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Benefit of carotid revascularisation for women with symptomatic carotid stenosis: protocol for a systematic review

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ABSTRACT

Introduction Carotid intervention in the form of endarterectomy or stenting is the current standard of care for the majority of patients with symptomatic high-grade carotid stenosis. However, some randomised controlled trials (RCT) have demonstrated that women benefited significantly less from intervention than men. It is unclear if this is a true phenomenon or a study sampling artefact, as women were severely under-represented in all RCTs of carotid revascularisation. A systematic review is needed to summarise the existing data and to answer the question of whether a women-only trial for symptomatic patients with ipsilateral carotid stenosis is scientifically necessary and ethically permissible.

Methods and analysis We will systematically search Medline, Embase, PubMed and the Cochrane libraries for all studies with data from RCTs that included women and compared either endarterectomy with stenting or revascularisation (by means of endarterectomy or stenting) with medical therapy in patients with symptomatic carotid stenosis. Search dates will be restricted to 1991–2018. Two reviewers will conduct screening search results, study selection, data extraction and quality assessment. We will include all studies reporting outcomes of interest. Planned subgroup analysis based on revascularisation technique, degree of stenosis and timing of intervention from the index event will be conducted with enough data.

Ethics and dissemination This research is exempt of ethics approval as no primary data will be collected. The results will be published in peer-reviewed journals and disseminated through national and international-level conferences and scientific meetings. The result of this comprehensive review will provide useful information on whether further RCTs are required to study a women-only population with symptomatic carotid disease.

PROSPERO registration number CRD42019134967.

Strengths and limitations of this study

- This protocol was developed and prepared according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement.
- This study benefits from a comprehensive search strategy, designed to retrieve a broad spectrum of relevant randomised controlled trials for the research question.
- Heterogeneity will be explored using subgroup analysis based on a priori defined factors.
- Depending on our ability to extract sufficiently detailed sex-based data, individual patient data analysis and network meta-analysis may be needed to analyse data in previously published trials.

BACKGROUND

Carotid intervention (either endarterectomy or stenting) is the current standard of care for the majority of patients with symptomatic high-grade carotid stenosis.[1] The benefits of surgical intervention appear to be highly time dependent, declining rapidly after the symptomatic event.[2] However, the management of carotid stenosis in women remains a topic of some controversy due to apparent differences in the likelihoods of benefit for men and women.[3–5] It is not clear whether the observed difference between men and women is a true phenomenon or an artefact of study sampling, in that women were consistently under-represented in early randomised controlled trials (RCT).[6 7] If there is indeed a difference, it may reflect biological, psychological or sociological factors. For example, it is recognised that women take longer to get to hospital after onset of stroke, but they are also less likely to receive diagnostic tests and to receive secondary prevention drugs.[8 9] As a consequence, women have worse outcomes, increased disability and decreased quality of life after ischaemic stroke.[10 11] Women appear to experience their strokes earlier after the transient ischaemic attack (TIA) or minor stroke, potentially shortening the time window for effective intervention.[11 12]

In light of these potential differences, it is not clear whether stroke prevention strategies for women and men should be different, particularly in the setting of symptomatic carotid stenosis. Some experts have called for repeating landmark trials, only with female patients.[4 5] Is such a step necessary and ethical based on available knowledge?

Rothwell *et al*[2] were the first to report significant sex-related differences for surgical intervention of symptomatic carotid disease with combined analysis from the two earliest RCTs (European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial (NASCET)). This analysis showed that women in the medical group had a more rapid decline in the incidence of ipsilateral ischaemic stroke after TIA/minor stroke than did men. According to this analysis, the clear benefit of carotid endarterectomy (CEA) in women with 70% stenosis was present only for the first 2 weeks after the last clinical event, whereas men could benefit up to 12 weeks after the last event.[2] Alternatively, there has been a suggestion that rates of poor outcomes are higher in women who undergo CEA. In Rothwell *et al*'s analysis, the 30-day risk of perioperative stroke or death was higher in women compared with men (8.7% vs 6.8%; p=0.004).[2] Combination analysis from NASCET and the ASA and Carotid Endarterectomy studies showed an increased 30-day mortality in women versus men (2.3% vs 0.8%; p=0.002). However, perioperative risk of stroke or death was not significantly different.[13]

