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Protocol

12 kinds of Chinese medicine injections for acute cerebral infarction: Protocol for a systematic review and network meta-analysis

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ABSTRACT

Introduction: Chinese medicine injections (CMIs) are widely used in the treatment of acute cerebral infarction (ACI) in mainland China. Up to 20 different kinds of CMIs are reportedly often used for treating cerebral infarction, however, there are very few head-to-head comparative trials to determine the relative efficacy between different CMIs. Due to the fact that various CMIs are used in clinic, it is difficult for clinicians to choose the optimal CMIs for patients with ACI. We will conduct a network meta-analysis (NMA) to compare the efficacy of 12 kinds of different CMIs, including direct and indirect comparisons between CMIs. It is hoped that this NMA could provide the best currently available evidence base to guide the choice regarding CMIs treatment for patients with ACI.

Methods: A systematic and comprehensive literature search will be performed from inception to August 2018 in both English and Chinese databases, involving Medline, Cochrane Library, Embase, China National Knowledge Infrastructure Database, Wanfang Database, Chongqing VIP information, and SinoMed. Randomized controlled trials related to CMIs in the treatment of ACI will be included. Quality of included trials will be assessed according to the risk of bias tool of Cochrane Handbook 5.1.0. The GRADE approach will be used to rate the certainty of evidence of estimates derived from NMA. Data analysis will be conducted by using STATA 13.1.

Results: This systematic review and NMA aims to summarise the direct and indirect evidence for 12 kinds of different CMIs and to rank these CMIs. The findings of this NMA will be reported according to PRISMA-NMA statement.The results of the NMA will be submitted to a peer-reviewed journal once completed.

Conclusion: Using NMA, this study will provide an evidence profile which will be helpful to inform the selection of CMIs for treating patients with ACI. The results will inform clinicians, bridge the evidence gaps, and identify promising CMIs for future trials.

1. Introduction

Cerebral infarction is an area of necrosis in the cerebrum caused by an insufficiency of arterial or venous blood flow according to the definition of Mesh Terms of Pubmed (https://www.ncbi.nlm.nih.gov/pubmed). Acute cerebral infarction is a clinical classification of cerebral infarction. The acute phase of ACI generally occurs 2 weeks after the onset of disease [1]. As one of the major public health problems and the third costliest health condition in developed countries, ACI has a high disability, mortality and recurrence rate and usually leads to serious damage of central nervous system [2]. One study reported that the brain loses 1.9 million neurons, 14 billion synapses, and 7.5 miles of myelinated nerve fibres every minute in a typical acute ischemic stroke [3]. According to the top 10 causes of death reported by World Health Organisation (WHO), ischaemic heart disease and stroke are the world's biggest killers, and have remained the leading causes of death globally in the last 15 years (http://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death). In China, cerebrovascular disease is the second leading cause of death (http://www.docin.com/p-6587220.html). Besides, ACI has a sudden onset and can develop rapidly. Early detection and rapid treatment are recommended in treating ACI. It is particularly important to quickly select appropriate and optimal treatments among various therapies for patients with ACI.

Currently, conventional treatment recommended by clinical practice guideline mainly includes thrombolytics, antithrombotics and anticoagulants [4]. Although these medications can give the necessary

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Table 1
Basic information on the 12 kinds of CMIs to be included.

Number	Generic name	Chemical composition	Botanical/Animal name
1	Shuxuening injection	ginkgo biloba leaves are extracted from a sterile aqueous solution, excipients are sorbitol, 95% ethanol, methyl sulfide	ginkgo biloba extract
2	Xiangdan injection	salvia, fragrant, excipient is polysorbate 80	salvia miltiorrhiza bunge, dalbergia odorifera
3	Shuxuetong injection	hirudo, pheretima	hirudo nipponica whitman, pheretima aspergillum
4	Kudiezi injection	ixeris sonchifolia	ixeris sonchifolia
5	Xuesaitong injection	panax notoginsenosides, excipient is sodium chloride	panax notoginseng extract
6	Xueshuantong injection	panax notoginsenosides, excipient is sodium chloride and sodium citrate	panax notoginseng extract
7	Dengzhanhuasu injection	breviscapine, excipient is ethylenediamine tetraacetic acid disodium	erigeron breviscapus
8	Danhong injection	salvia miltiorrhiza, safflower, water for injection	salvia miltiorrhiza bunge, carthamus tinctorius
9	Dengzhanxixin injection	wild baicalin ($C_{21}H_{18}O_{12}$) and total caffeate; excipients: sodium chloride	erigeron breviscapus extract
10	Danshen injection	salvia miltiorrhiza	salvia miltiorrhiza bunge
11	Mailuoning injection	honeysuckle, achyranthes, dendrobium, scrophularia and excipient is polysorbate 80	lonicera japonica, achyranthes bidentata blume, dendrobium nobile, scrophularia ningpoensis hemsl
12	Xingnaojing injection	artificial musk, gardenia, turmeric, borneol and accessories for poly yamanashi ester 80, sodium chloride	moschus,gardenia jasminoides ellis, curcumakwangsiensis

