischemic Stroke (AIS); (2) Randomized controlled trials (RCTs); (3) SAFI plus CT versus CT, including statins, aspirin, edaravone, clopidogrel, citicoline sodium, nitrate esters, cerebrolysin vial; (4) Primary outcome is total effective rate (cured: NIHSS score decreased 91~100%; significant effectiveness: NIHSS score decreased 46~90%; effective: NIHSS score decreased 18~45%; inefficacy: NIHSS score decreased by 0~17%; deterioration: NIHSS score increased), total effective rate=(number of effective cases)/total number of cases×100%; and (5) Secondary outcomes including NIHSS score, ability of daily living (ADL: Barthel index, BI; modified Rankin Scale, MRS score), hemorheology (LBV, HBV, PV), mini-mental state examination (MMSE) score, Montreal cognitive assessment (MoCA) score, C-reactive protein (CRP) and any adverse drugs events/reactions (ADEs/ADRs).

The exclusion criteria were: (1) There was a serious error in the research data; (2) Unable to obtain full text; (3) Duplicate data; and (4) Intervention included other Chinese medicines, acupuncture, or massage.

Endnote was used to find duplicate studies among the retrieved studies. The titles, abstracts, and keywords of studies were browsed to determine if they met the inclusion criteria. Full contents of studies were scanned to further assess whether they met the inclusion criteria. If there was a disagreement between reviewers, the decision was made by consulting a third team (ZFW and YMX).

Data extraction and management

JL and LXW were independently responsible for extraction of intervention and outcomes, and disagreements were resolved by the third author (YMX). The number of events and sample size in each group were extracted from binary outcomes. The mean, standard deviation (SD), and sample size of each group were extracted from continuous outcomes. The data extracted included: (1) general information: the first author, year of publication; (2) study characteristics: study design, method of randomization and blinding; (3) patients: number, sex, age in comparison groups, and total number; (4) intervention: dosage and course of treatment of experimental and control groups; (5) outcomes: primary outcome, secondary outcomes, and any adverse reactions or events.

Quality assessment

The Cochrane Handbook was used to assess methodological quality of trials [28]. All included studies were assessed in 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. The risk of bias was classified as low, high, or unclear. Any disagreements were resolved by discussion to reach consensus.

Statistical analysis

The data analysis was carried out using RevMan 5.3. If I^2 statistics <50%, the homogeneity was better, and the fixed-effects model was used. If I^2 statistics ≥50%, significant statistical heterogeneity was identified, and the random-effects model was used. For binary outcome, relative risk (RR) with 95% confidence interval (CI) was used. The weighted mean difference (WMD) was used for continuous outcomes. The Cochrane Handbook was used to convert multiple-arms trials to two-arm trials if there were multiple arms [28]. Publication bias was assessed by funnel plot.

Subgroup analysis and sensitivity analysis

Subgroup analysis was based on different doses (100 mg/130 mg), NIHSS score, Barthel index, and specific index of hemorheology (LBV, HBV, PV) to manage heterogeneity. Sensitivity analysis was performed to detect the influence of a single study on the overall pooled estimate by removing 1 study at a time.

GRADE for evidence quality

Based on the systematic review results, the evidence quality grading method (GRADE) introduced by the GRADE Working Group in 2004 was used to evaluate the total effective rate, NIHSS score, and Barthel index. In the GRADE classification method, randomized controlled trials were initially classified as high-quality evidence whose quality could be reduced by 5 factors (risk of bias, inconsistency, indirectness, imprecision, and publication bias), and the quality of the final evidence was classified as high, moderate, low, and very low. Four key factors influence the recommendations: balance between desirable and undesirable effects, quality of the evidence, values and preferences, and costs (resource utilization). Based on these 4 factors, the GRADE system classifies recommendations into strong and weak levels [29,30].

Patient and public involvement

There was no direct patient or public involvement in this review.

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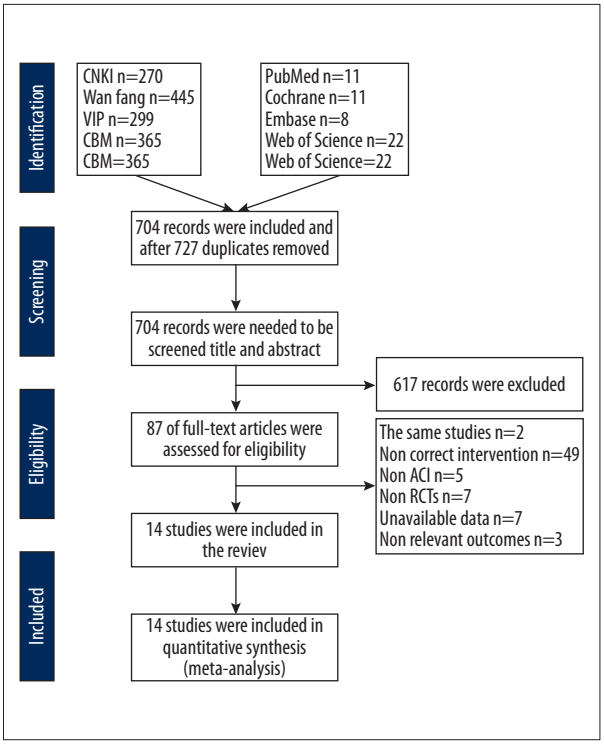

Figure 1. PRISMA flow diagram of included and excluded articles. PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Results

Literature search results

The initial literature search identified 1431 studies. After duplicates among different databases were removed, we read the titles and abstracts of all identified studies, and based on inclusion and exclusion criteria, 87 studies were downloaded for full-text assessment. We excluded 73 of these 87 studies for the following reasons: duplicate study (n=2); not using intervention measures correctly (n=49); not ACI (n=5); not RCTs (n=7); unavailable data (n=7); and not reporting relevant outcomes (n=3). A total of 14 trials included in this review and all were published in Chinese (Figure 1).

Characteristics of included studies

In total, 14 studies were included and all were conducted in China. All 14 studies reported that the baseline conditions in the experimental group and control group were balanced, 3 of which provided a comparative table for the general characteristics of the 2 groups [33,43,44]. The total sample size was 1309 participants, the sample size ranged from 60 to 150, the experimental groups included 650 cases, and the control groups included 659 cases. All of the studies compared SAFI plus CT *vs.* CT. The treatment regimen of SAFI was divided into 100 mg/day (7 studies) and 130 mg/day (7 studies). Only 1 study [33] administered treatment for 21 days, and the other studies administered treatment for 14 days. Eleven trials observed adverse reactions or events. Characteristics of the 14 included trials are listed in Table 2.

