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Identifying sex-specific differences in the carotid revascularisation literature: findings from a scoping review

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ABSTRACT

Objective No systematic review of the literature has dedicated itself to looking at the management of symptomatic carotid stenosis in female patients. In this scoping review, we aimed to identify all randomised controlled trials (RCTs) that reported sex-specific outcomes for patients who underwent carotid revascularisation, and determine whether sufficient information is reported within these studies to assess short-term and long-term outcomes in female patients.

Design, setting and participants We systematically searched Medline, Embase, Pubmed and Cochrane libraries for RCTs published between 1991 and 2020 that included female patients and compared either endarterectomy with stenting, or any revascularisation (endarterectomy or stenting) with medical therapy in patients with symptomatic high-grade (>50%) carotid stenosis.

Results From 1537 references examined, 27 eligible studies were identified. Sex-specific outcomes were reported in 13 studies. Baseline patient characteristics of enrolled female patients were reported in 2 of those 13 studies. Common outcomes reported included stroke and death, however, there was significant heterogeneity in the reporting of both periprocedural and long-term outcomes. Sex-specific differences relating to the degree of stenosis and time from index event to treatment are largely limited to studies comparing endarterectomy to medical therapy. Adverse events were not reported by sex.

Conclusions Only half of the previously published RCTs and systematic reviews report sex-specific outcomes. Detailed analyses on the results of carotid artery intervention for female patients with symptomatic stenosis are limited.

INTRODUCTION

Carotid revascularisation can benefit select patients with symptomatic carotid stenosis. However, there is debate within the community regarding the degree of benefit observed in female patients.[1 2] Interpretation of extant trial data is challenging, as the trials were not designed to study sex differences, and it is unknown whether observed differences reflect true biological differences or relate to study sampling.[3–5] In addition, while interaction terms have been non-significant in many of the major trials, there has been, in general, an under-representation of female patients within carotid stenosis trials. A failure to see an interaction effect may therefore reflect inadequate statistical power.[6] This has led to the proposal of novel randomised controlled trials (RCTs) of carotid revascularisation versus best medical therapy (BMT) in women only.[2] These RCTs would randomise female patients away from standard-of-care interventions and would need to have a strong scientific foundation to be ethically justifiable.

While prior systematic reviews have looked at sex-based differences in carotid stenosis management, they have focused on carotid endarterectomy (CEA) in asymptomatic and symptomatic patients, or included non-randomised data, resulting in heterogenous findings. No systematic review has yet addressed the optimal management (CEA, carotid stenting (CAS) or BMT) of female patients with recently symptomatic high-grade carotid stenosis.

The goal of this scoping review is to determine whether the benefit of carotid revascularisation in female patients can be reliably assessed using existing RCT data, and whether there are sufficient data on outcomes to assess the need for future trials.

METHODS

The authors declare that all supporting data and methodological detail are available within the article and online-only supplement. The protocol for this study was previously published,[7] and this study complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for scoping reviews.[8] As a scoping review, our aim was to identify publications of RCTs or related material (systematic reviews, meta-analyses) that reported sex-specific data in relation to the management

