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Keywords:	Stroke < NEUROLOGY, NEUROSURGERY, STROKE MEDICINE

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Safety and Efficacy of Transcarotid Artery Revascularization Versus Carotid Endarterectomy: protocol for a systematic review and meta-analysis

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Word count: **2199**

ABSTRACT

Introduction In recent years, transcarotid artery revascularization (TCAR) with flow reversal has been developed to treat carotid artery stenosis. The superiority of TCAR over transfemoral carotid artery stenting (TFCAS) has been demonstrated. However, the safety and efficacy between TCAR and carotid endarterectomy (CEA) remains uncertain. This study aims to introduce a protocol for a systemic review and meta-analysis to compare the morbidity and mortality rates between TCAR and CEA in treating atherosclerotic carotid artery stenosis.

Methods and analysis This protocol was conducted in term of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement. Major databases will be searched, including Medline, Web of Science, Embase, and the Cochrane Library. Randomized controlled trials and high-quality observational studies will be included. We will screen the studies published from January 2000 to March 2021. Bias risk will be evaluated with usage of the Cochrane Collaboration criteria or Newcastle–Ottawa Scale depending on the study type. Two reviewers will select eligible studies and extract data independently. The primary outcome will include stroke or death during perioperative period and follow-up. I^2 statistic will be used for evaluation of heterogeneity. Subgroup analysis and sensitivity analysis will be performed to explore any potential sources of heterogeneity. Specific results will be described in narrative form when available eligible studies are not enough for meta-analysis. Publication bias will be assessed by performing a funnel plot.

Ethics and dissemination This study will summarize and analyze the existing literature, so ethics approval will not be required. The final results may be published at relevant academic conference or journal.

PROSPERO registration number 42020178691

Keywords carotid artery stenosis, transcarotid artery revascularization, carotid endarterectomy, systematic review, meta-analysis

Strengths and limitations of this study

- This systemic review and meta-analysis will summarize the current literatures and compare both primary and secondary outcomes between TCAR and CEA
- This study will also compare the outcomes based on studies eliminating baseline discrepancy of comorbidities and anatomic factors
- Observational studies will be included, with the aim of providing adequate statistical power when evaluating primary and secondary outcomes
- Inclusion of observational studies will increase the bias risk, but our assessments and methods will be meticulous to ensure the accuracy of our results
- Subgroup and sensitivity analyses will be conducted if level of heterogeneity is high

INTRODUCTION

Stroke is a major cause of mortality and morbidity globally,[1] and carotid artery disease is the major pathophysiology process leading to stroke.[2] Carotid endarterectomy (CEA) has been the golden standard surgical intervention to treat atherosclerotic carotid artery stenosis for many decades.[2 3] With rapid development of endovascular techniques, carotid artery stenting (CAS) has been considered as a less invasive intervention and an effective alternative of CEA. However, during traditional approach with transfemoral carotid artery stenting (TFCAS), sheath position distal to common carotid artery (CCA) is often required for placement of embolic protection devices (EPDs). This approach entails traversing the aorta, aortic arch, and the culprit lesion at CCA bifurcation crossed by a wire and EPD delivery catheter, which may increase the risk of plaque rupture and result in emboli shower during distal access.[4] Thus, TFCAS might paradoxically lead to a higher peri-procedural stroke risk compared to CEA.[2 5]

In recent years, the new technique of transcarotid artery revascularization (TCAR) with flow reversal has been developed to treat carotid artery stenosis.[4 6-8] TCAR is performed through direct carotid access via a small incision at the base of the neck. This cervical approach has many advantages - it avoids catheter manipulation in the aortic arch, supra-aortic vessels, and CCA, thereby decreasing risk of cerebral emboli. Additionally, it uses flow reversal system to synergistically reduce perioperative embolic stroke risks. With the aforementioned advantages, the superiority of TCAR over TFCAS has been clearly demonstrated in a series of studies.[8 9]

Nevertheless, high-level evidence regarding outcome comparison between TCAR and CEA, which is the golden standard of treatment of carotid stenosis, is lacking. Although previous meta-analyses showed TCAR had similar 30-day risk of stroke/myocardial infarction(MI)/death and a significantly lower risk of cranial nerve injury (CNI) when compared with CEA,[10 11] the evidence was synthesized in the context of limited number of studies and lack of long-term results. Since the last meta-analysis, numerous new studies with long-term outcomes have been published, which warrants a repeat systematic review incorporating those results. [8 12] Also, TCAR were shown with shorter operative time than CEA in some studies,[4 12 13] but this was not analyzed in both meta-analyses.[10 11] In addition, as patients were usually considered for TCAR when they were regarded as high risk CEA candidates due to comorbidities such as chronic renal disease or coronary artery disease,[10] thus the results of previous meta-analyses could not be generalized to patients with standard surgical risk.[10 11] Therefore, the comparative safety and efficacy between TCAR and CEA needs to be further analyzed based on studies with acceptable treatment equipoise between the two interventions.[4 12]