first line treatment for patients with ACI, side effects and drug resistance have been found with their use in practice. Thus, CMIs are increasingly widely used as a complementary therapeutic approach for patients with ACI in China due to their remarkable effectiveness, rapid action, and high bioavailability [5]. According to Traditional Chinese Medicine (TCM) theory, cerebral infarction pertains to *apoplexy*, primarily due to blood stasis syndrome. The therapeutic principle of TCM is promoting blood circulation to remove blood stasis [6]. At present, it is reported that up to 20 kinds of CMIs are commonly used in the treatment of cerebral infarction by invigorating blood circulation [7]. These kinds of CMIs can dilate blood vessels, improve blood circulation and increase blood flow to the brain arteries. Since various CMIs are used in clinic, it poses a challenge for clinicians to choose the optimal CMIs for patients with ACI.

There are many randomised controlled trials (RCTs) and systematic reviews that have evaluated the efficacy of various CMIs for ACI. However, most of these studies were designed in comparison with conventional western medicine. There are rarely studies to compare different CMIs head to head. Therefore, there remains uncertainty regarding the comparative efficacy among different CMIs. Thus, we plan to conduct a systematic review and network meta-analysis to compare the efficacy among 12 different CMIs and rank their benefits relative to each other. It is hoped that the findings of this study will facilitate the management and application of CMIs in the treatment of ACI.

2. Methods

2.1. Study registering and reporting

The study protocol has been registered on PROSPERO (International Prospective Register of Systematic Reviews) (CRD42018109188). This protocol is developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) [8]. Any protocol modifications made during the performing of the review will be recorded in the publication of the final report. The PRISMA Extension Statement is used to ensure all aspects of methods and findings are reported [9].

2.2. Eligibility criteria

The PICOS (Population-Intervention-Comparators-Outcomes-Study design) framework was adopted as the eligibility criteria for the review as following.

2.2.1. Study design

Regardless of whether blinding is used or not, randomized controlled trials (RCTs) related to CMIs in the treatment of ACI will be included for analysis. Duplicate studies with insufficient information to compute effect estimates will be excluded. No language or other restrictions will be applied.

2.2.2. Population

RCTs with a definite diagnosis of ACI will be taken into consideration. Most studies published in China will have adopted the standards revised by the Fourth National Conference on Cerebrovascular Disease by the Chinese Medical Association in 1995 [10]. The acute phase of ACI generally refers to 2 weeks after the onset of disease. There will be no limits on age, gender, race or nationality.

2.2.3. Interventions/comparators

In our preliminary analysis of the relevant literature on the treatment of acute cerebral infarction we found that 12 kinds of CMIs were the most commonly used to treat acute cerebral infarction to promote blood circulation and remove blood stasis. All of these 12 kinds of CMIs can dilate blood vessels, improve blood circulation and increase blood flow to the brain arteries. The basic information on the 12 kinds of CMIs is listed in Table 1. To facilitate data analysis, conventional treatment has been defined as thrombolytic therapy, anticoagulant therapy and antiplatelet aggregation therapy [5]. Furthermore, some symptomatic supportive treatments, such as control of blood pressure and adjustment of blood lipids will also be included. Eligible comparisons are as follows: a. CMI a + conventional treatment versus CMI b + conventional treatment; b. CMI + conventional treatment versus conventional treatment. Considering that western medicines are updated quickly some of which are withdrawn from the market, studies of CMIs combined with a specific non-commonly used western medicine will be excluded. There will be no limitations on drug dosages or treatment courses.

