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Treatment strategies for asymptomatic carotid artery stenosis in the era of lipid-lowering drugs: protocol for a systematic review and network meta-analysis

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ABSTRACT

Introduction Carotid endarterectomy (CEA), carotid artery stenting (CAS) and best medical therapy (BMT) are the major treatments used for significant asymptomatic carotid artery stenosis (ACAS, ≥50%). However, the widespread use of lipid-lowering drugs in this century has improved BMT outcomes. This study aims to compare the treatment efficacy of current BMT, CEA+BMT and CAS+BMT in patients with significant ACAS.

Methods and analysis This protocol was designed based on the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols. Publication time for studies will be set from 1 January 2000 to 1 June 2020. We will search three databases: PubMed, EMBASE and The Cochrane Library. Suitable randomised controlled studies will be screened. The primary outcomes will include short-term and long-term mortality, stroke and myocardial infarction. OR and HR for dichotomous data and time-to-event data with 95% CIs will be calculated. Treatment effects among different therapies will be ranked according to the surface under the cumulative ranking curve and mean rank. A comprehensive evaluation of the risk of bias, heterogeneity and transitivity will be performed before data synthesis. Consistency and evidence quality will also be assessed.

Ethics and dissemination There will be no need for ethics approval as this systematic review is a summary and analysis of existing literature. Final results may be presented in international conferences or a peer-reviewed journal.

PROSPERO registration number CRD42019138942.

Strengths and limitations of this study

- This network meta-analysis will comprehensively compare the safety and efficacy of best medical therapy (BMT), carotid endarterectomy+BMT and carotid artery stenting+BMT in patients with significant asymptomatic carotid artery stenosis in the era of lipid-lowering drugs.
- The reporting of the protocol is based on the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols and has been registered in the International Prospective Register of Systematic Reviews.
- Two independent reviewers will perform study selection, data extraction and quality assessment to minimise personal bias.
- The heterogeneity among studies may be high, which may impact the final results.

INTRODUCTION

Significant asymptomatic carotid artery stenosis (ACAS, ≥50%) is not uncommon and remains a worldwide concern due to the unignorable rate of disability and death.[1–4] The prevalence of significant ACAS varies among studies, ranging from 2.2% to 5.2%.[3–5] Risk factors include age,[3 4] male sex, diabetes mellitus,[3 4 6] hypertension,[3 4 7] hyperhomocysteinaemia,[8 9] dyslipidaemia,[4 5] smoking[4] and metabolic syndrome.[10] This condition can also lead to cerebrovascular reserve impairment and hypoperfusion due to artery stenosis.[11] Approximately half of the patients show impairment in at least two neuropsychological domains and primarily reduced motor/processing speed and learning/memory capacity.[11] In addition, it may increase the risk of cerebrovascular events, especially brain infarction.[12] Previous randomised controlled studies (RCTs) have shown that the incidence risk of combined neurological events is 10%–20%.[13 14]

Carotid endarterectomy (CEA), carotid artery stenting (CAS) and best medical therapy (BMT) are the main therapeutic modalities for ACAS. Previous trials, including the Veterans Affairs Cooperative Study Group trial,[15] ACAS trial[14 16] and ACST-1 trial (Asymptomatic Carotid Surgery Trial),[17] demonstrated that the outcomes of

BMT were unsatisfactory. However, later studies showed that a reduction in the stroke risk could be achieved with BMT, mainly due to lipid-lowering drug use in this century.[18–20] At the same time, CEA and CAS need to be performed by experienced surgeons, ensuring a perioperative stroke rate lower than 3%.[21–23] In addition, although CEA has been shown to have a lower perioperative stroke risk than stenting, it has the potential to induce higher cranial nerve injury and myocardial infarction (MI).[22]

Choosing the best treatment for patients with ACAS is still a matter of debate. The widespread usage of lipid-lowering drugs, especially statins, over the last two decades, has led to great improvements in patient outcomes using medicine therapy alone.[24] One Cochrane systematic review showed that statins could reduce all-cause mortality and major vascular events without increasing adverse events.[25] Statins may decrease the levels of receptor activator of NF-κB ligand and inhibit neutrophil activation.[26] They may also stabilise plaques' fibrotic cap to avoid rupture.[27] However, the CEA procedural recommendations in the current guidelines mainly refer to the evidence of trials conducted decades ago before the use of lipid-lowering drugs.[18 28 29] Hence, currently, costly carotid surgical procedures may not be beneficial to patients with ACAS.[28]Furthermore, interim results of the Stent-Protected Angioplasty versus Carotid Endarterectomy-2 (SPACE-2) study provided new evidence of the non-inferiority of contemporary BMT in treating patients with ACAS.[30] Although comprehensive comparisons were reported by the previous meta-analyses of Galyfos *et al*[31] and Barkat *et al*,[32] they did not clarify the impact of lipid-lowering drugs on current BMT when compared with carotid interventions.

