

# BMJ Open Safety and efficacy of transcrotid artery revascularisation versus carotid endarterectomy: protocol for a systematic review and meta-analysis study

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## ABSTRACT

**Introduction** In recent years, the transcrotid 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 Review 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.

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## INTRODUCTION

Stroke is a major cause of mortality and morbidity globally,<sup>1</sup> and carotid artery disease is the major pathophysiological process leading to stroke.<sup>2</sup> Carotid endarterectomy

## 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 transcrotid artery revascularisation and carotid endarterectomy.
- This study will also compare the outcomes based on studies that eliminate baseline discrepancies in comorbidities and anatomical 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.

(CEA) has been the gold standard surgical intervention to treat atherosclerotic carotid artery stenosis for many decades.<sup>2,3</sup> 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.<sup>4</sup> Thus, TFCAS may paradoxically lead to a higher periprocedural stroke risk than CEA.<sup>2,5</sup>

In recent years, a new technique—transcarotid artery revascularisation (TCAR)—with flow reversal has been developed to treat carotid artery stenosis<sup>4–8</sup>; 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.<sup>8,9</sup>

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,<sup>10,11</sup> 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.<sup>8,12</sup> In addition, TCAR was shown to have a shorter operative time than CEA in some studies,<sup>4,12,13</sup> but this was not analysed in either meta-analyses.<sup>10,11</sup> 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.<sup>10</sup> Thus, the results of previous meta-analyses could not be generalised to patients with standard surgical risk.<sup>10,11</sup> Therefore, the comparative safety and efficacy between TCAR and CEA need to be further analysed based on studies with acceptable treatment equipoise between the two interventions.<sup>4,12</sup>

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 were registered in the International Prospective Register of Systematic Reviews, and the protocol was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (online supplemental table 1).<sup>14</sup> 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  $\geq 18$  years old) with atherosclerotic carotid artery stenosis, who were diagnosed using carotid ultrasonography, CT 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 old; 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 micro-puncture 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.<sup>15,16</sup> 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.<sup>10,17</sup>

### 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, TIAs, 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.<sup>5,18</sup> 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', and 'revascularisation'. 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<sup>19</sup> (online supplemental 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.<sup>20</sup> 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 anatomical 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.<sup>21–23</sup> The methodological quality and synthesis of case series and case reports will be used for case series.<sup>24</sup> 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

$\chi^2$  test and  $I^2$  statistics will be used to measure the heterogeneity before any outcome is pooled.<sup>25 26</sup> We will assign the degree of low, moderate and high heterogeneity to the  $I^2$  statistic of 25%, 50% and 75%.<sup>25 27</sup>

### Measures of treatment effect and data synthesis

Both primary and secondary outcomes between TCAR and CEA will be compared based not only on all eligible studies but also on studies eliminating baseline discrepancy of comorbidities and anatomical 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. ORs with 95% CIs 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% CIs. 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-effect model will be used. In contrast, a fixed-effect model will be performed.<sup>28</sup> 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 used to appreciate studies with a high risk of bias through stepwise 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 V.14 (StataCorp, USA) will be used as a tool for all statistical analyses.

### Publication bias assessment

The trial 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<sup>29</sup> and the Grading of Recommendations Assessment, Development and Evaluation system for assessment of observational studies and RCTs, respectively.<sup>30</sup>

### 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 min of flow reversal, which will not be tolerated by some patients undergoing carotid revascularisation.<sup>7</sup> Many studies were performed under the supervision of the Silk Road Medical company.<sup>31</sup> However, the safety and efficacy of TCAR and the gold standard for treatment of CEA remain uncertain. In addition, a systematic review and meta-analysis of high-quality studies that eliminate the baseline discrepancy of comorbidities and anatomical factors will be performed for the decision-making process for patients with carotid artery stenosis.