2.3. Outcome measures

By reviewing clinical trials of ACI published in academic journals, we found that outcomes reported regularly are: imaging surrogate markers, initial stroke severity, functional outcome, and short-term mortality in human AIS [11]. However, in Chinese studies, the markedly effective rate which depends predominantly on the change of neurological deficit score is most used [10]. Thus we adopted the following standard for defining outcomes in advance. The primary outcome of interest will include: mortality and the rate of cerebrovascular event including a recurrence event. The secondary outcome of interest will include National Institutes of Health Stroke Scale (NIHSS) and adverse drug event.

2.4. Data sources and search strategy

The literature search will be conducted in three English databases (Medline, Cochrane Library and Embase) and four Chinese databases (China National Knowledge Infrastructure Database, Wanfang Database, Chongqing VIP information and Sinomed) from inception to August 2018. A separate search for systematic reviews will be performed to compare the included studies from existing reviews against those retrieved from the current RCT searching. We will also undertake a targeted gray literature search on Clinical Trials.gov and the International Clinical Trials Registry Platform search portal to identify in-progress and completed trials. In addition, the search will include: Google Scholar, CINHAL, Web of Science, and Baidu Scholar to identify trial protocols and other information. Further studies will be identified by examining the reference lists of all included studies.

Search strategy of Medline is as follows:

#1 Search ("Cerebral Infarction"[Mesh]) OR (("Cerebral Infarctions" or "Infarctions, Cerebral" or "Infarction, Cerebral" or "Cerebral Infarction, Left Hemisphere" or "Left Hemisphere, Infarction, Cerebral" or "Infarction, Left Hemisphere, Cerebral" or "Left Hemisphere, Cerebral Infarction" or "Cerebral, Left Hemisphere, Infarction" or "Infarction, Cerebral, Left Hemisphere" or "Subcortical Infarction" or "Infarction, Subcortical" or "Infarctions, Subcortical" or "Subcortical Infarctions" or "Posterior Choroidal Artery Infarction" or "Anterior Choroidal Artery Infarction" or "Cerebral Infarction, Right Hemisphere" or "Infarction, Right Hemisphere, Cerebral" or "Infarction, Cerebral, Right Hemisphere" or "Cerebral, Right Hemisphere, Infarction" or "Right Hemisphere, Infarction, Cerebral" or "Right Hemisphere, Cerebral Infarction"))

#2 Search ("Medicine, Chinese Traditional"[Mesh]) OR (("Traditional Chinese Medicine" or "Chung I Hsueh" or "Hsueh, Chung I" or "Traditional Medicine, Chinese" or "Zhong Yi Xue" or "Chinese Traditional Medicine" or "Chinese Medicine, Traditional" or " Chinese patent medicine" or "Chinese patent drug" or "proprietary Chinese medicine" or "proprietary Chinese drug" or "Chinese heral injection" or "Chinese medicine injection"))

#3 Search ("Injections"[Mesh]) OR (("Injection" or "Injectables" or "Injectable"))

#4 #2 AND #3

#5 Search (("Shuxuening injecton " or " Xiangdan injection " or " Danshen injection " or " Mailuoning injection " or " Shuxuetong injection " or " Kudiezi injection " or " Xuesaitong injection " or " Xueshuantong injection " or " Danhong injection " or " Xingnaojing injection " or " Dengzhanhuasu injection " or " Dengzhanxixin injection "))

#6 #4 OR #5

#7 #1 AND #6

2.5. Study selection and data extraction

Records downloaded from seven databases will be managed by NoteExpress software (V3.2.0.7253). Two researchers will independently screen the included studies, extract data, evaluate quality of included studies and cross-check with each other according to the established selection criteria. Disagreements will be resolved by discussion or consultation with a third author (XL or NR). First, preliminary screening will be performed by reading the title and abstract of the obtained literature. Studies that fail to meet the eligibility criteria will be excluded. Then full text of the articles will be retrieved to further determine whether they are included. The screening process will be presented with reference to the PRISMA statement as Fig. 1. Microsoft Excel 2010 will be used to extract data and collect relevant information. The extracted information will be classified into five parts: a. publication information: first author, publication year, journal and publication country ; b. general characteristics of patients: disease, sample size, gender, age, eligibility criteria, baseline information and numbers of dropouts; c. details of intervention and control therapy: drugs, dosages, treatment course, follow up; d. details of outcomes: mortality, the rate of cerebrovascular events including recurrence event, National Institutes of Health Stroke Scale (NIHSS), adverse drug events, and bias risk assessment information.

