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

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- 1 Sex differences in Outcome after Carotid Revascularization in Symptomatic and
- 2 Asymptomatic Carotid Artery Stenosis
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18	Appendix II, Supplemental File 2: Prisma Checklist
19	Appendix III, Supplemental Tables 1-4
20	Appendix IV, Supplemental Figures S1-S2
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1 Abstract

2 Objective: Sex differences regarding the safety and efficacy of carotid revascularization in 3 carotid artery stenosis have been addressed in several studies with conflicting results. 4 Moreover, women are underrepresented in clinical trials leading to limited conclusions 5 regarding the safety and efficacy of acute stroke treatments. 6 **Methods:** A systematic review and meta-analysis was performed by literature search 7 including 4 databases from January 1985 to December 2021. Sex differences in the efficacy 8 and safety of revascularization procedures, including carotid endarterectomy (CEA) and 9 carotid artery stenting (CAS), for symptomatic and asymptomatic carotid artery stenoses were 10 analyzed. 11 Results: Regarding carotid endarterectomy (CEA) in symptomatic carotid artery stenosis, the 12 stroke risk in men (3.6%) and women (3.9%) based on 99,495 patients (30 studies) did not 13 differ (p=0.16). There was also no difference in the stroke risk by different time frames up to 14 10 years. Compared with men, women treated with CEA had a significantly higher stroke or 15 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 16 17 2.81,95% CI 1.66-4.75; p=0.0001). For carotid stenting (CAS) in symptomatic artery stenosis 18 data showed a non-significant tendency toward higher peri-procedural stroke in women. 19 Whereas, for asymptomatic carotid artery stenosis, data based on 332,344 patients showed 20 that women compared to men after CEA had similar rates of stroke, stroke or death and the 21 composite outcome stroke/death/myocardial infarction. The rate of restenosis at 1 year was 22 significantly higher in women compared to men (1 study, 372 patients; 10.8% vs 3.2%; OR 23 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

1	infarction in women than me	en (8445 pa	tients, 1.2%	vs. 0.6%,	OR 2.01, 9	95%CI 1.23	-3.28,
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 $I^2=0\%$, 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

- human

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2

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1 Introduction

2	Stroke and transient ischemic attack (TIA) due to atherosclerotic carotid artery disease
3	accounts for around 15 % of all cases according to the definition of stroke etiology and
4	stenosis classification used.(1) In the Caucasian population, the prevalence of carotid
5	atherosclerotic disease, defined as \geq 50% stenosis of the carotid arteries, increases with age
6	and is higher for men. (2)
7	Women have a higher risk of stroke during and after menopause, probably due to changes in
8	the vascular microstructure with increasing arterial stiffness and a higher risk of
9	hypertension.(3) Recurrent carotid artery stenosis after revascularization is more prevalent in
10	women(4). Carotid plaque morphology is different in women compared to men who show
11	higher percentages of intraplaque hemorrhage and larger necrotic cores.(5)
12	Sex differences in anatomy with a smaller diameter of the carotid artery in women and sex-
13	specific risk factors during interventions can affect outcome. (6) Biological differences,
14	including hormonal changes, are not well studied and likely contribute to sex differences in
15	outcome after carotid revascularization.(7)
16	Moreover, women are underrepresented in randomized controlled trials (RCTs) leading to
17	conflicting results and low evidence for interventions in women. (8)
18	Therefore, the aim of this study was to investigate sex differences in the efficacy and safety of
19	revascularization procedures, including carotid endarterectomy (CEA) and carotid artery
20	stenting (CAS), for symptomatic and asymptomatic carotid artery stenoses by performing a
21	systematic review and meta-analysis.
22 23	Methods
24	A professional methodologist (AL) prepared and executed search algorithms and strategies in
25	four databases (MEDLINE, EMBASE, CINAHL, SCOPUS) using a combination of

26 controlled vocabulary, free text terms, and their corresponding Medical Subject Heading

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1 (MeSH) terms (Supplemental File 1). Potentially eligible RCTs, meta-analyses, and 2 observational studies were identified, and citations were loaded on COVIDENCE software. 3 Only original articles in English from January 1985 to December 2021 were included. 4 The selection of studies were performed by two members of the group independently 5 according to pre-defined inclusion/exclusion criteria (Supplemental File 1). In case of 6 conflict, the disagreement was resolved by a third member. 7 The relevant outcomes for both carotid endarterectomy (CEA) and Carotid Stenting (CAS) of 8 symptomatic and asymptomatic carotid artery stenoses selected were: Ischemic Stroke, 9 Transitory ischemic attack (TIA), mortality, myocardial infarction (MI) and/or cardiac heart 10 failure, cranial nerve palsy, complications of revascularization: re-intervention, and restenosis. 11 After screening the titles and abstracts, the full text of potentially relevant studies was loaded 12 onto the software and assessed following the same inclusion/exclusion criteria. The selection 13 process is shown in the PRISMA-chart (Figure 1, checklist see Supplemental File 2). Sex-14 specific relevant data were extracted from eligible studies, and patients` outcomes were 15 compared between the sexes. Due to the lack of sex-specific data in most RCTs, observational 16 studies were also included. 17 Where applicable, meta-analyses were performed by using the RevMan software, using a 18 Random-effects model. Odds ratio (OR) was calculated for dichotomous variables and mean 19 differences (MD) for continuous variables, along with their 95% confidence interval (CI). A 20 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. 21 22

- 23 **Results**
- 24 Symptomatic carotid artery stenosis

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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)

8 The overall death rate based on 87,163 patients (31,021 women, 56,142 men) was not 9 significantly different between women (1.5%) and men (1.4%) (OR 0.95, 95% CI 0.80-1.12; 10 $I^2=28\%$; p=0.53) (Supplemental Figure S1), whereas the death rate at 10 years was greater in 11 men (27.1% versus 37.8% in men, p=0.006) (Supplemental Table 1 and Supplemental Figure 12 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; 13 $I^2=0\%$; p=0.03), and a slightly longer mean hospital stay (2 studies, 21,117 patients; 6.4 days 14 vs 5.8 days; OR 0.52, 95% CI 0.21, 0.83; $I^2=0\%$; p=0.001).(14, 34) Women had a 15 16 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 17 2.81,95% CI 1.66-4.75; p=0.0001).(33) A higher rate of cranial nerve palsy as post-procedural 18 19 complication was found in women (1 study, 821 patients; 8.2% vs 4.3%; OR 1.98, 95% CI 20 1.08-3.64; *p*=0.03) (Supplemental Table 1).

