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Endovascular treatment for symptomatic intracranial artery stenosis: protocol for a systematic review and network meta-analysis

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Keywords: Endovascular treatment, balloon angioplasty, balloon-mounted stent, self-expanding stent, intracranial artery stenosis, network meta-analysis.

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Abstract

Introduction Atherosclerotic intracranial artery stenosis (ICAS) is one of most common causes of stroke, which is the second-leading cause of death worldwide. Medical, surgical, and endovascular therapy are three major treatments for ICAS. Currently, medical therapy is considered as the standard of care for most patients with ICAS, while extracranial to intracranial bypass is only used rare situations. Balloon angioplasty alone (BA), balloon-mounted stent (BMS), and self-expanding stent (SES), collectively called endovascular treatment, have showed promising potentials in treating specific subgroups of patients with symptomatic ICAS, however, their comparative safety and efficacy is still unclear. Therefore, a systematic review with network meta-analysis is needed to establish a hierarchy of these endovascular treatments.

Methods and analysis The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols was followed to establish this protocol. Major databases including Cochrane Library, MEDLINE, EMBASE, Chinese Biomedical Literature Database, conference proceedings and grey literature database will be searched for clinical studies comparing at least two interventions for symptomatic ICAS patients. Primary outcomes include short- and long-term mortality or stroke rate. Random effects pairwise and network meta-analyses of included studies will be performed on STATA (Vision 14, StataCorp. 2015). The surface under the cumulative ranking curve and mean rank will be calculated in order to establish a hierarchy of the endovascular treatments. Evaluation of the risk of bias, heterogeneity, consistency, transitivity and quality of evidence will follow the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.

Ethics and dissemination: Ethics approval is not needed for systematic review is based on published studies. Study findings will be presented at international conferences and published on a peer-reviewed journal.

PROSPERO registration number: CRD42018084055.

Strengths and limitations of this study

To the best of our knowledge, this study will be the first systematic review and network meta-analysis of safety and efficacy of three subtypes of endovascular treatment for patients with symptomatic intracranial stenosis.

Besides randomized controlled studies, observational studies will also be included in order to obtain sufficient data for the network meta-analysis and improve the precision of estimates of adverse events.

The present study has a clearly established aim, state of the art methods for data collection, quality evaluation and quantitative synthesis.

The major challenge may come from unexpected heterogeneity from observational study designs. Stringent evaluation of transitivity will be conducted before data pooling for network meta-analysis.

Background

Description of the condition

Stroke is currently the second-leading cause of death just behind ischemic heart disease, causing 6.2 million death in 2015 worldwide [1, 2]. Atherosclerotic intracranial artery stenosis (ICAS), one of most common causes of stroke, accounted for 10-54% of all ischemic strokes. Stroke mortality presented with regional variation, with a disproportionately high mortality in Asian countries, which might be partially attributable to higher prevalence of intracranial atherosclerosis these regions [3]. Great economic and family burden have been caused by stroke globally, especially in low- and middle-income countries [4].

Description of the intervention

Contemporary treatments for ICAS can be broadly categorized into medical, surgical, and endovascular therapy. Currently, medical treatment remains the standard of care for patients with ICAS [5]. Aggressive medical management (i.e., dual anti-platelet therapy along with intensive modifiable risk factor management) is supported by the latest studies [6-8] and recommended as the first-line therapy for symptomatic ICAS by the American Heart Association stroke prevention guidelines [9]. Extracranial to intracranial bypass surgery (EC-IC bypass) has been used to treatment for ICAS since 1980s, but it was proven to be associated with a worse prognosis versus medical treatment for ICAS patients in a RCT published in 1985 [10]. Ever since, EC-IC bypass is used in very few situations, such as stenoses progressing to occlusions with major hemodynamic impairment or in non atherosclerotic lesions like Moyamoya disease [11]. Endovascular therapy, also called percutaneous transluminal angioplasty and stenting (PTAS), was adopted from management of coronary heart disease and the first cases of its use in ICAS were reported in the 1980s [12]. It was considered as a minimally-invasive approach to treat symptomatic ICAS patients and was found to have an acceptable periprocedural complication rate and potential benefit in initial studies [8, 13-15]. Although results of SAMMPRIS and VISSIT trials didn't favor the use of PTAS in ICAS patients, many neurovascular practitioners and academics still believe that there is a role for endovascular treatment of ICAD [16]. Specific subgroups of patients, for example, African-American, Asian and Hispanic patients [17-20], high-risk subgroup of patients who do not respond well to intensive medical treatment [21, 22], and patients with hypoperfusion symptoms [22], which still needs to be confirmed by future studies.

Rationale for the current systematic review

Endovascular therapy can be generally divided into three subtypes: balloon angioplasty alone (BA), balloon-mounted stent (BMS), or self-expanding stent (SES) [23]. So far, none of them has been established to be the primary option of endovascular therapy for specific subgroups of ICAS patients. Early studies comparing BA with stent placement showed comparable recurrent stroke or mortality rate, but stent treatment showed a lower rate of postoperative residual stenosis [24, 25]. Comparable immediate procedural outcomes were reported by another study [26]. A recent study, however, reported a significantly higher mortality (17.6% vs. 8.4%, P<0.001) but no difference of iatrogenic stroke rate (3.4% vs. 3.6%, P=0.826) in BA group, compared to stent group [27]. Therefore, the safety and efficacy of BA versus stent placement is still unclear. As for the efficacy of

BMS versus SES, the restenosis rate was showed to be higher in the SES than the BMS group [28-30]. However, whether the other major complication rates are different between them is still needed to be clarified. In summary, a systematic review with network meta-analysis that allows for both direct and indirect comparisons of multiple interventions is needed to decide the comparative effects of the three subtypes of endovascular therapy. To our knowledge, this kind of systematic review has not been previously completed.

Objective

The primary objectives of this study are to (1) determine the effects of different endovascular treatments (i.e., balloon angioplasty alone, balloon-mounted stent or self-expanding stent) on patients with symptomatic intracranial artery stenosis, and (2) establish a hierarchy of endovascular treatments for treating symptomatic intracranial artery stenosis, through a systematic review with network meta-analysis of randomized trials and observational studies.

Methods

This protocol was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (see **Supplement 1.** PRISMA-P Checklist) [31]. This systematic review has been perspectively registered on the PROSPERO database (CRD42018084055, available at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018084055). Any revision of this protocol and the whole review process will be updated timely on the PROSPERO registration. The conduction and reporting of this systematic review will follow the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions [32, 33].

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) and quasi-RCTs (non-blinded, interrupted time series) will be included. Observational cohort, case-control and registry studies will be included to obtain adequate statistical power, because rare outcomes will be included in our review and identifying these rare adverse events are important to assess the intervention safety, and RCTs lack adequate statistical power to evaluate these uncommon/rare safety outcomes due to Type II (i.e., false negative) error [34]. Other types of studies including case series and case reports will be excluded. Studies published in Chinese journals will not be considered due to inappropriate randomization procedures have been reported in many of these studies [35].

