Risk Factors for Restenosis After Carotid Revascularization: A Meta-Analysis of Hazard Ratios

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Key words
- Carotid artery stenting
- Carotid endarterectomy
- Carotid restenosis
- Risk factors

Abbreviations and Acronyms
CAD: Coronary artery disease
CAS: Carotid artery stenting
CEA: Carotid endarterectomy
CI: Confidence interval
CKD: Chronic kidney disease
HR: Hazard ratio

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BACKGROUND: **Carotid artery restenosis after carotid endarterectomy (CEA) or carotid artery stenting (CAS) will occur in 3%–30% of cases. Restenosis can lead to more frequent clinical and imaging monitoring and the potential for reoperation. We sought to define the demographic, clinical, and radiographic characteristics that influence the restenosis risk after carotid revascularization.**

METHODS: **The present study was performed in accordance with the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines. A random effects model meta-analysis of hazard ratios (HRs) was conducted.**

RESULTS: **Eighteen studies with 17,106 patients were included. Diabetes (HR, 1.68; 95% confidence interval [CI], 1.00–2.83; I^2, 76.7%), dyslipidemia (HR, 1.77; 95% CI, 1.08–2.91; I^2, 22.5%), female gender (HR, 1.50; 95% CI, 1.14–1.98, I^2, 0%), chronic kidney disease (HR, 4.15; 95% CI, 1.69–10.19; I^2, 44.5%), hypertension (HR, 1.99; 95% CI, 1.07–3.72; I^2, 68%), smoking (HR, 1.65; 95% CI, 1.15–2.37; I^2, 54.3%), and pretreatment stenosis >70% (HR, 1.04; 95% CI, 1.0–1.08; I^2, 0%) showed a statistically significant increase in restenosis risk after carotid revascularization. Subgroup analyses of CEA and CAS showed that female gender and smoking status were significantly associated with recurrent stenosis after CEA but not after CAS. In contrast, hypertension was associated with restenosis after CAS but not after CEA. Patch endarterectomy (HR, 0.33; 95% CI, 0.22–0.50; I^2, 0%) and symptomatic status at presentation in the CAS group (HR, 0.61; 95% CI, 0.41–0.90; I^2, 0%) were associated with a decreased risk of restenosis. Antiplatelet use and coronary artery disease were not associated with restenosis risk.**

CONCLUSIONS: **Diabetes, dyslipidemia, female gender, renal failure, hypertension, and smoking were associated with an increased risk of restenosis, and patch endarterectomy and symptomatic status at presentation were associated with a decreased risk of carotid restenosis. Both female gender and current smoking status were only associated with recurrent stenosis after CEA, and hypertension was only associated with restenosis after CAS.**

INTRODUCTION

Carotid artery restenosis is a potential short- and long-term complication after carotid revascularization using carotid artery endarterectomy (CEA) or carotid artery stenting (CAS). The incidence of restenosis after CEA has been reported to be from 5% to 22%, and the occurrence of in-stent restenosis has ranged from 2.7% to 33%.[1-6] Several studies have demonstrated the temporal component of carotid restenosis, suggesting that early restenosis (<3 years) will be caused by myointimal hyperplasia, and late restenosis (>3 years) will be a consequence of recurrent carotid atherosclerosis.[7-10]

The clinical effect of carotid restenosis can be severe, including recurrent stroke and neurologic morbidity. Patients who develop carotid restenosis after CEA or CAS could require a second revascularization procedure. This, in turn, will lead to increased healthcare costs, the additional risk of procedure-related complications, and patient inconvenience.[11,12] Several risk factors that affect the long-term durability of revascularization have been identified, including active smoking, diabetes mellitus, female gender, and stent type used in CAS.[13,14] Patient selection according to anatomic factors and clinical variables could help develop risk stratification tools to accurately select the safest and most efficacious carotid revascularization strategy for each patient.

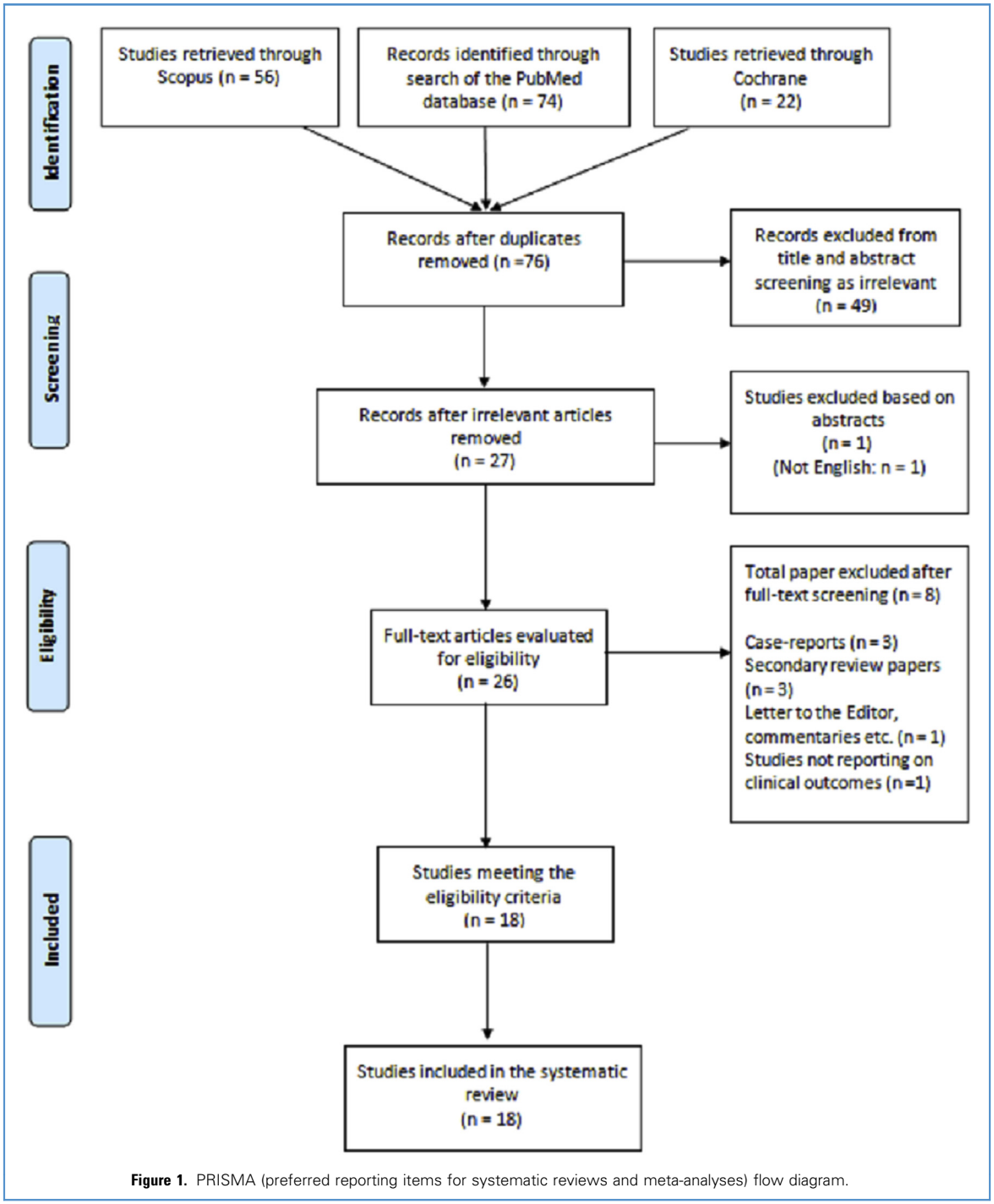

Figure 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram.