Methodological quality

All of the studies described the randomization method used. The allocation sequence being generated from random alphabet method, random number tables, and a computer random number generator was described in 8 studies [31,32,34–36,39,40,42]. No study mentioned the blinding and allocation concealment methods. Three studies reported on follow-up after treatment [32,43,44]. Four studies reported that they had received ethics committee approval [31,34,40,43]. Eight studies reported that all patients signed the informed consent [33,34,36,39–43]. There were no withdrawals or losses in any of the studies. No study protocols were reported. No selective reporting was mentioned in any of the included studies. There were no other potential sources of bias because the age, sex, dosage, and duration in different treatment groups were similar at baseline in all studies. The quality of the included studies is displayed in Figures 2 and 3.

Meta-analysis

Total effective rate, improvement of NIHSS score, Barthel Index, and hemorheology were the key outcomes in all included studies. For comprehensive and systematic evaluation of effects of interventions, the MRS score, MMSE score, MoCA score, and CRP were analyzed as well. In the pooled estimates of hemorheology, the studies were separated into 3 subgroups (LBV, HBV, and PV).

Total effective rate

The total effective rate was assessed for 967 patients in 10 studies [32–35,37–39,41,43,45]. The heterogeneity test shows that there was good homogeneity among the studies (P=0.95, I^2=0%), and the fixed-effects model was used for analyses. The meta-analysis demonstrated that SAFI plus CT has a better total effective rate than does CT alone (RR=1.35, 95% CI 1.25 to 1.44, P<0.00001, Figure 4).

Improvement of NIHSS score

The NIHSS score was assessed for 936 patients in 11 studies [31,32,34–37,39,40,42–44]. The random-effects model was used for analysis (130 mg: P=0.009, I^2=68%). The meta-analysis demonstrated that SAFI plus CT has a better effect on the reduction of NIHSS score compared with CT alone (130 mg: WMD=–3.31, 95% CI –3.80 to –2.47, P<0.00001; 100 mg: WMD=–1.91, 95% CI –2.28 to –1.54, P<0.00001; Figure 5).

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Table 2. characteristics of included trials.

Study ID	Sample size			Gender (T/C)	Age/(year) (T/C)	Treatment group			Control group	Duration/ day	Outcomes
	T	C	Total			Baseline	Dose of SAFI/mg	Combined with treatment			
Zheng et al. (2018) [31]	43	43	86	T: 27/16 C: 25/18	T: 41~79 (64.00±12.06) C: 42~79 (64.09±10.28)	B	100	SAFI+CT	CT	14	2),3),9)
Wei et al. (2018) [32]	63	63	126	T: 40/23 C: 39/24	T: (58.30±6.20) C: (57.70±5.80)	B	130	SAFI+CT	CT	21	1),2),3)
Li (2018) [33]	67	76	143	T: 49/18 C: 55/21	T: 50~73 (61.00) C: 55.25~75.75 (63.50)	B	130	SAFI+CT	CT	14	1)
He (2018) [34]	39	39	78	T: 23/16 C: 22/17	T: 44~72 (57.20±6.20) C: 42~73 (56.80±6.40)	B	100	SAFI+CT	CT	14	1),2),9)
Zhang et al. (2017) [35]	30	30	60	T: 20/10 C: 18/12	T: 45~76 (60.50±6.20) C: 47~78 (61.30±6.10)	B	130	SAFI+CT	CT	14	1),2),4), 8),9)
Yan (2017) [36]	48	48	96	T: 26/22 C: 25/23	T: 33~75 (55.34±5.67) C: 34~76 (56.16±6.39)	B	130	SAFI+CT	CT	14	2),3),5), 6),7),9)
Liu et al. (2017) [37]	43	43	86	T: 30/13 C: 26/17	T: 53~69 (62.40±3.00) C: 55~68 (62.30±3.10)	B	100	SAFI+CT	CT	14	1),2),6), 7),9)
Fang (2017) [38]	75	75	150	T: 32/43 C: 34/41	T: 39~76 (57.83±7.79) C: 40~78 (56.91±7.62)	B	100	SAFI+CT	CT	14	1),4),9)
Wang (2016) [39]	40	40	80	T: 25/15 C: 24/16	T: 31~82 (64.80±3.20) C: 30~81 (65.20±3.40)	B	130	SAFI+CT	CT	14	1),2),3),9)
Cui (2016) [40]	45	45	90	58/42	38~74 (62.50±5.80)	B	130	SAFI+CT	CT	14	2),3),9)
An (2016) [41]	40	40	80	T: 23/17 C: 22/18	T: 44~81 (65.32±9.34) C: 44~80 (65.31±9.35)	B	100	SAFI+CT	CT	14	1),8)
Zhang et al. (2015) [42]	35	35	70	T: 24/16 C: 22/18	T: 47~79 (62.50±4.50) C: 45~82 (60.50±4.80)	B	100	SAFI+CT	CT	14	2),3),5), 6),7),9)
Li (2015) [43]	50	50	100	T: 34/16 C: 31/19	T: (62.40±4.50) C: (60.30±4.30)	B	130	SAFI+CT	CT	14	1),2),3), 4),9)
Chen (2015) [44]	32	32	64	T: 21/11 C: 20/12	T: (54.23±9.60) C: (53.67±10.3)	B	100	SAFI+CT	CT	14	1),2),3),9)

T – treatment group; C – control group; 1) – total effective rate of NIHSS score; 2) – NIHSS; 3) – Barthel Index; 4) – hemorheology; 5) – MRS; 6) – MMSE; 7) – MOCA; 8) – CRP; 9) – ADEs/ADRs; B – balanced; SAFI – Salvianolic acids for injection; CT – conventional treatment: aspirin, clopidogrel, edaravone, statins, citicoline sodium, nitrate esters, cerebrolysin Vial.

In the forest plot, the confidence interval of 1 trial [32] did not overlap with other 5 trials in the first subgroup (130 mg). From the original study, we observed that the trial's duration of treatment was 21 days, but the duration of the others was 14 days. This appears to be the main source of heterogenicity, so we removed that study and pooled the other 5 studies (WMD=–2.87, 95% CI –3.45 to –2.30, I^2=27%, P<0.00001).

Improvement of ADL

Barthel index

The BI was assessed for 712 patients in 8 studies [31,32,36,39,40,42–44]. The heterogeneity test showed that random-effects model should be used (130 mg: P=0.0002, I^2=82%). The meta-analysis demonstrated that SAFI plus CT has a better therapeutic effect on the improvement of BI compared with CT alone (130 mg: WMD=13.61, 95% CI 9.00 to 18.21, P<0.00001; 100 mg: WMD=8.21, 95% CI 5.46 to 10.95, P<0.00001; Figure 6).