Types of participants

Patients with symptomatic intracranial arterial stenosis (ICAS) and degree of stenosis more than 50% (verified by angiography) will be included. The stenosis is located in at least one major intracranial artery (intracranial internal carotid artery, vertebral artery, or basilar artery and their major branches). ICAS patients with a transient ischemic attack (TIA) or

stroke are defined as symptomatic. A TIA was defined as a transient episode of neurological dysfunction (focal weakness or language disturbance, transient monocular blindness, or required assistance in walking) caused by focal brain or retinal ischemia that lasts for at least 10 minutes but resolves within 24 hours [36]. Intracranial arterial stenosis related to the following factors will be excluded: arterial dissection, moya-moya disease, vasculitic disease, radiation-induced vasculopathy, fibromuscular dysplasia, sickle cell disease, neurofibromatosis, suspected vasospastic process, and suspected recanalized embolus.

Types of interventions

All competing interventions including any endovascular treatment as well as non-endovascular treatment strategy that can be administered for symptomatic ICAS are eligible for the analysis. Studies comparing at least two of the following eligible interventions will be considered in the analysis. We assume that any of the eligible interventions are, in principle, jointly randomizeable among any patients that meets the inclusion criteria. If we identify any interventions that we are not aware of, we will consider them as eligible and include them in the network after assessing their comparability with those named below.

1. Interventions of direct interest

   Studies that evaluated one or more of the following endovascular therapies, namely balloon angioplasty alone (BA), self-expanding stent (SES), and balloon-mounted stent (BMS) will be included. We will estimate the relative ranking of these interventions in the network meta-analysis according to primary outcomes.

2. Inclusion of additional interventions to supplement the analysis

   Studies that evaluated non-endovascular treatment, namely medical treatment alone, and extracranial-intracranial bypass, will also be included to increase the amount of available (indirect) information in the analysis.

Types of outcome measures

Studies that reported at least one of the following outcomes will be included.

1. Primary outcomes

(1) Short-term mortality or stroke rate (peri-procedural, or mean follow-up ≤ 3 month)

(2) Long-term mortality or stroke rate (mean follow-up ≥ 6 month)

2. Secondary outcomes

(1) Long-term restenosis (≥ 50% stenosis verified by angiography, mean follow-up ≥ 6 month)

(2) TIA rate (short- or long-term)

(3) Other major complications

Search methods for identification of studies

Literature search will mainly be executed in three databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL). Search strategy has been drafted by an experienced librarian and revised by another librarian according to the Peer Review of Electronic Search Strategies checklist (see **Supplement 2.** Search strategy) [37]. In addition, we will also search other databases such as Chinese Biomedical Literature Database (CBM), Web of Science (WOS), and Open Grey (OG), and conference proceedings for relevant abstracts, the ISRCTN registry (http://www.isrctn.com), government registries (http://www.clinicaltrials.gov), and World Health Organization registries (http://www.who.int/ trialsearch/) for on-going and recently completed studies. There will be no restrictions on study type, language or publication type. We will search the bibliography of all included studies and request original data from the primary authors when necessary.

Data collection and analysis

Selection of studies

Two reviewers will independently complete the two levels of study screening and selection. In level one screening, reviewers will determine if a study is eligible for inclusion by screening the title and abstract of articles retrieved from the literature search. In level two screening, the full-text of articles retained from level one screening will then be obtained and those meet the eligible criteria will be included. When multiple studies report data from the same study population, or multiple articles of the same study series are published in chronological order, the study with the interventions of direct interest or the largest sample size will be retained. Before each level of screening, a pilot-test, based on the pre-designed test forms (see **Supplement 3.** Screening pilot-test form; adapted from Tricco, et al. [38]), will be conduct to calculate inter-rater reliability and high agreement (≥ 80%) is required to launch the formal screening. Discrepancies between the two reviewers will be resolved by discussion or otherwise a third reviewer. In cases of any ambiguity or insufficient data, study authors will be contacted for further information.

Data extraction and management

Similar with the screening process, data extraction will also be conducted by two reviewers, independently. A data abstraction form will be created in Excel and include two types of data:

1. Outcome data

   Number of primary and secondary outcome events, total number of patients, the interventions being compared, and follow-up duration will be extracted from included studies. Arm level data will be extracted.

2. Data on potential effect modifiers

   Data that may act as effect modifiers will be extracted from included studies, including: (1). study characteristics (e.g., study design, volume of study center, date of publication, journal of publication, study location(s), study funding); (2). population characteristics (e.g., mean or median age, proportion of male patients, degree of pre-procedural stenosis, functional status at presentation, past medical history, drinking

and smoking status, stenosis site of the intracranial artery); (3). intervention characteristics (e.g., placement success rate, residual stenosis).

And a similar pilot-test to calculate inter-rater reliability is required to confirm high agreement (≥ 80%) between two reviewers. Similarly, two reviewers will be resolve disagreements by discussion or otherwise a third reviewer. And we will contact study authors for further information in case of any ambiguity or insufficient data.

Assessment of risk of bias in included studies

Similarly, two reviewers will independently assess risk of bias, and conflicts will be resolved through discussion or otherwise a third reviewer. The risk of bias of RCTs and quasi-RCTs will be assessed with items in the Cochrane Collaboration's tool [32], while that of non-RCTs (observational cohort and case-control studies) will be assessed with the Newcastle-Ottawa Scale (see **Supplement 4.** Newcastle-Ottawa Scale) [39].

Measures of treatment effect

As primary and secondary outcomes are all dichotomous data, odds ratios (ORs) will be used as the measure of treatment effect. Relative treatment effects will be presented as the summary relative effect sizes (ORs) and associated 95% credible intervals (CIs) for each possible pairwise comparison. Relative treatment ranking will also be estimated using the surface under the cumulative ranking curve (SUCRA) and mean ranks [40].

Dealing with missing data

Some of the outcomes are assumed to be rare. Thus, zero events in one arm might be reported. In this case, 0.5 will be added to the numerator and 1 will be added to the denominator. Studies reporting zero events in all arms for primary outcomes will be excluded [41, 42]. When encountering missing data in the included studies, we will contact the study authors for these data first. If the data are still unavailable upon requests, we will impute missing data using established methods, including informative missing odds ratios (IMORs) for dichotomous outcomes and informative missingness difference of means (IMDoM) for continuous outcomes [43] [44]. Further more, a sensitivity analysis will be conduct to ensure that our imputations do not bias the final results [45].