The aim of the present meta-analysis was to define the clinical characteristics that can influence the risk of restenosis after carotid revascularization using CEA or CAS to optimize the patient selection criteria for each approach.

METHODS

Search Strategy and Selection Criteria

Systematic searches were conducted in PubMed, Scopus, and Cochrane Central. The keywords used for the database searches included carotid, restenosis, hazard ratio, endarterectomy, and stenting. The search was conducted by 2 of us (P.T., S.G.) independently. Disagreements were resolved by a third investigator (D.G.K.). The references of the included

Table 1. Baseline Characteristics

Investigator	Study Design	Mean Age (years)	Female Gender (%)	Symptomatic Patients Before Procedure (%)	HTN (%)	Diabetes (%)	Dyslipidemia (%)	Smoking (%)
CEA								
De Letter et al.,[24] 1993	RCT	NR	27	NR	NR	NR	NR	NR
Cao et al.,[22] 2000	RCT	NR	NR	NR	NR	NR	NR	NR
Mannheim et al.,[23] 2005	RCT	70	34	46	75	48	48	46
Reina-Gutiérrez et al.,[21] 2005	OBS	71	22	58	68	29	46	72
Goodney et al.,[20] 2010	OBS	73	41	32	86	30	NR	79
Fluri et al.,[37] 2010	OBS	66	27	82	75	16	47	47
Lal et al.,[18] 2012*	RCT	69	33	53	86	31	86	26
Malas et al.,[19] 2015	RCT	69	33	54	86	31	85	26
Avgerinos et al.,[36] 2016	OBS	71	44	35	86	32	71	24
CAS								
de Donato et al.,[34] 2008	OBS	72	33	41	72	26	62	38
Bonati et al.,[35] 2009	RCT	67	34	96	48	16	26	72
Verzini et al.,[30] 2016	OBS	72	29	25	84	31	61	NR
Lal et al.,[18] 2012*	RCT	69	35	53	85	30	85	27
Yamagami et al.,[29] 2012	OBS	71	14	55	75	47	47	27
Misaki et al.,[32] 2016	OBS	70	15	69	73	46	42	69
Zapata-Arriaza et al.,[28] 2016	OBS	69	20	74	77	47	62	44
Hung et al.,[33] 2016	OBS	73	19	58	85	36	48	56
Dai et al.,[26] 2018	OBS	66	14	36	83	37	44	39
Dai et al.,[27] 2019	OBS	67	14	54	84	38	43	41

HTN, hypertension; CEA, carotid endarterectomy; RCT, randomized controlled trial; NR, not reported; OBS, observational; CAS, carotid artery stenting.
*The study by Lal et al.[18] was included in both the CEA and the CAS subgroups.

studies were also manually reviewed to identify further eligible articles.

A study was included in the present meta-analysis if it had fulfilled 2 predefined criteria: 1) randomized controlled trial or prospective or retrospective observational analysis providing ≥1 hazard ratio (HR) estimate for the risk factors associated with restenosis after CAS or CEA; and 2) studies reported in English up to October 2018. Studies with a high risk of bias or studies reporting irrelevant outcomes were excluded.

Data Extraction and Outcomes

Two reviewers (P.T., S.G.), who were unaware of the other's findings, independently extracted the relevant data from the eligible studies. All disagreements were resolved after discussion, and a final decision was reached by consensus with the addition of a third reviewer (D.G.K.). The primary outcome was the HR of restenosis for risk factors that included gender, coronary artery disease (CAD), hypertension, diabetes mellitus, use of antiplatelet agents, glomerular filtration rate <30 mL/min, smoking, primary stenosis of >70%, symptomatic status at presentation, and patch use in CEA.

Risk of Bias Assessment

The risk of bias was assessed by 2 of us (P.T., S.G.) with the Cochrane tool for the randomized studies and the Robins-I tool for nonrandomized studies.[15,16] The following domains for the nonrandomized studies were evaluated: confounding, selection of participants, departure from intended interventions, missing data, measurement of outcomes, and selective reporting. Randomized control trials were evaluated in terms of random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, and selective reporting. Discrepancies in quality assessment were resolved via consensus.

Statistical Synthesis and Analysis

HRs with the corresponding 95% confidence intervals (CIs) were used for the outcomes. A random effects model was used to account for heterogeneity among studies. Heterogeneity was assessed using the Higgins I^2 statistic.[17] An I^2 >50% indicated significant heterogeneity.[17] Forest plots were used to graphically display the effect size in each study and the pooled estimates. Sensitivity analyses

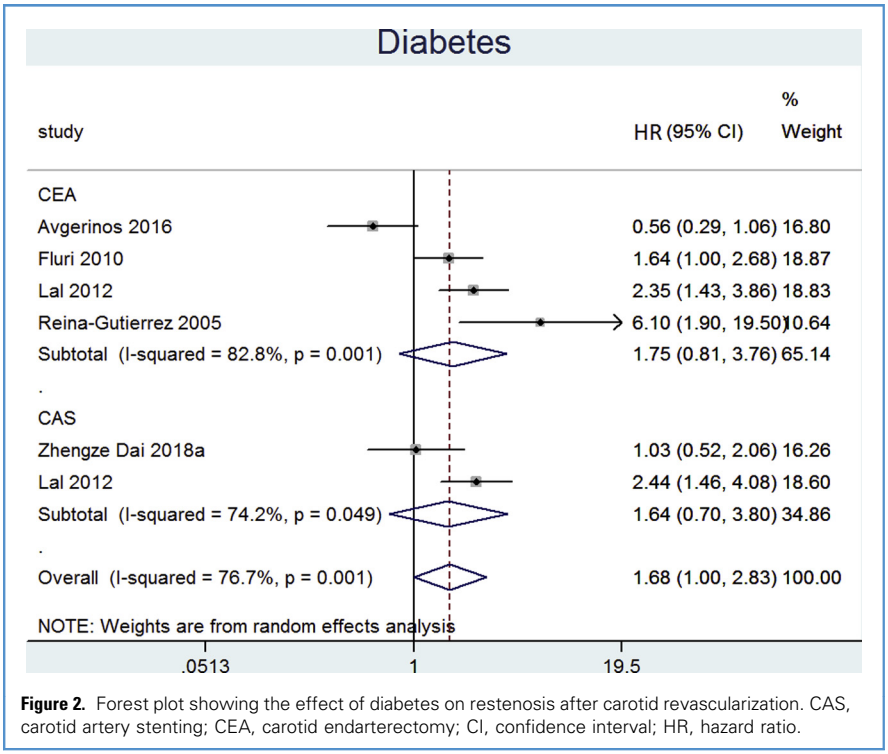

Figure 2. Forest plot showing the effect of diabetes on restenosis after carotid revascularization. CAS, carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; HR, hazard ratio.

were conducted for all the outcomes, stratified by CEA and CAS. A *P* value <0.05 was considered statistically significant. STATA, version 14.1 (StataCorp, College Station, Texas, USA), was used as the statistical software.