21 Regarding CAS of symptomatic carotid artery stenosis, the Carotid Revascularization

22 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

24 Angioplasty versus Carotid Endarterectomy (SPACE) trial showed a non-significant increase

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1	in the periprocedural ipsilateral stroke/death for women with symptomatic carotid artery
2	stenosis (who accounted for 28% of enrolled patients) after CAS in the subgroup analyses
3	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
4	(p=0.85) in the CEA arm. (36) Based on the results of our meta-analyses, the overall stroke
5	rate of 4650 patients (1703 women, 2947 men) did not differ between men (7.6%) and women
6	(8.0%) receiving CAS (OR 1.04, 95% CI 0.79-1.38; <i>I</i> ² =18%; <i>p</i> =0.77) (Figure 2B). This trend
7	was consistent for the in-hospital stroke rate ($P=0.67$) and for the stroke rate at 1 month
8	(p=0.28), at 2 $(p=0.58)$, and 4 years $(p=0.08)$ from stenting. (10, 25) (Supplemental Table 2)
9	The risk of death (n=7405, 2477 women, 4928 men) was also comparable between men and
10	women (OR 1.04, 95% CI 0.66-1.64; <i>I</i> ² =31%; <i>p</i> =0.87) (Supplemental Figure S2) as well as
11	stroke or death (n=9615) (OR 1.09, 95% CI 0.91-1.30; <i>I</i> ² =0%; <i>p</i> =0.37). (17, 23, 36, 37, 38,
12	39, 40, 41, 42, 43)

13

14 Asymptomatic carotid artery stenosis

15 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

17 observational studies. (9, 11, 12, 15, 17, 21, 22, 23, 24, 35, 43, 44, 45, 46, 47, 48, 49, 50, 51,

18 52, 53, 54) Overall, compared to men, women had similar rates of stroke (21 studies, 332,344

19 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,

21 3.4% vs 3.2%, OR 1.17, 95% CI 0.75-1,.3; *I*²=33; *p*=0.49).

22 Although the overall risk of death was slightly significantly lower in women than in men (13

23 studies, 313,453 patients, 136,760 women, 176,693 men;0.35% vs 0.42%, OR 0.87, 95% CI

24 0.78-0.98; $I^2=0\%$; p=0.02), the overall risk of the composite endpoint stroke or death resulted

1 slightly higher in women (8 studies, 65,340 patients, 2.0% vs 1.8%, OR 1.30, 95% CI 1.05-2 $1.63, I^2=39\%, p=0.02$) (Figure 3B). 3 Similarly, the rates of in-hospital MI (1 study, 49,042; OR 1.48, 95% CI 1.17-1.85; *p*=0.0008) 4 and of the composite outcome stroke/MI/death (1 study, 463 patients; 5.3% vs 1.6%; OR 3.43, 5 95% CI 1.10 - 10.69; p=0.03) were significantly higher in women than in men (Supplemental 6 Table 3). However, data on these outcome measures should be interpreted with caution since 7 they come from 1 study each. Perioperative (one-month) outcome events in terms of stroke 8 (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), 9 stroke or death (5 studies, 10,218 patients, 3.2% vs 2.1%, OR 1.44, 95% CI 1.13-1.85; $I^2=0\%$; 10 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, I²: 0%, 11 12 p=0.81) (Supplemental Table 3). The rate of restenosis at 1 year was significantly higher in 13 women compared to men (1 study, 372 patients; 10.8% vs 3.2%; OR 3.71, 95% CI 1.49, 9.2;

14 p=0.005) (Supplemental Table 3).

15 The absolute risk of stroke among asymptomatic women treated with CAS was 3%, with no

16 significant differences compared to men (2.9%) (9 studies, 14,155 patients, 5588 women,

17 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)

18 (Figure 4). There was no sex difference in the absolute risk of death in asymptomatic patients

19 treated with CAS (8 studies, 14,292 patients, 5351 women, 8941 men) OR 1.16, 95% CI 0.71-

20 2.89; *I*²⁼19%; *p*=0.55). (9, 11, 43, 50, 55, 57). However, this meta-analysis of observational

21 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%

23 CI 1.23-3.28, $I^2=0\%$, p=0.005) (Figure 5 and Supplemental Table 4). (9, 43, 55, 56, 57, 59)

24 The data on sex differences in the efficacy and safety of CAS in carotid stenosis comes from

25 observational analyses of registries. Stroke and death among asymptomatic women treated

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10	Discussion
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7	patients undergoing CAS. (9, 15, 43, 58) The risk of bias was acceptable.
6	Other studies showed no between-sex differences in stroke and death in asymptomatic
5	one of the strongest risk factors for death (OR 21.39, 95% CI 5.49-33.39, p<0.001). (56)
4	postoperative stroke (OR 12.59, 95% CI 8.25-18.38, $p < 0.001$) and, together with CAS, it was
3	56, 57, 61) In the study by Dua et al., female sex was associated with a high risk of
2	women were significantly more likely to develop stroke and death after CAS than men. (11,
1	with CAS were recorded in 2.6%-5.4% of cases. (9, 15, 55, 60) in some of these studies,

We present data from our meta-analysis that collected evidence addressing revascularization 11 12 of carotid artery stenosis in men and women covering the last 30 years of stroke evidence for 13 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 14 15 the outcome after carotid revascularization in men and women considering all endpoints. 16 Although there was a trend toward increased randomization of women over this period, 17 women continue to be underrepresented in RCTs and the percentage of women over 75 years 18 of age are still low compared to that observed in the real clinical practice. (62) This under-19 enrolment was confirmed by a recent meta-analysis, underlining that this disparity persisted 20 across all geographic regions, intervention types, and stroke types, apart from subarachnoid 21 hemorrhage. (63) 22 Women are underrepresented in carotid revascularization trials with the highest representation

- 23 in the CREST-trial (35%). Apart from a higher rate of carotid atherosclerosis in men, the
- 24 potential reasons for the underrepresentation of women in carotid revascularization trials may

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1 be the perceived technical difficulties (smaller ICA size in women) or a higher rate of peri-2 and postprocedural complications reported in women than in men. (8) 3 However, based on our data, we could not find a significant increased operative risk in 4 women. In a consensus document published in 2013 on the management of women with 5 carotid artery disease bearing in mind the anatomical and technical differences, and vascular 6 and non-vascular co-morbidities in men and women, a more tailored management for women 7 was called for. (64) Current guidelines on the treatment of extracerebral vascular disease by 8 the society for vascular surgery do not give any sex-specific recommendation.(65) This 9 applies also to the recently published guidelines on endarterectomy and stenting for carotid 10 artery stenosis of the European Stroke Organisation. Sub-group analyses according to sex was 11 performed, but due to the lack of interaction by sex for the main outcomes and low numbers 12 of women included in RCTs no specific recommendation for women was given. (66) 13 Considering the under-enrolment of women, there could be potential risks of under-treatment 14 and it is important to state that, even with some studies reporting a higher peri-operative risk 15 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 16 17 ongoing trials comparing modern medical therapy to modern medical therapy and CAS/CEA 18 in asymptomatic (CREST 2) (68) and at low-risk symptomatic patients (ECST2). (European 19 carotid surgery trial (ECST-2)). (69) 20 A large RCT with a more pragmatic design, including an elderly population, may answer 21 some questions about the risk and benefits of carotid intervention in women. (70)