Assessment of clinical and methodological heterogeneity and transitivity

Across all eligible trials that compare each pair of interventions, descriptive statistics for potential effect modifiers described above (i.e., study, population and intervention characteristics) will be generated. We will assess the presence of clinical and methodological heterogeneity both within and across treatment comparisons by calculating the I^2 within each pairwise comparison [46]. We will assess the assumption of transitivity across treatment comparisons by comparing the distribution of the potential effect modifiers across the different pairwise comparisons using boxplots or percentages [47, 48]. The above factors are ensured prior to conducting the following pairwise and network meta-analyses.

Data synthesis

As described above, if quantitative synthesis is not appropriate or the data are insufficient, the findings of our systematic review will be narratively reported. When quantitative analysis is plausible, the following pairwise and network meta-analyses will be conducted in STATA (Vision 14, StataCorp. 2015). We will first restrict our analysis to RCTs, then include data from quasi-RCTs, and finally, data from observational studies. This sequential approach of analyses will provide an understanding of the contribution of each type of study design to our summary estimates.

Methods for direct treatment comparisons

Initially, we will perform standard pairwise meta-analyses for every direct treatment comparison with at least two studies (see **Figure 1**). We will use Bayesian random-effects models to derive summary effect measures with associated 95% credible intervals [49]. The normal distribution will be used in the vague priors for all trial baselines, treatment effects, and between-study standard deviations.

Methods for indirect and mixed comparisons

We will perform network meta-analysis using the three-level hierarchical, random-effects model as described in Schmitz et al., due to both RCTs and non-RCTs are included [50]. The normal distribution will also be used as the vague priors. We will rank relative treatment effects using mean ranks and the SUCRA [40]. Rank-heat plots will be used to display the treatment rankings across multiple outcomes [51].

Assessment of statistical inconsistency

We will evaluate the inconsistency between direct and indirect data locally by using the loop-specific method [52, 53] and the node-splitting method [54], and globally by using the design-by-treatment interaction model [55].

Investigation of heterogeneity and inconsistency and sensitivity analyses

Subgroup analyses will be conducted to explore if sufficient data are available. The following effect modifiers will be included in subgroup analyses: age, sex, degree of pre-procedural stenosis, functional status at presentation, stenosis site of the intracranial artery. Network meta-regression will be used to explore the effect of study year and study country if more than 10 studies are available. Sensitivity analyses will be conducted to test the robustness of our study findings by incorporating only data from the following studies when adequate studies are available: RCTs, quasi-RCTs and cohort studies reporting effect measures that are adjusted for important confounders.

Discussion

The main anticipated challenge for the present systematic review and network meta-analysis is incorporating both randomized and observational studies. The rationale for including non-randomized studies is to obtain adequate statistical power to evaluate the outcomes, especially for the rare complications, because only a small amount of randomized studies were identified through an experimental search for eligible studies. Given that observational studies have inherited methodological limitations compared to randomized studies, another challenge is ensuring the treatment compari-

sons in our study maintain transitivity in our network meta-analyses while also remaining clinically meaningful to knowledge users.

It is expected that the study findings will address important questions about the relative safety and efficacy of different endovascular treatments for patients with symptomatic ICAS, allow patients and care-providers to make informed decisions, and provide comprehensive information for future study designs.

Contributors LJ, FL and YM developed the initial idea for this study. XW, TW and KY developed and revised the search strategy. TW, JZ and PG finished the study design. LJ, FL and YM were consulted about clinical issues. TW, JL and KY contributed to the original draft. PG, JZ and XW were responsible for the revision of the draft. TW and XW contributed equally to this article. All of the authors approved the final work prior to submission.

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Competing interests None declared.

Ethics approval No ethic approval is needed for published data.

Figure 1. Network of all possible pairwise comparisons between the eligible interventions. BA: balloon angioplasty; BMS: balloon mounted stent; SES: self-expanding stent; EC-IC bypass: extracranial-intracranial bypass.

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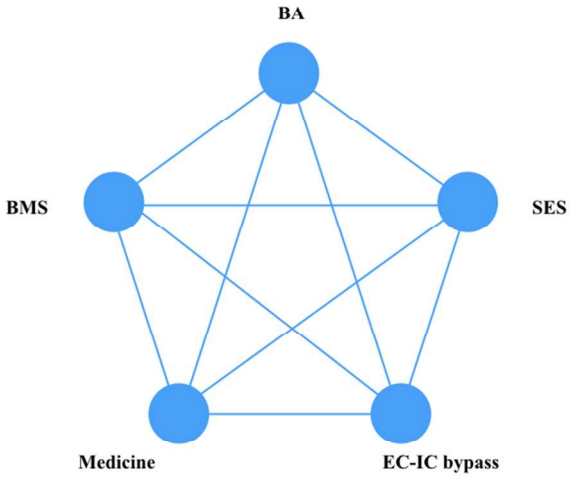

Figure 1. Network of all possible pairwise comparisons between the eligible interventions.

361x270mm (72 x 72 DPI)

Supplement 1. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Check results
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Yes
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Yes
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Yes
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Yes
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes

INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Yes
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes

Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Yes
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplement 2. Search strategy.

Search step	Search terms
#1	((((((((((((((((((((("Intracranial Arterial Diseases"[Mesh]) AND "Constriction, Pathologic"[Mesh]) OR "Intracranial Arteriosclerosis"[Mesh]) OR intracranial arterial stenosis) OR intracranial atherosclerosis) OR intracranial stenosis) OR intracranial atherosclerotic stenosis) OR intracranial atherosclerotic diseases) OR "Vertebrobasilar Insufficiency"[Mesh]) OR intracranial vertebral artery stenosis) OR intracranial vertebrobasilar artery stenosis) OR ischemic cerebrovascular disease caused by artery stenosis) OR basilar artery stenosis) OR cerebral artery stenosis) OR vertebral artery stenosis) OR atherosclerotic vertebrobasilar artery occlusion) OR (intracranial large artery stenoses and occlusions)) OR (intracranial large artery stenosis and occlusions)) OR intracranial vertebral artery atherosclerotic stenosis) OR vertebral atherosclerotic diseases) OR vertebral atherosclerosis diseases) OR intracranial internal carotid artery stenosis) OR atherosclerotic intracranial stenosis
#2	((((balloon expandable intracranial stent*) OR balloon expandable stent*) OR balloon dilatable stent*) OR balloon mounted stent*) OR balloon angioplasty with stent*
#3	(((self expanding stent*) OR self expanded stent*) OR self expandable stent*) OR primary stent*
#4	((((((((balloon angioplasty) OR balloon dilatation) OR balloon dilation) OR primary angioplasty) OR intracranial angioplasty alone) OR endovascular treatment alone) OR endovascular therapy alone) OR intravascular treatment alone) OR intravascular therapy alone

