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Sex differences in Outcome after Carotid Revascularization in Symptomatic and Asymptomatic Carotid Artery Stenosis

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Appendix I, Supplemental File 1: Methods

Appendix II, Supplemental File 2: Prisma Checklist

Appendix III, Supplemental Tables 1-4

Appendix IV, Supplemental Figures S1-S2

Abstract

Objective: Sex differences regarding the safety and efficacy of carotid revascularization in carotid artery stenosis have been addressed in several studies with conflicting results. Moreover, women are underrepresented in clinical trials leading to limited conclusions regarding the safety and efficacy of acute stroke treatments.

Methods: A systematic review and meta-analysis was performed by literature search including 4 databases from January 1985 to December 2021. Sex differences in the efficacy and safety of revascularization procedures, including carotid endarterectomy (CEA) and carotid artery stenting (CAS), for symptomatic and asymptomatic carotid artery stenoses were analyzed.

Results: Regarding carotid endarterectomy (CEA) in symptomatic carotid artery stenosis, the stroke risk in men (3.6%) and women (3.9%) based on 99,495 patients (30 studies) did not differ (p=0.16). There was also no difference in the stroke risk by different time frames up to 10 years. Compared with men, women treated with CEA had a significantly higher stroke or death rate at 4 months (2 studies, 2565; 7.2% vs 5.0%; OR 1.49, 95% CI 1.04-2.12; I^2=0%; p=0.03), and a significantly higher rate of restenosis (1 study, 615; 17.2% vs. 6.7%; OR 2.81,95% CI 1.66-4.75; p=0.0001). For carotid stenting (CAS) in symptomatic artery stenosis data showed a non-significant tendency toward higher peri-procedural stroke in women. Whereas, for asymptomatic carotid artery stenosis, data based on 332,344 patients showed that women compared to men after CEA had similar rates of stroke, stroke or death and the composite outcome stroke/death/myocardial infarction. The rate of restenosis at 1 year was significantly higher in women compared to men (1 study, 372 patients; 10.8% vs 3.2%; OR 3.71, 95% CI 1.49-9.2; p=0.005).

Furthermore, carotid stenting in asymptomatic patients was associated with low risk of a postprocedural stroke in both sexes, but a significantly higher risk of in-hospital myocardial

infarction in women than men (8445 patients, 1.2% vs. 0.6%, OR 2.01, 95%CI 1.23-3.28, I^2=0%, p=0.005).

Conclusions: A few sex-differences in short term outcomes after carotid revascularization for symptomatic and asymptomatic carotid artery stenosis were found, although there were no significant differences in the overall stroke. This indicates a need for larger multicenter prospective studies to evaluate these sex-specific differences. More women, including those aged over 80 years, need to be enrolled in RCTs, to better understand if sex differences exist and to tailor carotid revascularization accordingly.

Keywords: ischemic stroke; carotid endarterectomy; carotid stenting; outcome; sex differences

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Introduction

Stroke and transient ischemic attack (TIA) due to atherosclerotic carotid artery disease accounts for around 15 % of all cases according to the definition of stroke etiology and stenosis classification used.(1) In the Caucasian population, the prevalence of carotid atherosclerotic disease, defined as ≥ 50% stenosis of the carotid arteries, increases with age and is higher for men. (2)

Women have a higher risk of stroke during and after menopause, probably due to changes in the vascular microstructure with increasing arterial stiffness and a higher risk of hypertension.(3) Recurrent carotid artery stenosis after revascularization is more prevalent in women(4). Carotid plaque morphology is different in women compared to men who show higher percentages of intraplaque hemorrhage and larger necrotic cores.(5)

Sex differences in anatomy with a smaller diameter of the carotid artery in women and sex-specific risk factors during interventions can affect outcome. (6) Biological differences, including hormonal changes, are not well studied and likely contribute to sex differences in outcome after carotid revascularization.(7)

Moreover, women are underrepresented in randomized controlled trials (RCTs) leading to conflicting results and low evidence for interventions in women. (8)

Therefore, the aim of this study was to investigate sex differences in the efficacy and safety of revascularization procedures, including carotid endarterectomy (CEA) and carotid artery stenting (CAS), for symptomatic and asymptomatic carotid artery stenoses by performing a systematic review and meta-analysis.

Methods

A professional methodologist (AL) prepared and executed search algorithms and strategies in four databases (MEDLINE, EMBASE, CINAHL, SCOPUS) using a combination of controlled vocabulary, free text terms, and their corresponding Medical Subject Heading

(MeSH) terms (Supplemental File 1). Potentially eligible RCTs, meta-analyses, and observational studies were identified, and citations were loaded on COVIDENCE software. Only original articles in English from January 1985 to December 2021 were included.

The selection of studies were performed by two members of the group independently according to pre-defined inclusion/exclusion criteria (Supplemental File 1). In case of conflict, the disagreement was resolved by a third member.

The relevant outcomes for both carotid endarterectomy (CEA) and Carotid Stenting (CAS) of symptomatic and asymptomatic carotid artery stenoses selected were: Ischemic Stroke, Transitory ischemic attack (TIA), mortality, myocardial infarction (MI) and/or cardiac heart failure, cranial nerve palsy, complications of revascularization: re-intervention, and restenosis.

After screening the titles and abstracts, the full text of potentially relevant studies was loaded onto the software and assessed following the same inclusion/exclusion criteria. The selection process is shown in the PRISMA-chart (Figure 1, checklist see Supplemental File 2). Sex-specific relevant data were extracted from eligible studies, and patients` outcomes were compared between the sexes. Due to the lack of sex-specific data in most RCTs, observational studies were also included.

Where applicable, meta-analyses were performed by using the RevMan software, using a Random-effects model. Odds ratio (OR) was calculated for dichotomous variables and mean differences (MD) for continuous variables, along with their 95% confidence interval (CI). A value of $P< 0.05$ was considered for statistical significance. The heterogeneity was checked by a high value of I^2 and $P< 0.05$.

Results

Symptomatic carotid artery stenosis

Our meta-analysis based on 99,495 patients (35,160 women, 64,335 men) with symptomatic carotid artery stenosis (5 RCTs [NASCET, ECST, CREST, SPACE, CAVATAS] and 25 observational studies) treated with CEA demonstrated that the overall stroke risk did not differ between men (3.6%) and women (3.9%) (OR 1.07, 95% CI 0.97-1.17; I^2=14%; p=0.16) (Figure 2A). There was also no difference in the stroke risk by different timeframes (Figure 2A, Supplemental Table 1). (9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32)

The overall death rate based on 87,163 patients (31,021 women, 56,142 men) was not significantly different between women (1.5%) and men (1.4%) (OR 0.95, 95% CI 0.80-1.12; I^2=28%; p=0.53) (Supplemental Figure S1), whereas the death rate at 10 years was greater in men (27.1% versus 37.8% in men, p=0.006) (Supplemental Table 1 and Supplemental Figure S1).(33) Compared with men, women treated with CEA had a significantly higher stroke or death rate at 4 months (2 studies, 2565 patients; 7.2% vs 5.0%; OR 1.49, 95% CI 1.04-2.12; I^2=0%; p=0.03), and a slightly longer mean hospital stay (2 studies, 21,117 patients; 6.4 days vs 5.8 days; OR 0.52, 95% CI 0.21, 0.83; I^2=0%; p=0.001).(14, 34) Women had a significantly higher rate of restenosis compared to men at both 5 (1study, 615 patients; 11.4% vs. 3.3% in men; OR 3.79,95% CI 1.89-7.61, p=0.0002) and 10 years (17.2% vs. 6.7%; OR 2.81,95% CI 1.66-4.75; p=0.0001).(33) A higher rate of cranial nerve palsy as post-procedural complication was found in women (1 study, 821 patients; 8.2% vs 4.3%; OR 1.98, 95% CI 1.08-3.64; p=0.03) (Supplemental Table 1).