Table 1 List of studies with sex-specific outcomes

Study	Female/male	Interventions	Per cent stenosis	Outcome(s) assessed
ECST[11]	850/2168	CEA/BMT	0%–99%	Model of stroke-free life expectancy stratified by age and per cent stenosis
NASCET[12]	873/2012	CEA/BMT	>70%; 50%–69%;<50%	5-year risk of ipsilateral stroke stratified by per cent stenosis
SPACE[13 14]	338/858	CEA/CAS	>50%	► 30-day risk of death of any cause, ipsilateral stroke or haemorrhage ► 30-day risk of stroke and death and 2-year risk of ipsilateral ischaemic stroke (combined)
EVA-3S[15]	130/397	CEA/CAS	>60%	30-day risk of death, any stroke and 4-year risk of ipsilateral stroke (combined)
CAVATAS[16]	152/352	CEA/CAS	>60%	8-year risk of any stroke or perioperative death (combined)
ICSS[17]	503/1207	CEA/CAS	>50%	120-day risk of stroke, death or myocardial infarction (combined)
CREST[3 18]	872/1630	CEA/CAS	>50% >60%	► 30-day risk of myocardial infarction, stroke or death ► 4-year risk of myocardial infarction, stroke or death ► 30-day (myocardial infarction, stroke or death) and 10-year risk of ipsilateral stroke (combined)
Pooled individual patient data meta-analysis				
NASCET and ESCT[4 5]	1718/4175	CEA/BMT	>50%	► 5-year relative risk of ipsilateral ischaemic stroke or death, stratified by time from last symptomatic event to randomisation ► 5-year risk of stroke and death in surgery patients, stratified by per cent stenosis and time from last symptomatic event to randomisation ► 5-year risk of ipsilateral ischaemic stroke and any stroke or death within 30 days of randomisation (combined) ► 5-year risk of ipsilateral ischaemic stroke and any stroke or death within 30 days of randomisation (combined), stratified by per cent stenosis
EVA-3S, SPACE, ICSS, CREST trials[9]	1437/3317	CEA/CAS	Multiple thresholds	► 120-day risk of any stroke or death and 5-year risk of ipsilateral stroke (combined) ► 5-year risk of ipsilateral stroke
EVA-3S, SPACE, BACASS, ICSS, CREST trials[10]	1466/3395	CEA/CAS	Multiple thresholds	30-day risk of death or any stroke (combined)

BACASS, Basel Carotid Artery Stenting Study; BMT, best medical therapy; CAS, carotid artery stenting; CAVATAS, Carotid And Vertebral Artery Transluminal Angioplasty Study; CEA, carotid endarterectomy; CREST, Carotid Revascularisation Endarterectomy Versus Stenting Trial; ECST, European Carotid Surgery Trial; EVA-3S, Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis; ICSS, International Carotid Stenting Study; NASCET, North American Symptomatic Carotid Endarterectomy Trial; SPACE, Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy.

of symptomatic carotid stenosis (surgical intervention (CEA, CAS) and/or BMT). Symptomatic stenosis was defined as carotid narrowing greater than 50% (or equivalent measurement) associated with an ipsilateral transient ischemic attack (TIA), amaurosis fugax or stroke.

We relied on individual trial reporting of carotid stenosis and outcomes, or summary analysis reported by systematic reviews. Four databases were searched: Ovid Medline, Embase, PubMed and the Cochrane Library on Wiley from 1991 to 2018, as per our protocol[7] with an updated

search of Ovid Medline from 2018 to 2020 (search terms are listed in online supplemental table I). We collected publication information, study population information, severity of ipsilateral carotid stenosis, type of ipsilateral event, treatment allocation, follow-up time and outcome data. These results were described qualitatively. As per scoping review guidelines, a formal assessment of methodological quality was not performed.[8]

RESULTS

We identified 13 studies reporting sex-specific outcomes (table 1 and online supplemental figure 1 and table II) representing eight RCTs, three individual patient-data meta-analyses and 3184 female patients.[3 4 9–18] Inclusion criteria were largely consistent across studies with the majority recruiting symptomatic patients (TIA, non-disabling ipsilateral stroke or retinal infarction), with carotid stenosis >50% based on either North American Symptomatic Carotid Endarterectomy Trial (NASCET) Collaborators or European Carotid Surgery Trialists' (ESCT) Collaborative Group criteria. Asymptomatic patients were also recruited in Carotid Revascularisation Endarterectomy Versus Stenting Trial (CREST).[3] Baseline patient characteristics by sex were reported in two sub-analyses of the NASCET and CREST (online supplemental table III).[3 12] Individual patient data meta-analyses that compared CEA to BMT[4] or CEA to CAS[9 10] did not evaluate sex-specific baseline characteristics.