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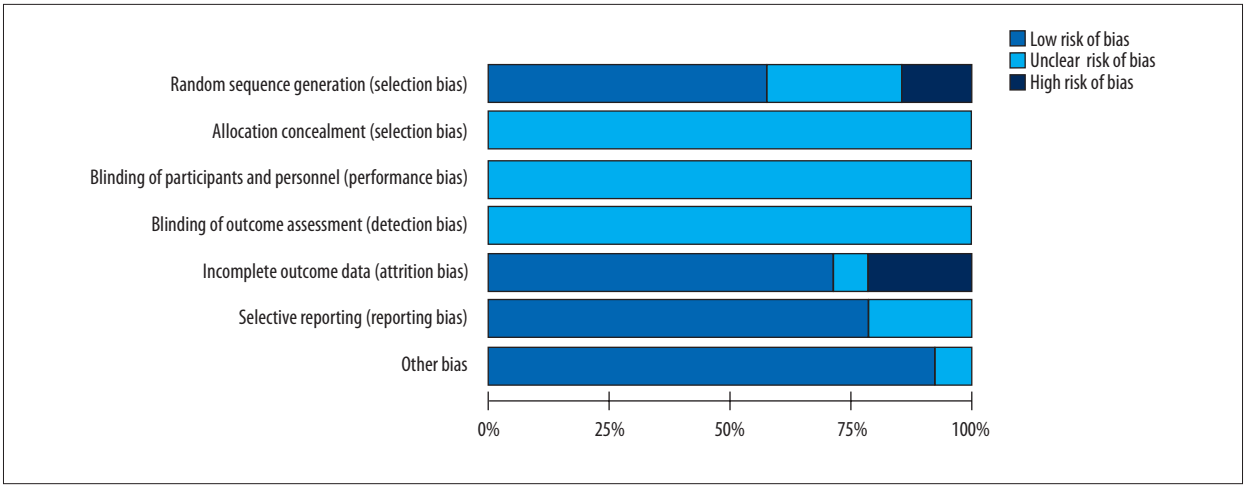

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

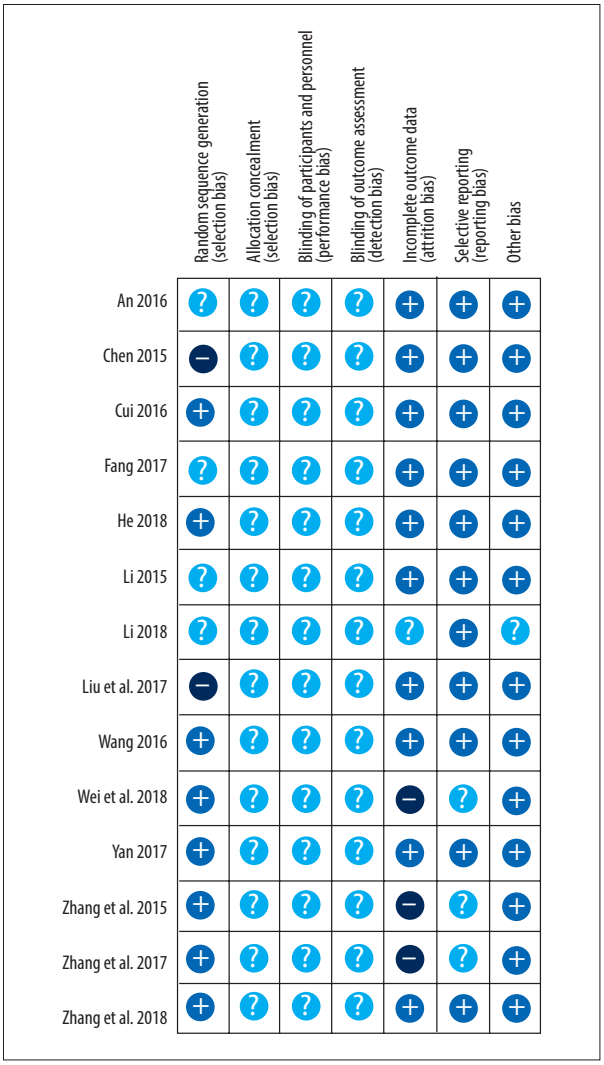

Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

In the forest plot, the confidence intervals of 2 studies [32, 40] did not overlap with the first subgroup (130 mg) of the 3 other studies, which was closely related to the duration of treatment (21 days) [32] and differences in gender and age [40]. Therefore, we also pooled other 3 studies (WMD=13.20, 95% CI 9.97 to 16.44, I^2=0%, P<0.00001).

MRS score

The MRS scores were assessed for 166 patients in 2 studies [36,42]. The heterogeneity test showed that there was good homogeneity between the studies (P=0.41, I^2=0%), and the fixed-effect model should be used. The meta-analysis demonstrated that SAFI plus CT has a better therapeutic effect on the reduction of MRS score compared with CT alone (WMD=–0.73, 95% CI –0.85 to –0.61, P<0.00001, Figure 7).

Improvement of cognitive function

MoCA score

MoCA scores were assessed for 252 patients in 3 studies [36,37,42], and the fixed-effects model should be used (P=0.80, I^2=0%). The meta-analysis of the 3 studies showed that SAFI plus CT has a better therapeutic effect on the improvement of MoCA score compared with CT alone (WMD=2.49, 95% CI 1.62 to 3.35, P<0.00001, Figure 8).

MMSE score

Three studies [36,37,42] with 252 patients assessed the MMSE score. The fixed-effects model was used (P=0.75, I^2=0%). The meta-analysis demonstrated that SAFI plus CT has a better therapeutic effect on the improvement of MMSE score