This systemic review and meta-analysis will summarize the current literatures and compare both primary and secondary outcomes between the two modalities in treatment

of atherosclerosis carotid artery stenosis. We anticipate provision of valuable clinical evidence for decision-making process in treatment selection for carotid artery stenosis patients.

METHODS AND ANALYSIS

The registration of this systematic review and meta-analysis has been completed in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD 42020178691). This protocol was conducted in term of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (Supplement Table 1).[14] If any changes were made to this protocol, PROSPERO registration information will be updated in a timely fashion.

Inclusion criteria for selecting study

Participants

We will include adult participants (age ≥18 years old) with atherosclerotic carotid artery stenosis, which were diagnosed by carotid ultrasound, Computed Tomography Angiography (CTA), Magnetic Resonance Angiography (MRA) or Digital Subtraction Angiography (DSA), and treated with TCAR or CEA. We will exclude participants when one of the following criteria is met: aged under 18 years; carotid artery stenosis due to nonatherosclerotic etiologies, such as vasculitis, radiation, vasospasm and fibromuscular dysplasia; missing or unclear clinical, imaging, or follow-up data.

Primary Intervention of Interest

The primary intervention of interest will be TCAR with flow reversal for atherosclerotic carotid artery stenosis. TCAR is a type of CAS performed through direct carotid access via a small incision at the base of the neck. Micropuncture set is used to perform arterial puncture, then guidewire and arterial sheath will pass through it. Venous access could be used by common femoral vein or internal jugular vein.[15 16] Then, the common femoral vein will be punctured and sheath insertion will be performed. Connection of the sheaths with 'flow controller' is conducted to complete the circuit. The blood reversal is achieved by occlusion of the proximal to the arterial puncture site and the flow controller could regulate the blood flow.[10 17]

Comparison Intervention

The comparison intervention will be CEA, which contains primary closure CEA and eversion CEA, with or without shunt and arterioplasty.

Outcome

At least one of the following items is reported.

Primary outcomes:

1. Stroke or death during the perioperative (within 30 days) period
2. Stroke or death during follow-up (such as 1 year and 2 years) period

We will classify the causes of stroke or death into culprit lesion induced, non-culprit lesion induced, and non-vascular cause.

Secondary outcomes:

1. Operative duration, CNI, myocardial infarction (MI), transient ischemic attacks (TIAs), hematoma and intracranial hemorrhage during perioperative period
2. MI, TIAs, hematoma, intracranial hemorrhage and restenosis during follow-up period

Studies

Studies included in the systematic review will be randomized controlled trials (RCTs) and high-quality observational studies including case-control or cohort studies. The reason for inclusion of observational studies is to minimize type II error caused by lack of statistical power due to limited number of RCTs.[5 18] Conference abstracts, case reports and case series (no more than 10 patients) will be excluded.

Search strategy

Literature search will be performed using the following main databases, including Medline, Embase, Web of Science, and the Cochrane Library. We will search and screen the studies published between January 2000 and March 2021. The explicit search strategy will be constructed for each database using the following related terms: "carotid artery stenosis", "carotid endarterectomy", "transcarotid artery", "transcervical", "revascularization". Additionally, ClinicalTrials.gov will be searched for any ongoing studies to assure that we include all eligible data. The search strategy for Medline was drafted and revised in accordance with the standards of search strategies checklist[19] (Supplementary Table 2, Search strategy for Medline).

Data selection and analysis

Study selection

Two independent reviewers (YW and XW) will screening all results after searching the databases for selection of eligible studies (see Figure 1. Study flow diagram). First, titles, key words and abstracts will be screened by reviewers, and they will rule out the irrelevant studies. Second, reviewers will evaluate eligible studies from the remaining studies by reading through the full articles. We will document the causes of all included and excluded studies. If conflicts result, reconciliation with consultation from a third reviewer (TW) will be sought.