#5	((((((((((("Drug Therapy"[Mesh]) OR drug therapy) OR pharmacotherapy) OR chemotherapy) OR medication)) OR ((((((((((((((((("Aspirin"[Mesh]) OR aspirin) OR acetylsalicylic acid) OR ASA) OR "2-acetyloxy benzoic acid") OR acylpyrin) OR aloxiprinum) OR colfarit) OR disopril) OR ecotrin) OR endosprin) OR magnecyl) OR micristin) OR polopirin) OR polopiryna) OR solprins) OR solupsan) OR zorprin) OR acetysal)) OR ((((((((((("clopidogrel" [Supplementary Concept]) OR clopidogrel) OR iscover) OR pcr 4099) OR pcr-4099) OR pcr4099) OR plavix) OR sr 25989) OR sr-25989) OR sr25989) OR sr 25990c) OR sr-25990c) OR sr25990c)) OR ((((((((((("Warfarin"[Mesh]) OR warfarin) OR aldocumar) OR warfant) OR coumadin) OR coumarin) OR marevan) OR coumadine) OR tedicumar) OR jantoven) OR waran)) OR ((((((((("cilostazol" [Supplementary Concept]) OR cilostazol) OR pletal) OR pletaal) OR OPC 13013) OR OPC-13013) OR OPC13013) OR OPC 21) OR OPC-21) OR OPC21)) OR (((((("Ticagrelor" [Supplementary Concept]) OR ticagrelor) OR brilinta) OR brilique) OR AZD 6140) OR AZD-6140) OR AZD6140)) OR ((((((((("Ticlopidine"[Mesh]) OR ticlopidine) OR ticlid) OR tiklid) OR ticlodix) OR ticlodone) OR panaldine) OR 53 32C) OR 53-32C) OR 5332C)) OR ((((((((("Prasugrel Hydrochloride"[Mesh]) OR prasugrel) OR efient) OR effient) OR CS 747) OR CS-747) OR CS747) OR LY 640315) OR LY-640315) OR LY640315)) OR (("Thienopyridines"[Mesh]) OR thienopyridine) OR thienopyridines)) OR (((((("Aspirin, Dipyridamole Drug Combination"[Mesh]) OR aspirin-dipyridamole drug combination) OR aspirin dipyridamole drug combination) OR TX 3301) OR TX-3301) OR TX3301) OR asasantin) OR aggrenox)
#6	(((((((("Cerebral Revascularization"[Mesh]) OR extracranial-intracranial) OR extracranial intracranial) OR extra-intracranial) OR extra intracranial) OR EC-IC) OR ECIC) OR graft) OR bypass) OR bypasses
#7	#1 AND #2 AND #3 AND #4
#8	#1 AND (#2 OR #3 OR #4)
#9	#1 AND #5 AND #6
#10	Filters: Publication date from 2000/01/01; English
#11	(#7 OR #8 OR #9) AND #10

Supplement 3. Screening pilot-test form

Level 1 screening

1. Does the study include patients with intracranial stenosis?

   YES____ NO____ UNCLEAR____

2. Were the patients treated with medical treatment alone, endovascular treatment, or extracranial-intracranial bypass?

   YES____ NO____ UNCLEAR____

3. Were the patients treated with one of the above treatments compared to each other?

   YES____ NO____ UNCLEAR____

4. Is this a relevant study design (e.g., experimental, quasi-experimental, observational studies)?

   YES____ NO____ UNCLEAR____

If you answer NO to any of these questions, the citation will be excluded. All other citations will be included in L2 screening.

Level 2 screening

1. Does the study include patients with symptomatic intracranial stenosis (≥ 50%) ?

   YES____ NO____ UNCLEAR____

2. Were the women treated with medical treatment alone, balloon angioplasty alone, balloon-mounted stent, self-expandable stent, or extracranial-intracranial bypass.

   YES____ NO____ UNCLEAR____

3. Were the patients treated with one of the above treatments compared to each other?

   YES____ NO____ UNCLEAR____

4. Does the study report at least one of our safety outcomes of interest (e.g., short-term mortality or stroke rate (peri-procedural, or mean follow-up ≤ 3 month), long-term mortality or stroke rate (mean follow-up ≥ 6 month), long-term restenosis (≥ 50% stenosis verified by angiography, mean follow-up ≥ 6 month), TIA rate (short- or long-term), other major complications)?

   YES____ NO____ UNCLEAR____

5. Is this a relevant study design (experimental, quasi-experimental, observational cohort, case-control or registry studies)?

   YES____ NO____ UNCLEAR____

If you answer NO to any of these questions, the citation/study will be excluded. All other full-text articles will be included.

Supplement 4. Adapted Newcastle-Ottawa Scale for observational studies.

1. Adapted Newcastle-Ottawa Scale for cohort studies:

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average symptomatic intracranial stenosis in the community ✵
   b) somewhat representative of the average symptomatic intracranial stenosis in the community ✵
   c) selected group of patients
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✵
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✵
   b) structured interview ✵
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✵
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for treatments of symptomatic intracranial stenosis ✵
   b) study controls for any additional factor ✵ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✵
   b) record linkage ✵
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✵
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✵
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > 80 % follow up, or description provided of those lost) ✵
   c) follow up rate < 80% and no description of those lost

d) no statement

2. Adapted Newcastle-Ottawa Scale for case-control studies:

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✵
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✵
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✵
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✵
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for treatments of symptomatic intracranial stenosis ✵
   b) study controls for any additional factor ✵ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✵
   b) structured interview where blind to case/control status ✵
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✵
   b) no

3) Non-Response rate
   a) same rate for both groups ✵
   b) non respondents described
   c) rate different and no designation

Note from the Editors: Instructions for reviewers of study protocols

Since launching in 2011, BMJ Open has published study protocols for planned or ongoing research studies. If data collection is complete, we will not consider the manuscript.

Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study.

The scientific integrity and the credibility of the study data depend substantially on the study design and methodology, which is why the study protocol requires a thorough peer-review.

BMJ Open will consider for publication protocols for any study design, including observational studies and systematic reviews.

Some things to keep in mind when reviewing the study protocol:

- Protocol papers should report planned or ongoing studies. The dates of the study should be included in the manuscript.
- Unfortunately we are unable to customize the reviewer report form for study protocols. As such, some of the items (i.e., those pertaining to results) on the form should be scored as Not Applicable (N/A).
- While some baseline data can be presented, there should be no results or conclusions present in the study protocol.
- For studies that are ongoing, it is generally the case that very few changes can be made to the methodology. As such, requests for revisions are generally clarifications for the rationale or details relating to the methods. If there is a major flaw in the study that would prevent a sound interpretation of the data, we would expect the study protocol to be rejected.

BMJ Open

Endovascular treatment for symptomatic intracranial artery stenosis: protocol for a systematic review and network meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022359.R1
Article Type:	Protocol
Date Submitted by the Author:	27-Mar-2018

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Evidence based practice, Surgery
Keywords:	endovascular treatment, balloon angioplasty, balloon-mounted stent, self-expanding stent, intracranial artery stenosis, network meta-analysis

Endovascular treatment for symptomatic intracranial artery stenosis: protocol for a systematic review and network meta-analysis

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Keywords: Endovascular treatment, balloon angioplasty, balloon-mounted stent, self-expanding stent, intracranial artery stenosis, network meta-analysis.