Regarding CAS of symptomatic carotid artery stenosis, the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) did not find a significant sex-related difference by treatment in primary endpoint rates at 4 years (p=0.34).(35) The Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial showed a non-significant increase

in the periprocedural ipsilateral stroke/death for women with symptomatic carotid artery stenosis (who accounted for 28% of enrolled patients) after CAS in the subgroup analyses stratified by sex: 8.2% vs 6.4% in men (p=0.48), in the CAS arm and 6.6% vs 6.0% in men (p=0.85) in the CEA arm. (36) Based on the results of our meta-analyses, the overall stroke rate of 4650 patients (1703 women, 2947 men) did not differ between men (7.6%) and women (8.0%) receiving CAS (OR 1.04, 95% CI 0.79-1.38; I^2=18%; p=0.77) (Figure 2B). This trend was consistent for the in-hospital stroke rate (P=0.67) and for the stroke rate at 1 month (p=0.28), at 2 (p=0.58), and 4 years (p=0.08) from stenting. (10, 25) (Supplemental Table 2) The risk of death (n=7405, 2477 women, 4928 men) was also comparable between men and women (OR 1.04, 95% CI 0.66-1.64; I^2=31%; p=0.87) (Supplemental Figure S2) as well as stroke or death (n=9615) (OR 1.09, 95% CI 0.91-1.30; I^2=0%; p=0.37). (17, 23, 36, 37, 38, 39, 40, 41, 42, 43)

Asymptomatic carotid artery stenosis

Regarding CEA for asymptomatic carotid artery stenosis, we included in our analysis sex-specific data from 5 RCTs [ACAS, ACST, ACST 2010, CREST, ACST 2] and 17 observational studies. (9, 11, 12, 15, 17, 21, 22, 23, 24, 35, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54) Overall, compared to men, women had similar rates of stroke (21 studies, 332,344 patients (144,022 women,188,322 men; 0.9% vs 0.8%, OR 1.12, 95% CI 0.96-1.30, I^2=42%; p=0.14) (Figure 3A) and of the composite endpoint stroke/death/MI (3 studies, 5,675 patients, 3.4% vs 3.2%, OR 1.17, 95% CI 0.75-1,.3; I^2=33; p=0.49).

Although the overall risk of death was slightly significantly lower in women than in men (13 studies, 313,453 patients, 136,760 women, 176,693 men;0.35% vs 0.42%, OR 0.87, 95% CI 0.78-0.98; I^2=0%; p=0.02), the overall risk of the composite endpoint stroke or death resulted

slightly higher in women (8 studies, 65,340 patients, 2.0% vs 1.8%, OR 1.30, 95% CI 1.05-1.63, I^2=39%, p=0.02) (Figure 3B).

Similarly, the rates of in-hospital MI (1 study, 49,042; OR 1.48, 95% CI 1.17-1.85; p=0.0008) and of the composite outcome stroke/MI/death (1 study, 463 patients; 5.3% vs 1.6%; OR 3.43, 95% CI 1.10 - 10.69; p=0.03) were significantly higher in women than in men (Supplemental Table 3). However, data on these outcome measures should be interpreted with caution since they come from 1 study each. Perioperative (one-month) outcome events in terms of stroke (12 studies, 218,116 patients, 0.7% vs 0.6%, OR 1.19, 95% CI 1.01-1.40; I^2=9%; p=0.03), stroke or death (5 studies, 10,218 patients, 3.2% vs 2.1%, OR 1.44, 95% CI 1.13-1.85; I^2=0%; p=0.004) occurred more frequently in women than in men, except for the composite outcome stroke/death/MI (2 studies, 4,625 patients, 3.1% vs 3.2%, OR 0.96, 95% CI 0.69-1.34, I^2: 0%, p=0.81) (Supplemental Table 3). The rate of restenosis at 1 year was significantly higher in women compared to men (1 study, 372 patients; 10.8% vs 3.2%; OR 3.71, 95% CI 1.49, 9.2; p=0.005) (Supplemental Table 3).

The absolute risk of stroke among asymptomatic women treated with CAS was 3%, with no significant differences compared to men (2.9%) (9 studies, 14,155 patients, 5588 women, 8567 men; OR 1.09, 95% CI 0.88-1.35; I^2 =7%; p=0.42). (9, 11, 15, 43, 55, 56, 57, 58) (Figure 4). There was no sex difference in the absolute risk of death in asymptomatic patients treated with CAS (8 studies, 14,292 patients, 5351 women, 8941 men) OR 1.16, 95% CI 0.71-2.89; $I^{2=}$19%; p=0.55). (9, 11, 43, 50, 55, 57). However, this meta-analysis of observational studies showed that asymptomatic women treated with CAS had a significantly higher risk of in-hospital and 1-month MI than men (6 studies, 8,445 patients, 1.2% vs. 0.6%, OR 2.01, 95% CI 1.23-3.28, I^2=0%, p=0.005) (Figure 5 and Supplemental Table 4). (9, 43, 55, 56, 57, 59)

The data on sex differences in the efficacy and safety of CAS in carotid stenosis comes from observational analyses of registries. Stroke and death among asymptomatic women treated

with CAS were recorded in 2.6%-5.4% of cases. (9, 15, 55, 60) In some of these studies, women were significantly more likely to develop stroke and death after CAS than men. (11, 56, 57, 61) In the study by Dua et al., female sex was associated with a high risk of postoperative stroke (OR 12.59, 95% CI 8.25-18.38, p <0.001) and, together with CAS, it was one of the strongest risk factors for death (OR 21.39, 95% CI 5.49-33.39, p<0.001). (56) Other studies showed no between-sex differences in stroke and death in asymptomatic patients undergoing CAS. (9, 15, 43, 58) The risk of bias was acceptable.

Discussion

We present data from our meta-analysis that collected evidence addressing revascularization of carotid artery stenosis in men and women covering the last 30 years of stroke evidence for this treatment. Although in some studies a higher peri-operative risk with CAS, and a higher stroke and death rate with CEA were reported, this did not result in a significant difference in the outcome after carotid revascularization in men and women considering all endpoints. Although there was a trend toward increased randomization of women over this period, women continue to be underrepresented in RCTs and the percentage of women over 75 years of age are still low compared to that observed in the real clinical practice. (62) This under-enrolment was confirmed by a recent meta-analysis, underlining that this disparity persisted across all geographic regions, intervention types, and stroke types, apart from subarachnoid hemorrhage. (63)

Women are underrepresented in carotid revascularization trials with the highest representation in the CREST-trial (35%). Apart from a higher rate of carotid atherosclerosis in men, the potential reasons for the underrepresentation of women in carotid revascularization trials may

be the perceived technical difficulties (smaller ICA size in women) or a higher rate of peri- and postprocedural complications reported in women than in men. (8)

However, based on our data, we could not find a significant increased operative risk in women. In a consensus document published in 2013 on the management of women with carotid artery disease bearing in mind the anatomical and technical differences, and vascular and non-vascular co-morbidities in men and women, a more tailored management for women was called for. (64) Current guidelines on the treatment of extracerebral vascular disease by the society for vascular surgery do not give any sex-specific recommendation.(65) This applies also to the recently published guidelines on endarterectomy and stenting for carotid artery stenosis of the European Stroke Organisation. Sub-group analyses according to sex was performed, but due to the lack of interaction by sex for the main outcomes and low numbers of women included in RCTs no specific recommendation for women was given. (66)

Considering the under-enrolment of women, there could be potential risks of under-treatment and it is important to state that, even with some studies reporting a higher peri-operative risk in women, both sexes benefit likewise from revascularization. This was highlighted by a recently published algorithm for carotid stenosis in women. (67) There are currently two ongoing trials comparing modern medical therapy to modern medical therapy and CAS/CEA in asymptomatic (CREST 2) (68) and at low-risk symptomatic patients (ECST2). (European carotid surgery trial (ECST-2)). (69)

A large RCT with a more pragmatic design, including an elderly population, may answer some questions about the risk and benefits of carotid intervention in women. (70)

Limitations

Our systematic review is not without limitations. First, data are mostly based on cohort studies with possible inclusion bias. Although there are few RCTs in this systematic review, in these studies, patients were not randomized to men and women. Second, the authors were

not contacted for the missing information and individual-based data of men and women due to the large number of studies included in this systematic review. Also, the management of carotid artery stenoses might have changed over time.

Conclusions

Overall, even considering the risk of bias, our data showed no significantly different outcomes in men and women after revascularization of symptomatic and asymptomatic carotid artery stenosis.

Further larger multicenter prospective research into these sex-specific differences is needed. More women have to be enrolled in RCTs, including those aged over 80 years, to better understand why these sex differences still exist and how we can tailor stroke treatment for both sexes.