Data extraction and management

EndNote X7 (Clarivate Analytics, Philadelphia, USA) will be used to manage included studies. The data extraction will be independently conducted by two reviewers (YW and XW) on the basis of a standardized data extraction form.[20] The extracted information is as follows:

1. Study characteristics: type of study, authors, year of publication, location, sample size, number of procedures

2. Patient characteristics: mean age, age range, gender, medical history, symptom status, anatomic characteristics
3. Operative characteristics: type of treatment, anesthesia type and the use of anticoagulation
4. Data of outcomes: number of cases with aforementioned outcomes, number of participants and follow-up time

Discrepancy in data extraction between two reviewers will be settled by a discussion. For missing or unclear information, we will try to contact the corresponding authors via email. If no responses after two emails, we will exclude this study for meta-analysis and record this case in the PRISMA flow chart.

Bias risk assessment

Two independent reviewers (YW and KY) will assess the bias risk of included studies. Cochrane Collaboration criteria and Newcastle-Ottawa scale will be performed for assessing the bias risk of RCTs and observational studies, respectively.[21 22] The Methodological Quality and Synthesis of Case Series and Case Reports will be used for case series.[23] Each domain of included studies will be given a score based on the bias risk. The level of bias risk will be ranked as high, unclear or low. Any disagreements will be discussed by the two reviewing authors and a group discussion will be organized if necessary.

Heterogeneity assessment

χ^2test and I^2statistic will be used for measuring the heterogeneity before any outcome is pooled.[24 25] I^2statistic > 60% will be determined as having substantial heterogeneity, and the I^2statistics <40% and 40%–60% will be considered as mild and moderate heterogeneity.[26]

Measures of treatment effect and data synthesis

Both primary and secondary outcomes between TCAR and CEA will be compared not only based on all eligible included studies, but also on studies eliminating baseline discrepancy of comorbidities and anatomic factors to minimize selection bias.

If effect size is sufficient (more than 2 included studies), meta-analyses will be performed for pooled results of included studies. Odds ratio (OR) with 95% confidence intervals (CIs) will be used to present the treatment effect for outcomes reported in dichotomous form. For continuous data, we will report in mean differences with 95% CIs. The level of statistical significance is $p < 0.05$. The fixed-effects model will be applied when there is mild or moderate evidence of heterogeneity ($I^2 \leq 60\%$). On the contrary, the random-effects model will be used in studies with substantial heterogeneity ($I^2 > 60\%$).[27] If there is substantial heterogeneity and sufficient studies, subgroup analyses will be performed to examine the potential sources of heterogeneity by symptomatic or asymptomatic patients. Sensitivity analysis is also utilized to appreciate studies with high risk of bias through step-wise exclusion of studies and

observation of combined bias in remaining studies. In case that data is insufficient and meta-analysis is infeasible, the solely narrative presentation of study results will be presented. The STATA (version 14, StataCorp LLC, USA) will be used as a tool for all statistical analysis.

Publication bias assessment

The trail protocols will be checked for assessing publication bias of eligible studies. Provided that more than 10 studies are included, publication bias will be assessed by visualization of funnel plot.

Assessment of pooled effect estimates

For pooled effect estimates, we will used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[28] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for assessment of observational studies and RCTs, respectively.[29]

Patient and public involvement

Patient and public will not be involved in the process of this systematic review and meta-analysis because this study will be conducted on the basis of published data.

DISCUSSION

This study aims to summarize the current literatures and compare both primary and secondary outcomes between TCAR and CEA in treating atherosclerotic carotid artery stenosis. TCAR with flow reversal was recently developed to treat carotid artery stenosis. However, the safety and efficacy between TCAR and the golden therapy of CEA remains uncertain. Also, a systemic and meta-analysis of high-quality based on studies eliminating the baseline discrepancy of comorbidities and anatomic factors will be performed for decision-making process for carotid artery stenosis patients.

ETHICS AND DISSEMINATION

There is no need for ethical approval because primary data will not be obtained. The systematic review will be presented at international conferences and published in peer-reviewed journals.

Abbreviations: CEA, Carotid endarterectomy; CAS, carotid artery stenting; TFCAS, transfemoral carotid artery stenting; CCA, common carotid artery; EPDs, embolic protection devices; TCAR, transcarotid artery revascularization; CNI, cranial nerve injury; PROSPERO, International Prospective Register of Systematic Reviews; PRISMA-P, Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols; PICO, Population Intervention Comparison Outcome; CTA, computed tomography angiography; MRA, magnetic resonance angiography; DSA, digital

subtraction angiography; MI, myocardial infarction; TIAs, transient ischemic attacks; RCTs, randomized controlled trials; OR, odds ratio; CIs, confidence intervals; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology statement; GRADE, Grading of Recommendations Assessment, Development and Evaluation system.