2.6. Quality assessment

The Risk of Bias Tool (ROB) in Cochrane Handbook 5.1.0 [12] will be used to assess the methodological quality of included studies by two independent reviewer (DDY and RZC). Disagreements will be resolved by discussion with a third reviewer (XL or NR). Seven items are included in the Cochrane collaboration's risk of bias tool: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. Judgment of each item is divided into three levels: low risk of bias, high risk of bias and unclear risk of bias.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system will be used to assess the certainty of evidence contributing to network estimates of the primary outcome [13]. Based on five key domains (risk of bias, indirectness, inconsistency, imprecision and publication bias), the quality of evidence will be classified in one of four levels: high, moderate, low and very low.

2.7. Statistical analysis

2.7.1. Pairwise meta-analysis

The conventional pairwise meta-analysis will be performed by using STATA 13.1 software. The pooled odds ratios (ORs) with 95% confidence interval(95%CI) will be calculated for dichotomous data(mortality, the rate of cerebrovascular event including recurrence event and adverse drug event). Mean difference (MD) or standardised mean difference (SMD) with 95% confidence interval(95%CI) will be calculated for continuous data(NIHSS). The χ^2 test and I^2 test will be conducted to detect the potential heterogeneity across the included studies. If $I^2 < 50\%$ and $P > 0.1$, it suggests that heterogeneity is not important and the Mantel–Haenszel fixed model will be employed for meta-analysis. If $I^2 \geq 50\%$ and $P \leq 0.1$, it manifests that heterogeneity needs to be analyzed. Heterogeneity is divided into three types—statistical heterogeneity, clinical heterogeneity and methodological heterogeneity [12]. The random-effects model will be used for statistical heterogeneity. Subgroup analysis or meta-regression will be conducted if clinical and methodological heterogeneity exists. In addition, if the source of heterogeneity is unknown, we will give up synthetic analysis and adopt descriptive analysis instead. Sensitivity analysis will be employed for the robustness of results of the included studies. Funnel plot will be used to detect publication bias in trials included in the current NMA if the number of studies is not less than 10. Egger's test for detecting asymmetry in a funnel plot will be performed mathematically [14,15].

2.7.2. Network meta-analysis

The network meta-analysis will be conducted using the network command in STATA [16–19]. To rank probabilities of treatments, surface under the cumulative ranking (SUCRA) will be used to summarize the probability values. A SUCRA value of 100% is assigned to the best treatment and 0% for the worst treatment [20]. We will employ the inconsistency factor (IF) to evaluate heterogeneity among the included studies if a closed loop exists. If the 95% CIs of the IF values are truncated at zero, it indicates that direct and indirect evidences are in agreement [20]. A comparison-adjusted funnel plot will be conducted to assess the presence of small-study effect [21]. All analyses will be performed using STATA software version 13.1.