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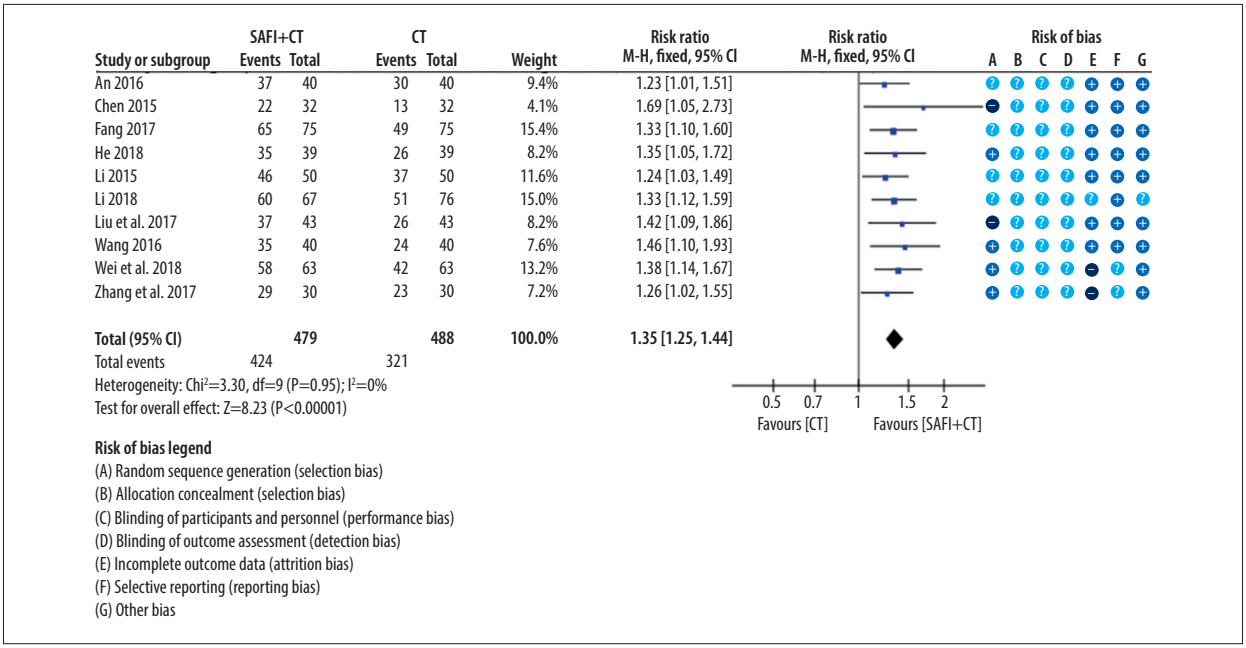

Figure 4. SAFI plus CT versus CT: total effective rate.

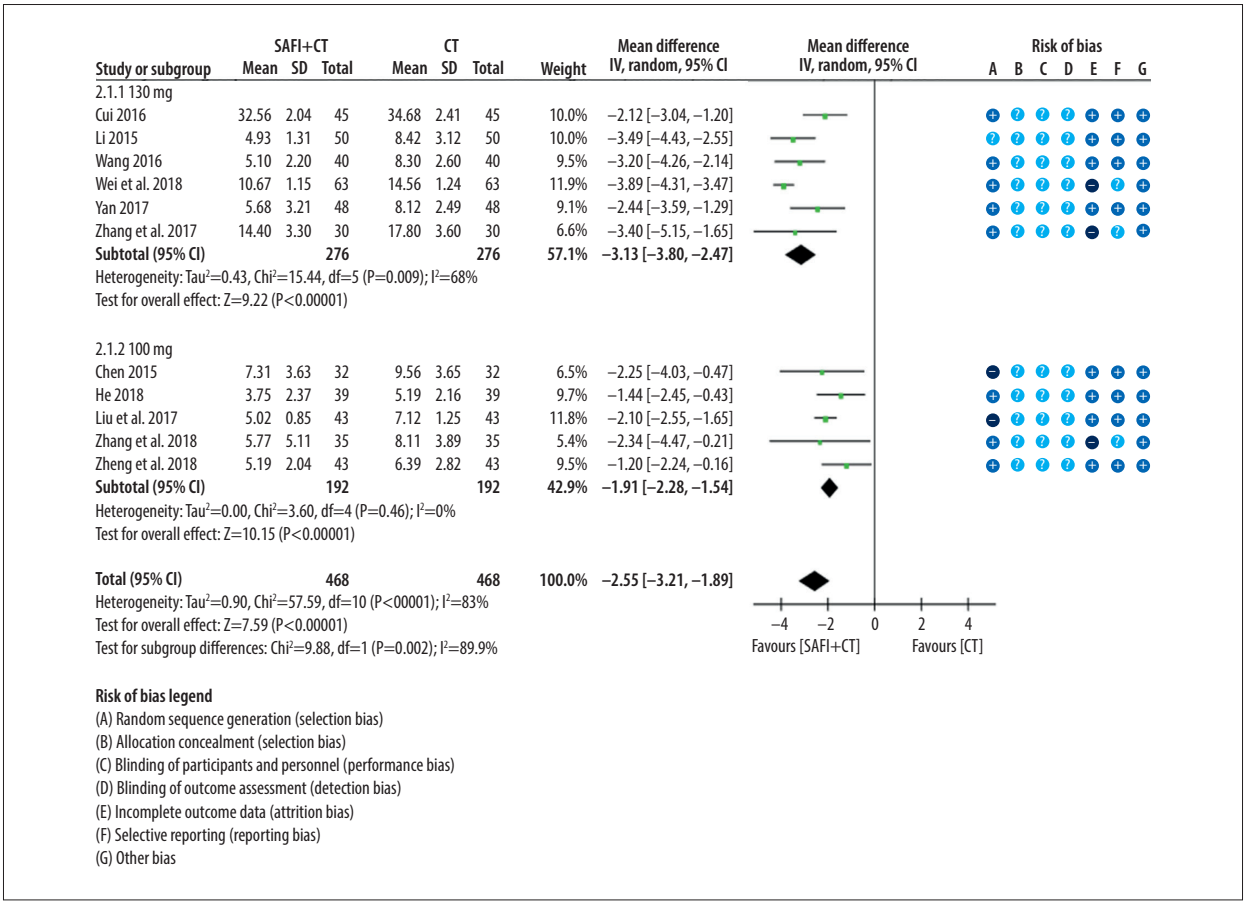

Figure 5. SAFI plus CT versus CT: reduction of NIHSS score.