22 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

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- 1 not contacted for the missing information and individual-based data of men and women due to
- 2 the large number of studies included in this systematic review. Also, the management of
- 3 carotid artery stenoses might have changed over time.
- 4

5 **Conclusions**

- 6 Overall, even considering the risk of bias, our data showed no significantly different outcomes
- 7 in men and women after revascularization of symptomatic and asymptomatic carotid artery
- 8 stenosis.
- 9 Further larger multicenter prospective research into these sex-specific differences is needed.
- 10 More women have to be enrolled in RCTs, including those aged over 80 years, to better
- 11 understand why these sex differences still exist and how we can tailor stroke treatment for
- 12 both sexes.
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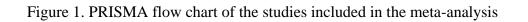
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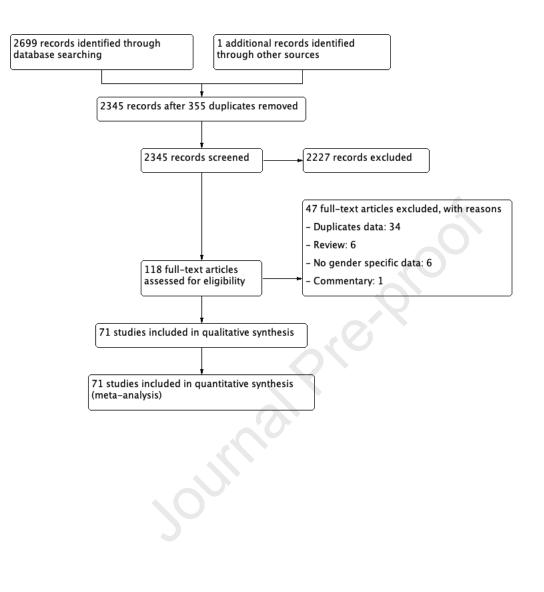


Figure 2. Stroke in men and women after carotid endarterectomy (A) and after stenting (B) of symptomatic carotid artery stenosis

A.

Study or Subgroup 2.1.1 Hospital, Symptomatic	Women Events	Me Total Events		Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% Cl
Bisdas 2012	66 2	2164 79	2164	6.4%	1.12 [0.82, 1.52]	_
Menyhei 2011 < 75 Y		8667 361		11.6%	0.85 [0.70, 1.03]	-
Menyhel 2011, > 75 Y		6078 190	11408	9.7%	1.20 [0.95, 1.51]	-
Rockman 2011, Symptomatic		1037 30	1449	3.0%	1.65 [1.01, 2.71]	
Sarac 2002, Sympotmatic	12	361 20	688	1.5%	1.15 [0.55, 2.38]	
Subtotal (95% CI)		8547	36038	32.3%	1.11 [0.89, 1.38]	L
	398	700	30030	32.3/0	1.11 [0.05, 1.50]	T
Total events Heteropenation Touris - 0.02, Ch			E). 12 _ 1	- 78		
Heterogeneity: Tau ² = 0.03; Ch Test for overall effect: Z = 0.91		IT = 4 (F = 0.0	ы); г = :) /7		
2.1.2 1 month, Symptomatic						
Alamowitch 2005	40	753 93	1810	4.6%	1.04 [0.71, 1.52]	+
Bonati 2010	5	31 13	76	0.6%	0.93 [0.30, 2.66]	
CREST 2011, Howard	6	226 15	427	0.9%	0.75 [0.29, 1.96]	
Frawley 2000	6	312 9	666	0.7%	1.48 [0.52, 4.19]	
Guzman 2014	4	243 9	438	0.6%	0.80 [0.24, 2.62]	
im 2014	43	960 56	1494	4.2%	1.20 [0.80, 1.81]	+-
Kapral 2000	34	506 64	1140	3.6%	1.21 [0.79, 1.86]	4
Kuy 2014, Symptomatic		8254 669	12112	17.8%	1.08 [0.96, 1.22]	
Lane 2003, Symptomatic	4	57 3	104	0.3%	2.54 [0.55, 11.77]	
	6		496			
Lee 2003, Symptomatic		315 13		0.6%	0.72 [0.27, 1.92]	
Lubke 2015, Symptomatic	4	128 11	328	0.6%	0.93 [0.29, 2.97]	
Mattos 2001, Symptomatic	1	311 4	492	0.2%	0.39 [0.04, 3.54]	
Maxwell 1990, < 75 Y	7	265 2	366	0.3%	4.94 [1.02, 23.96]	
Maxwell 1990, > 75 Y	1	70 2	63	0.1%	0.44 [0.04, 5.00]	
Riles 1994	27	636 39	1527	2.9%	1.27 [0.77, 2.09]	
Rockman 2001, Symptomatic	20	659 25	1041	2.1%	1.27 [0.70, 2.31]	
Schneider 1997	5	155 4	271	0.5%	2.23 [0.59, 8.41]	
Tsivgoulis 2014, Symptoma	4	96 4	69	0.4%	0.71 [0.17, 2.93]	
Weise 2004	5	56 8	156	0.6%	1.81 [0.57, 5.80]	
Subtotal (95% CI)		4235	23098	42.0%	1.10 [1.00, 1.22]	-
Total events	712	1043				ſ
Heterogeneity: Tau ² = 0.00; Ch			A 881. 12	- 04		
Test for overall effect: Z = 1.97		QI = 18 (P = 1	v.aa <u>,</u> i	- 04		
2.1.3 1 year, Symptomatic						
Park 2008	0	40 1	53	0.1%	0.43 [0.02, 10.89]	
Subtotal (95% CI)		40	53	0.1%	0.43 [0.02, 10.89]	
Total events	0	1				
Heterogeneity: Not applicable Test for overall effect: Z = 0.51	(P = 0.61)					
2.1.4 2 years, Symptomatic						
Eckstein 2008, SPACE	11	167 39	422	1.6%	0.69 [0.35, 1.39]	
Schneider 1997	6	155 6	271	0.6%	1.78 [0.56, 5.61]	- -
Subtotal (95% CI)		322	693	2.2%	0.99 [0.40, 2.42]	-
Total events	17	45				T
Heterogeneity: $Tau^2 = 0.21$; Ch Test for overall effect: $Z = 0.02$	1² = 1.90, d		.7); i ² = 4	17%		
2.1.5 4 years, Symptomatic						
CREST 2011, Howard	14	226 23	427	1.6%	1.16 [0.58, 2.30]	_
Rong 2016	15	102 12	171	1.2%	2.28 [1.02, 5.10]	
Subtotal (95% CI)	~~	328	598	2.8%	1.57 [0.81, 3.05]	
Total events	29	35				-
Heterogeneity: Tau ² = 0.08; Ch Test for overall effect: Z = 1.35	l ² = 1.58, d		:1);	37%		
2.1.6 5 years, Symptomatic						
Alamowitch 2005	64	424 143	1012	6.1%	1.08 [0.79, 1.49]	+-
Lane 2003, Symptomatic Subtotal (95% CI)	4	57 3 481	104 1116	0.3X 6.5%	2.54 [0.55, 11.77] 1.18 [0.71, 1.94]	•
Total events	68	146				Г
Heterogeneity: $Tau^2 = 0.05$; Ch Test for overall effect: $Z = 0.63$	ıř = 1.15, d		:6); I ² = :	13%		
1 7 10 years from the second						
2.1.7 10 years, Symptomatic						
Cunningham 2002	22	476 61	1250	3.1%	0.70 [0.43, 1.13]	
Mattos 2001, Symptomatic	40	311 94	492	4.3%	0.62 [0.42, 0.93]	
NASCET 1999, Ferguson	76	418 166	997 2739	6.6X	1.11 [0.82, 1.50]	
Subtotal (95% CI)		1207	2739	14.1%	0.81 [0.55, 1.19]	-
Total events Heterogeneity: Tau ² = 0.08; Ch Test for overall effect: Z = 1.08		341 f = 2 (P = 0.0	15); I ² = (9 7%		
rescior overall effect: $Z = 1.06$						l
				100 00/	1.07 [0.97, 1.17]	1
Total (95% CI)	35	5160	64335	100.0%	1.07 [0.57, 1.17]	· · · · · · · · · · · · · · · · · · ·
Total events	1362	2311			1.07 [0.57, 1.17]	ſ
	1362	2311			107 [0.57, 117]	0.02 0.1 1 10 5