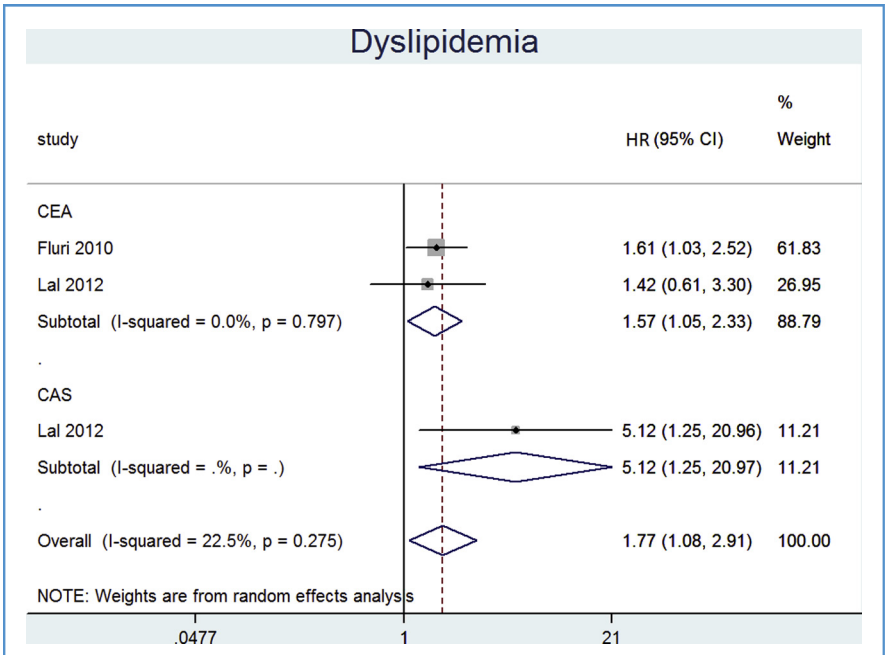

Figure 3. Forest plot showing the effect of dyslipidemia on restenosis after carotid revascularization. CAS, carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; HR, hazard ratio.

RESULTS

Search Results

The literature search yielded 103 potentially relevant records after the duplicates had been removed. After screening the titles and abstracts, 28 studies were retrieved for full-text evaluation, and 18 studies had satisfied the predetermined search criteria and were included in the present meta-analysis as shown in the PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram (**Figure 1**).

Characteristics of Studies and Patients

Of the 18 included studies, 6 were randomized trials and 12 were observational cohort analyses.[18-37] The assessment of the risk of bias is presented in **Supplemental Tables 1** and **2**. Overall 17,106 patients were included in the present meta-analysis. Detailed patient and study characteristics are presented in **Table 1**. Nine studies[18-24,36,37] reported the HRs of restenosis after CEA and 10 after CAS.[18,26-30,32-35] One of these studies reported the HRs for both CEA and CAS.[18] All the studies had reported the adjusted HRs from multivariate analyses, except for 3 studies, which had provided unadjusted HRs only.[18,32,33] Restenosis after carotid revascularization was defined as stenosis ≥50% in 11 studies,[22,24,26,27,29,30,32-35,37] ≥70% in 6 studies,[18,19,21,23,28,36] and >80% in 1 study.[20]

Factors with a Statistically Significant Association with Restenosis

Diabetes mellitus showed a statistically significant association with restenosis after carotid revascularization (HR, 1.68; 95% CI, 1.00–2.83; I^2, 76.7%) but was without statistical significance in the subgroup analyses for CEA and CAS (CEA: HR, 1.75; 95% CI, 0.81–3.76; and CAS: HR, 1.64; 95% CI, 0.70–3.80; **Figure 2**). Dyslipidemia was associated with restenosis after carotid revascularization (HR, 1.77; 95% CI, 1.08–2.91; I^2, 22.5%), both after CEA (HR, 1.57; 95% CI, 1.05–2.33; I^2, 0%) and after CAS (HR, 5.12; 95% CI, 1.25–20.97; **Figure 3**). Female gender demonstrated a statistically significant association with restenosis after carotid interventions (HR, 1.50; 95% CI, 1.14–1.98; I^2, 0%). Subgroup analyses

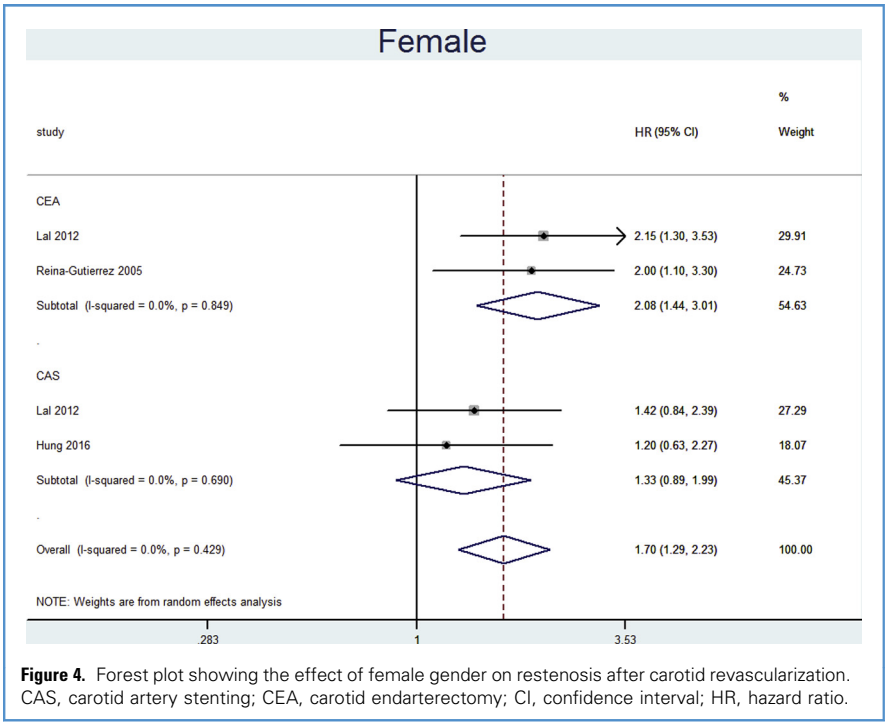

Figure 4. Forest plot showing the effect of female gender on restenosis after carotid revascularization. CAS, carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; HR, hazard ratio.

for CEA and CAS showed a significant association for CEA (HR, 1.67; 95% CI, 1.14–2.44; I^2, 0%) but not for CAS (HR, 1.33; 95% CI; 0.89–1.99; I^2, 0%; Figure 4). Chronic kidney disease (CKD) stage 4 or 5 (defined as glomerular filtration rate <30 mL/min) was also associated with restenosis (HR, 4.15; 95% CI, 1.69–10.19; I^2, 44.5%). The results were significant for both CEA (HR, 2.92; 95% CI, 1.50–5.70; I^2, 0%) and CAS (HR, 17.73; 95% CI, 2.95–106.64; Figure 5). The presence of hypertension in patients who had undergone carotid revascularization was associated with restenosis (HR, 1.99; 95% CI, 1.07–3.72; I^2, 68%). Patients in the CAS group demonstrated a significant association with restenosis (HR, 3.51; 95% CI, 1.71–7.19; I^2, 0%) compared with the patients in the CEA group (HR, 1.51; 95% CI, 0.78–2.90; I^2, 60.9%), for whom no association was found (Figure 6). Active smokers had a statistically significant hazard for restenosis after carotid revascularization (HR, 1.65; 95% CI, 1.15–2.37; I^2, 54.3%). Smoking was associated with restenosis in the CEA group (HR, 1.79; 95% CI, 1.22–2.62; I^2, 29.6%) but not the CAS group (HR, 1.52; 95% CI, 0.78–2.98; I^2, 71.2%; Figure 7). Patch closure of the carotid arteriotomy was associated with a statistically significant lower risk of restenosis (HR, 0.33; 95% CI, 0.22–0.50; I^2, 0%; Figure 8). Symptomatic patients at presentation were at a statistically significant lower risk of restenosis after carotid revascularization (HR, 0.68; 95% CI, 0.50–0.93; I^2, 0%). This association was significant for the CAS group (HR, 0.61; 95% CI, 0.41–0.90; I^2, 0%) but not the CEA group (HR, 0.82; 95% CI, 0.50–1.34; Figure 9). Pretreatment stenosis >70% showed a statistically significant association with restenosis (HR, 1.04; 95% CI, 1.00–1.08; I^2, 0%; Figure 10).