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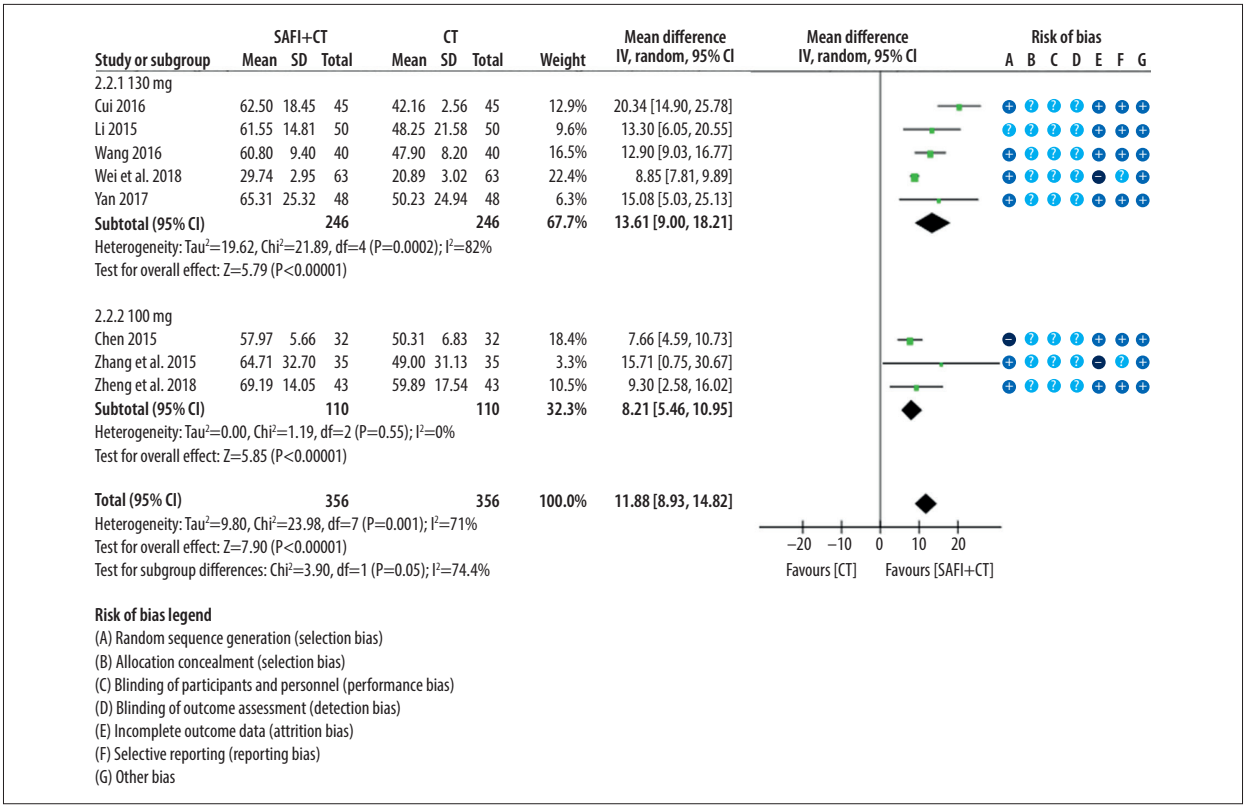

Figure 6. SAFI plus CT versus CT: improvement of BI.

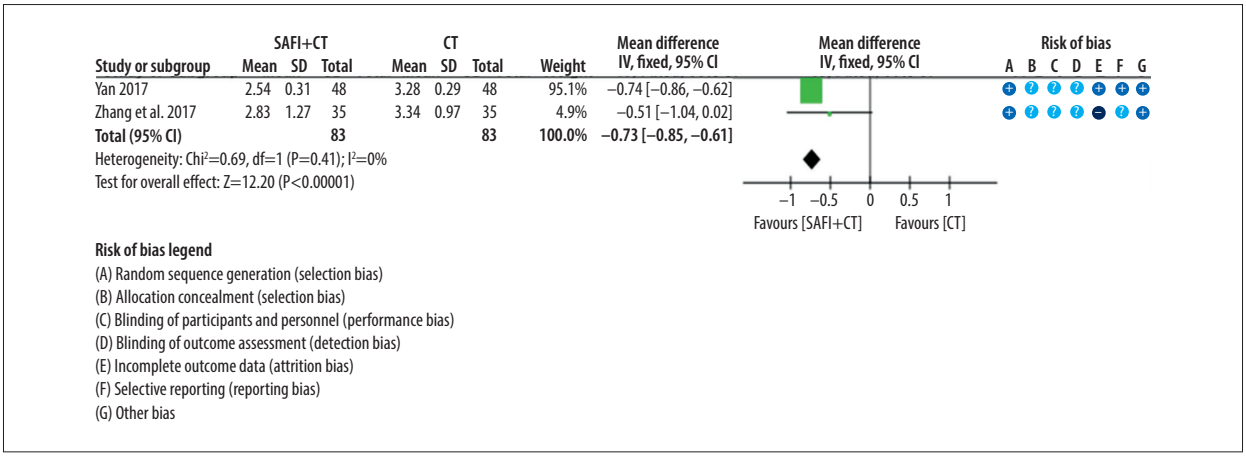

Figure 7. SAFI plus CT versus CT: reduction of MRS score.

compared with CT alone (WMD=2.46, 95% CI 1.66 to 3.26, *P*<0.00001, Figure 9).

Hemorheology

Hemorheology was assessed for 770 patients in 7 studies. The random-effects model was used to conduct subgroup analysis (HBV: *P*=0.07, I^2=70%; PV: *P*<0.00001, I^2=98%). Three studies [35,38,43] showed that SAFI plus CT has a better therapeutic effect on the improvement of LBV compared with CT alone (WMD=–1.85, 95% CI –2.15 to –1.54, *P*<0.00001, Figure 10). Two studies [38,43] showed that SAFI plus CT has a better therapeutic effect on the improvement of HBV compared with CT alone (WMD=–0.97, 95% CI –1.20 to –0.74, *P*<0.00001, Figure 10). Two studies [35,38] showed that SAFI plus CT has a better therapeutic effect on the improvement of PV compared with CT alone (WMD=–0.81, 95% CI –0.84 to –0.78, *P*<0.00001, Figure 10).

In the subgroup of HBV and PV, the heterogenicity between studies was obvious in each subgroup, and was closely related

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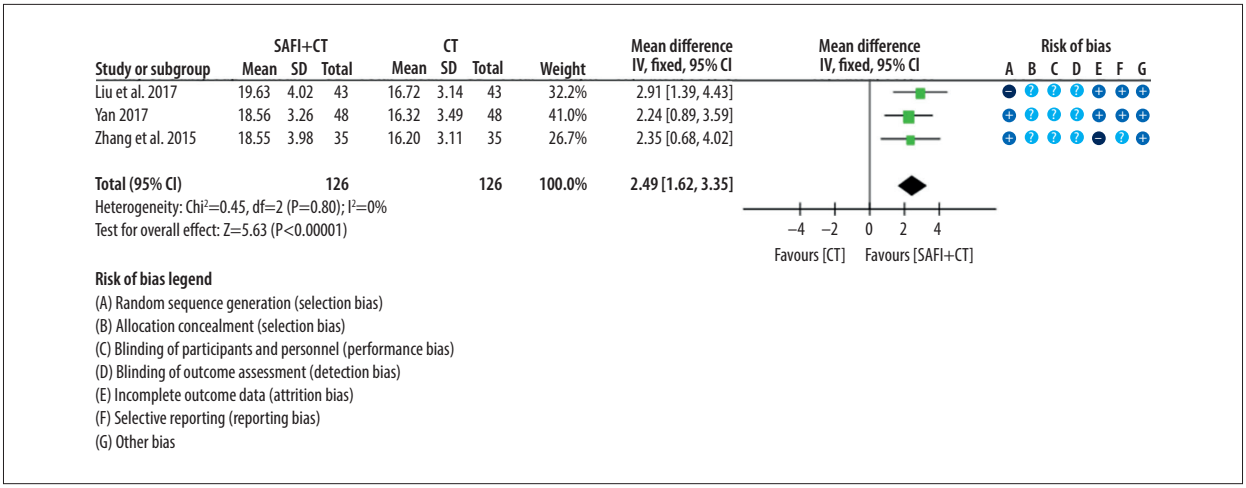

Figure 8. SAFI plus CT versus CT: improvement of MoCA score.