Word count: 3247 words.

Abstract

Introduction Atherosclerotic intracranial artery stenosis (ICAS) is one of most common causes of stroke, which is the second-leading cause of death worldwide. Medical, surgical, and endovascular therapy are three major treatments for ICAS. Currently, medical therapy is considered as the standard of care for most patients with ICAS, while extracranial to intracranial bypass is only used rare situations. Balloon angioplasty alone (BA), balloon-mounted stent (BMS), and self-expanding stent (SES), collectively called endovascular treatment, have showed promising potentials in treating specific subgroups of patients with symptomatic ICAS, however, their comparative safety and efficacy is still unclear. Therefore, a systematic review with network meta-analysis is needed to establish a hierarchy of these endovascular treatments.

Methods and analysis The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols was followed to establish this protocol. The search will be limited to studies published from January 1st, 2000 to the formal search date. Major databases including Cochrane Library, MEDLINE, EMBASE, Chinese Biomedical Literature Database, conference proceedings and grey literature database will be searched for clinical studies comparing at least two interventions for symptomatic ICAS patients. Primary outcomes include short- and long-term mortality or stroke rate. Random effects pairwise and network meta-analyses of included studies will be performed on STATA (Vision 14, StataCorp. 2015). The surface under the cumulative ranking curve and mean rank will be calculated in order to establish a hierarchy of the endovascular treatments. Evaluation of the risk of bias, heterogeneity, consistency, transitivity and quality of evidence will follow the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.

Ethics and dissemination: Ethics approval is not needed for systematic review is based on published studies. Study findings will be presented at international conferences and published on a peer-reviewed journal.

PROSPERO registration number: CRD42018084055.

Strengths and limitations of this study

To the best of our knowledge, this study will be the first systematic review and network meta-analysis of safety and efficacy of three subtypes of endovascular treatment for patients with symptomatic intracranial stenosis.

Besides randomized controlled studies, observational studies will also be included in order to obtain sufficient data for the network meta-analysis and improve the precision of estimates of adverse events.

The present study has a clearly established aim, state of the art methods for data collection, quality evaluation and quantitative synthesis.

The major challenge may come from unexpected heterogeneity from observational study designs. Stringent evaluation of transitivity will be conducted before data pooling for network meta-analysis.

Background

Description of the condition

Stroke is currently the second-leading cause of death just behind ischemic heart disease, causing 6.2 million death in 2015 worldwide [1, 2]. Atherosclerotic intracranial artery stenosis (ICAS), one of most common causes of stroke, accounted for 10-54% of all ischemic strokes. Stroke mortality presented with regional variation, with a disproportionately high mortality in Asian countries, which might be partially attributable to higher prevalence of intracranial atherosclerosis these regions [3]. Great economic and family burden have been caused by stroke globally, especially in low- and middle-income countries [4].

Description of the intervention

Contemporary treatments for ICAS can be broadly categorized into medical, surgical, and endovascular therapy. Currently, medical treatment remains the standard of care for patients with ICAS [5]. Aggressive medical management (i.e., dual anti-platelet therapy along with intensive modifiable risk factor management) is supported by the latest studies [6-8] and recommended as the first-line therapy for symptomatic ICAS by the American Heart Association stroke prevention guidelines [9]. Extracranial to intracranial bypass surgery (EC-IC bypass) has been used to treatment for ICAS since 1980s, but it was proven to be associated with a worse prognosis versus medical treatment for ICAS patients in a RCT published in 1985 [10]. Ever since, EC-IC bypass is used in very few situations, such as stenoses progressing to occlusions with major hemodynamic impairment or in non atherosclerotic lesions like Moyamoya disease [11]. Endovascular therapy, also called percutaneous transluminal angioplasty and stenting (PTAS), was adopted from management of coronary heart disease and the first cases of its use in ICAS were reported in the 1980s [12]. It was considered as a minimally-invasive approach to treat symptomatic ICAS patients and was found to have an acceptable periprocedural complication rate and potential benefit in initial studies [8, 13-15]. Although results of SAMMPRIS and VISSIT trials didn't favor the use of PTAS in ICAS patients, many neurovascular practitioners and academics still believe that there is a role for endovascular treatment of ICAD [16]. Specific subgroups of patients, for example, African-American, Asian and Hispanic patients [17-20], high-risk subgroup of patients who do not respond well to intensive medical treatment [21, 22], and patients with hypoperfusion symptoms [22], which still needs to be confirmed by future studies.

Rationale for the current systematic review

Endovascular therapy can be generally divided into three subtypes: balloon angioplasty alone (BA), balloon-mounted stent (BMS), or self-expanding stent (SES) [23]. So far, none of them has been established to be the primary option of endovascular therapy for specific subgroups of ICAS patients. Early studies comparing BA with stent placement showed comparable recurrent stroke or mortality rate, but stent treatment showed a lower rate of postoperative residual stenosis [24, 25]. Comparable immediate procedural outcomes were reported by another study [26]. A recent study, however, reported a significantly higher mortality (17.6% vs. 8.4%, P<0.001) but no difference of iatrogenic stroke rate (3.4% vs. 3.6%, P=0.826) in BA group, compared to stent group [27]. Therefore, the safety and efficacy of BA versus stent placement is still unclear. As for the efficacy of

BMS versus SES, the restenosis rate was showed to be higher in the SES than the BMS group [28-30]. However, whether the other major complication rates are different between them is still needed to be clarified. In summary, a systematic review with network meta-analysis that allows for both direct and indirect comparisons of multiple interventions is needed to decide the comparative effects of the three subtypes of endovascular therapy. To our knowledge, this kind of systematic review has not been previously completed.

Objective

The primary objectives of this study are to (1) determine both the safety and efficacy of different endovascular treatments (i.e., balloon angioplasty alone, balloon-mounted stent or self-expanding stent) on patients with symptomatic intracranial artery stenosis, and (2) establish a hierarchy of endovascular treatments for treating symptomatic intracranial artery stenosis, through a systematic review with network meta-analysis of randomized trials and observational studies.

Methods

This protocol was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (see **Supplement 1.** PRISMA-P Checklist) [31]. This systematic review has been perspectively registered on the PROSPERO database (CRD42018084055, available at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018084055). Any revision of this protocol and the whole review process will be updated timely on the PROSPERO registration. The conduction and reporting of this systematic review will follow the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions [32, 33].