Contributors XB, XZ, LJ and YM contributed to the initial idea for this study. XW, TW, YW and YF developed and revised the search strategy. XB, XZ, and WY completed the study design. LJ and YM contributed to consults about clinical issues. XB, XZ and WY contributed to the original draft. LJ, YM, XB, XZ, WY, TW and KY contributed to the revision of the draft. XB, XZ and WY contributed equally to this article. All of the authors approved the final work prior to submission.

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Competing interests None declared.

Patient consent Not required.

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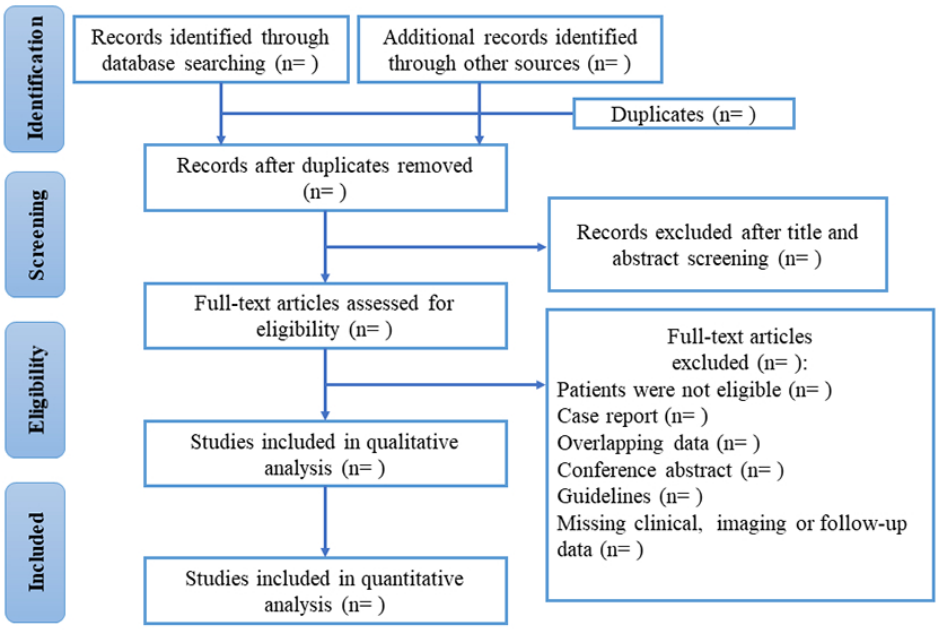

Flow diagram of literature for systematic review and meta-analysis.

75x56mm (300 x 300 DPI)

Supplementary file 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:			P1, L1-3
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 P2, L25
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes P1, L4-32
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes P9, L3-7
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:			P9, L9-11
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 P4, L2-38
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes P4, L40-P5, L1
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 P5, L3- P6, L12
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 P6, L14-L23
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 Supplementary Table 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes P6, L36-L37
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 P6, L26-33

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 P6, L37-L38
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 P6, L38-P7, L8
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 P5, L36-P6, L5
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 P7, L10-18
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Yes P7, L27-32
	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 P7, L32-38
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes P7, L38-42
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes P7, L42-P8, L1
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes P8, L4-7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes P8, L9-13

***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.

Supplementary Table 2 Search strategy for Medline

1. carotid artery diseases/ or carotid artery thrombosis/ or carotid stenosis/
2. carotid arteries/ or carotid artery, common/ or carotid artery, external/ or carotid artery, internal/
3. constriction, pathologic/
4. 2 and 3
5. (carotid adj5 (stenosis or thrombo$ or disease$ or arter$ narrow$ or plaque$ or arterioscler$ or atheroscler$)).tw.
6. 1 or 4 or 5
7. Endarterectomy/
8. Vascular Surgical Procedures/
9. 7 or 8
10. 6 and 9
11. Endarterectomy, Carotid/
12. (carotid adj5 (endarterectomy or surgery)).tw.
13. cea.tw.
14. 10 or 11 or 12 or 13
15. angioplasty/ or angioplasty, balloon/ or angioplasty, balloon, laser-assisted/ or angioplasty, laser/
16. Stents/
17. (angioplasty or stent$ or endovascular).tw.
18. (balloon adj5 (dilat$ or catheter$)).tw.
19. ((endoluminal or transluminal) adj5 repair$).tw.
20. (revasculariz$ or recanali$).tw.
21. 15 or 16 or 17 or 18 or 19 or 20
22. (trans adj5 (carotid or cervical)).tw.
23. 21 and 22
24. 14 and 23