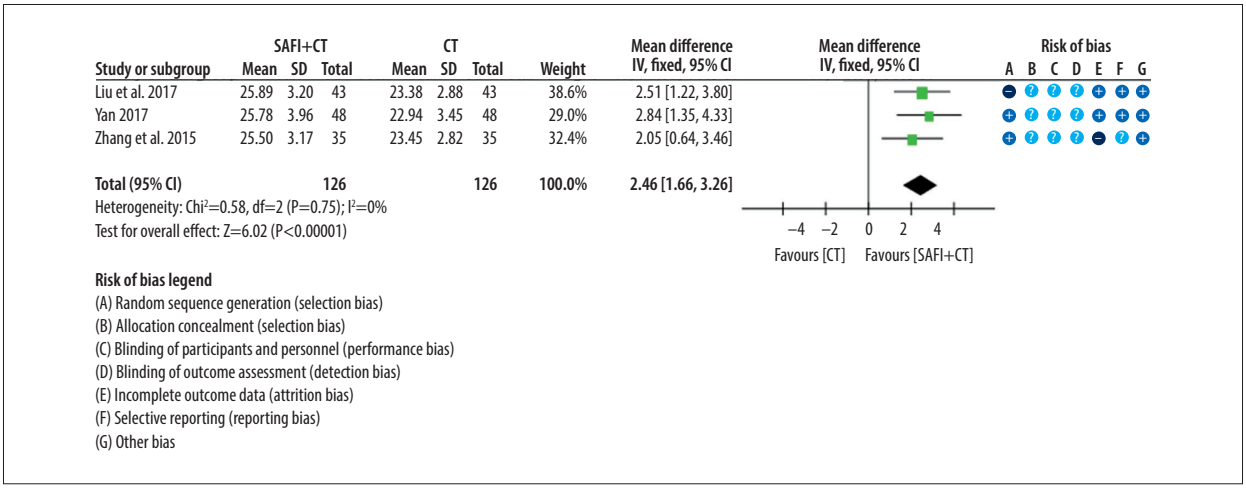

Figure 9. SAFI plus CT versus CT: improvement of MMSE score.

to the different doses between studies in each group (HBV: Fang 2017 100 mg, Li 2015 130 mg; PV: Fang 2017 100 mg, Zhang et al. 2017 130 mg).

CRP

Two studies [35,41] with 140 patients assessed the C-reactive protein. There was good homogeneity between the 2 studies (P=0.98, I^2=0%), and the fixed-effects model was used. The meta-analysis demonstrated that SAFI plus CT has a better therapeutic effect on the improvement of CRP compared with CT alone (WMD=–1.44, 95% CI –1.88 to –0.99, P<0.00001, Figure 11).

Adverse drug events/reactions

Eleven studies observed ADEs/ADRs, and 4 studies reported no ADEs/ADRs. One study [35] reported 3 cases of liver function damage and 1 case of hyperuricemia in the treatment group. One study [36] reported 2 cases of mild adverse reactions in the treatment group. One study [37] reported 1 case of nosebleed and 1 case of itchy skin in the treatment group and 1 case of vomiting and diarrhea in the control group. One study [38] reported blood routine, urine routine abnormality, liver and kidney function damage, heart rate anomaly, and dysarteriotony in 2 groups, but the difference was not statistically significant (P>0.05). One study [42] reported 1 case of upper gastrointestinal bleeding, 3 cases of liver function damage, and 1 case of hyperuricemia in the treatment group. One study [43] reported 1 case of nosebleed and 1 case of itchy skin in the treatment group. One study [44] reported 1 case of ALT rise and 1 case of chest distress and palpitation in the treatment group, and 1 case of mild AST rise in the control group.

Adverse reactions in both groups in all studies were minor or tolerable, and were relieved by symptomatic treatment or disappeared after drug withdrawal, or resolved without additional intervention.

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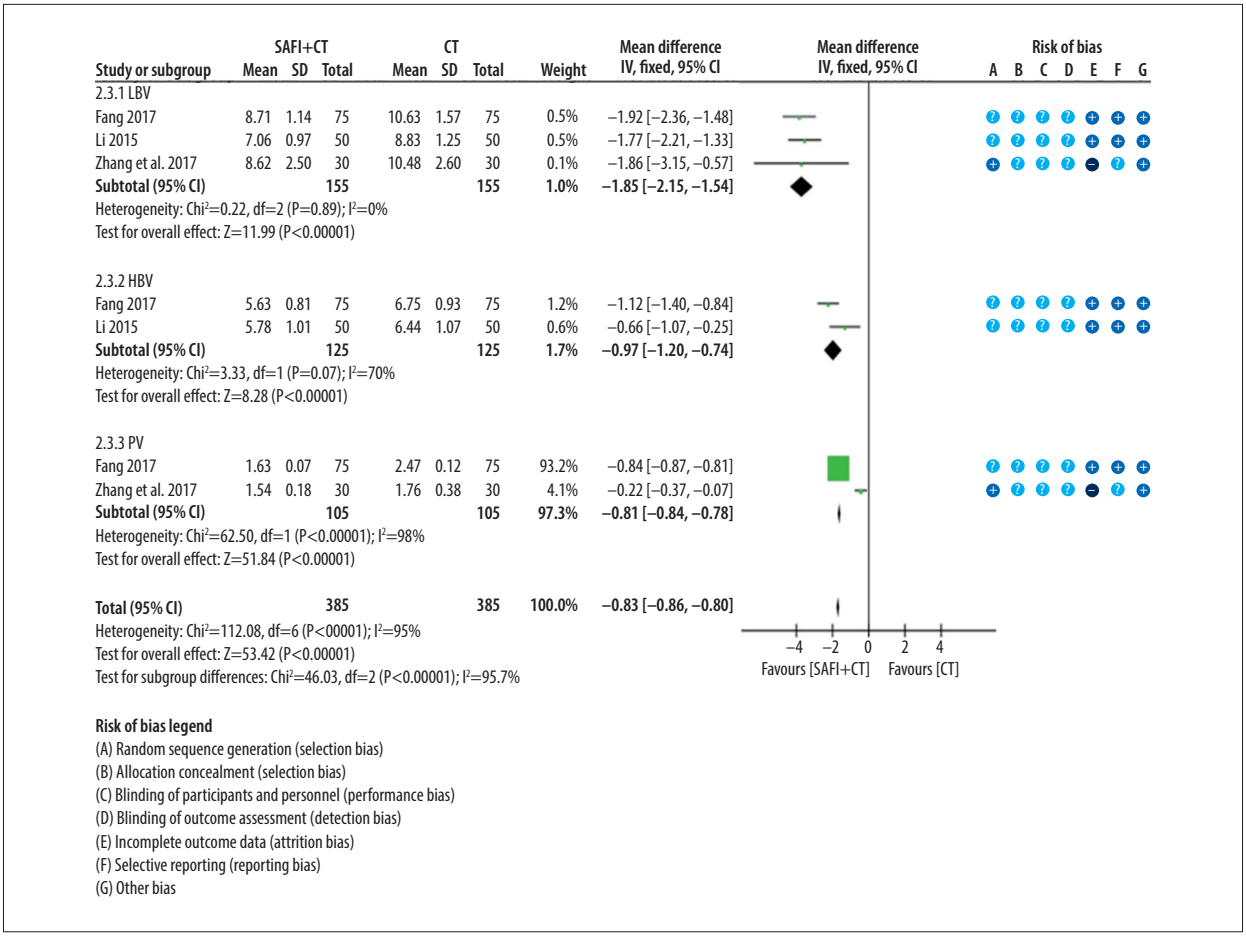