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) and quasi-RCTs (non-blinded, interrupted time series) will be included. Observational cohort, case-control and registry studies will be included to obtain adequate statistical power, because rare outcomes will be included in our review and identifying these rare adverse events are important to assess the intervention safety, and RCTs lack adequate statistical power to evaluate these uncommon/rare safety outcomes due to Type II (i.e., false negative) error [34]. Other types of studies including case series and case reports will be excluded. Studies published in Chinese journals will not be considered due to inappropriate randomization procedures have been reported in many of these studies [35].

Types of participants

Patients with symptomatic intracranial arterial stenosis (ICAS) and degree of stenosis more than 50% (verified by angiography) will be included. The stenosis is located in at least one major intracranial artery (intracranial internal carotid artery, vertebral artery, or basilar artery and their major branches). ICAS patients with a transient ischemic attack (TIA) or

stroke are defined as symptomatic. A TIA was defined as a transient episode of neurological dysfunction (focal weakness or language disturbance, transient monocular blindness, or required assistance in walking) caused by focal brain or retinal ischemia that lasts for at least 10 minutes but resolves within 24 hours [36]. Intracranial arterial stenosis related to the following factors will be excluded: arterial dissection, moya-moya disease, vasculitic disease, radiation-induced vasculopathy, fibromuscular dysplasia, sickle cell disease, neurofibromatosis, suspected vasospastic process, and suspected recanalized embolus.

Types of interventions

All competing interventions including any endovascular treatment as well as non-endovascular treatment strategy that can be administered for symptomatic ICAS are eligible for the analysis. Studies comparing at least two of the following eligible interventions will be considered in the analysis. We assume that any of the eligible interventions are, in principle, jointly randomizable among any patients that meets the inclusion criteria. If we identify any interventions that we are not aware of, we will consider them as eligible and include them in the network after assessing their comparability with those named below.

1. Interventions of direct interest

   Studies that evaluated one or more of the following endovascular therapies, namely balloon angioplasty alone (BA), self-expanding stent (SES), and balloon-mounted stent (BMS) will be included. We will estimate the relative ranking of these interventions in the network meta-analysis according to primary outcomes.

2. Inclusion of additional interventions to supplement the analysis

   Studies that evaluated non-endovascular treatment, namely medical treatment alone, and extracranial-intracranial bypass, will also be included to increase the amount of available (indirect) information in the analysis.

Types of outcome measures

Studies that reported at least one of the following outcomes will be included.

1. Primary outcomes

(1) Short-term mortality or stroke rate (peri-procedural, or mean follow-up ≤ 3 month)

(2) Long-term mortality or stroke rate (mean follow-up ≥ 6 month)

2. Secondary outcomes

(1) Long-term restenosis (≥ 50% stenosis verified by angiography, mean follow-up ≥ 6 month)

(2) TIA rate (short- or long-term)

(3) Other major complications

Search methods for identification of studies

Literature search will mainly be executed in three databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL). Search strategy has been drafted by an experienced librarian and revised by another librarian according to the Peer Review of Electronic Search Strategies checklist (see **Supplement 2.** Search strategy) [37]. The search will be limited to studies published from January 1st, 2000 to the formal search date. In addition, we will also search other databases such as Chinese Biomedical Literature Database (CBM), Web of Science (WOS), and Open Grey (OG), and conference proceedings for relevant abstracts, the ISRCTN registry (http://www.isrctn.com), government registries (http://www.clinicaltrials.gov), and World Health Organization registries (http://www.who.int/ trialsearch/) for on-going and recently completed studies. There will be no restrictions on study type, language or publication type. We will search the bibliography of all included studies and request original data from the primary authors when necessary.

Data collection and analysis

Selection of studies

Two reviewers will independently complete the two levels of study screening and selection. In level one screening, reviewers will determine if a study is eligible for inclusion by screening the title and abstract of articles retrieved from the literature search. In level two screening, the full-text of articles retained from level one screening will then be obtained and those meet the eligible criteria will be included. When multiple studies report data from the same study population, or multiple articles of the same study series are published in chronological order, the study with the interventions of direct interest or the largest sample size will be retained. Before each level of screening, a pilot-test, based on the pre-designed test forms (see **Supplement 3.** Screening pilot-test form; adapted from Tricco, et al. [38]), will be conduct to calculate inter-rater reliability and high agreement (≥ 80%) is required to launch the formal screening. Discrepancies between the two reviewers will be resolved by discussion or otherwise a third reviewer. In cases of any ambiguity or insufficient data, study authors will be contacted for further information.

Data extraction and management

Similar with the screening process, data extraction will also be conducted by two reviewers, independently. A data abstraction form will be created in Excel and include two types of data:

1. Outcome data

   Number of primary and secondary outcome events, total number of patients, the interventions being compared, and follow-up duration will be extracted from included studies. Arm level data will be extracted.

2. Data on potential effect modifiers

   Data that may act as effect modifiers will be extracted from included studies, including: (1). study characteristics (e.g., study design, volume of study center, date of publication, journal of publication, study location(s), study funding); (2). population characteristics (e.g., mean or median age, proportion of male patients, degree of pre-

procedural stenosis, functional status at presentation, past medical history, drinking and smoking status, stenosis site of the intracranial artery); (3). intervention characteristics (e.g., placement success rate, residual stenosis).

And a similar pilot-test to calculate inter-rater reliability is required to confirm high agreement (≥ 80%) between two reviewers. Similarly, two reviewers will be resolve disagreements by discussion or otherwise a third reviewer. And we will contact study authors for further information in case of any ambiguity or insufficient data.

Assessment of risk of bias in included studies

Similarly, two reviewers will independently assess risk of bias, and conflicts will be resolved through discussion or otherwise a third reviewer. The risk of bias of RCTs and quasi-RCTs will be assessed with items in the Cochrane Collaboration's tool [32], while that of non-RCTs (observational cohort and case-control studies) will be assessed with the Newcastle-Ottawa Scale (see **Supplement 4.** Newcastle-Ottawa Scale) [39].

Measures of treatment effect

As primary and secondary outcomes are all dichotomous data, odds ratios (ORs) will be used as the measure of treatment effect. Relative treatment effects will be presented as the summary relative effect sizes (ORs) and associated 95% credible intervals (CIs) for each possible pairwise comparison. Relative treatment ranking will also be estimated using the surface under the cumulative ranking curve (SUCRA) and mean ranks [40].

Dealing with missing data

Some of the outcomes are assumed to be rare. Thus, zero events in one arm might be reported. In this case, 0.5 will be added to the numerator and 1 will be added to the denominator. Studies reporting zero events in all arms for primary outcomes will be excluded [41, 42]. When encountering missing data in the included studies, we will contact the study authors for these data first. If the data are still unavailable upon requests, we will impute missing data using established methods, including informative missing odds ratios (IMORs) for dichotomous outcomes and informative missingness difference of means (IMDoM) for continuous outcomes [43] [44]. Further more, a sensitivity analysis will be conduct to ensure that our imputations do not bias the final results [45].