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Figure 1. PRISMA flow chart of the studies included in the meta-analysis

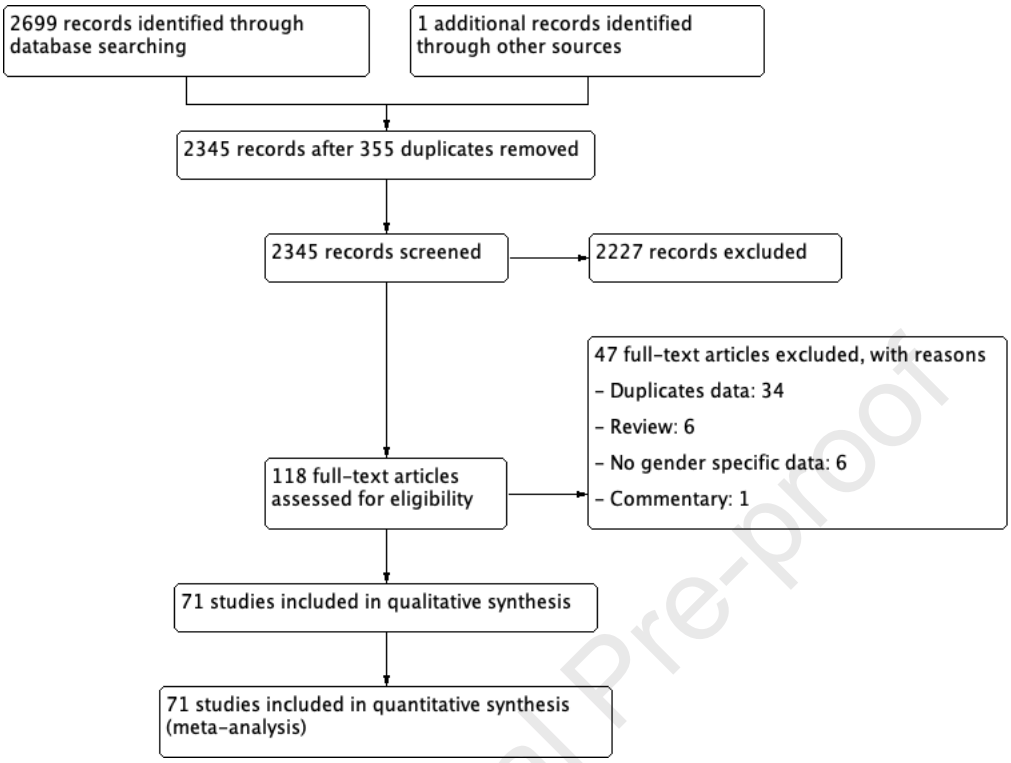
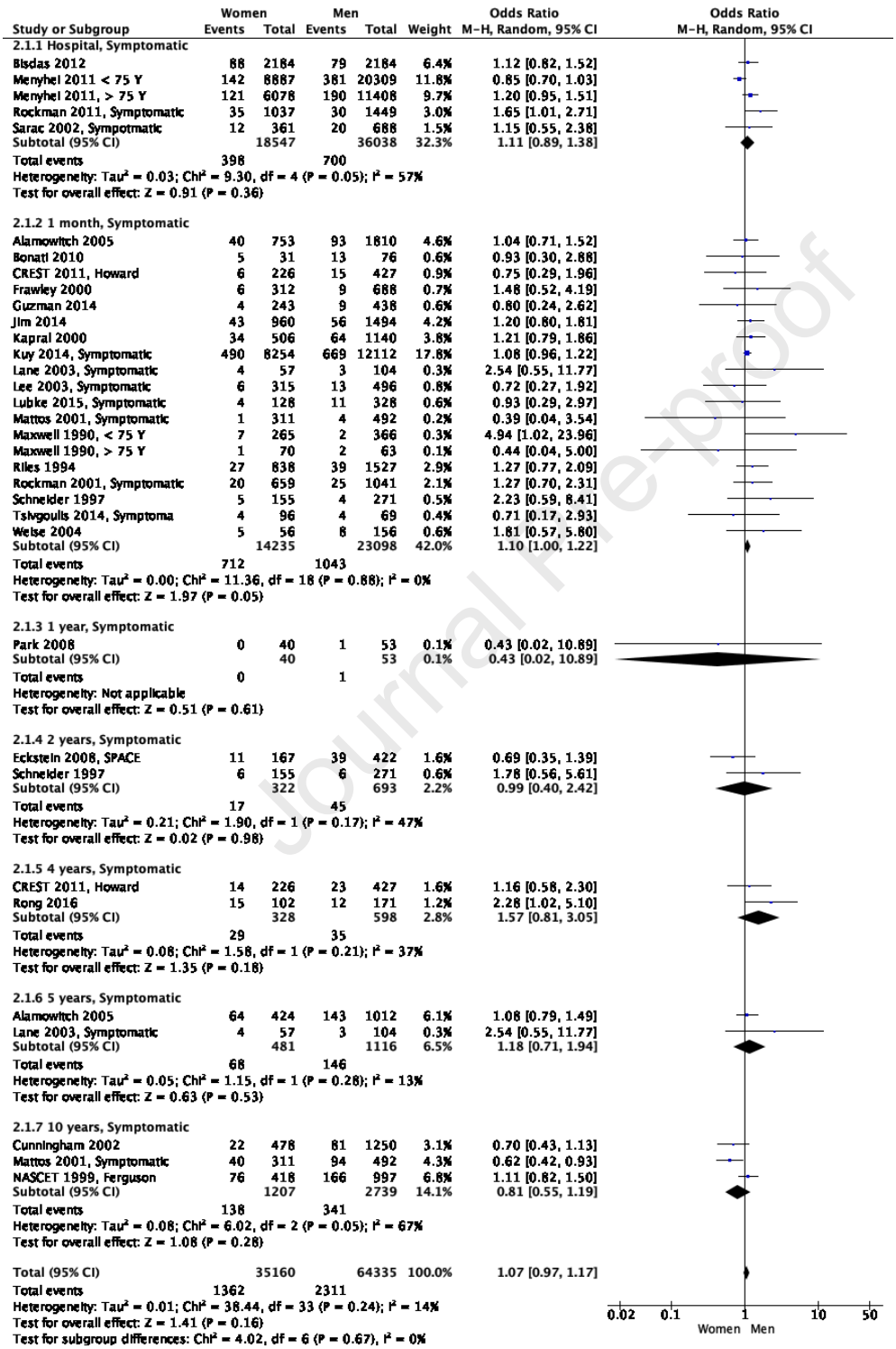
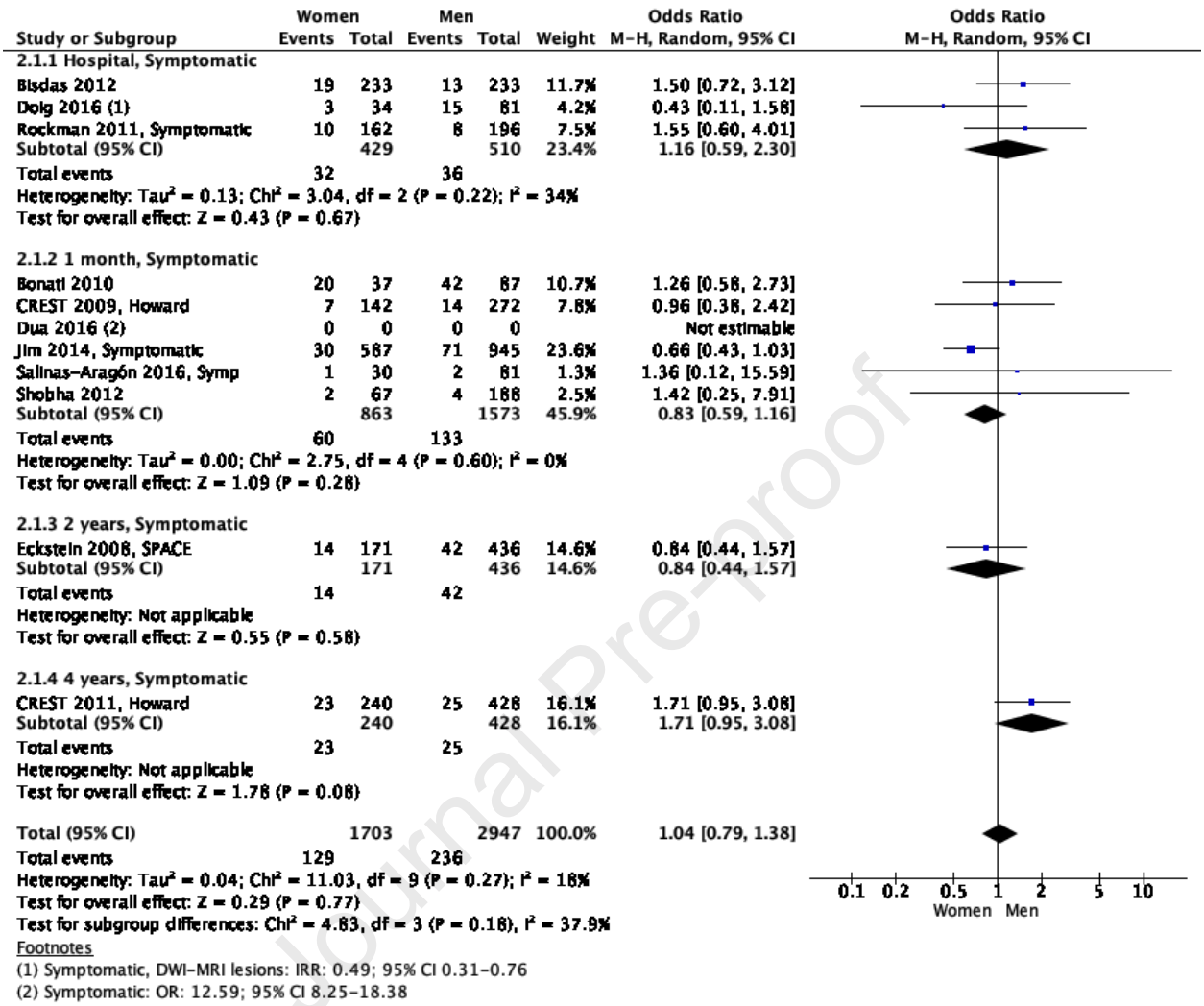