Figure 10. SAFI plus CT versus CT: improvement of Hemorheology.

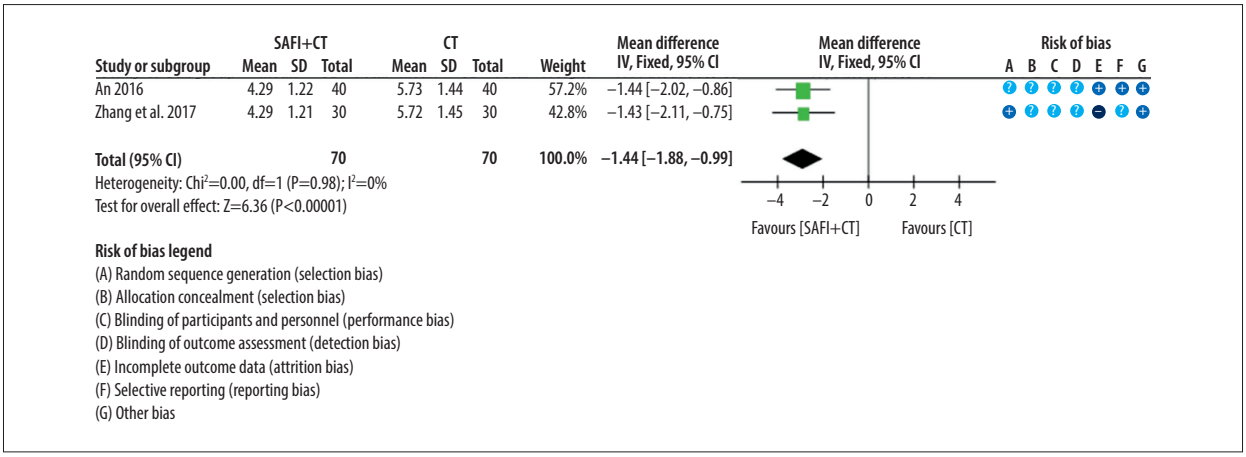

Figure 11. SAFI plus CT versus CT: improvement of CRP.

Publication bias

The funnel plot was asymmetric when pooling 10 trials on the total effective rate (Figure 12) and 11 trials on improvement of NIHSS score (Figure 13). The potential publication bias might have been due to the high proportion of published positive results in China. All studies included were in Chinese language, which might have contributed to linguistic publication bias.

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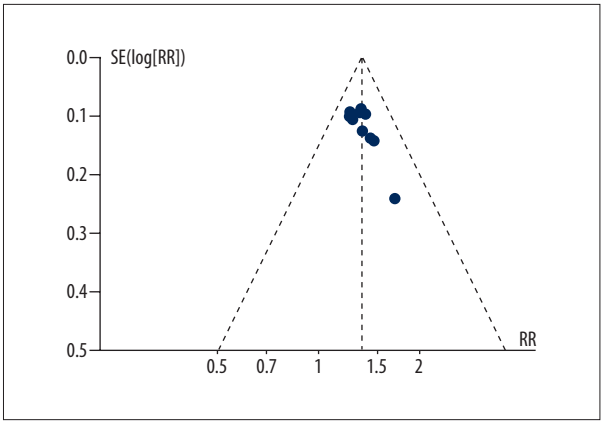

Figure 12. Funnel plot of publication bias according to the total effective rate.

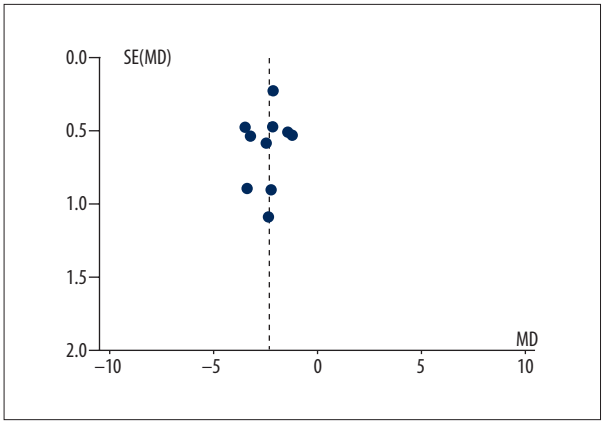

Figure 13. Funnel plot of publication bias according to improvement of NIHSS score.

Table 3. GRADE evidence profile:SAFI+CT for ACI.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SAFI+CT	CT	Relative (95% CI)	Absolute		
Total effective rate (follow-up mean 14 days)												
10	Randomised trials	Serious 1),2)	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias 4)	424/479 (88.5%)	321/488 (65.8%)	RR 1.35 (1.25 to 1.44)	230 more per 1000 (from 164 more to 289 more)	⊕⊕OO Low	Critical
								66.7%		233 more per 1000 (from 167 more to 293 more)		
NIHSS –130 mg (follow-up mean 14 days; Better indicated by lower values)												
6	randomised trials	Serious 1),2),3)	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias 4)	276	276	–	MD 3.13 lower (3.8 to 2.47 lower)	⊕OOO Very low	Important
NIHSS –100 mg (follow-up mean 14 days; Better indicated by lower values)												
5	randomised trials	Serious 1),2)	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias 4)	192	192	–	MD 1.91 lower (2.28 to 1.54 lower)	⊕⊕OO Low	Important
Barthel index –130 mg (follow-up mean 14 days; Better indicated by lower values)												
5	randomised trials	Serious 1),2)	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias 4)	246	246	–	MD 13.61 higher (9 to 18.21 higher)	⊕⊕OO Low	Important
Barthel index –100 mg (follow-up mean 14 days; Better indicated by lower values)												
3	randomised trials	Serious 1),2)	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias 4)	110	110	–	MD 8.21 higher (5.46 to 10.95 higher)	⊕⊕OO Low	Important

GRADE – Working Group grades of evidence; High quality – further research is very unlikely to change our confidence in the estimate of effect; Moderate quality – further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality – further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality – we are very uncertain about the estimate; CI – confidence interval; RR – risk ratio; MD – mean difference. 1) Lack of allocation concealment; 2) lack of blinding; 3) incomplete accounting of patients and outcome events; 4) evaluation of the data suggested publication bias, and there may be the equivalent number of 'negative' trials that have not been included in this analysis.