Commonly reported outcomes included stroke (any or ipsilateral), death (any cause) or a combination thereof. The timepoints at which these outcomes were evaluated varied widely from trial to trial. Individual trials reported a range of follow-up times for long-term outcomes (2–10 years), often combining these measures with periprocedural events (30-day events; figure 1). A Cochrane analysis comparing CEA to CAS was able to assess 30-day periprocedural risk of death and stroke by acquiring individual patient data from five trials.[10] Sex-specific assessments of long-term outcomes were largely limited to 5-year risk of stroke (ipsilateral or any)±death.[4 5 9] Sex-specific differences relating to the degree of stenosis were only reported in studies comparing CEA to BMT.[4 5]

Overall, the individual patient data meta-analysis of NASCET and ESCT reported a lower absolute risk (ARR) for 5-year stroke and periprocedural death with CEA in women compared with men (2.8% (2.2–7.8) vs 11.0% (7.6–14.4)).[5] When stratified by per cent stenosis, women with ≥70% benefited from the procedure (ARR: 9.9%), while those with 50%–69% stenosis did not. A similar pattern was observed with time to procedure: only women who had a CEA performed within 2 weeks of the index event had a significant reduction in recurrent stroke.[4] Comparing CEA to CAS at 30 days, there was a non-significant trend towards an increased hazard with CAS.[10] No study compared CAS to BMT. Adverse events were not reported by sex.

DISCUSSION

We sought to perform a scoping review of the literature to determine the type and amount of information available relating to different management strategies for female patients with symptomatic carotid stenosis. Individual patient data analyses from high quality trials have reported on female outcomes for only select comparisons (CEA to BMT and CEA to CAS) in relation to specific outcome measures, (eg, 30-day outcome and 5-year ipsilateral stroke). No conclusions can be drawn about CAS versus CEA, or in relation to per cent stenosis or time to treatment. However, our appraisal of data available within individual trials indicates that a detailed, aggregated

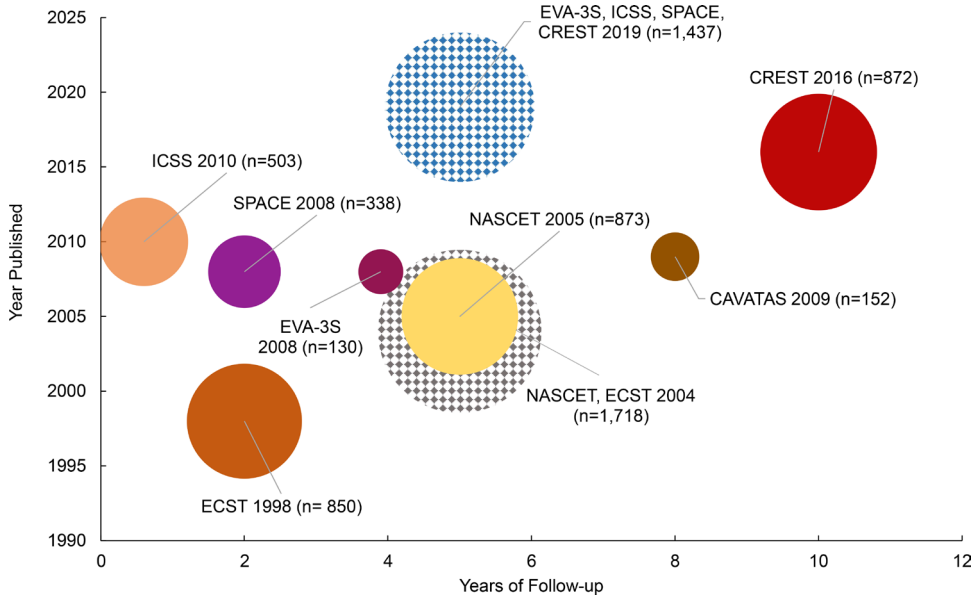

Figure 1 Sex-specific long-term outcomes. n represents the number of female patients. Pattern areas represent pooled individual patient data analysis.

subgroup analysis in female compared to male patients is possible (table 1 and online supplemental table II). We contend that such an analysis would be necessary before female-only RCTs of carotid revascularisation are considered. A trial that would randomise female patients with symptomatic carotid stenosis away from standard revascularisation would need a strong scientific argument to be ethically justified,[19] and we believe our scoping review demonstrates that more work is needed to draw any conclusions from the available scientific evidence.