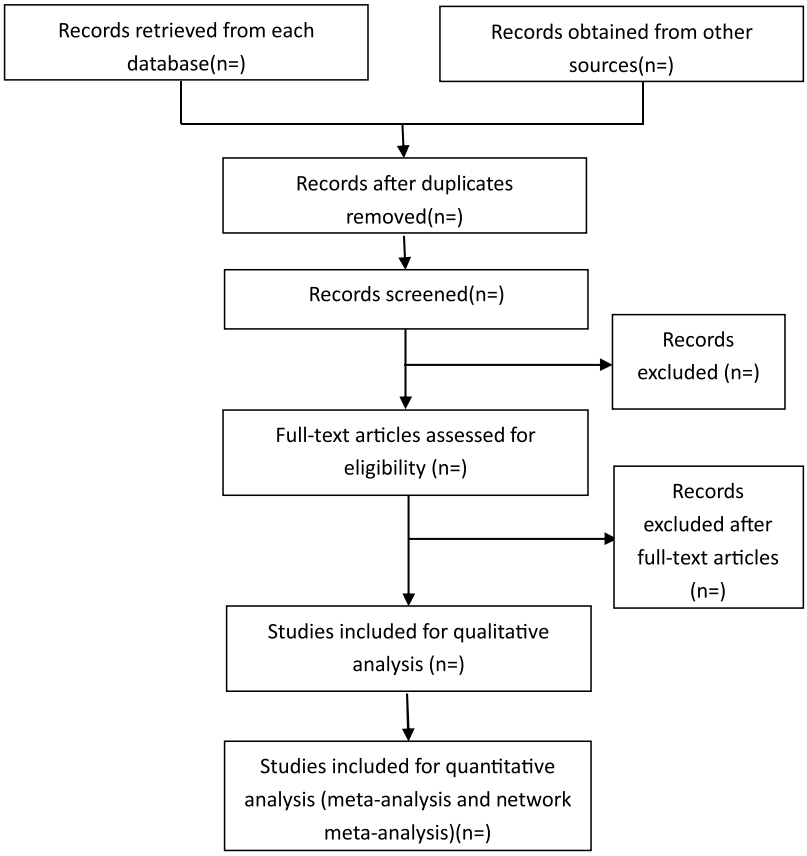

Fig. 1. Flow chart of searching and screening studies.

2.8. Patient and public involvement

This part is not covered in this study.

3. Discussion

Chinese herbal injections (CHIs) are prepared by extracting and purifying effective substances from herbs (or decoction pieces) using modern scientific techniques and methods. Chinese medicine injections (CMIs) have a wider range of sources. They can not only be made from plants or herbs, but also from animals. The latter is less common. One of the 12 CHIs in the current systematic review and network meta analysis includes animal extracts. During the process of retrieving literature, two NMAs about Chinese herbal injections(CHIs) for cerebral infarction were detected [22,23]. To demonstrate the differences, we made a comparison between the current NMA and the other 2 NMAs. The details of the comparison can be seen in Table 2.

From the comparison shown in Table 2, the current NMA will update literature searching and focus on two different kinds of interventions treating ACI. With GRADE evaluation, the certainty of evidence in the main results of the current NMA will be incorporated to highlight the most robust findings for further use.

Despite availability of randomized controlled trials and systematic reviews about CMIs treatment for ACI, it is still a challenge for clinicians to choose the optimal CMIs when it comes to the management of ACI. Because head-to-head comparisons between CMIs for ACI is insufficient. The emerging network meta-analysis can compare multiple interventions simultaneously and analyze studies by making different comparisons in the same analysis. NMA has been applied in evaluating CHIs for cerebral infarction, just like the two NMAs obave [22,23]. However, the literature retrieval time for both studies was until June of 2016. Moreover, both studies included chemical drugs which are extracts from traditional Chinese medicine ingredients, such as salviae miltiorrhizae, ligustrazine hydrochloride injection, ginkgo leaf extract and dipyridamole injection, etc. These injections are classified as chemical drugs by China Food and Drug Administration (CFDA). Thus they are not part of CHIs. Neither of them performed the GRADE evaluating to report the certainty of the evidence. For the above reason, we will update literature search strategy and make adjustments based on the two NMAs. A comprehensive comparative appraisal of the efficacy of CMIs used in the management of ACI will be performed. We believe that our network meta-analysis will provide a comprehensive evidence profile to facilitate the application of CMIs in the treatment of ACI. The results of our NMA will reflect the relative efficacy of different CMIs for treating ACI in clinic.

Three issues will need specific attention in this study. Firstly, we have found that randomization was not designed rigorously in most studies published in Chinese journals based on our experience. Predictably, most of the randomized controlled trials included in this study will be rated as low level quality. Secondly, this study is based on literature analysis, which is not a direct head to head comparative study. The relative efficacy between CMIs will be estimated from a common comparator indirectly using a network meta-analysis. The presence of heterogeneity is an inherent problem in meta-analysis, which would affect the estimate. It results from the diversity in clinical and methodological characteristics, and variations between studies. Thirdly, as an emerging statistical method, some limitations remain in the use of NMA. A good NMA depends on three conditions—network connectivity, similarity of trials with respect to study design and populations, and network consistency. It is imperative that these conditions be assessed and appropriate adjustments be made when conditions are not met, such as meta-regression. Thus, we cannot guarantee that the relative efficacy of the difference among CMIs is the true value as it is in practice. Consequently, further head to head comparisons are

Table 2
Comparison of basic information between the current NMA and the other 2 NMAs.