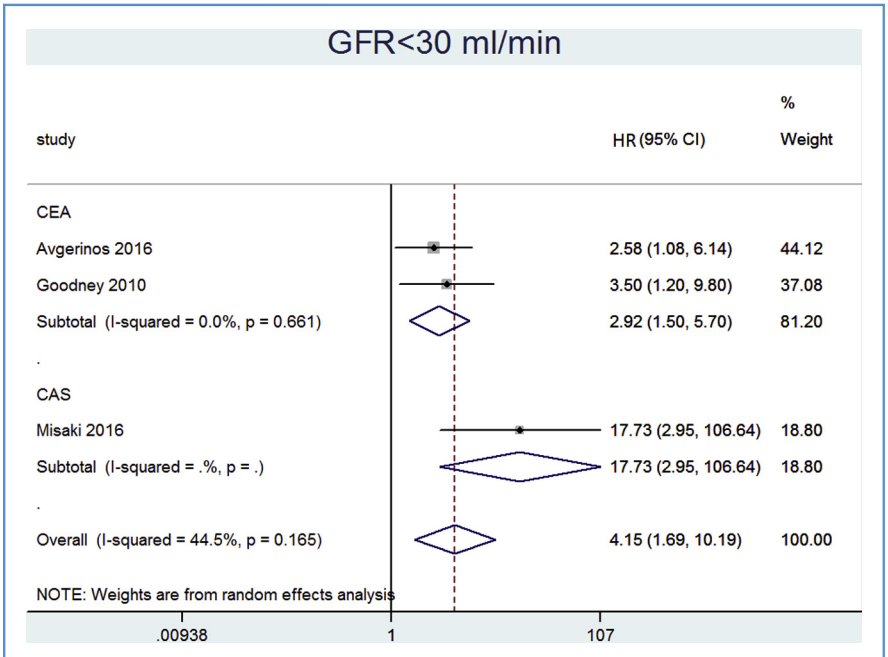

Figure 5. Forest plot showing the effect of chronic kidney disease stage 4 or 5 (glomerular filtration rate [GFR] <30 mL/min) on restenosis after carotid revascularization. CAS, carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; HR, hazard ratio.

Factors without a Statistically Significant Association with Restenosis

Antiplatelet medication did not reduce the risk of restenosis after carotid revascularization (HR, 0.65; 95% CI, 0.26–1.59; I^2, 36.3%). This was consistent in the subgroups of CEA (HR, 0.78; 95% CI, 0.34–1.80) and CAS (HR, 0.63; 95% CI, 0.10–4.08; I^2, 62.2%; Figure 11). CAD did not increase the risk of restenosis significantly in the pooled analysis (HR, 1.18; 95% CI, 0.86–1.61; I^2, 14%), the CEA subgroup (HR, 1.06; 95% CI, 0.75–1.49; I^2, 0%) or the CAS subgroup (HR, 2.16; 95% CI, 0.50–9.31; I^2, 60.2%; Figure 12).

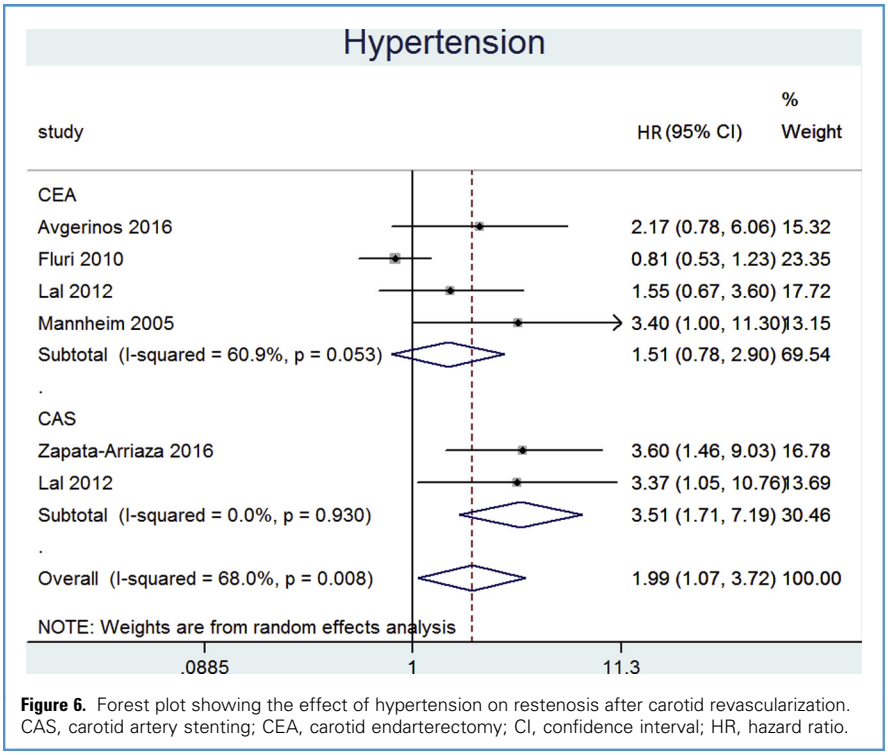

Figure 6. Forest plot showing the effect of hypertension on restenosis after carotid revascularization. CAS, carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; HR, hazard ratio.

DISCUSSION

The present meta-analysis investigated the effect of various baseline demographic, clinical, and radiographic factors on carotid restenosis after CEA or CAS. Our results have demonstrated that diabetes, dyslipidemia, female gender, renal failure, pretreatment stenosis >70%, hypertension, and smoking were associated with an increased risk of restenosis and that patch endarterectomy and symptomatic status at baseline were associated with a decreased risk of restenosis. Furthermore, the use of antiplatelet medication and the presence of CAD did not show a statistically significant association with restenosis after carotid revascularization.

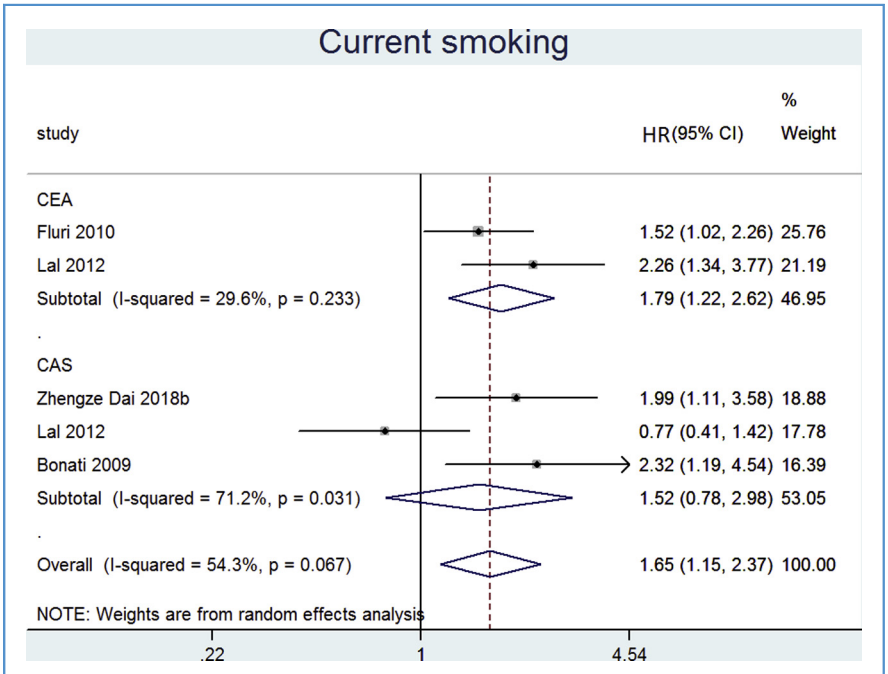

Figure 7. Forest plot showing the effect of smoking on restenosis after carotid revascularization. CAS, carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; HR, hazard ratio.