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Contributors Study was designed and conceptualised by VY, MS and OB. Search and screening was performed by BD, CH and OB. Manuscript was drafted by VY. Critical manuscript revision was performed by DD, SG, MF, PR and VH for intellectual content.

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SUPPLEMENTAL MATERIAL

Supplemental Methods and Search Results:

Eligibility Criteria:

Studies related to asymptomatic carotid stenosis, carotid artery occlusions or near-occlusions, were excluded. Meta-analysis or systematic reviews reporting individual patient data from RCTs were also included, however observational studies, case series, and reports were not included due to the elevated risk of bias associated with non-randomized data. We had no restrictions on country of study, ethnicity, sex, socio-economic status of study populations, or healthcare location of research. We only included studies presented in the English and French language.

Information Sources and Search:

Supplementary searches included scanning the reference list of included studies and reviews identified through the primary search and ClinicalTrials.gov. The detailed search strategy using keywords and Medical Subject Headings (MeSH) terms is provided in Supplement Table I.

Study Selection:

Screening and full-text review was conducted using Covidence Systematic Review software (Covidence, Melbourne, Australia). A two-stage screening was performed by two independent reviewers (OB and BD). In stage one, both abstracts and titles were screened for potentially relevant articles. In stage two, full-text screening was performed using a screening form created a priori. A liberal accelerated method was utilized, requiring two reviewers to exclude a study. A pilot screening exercise was performed at both levels, with 100 records piloted for level 1 and 25 records piloted at level 2. Disputes were resolved by author, MS.

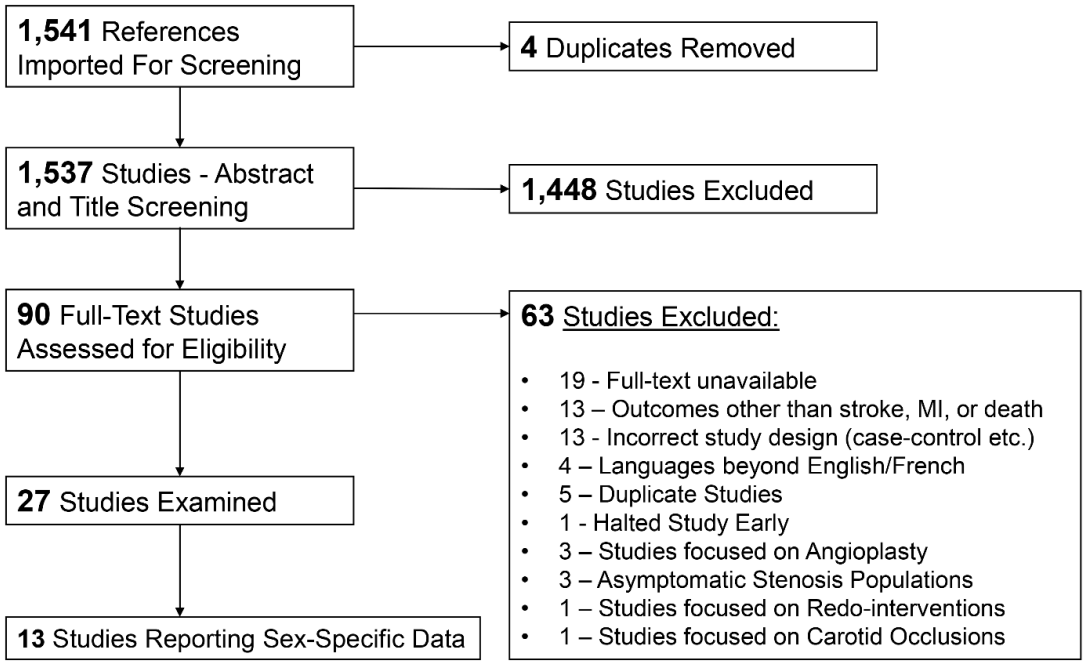
Data Charting Process and Selected Items:

Data extraction was conducted independently by each reviewer using an *a priori* collection form. We collected publication information, study population information, severity of ipsilateral carotid stenosis, type of ipsilateral event, treatment allocation, follow-up time, and outcome data.