Assessment of clinical and methodological heterogeneity and transitivity

Across all eligible trials that compare each pair of interventions, descriptive statistics for potential effect modifiers described above (i.e., study, population and intervention characteristics) will be generated. We will assess the presence of clinical and methodological heterogeneity both within and across treatment comparisons by calculating the I^2 within each pairwise comparison [46]. We will assess the assumption of transitivity across treatment comparisons by comparing the distribution of the potential effect modifiers across the different pairwise comparisons using boxplots or percentages [47, 48]. The above factors are ensured prior to conducting the following pairwise and network meta-analyses.

Data synthesis

As described above, if quantitative synthesis is not appropriate or the data are insufficient, the findings of our systematic review will be narratively reported. When quantitative analysis is plausible, the following pairwise and network meta-analyses will be conducted in STATA (Vision 14, StataCorp. 2015). We will first restrict our analysis to RCTs, then include data from quasi-RCTs, and finally, data from observational studies. This sequential approach of analyses will provide an understanding of the contribution of each type of study design to our summary estimates.

Methods for direct treatment comparisons

Initially, we will perform standard pairwise meta-analyses for every direct treatment comparison with at least two studies (see **Figure 1**). We will use Bayesian random-effects models to derive summary effect measures with associated 95% credible intervals [49]. The normal distribution will be used in the vague priors for all trial baselines, treatment effects, and between-study standard deviations.

Methods for indirect and mixed comparisons

We will perform network meta-analysis using the three-level hierarchical, random-effects model as described in Schmitz et al., due to both RCTs and non-RCTs are included [50]. The normal distribution will also be used as the vague priors. We will rank relative treatment effects using mean ranks and the SUCRA [40]. Rank-heat plots will be used to display the treatment rankings across multiple outcomes [51].

Assessment of statistical inconsistency

We will evaluate the inconsistency between direct and indirect data locally by using the loop-specific method [52, 53] and the node-splitting method [54], and globally by using the design-by-treatment interaction model [55].

Investigation of heterogeneity and inconsistency and sensitivity analyses

Subgroup analyses will be conducted to explore if sufficient data are available. The following effect modifiers will be included in subgroup analyses: age, sex, degree of pre-procedural stenosis, functional status at presentation, stenosis site of the intracranial artery. Network meta-regression will be used to explore the effect of study year and study country if more than 10 studies are available. Sensitivity analyses will be conducted to test the robustness of our study findings by incorporating only data from the following studies when adequate studies are available: RCTs, quasi-RCTs and cohort studies reporting effect measures that are adjusted for important confounders.

Patient and Public Involvement

As the present study is a systematic review based on published data, patient and public are not involved in the study design, conduct, data analysis and result dissemination.

Discussion

The main anticipated challenge for the present systematic review and network meta-analysis is incorporating both randomized and observational studies. The rationale for including non-randomized studies is to obtain adequate statistical power to evaluate the outcomes, especially for the rare com-

plications, because only a small amount of randomized studies were identified through an experimental search for eligible studies. Given that observational studies have inherited methodological limitations compared to randomized studies, another challenge is ensuring the treatment comparisons in our study maintain transitivity in our network meta-analyses while also remaining clinically meaningful to knowledge users.

It is expected that the study findings will address important questions about the relative safety and efficacy of different endovascular treatments for patients with symptomatic ICAS, allow patients and care-providers to make informed decisions, and provide comprehensive information for future study designs.

Ethics and dissemination

Ethics approval is not needed for systematic review is based on published studies. Study findings will be presented at international conferences and published on a peer-reviewed journal.

Contributors LJ, FL and YM developed the initial idea for this study. XW, TW and KY developed and revised the search strategy. TW, JZ and PG finished the study design. LJ, FL and YM were consulted about clinical issues. TW, JL and KY contributed to the original draft. PG, JZ and XW were responsible for the revision of the draft. TW and XW contributed equally to this article. All of the authors approved the final work prior to submission.

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Competing interests None declared.

Figure 1. Network of all possible pairwise comparisons between the eligible interventions. BA: balloon angioplasty; BMS: balloon mounted stent; SES: self-expanding stent; EC-IC bypass: extracranial-intracranial bypass.

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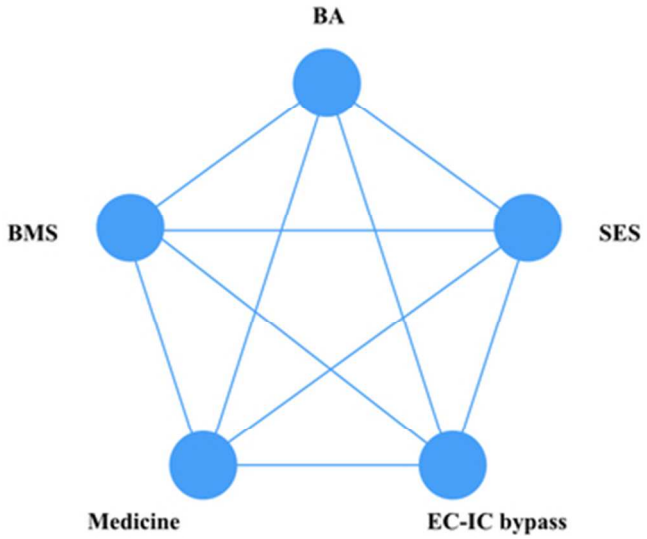

Network of all possible pairwise comparisons between the eligible interventions. BA: balloon angioplasty; BMS: balloon mounted stent; SES: self-expanding stent; EC-IC bypass: extracranial-intracranial bypass.

48x36mm (300 x 300 DPI)

Supplement 1. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Check results
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Yes Page 1, line 2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes Page 2, line 35; Page 5, line 26
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes Page 1, line 11
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes Page 10, line 17
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Yes Page 5, line 28
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Yes Page 10, line 24
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes Page 10, line 24

Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes Page 10, line 25
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes Page 4, line 44
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes Page 5, line 10
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes Page 5, line 35
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes Page 7, line 1
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes Page 7, line 6
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes Page 7, line 39
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Yes Page 7, line 20
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes Page 7, line 39

Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes Page 7, line 45; Page 7, line 52
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes Page 6, line 37
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes Page 8, line 12
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes Page 8, line 44
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Yes Page 8, line 56
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes Page 9, line 34
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes Page 9, line 2
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes Page 9, line 34
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes Page 5, line 30

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplement 2. Search strategy.