Carotid restenosis after CEA or in-stent restenosis after CAS is a complication that can result in recurrent stroke and neurologic morbidity.[38,39] Thus, the identification of patients at an increased risk of restenosis is important to optimize patient selection for the most durable revascularization procedure and to develop the best strategy for postprocedural clinical and imaging surveillance. The results from the present meta-analysis suggest that female gender, diabetes, dyslipidemia, hypertension, smoking, and CKD stage 4 or 5 are potential risk factors for carotid restenosis. Although pretreatment stenosis >70% had a statistically significant association with restenosis, the pooled HR estimate was only 1.04, which calls into question the clinical significance. The results for female gender, dyslipidemia, and CKD stage 4 or 5 were consistent among the included studies. In contrast, the results for diabetes, hypertension, and smoking were inconsistent among the included studies, which was reflected by the high amount of heterogeneity identified. Furthermore, the subgroup analyses for CEA and CAS could potentially provide insight on the optimal treatment modality for patients who require carotid revascularization. Female gender was a statistically significant risk factor for restenosis for patients in the CEA group (HR, 1.67; 95% CI, 1.14–2.44) but not for those in the CAS group (HR, 1.33; 95% CI, 0.89–1.99; I^2, 0%). Several studies have reported that female gender is a risk factor for restenosis after CEA.[9,21,40] In contrast, reported data have indicated no differences exists between men and women in terms of in-stent restenosis after CAS.[41] The varying effect of female gender on CEA versus CAS could be because women generally will have smaller carotid artery diameters.[42] This might render their carotid vasculature more vulnerable to restenosis after CEA secondary to suturing of the arteriotomy compared with the general expansile

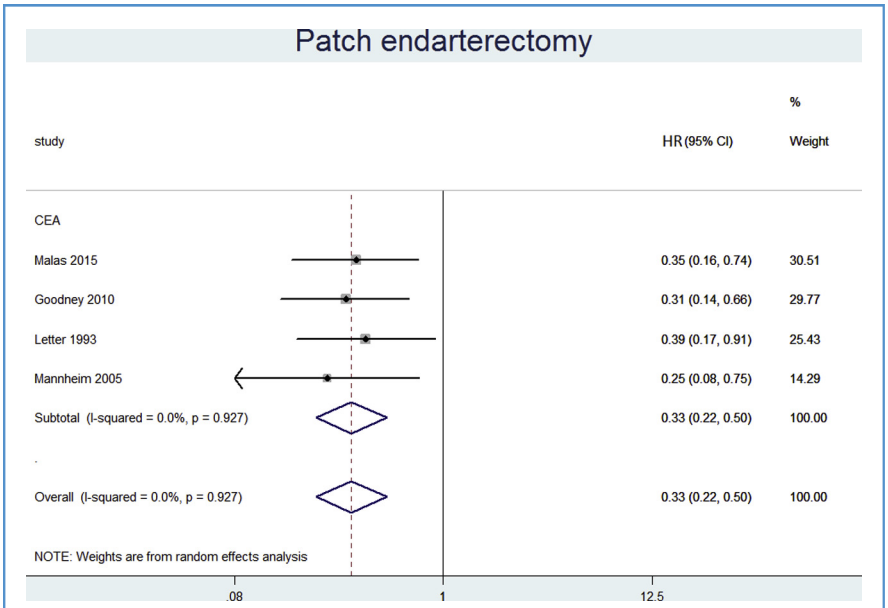

Figure 8. Forest plot showing the effect of patch closure on restenosis after carotid endarterectomy. CAS, carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; HR, hazard ratio.

force of angioplasty and stenting. In addition, the effect of sex hormones on the nature of atheromatous plaque could play a role. Similarly, current smoking was associated with restenosis after CEA (HR, 1.79; 95% CI, 1.22–2.62) but not after CAS (HR, 1.52; 95% CI, 0.78–2.98). This is agreement with the results of a secondary analysis of the CREST (carotid revascularization endarterectomy vs. stenting trial), which showed that smoking is in independent risk factor for restenosis only after CEA.[18] This could be explained by the potentially different effect of smoking on the healing process after CAS versus after CEA, given the different nature of carotid injury between the 2 revascularization strategies.[18] In contrast, hypertension was a risk factor of restenosis after CAS (HR, 3.51; 95% CI, 1.71–7.19) but not after CEA (HR, 1.51; 95% CI, 0.78–2.90) in the present meta-analysis. Zapata-Arriaza et al.[28] showed that hypertension is associated with carotid restenosis after CAS. They attributed this to the harmful effect of hypertension on the endothelium, which accelerates inflammation and smooth muscle cell proliferation at the site of stent placement.[28] However, the results from studies investigating the association of hypertension with the progression of carotid disease after CEA have been inconclusive.[36,37] These results suggest that female patients and smokers might have a lower risk of restenosis if they undergo CAS and that patients with hypertension might have a lower risk of restenosis if they undergo CEA. Nevertheless, further studies directly comparing CEA versus CAS for female patients, smokers, and those with hypertension are warranted to validate our results.

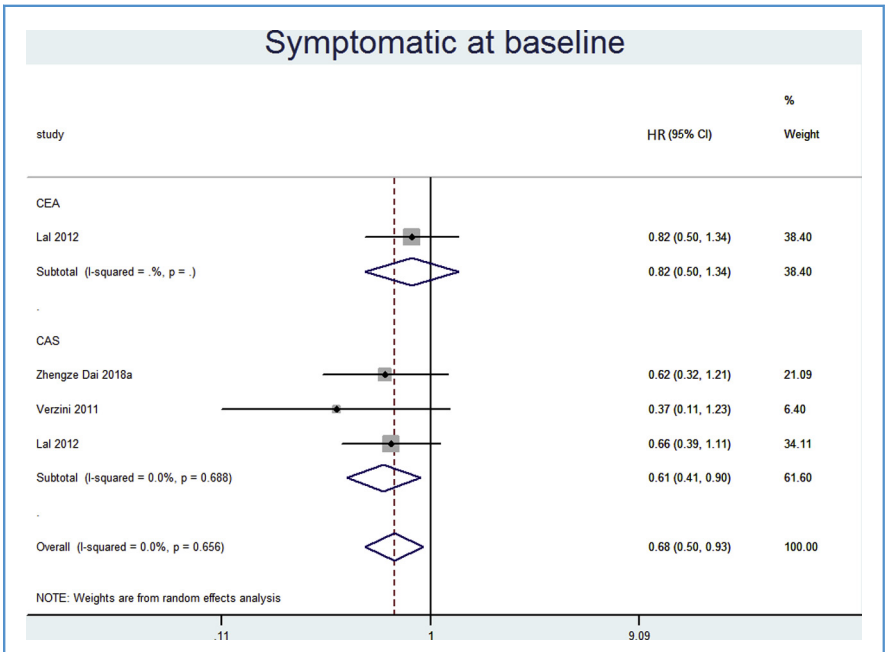

Figure 9. Forest plot showing the effect of symptomatic status at baseline on restenosis after carotid revascularization. CAS, carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; HR, hazard ratio.