Article Selection:

Among the 1,537 records retrieved, title and abstract screening narrowed our search to 90 articles that underwent full text screening. Reasons for exclusion included: assessment of different outcome, alternate study designs, and lack of full-text availability (i.e. published abstracts). All included studies were peer-reviewed original research contributions using clinical trial data.

Supplemental Figure 1: PRISMA Diagram



Supplemental Table I: Sample Search Strategy

1 Carotid Stenosis/ or carotid stenosis.kw.
2 (carotid adj3 (stenos$ or ulcer$ or plaque$ or narrow$ or obstruct$ or occlus$ or constrict$)).tw.
3 1 or 2
4 Endarterectomy, Carotid
5 endarterectom*.tw,kw.
6 STENTS/ or stent*.tw,kw.
7 carotid revascularization.tw,kw.
8 or/4-7
9 3 and 8
10 WOMEN
11 Sex Characteristics
12 sex factors
13 (female or women).tw
14 (sex or gender or women or female).ti.
15 (gender based or gender specific).tw.
16 ((sex or gender) adj2 (difference* or disparit*)).tw.
17 or/10-16
18 9 and 17
19 randomized controlled trial.pt.
20 controlled clinical trial.pt.
21 randomi?ed.ab.
22 placebo.ab.
23 clinical trials as topic.sh.
24 randomly.ab.
25 trial.ti.
26 groups.ab.
27 or/19-26
28 9 and 27
29 symptomatic.tw,kw.
30 28 and 29
31 18 and 27
32 30 or 31
33 limit 32 to yr="1990 -Current"
34 case reports.pt.
35 33 not 34
36 limit 35 to (english or french)

Supplemental Table II: Full List of Included Studies (n=27)

Study	Study Type	Interventions	Percent Stenosis	Outcome Assessed
North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET)	RCT	CEA / BMT	70-99%	- 2-year longitudinal collection of death and stroke events[1] - 8-year longitudinal collection of stroke events (disabling, ipsilateral)[2] - 5-year risk of ipsilateral stroke stratified by percent stenosis (sex-specific data available)[3]
European Carotid Surgery Trialists' Collaborative Group (ECST)	RCT	CEA / BMT	70-99% 0-29%	- 30-day risk of death or disabling stroke[4] - 3-year longitudinal collection of death and stroke events[4] - 8-year longitudinal collection of death and stroke events[5] - Model of stroke-free life expectancy stratified by age and percent stenosis[6]
Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)	RCT	CEA / CAS	70-99% 50-69% 0-49%	- 30-day risk of death or disabling stroke[7] - 3-year longitudinal collection of death and stroke[7] - Sex-specific 8-year longitudinal collection of stroke events (disabling, TIA) and/or death[8]
Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE)	RCT	CEA / CAS	> 50%* > 80%†	Death, stroke, myocardial infarction + Composite at 1 year[9]
Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE)	RCT	CEA / CAS	> 50%	- 30-day risk of death, stroke, bleeding, or composite[10] - Sex-specific 30 day risk of composite outcome[10]

Study	Study Type	Interventions	Percent Stenosis	Outcome Assessed
				- 2-year risk of ipsilateral ischemic stroke plus 30-day risk of stroke and death[11] - Sex-specific 2-year risk of ipsilateral ischemic stroke plus 30-day risk of stroke and death[11] - Study aimed at identifying risk factors associated with outcome[12]
Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S)	RCT	CEA / CAS	> 60%	- Stroke or death within 30 days of procedure and at 6 months[13] - stroke or death within 30 days of procedure and at 4 years[14] - Sex-specific 30-day risk of death, any stroke and 4 year risk of ipsilateral stroke (combined) [14] - Stroke or death at 5 years and 10 years[15]
Basel Carotid Artery Stenting Study (BACCAS)	RCT	CEA / CAS	> 70%	- 30-day risk of stroke, death, and myocardial infarction[16] - patency of vessel after 2 years[16]
Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST)	RCT	CEA / CAS	> 50%* > 60%†	- stroke, myocardial infarction, death within 30 days of randomization[17] - ipsilateral stroke at 4 years[17] - Sex-specific 30-day and 4 year risk of myocardial infarction, stroke, or death (composite and individual components)[18] - Myocardial infarction, stroke, death and other adverse events during the periprocedural period[19] - 30-day and/or 10-year risk stroke, myocardial infarction, death (composite outcome)[20]