B.

	Wom	en	Mer	1		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
2.1.1 Hospital, Symptomatic							
Bisdas 2012	19	233	13	233	11.7%	1.50 [0.72, 3.12]	
Dolg 2016 (1)	3	34	15	81	4.2%	0.43 [0.11, 1.58]	
Rockman 2011, Symptomatic	10	162	6	196	7.5%	1.55 [0.60, 4.01]	
Subtotal (95% CI)		429		510	23.4%	1.16 [0.59, 2.30]	-
Total events	32		36				
Heterogeneity: Tau ² = 0.13; Cl			2 (P = 0.	22); i ² (34%		
Test for overall effect: $Z = 0.43$	B (P = 0.6)	7)					
2.1.2 1 month, Symptomatic							
Bonati 2010	20	37	42	87	10.7%	1.26 [0.58, 2.73]	_
CREST 2009, Howard	7	142	14	272	7.8%	0.96 [0.38, 2.42]	
Dua 2016 (2)	0	0	0	0	-	Not estimable	
Jim 2014, Symptomatic	30	587	71	945	23.6X	0.66 [0.43, 1.03]	
Salinas–Aragón 2016, Symp	1	30	2	81	1.3×	1.36 [0.12, 15.59]	
Shobha 2012	2	67	4	166	2.5%	1.42 [0.25, 7.91]	
Subtotal (95% CI)		863		1573	45.9%	0.83 [0.59, 1.16]	◆
Total events	60		133				
Test for overall effect: Z = 1.09 2.1.3 2 years, Symptomatic	, - .						
Eckstein 2008, SPACE Subtotal (95% CI)	14	171 171	42	436 436	14.6X 14.6%	0.84 [0.44, 1.57] 0.84 [0.44, 1.57]	-
T	14		42				
i otal events	T-4						
	14		42				
Heterogeneity: Not applicable		6)	42				
Heterogeneity: Not applicable Test for overall effect: Z = 0.55		6)	42				
Heterogeneity: Not applicable Test for overall effect: Z = 0.55 2.1.4 4 years, Symptomatic		8) 240	25	428	16.1%	1.71 [0.95, 3.08]	
Heterogeneity: Not applicable Test for overall effect: Z = 0.55 2.1.4 4 years, Symptomatic CREST 2011, Howard	5 (P = 0.5			428 428	16.1% 16.1%	1.71 [0.95, 3.08] 1.71 [0.95, 3.08]	
Total events Heterogenelty: Not applicable Test for overall effect: Z = 0.55 2.1.4 4 years, Symptomatic CREST 2011, Howard Subtotal (95% CI) Total events	5 (P = 0.5	240					•
Heterogeneity: Not applicable Test for overall effect: Z = 0.55 2.1.4 4 years, Symptomatic CREST 2011, Howard Subtotal (95% Cl) Total events	5 (P = 0.5 23	240	25				-
Heterogeneity: Not applicable Test for overall effect: Z = 0.55 2.1.4 4 years, Symptomatic CREST 2011, Howard Subtotal (95% CI) Total events Heterogeneity: Not applicable	5 (P = 0.5 23 23	240 240	25				-
Heterogeneity: Not applicable Test for overall effect: Z = 0.55 2.1.4 4 years, Symptomatic CREST 2011, Howard Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.76	5 (P = 0.5 23 23	240 240	25	428			
Heterogeneity: Not applicable Test for overall effect: Z = 0.55 2.1.4 4 years, Symptomatic CREST 2011, Howard Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.76 Total (95% CI)	5 (P = 0.5 23 23	240 240 8)	25 25	428	16.1%	1.71 (0.95, 3.08)	•
Heterogeneity: Not applicable Test for overall effect: Z = 0.55 2.1.4 4 years, Symptomatic CREST 2011, Howard Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.76 Total (95% CI) Total events	5 (P = 0.5 23 23 8 (P = 0.0 129	240 240 6) 1703	25 25 236	428	16.1% 100.0%	1.71 (0.95, 3.08)	
Heterogeneity: Not applicable Test for overall effect: Z = 0.55 2.1.4 4 years, Symptomatic CREST 2011, Howard Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.76 Total (95% CI) Total events Heterogeneity: Tau ² = 0.04; Ci	5 (P = 0.5 23 23 8 (P = 0.0 129 ht ² = 11.0	240 240 8) 1703 3, df =	25 25 236	428	16.1% 100.0%	1.71 (0.95, 3.08)	
Heterogeneity: Not applicable Test for overall effect: Z = 0.55 2.1.4 4 years, Symptomatic CREST 2011, Howard Subtotal (95% CI)	5 (P = 0.5) 23 23 $8 (P = 0.0)$ 129 $ht2 = 11.0$ $9 (P = 0.7)$	240 240 8) 1703 3, df = 7)	25 25 236 9 (P = 1	428 2947 ().27); ř	16.1% 100.0% = 18%	1.71 (0.95, 3.08) 1.04 (0.79, 1.38)	0.1 0.2 0.5 1 2 5 10 Women Men

(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.