Supplementary file 3

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
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 _____ (Select the most important factor.) ✸
   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

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
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 _____ (describe) in the community ✸
   b) somewhat representative of the average _____ in the community ✸
   c) selected group of users eg nurses, volunteers
   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 _____ (select the most important factor) ✸
   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 - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Note: 1 ✸ means 1 point, and studies with scores of 0–4 points were identified as low quality and 5–9 points as high quality and only high-quality literature will be in our analysis.

BMJ Open

Safety and Efficacy of Transcarotid Artery Revascularisation Versus Carotid Endarterectomy: Protocol for a Systematic Review and Meta-analysis Study

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Keywords:	Stroke < NEUROLOGY, NEUROSURGERY, STROKE MEDICINE

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Safety and Efficacy of Transcarotid Artery Revascularisation Versus Carotid Endarterectomy: Protocol for a Systematic Review and Meta-analysis Study

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ABSTRACT

Introduction: In recent years, the transcarotid artery revascularisation (TCAR) with flow reversal technique has been developed to treat carotid artery stenosis. The superiority of TCAR over transfemoral carotid artery stenting has been demonstrated. However, the safety and efficacy of TCAR and carotid endarterectomy remain unclear. This study aims to introduce a protocol for a systematic review and meta-analysis to compare the morbidity and mortality rates between TCAR and carotid endarterectomy in the treatment of atherosclerotic carotid artery stenosis.

Methods and analysis: This protocol was drafted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols statement. Herein, major databases will be searched, including Medline, Web of Science, Embase, and the Cochrane Library, and randomised controlled trials and high-quality observational studies will be included. We will screen all studies published from January 2000 to March 2021. Bias risk will be evaluated using the Cochrane Collaboration criteria or Methodological Index for Non-randomised Studies criteria, depending on the study type. Two reviewers will select eligible studies and extract the data independently. The primary outcome will include stroke or death during the perioperative period and follow-up. Subgroup and sensitivity analyses will be performed to explore any potential sources of heterogeneity. Specific results will be described in a narrative form when available eligible studies are insufficient for meta-analysis. Publication bias will be assessed using a funnel plot.

Ethics and dissemination: This study will summarise and analyse the existing literature; hence, ethics approval will not be required. The final results may be published at a relevant academic conference or in a journal.

PROSPERO registration number: 42020178691,

Keywords carotid artery stenosis, transcarotid artery revascularization, carotid endarterectomy, systematic review, meta-analysis

Strengths and limitations of this study

- This systematic review and meta-analysis will summarise the current literature and compare the primary and secondary outcomes between transcarotid artery revascularisation and carotid endarterectomy.
- This study will also compare the outcomes based on studies that eliminate baseline discrepancies in comorbidities and anatomic factors.
- Observational studies will be included, with the aim of providing adequate statistical power to evaluate primary and secondary outcomes.
- The inclusion of observational studies will increase the risk of bias, but our assessments and methods will be meticulous to ensure the accuracy of our results.
- Subgroup and sensitivity analyses will be conducted if the level of heterogeneity is high.

INTRODUCTION

Stroke is a major cause of mortality and morbidity globally,[1] and carotid artery disease is the major pathophysiological process leading to stroke.[2] Carotid endarterectomy (CEA) has been the gold standard surgical intervention to treat atherosclerotic carotid artery stenosis for many decades.[2 3] However, with the rapid development of endovascular techniques, carotid artery stenting (CAS) has been considered as a less-invasive intervention and an effective alternative to CEA. However, during traditional approaches with transfemoral carotid artery stenting (TFCAS), a sheath position distal to the common carotid artery (CCA) is often required for placement of embolic protection devices. This approach entails traversing the aorta, aortic arch, and culprit lesion at the CCA bifurcation crossed by a wire and embolic protection device delivery catheter, which may increase the risk of plaque rupture and result in an emboli shower during distal access.[4] Thus, TFCAS may paradoxically lead to a higher periprocedural stroke risk than CEA.[2 5]