Figure 2. Stroke in men and women after carotid endarterectomy (A) and after stenting (B) of symptomatic carotid artery stenosis

A.



B.



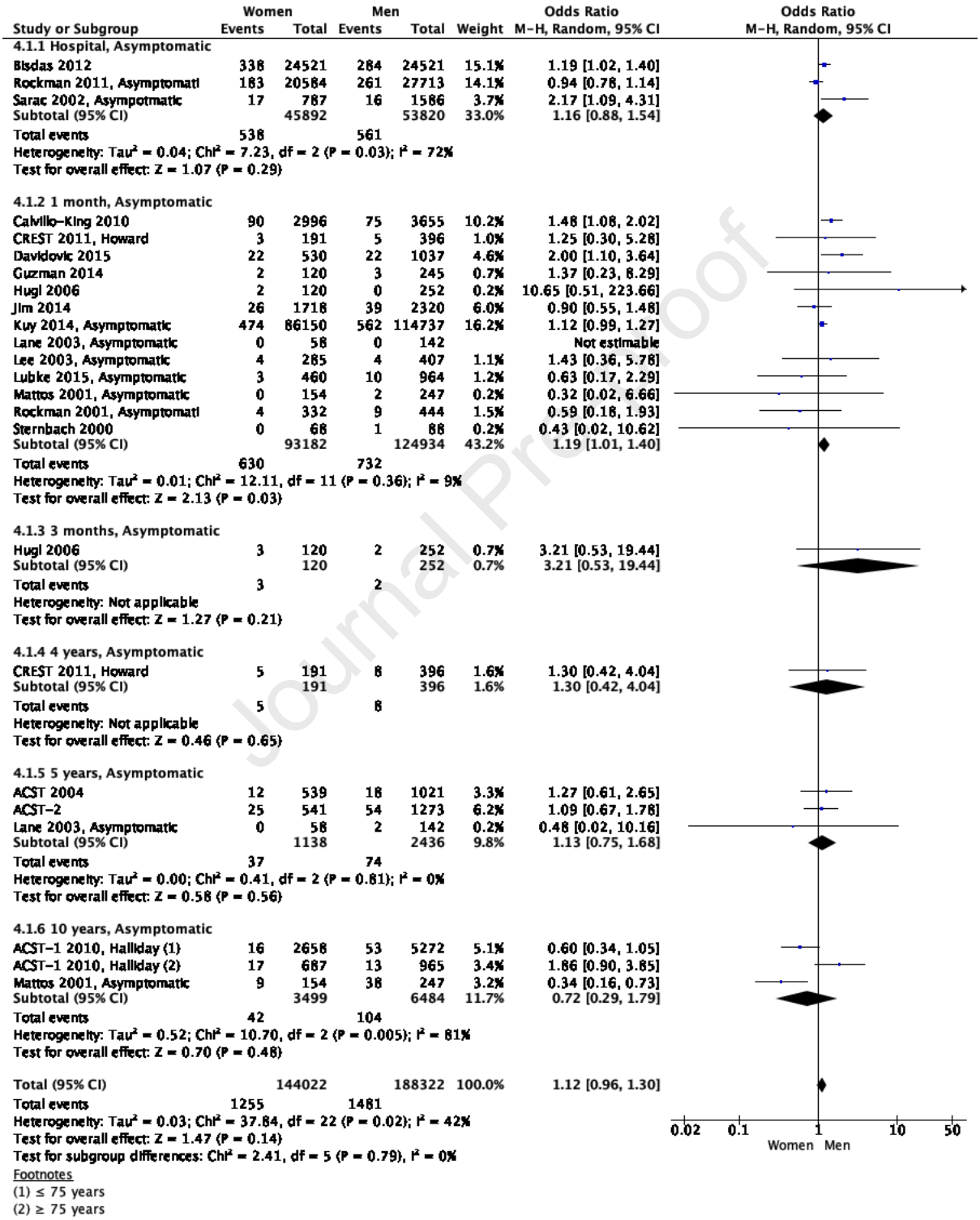
Footnotes

(1) Symptomatic, DWI-MRI lesions: IRR: 0.49; 95% CI 0.31-0.76

(2) Symptomatic: OR: 12.59; 95% CI 8.25-18.38

Figure 3. Stroke (A) and Mortality (B) in men and women after endarterectomy of asymptomatic carotid artery stenosis

A.



B.