Based on the findings from a systematic review of 28 guidelines on the management of ACAS, carotid interventions are more likely to be recommended than BMT for these patients,[28] due to evidence from clinical trials performed decades ago when lipid-lowering drugs were underused. Further, recent RCTs such as the Aggressive Medical Treatment Evaluation for ACAS Study[33] and SPACE-2[30] have also shown different results. Ongoing RCTs such as the Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis trial[34] are still under recruitment. Hence, considering that there are biased recommendations from guidelines and evidence that has shown great improvements in BMT with lipid-lowering drugs, this network meta-analysis (NMA) will provide new evidence for best therapy selection for significant ACAS.

OBJECTIVE

This systematic review and NMA aims to compare the short-term safety and long-term efficacy of ACAS treatment modalities, including CEA+BMT, CAS+BMT and current BMT.

Methods

The protocol design of this NMA was in accordance with standards from Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (online supplementary 1).[35] We will update the PROSPERO record if any revision is made.

Patient and public involvement

This NMA aims to systemically review and summarise results of the existing literature. Patients and the public will not be involved.

Eligibility criteria

Types of studies

Full-text RCTs will be included, while other study types, such as case reports, will be excluded. Abstract-only studies will also not be eligible. The minimum number of patients within a study should be over 50 and hence, no case series will be included. There will be no language restrictions.

Types of participants

Patients with significant ACAS (≥50%, diagnosed with Duplex ultrasonography, CT/magnetic resonance angiography or angiography) due to atherosclerotic disease will be included. Asymptomatic status was defined as being free from any ipsilateral hemisphere vascular events (eg, stroke, transient ischaemic attack (TIA) and amaurosis fugax) for 6 months before study enrolment or admission.[36] Carotid artery stenosis caused by other reasons, including vasculitis, fibromuscular dysplasia, Moyamoya disease, vasospasm and dissection will not be included.[37]

Types of interventions

The type of interventions will include CEA+BMT, CAS+BMT and BMT alone. Suitable studies should contain a comparison of at least two therapeutic methods for ACAS. At the same time, BMT should include lipid-lowering agents as well as other traditional methods such as antiplatelets and antihypertensive drugs.[20] For CEA, we will include any type such as traditional, eversion or modified eversion CEA. CAS with or without embolism protection device will be considered.

Types of outcome measures

Primary and secondary outcomes will be compared in this NMA.[37]

Primary outcomes

1. Mortality, stroke or MI rates in the periprocedural period or during the postoperative period of 30 days.
2. Mortality, stroke or MI rates during follow-up (the mean time of follow-up should not be less than 6 months).

Secondary outcomes

1. TIA during the periprocedural period and follow-up.
2. Any other major complications (eg, cranial nerve injury, wound bleeding and lung infection).

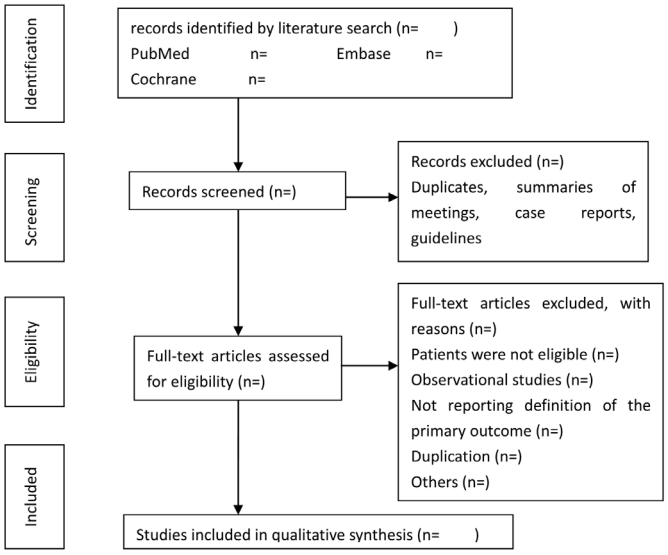

Figure 1 Flowchart of the study selection for this network meta-analysis.

Search strategy

Three electronic databases, including PubMed, EMBASE and The Cochrane Library, will be searched. A detailed search strategy for PubMed is shown in online supplementary 2. There will be no language limitation for the included studies. Publication time of suitable studies will be set from 1 January 2000 to 1 June 2020.

Data collection and analysis

Study screening

EndNote V.X7 literature management software will be used for study screening and data extraction. At initial search and screening, two reviewers (JL and XW) will independently review the titles and abstracts of search results to select possible eligible articles. Further screening of the full text by two reviewers (JL and XW) will then confirm whether the above selected researches are suitable and meet the eligibility criteria for inclusion. In case of any duplicated studies, group discussion to identify the study providing the most valuable information for final analysis will be held. According to a previously published pilot test,[37] we will adopt a revised form as shown in online supplementary 3 for the reviewers to calculate inter-rater reliability and ensure high agreement (≥80%) when performing screening. If there was any disagreement or discrepancies between the two reviewers in the screening process, discussion or consultation with a third reviewer will be conducted. We will demonstrate the process of study selection as shown in figure 1.