In recent years, a new technique- transcarotid artery revascularisation (TCAR) with flow reversal has been developed to treat carotid artery stenosis[4 6-8]; this involves direct carotid access via a small incision at the base of the neck. This cervical approach has many advantages: it avoids catheter manipulation in the aortic arch, supra-aortic vessels, and CCA, thereby decreasing the risk of cerebral emboli. Additionally, it uses a flow reversal system to synergistically reduce perioperative embolic stroke risks. With the aforementioned advantages, the superiority of TCAR over TFCAS has been clearly demonstrated in a series of studies.[8 9]

Nevertheless, high-level evidence regarding outcome comparison between TCAR and CEA, which is the gold standard in the treatment of carotid stenosis, is lacking. Although previous meta-analyses showed that TCAR had a similar 30-day risk of stroke/myocardial infarction (MI)/death and a significantly lower risk of cranial nerve injury when compared with CEA,[10 11] the evidence was synthesised in the context of a limited number of studies and a lack of long-term results. Since the last meta-analysis, numerous new study outcomes beyond 30 days after surgery have been published, which warrant a repeat systematic review incorporating these results. [8 12] In addition, TCAR was shown to have a shorter operative time than CEA in some studies,[4 12 13] but this was not analysed in either meta-analyses.[10 11] In addition, patients were usually considered for TCAR when they were regarded as high-risk CEA candidates because of comorbidities such as chronic renal disease or coronary artery disease.[10] Thus, the results of previous meta-analyses could not be generalised to patients with standard surgical risk.[10 11] Therefore, the comparative safety and efficacy between TCAR and CEA needs to be further analysed based on studies with acceptable treatment equipoise between the two interventions.[4 12]

This systematic review and meta-analysis will summarise the current literature and compare both the primary and secondary outcomes between the two modalities in the

treatment of atherosclerotic carotid artery stenosis. We anticipate the provision of valuable clinical evidence for decision-making processes in treatment selection for patients with carotid artery stenosis.

METHODS AND ANALYSIS

This systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD 42020178691), and the protocol was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (Supplement Table 1).[14] If any changes were made to this protocol, PROSPERO registration information will be updated in a timely fashion.

Inclusion criteria for the selection study

Participants

We will include adult participants (age ≥18 years old) with atherosclerotic carotid artery stenosis, who were diagnosed using carotid ultrasonography, computed tomography angiography, magnetic resonance angiography or digital subtraction angiography, and treated with TCAR or CEA. We will exclude participants when one of the following criteria is met: age under 18 years; carotid artery stenosis due to nonatherosclerotic aetiologies, such as vasculitis, radiation, vasospasm and fibromuscular dysplasia; and missing or unclear clinical, imaging, or follow-up data.

Primary Intervention of Interest

The primary intervention of interest will be TCAR with flow reversal for atherosclerotic carotid artery stenosis. TCAR is a type of CAS performed through direct carotid access via a small incision at the base of the neck. A micropuncture set is used to perform arterial puncture, and the guidewire and arterial sheath are passed through it. Venous access can be performed via the common femoral vein or internal jugular vein.[15 16] Then, the common femoral vein is punctured and sheath insertion is performed. Connection of the sheaths with a 'flow controller' is conducted to complete the circuit. Blood reversal is achieved by occlusion of the proximal to the arterial puncture site, and the flow controller can thus regulate the blood flow.[10 17]

Comparison Intervention

The comparison intervention will involve CEA, which includes primary closure CEA and eversion CEA, with or without shunt and arterioplasty.

Outcome

At least one of the following items will be reported.

Primary outcomes:

1. Stroke or death during the perioperative (within 30 days) period
2. Stroke or death during follow-up (such as 1 year and 2 years) period

We will classify the causes of stroke or death as either culprit lesion-induced, non-culprit lesion-induced, or non-vascular.

Secondary outcomes:

1. Operative duration, cranial nerve injury, MI, transient ischaemic attacks (TIAs), haematoma and intracranial haemorrhage during the perioperative period
2. MI, transient ischaemic attacks, haematoma, intracranial haemorrhage and restenosis during the follow-up period beyond 30 days

Studies

Studies included in the systematic review will be randomised controlled trials (RCTs) and high-quality observational studies, including case-control or cohort studies. Observational studies will be included to minimise type II error caused by lack of statistical power due to the limited number of RCTs.[5 18] Conference abstracts, case reports and case series (no more than 10 patients) will be excluded.