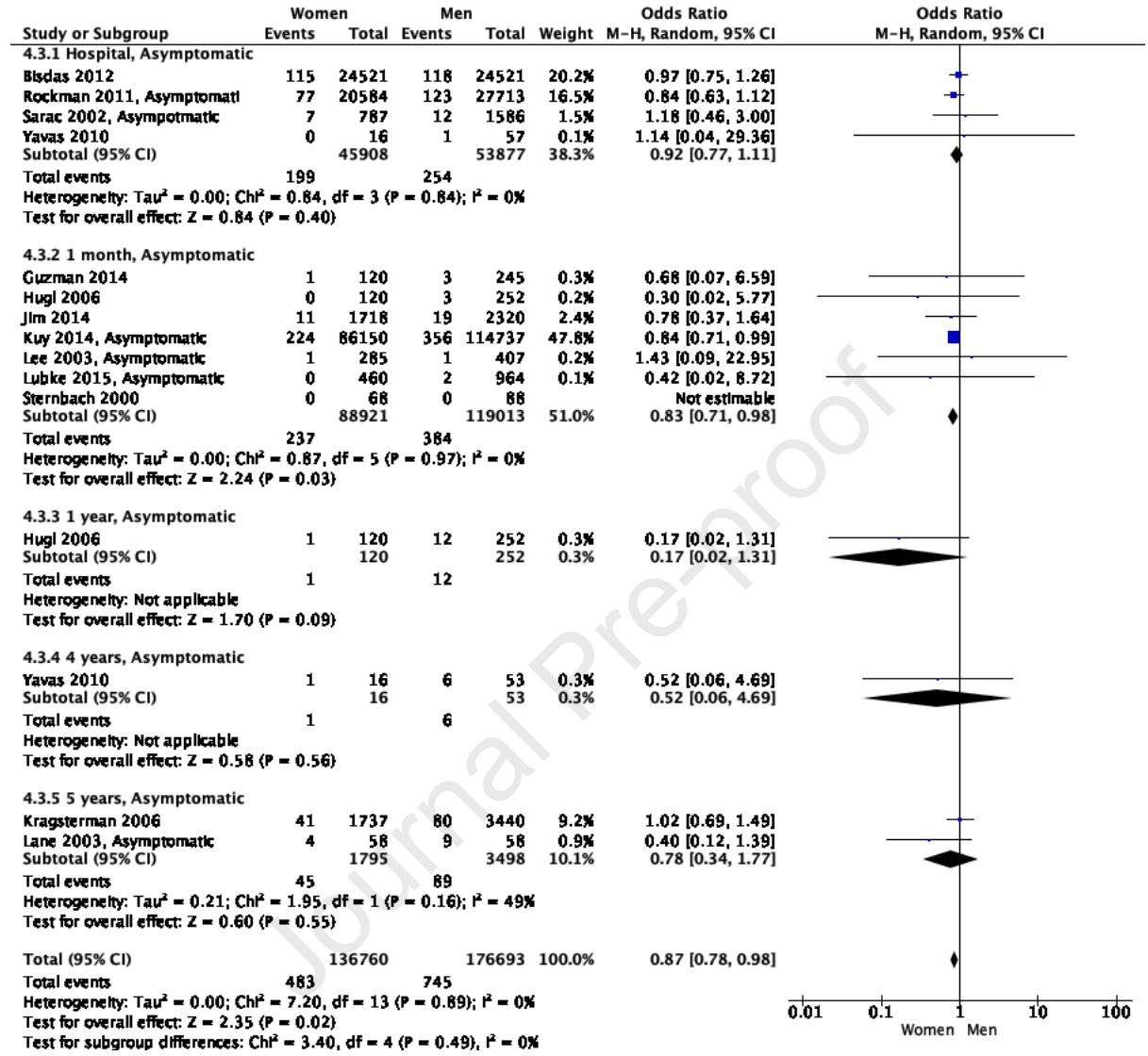
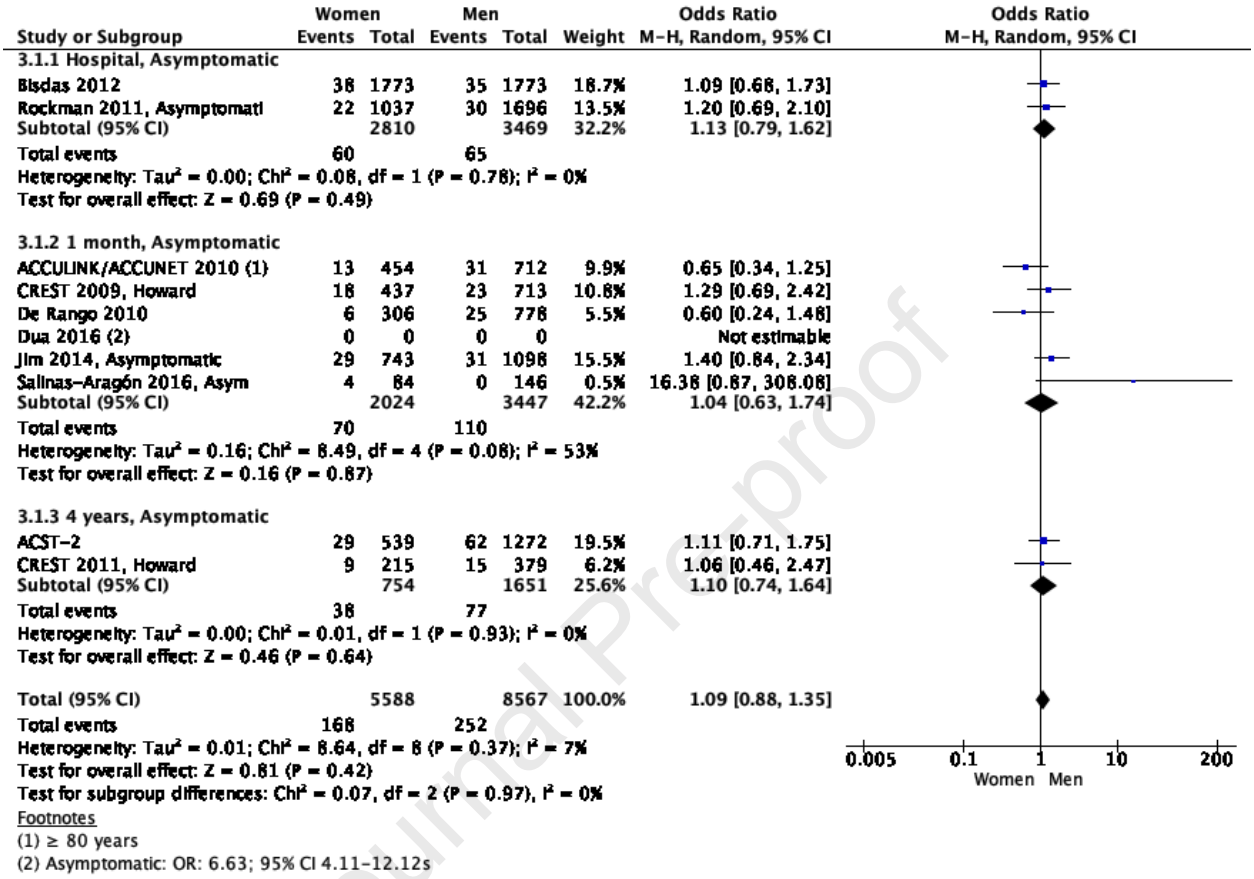


Figure 4. Stroke in men and women after stenting of asymptomatic carotid artery stenosis

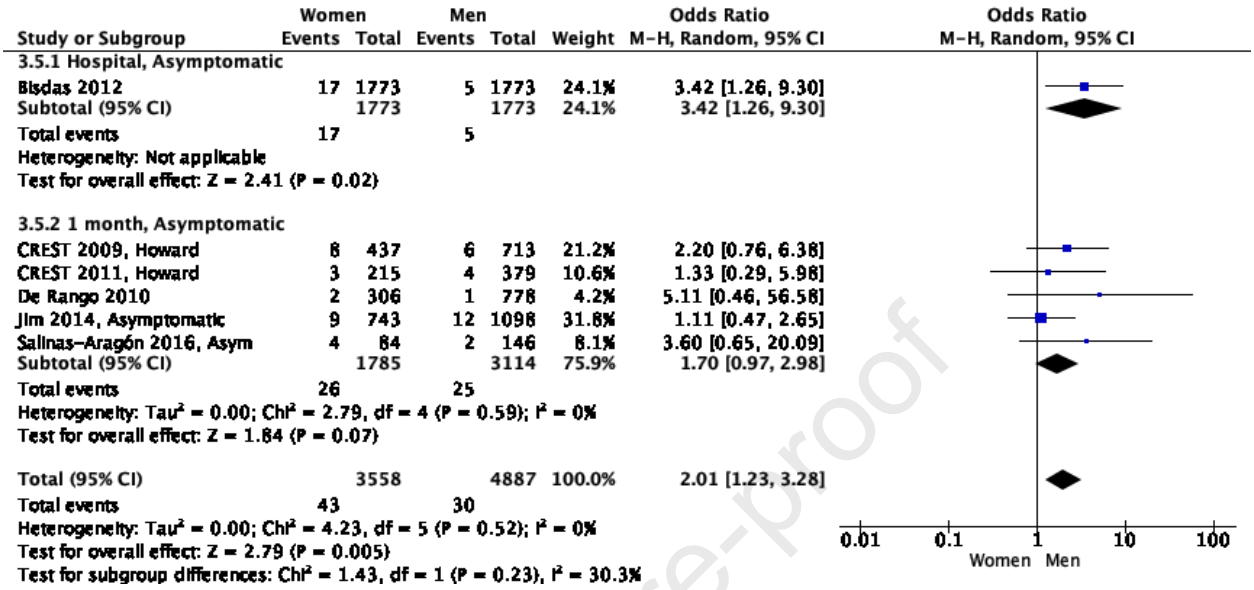


Footnotes

(1) ≥ 80 years

(2) Asymptomatic: OR: 6.63; 95% CI 4.11-12.12s

Figure 5. Myocardial infarction in men and women after stenting of asymptomatic carotid artery stenosis



Supplemental File 1.