Dyslipidemia and renal failure were independently associated with restenosis after both CEA and CAS. Hypercholesterolemia is a well-established risk factor for atherosclerotic disease. Evidence has shown a significant association between hyperlipidemia and carotid restenosis after both CEA and CAS.[43] The pathophysiologic mechanism involves vascular damage by oxidation of low-density lipoprotein and formation of unstable, foamy, necrotic, atherosclerotic carotid plaques.[44] Moreover, uremia and diabetes are known universal factors implicated in the development of atherosclerotic disease.[45-47] Patients with end-stage renal disease can develop endothelial dysfunction through several mechanisms, including elevated low-density lipoprotein, decreased adiponectin levels, and decreased clearance of proinflammatory and oxidative substances.[48] Our results have demonstrated that diabetes was a significant risk factor for restenosis only

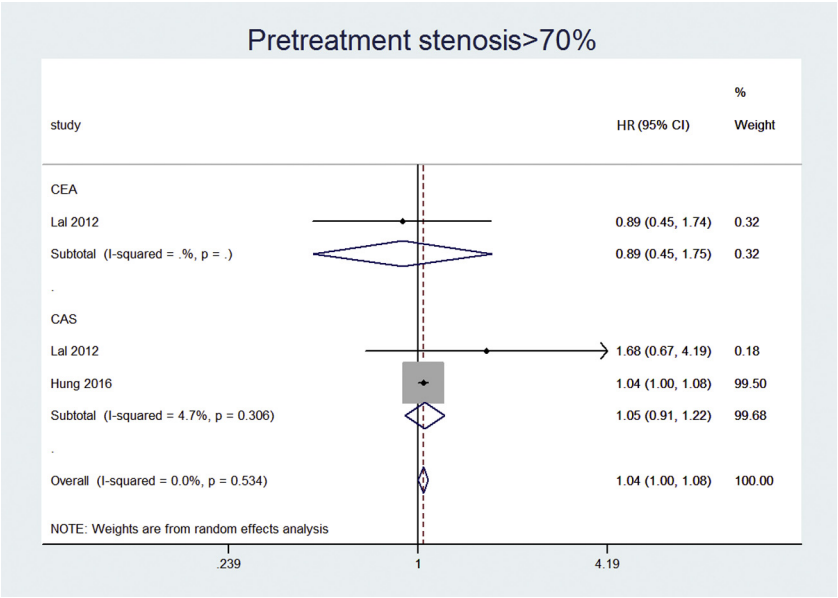

Figure 10. Forest plot showing the effect of pretreatment stenosis >70% on restenosis after carotid revascularization. CAS, carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; HR, hazard ratio.

in the pooled analysis and not in the CEA and CAS subgroups. However, it is likely that the subgroup analyses were underpowered to detect such a difference. Diabetes can increase the risk of atherosclerosis by conventional mechanisms, including dyslipidemia and hypertension, and through diabetes-specific factors, including increased production of reactive oxygen species

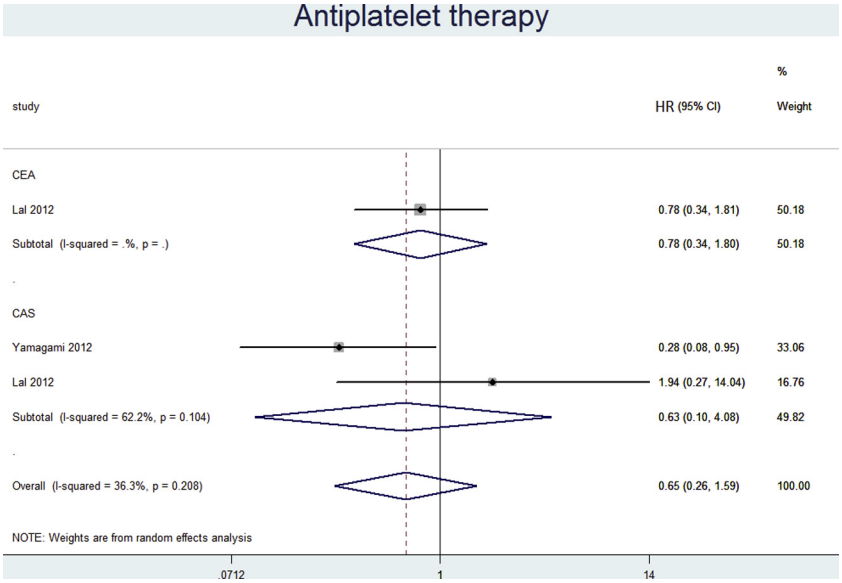

Figure 11. Forest plot showing the effect of antiplatelet medication on restenosis after carotid revascularization. CAS, carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; HR, hazard ratio.

secondary to hyperglycemia and dysregulated matrix protein production.[49]

Patch closure of the endarterectomy was associated with a statistically significant lower risk of restenosis compared with primary closure, consistent with previous reported data.[19,23,50] Symptomatic status at presentation was also found to be associated with a significantly lower risk of restenosis after carotid revascularization. However, none of the individual included studies for this comparison reported a statistically significant association, which could be explained by the increased statistical power a meta-analysis provides compared with that of individual studies. Nevertheless, we believe this could have been a confounded result, given that symptomatic patients might receive more comprehensive medical therapy (e.g., statins) compared with those without presenting symptoms. Statins are known to delay progression in atherosclerotic carotid arteries, reduce postoperative complications after CAS and CEA, and, potentially, induce regression of stenosis.[51-54] Also, the statin-mediated lipid-lowering effect is known to provide a reduction of carotid intima media thickness by 0.73% annually (95% CI, 0.27–1.19) for every 10% reduction in low-density lipoprotein cholesterol.[55] Nevertheless, none of the included studies provided a HR for statins; therefore, their effect on restenosis could not be investigated in the present meta-analysis.

The present study found no association between coexisting CAD and antiplatelet therapy with carotid restenosis in either the CAS or the CEA subgroups. One of the 2 studies that reported the effect of antiplatelet therapy provided the HR for cilostazol and showed a preventive effect on restenosis.[29] However, the second study did not specifically report the exact antiplatelet that was used, which limited the generalizability of our pooled estimate.[18] Finally, the included studies consistently reported no significant association of CAD with recurrent carotid stenosis after CEA or CAS.[18,32,37]

Study Limitations

Our results should be interpreted in the context of several limitations. First, our meta-analysis was limited by the observational design used for most of the

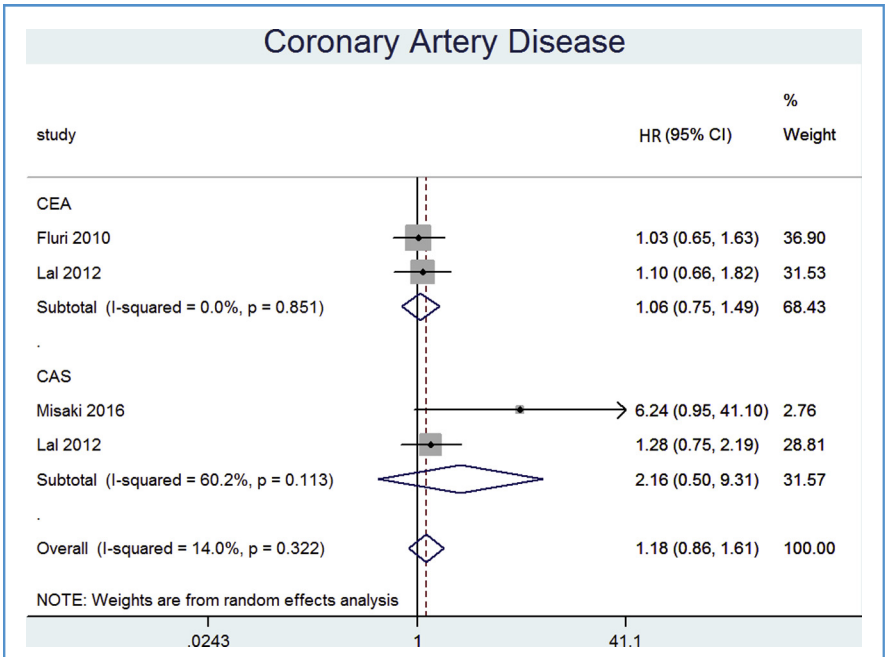

Figure 12. Forest plot showing the effect of coronary artery disease on restenosis after carotid revascularization. CAS, carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; HR, hazard ratio.

included studies. Second, not all studies reported the multivariate HRs; therefore, univariate HRs were used for these studies. Third, the follow-up intervals were not standardized among the included studies. Fourth, individual centers or surgeons could have caused heterogeneity in our results, for which we could not account. Finally, restenosis was defined by multiple definitions, and a critical threshold for restenosis has not been established.

