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Risk factors for new ischaemic cerebral lesions after carotid artery stenting: protocol for a systematic review and meta-analysis

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Strengths and limitations of this study

- As far as we are concerned, this study will be the first systematic review and meta-analysis for the risk factors of the occurrence of new cerebral ischaemic lesions.
- Besides randomised controlled trials study, the high-quality case–control study or cohort study will also be included in case of insufficient data to draw a solid conclusion.
- Subgroup analysis will be used when there is significant evidence of heterogeneity.
- Polling these data is at risk of inherent uncertainty due to different outcomes and methods used.

ABSTRACT

Introduction New ischaemic cerebral lesions (NICL) detected by diffusion-weighted imaging MRI are common after carotid artery stenting (CAS), with an occurrence rate ranging from 18% to 57%. Many studies reported occurrence of NICL could increase risk of future cerebrovascular events and cognitive impairment. However, controversies about determinants for occurrence of NICL after CAS exist among studies, and one risk factor embodied in an article may not be in another. Aim of this study is to introduce a protocol for a systematic review and meta-analysis to identify risk factors associated with occurrence of NICL after CAS.

Methods and analysis All relevant literature referring to risk factors for occurrence of NICL after CAS will be searched on the major databases, such as PubMed, Embase, Web of Science and the Cochrane Library until 31 December 2018. Literature, which must be randomised controlled trials, case–control studies or cohort studies, will be included in accordance with the prespecified eligibility criteria. The risk of bias will be assessed using the Cochrane Collaboration criteria and the quality of evidence will be assessed with the corresponding scale. Data will be extracted with a form prepared before and analysed using RevMan V.5.3 analyses software. Heterogeneity will be assessed using I² statistic. Our systematic review will be performed according to the guidance from the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

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

PROSPERO registration number CRD42019121129

INTRODUCTION

A new guideline from American Heart Association reported that approximately 79,500 people experience a new or recurrent stroke. Of all strokes, 87% are ischaemic and 10% are intracerebral haemorrhage strokes, whereas 3% are subarachnoid haemorrhage strokes. Atherosclerotic carotid stenosis is an important risk factor for ischaemic stroke. Nowadays, carotid artery stenting (CAS) has been an alternative to carotid endarterectomy for the treatment of carotid artery stenosis. CAS is considered as a less invasive procedure with favourable successful rate for treatment of internal carotid artery stenosis. However, even with widespread use of embolic protection devices, new ischaemic cerebral lesions (NICL) after CAS detected by diffusion-weighted imaging MRI (DWI-MRI) are common, ranging from 18% to 57%. Although most are silent, NICL on DWI-MRI after CAS increased the risk of future cerebrovascular events reported by recent study. Besides, Maggio et al and Huang et al observed NICL could lead to cognitive impairment. People with NICL may benefit from more aggressive and prolonged antiplatelet therapy after CAS. So, determinants for the occurrence of NICL are important in clinical strategy for prevention...
and evaluation, but controversies exist among studies. For example, using embolic protection device is a risk factor for NICL in one study, but contradicts to many others. Other predictors such as age, symptomatic lesions, lesion side and so on are inconsistent in different literature. As most related researches are observational studies with low level of evidence, it is necessary to perform a systematic review and meta-analysis of English studies and databases for NICL occurrence determinants exploration. A recently published article tried to clarify this issue. However, risk factors studied were limited and some important factors such as type of stents and embolic protection devices were not included. So, in our study, we will include all accessible risk factors suitable for meta-analysis and try to provide a more comprehensive view about this issue.

METHODS
This systematic review and meta-analysis adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols (see online supplementary file 1).

Inclusion criteria for study selection

Studies
Any randomised clinical trial, as well as high-quality case–control study or cohort study will be included in our systematic review. All studies must be published in English. Case report, conference report and abstract will be excluded.

Participants
Studies that have patients with carotid artery atherosclerosis stenosis treated with CAS will be included. Carotid artery stenosis in studies should be defined as degree of stenosis more than 50% for symptomatic patients or more than 70% for asymptomatic patients according to the North American Symptomatic Carotid Endarterectomy Trial standard. Carotid artery stenosis related to the following factors will be excluded: arterial dissection, vasculitis disease, radiation-induced vasculopathy, fibromuscular dysplasia or suspected embolus.