Data extraction

After the two screening processes, two reviewers (JL and XW) will independently extract data and document details. Data will be extracted according to a standardised form, including study characteristics (study type, author name, study period and publication year), participants (race, demographic characteristics, lesion features, etc), details for each intervention (drug dosage, CEA type, embolic protection device use, etc), comparisons (intervention compared, study period, sample size, etc) and outcomes (both primary and secondary outcomes). Group discussion will solve disagreements between the two reviewers. If there is any missing information in a study, we will try to contact the authors. We will exclude the study if no response is received. The extracted data will be documented in two formats according to its type. Continuous data will be presented as mean and SD, while dichotomous data will be presented as frequencies for both events in each study arm.

Assessment of risk of bias

Another two reviewers (TW and LL) will independently assess risk of bias. A third reviewer (LJ) will be in charge of resolving the different opinions between the two reviewers. Risk assessment of RCTs will be according to the Grading of Recommendations, Assessment, Development and Evaluation criteria for NMA.[38]

Heterogeneity and transitivity assessment

Clinical heterogeneity will be analysed based on the variability in different aspects involving study types, treatment methods, follow-up periods and patients' characteristics among studies.[39] Methodological heterogeneity will be evaluated through I^2 calculation for each pairwise comparison. If there are high levels of heterogeneity ($I^2 \geq 50\%$ or $p<0.1$), the source of heterogeneity will be further clarified by subgroup or sensitivity analyses.[40] Assumption of transitivity across different treatment methods will be assessed through possible confounding factors among pairwise comparisons[41] and boxplots or percentages will be used.[37 42 43] Further, data synthesis and analysis will be performed only when the above factors are guaranteed.

Data synthesis

Measures of outcomes

In this NMA, pairwise comparisons will be performed to calculate OR and HR for dichotomous data and time-to-event data, respectively.[37 44 45] Additionally, 95% CIs will be presented. The hierarchy among different treatments will be estimated by the surface under the cumulative ranking curve (SUCRA) and mean rank.[41 46] In case of inadequate studies for any comparison or observed outcomes, a narrative description will be performed rather than a quantitative synthesis. Stata V.14 (StataCorp, 2015) will be used by a statistician for quantitative synthesis in each pairwise and network meta-analysis (figure 2). Summary effects will be presented in the forms of forest plots, league tables, and rankograms.

Direct treatment comparisons

Direct treatment comparisons will initially be conducted for any direct comparison containing more than one study. The summary effect with the associated 95% CI will be analysed by Bayesian random-effects models.[47]

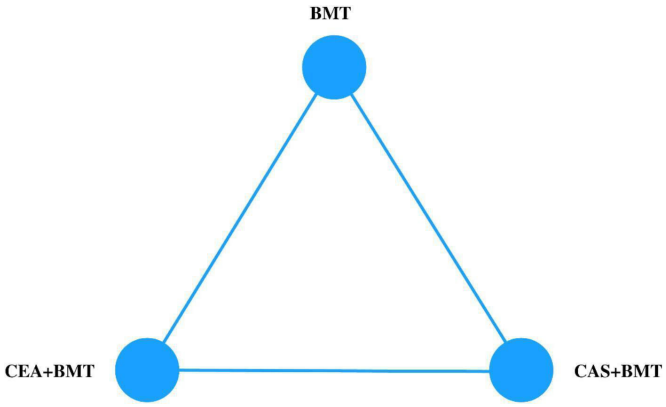

Figure 2 Network of all possible pairwise comparisons between the eligible interventions. BMT, best medical therapy (containing lipid-lowering drugs); CAS, carotid artery stenting; CEA, carotid endarterectomy.

Indirect and mixed comparisons

A three-level hierarchical, random-effects model will be used for data analysis.[48] Mean rank and SUCRA will be used to estimated relative effectiveness among different treatments. For treatment rankings with multiple outcomes, rank-heat plots will be applied.[49] For direct, indirect and mixed comparisons, the normal distribution will be used as the vague prior.

Assessment of statistical inconsistency

The loop-specific[50] and the node-splitting methods[51] will be used for local evaluation of data used in direct and indirect comparisons. The design-by-treatment interaction model[52] will be used for global evaluation.

Subgroup and sensitivity analysis

If data are sufficient, subgroup analyses will be performed. Some confounding factors, such as gender, race and types of lipid-lowering drugs used may be investigated for subgroup analysis. We will conduct network meta-regression analysis to explore the effect of research year and country if more than 10 studies were available. Sensitivity analysis will be conducted by excluding studies one by one to observe the impact on the final results.[37 40]

Assessment of publication bias

Publication bias will be evaluated using network funnel plots.

DISCUSSION

This NMA will comprehensively compare treatment effects among different therapies for ACAS in the era of lipid-lowering drugs. We hope the hierarchy established among different therapies will provide clinicians valuable evidence to aid decision-making for patients with ACAS, as well as guide future studies. However, some limitations in this study must be considered. The heterogeneity among studies may be high, which may impact the final results.

ETHICS AND DISSEMINATION

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

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

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