CONCLUSIONS

The results of the present meta-analysis have shown that diabetes, dyslipidemia, female gender, CKD stage 4 and 5, hypertension, and smoking are associated with an increased risk of restenosis and that patch endarterectomy and symptomatic status at presentation can lead to a lower risk of restenosis after carotid revascularization. Further studies are needed to validate our results.

REFERENCES

1. LaMuraglia GM, Stoner MC, Brewster DC, et al. Determinants of carotid endarterectomy anatomic durability: effects of serum lipids and lipid-lowering drugs. *J Vasc Surg*. 2005;41:762-768.
2. Sadideen H, Taylor PR, Padayachee TS. Restenosis after carotid endarterectomy. *Int J Clin Pract*. 2006;60:1625-1630.
3. Bekelis K, Moses Z, Missios S, Desai A, Labropoulos N. Indications for treatment of recurrent carotid stenosis. *Br J Surg*. 2013;100:440-447.
4. Zierler RE, Bandyk DF, Thiele BL, Strandness DEJ. Carotid artery stenosis following endarterectomy. *Arch Surg*. 1982;117:1408-1415.
5. Wasser K, Schnaudigel S, Wohlfahrt J, et al. Clinical impact and predictors of carotid artery in-stent restenosis. *J Neurol*. 2012;259:1896-1902.
6. Wasser K, Gröschel S, Wohlfahrt J, Gröschel K. Predictors of carotid artery in-stent restenosis. *Perspect Med*. 2012;1:122-128.
7. Hunter GC. Edgar J. Poth Memorial/W.L. Gore and Associates, Inc. Lectureship. The clinical and pathological spectrum of recurrent carotid stenosis. *Am J Surg*. 1997;174:583-588.
8. Edwards JM, AbuRahma AF, Hannay RS, et al. Prospective randomized study of carotid endarterectomy with polytetrafluoroethylene versus collagen-impregnated Dacron (Hemashield) patching: perioperative (30-day) results. *J Vasc Surg*. 2002;35:125-130.
9. Trisal V, Paulson T, Hans SS, Mittal V. Carotid artery restenosis: an ongoing disease process. *Am Surg*. 2002;68:275-280.
10. AbuRahma AF, Abu-Halimah S, Hass SM, et al. Carotid artery stenting outcomes are equivalent to carotid endarterectomy outcomes for patients with post-carotid endarterectomy stenosis. *J Vasc Surg*. 2010;52:1180-1187.
11. Texakalidis P, Giannopoulos S, Jonnalagadda AK, et al. Carotid artery endarterectomy versus carotid artery stenting for restenosis after carotid artery endarterectomy: a systematic review and meta-analysis. *World Neurosurg*. 2018;115:421-429.e1.
12. Van Haaften AC, Bots ML, Moll FL, De Borst GJ. Therapeutic options for carotid in-stent restenosis: review of the literature. *J Vasc Interv Radiol*. 2010;21:1471-1477.
13. Callow AD. Recurrent stenosis after carotid endarterectomy. *Arch Surg*. 1982;117:1082-1085.
14. Texakalidis P, Giannopoulos S, Kokkinidis DG, Lanzino G. Effect of open- vs closed-cell stent design on periprocedural outcomes and restenosis after carotid artery stenting: a systematic review and comprehensive meta-analysis. *J Endovasc Ther*. 2018;25:523-533.
15. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011;343:d4002.
16. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
17. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
18. Lal BK, Beach KW, Roubin GS, et al. Restenosis after carotid artery stenting and endarterectomy: a secondary analysis of CREST, a randomised controlled trial. *Lancet Neurol*. 2012;11:755-763.
19. Malas M, Glebova NO, Hughes SE, et al. Effect of patching on reducing restenosis in the carotid revascularization endarterectomy versus stenting trial. *Stroke*. 2015;46:757-761.
20. Goodney PP, Nolan BW, Eldrup-Jorgensen J, Likosky DS, Cronenwett JL. Restenosis after carotid endarterectomy in a multicenter regional registry. *J Vasc Surg*. 2010;52:897-904, 905.e1-2 [discussion: 904-905].
21. Reina-Gutiérrez T, Serrano-Hernando FJ, Sánchez-Hervás L, Ponce A, Vega de Ceniga M, Martín A. Recurrent carotid artery stenosis following endarterectomy: natural history and risk factors. *Eur J Vasc Endovasc Surg*. 2005;29:334-341.
22. Cao P, Giordano G, Rango P, et al. Eversion versus conventional carotid endarterectomy: late results of a prospective multicenter randomized trial. *J Vasc Surg*. 2000;31(Pt 1):19-30.
23. Mannheim D, Weller B, Vahadim E, Karmeli R. Carotid endarterectomy with a polyurethane patch versus primary closure: a prospective randomized study. *J Vasc Surg*. 2005;41:403-408.
24. De Letter JAM, Moll FL, Welten RJT, et al. Benefits of carotid patching: a prospective randomized study with long-term follow-up. *Ann Vasc Surg*. 1994;8:54-58.

25. Bonati LH, Ederle J, Dobson J, et al. Length of carotid stenosis predicts peri-procedural stroke or death and restenosis in patients randomized to endovascular treatment or endarterectomy. *Int J Stroke*. 2014;9:297-305.

26. Dai Z, Gao J, Li S, et al. Mean platelet volume as a predictor for restenosis after carotid angioplasty and stenting. *Stroke*. 2018;49:872-876.

27. Dai Z, Li R, Zhao N, et al. Neutrophil to lymphocyte ratio as a predictor of restenosis after angioplasty and stenting for asymptomatic carotid stenosis. *Angiology*. 2019;70:160-165.

28. Zapata-Arriaza E, Moniche F, Gonzalez A, et al. Predictors of restenosis following carotid angioplasty and stenting. *Stroke*. 2016;47:2144-2147.

29. Yamagami H, Sakai N, Matsumaru Y, et al. Periprocedural cilostazol treatment and restenosis after carotid artery stenting: the Retrospective Study of In-Stent Restenosis after Carotid Artery Stenting (ReSISteR-CAS). *J Stroke Cerebrovasc Dis*. 2012;21:193-199.

30. Verzini F, De Rango P, Parlani G, et al. Effects of statins on early and late results of carotid stenting. *J Vasc Surg*. 2011;53:71-79 [discussion: 79].

31. Mousa AY, AbuRahma AF, Bozzay J, et al. Long-term comparative outcomes of carotid artery stenting following previous carotid endarterectomy vs de novo lesions. *J Endovasc Ther*. 2015;22:449-456.