The Carotid Revascularization Endarterectomy vs Stenting Trial (CREST)[14 15] is the most recent and largest RCT comparing carotid artery stenting (CAS) to CEA for patients with symptomatic and asymptomatic carotid stenoses. Unlike earlier RCTs, CREST had a preplanned secondary subgroup analysis to address sex differences. Specifically, CREST was designed to achieve 90% power to detect an effect of sex on outcomes.[14] According to this analysis, there were no increased periprocedural risks in symptomatic women in the CEA arm of CREST.[16] However, there was a higher periprocedural stroke risk in women for CAS than for CEA (5.5% vs 2.2%; p=0.013), while there were no significant differences in men (3.3% vs 2.4%; p=0.26).[15 16]

Other individual RCTs focusing on sex differences in outcomes of CAS versus CEA have provided limited and conflicting data for women with carotid stenosis.[17–19] A combined sex-stratified analysis of patient data at 120 days after treatment from the three major European RCTs on carotid stenting in symptomatic patients performed by the Carotid Stenting Trialists' Collaboration found that surgical risk was higher in women than in men, whereas risk of stenting was virtually unaffected by sex.[20] However, their most recent long-term pooled analysis did not detect any significant treatment differences between sexes.[21]

Interpreting these results is challenging because women were severely under-represented in all major carotid revascularisation trials, with most trials enrolling less than 30% women.[22] Although the most successful RCT representing women in carotid intervention was the CREST trial, its population only included 35% women.

Moreover, modern medical management of carotid disease has significantly advanced over the last 30 years. While high-potency statins, tight blood pressure control, antithrombotic agents, along with lifestyle modifications and smoking cessation are now standard of care, only 15% of all patients in the NASCET trial were on any lipid-lowering agent.[23]

There are currently two ongoing trials comparing modern medical therapy to modern medical therapy and CAS/CEA in asymptomatic (CREST2)[24] and lower risk symptomatic patients (ECST2).[25] Overall, management of carotid stenosis in women is receiving an increased amount of attention. Several researchers have recently called for a sex-specific trial of carotid intervention in women with symptomatic stenosis.[4 5] A modern, large RCT with a more pragmatic design, including an elderly population, may answer some questions related to the risk and benefits of carotid intervention in women. However, before proposing and conducting new research, a systematic review and meta-analysis should be done to identify whether the answer to the question is already available through existing data.[26] To conduct a novel RCT when available data provide an answer to a clinical question would be unethical, in that it would deprive patients of standard therapies for multiple reasons: patients may be harmed, and resources would be wasted.

To date, few systematic reviews have investigated sex-related differences in the management of carotid stenosis. None has definitively answered the question of whether symptomatic women derive less benefit from carotid intervention. Some used combined data from asymptomatic and symptomatic patients or did not include sex-related differences in their primary outcome.[27 28] Others were weakened by the poor quality of analysed papers and included case series and very heterogeneous non-randomised studies.[29]

Therefore, we propose to perform a systematic review of all RCTs for symptomatic carotid stenosis comparing surgical intervention (CEA or CAS) and/or medical management that included women. Anticipating significant between-trial heterogeneity, network meta-analysis (NMA) and individual patient data analysis may be necessary.

REVIEW QUESTION

What are the benefits and harms of carotid intervention (endarterectomy and/or stenting) for women with symptomatic carotid stenosis?

OBJECTIVES

The objective is to perform a systematic review of the evidence of carotid intervention in women with symptomatic carotid disease. The results from this review will help determine whether another trial is scientifically necessary and ethically permissible, and may help to inform the design of such a trial.