	Wom	on	Me	'n		Odds Ratio	Odds Ratio
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
4.1.1 Hospital, Asymptomatic	220	24524	201	245.24	10 10	1 10 11 00 1 10	
Bisdas 2012 Rockman 2011, Asymptomati	336 163	24521 20584	264 261	24521 27713	15.1% 14.1%	1.19 [1.02, 1.40] 0.94 [0.78, 1.14]	Ţ
Sarac 2002, Asymptomatic	105	20304	16	1586	3.7%	2.17 [1.09, 4.31]]
Subtotal (95% CI)		45892	-	53820	33.0%	1.16 [0.88, 1.54]	•
Total events	538	15	561		,		
Heterogeneity: $Tau^2 = 0.04$; Chi Test for overall effect: Z = 1.07			° = 0.03)); i* = 729	6		
4.1.2 1 month, Asymptomatic							
Calvillo-King 2010	90	2996	75	3655	10.2%	1.46 [1.06, 2.02]	C +
CREST 2011, Howard	3	191	5	396	1.0%	1.25 [0.30, 5.28]	
Davidovic 2015	22	530	22	1037	4.6%	2.00 [1.10, 3.64]	
Guzman 2014 Hugi 2006	2	120 120	3	245 252	0.7%	1.37 [0.23, 8.29]	
jim 2014	26	1718	39	2320	6.0%	10.65 [0.51, 223.66] 0.90 [0.55, 1.48]	
Kuy 2014, Asymptomatic	474	86150		114737	16.2%	1.12 [0.99, 1.27]	
Lane 2003, Asymptomatic	0	56	0	142		Not estimable	
Lee 2003, Asymptomatic	Å.	285	Å	407	1.1%	1.43 [0.36, 5.78]	
Lubke 2015, Asymptomatic	3	460	10	964	1.2%	0.63 [0.17, 2.29]	
Mattos 2001, Asymptomatic	Ő	154	2	247	0.2%	0.32 [0.02, 6.66]	
Rockman 2001, Asymptomati	4	332	9	444	1.5%	0.59 [0.18, 1.93]	
Sternbach 2000	0	68	1	66	0.2%	0.43 [0.02, 10.62]	
Subtotal (95% CI)		93182		124934	43.2%	1.19 [1.01, 1.40]	•
Total events	630		732				
Heterogeneity: $Tau^2 = 0.01$; Chi Test for overall effect: $Z = 2.13$			L (P = 0.)	36);	176		
4.1.3 3 months, Asymptomati	c						
Hugi 2006 Subtotal (95% CI)	3	120 120	2	252 252	0.7% 0.7%	3.21 [0.53, 19.44] 3.21 [0.53, 19.44]	
Total events	3	120	2	2.52	0.770	5.21 [0.55, 15.44]	
Heterogeneity: Not applicable Test for overall effect: $Z = 1.27$.)	8				
4.1.4 4 years, Asymptomatic							
CREST 2011, Howard Subtotal (95% CI)	5	191 191	6	396 396	1.6% 1.6%	1.30 [0.42, 4.04] 1.30 [0.42, 4.04]	
Total events	5		6	550	110/0	100 [0112, 101]	
Heterogeneity: Not applicable			-				
Test for overall effect: $Z = 0.46$	(P = 0.65	i)					
4.1.5 5 years, Asymptomatic							
ACST 2004	12	539	16	1021	3.3%	1.27 [0.61, 2.65]	_
ACST-2	25	541	54	1273	6.2%	1.09 [0.67, 1.78]	- -
Lane 2003, Asymptomatic	0	58	2	142	0.2%	0.48 [0.02, 10.16]	
Subtotal (95% CI)	-	1138		2436	9.8%	1.13 [0.75, 1.68]	◆
Total events	37		74				
Heterogeneity: Tau ² = 0.00; Chi Test for overall effect: Z = 0.58			· = 0.81)	r; r = 0%			
4.1.6 10 years, Asymptomatic							
ACST-1 2010, Halliday (1)	16	2658	53	5272	5.1%	0.60 [0.34, 1.05]	_
ACST-1 2010, Hallkday (2)	17	687	13	965	3.4%	1.86 [0.90, 3.85]	↓ →−
Mattos 2001, Asymptomatic	9	154	38	247	3.2%	0.34 [0.16, 0.73]	
Subtotal (95% CI)		3499		6484	11.7%	0.72 [0.29, 1.79]	-
Total events	42		104				
Heterogeneity: Tau ² = 0.52; Chi Test for overall effect: Z = 0.70			(P = 0.0)	05);	11		
Total (95% CI)		144022		188322	100.0%	1.12 [0.96, 1.30]	•
Total events	1255		1481				ľ
Heterogeneity: Tau ² = 0.03; Chi		l, df = 22		02);	2%		0.02 0.1 1 10
Test for overall effect: Z = 1.47 Test for subgroup differences: C	(P = 0.14)	9	-				0.02 0.1 1 10 Women Men
Footnotes		-,	.	-/1 •/	-		
(1) ≤ 75 years							

 $(1) \le 75$ years $(2) \ge 75$ years B.

•	Wom	en	Me	en		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
4.3.1 Hospital, Asymptomatic							
Bisdas 2012	115	24521	116	24521	20.2%	0.97 [0.75, 1.26]	
Rockman 2011, Asymptomati	77	20584	123	27713	16.5%	0.84 [0.63, 1.12]	
Sarac 2002, Asympotmatic	7	787	12	1586	1.5%	1.18 [0.46, 3.00]	
Yavas 2010	ó	16	1	57	0.1%	1.14 [0.04, 29.36]	
Subtotal (95% CI)	•	45908	-	53877		0.92 [0.77, 1.11]	4
Total events	199		254				1
Heterogeneity: Tau ² = 0.00; Ch		df = 3 ()		. P = 0¥			
Test for overall effect: Z = 0.84			••••				
4.3.2 1 month, Asymptomatic	c						
Guzman 2014	1	120	3	245	0.3%	0.68 [0.07, 6.59]	
lugi 2006	0	120	3	252	0.2%	0.30 [0.02, 5.77]	
Im 2014	11	1718	19	2320	2.4%	0.78 [0.37, 1.64]	
(uy 2014, Asymptomatic	224	86150	-	114737	47.8%	0.64 [0.71, 0.99]	
ee 2003, Asymptomatic	1	285	1	407	0.2%	1.43 [0.09, 22.95]	
ubke 2015, Asymptomatic	0	460	2	964	0.1%	0.42 [0.02, 8.72]	
iternbach 2000	Ó	68	0	66		Not estimable	
Subtotal (95% CI)	-	88921	-	119013	51.0%	0.83 [0.71, 0.98]	•
fotal events	237		364				
teterogeneity: $Tau^2 = 0.00$; Ci fest for overall effect: $Z = 2.24$			P = 0.97);			
1.3.3 1 year, Asymptomatic							,
lugi 2006	1	120	12	252	0.3%	0.17 [0.02, 1.31]	
ubtotal (95% CI)		120		252	0.3%	0.17 [0.02, 1.31]	
fotal events	1		12				
leterogeneity: Not applicable lest for overall effect: Z = 1.70) (P = 0.09)					
1.3.4 4 years, Asymptomatic							
ravas 2010	1	16	6	53	0.3%	0.52 [0.06, 4.69]	
ubtotal (95% CI)		16		53	0.3%	0.52 [0.06, 4.69]	
otal events	1		6				
leterogeneity: Not applicable fest for overall effect: Z = 0.56	3 (P = 0.56)					
.3.5 5 years, Asymptomatic							
ragsterman 2006	41	1737	80	3440	9.2%	1.02 [0.69, 1.49]	+
ane 2003, Asymptomatic	4	58	9	58	0.9%	0.40 [0.12, 1.39]	
ubtotal (95% CI)		1795		3498	10.1%	0.78 [0.34, 1.77]	
otal events	45		69				
leterogeneity: $Tau^2 = 0.21$; Cl est for overall effect: $Z = 0.60$			P = 0.16); I ² = 49)	6		
Total (95% CI)		136760		176693	100.0%	0.87 [0.78, 0.98]	•
fotal events	463		745				
leterogeneity: Tau ² = 0.00; Cl	ht ² = 7.20,	df = 13	(P=0.8)	9); t ² = 07	"		0.01 0.1 1 10 10
est for overall effect: Z = 2.35			-				U.UI U.I I IU IU Women Men
Test for subgroup differences:			(P = 0.4)	9), $t^2 = 0$	×		women wen