### 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.

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### REFERENCES

- 1 Powers WJ, Rabinstein AA, Ackerson T, *et al*. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American heart Association/American stroke association. *Stroke* 2018;49:e46–110.
- 2 International Carotid Stenting Study investigators, Ederle J, Dobson J, *et al*. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International carotid stenting study): an interim analysis of a randomised controlled trial. *Lancet* 2010;375:985–97.
- 3 Feng Y, Bai X, Wang T, *et al*. Thirty-day outcomes of carotid endarterectomy in the elderly: a 17-year single-center study. *J Clin Neurosci* 2020;78:86–90.
- 4 Kashyap VS, King AH, Foteh MI, *et al*. A multi-institutional analysis of transcrotid artery revascularization compared to carotid endarterectomy. *J Vasc Surg* 2019;70:123–9.
- 5 Feng Y, Li L, Bai X, *et al*. Risk factors for new ischaemic cerebral lesions after carotid artery stenting: protocol for a systematic review and meta-analysis. *BMJ Open* 2019;9:e030025.
- 6 Alvarez B, Ribo M, Maeso J, *et al*. Transcervical carotid stenting with flow reversal is safe in octogenarians: a preliminary safety study. *J Vasc Surg* 2008;47:96–100.
- 7 Plessers M, Van Herzele I, Hemelsoet D, *et al*. Transcervical carotid stenting with dynamic flow reversal demonstrates embolization rates comparable to carotid endarterectomy. *J Endovasc Ther* 2016;23:249–54.
- 8 Dakour-Aridi H, Kashyap VS, Wang GJ, *et al*. The impact of age on in-hospital outcomes after transcrotid artery revascularization, Transfemoral carotid artery stenting, and carotid endarterectomy. *J Vasc Surg* 2020;72:931–42.
- 9 Schermerhorn ML, Liang P, Eldrup-Jorgensen J, *et al*. Association of Transcarotid artery revascularization vs Transfemoral carotid artery stenting with stroke or death among patients with carotid artery stenosis. *JAMA* 2019;322:2313–22.
- 10 Conway AM, Nguyen Tran NT, Qato K, *et al*. Complexity of aortic arch anatomy affects the outcomes of transcrotid artery revascularization versus Transfemoral carotid artery stenting. *Ann Vasc Surg* 2020;67:78–89.
- 11 Naazie IN, Cui CL, Osaghae I, *et al*. A systematic review and meta-analysis of Transcarotid artery revascularization with dynamic flow reversal versus Transfemoral carotid artery stenting and carotid endarterectomy. *Ann Vasc Surg* 2020;69:426–36.
- 12 Yee EJ, Wang SK, Timsina LR, *et al*. Propensity-Matched outcomes of Transcarotid artery revascularization versus carotid endarterectomy. *J Surg Res* 2020;252:22–9.
- 13 Schermerhorn ML, Liang P, Dakour-Aridi H, *et al*. In-Hospital outcomes of transcrotid artery revascularization and carotid endarterectomy in the Society for vascular surgery vascular quality initiative. *J Vasc Surg* 2020;71:87–95.
- 14 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.

- 15 Matas M, Alvarez B, Ribo M, *et al.* Transcervical carotid stenting with flow reversal protection: experience in high-risk patients. *J Vasc Surg* 2007;46:49–54.
- 16 Leal I, Orgaz A, Flores Ángel, *et al.* A diffusion-weighted magnetic resonance imaging-based study of transcervical carotid stenting with flow reversal versus Transfemoral filter protection. *J Vasc Surg* 2012;56:1585–90.
- 17 Luk Y, Chan YC, Cheng SW. Transcarotid artery revascularization as a new modality of treatment for carotid stenosis. *Ann Vasc Surg* 2020;64:397–404.
- 18 Bai X, Feng Y, Yang K, *et al.* Extracranial-Intracranial bypass surgery for occlusive atherosclerotic disease of the anterior cerebral circulation: protocol for a systematic review and meta-analysis. *Syst Rev* 2020;9:70.
- 19 Wang T, Wang X, Yang K, *et al.* Endovascular treatment for symptomatic intracranial artery stenosis: protocol for a systematic review and network meta-analysis. *BMJ Open* 2018;8:e022359.
- 20 Bai X, Feng Y, Li L, *et al.* Treatment strategies for asymptomatic carotid artery stenosis in the era of lipid-lowering drugs: protocol for a systematic review and network meta-analysis. *BMJ Open* 2020;10:e035094.
- 21 Higgins J, Green S. Cochrane Handbook for systematic reviews of interventions, version 5.1.0. The Cochrane collaboration 2013.
- 22 Wells GA, Shea B, O'Connell J. The Newcastle-Ottawa scale (NOS) for assessing the quality of Nonrandomised studies in meta-analyses 2014.
- 23 Slim K, Nini E, Forestier D, *et al.* Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg* 2003;73:712–6.
- 24 Murad MH, Sultan S, Haffar S, *et al.* Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med* 2018;23:60–3.
- 25 Higgins JPT, Thompson SG, Deeks JJ, *et al.* Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
- 26 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
- 27 Zhang X, Yu Y, Yang K, *et al.* Clinical outcomes of radiation-induced carotid stenosis: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis* 2020;29:104929.
- 28 Cooper HM, Hedges LV, Valentine JC. *The Handbook of research synthesis and meta-analysis*. 2nd edn, 2009.
- 29 von Elm E, Altman DG, Egger M, *et al.* Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;335:806–8.
- 30 Guyatt GH, Oxman AD, Vist GE, *et al.* Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
- 31 Coelho A, Prassaparo T, Mansilha A, *et al.* Critical appraisal on the quality of reporting on safety and efficacy of Transcarotid artery stenting with flow reversal. *Stroke* 2020;51:2863–71.