Search step	Search terms
#1	((((((((((((((((((((("Intracranial Arterial Diseases"[Mesh]) AND "Constriction, Pathologic"[Mesh]) OR "Intracranial Arteriosclerosis"[Mesh]) OR intracranial arterial stenosis) OR intracranial atherosclerosis) OR intracranial stenosis) OR intracranial atherosclerotic stenosis) OR intracranial atherosclerotic diseases) OR "Vertebrobasilar Insufficiency"[Mesh]) OR intracranial vertebral artery stenosis) OR intracranial vertebrobasilar artery stenosis) OR ischemic cerebrovascular disease caused by artery stenosis) OR basilar artery stenosis) OR cerebral artery stenosis) OR vertebral artery stenosis) OR atherosclerotic vertebrobasilar artery occlusion) OR (intracranial large artery stenoses and occlusions)) OR (intracranial large artery stenosis and occlusions)) OR intracranial vertebral artery atherosclerotic stenosis) OR vertebral atherosclerotic diseases) OR vertebral atherosclerosis diseases) OR intracranial internal carotid artery stenosis) OR atherosclerotic intracranial stenosis
#2	((((balloon expandable intracranial stent*) OR balloon expandable stent*) OR balloon dilatable stent*) OR balloon mounted stent*) OR balloon angioplasty with stent*
#3	(((self expanding stent*) OR self expanded stent*) OR self expandable stent*) OR primary stent*
#4	((((((((balloon angioplasty) OR balloon dilatation) OR balloon dilation) OR primary angioplasty) OR intracranial angioplasty alone) OR endovascular treatment alone) OR endovascular therapy alone) OR intravascular treatment alone) OR intravascular therapy alone

#5	((((((((((("Drug Therapy"[Mesh]) OR drug therapy) OR pharmacotherapy) OR chemotherapy) OR medication)) OR ((((((((((((((((("Aspirin"[Mesh]) OR aspirin) OR acetylsalicylic acid) OR ASA) OR "2-acetyloxy benzoic acid") OR acylpyrin) OR aloxiprinum) OR colfarit) OR disopril) OR ecotrin) OR endosprin) OR magnecyl) OR micristin) OR polopirin) OR polopiryna) OR solprins) OR solupsan) OR zorprin) OR acetysal)) OR ((((((((((("clopidogrel" [Supplementary Concept]) OR clopidogrel) OR iscover) OR pcr 4099) OR pcr-4099) OR pcr4099) OR plavix) OR sr 25989) OR sr-25989) OR sr25989) OR sr 25990c) OR sr-25990c) OR sr25990c)) OR ((((((((((("Warfarin"[Mesh]) OR warfarin) OR aldocumar) OR warfant) OR coumadin) OR coumarin) OR marevan) OR coumadine) OR tedicumar) OR jantoven) OR waran)) OR ((((((((("cilostazol" [Supplementary Concept]) OR cilostazol) OR pletal) OR pletaal) OR OPC 13013) OR OPC-13013) OR OPC13013) OR OPC 21) OR OPC-21) OR OPC21)) OR (((((("Ticagrelor" [Supplementary Concept]) OR ticagrelor) OR brilinta) OR brilique) OR AZD 6140) OR AZD-6140) OR AZD6140)) OR ((((((((("Ticlopidine"[Mesh]) OR ticlopidine) OR ticlid) OR tiklid) OR ticlodix) OR ticlodone) OR panaldine) OR 53 32C) OR 53-32C) OR 5332C)) OR ((((((((("Prasugrel Hydrochloride"[Mesh]) OR prasugrel) OR efient) OR effient) OR CS 747) OR CS-747) OR CS747) OR LY 640315) OR LY-640315) OR LY640315)) OR (("Thienopyridines"[Mesh]) OR thienopyridine) OR thienopyridines)) OR (((((((("Aspirin, Dipyridamole Drug Combination"[Mesh]) OR aspirin-dipyridamole drug combination) OR aspirin dipyridamole drug combination) OR TX 3301) OR TX-3301) OR TX3301) OR asasantin) OR aggrenox)
#6	(((((((("Cerebral Revascularization"[Mesh]) OR extracranial-intracranial) OR extracranial intracranial) OR extra-intracranial) OR extra intracranial) OR EC-IC) OR ECIC) OR graft) OR bypass) OR bypasses
#7	#1 AND #2 AND #3 AND #4
#8	#1 AND (#2 OR #3 OR #4)
#9	#1 AND #5 AND #6
#10	Filters: Publication date from 2000/01/01; English
#11	(#7 OR #8 OR #9) AND #10

Supplement 3. Screening pilot-test form

Level 1 screening

1. Does the study include patients with intracranial stenosis?

   YES____ NO____ UNCLEAR____

2. Were the patients treated with medical treatment alone, endovascular treatment, or extracranial-intracranial bypass?

   YES____ NO____ UNCLEAR____

3. Were the patients treated with one of the above treatments compared to each other?

   YES____ NO____ UNCLEAR____

4. Is this a relevant study design (e.g., experimental, quasi-experimental, observational studies)?

   YES____ NO____ UNCLEAR____

If you answer NO to any of these questions, the citation will be excluded. All other citations will be included in L2 screening.

Level 2 screening

1. Does the study include patients with symptomatic intracranial stenosis (≥ 50%) ?

   YES____ NO____ UNCLEAR____

2. Were the women treated with medical treatment alone, balloon angioplasty alone, balloon-mounted stent, self-expandable stent, or extracranial-intracranial bypass.

   YES____ NO____ UNCLEAR____

3. Were the patients treated with one of the above treatments compared to each other?

   YES____ NO____ UNCLEAR____

4. Does the study report at least one of our safety outcomes of interest (e.g., short-term mortality or stroke rate (peri-procedural, or mean follow-up ≤ 3 month), long-term mortality or stroke rate (mean follow-up ≥ 6 month), long-term restenosis (≥ 50% stenosis verified by angiography, mean follow-up ≥ 6 month), TIA rate (short- or long-term), other major complications)?

   YES____ NO____ UNCLEAR____

5. Is this a relevant study design (experimental, quasi-experimental, observational cohort, case-control or registry studies)?

   YES____ NO____ UNCLEAR____

If you answer NO to any of these questions, the citation/study will be excluded. All other full-text articles will be included.

Supplement 4. Adapted Newcastle-Ottawa Scale for observational studies.

1. Adapted Newcastle-Ottawa Scale for cohort studies:

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average symptomatic intracranial stenosis in the community ✵
   b) somewhat representative of the average symptomatic intracranial stenosis in the community ✵
   c) selected group of patients
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✵
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✵
   b) structured interview ✵
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✵
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for treatments of symptomatic intracranial stenosis ✵
   b) study controls for any additional factor ✵ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✵
   b) record linkage ✵
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✵
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✵
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > 80 % follow up, or description provided of those lost) ✵
   c) follow up rate < 80% and no description of those lost

d) no statement

2. Adapted Newcastle-Ottawa Scale for case-control studies:

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✵
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✵
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✵
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✵
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for treatments of symptomatic intracranial stenosis ✵
   b) study controls for any additional factor ✵ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✵
   b) structured interview where blind to case/control status ✵
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✵
   b) no

3) Non-Response rate
   a) same rate for both groups ✵
   b) non respondents described
   c) rate different and no designation