Search strategy

A literature search will be performed using the following main databases: Medline, Embase, Web of Science, and the Cochrane Library. We will search and screen studies published between January 2000 and March 2021. An explicit search strategy will be constructed for each database using the following related terms: 'carotid artery stenosis', 'carotid endarterectomy', 'transcarotid artery', 'transcervical', 'revascularization'. Additionally, ClinicalTrials.gov will be searched for ongoing studies to ensure that we include all eligible data. The search strategy for Medline was drafted and revised in accordance with the standards of the search strategy checklist[19] (Supplementary Table 2, search strategy for Medline).

Data selection and analysis

Study selection

Two independent reviewers (YW and XW) will screen all the results after searching the databases for the selection of eligible studies. First, the titles, keywords, and abstracts will be screened by reviewers, and all irrelevant studies will be ruled out. Second, reviewers will evaluate the eligible studies from the remaining studies by reading the full articles. We will then document the causes of all the included and excluded studies. If conflicts occur as a result, reconciliation with consultation from a third reviewer (TW) will be sought.

Data extraction and management

EndNote X7 (Clarivate Analytics, Philadelphia, USA) will be used to manage the included studies. The data extraction will be independently conducted by two reviewers (YW and XW) on the basis of a standardised data extraction form.[20] The extracted information is as follows:

1. Study characteristics: type of study, authors, year of publication, location, sample size, and number of procedures

2. Patient characteristics: mean age, age range, sex, medical history, symptom status, and anatomic characteristics
3. Operative characteristics: type of treatment, anaesthesia type, and use of an anticoagulant
4. Data of outcomes: number of cases with aforementioned outcomes, number of participants, and follow-up time

Discrepancies in data extraction between the two reviewers will be settled with a discussion. For missing or unclear information, we will try to contact the corresponding authors via email. If there are no responses after two emails, we will exclude this study from the meta-analysis and record this case in the Preferred Reporting Items for Systematic Review and Meta-Analysis flow chart.

Bias risk assessment

Two independent reviewers (YW and KY) will assess the bias risk of the included studies. Cochrane Collaboration criteria and Methodological Index for Non-randomised Studies criteria will be performed to assess the bias risk of RCTs and observational studies, respectively.[21-23] The methodological quality and synthesis of case series and case reports will be used for case series.[24] Each domain of included studies will be given a score based on the bias risk. The level of bias risk will be ranked as high, unclear or low. Any disagreements will be discussed by the two reviewing authors, and a group discussion will be organised if necessary.

Heterogeneity assessment

χ^2test and I^2statistics will be used to measure the heterogeneity before any outcome is pooled.[25 26] We will assign the degree of low, moderate and high heterogeneity to the I^2 statistic of 25%, 50%, and 75%.[25 27]

Measures of treatment effect and data synthesis

Both primary and secondary outcomes between TCAR and CEA will be compared not only based on all eligible studies, but also on studies eliminating baseline discrepancy of comorbidities and anatomic factors to minimise selection bias.

If the effect size is sufficient (more than two included studies), meta-analyses will be performed for the pooled results of the included studies. Odds ratios with 95% confidence intervals will be used to present the treatment effect for outcomes reported in dichotomous form. For continuous data, we will report the mean differences with 95% confidence intervals. The level of statistical significance is at $P < 0.05$. If the included studies are associated with different characteristics, such as differences in included patients, treatment, and follow-up, a random-effects model will be used. In contrast, a fixed effect model will be performed.[28] If there is moderate to substantial heterogeneity (I^2>50%) and sufficient studies (at least 10), subgroup analyses will be performed to examine the potential sources of heterogeneity, which will include characteristics of the patients, treatments, and clinical outcomes. For instance, one can expect a difference

between symptomatic and asymptomatic participants, and we will therefore divide them into two groups and analyse the safety and efficacy outcomes of either group of participants. Sensitivity analysis will also be utilised to appreciate studies with a high risk of bias through step-wise exclusion of studies and observation of combined bias in the remaining studies. Meta-regression analysis will be performed on the condition that there are at least 10 included studies. In cases where data are insufficient and meta-analysis is infeasible, the sole narrative presentation of the study results will be presented. STATA (version 14, StataCorp LLC, USA) will be used as a tool for all statistical analyses.

Publication bias assessment

The trail protocols will be checked to assess the publication bias of the eligible studies. Provided that more than 10 studies are included, publication bias will be assessed by visualisation of the funnel plot. In addition, Egger's intercept and Begg and Mazumdar's text will also be used to assess publication bias.