METHODS

This protocol was developed and prepared according to the Preferred Reporting Items for Systematic Review

Table 1 Inclusion and exclusion criteria

	Inclusion	Exclusion
Participants	Participants with symptomatic (A) carotid stenosis (B) A. Symptomatic is defined as ipsilateral TIA or minor stroke within 6 months. B. Carotid stenosis is defined as greater than 50% stenosis (or the equivalent measurement).	Participants with asymptomatic carotid stenosis, carotid artery occlusions, carotid near-occlusion, concomitant coronary bypass surgery and redo surgeries for carotid stenosis
Interventions	Management by endarterectomy and/or stenting	Intervention done for tandem occlusions in the setting of acute ischaemic stroke, redo interventions, concomitant interventions with other surgery, comparisons of types or approaches for the same intervention
Comparators	Medical therapy, endarterectomy and stenting	
Outcomes	*Primary outcomes*: composite of any stroke or death at 30 days *Secondary outcomes*: 1. 30-day disabling stroke or death, myocardial infarction, different types of stroke. Disabling stroke is defined as any stroke resulting in new or increased disability with a score on the modified Rankin Scale (mRS) of 3 or greater, 30 days or more after stroke onset. 2. Intermediate and long-term outcome, including stroke recurrence, death and rates of restenosis according to individual studies' prespecified outcomes	
Timing	Studies published from 1990 onwards.	
Study design	Randomised controlled trials (RCT), meta-analysis or systematic reviews reporting individual patient data from RCTs	Systematic reviews/meta-analysis, observational studies (eg, cohorts, case–controls, cross sections), case series/reports and non-empirical studies (eg, editorials, comments, letters)
Language	English and French	

TIA, transient ischaemic attack.

and Meta-analysis Protocols (PRISMA-P) statement[30] (see online supplementary appendix).

Eligibility criteria

The inclusion and exclusion criteria are presented in table 1.

Data sources and search for studies

A search strategy will be developed through an iterative process with the review team, including a medical library scientist. We will search Ovid Medline, Embase and PubMed. We will also search the Cochrane Library on Wiley. Search dates will be restricted to 1991–2018, based on the start of the modern era of carotid intervention with the NASCET trial published in 1991.[31] Strategies used a combination of controlled vocabulary (eg, 'carotid stenosis', 'symptomatic stenosis', 'carotid revascularization', 'carotid endarterectomy', 'carotid stenting', 'sex characteristics', 'carotid endarterectomy', 'stenting') and keywords (eg, 'women', 'female', 'sex', 'gender', 'symptomatic') (see online supplementary appendix).

Database searches will be supplemented by searching relevant websites, including ClinicalTrials.gov. Bibliographies from relevant systematic reviews and meta-analysis will be searched to ensure relevant RCTs are captured.

Study selection

Duplicates across searches will be identified and removed using Covidence. Two authors will independently screen articles in a two-level process. Level 1 will involve screening based on title and abstract. Studies that score 'Yes' or 'Maybe' after two reviews in this phase will be brought forward for full-text (level 2) evaluation. Full-text screening will use a procreated article screening form (see online supplementary appendix). We will use a 'liberal accelerated' method at this level, meaning that two reviews are required to exclude a study. The process of study selection will be described using a PRISMA flow diagram. A pilot exercise will occur at both levels, with 100 records piloted at level 1 and 25 records piloted at level 2. This allows for testing of the screening questions and for calibration among reviewers. Articles not available electronically will be ordered through interlibrary loan. Those not received within 30 days of the request will be excluded with the reason for exclusion labelled

'full text not available'. Where study eligibility is unclear during full-text screening, authors will be contacted twice, 2 weeks apart, for additional information. If no response is received, the article will be excluded.

Data collection process

Data will be independently extracted by two reviewers using a standardised data extraction form. We will pilot-test the data extraction form with five randomly selected articles to train data extractors as well as to assess the sufficiency of the data extraction manual to ensure inter-rater reliability. We aim to achieve high agreement (≥80%) between two reviewers.