Methods: supplemental information

Medical Subject Headings (MeSH) for the search used

'Carotid stenosis' OR 'carotid artery stenosis' OR 'carotid artery obstruction' AND 'carotid artery surgery' OR ('carotid artery' AND 'surgery') OR 'angioplasty' OR 'stent*' OR 'angioplasty, balloon' OR 'percutaneous transluminal angioplasty' OR 'endarterectomy'' AND 'treatment outcome' OR 'postoperative complications' OR 'myocardial infarction' OR 'heart infarction' OR 'stroke' OR 'brain ischemia' OR 'cerebrovascular accident' OR 'death' OR 'death, sudden, cardiac' OR 'mortality' OR 'sudden death' AND 'females' OR 'males' OR 'women' OR 'men' OR 'gender difference' OR 'sex difference' OR 'sex factor*' OR 'gender factor'.

Inclusion and exclusion criteria for the search used

Symptomatic carotid artery stenosis

Women and men with symptomatic carotid artery stenosis; Carotid endarterectomy in women; Carotid endarterectomy in men; Stroke, hemorrhage, mortality.

Women and men with symptomatic carotid artery stenosis; Carotid stenting in women; Carotid stenting in men; Stroke, hemorrhage, mortality.

Asymptomatic carotid artery stenosis

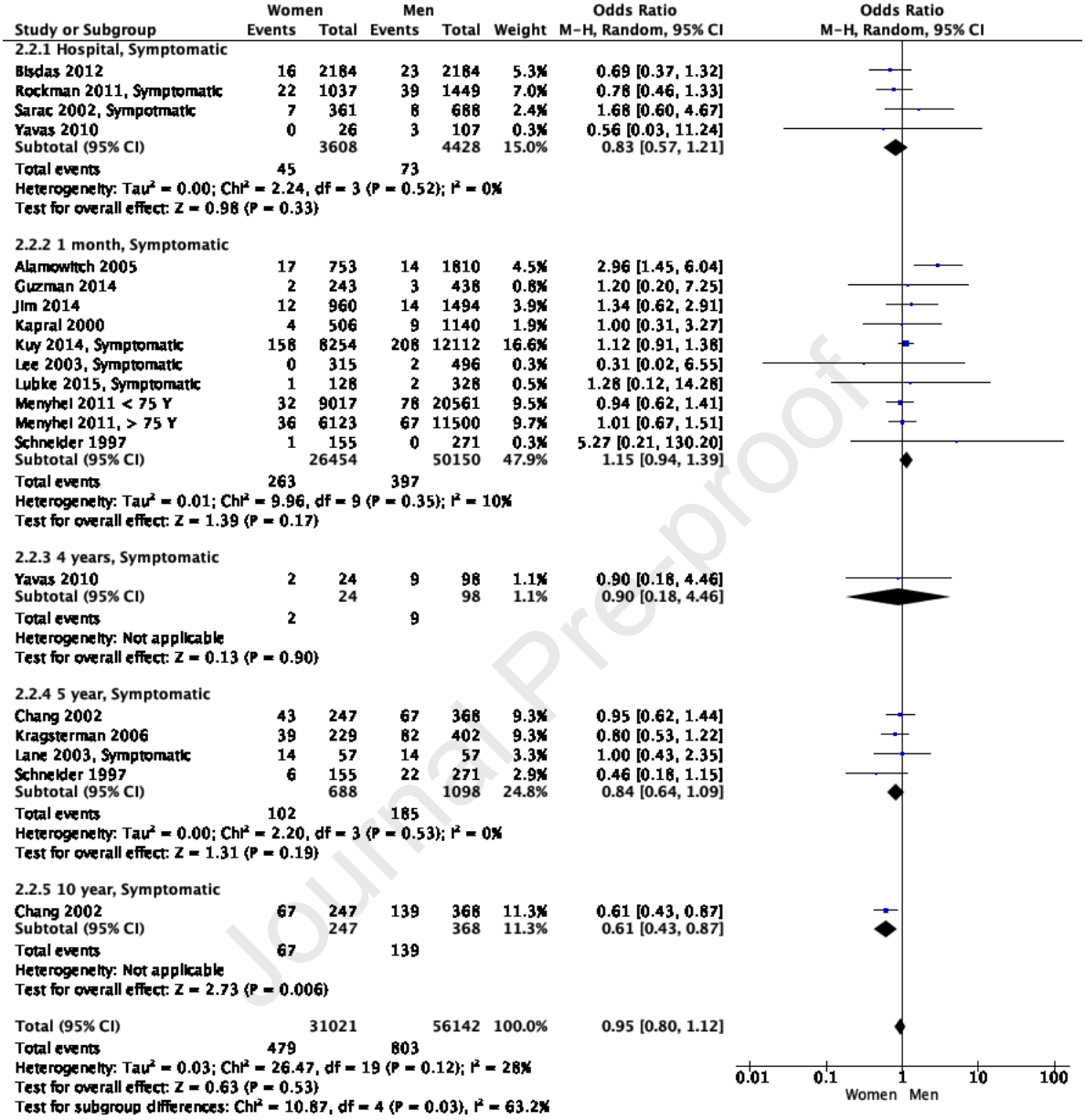
Women and men with asymptomatic carotid artery stenosis; Carotid endarterectomy in women; Carotid endarterectomy in men; Stroke, hemorrhage, mortality.

Women and men with asymptomatic carotid artery stenosis; Carotid stenting in women; Carotid stenting in men; Stroke, hemorrhage, mortality.

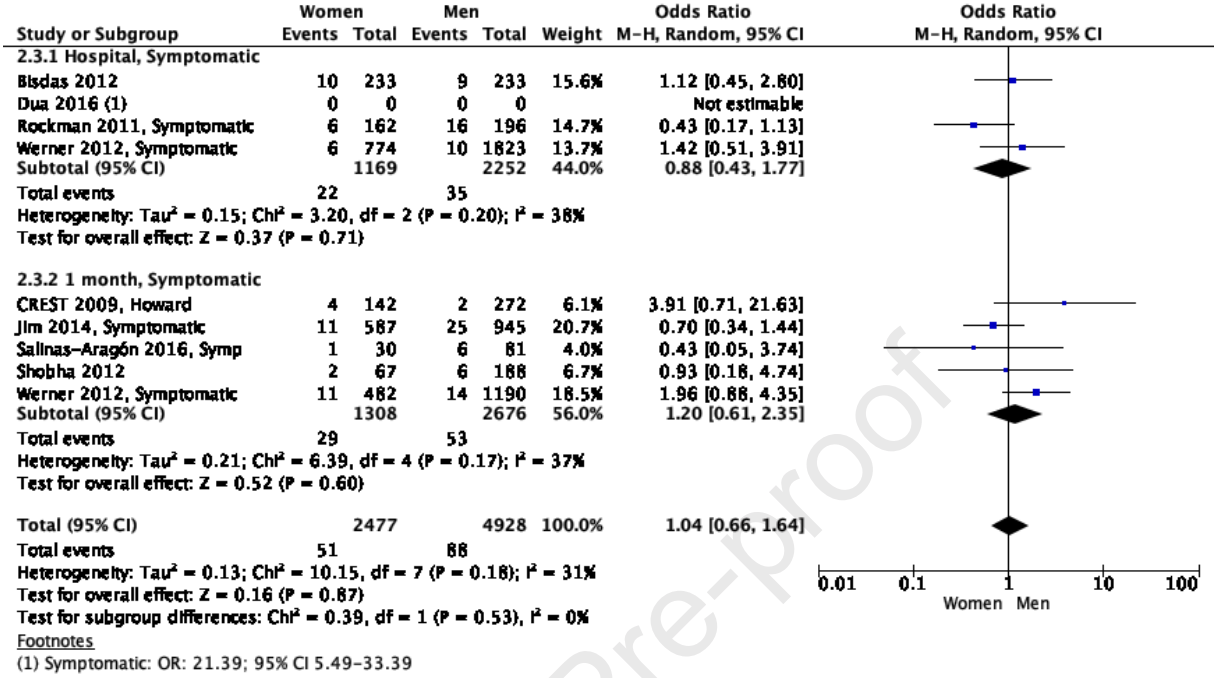
Exclusion criteria

Patients: Women and men without carotid artery stenosis; Did not evaluate carotid endarterectomy or carotid stenting; Did not study Stroke, hemorrhage, mortality. Study designs such as reviews, letter to editor, case report, commentary, or editorial.