Summary of evidence quality in GRADE

The evidence quality of total effective rate was low because of the lack of allocation concealment and blinding and publication bias. The evidence quality of NIHSS score (130 mg) was very low because of the lack of allocation concealment and blinding, incomplete accounting of patients and outcome events, and publication bias. The evidence quality of NIHSS score (100 mg) and Barthel index (130 mg/100 mg) was low because of the lack of allocation concealment and blinding and publication bias. The GRADE evidence profiles are shown in Table 3.

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Discussion

Summary of therapy effectiveness

This study performed systematic evaluation of the efficacy of SAFI plus CT in the treatment of ACI. The results of our meta-analysis show that under the same standard of curative effect, the curative effect of SAFI plus CT for ACI was better than CT alone. It can effectively improve the total effective rate of NIHSS score, improve the neurological impairment and degree of disability, improve the ability to perform activities of daily living and cognitive function, improve the LBV, HBV, and PV in hemorheology, and also had a good therapeutic effect on C-reactive protein. The Guidelines for the Diagnosis and Treatment of Cerebral Infarction in China (2017) [6], formulated by the Professional Committee of Neurology of the Chinese Society of Integrated traditional Chinese and Western Medicine, recommended SAFI for the treatment of ACI. The results of the present study confirmed that SAFI plus CT has a good therapeutic effect on ACI, in accordance with the recommendations of the 2017guidelines.

ACI is caused by atherosclerosis and thrombosis of the arteries supplying blood to the brain, which makes the luminal tube narrow and even occluded, resulting in acute cerebral insufficiency of blood supply [45]. SAFI is a water-soluble salvianolic acids compound extracted from the plant *Salvia miltiorrhiza*, in which the content of salvianolic acid B (Sal B) is the highest [46,47]. Its mechanisms of action include [48]: improving energy metabolism, reducing brain edema, antioxidation, inhibiting lipid peroxidation, inhibiting inflammatory reaction, affecting gene expression, anti-apoptosis, and promoting vascular and neural regeneration.

Summary of therapy safety

Among the included studies, 11 studies reported ADEs/ADRs, and 4 studies reported no adverse reactions in the 2 groups. Seven studies reported nosebleed, pruritus, vomiting and diarrhea, abnormal routine blood test, function of liver and kidney injury, upper gastrointestinal bleeding, and chest tightness. These symptoms were tolerable, disappeared after withdrawal, or disappeared by later follow-up, and there were no serious adverse reactions in the 2 groups. However, due to the combined use of drugs, the research information is incomplete, the quality of methodology is not high, and its safety needs to be further studied and clarified. Our study suggests value of clinical use of SAFI with standardized monitoring and standardized records, and combined use of drugs should be avoided to reduce the risk of adverse drug reactions.

Evidence quality

After performing the systematic review, the GRADE system was used to evaluate the evidence quality of the 3 key outcome measures: total effective rate, NIHSS score, and Barthel index. In terms of total effective rate, NIHSS score, and Barthel index, the experimental group did significantly better than the control group. However, there was lack of data on allocation concealment and blinding, as well as incomplete accounting of patients and outcome events, and evaluation of the data suggested publication bias. In addition, there may be an equivalent number of "negative" trials that were not included in this analysis. Thus, the evidence quality of the total effective rate, NIHSS score (130 mg), NIHSS score (100 mg), Barthel index (130 mg), and Barthel index (100 mg) were low, very low, low, and low, respectively. The recommendations for total effective rate, NIHSS score, and Barthel index should be considered further in the absence of high-quality evidence, and uncertain or different values and preferences, and it is unclear if the net benefits are worth the costs. These evidence quality results of the key outcome indicators provide a reference basis for guiding clinical practice.

Limitations

The quality of the included studies was not high: (a) Only 8 studies provided methods of randomized, while in the other 6 studies it was impossible to know whether random and blind methods were actually achieved; (b) None of these studies used distributive concealment and all were prone to selection bias, implementation bias, measurement bias, and other issues; (c) None of the included studies reported the protocol or sample size estimation, and only 3 studies reported details of follow-up; (d) Only 4 studies had sample sizes of more than 100 cases, and the minimum sample size was 60 cases; (e) In some studies, because the sample size was too small, the curative effect index was not stable, and the power of test was low; (f) According to the non-symmetrical distribution of the funnel graph, there was publication bias, which indicates that the researchers had a subjection bias, thus overstating the effect of the treatment group on the ACI. The present study suggests that large-scale, low-bias randomized controlled trials should first apply the CONSORT criteria.

There are differences in the specific contents of conventional treatment mentioned in the included studies, which resulted in heterogeneity and affected the results of the study. There were differences in curative effect standard in a few studies, and this may have affected our results. With the exception of 21 days for 1 study and 14 days for another study, most of the studies did not have long-term follow-up, and the long-term efficacy could not be evaluated.

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Implications and future directions

This meta-analysis shows that SAFI plus CT may have positive effects on improving the neurological impairment and degree of disability, as well as improving cognitive function and the ability to perform activities of daily living. The results of this study suggest that we should consider adding SAFI on the basis of CT in the treatment of ACI in clinical practice, which has a synergistic effect. However, the results need to be confirmed further because of the low methodological quality of the studies we analyzed.

The following aspects should be considered in high-quality clinical research: (a) Complete and transparent reporting in quality and methodology should adhere to internationally recognized standards; (b) Clinical trials should be registered on an international platform to make the protocol available; (c) Mortality, disability, recurrence, and quality of life from long-term follow-up should be reported; and (d) Outcome measures should be assessed in accordance with international criteria.

Conclusions

The available data and methods show that SAFI plus CT in the treatment of ACI can improve the total effective rate, neurological deficit, and ability to perform activities of daily living, and there were no serious adverse reactions reported. Based on the GRADE system, the evidence quality is low. More large-scale, well-designed, and high-quality RCTs are required to confirm the present results. Long-term follow-up is needed to evaluate the long-term efficacy and safety of SAFI plus CT for ACI.

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Data sharing statement

Extracted data are available from the corresponding author upon request.

Conflict of interests

None.

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