A data abstraction form will capture four types of data:

1. Bibliographic data. First author last name, publication year, country, funding source.
2. Study population data. Demographics (including age, sex), number of participants randomised to each group, relevant medical history, severity of ipsilateral carotid stenosis, type (TIA, retinal ischaemia, hemispheric stroke) of most recent ipsilateral event, days elapsed between most recent event and treatment.
3. Outcome data. Combination of any stroke or death at 30 days, disabling stroke or death, different types of stroke, myocardial infarction, local access complications, restenosis. Total number of randomised patients, the interventions being compared, and follow-up duration will be extracted from included studies.
4. Effect modifier data will be extracted on a per-trial basis (see the text that follows).

Data that may act as effect modifiers include:

1. Population characteristics (eg, mean or median age, proportion of female participants, functional status at presentation, medical history, smoking history, stenosis characteristics, including degree, location and presence of contralateral carotid stenosis).
2. Intervention characteristics (eg, CEA vs carotid stenting/angioplasty vs medical management only, revascularisation success rate, residual stenosis, restenosis rate).

After data extraction, two reviewers will resolve disagreements by discussion. A third reviewer will adjudicate in the event of unresolved disagreements.

Risk of bias assessment

Risk of bias will be assessed by one reviewer, with verification done by a second reviewer, using the Cochrane Risk of Bias Tool.[32] We will determine an overall judgement per study and outcome class using the Cochrane guidance. The studies' level of quality will be presented in a table and narrative summary. The impact of study quality will be evaluated in the discussion. Where appropriate, a sensitivity analysis will be conducted excluding poor quality trials.

Strategy for data synthesis

We will assess patient characteristics, study design information and event rates of the comparator arms. We will use various measures (I^2) to assess for statistical heterogeneity. If quantitative synthesis is not appropriate or if the data are insufficient, the findings of our systematic review will be narratively reported. If quantitative analysis is possible, the results of individual outcomes will be pooled and meta-analysis will be performed using STATA. Furthermore, in case of a significant between-study heterogeneity, an NMA will be performed to establish multilevel comparisons among interventions. We will use the NMA PRISMA Extension to guide report preparation.[33] Grading of Recommendations Assessment, Development and Evaluation methods will be used for NMA to appraise the strength of evidence for all analyses.[34]

Analysis of subgroups or subsets

Planned subgroup analyses will be conducted where possible given available data. Specifically, we will examine the following comparisons:

1. Women with any intervention versus men with any intervention.
2. Women with any intervention versus women without intervention.
3. The above, stratified by degree of stenosis, with 50%–69% and 70%–99% being commonly reported thresholds.
4. The above, based on the intervention technique (endarterectomy or stenting).
5. The above, based on timing of intervention after the index event (within 48 hours, within 2 weeks, within 4 weeks, within 12 weeks and greater than 12 weeks).

PATIENT AND PUBLIC INVOLVEMENT

No patients will be involved.

CONCLUSION

We aim to compare treatment outcomes between sexes in patients with symptomatic carotid artery stenosis. The results of this work may help clinicians to guide management of symptomatic carotid stenosis in women and may also act as a useful tool in patient selection for intervention in this group population. We also hope that this work will provide useful information on whether an RCT for women with symptomatic carotid stenosis is scientifically necessary and ethically permissible.

Contributors OB, BD and MS drafted the manuscript protocol. OB, BD, CH and MS contributed to the development of the selection criteria, article screening strategy and data extraction criteria. OB and MS developed the search strategy. OB, BD, DD, VH, CH, SG, MF and MS read, provided feedback and approved the final protocol. OB acts as guarantor of the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Formal ethics approval is not required as no primary data will be collected. The results will be published in a peer-reviewed journal. We will also disseminate our results through conference presentations and the popular press.

Provenance and peer review Not commissioned; externally peer reviewed.

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