Supplemental Figure S1. Mortality in men and women after endarterectomy of symptomatic carotid artery stenosis



Supplemental Figure S2. Mortality in men and women after stenting of symptomatic carotid artery stenosis



Footnotes

(1) Symptomatic: OR: 21.39; 95% CI 5.49-33.39

Supplemental Table 1. Vascular events, length of stay, and complications, in men and women after endarterectomy of symptomatic carotid artery stenosis

Outcome	Incidence (%)		n (N)	OR [95% CI]	I^2, p	P value
	Women	Men				
Stroke						
Hospital	2.1%	1.9%	5(54585)	1.11 [0.89, 1.38]	57%, 0.05	0.36
1 month	5.0%	4.5%	19(37333)	1.10 [1.00, 1.22]	0%, 0.88	0.05
1 year	0.0%	1.9%	1(93)	0.43 [0.02, 10.89]	NA	0.61
2 years	5.3%	6.5%	2(1015)	0.99 [0.40, 2.42]	47%, 0.17	0.98
4 years	8.8%	5.9%	2(926)	1.57 [0.81, 3.05]	37%, 0.21	0.18
5 years	14.1%	13.1%	2(1597)	1.18 [0.71, 1.94]	13%, 0.28	0.53
10 years	11.4%	12.4%	3(3946)	0.81 [0.55, 1.19]	67%, 0.05	0.28
TIA						
Hospital	0.6%	0.3%	1(1049)	1.91 [0.27, 13.62]	NA	0.52
1 month	1.9%	1.4%	3(1449)	1.64 [0.71, 3.80]	0%, 0.95	0.25
2 years	3.9%	4.8%	1(426)	0.80 [0.30, 2.15]	NA	0.66
Death						
Hospital	1.2%	1.6%	4(8036)	0.83 [0.57, 1.21]	0%, 0.52	0.33
1 month	1.0%	0.8%	10(76604)	1.15 [0.94, 1.39]	10%, 0.35	0.17
1 year	NR	NR	NR	NR	NR	NR
2 years	NR	NR	NR	NR	NR	NR
4 years	8.3%	9.2%	1(122)	0.90 [0.18, 4.46]	NA	0.9
5 years	14.8%	16.8%	4(1786)	0.84 [0.64, 1.09]	0%, 0.53	0.19
10 years	27.1%	37.8%	1(615)	0.61 [0.43, 0.87]	NA	0.006
Stroke or death						
Hospital	4.4%	3.9%	2(5417)	1.09 [0.84, 1.43]	0%, 0.84	0.51
1 month	9.4%	8.9%	13(14360)	1.08 [0.93, 1.27]	8%, 0.37	0.3
4 months	7.2%	5.0%	2(2565)	1.49 [1.04, 2.12]	0%, 0.34	0.03
3 years	NR	NR	NR	NR	NR	NR
4 years	6.2%	5.4%	1(653)	1.16 [0.58, 2.30]	NA	0.67
5 years	12.4%	8.9%	3(2331)	1.47 [0.94, 2.29]	59%, 0.09	0.09
MI						
Hospital	1.3%	1.0%	1(4368)	1.34 [0.76, 2.36]	NA	0.32
1 month	1.5%	1.4%	4(24284)	0.98 [0.61, 1.56]	33%, 0.21	0.92
Stroke, MI or death						
Hospital	8.2%	8.6%	1(697)	0.95 [0.54, 1.65]	NA	0.85
1 month	5.7%	5.0%	3(3928)	1.14 [0.67, 1.95]	59%, 0.09	0.62
4 years	7.5%	7.7%	1(653)	0.97 [0.53, 1.78]	NA	0.92
LOS, hospital, d						
Overall	6.4±11.8	5.8±11.7	2(21177)	0.52 [0.21, 0.83]	0%, 0.55	0.001
Restenosis						
1 month	3.6%	3.2%	1(212)	1.12 [0.21, 5.94]	NA	0.9
1 year	NR	NR	NR	NR	NR	NR
5 years	11.4%	3.3%	1(615)	3.79 [1.89, 7.61]	NA	0.0002
10 years	17.2%	6.7%	1(615)	2.81 [1.66, 4.75]	NA	0.0001
Reintervention						

Outcome	Incidence (%)		n (N)	OR [95% CI]	I^2, p	P value
	Women	Men				
1 month	3.2%	2.4%	1(811)	1.32 [0.56, 3.10]	NA	0.52
CHF						
1 month	0.6%	0.6%	1(811)	1.05 [0.17, 6.32]	NA	0.96
Cranial nerve palsy						
Overall	8.2%	4.3%	1(821)	1.98 [1.08, 3.64]	NA	0.03
Hematoma						
Overall	8.2%	5.2%	1(821)	1.64 [0.91, 2.95]	NA	0.1

CHF: Congestive heart failure; CI: Confidence interval; d: days; I^2: Heterogeneity; ICU: Intensive care unit; LOS: Length of stay; MI: Myocardial infarction; n: Number of studies; N: Number of patients; NA: Not applicable; NE: Not estimable; p: Statistical significance value; OR: Odds Ratio

Supplemental Table 2. Vascular events, length of stay, and complications in men and women after stenting of symptomatic carotid artery stenosis

Outcome	Incidence (%)		n (N)	OR [95% CI]	I^2, p	P value
	Women	Men				
Stroke						
Hospital	7.5%	7.1%	3(939)	1.16 [0.59, 2.30]	34%, 0.22	0.67
1 month	7.0%	8.5%	5(2436)	0.83 [0.59, 1.16]	0%, 0.60	0.28
2 years	8.2%	9.6%	1(607)	0.84 [0.44, 1.57]	NA	0.58
4 years	9.6%	5.8%	1(668)	1.71 [0.95, 3.08]	NA	0.08
TIA						
1 month	4.5%	5.3%	1(255)	0.83 [0.22, 3.13]	NA	0.79
Death						
Hospital	1.9%	1.6%	3(3421)	0.88 [0.43, 1.77]	38%, 0.20	0.71
1 month	2.2%	2.0%	5(3984)	1.20 [0.61, 2.35]	37%, 0.17	0.60
Stroke or death						
Hospital	5.3%	4.8%	2(2961)	0.97 [0.64, 1.48]	21%, 0.26	0.9
1 month	7.7%	6.9%	6(3661)	1.15 [0.87, 1.51]	0%, 0.61	0.33
4 months	8.5%	9.0%	1(1725)	0.93 [0.64, 1.36]	NA	0.72
4 years	9.6%	5.8%	1(668)	1.71 [0.95, 3.08]	NA	0.08
MI						
Hospital	1.7%	2.6%	1(466)	0.66 [0.18, 2.37]	NA	0.53
1 month	1.7%	4.5%	5(2980)	0.59 [0.05, 6.74]	88%, < 0.001	0.67
Stroke, MI or death						
1 month	7.8%	7.8%	4(2725)	1.07 [0.67, 1.70]	42%, 0.16	0.79
4 months	7.9%	8.7%	1(853)	0.91 [0.53, 1.56]	NA	0.73
LOS, hospital, d						
Overall	6.7±1.4	5.4±1.2	2(721)	-0.09 [-0.27, 0.08]	0%, 0.80	0.29

CI: Confidence interval; d: days; I^2: Heterogeneity; ICU: Intensive care unit; LOS: Length of stay; MI: Myocardial infarction; n: Number of studies; N: Number of patients; NA: Not applicable; NE: Not estimable p: Statistical significance value; OR: Odds Ratio

Supplemental Table 3. Vascular events, length of stay, and complications in men and women after endarterectomy of asymptomatic carotid artery stenosis