32. Misaki K, Uchiyama N, Mohri M, Hayashi Y, Ueda F, Nakada M. Prediction of carotid artery in-stent restenosis by quantitative assessment of vulnerable plaque using computed tomography. *J Neuroradiol*. 2016;43:18-24.

33. Hung CS, Lin MS, Chen YH, Huang CC, Li HY, Kao HL. Prognostic factors for neurologic outcome in patients with carotid artery stenting. *Acta Cardiol Sin*. 2016;32:205-214.

34. de Donato G, Setacci C, Deloose K, Peeters P, Cremonesi A, Bosiers M. Long-term results of carotid artery stenting. *J Vasc Surg*. 2008;48:1431-1441.

35. Bonati LH, Ederle J, McCabe DJH, et al. Long-term risk of carotid restenosis in patients randomly assigned to endovascular treatment or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial. *Lancet Neurol*. 2009;8:908-917.

36. Avgerinos ED, Chaer RA, Naddaf A, El-Shazly OM, Marone L, Makaroun MS. Primary closure after carotid endarterectomy is not inferior to other closure techniques. *J Vasc Surg*. 2016;64:678-683.e1.

37. Fluri F, Hatz F, Voss B, Lyrer PA, Engelter ST. Restenosis after carotid endarterectomy: significance of newly acquired risk factors. *Eur J Neurol*. 2010;17:493-498.

38. Bonati LH, Gregson J, Dobson J, et al. Restenosis and risk of stroke after stenting or endarterectomy for symptomatic carotid stenosis in the International Carotid Stenting Study (ICSS): secondary analysis of a randomised trial. *Lancet Neurol*. 2018;17:587-596.

39. Daou B, Chalouhi N, Starke RM, et al. Predictors of restenosis after carotid artery stenting in 241 cases. *J Neurointerv Surg*. 2016;8:677-679.

40. Ouriel K, Green RM. Clinical and technical factors influencing recurrent carotid stenosis and occlusion after endarterectomy. *J Vasc Surg*. 1987;5:702-706.

41. Skelly CL, Gallagher K, Fairman RM, et al. Risk factors for restenosis after carotid artery angioplasty and stenting. *J Vasc Surg*. 2006;44:1010-1015.

42. Krejza J, Arkuszewski M, Kasner SE, et al. Carotid artery diameter in men and women and the relation to body and neck size. *Stroke*. 2006;37:1103-1105.

43. Volteas N, Labropoulos N, Leon M, Kalodiki E, Chan P, Nicolaides AN. Risk factors associated with recurrent carotid stenosis. *Int Angiol*. 1994;13:143-147.

44. Mughal MM, Khan MK, Demarco JK, Majid A, Shamoun F, Abela GS. Symptomatic and asymptomatic carotid artery plaque. *Expert Rev Cardiovasc Ther*. 2011;9:1315-1330.

45. Olechnowicz-Tietz S, Gluba A, Paradowska A, Banach M, Rysz J. The risk of atherosclerosis in patients with chronic kidney disease. *Int Urol Nephrol*. 2013;45:1605-1612.

46. Kon V, Linton MF, Fazio S. Atherosclerosis in chronic kidney disease: the role of macrophages. *Nat Rev Nephrol*. 2010;7:45-54.

47. Wagenknecht LE, Zaccaro D, Espeland MA, Karter AJ, Leary DHO, Haffner SM. Diabetes and progression of carotid atherosclerosis: the insulin resistance atherosclerosis study. *Arterioscler Thromb Vasc Biol*. 2003;23:1035-1041.

48. Amann K, Wanner C, Ritz E. Cross-talk between the kidney and the cardiovascular system. *J Am Soc Nephrol*. 2006;17:2112-2119.

49. Goldberg IJ. Why does diabetes increase atherosclerosis? I don't know!. *J Clin Invest*. 2004;114:613-615.

50. Bond R, Rerkasem K, AbuRahma AF, Naylor AR, Rothwell PM. Patch angioplasty versus primary closure for carotid endarterectomy. *Cochrane Database Syst Rev*. 2004:CD000160.

51. Hegland O, Kurz MW, Munk PS, Larsen JP. The effect of statin therapy on the progression of carotid artery stenosis in relation to stenosis severity. *Acta Neurol Scand*. 2010;121:11-15.

52. Texakalidis P, Giannopoulos S, Kokkinidis DG, Jabbour P, Reavey-Cantwell J, Rangel-Castilla L. Outcome of carotid artery endarterectomy in statin users versus statin-naive patients: a systematic review and meta-analysis. *World Neurosurg*. 2018;116:444-450.

53. Texakalidis P, Giannopoulos S, Jonnalagadda AK, et al. Preoperative use of statins in carotid artery stenting: a systematic review and meta-analysis. *J Endovasc Ther*. 2018;25:624-631.

54. Paraskevas KI, Mikhailidis DP, Veith FJ. Statins induce regression of carotid artery stenosis: fact or fiction? *Int J Cardiol*. 2016;220:680.

55. Amarenco P, Labreuche J, Lavallee P, Touboul P-J. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. *Stroke*. 2004;35:2902-2909.

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Supplemental Table 1. Risk of Bias Assessment for Randomized Studies (Cochrane Tool)

Investigator	Random Sequence Generation	Allocation Concealment	Blinding of Participants	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
CEA						
De Letter et al.,[24] 1993	Yes	Yes	Yes	Yes	No	No
Cao et al.,[22] 2000	Yes	No	Yes	Yes	No	No
Mannheim et al.,[23] 2005	Yes	No	Yes	Yes	No	No
Lal et al.,[18] 2012*	Yes	Yes	Yes	Yes	No	Yes
Malas et al.,[19] 2015	Yes	No	Yes	Yes	No	No
CAS						
Bonati et al.,[35] 2009	Yes	Yes	Yes	Yes	Yes	Yes
Lal et al.,[18] 2012*	Yes	Yes	Yes	Yes	No	Yes

CEA, carotid endarterectomy; CAS, carotid artery stenting.
*The study by Lal et al.[18] was included in both the CEA and the CAS subgroups.

Supplemental Table 2. Risk of Bias Assessment for Observational Studies (Robins-I Tool)

Investigator	Confounding	Selection	Measurement of Interventions	Deviations From Intended Interventions	Missing Data	Measurement of Data	Selection of Reported Result
CEA							
Reina-Gutiérrez et al.,[21] 2005	Moderate	Low	Low	Low	Low	Low	Low
Goodney et al.,[20] 2010	Moderate	Low	Low	Low	Low	Low	Low
Fluri et al.,[37] 2010	Moderate	Low	Low	Low	Moderate	Low	Low
Avgerinos et al.,[36] 2016	Moderate	Low	Low	Low	Low	Low	Low
CAS							
de Donato et al.,[34] 2008	Moderate	Low	Low	Low	Low	Low	Low
Verzini et al.,[30] 2016	Moderate	Low	Low	Low	Moderate	Low	Low
Yamagami et al.,[29] 2012	Moderate	Low	Low	Low	Low	Low	Low
Misaki et al.,[32] 2016	Moderate	Low	Low	Low	Low	Low	Moderate
Zapata-Arriaza et al.,[28] 2016	Moderate	Low	Low	Low	Low	Low	Low
Hung et al.,[33] 2016	Moderate	Low	Low	Low	Low	Low	Moderate
Dai et al.,[26] 2018 (2004—2016)	Moderate	Low	Low	Low	Low	Low	Low
Dai et al.,[27] 2019 (2005—2016)	Moderate	Low	Low	Low	Low	Low	Low

CEA, carotid endarterectomy; CAS, carotid artery stenting.