	Wom	en	Me	n		Odds Ratio		Odds Rat	io	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random,	95% CI	
3.1.1 Hospital, Asymptomatic										
Bisdas 2012		1773	35	1773	16.7%	1.09 [0.66, 1.73]		_ - _		
Rockman 2011, Asymptomati	22	1037	30	1696	13.5%	1.20 [0.69, 2.10]				
Subtotal (95% CI)		2810		3469	32.2%	1.13 [0.79, 1.62]		•		
Total events	60		65							
Heterogeneity: Tau ² = 0.00; Chi	l ² = 0.08	, df = 1	. (P = 0.)	78); i² =	0%					
Test for overall effect: Z = 0.69	(P=0.4)	9)								
3.1.2 1 month, Asymptomatic										
ACCULINK/ACCUNET 2010 (1)	13	454	31	712	9.9%	0.65 [0.34, 1.25]				
CREST 2009, Howard	16	437	23	713	10.6%	1.29 [0.69, 2.42]		- -		
De Rango 2010	6	306	25	778	5.5%	0.60 [0.24, 1.48]				
Dua 2016 (2)	0	0	0	0		Not estimable				
im 2014, Asymptomatic	29	743	31	1098	15.5%	1.40 [0.84, 2.34]		· +		
Salinas–Aragón 2016, Asym	4	64	0		0.5%	16.38 [0.87, 308.08]		+	-	
Subtotal (95% CI)		2024		3447	42.2%	1.04 [0.63, 1.74]		•		
Total events	70		110							
Heterogeneity: Tau ² = 0.16; Chi Test for overall effect: Z = 0.16			$\langle P = 0.0$	08); I ² =	53%					
1 = 0.10	(r = 0.0.	"								
3.1.3 4 years, Asymptomatic										
ACST-2	29	539	62	1272	19.5%	1.11 [0.71, 1.75]				
CREST 2011, Howard	9	215	15	379	6.2%	1.06 [0.46, 2.47]				
Subtotal (95% CI)		754		1651	25.6%	1.10 [0.74, 1.64]		•		
Total events	36		77							
Heterogeneity: Tau ² = 0.00; Chi	r² = 0.01	, df = 1	(P = 0.9)	93); 🖻 =	• 0%					
Test for overall effect: $Z = 0.46$	(P = 0.6)	4)								
Total (95% CI)		5588		8567	100.0%	1.09 [0.88, 1.35]		•		
Total events	168		252					1		
Heterogeneity: Tau ² = 0.01; Chi	l ² = 8.64	, df = 6	$(\mathbf{P}=0.)$	37); 🖻 =	- 7%		0.005	0.1 1	10	20
Test for overall effect: Z = 0.81							0.003	Women Me		20
Test for subgroup differences: C	$h^2 = 0.0$	7, df =	2 (P = 0).97), ľ	= 0%			and the second second		
Footnotes										
(1) ≥ 80 years										
(2) Asymptomatic: OR: 6.63; 95	% CI 4.11	-12.12	s							

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

Study or SubgroupEvid3.5.1 Hospital, AsymptomaticBisdas 2012Subtotal (95% CI)Total eventsHeterogeneity: Not applicableTest for overall effect: Z = 2.41 (P3.5.2 1 month, AsymptomaticCREST 2009, HowardCREST 2011, HowardDe Rango 2010Jim 2014, AsymptomaticSalinas-Aragón 2016, AsymSubtotal (95% CI)Total eventsHeterogeneity: Tau ² = 0.00; Chi ² Test for overall effect: Z = 1.64 (P	17 17 - 0 8 3 2 9 4 26	1773 1773	5 5 6 4 1	1773 1773 713 379 776	24.1% 24.1%	M-H, Random, 95% Cl 3.42 [1.26, 9.30] 3.42 [1.26, 9.30] 2.20 [0.76, 6.38] 1.33 [0.29, 5.98]		M-H, Rar	ndom, 95% CI	
Bisdas 2012 Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 2.41 (P 3.5.2 1 month, Asymptomatic CREST 2009, Howard CREST 2011, Howard De Rango 2010 Jim 2014, Asymptomatic Salinas–Aragón 2016, Asym Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ²	17 - 0 - - - - - - - - - - - - -	1773 .02) 437 215 306 743 84	5 6 4 1 12	1773 713 379 778	24.1% 21.2% 10.6%	3.42 [1.26, 9.30] 2.20 [0.76, 6.38] 1.33 [0.29, 5.98]			•	
Subtotal (95% CI) Total events Heterogeneity: Not applicable Test for overall effect: Z = 2.41 (P 3.5.2 1 month, Asymptomatic CREST 2009, Howard CREST 2011, Howard De Rango 2010 Jim 2014, Asymptomatic Salinas–Aragón 2016, Asym Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ²	17 - 0 - - - - - - - - - - - - -	1773 .02) 437 215 306 743 84	5 6 4 1 12	1773 713 379 778	24.1% 21.2% 10.6%	3.42 [1.26, 9.30] 2.20 [0.76, 6.38] 1.33 [0.29, 5.98]			•	
Heterogeneity: Not applicable Test for overall effect: Z = 2.41 (P 3.5.2 1 month, Asymptomatic CREST 2009, Howard CREST 2011, Howard De Rango 2010 Jim 2014, Asymptomatic Salinas-Aragón 2016, Asym Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.00; Chi ²	e = 0 8 3 2 9 4 26	437 215 306 743 84	6 4 1 12	713 379 778	10.6X	1.33 [0.29, 5.98]				
Test for overall effect: Z = 2.41 (P 3.5.2 1 month, Asymptomatic CREST 2009, Howard CREST 2011, Howard De Rango 2010 Jim 2014, Asymptomatic Salinas-Aragón 2016, Asym Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.00; Chi ²	6 3 2 9 4 26	437 215 306 743 84	4 1 12	379 778	10.6X	1.33 [0.29, 5.98]				
3.5.2 1 month, Asymptomatic CREST 2009, Howard CREST 2011, Howard De Rango 2010 Jim 2014, Asymptomatic Salinas-Aragón 2016, Asym Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.00; Chi ²	6 3 2 9 4 26	437 215 306 743 84	4 1 12	379 778	10.6X	1.33 [0.29, 5.98]				
CREST 2009, Howard CREST 2011, Howard De Rango 2010 Jim 2014, Asymptomatic Salinas-Aragón 2016, Asym Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.00; Chi ²	3 2 9 4 26	215 306 743 84	4 1 12	379 778	10.6X	1.33 [0.29, 5.98]				
CREST 2011, Howard De Rango 2010 Jim 2014, Asymptomatic Salinas–Aragón 2016, Asym Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ²	3 2 9 4 26	215 306 743 84	4 1 12	379 778	10.6X	1.33 [0.29, 5.98]				
De Rango 2010 Jim 2014, Asymptomatic Salinas–Aragón 2016, Asym Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ²	2 9 4 26	306 743 84	1 12	778						
Jim 2014, Asymptomatic Salinas–Aragón 2016, Asym Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ²	9 4 26	743 84	12	-	4.76					
Salinas-Aragón 2016, Asym Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ²	4 26	64			-	5.11 [0.46, 56.58]		-		
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ² :	26		2	1098	31.6×	1.11 [0.47, 2.65]		-		
Total events Heterogeneity: Tau ² = 0.00; Chi ² :		1785	-		6.1×	3.60 [0.65, 20.09]				_
Heterogeneity: Tau ² = 0.00; Chi ²				3114	75 .9 %	1.70 [0.97, 2.98]			-	
	= 2.7		25		_					
Test for overall effect: Z = 1.64 (P			• 4 (P = •	0.59); I	* = 0 %					
) = 0.	.07)								
Total (95% CI)		3558		4887	100.0%	2.01 [1.23, 3.28]			•	
Total events	43		30							
Heterogeneity: Tau ² = 0.00; Chl ²	= 4.2	23, df -	5 (P =	0.52); I	² = 0%		0.01	0.1	1 10	100
Test for overall effect: Z = 2.79 (P	· = 0.	.005)					0.01		n Men	TŬ
Test for subgroup differences: Chi	ř = 1	.43, df	= 1 (P -	= 0.23)	, i ² = 30.3	3%		wonie	in wen	