Outcome	Incidence (%)		n (N)	OR [95% CI]	I^2, p	P value
	Women	Men				
Stroke						
Hospital	1.2%	1.0%	3(99712)	1.16 [0.88, 1.54]	72%, 0.03	0.29
1 month	0.7%	0.6%	12(218116)	1.19 [1.01, 1.40]	9%, 0.36	0.03
3 months	2.5%	0.8%	1(372)	3.21 [0.53, 19.44]	NA	0.21
1 year	NR	NR	NR	NR	NR	NR
2 years	NR	NR	NR	NR	NR	NR
4 years	2.6%	2.0%	1(587)	1.30 [0.42, 4.04]	NA	0.65
5 years	3.3%	3.0%	3(3574)	1.13 [0.75, 1.68]	0%, 0.81	0.56
10 years	1.2%	1.6%	3(9983)	0.72 [0.29, 1.79]	81%, 0.005	0.48
TIA						
Hospital	0.9%	0.6%	1(2373)	1.57 [0.58, 4.24]	NA	0.37
1 month	0.6%	0.1%	3(1220)	3.56 [0.46, 27.67]	0%, 0.34	0.23
3 months	2.5%	0.0%	1(372)	15.04 [0.77, 293.58]	NA	0.07
2 years						
Death						
Hospital	0.4%	0.5%	4(99785)	0.92 [0.77, 1.11]	0%, 0.84	0.4
1 month	0.27%	0.32%	7(207934)	0.83 [0.71, 0.98]	0%, 0.97	0.03
3 months	NR	NR	NR	NR	NR	NR
1 year	0.8%	4.8%	1(372)	0.17 [0.02, 1.31]	NA	0.09
2 years	NR	NR	NR	NR	NR	NR
4 years	6.3%	11.3%	1(69)	0.52 [0.06, 4.69]	NA	0.56
5 years	2.5%	2.5%	2(5293)	0.78 [0.34, 1.77]	49%, 0.16	0.55
10 years	NR	NR	NR	NR	NR	NR
Stroke or death						
Hospital	1.7%	1.6%	2(51415)	1.35 [0.68, 2.71]	82%, 0.02	0.39
1 month	3.2%	2.1%	5(10218)	1.44 [1.13, 1.85]	0%, 0.53	0.004
4 months	NR	NR	NR	NR	NR	NR
3 years	2.2%	1.8%	1(1560)	1.27 [0.61, 2.65]	NA	0.53
4 years	2.6%	2.0%	1(587)	1.30 [0.42, 4.04]	NA	0.65
5 years	5.4%	4.0%	1(1560)	1.36 [0.83, 2.21]	NA	0.22
MI						
Hospital	0.8%	0.5%	1(49042)	1.48 [1.17, 1.85]	NA	0.0008
1 month	0.90%	0.85%	5(206360)	1.06 [0.96, 1.16]	0%, 0.72	0.23
Stroke, MI or death						
Hospital	5.3%	1.6%	1(463)	3.43 [1.10, 10.69]	NA	0.03
1 month	3.1%	3.2%	2(4625)	0.96 [0.69, 1.34]	0%, 0.86	0.81
LOS, hospital, d						
Overall	2.6±16.0	2.3±16.0	2(201579)	0.24 [0.10, 0.38]	0%, 0.87	0.0006
Restenosis						
1 month	NR	NR	NR	NR	NR	NR
1 year	10.8%	3.2%	1(372)	3.71 [1.49, 9.20]	NA	0.005
5 years	NR	NR	NR	NR	NR	NR
10 years	NR	NR	NR	NR	NR	NR

Outcome	Incidence (%)		n (N)	OR [95% CI]	I^2, p	P value
	Women	Men				
Reintervention						
1 month	2.4%	2.9%	3(1264)	0.80 [0.39, 1.67]	0%, 0.74	0.56
CHF						
1 month	1.7%	0.8%	2(848)	2.07 [0.58, 7.42]	0%, 0.95	0.26
Arrhythmia						
1 month	0.0%	1.1%	1(156)	0.43 [0.02, 10.62]	NA	0.6
Cranial nerve palsy						
Overall	2.5%	2.8%	1(372)	0.90 [0.23, 3.53]	NA	0.88
Hematoma						
Overall	1.7%	2.0%	1(372)	0.84 [0.16, 4.38]	NA	0.83
Wound infections						
Overall	0.8%	0.8%	1(372)	1.05 [0.09, 11.70]	NA	0.97

CHF: Congestive heart failure; CI: Confidence interval; d: days; I^2: Heterogeneity; ICU: Intensive care unit; LOS: Length of stay; MI: Myocardial infarction; n: Number of studies; N: Number of patients; NA: Not applicable; NE: Not estimable; p: Statistical significance value; OR: Odds Ratio

Supplemental Table 4. Vascular events, length of stay, and complications in men and women after stenting of asymptomatic carotid artery stenosis

Outcome	Incidence (%)		n (N)	OR [95% CI]	I^2, p	P value
	Women	Men				
Stroke						
Hospital	2.1%	1.9%	2(6279)	1.13 [0.79, 1.62]	0%, 0.78	0.49
1 month	3.5%	3.2%	5(5471)	1.04 [0.63, 1.74]	53%, 0.08	0.87
2 years	NR	NR	NR	NR	NR	NR
4 years	5.0%	4.7%	2(2405)	1.10 [0.74, 1.64]	0%, 0.93	0.64
TIA						
1 month	3.3%	3.7%	1(1084)	0.87 [0.42, 1.81]	NA	0.71
Death						
Hospital	0.7%	0.6%	3(8404)	1.09 [0.61, 1.95]	0%, 0.47	0.78
1 month	1.1%	0.9%	5(5888)	1.12 [0.43, 2.86]	49%, 0.12	0.82
Stroke or death						
Hospital	2.5%	2.5%	2(5600)	0.99 [0.69, 1.42]	0%, 0.34	0.95
1 month	2.7%	3.3%	5(7479)	0.84 [0.60, 1.17]	15%, 0.32	0.3
4 years	4.2%	4.0%	1(594)	1.06 [0.46, 2.47]	NA	0.89
MI						
Hospital	1.0%	0.3%	1(3546)	3.42 [1.26, 9.30]	NA	0.02
1 month	1.5%	0.8%	5(4899)	1.70 [0.97, 2.98]	0%, 0.59	0.07
Stroke, MI or death						
1 month	5.7%	4.1%	4(3815)	1.46 [0.95, 2.24]	36%, 0.19	0.09
LOS, hospital, d						
Overall	3.1±3.0	2.7±3.0	1(3546)	0.40 [0.20, 0.60]	NA	0.29
Hematoma						
1 month	1.6%	1.3%	1(1084)	1.28 [0.43, 3.76]	NA	0.66

CI: Confidence interval; d: days; I^2: Heterogeneity; ICU: Intensive care unit; LOS: Length of stay; MI: Myocardial infarction; n: Number of studies; N: Number of patients; NA: Not applicable; NE: Not estimable; NR: Not reported; p: Statistical significance value; OR: Odds Ratio

Supplemental file 2: Kremer et al. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p. 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p. 3-4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Suppl.File 1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p. 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	p.4 Suppl.File1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p.4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p.4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p.4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p.4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p.4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	p.4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	p.4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p.4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p.4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	p.4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	n.a.
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	p. 4

Supplemental file 2: Kremer et al. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	p. 4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	p.4 and figures
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Fig. 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Fig. 1
Study characteristics	17	Cite each included study and present its characteristics.	p. 11
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p.5 cont.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	p.5 cont.
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	p.5 cont.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Fig. 1-5 and suppl.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	p. 5 cont.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	p.5 cont.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	p. 5 cont.
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	p. 5 cont.
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p.8 cont.
	23b	Discuss any limitations of the evidence included in the review.	p.8
	23c	Discuss any limitations of the review processes used.	p.9
	23d	Discuss implications of the results for practice, policy, and future research.	p.9
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p.4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	n/a
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p.10
Competing	26	Declare any competing interests of review authors.	p. 10

Supplemental file 2: Kremer et al. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
interests			
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	p.5 cont.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

Figure Legends:

Figure 1: PRISMA Flow chart of the studies included in the meta-analyis

Figure 2: Stroke in men and women after carotid endarterectomy (A) and stenting (B)

Figure 3: Stroke (A) and Mortality (B) in men and women after endarterectomy of asymptomatic carotid artery stenosis

Figure 4: Stroke in men and women after stenting of asymptomatic carotid artery stenosis

Figure 5: Myocardial infarction in men and women after stenting of asymptomatic carotid artery stenosis