Study	Database	Retrieval time	Disease	Intervention VS control	Outcome	GRADE evaluation
Liu S2018 [19]	PubMed, Cochrane Library, Embase, CNKI, Wanfang Database, CBM	Inception to June 2016	acute cerebral infarction (ACI)	1.CHIs① + AADN regimen VS AADN regimen 2. CHI a + AADN regimen VS CHI b + AADN regimen	1.the markedly effective rate 2.improvement of neurological impairment 3.activities of daily living function 4.death from all causes within the treatment and during the follow-up	no
Xiang Y2017 [20]	PubMed, Cochrane Library, Embase, CNKI, Wanfang Database, CBM, Chongqing VIP	Inception to June 2016	Stroke	1.CMIs② + conventional treatment VS conventional treatment 2. CMIs + conventional treatment VS placebo 3.CMIs + conventional treatment VS other CMIs 4.CMIs + conventional treatment VS western medicine	1. the markedly effective rate 2. neurological deficit score 3. daily activity ability score 4. adverse event rate 5.mortality 6.cerebral hematoma changes 7.safety evaluation of adverse/reactive events 8.disability rate 9.quality of life	no
the current NMA	Medline, Cochrane Library, Embase, CNKI, Wanfang Database, Sinomed, Chongqing VIP	Inception to August 2018	acute cerebral infarction(ACI)	1.CMI③ a + conventional treatment VS CMI b + conventional treatment 2.CMI + conventional treatment VS conventional treatment.	1. mortality 2. the rate of cerebrovascular event including recurrence event 3.NIHSS 4.adverse drug event	yes

PS: 1.AADN include: aspirin + anticoagulants + dehydrant + neuroprotectant.
2. CHIs① include: Ligustrazine injection, Xueshuantong injection, Xuesaitong injection, Shuxuening injection, Dengzhanxixin injection, Dengzhanhuasu injection, Shuxuetong injection, Danhong injection, Fufangdanshen injection, Ginkgo Leaf Extract and Dipyridamole Injection, Mailuoning injection, Honghuahuangsesu injection, Shenxiong glucose injection, salviae miltiorrhizae, ligustrazine hydrochloride injection, Danshen injection.
3. CMIs② include: Fufangdanshen injection, Danhong injection, Ginkgo Leaf Extract and Dipyridamole Injection, Dengzhanxixin injection, Dengzhanhuasu injection, Shuxuetong injection, salviae miltiorrhizae, ligustrazine hydrochloride injection, Shuxuening injection, Mailuoning injection, Gegensu injection, Kudiezi injection, Danshen injection, Danshen polyphenolate injection, Xueshuantong injection, Xuesaitong injection, Xinding injection, Extract of Ginkgo Biloba Leaves injection.
4. CMI③ include: Shuxuening injection, Xiangdan injection, Shuxuetong injection, Kudiezi injection, Xuesaitong injection, Xueshuantong injection, Dengzhanhuasu injection, Danhong injection, Dengzhanxixin injection, Danshen injection, Mailuoning injection, Xingnaojing injection.
5. Conventional treatment include: thrombolytic therapy, anticoagulant therapy, antiplatelet aggregation therapy and some other symptomatic supportive treatments, such as control of blood pressure and adjustment of blood lipids.

required to confirm the results.

As this study is secondary research based on literature, ethics approval and patient consent is not necessary. This protocol is designed in accordance with guidelines for NMA protocols [8]. It will be conducted and reported according to the PRISMA extension statement for NMA [9]. The results of this NMA will be submitted to a peer-reviewed journal once it is completed.

4. Conclusion

This study will offer helpful and informative evaluations of current CMIs for ACI. The results will inform clinicians, provide optimal CMI, bridge the evidence gaps, and identify promising CMIs in future trials.

Conflict of interests

The authors have declared no conflict of interest.

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