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.

Journal Prevention

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

						Odds Ratio
Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
16	2184	23	2184	5.3X	0.69 [0.37, 1.32]	
22	1037	39	1449	7.0%	0.78 [0.46, 1.33]	
7	361	8	666	2.4%	1.68 [0.60, 4.67]	
0	26	3	107	0.3%	0.56 [0.03, 11.24]	
	3608		4428	15.0%	0.83 [0.57, 1.21]	◆
45		73				
hľ = 2.24		(P = 0.5	2); I ² = (0%		
17	753	14	1810	4.5%	2.96 [1.45, 6.04]	_ _
2	243	3	438	0.6%		
12	960	14				_ _
4	506	9	1140	1.9%		
-						
-		_				
_						\perp
-		-				
1		v				
202	20434	207	30130	47.5%	1.15 [0.94, 1.39]	
		(P = 0.3	5);	10%		
		_				
	24 24	9	96 98	1.1% 1.1%	0.90 [0.18, 4.46] 0.90 [0.18, 4.46]	
2		9				
3 (P = 0.9	0)					
43	247	67	368	9.3%	0.95 [0.62, 1.44]	-
39	229	82	402	9.3%	0.80 [0.53, 1.22]	
14	57	14	57	3.3%	1.00 [0.43, 2.35]	_
6	155	22	271	2.9%	0.46 [0.18, 1.15]	
-	688		1098	24.8%	0.84 [0.64, 1.09]	•
102		185				•
hľ = 2.20			3); I ² = (0%		
67	247	139	368	11.3%	0.61 [0.43, 0.87]	
	247		368	11.3%	0.61 [0.43, 0.87]	◆
	06)	139				
	-]
	31021		56142	100.0%	0.95 [0.80, 1.12]	♦
479		603				
479 hľ² = 26.4	7, df =).12); P	- 28%		0.01 0.1 1 10 1
	Events 16 22 7 0 45 $(P = 0.3)$ 17 2 12 4 158 0 1 32 36 1 263 11 263 16 10 ² 2 4 48 10 ² 2 4 6 10 ² 2 4 6 10 ² 2.200 1 ² 2.200 1 ² 2.200 1 ² 2.200 1 ² 67 67 67	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Events Total Events 16 2184 23 22 1037 39 7 361 8 0 26 3 3608 73 45 73 17 753 14 2 243 3 12 960 14 4 506 9 158 8254 208 0 315 2 1 128 2 32 9017 76 36 6123 67 1 155 0 26454 263 397 16 9.96, df = 9 (P = 0.3 9 9.96, df = 9 (P = 0.3 9 2 2 16 9 9 2 24 9 2 24 9 3 247 67 39 229 82	Events Total Events Total 16 2184 23 2184 22 1037 39 1449 7 361 8 688 0 26 3 107 3608 4428 45 73 14 16 2184 23 2184 0 26 3 107 3608 4428 45 73 14 16 2243 3 438 12 960 14 1494 4 506 9 1140 158 8254 208 12112 0 315 2 496 1 128 2 328 32 9017 76 20561 36 6123 67 11500 263 397 14 50150 263 397 14 98 2	Events Total Events Total Weight 16 2184 23 2184 5.3% 22 1037 39 1449 7.0% 7 361 8 688 2.4% 0 26 3 107 0.3% 3608 4428 15.0% 45 73 14 1810 4.5% 2244 3 438 0.8% 12960 14 1494 3.9% 4 506 9 4 506 9 1140 1.9% 158 8254 208 12112 16.6% 0 315 2 496 0.3% 1 128 2 328 0.5% 36 6123 67 1500 9.7% 1 155 0 271 0.3% 263 397 14 98 1.1% 24 98 1.1%	Events Total Events Total Weight M-H, Random, 95% CI 16 2184 23 2184 5.3% 0.69 [0.37, 1.32] 22 1037 39 1449 7.0% 0.78 [0.46, 1.33] 7 361 8 688 2.4% 1.68 [0.60, 4.67] 0 26 3 107 0.3% 0.56 [0.03, 11.24] 3608 4428 15.0% 0.83 [0.57, 1.21] 45 45 73 14 1810 4.5% 2.96 [1.45, 6.04] 2 243 3 438 0.8% 1.20 [0.20, 7.25] 12 960 14 1494 3.9% 1.34 [0.62, 2.91] 4 506 9 1140 1.9% 1.00 [0.31, 3.22] 12 960 14 1494 3.9% 0.31 [0.02, 6.55] 1 128 2.328 0.5% 0.34 [0.62, 1.