Assessment of pooled effect estimates

For pooled effect estimates, we will use the Strengthening the Reporting of Observational Studies in Epidemiology statement[29] and the Grading of Recommendations Assessment, Development and Evaluation system for assessment of observational studies and RCTs, respectively.[30]

Patient and public involvement

Patients and the public will not be involved in the process of this systematic review and meta-analysis, as this study will be conducted solely on the basis of published data.

DISCUSSION

This study aims to summarise the current literature and compare both primary and secondary outcomes between TCAR and CEA in the treatment of atherosclerotic carotid artery stenosis. TCAR with flow reversal has recently been developed for the treatment of carotid artery stenosis. It is worth noting that despite many proposed advantages compared with TFCAS, TCAR may also have inherent disadvantages, such as anatomical restrictions from short thick necks and the need for at least 8 minutes of flow reversal, which will not be tolerated by some patients undergoing carotid revascularization.[7] Many studies were performed under the supervision of the Silk Road Medical company.[31] However, the safety and efficacy of TCAR and the gold standard for treatment of CEA remains uncertain. In addition, a systematic review and meta-analysis of high-quality studies that eliminate the baseline discrepancy of comorbidities and anatomic factors will be performed for the decision-making process for carotid artery stenosis patients.

ETHICS AND DISSEMINATION

There is no need for ethical approval because primary data will not be obtained. The systematic review will be presented at international conferences and published in peer-reviewed journals.

Abbreviations: CEA, Carotid endarterectomy; CAS, carotid artery stenting; TFCAS, transfemoral carotid artery stenting; CCA, common carotid artery; EPDs, embolic protection devices; TCAR, transcarotid artery revascularization; CNI, cranial nerve injury; PROSPERO, International Prospective Register of Systematic Reviews; PRISMA-P, Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols; CTA, computed tomography angiography; MRA, magnetic resonance angiography; DSA, digital subtraction angiography; MI, myocardial infarction; TIAs, transient ischemic attacks; RCTs, randomized controlled trials; MINORS, Methodological index for non-randomized studies criteria; OR, odds ratio; CIs, confidence intervals; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology statement; GRADE, Grading of Recommendations Assessment, Development and Evaluation system.

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Contributors XB, XZ, LJ and YM contributed to the initial idea for this study. XW, TW, YW and YF developed and revised the search strategy. XB, XZ, and WY completed the study design. LJ and YM contributed to consults about clinical issues. XB, XZ and WY contributed to the original draft. LJ, YM, XB, XZ, WY, TW and KY contributed to the revision of the draft. XB, XZ and WY contributed equally to this article. All of the authors approved the final work prior to submission.

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Competing interests None declared.

Patient consent Not required.

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Supplementary file 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:			P1, L1-10
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 P2, L39
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes P1, L12-49
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes P10, L7-13
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:			P10, L15-18
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 P4, L16-P5, 12
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes P5, L14-20
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 P5, L35- P6, L42
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 P6, L44-L57
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 Supplementary Table 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes P7, L17-L39
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 P7, L3-14

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 P7, L33-39
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 P7, L23-32
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 P6, L14-31
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 P7, L42-55
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	Yes P8, L18-25
	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 P8, L25-28
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes P8, L31-43
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes P8, L44-46
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes P8, L50-55
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes P9, L3-8

*** 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.**

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Supplementary Table 2 Search strategy for Medline

1. carotid artery diseases/ or carotid artery thrombosis/ or carotid stenosis/
2. carotid arteries/ or carotid artery, common/ or carotid artery, external/ or carotid artery, internal/
3. constriction, pathologic/
4. 2 and 3
5. (carotid adj5 (stenosis or thrombo$ or disease$ or arter$ narrow$ or plaque$ or arterioscler$ or atheroscler$)).tw.
6. 1 or 4 or 5
7. Endarterectomy/
8. Vascular Surgical Procedures/
9. 7 or 8
10. 6 and 9
11. Endarterectomy, Carotid/
12. (carotid adj5 (endarterectomy or surgery)).tw.
13. cea.tw.
14. 10 or 11 or 12 or 13
15. angioplasty/ or angioplasty, balloon/ or angioplasty, balloon, laser-assisted/ or angioplasty, laser/
16. Stents/
17. (angioplasty or stent$ or endovascular).tw.
18. (balloon adj5 (dilat$ or catheter$)).tw.
19. ((endoluminal or transluminal) adj5 repair$).tw.
20. (revasculariz$ or recanali$).tw.
21. 15 or 16 or 17 or 18 or 19 or 20
22. (trans adj5 (carotid or cervical)).tw.
23. 21 and 22
24. 14 and 23