Study	Study Type	Interventions	Percent Stenosis	Outcome Assessed
				- Sex-specific 30-day and 10 year risk of primary composite outcome[20]
International Carotid Stenting Study (ICSS) Investigators	RCT	CEA / CAS	> 50%	- 120-day risk of stroke, death, or myocardial infarction (composite)[21] - Sex-specific 120-day risk of the composite outcome[21] - 7-year longitudinal collection of stroke, death, or myocardial infarction events[22]
NASCET and ECST	IPD Meta-Analysis	CEA / BMT	0-99%	- Risk of ipsilateral ischemic stroke, determined in relation to time from the last symptomatic event to randomization (sex-specific data available)[23] - 5-year risk of ipsilateral ischemic stroke and any stroke or death within 30 days of randomization [combined][24] - 5-year risk of ipsilateral ischemic stroke and any stroke or death within 30 days of randomization [combined], stratified by percent stenosis[24]
EVA-3S, SPACE, ICSS, CREST trials	IPD Meta-Analysis	CEA / CAS	Multiple	Associations between perioperative and clinical variables and the 30-day risk of stroke or death[25] - Multiple outcomes assessed within 120 days and at 5 years[26] - Sex-specific outcomes of 120-day risk of any stroke or death

Study	Study Type	Interventions	Percent Stenosis	Outcome Assessed
				and 5-year risk of ipsilateral stroke (combined)[26] - Sex-specific outcome of 5 year risk of ipsilateral stroke[26]
EVA-3S, SPACE, BACASS, ICSS, CREST trials	IPD Meta-Analysis	CEA / CAS	Multiple	- Multiple outcomes assessed at 30 days after treatment (stroke, death, ipsilateral stroke, disabling stroke, myocardial infarction, restenosis etc.)[27] - Sex-Specific outcomes for death or any stroke within 30 days of treatment[27]

CEA: Carotid endarterectomy; IPD: individual patient data; RCT: randomized controlled trial
*Denotes Symptomatic Stenosis; †Denotes Asymptomatic Stenosis

Supplemental Table III: Baseline Female Patient Characteristics of the Primary Studies

	ECST (1998)[8]	Rothwell et al.[5]	Alamowitch et al.[9]*	SPACE (2006)[10]	Eckstein et al. (SPACE)[11]	Mas et al. (EVA-3S)[12]	Ederle et al. (CAVATAS)[13]	ICSS[14]	Howard et al. (CREST)[3]	Brott et al.[15]	Brott et al.[16]	Muller et al. (2020)[17]
n	850	1718	1208	334	338	130	152	503	872	872	1437	1466
Age (years)	NR	NR	34.8%†	NR	NR	NR	NR	NR	69.2 (9.2)	NR	NR	NR
Hypertension	NR	NR	66.6%	NR	NR	NR	NR	NR	88.3%	NR	NR	NR
Diabetes	NR	NR	22.7%	NR	NR	NR	NR	NR	31.6%	NR	NR	NR
Dyslipidemia	NR	NR	42.0%	NR	NR	NR	NR	NR	84.4%	NR	NR	NR
Present Smoker	NR	NR	34.3%	NR	NR	NR	NR	NR	27.7%	NR	NR	NR
Previous TIA/Stroke	NR	NR	18.1%	NR	NR	NR	NR	NR	NR	NR	NR	NR
50%-69% Stenosis	NR	NR	24.2%	NR	NR	NR	NR	NR	NR	NR	NR	NR
>70% Stenosis	NR	NR	41.8%	NR	NR	NR	NR	NR	NR	NR	NR	NR

NR: not reported

*Baseline patient characteristics for NASCET and ACE trials reported together

†Reported “Age older than 70 years” in percent

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