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

Study or Subgroup 2.3.1 Hospital, Symptomatic	Wom		Mer		W-!	Odds Ratio	Odds Ratio
	Events	rotal	Events	rotal	weight	M-H, Random, 95% CI	M–H, Random, 95% Cl
			-				
Bisdas 2012	10	233	9	233	15.6X		_
Dua 2016 (1)	0	0	0	0		Not estimable	
Rockman 2011, Symptomatic	6	162	16	196	14.7%		
Werner 2012, Symptomatic	6	774	10	1823	13.7%	1.42 [0.51, 3.91]	
Subtotal (95% CI)		1169		2252	44.0%	0.88 [0.43, 1.77]	
Total events	22		35				
Heterogeneity: $Tau^2 = 0.15$; C Test for overall effect: $Z = 0.3$			2 (P = 0.	.20); I ²	- 36%		
2.3.2 1 month, Symptomatic							
CREST 2009, Howard	4	142	2	272	6.1%	3.91 [0.71, 21.63]	
Jim 2014, Symptomatic	11	587	25	945	20.7%	0.70 [0.34, 1.44]	
Salinas–Aragón 2016, Symp	1	30	6	61	4.0%	0.43 [0.05, 3.74]	
	_		-	-			
Shobha 2012	2	67	6	166	6.7%	0.93 [0.18, 4.74]	
Werner 2012, Symptomatic	11	482	14	1190	18.5%	1.96 [0.88, 4.35]	
Subtotal (95% CI)		1308	- •	2676	56.0%	1.20 [0.61, 2.35]	—
Total events	29		53		0/		
Heterogeneity: $Tau^2 = 0.21$; C Test for overall effect: $Z = 0.57$			4 (P = Q.	.17); F	= 3/%		
Total (95% CI)		2477		4928	100.0%	1.04 [0.66, 1.64]	•
Total events	51		66				Ť
Footnotes (1) Symptomatic: OR: 21.39; 9	5% CI 5.4	9-33.3	9				

Journal Pre-proof

StrokeHospital1 month1 year2 years4 years5 years10 years	Women 2.1% 5.0% 0.0% 5.3% 8.8% 14.1% 11.4%	Men 1.9% 4.5% 1.9% 6.5% 5.9% 13.1% 12.4%	5(54585) 19(37333) 1(93) 2(1015) 2(926) 2(1597)	1.11 [0.89, 1.38] 1.10 [1.00, 1.22] 0.43 [0.02, 10.89] 0.99 [0.40, 2.42]	I ² , p 57%, 0.05 0%, 0.88 NA 47% 0.17	0.36 0.05 0.61
Hospital1 month1 year2 years4 years5 years10 years	5.0% 0.0% 5.3% 8.8% 14.1% 11.4%	4.5% 1.9% 6.5% 5.9% 13.1%	19(37333) 1(93) 2(1015) 2(926)	1.10 [1.00, 1.22]0.43 [0.02, 10.89]0.99 [0.40, 2.42]	0%, 0.88 NA	0.05
1 month1 year2 years4 years5 years10 years	5.0% 0.0% 5.3% 8.8% 14.1% 11.4%	4.5% 1.9% 6.5% 5.9% 13.1%	19(37333) 1(93) 2(1015) 2(926)	1.10 [1.00, 1.22]0.43 [0.02, 10.89]0.99 [0.40, 2.42]	0%, 0.88 NA	0.05
1 year2 years4 years5 years10 years	0.0% 5.3% 8.8% 14.1% 11.4%	1.9% 6.5% 5.9% 13.1%	1(93) 2(1015) 2(926)	0.43 [0.02, 10.89] 0.99 [0.40, 2.42]	NA	
2 years 4 years 5 years 10 years	5.3% 8.8% 14.1% 11.4%	6.5% 5.9% 13.1%	1(93) 2(1015) 2(926)	0.99 [0.40, 2.42]		0.61
4 years 5 years 10 years	8.8% 14.1% 11.4%	5.9% 13.1%	2(926)		470/ 017	
4 years 5 years 10 years	8.8% 14.1% 11.4%	5.9% 13.1%	2(926)		47%, 0.17	0.98
5 years 10 years	11.4%		2(1597)	1.57 [0.81, 3.05]	37%, 0.21	0.18
10 years		12.4%		1.18 [0.71, 1.94]	13%, 0.28	0.53
2			3(3946)	0.81 [0.55, 1.19]	67%, 0.05	0.28
TIA	0 604				,	
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	27.170	21.070	1(010)			0.000
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	12.170	0.770	0(2001)			0.07
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	110 /0	11170	(2:20:)		2270, 0.21	0.72
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	0.02
LOS, hospital,	1.570		1(000)	0.27 [0.00, 1.70]	1 12 1	0.72
d						
	6.4±11.8	5.8±11.7	2(21177)	0.52 [0.21, 0.83]	0%, 0.55	0.001
Restenosis	0.1_11.0	5.0_11.7	2(21177)	0.52 [0.21, 0.05]	070, 0.55	0.001
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	0.0002
Reintervention						

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				
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; I²: 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

, I². existical significant

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,	7.970	0.170	1(055)	0.91 [0.33, 1.30]		0.75
Overall	6.7±1.4	5.4±1.2	2(721)	-0.09 [-0.27, 0.08]	0%, 0.80	0.29

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

verall 6.7 ± 1.4 5.4 ± 1.2 2(721)-0.09[-0.27, 0.08]0%, 0.800.29CI: Confidence interval; d: days; I²: 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

Outcome	Incider	nce (%)	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	01170	11070	1(1000)	1.50 [0.05, 2.21]		0.22
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	0.0000
Stroke, MI or	0.2070	0.0570	5(200500)	1.00 [0.90, 1.10]	070, 0.72	0.23
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,	5.170	5.270	2(4023)	0.90 [0.09, 1.94]	070, 0.00	0.01
d						
Overall	2.6±16.0	2.3±16.0	2(201579)	0.24 [0.10, 0.38]	0%, 0.87	0.0006
Restenosis	2.0-10.0	2.2.10.0	2(201377)	0.2 1 [0.10, 0.30]	070,0.07	0.0000
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	<u> </u>	NR	
10 years	NR	NR	NR	NR	NR	NR
10 years			INIX	INK		TNIX

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

Outcome	Inciden	ice (%)	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				X		
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; I²: 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 .Æ

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Outcome	Inciden	ce (%)	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			0			
Overall	3.1±3.0	2.7±3.0	1(3546)	0.40 [0.20, 0.60]	NA	0.29
Hematoma				L / J		
1 month	1.6%	1.3%	1(1084)	1.28 [0.43, 3.76]	NA	0.66

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

CI: Confidence interval; d: days; I²: 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



Section and Topic	ltem #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT	1		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION	r		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	р. З
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p. 3-4
METHODS	1		
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

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Supplemental file 2: Kremer et al. PRISMA 2020 Checklist

Section and Topic	ltem #	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.			
	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.				
syntheses	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 INFORMA	TION					
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			



Journal Pre

Supplemental file 2: Kremer et al. PRISMA 2020 Checklist

Section and Topic	ltem #	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: <u>http://www.prisma-statement.org/</u>

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 gp://www.prisn.

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

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