Exposure factors
Data of demographics, laboratory test, imaging and so on observed in studies will be all extracted. For example, age, male gender, symptomatic lesions, hypertension, diabetes mellitus, cardiovascular disease, statin therapy, hyperlipidaemia and so on will be in our analysis. The patients will be divided into NICL-positive group and NICL-negative group according to the outcome of DWI-MRI.

Outcome measures
Our primary outcome of this meta-analysis will be NICL occurrence in included patients after CAS. NICL occurrence detected by DWI-MRI should be within a valid time window. The lesions are not seen before operation no more than 7 days but occur within 3 days on DWI-MRI after CAS. The secondary outcome is high occurrence rate of NICL (>40.5%). The cut-off is set according to previously reported literature and only patients from centres with high NICL occurrence will be studied. We will study risk factors for all patients with NICL and only patients from centres with high NICL occurrence rate, respectively.

Search strategy
Four English electronic bibliographic databases, namely PubMed, Embase, Web of Science and the Cochrane Library will be searched until 31 December 2018 to locate all relevant publications of the NICL detected by DWI-MRI after CAS. There will be no restriction to the publication year. A combination of the following keywords is going to be used: ‘carotid stenosis’, ‘carotid artery stenting’, ‘CAS’, ‘carotid angioplasty’, ‘ischemic lesion’, ‘cerebral embolism’, ‘diffusion-weighted imaging’, ‘DWI’. Search queries are optimised to fit the specific features of each database (see online supplementary file 2).

Data selection and analysis
Selection of studies
Initial screening of titles and abstracts was independently carried out by two reviewers (XB and XZ). The two reviewers’ lists of final included studies were compared by cross-checking. Inconsistencies were discussed and handled by a third reviewer (YC) when necessary. Two independent reviewers assessed whether articles met inclusion and exclusion criteria and evaluated the full text of selected articles. Two researchers extract data with discrepancies resolved by consensus. The process of study search strategy will be shown in a PRISMA-compliant flow chart (figure 1).

Figure 1 Flow diagram of literature for meta-analysis.
period and characteristics of the study population in total, including number of subjects with factors like age, sex, symptomatic lesions and so on which are referred in the literature. Two reviews (XZ and XB) will independently extract data from component studies and any disagreement will be resolved by consulting a third investigator.

Assessment of risk bias in included studies
Two reviewers will independently assess risk of bias for each included study according to the principle of the Grading of Recommendations Assessment, Development and Evaluation system for randomised controlled trials (RCTs) and the Newcastle-Ottawa Scale for observational studies (see online supplementary file 3, studies with scores of 5–9 points are identified as high-quality literature). The two authors will resolve any disagreements through discussion, with full review team if necessary. We will assess the risk of bias according to the following seven domains:
► Random sequence generation.
► Allocation concealment.
► Blinding of participants and personnel.
► Blinding of outcome assessment.
►Incomplete outcome data.
►Selective outcome reporting.
► Other possible bias.

We will grade the risk of bias for each domain as high, low or unclear and provide information from the study report together with a justification for our judgement.

Data analysis
If effect sizes are available or calculable in three or more studies for a specific outcome, a meta-analysis will be conducted using the software Review Manager. For continuous outcomes, we will use standardised mean difference with 95% CI, and for dichotomous outcomes, we will use the relative risk with 95% CI. If a meta-analysis is not feasible due to an insufficient number of studies, we will provide a narrative description of the study results alone. We will use a random-effects model to analyse included studies outcomes, but will use a fixed-effect model if there is little evidence of heterogeneity (I²<20%). What’s more, The χ² test will be used to test the heterogeneity. If I²>50%, we will explore the reason using subgroup based on studies, participants and exposure characteristics mentioned in the literature.

Subgroup analysis
Considering differences may exist between symptomatic and asymptomatic patients, we will stratify these two groups and analyse risk factors for either group patients, respectively.

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
This study aims to synthesise the extant literature on the association between risk factors and the occurrence of NICL after CAS and to provide a reliable evidence base for future research. The occurrence of NICL after CAS is common during procedure and is associated with poorer outcome. However, risk factors associated with NICL still remain uncertain due to inconsistent evidences and contradictory opinions. Therefore, it is necessary to perform a high-quality systemic review and meta-analysis, and our rigorous approach will provide a solid evidence for these issues.

Contributors
LJ and FL developed the initial idea for this study. YF, XB and XZ developed and revised the search strategy. TW, XZ and YC finished the study design. LJ, FL and YC were consulted about clinical issues. YF, WT and XB contributed to the original draft. YF and LL were responsible for the revision of the draft. YF and LL 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 for publication
Not required.

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