Carotid Revascularization in Older Adults: A Systematic Review and Meta-Analysis

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Key words

- Carotid
- Embolic protection
- Endarterectomy
- Octogenarians
- Older adults
- Stenting
- Stroke

Abbreviations and Acronyms

CAS: Carotid artery stenting
CEA: Carotid artery endarterectomy
CI: Confidence interval
CN: Cranial Nerve
CREST: Carotid Revascularization Endarterectomy versus Stenting Trial
MI: Myocardial infarction
OR: Odds ratio
RCT: Randomized controlled trial
TIA: Transient ischemic attack

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BACKGROUND: **Results from studies comparing carotid artery endarterectomy (CEA) with carotid artery stenting (CAS) in the elderly population are variable in the literature. The objective of this study was to investigate whether CEA or CAS is associated with a better safety profile in older adults (>80 years of age) for treatment of symptomatic and asymptomatic stenosis.**

METHODS: **A random-effects meta-analysis was performed, and the I^2 statistic was used to assess heterogeneity according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Subgroup analyses were performed as needed.**

RESULTS: **Nine studies comprising 5955 patients were included in this meta-analysis. No differences were identified in terms of 30-day stroke (CEA: 5.8% [n = 257/4415]; CAS: 10.5% [n = 81/767]; odds ratio [OR], 0.57; 95% confidence interval [CI], 0.30—1.08; I^2 = 26.1%), myocardial infarction (MI) (CEA: 1.1% [n = 4/357]; CAS: 0.5% [n = 2/355]; OR, 1.67; 95% CI, 0.37—7.46; I^2 = 0%), transient ischemic attack (TIA) (CEA: 0% [n = 0/98]; CAS: 4.2% [n = 7/166]; OR, 0.28; 95% CI, 0.03—2.52; I^2 = 0%), death (CEA: 1.5% [n = 8/523]; CAS: 0.9% [n = 4/431]; OR, 1.41; 95% CI, 0.43—4.58; I^2 = 0%), and cranial nerve injury (CEA: 5.8% [n = 3/51]; CAS: 0% [n = 0/51]; OR, 4.74; 95% CI, 0.5—44.98; I^2 =0%). A subgroup comparing CEA with transfemoral protected CAS showed that patients in the CEA group had a statistically significant lower risk of 30-day stroke (OR, 0.31; 95% CI, 0.17—0.57; I^2 = 30.8%).**

CONCLUSIONS: **This study shows that CEA is associated with a statistically significant lower risk of 30-day stroke in the elderly population compared with transfemoral CAS with distal or proximal protection. No differences were noted in the rates of periprocedural TIA, MI, death, and cranial nerve injury between CEA and CAS in the original pooled analysis.**

INTRODUCTION

Carotid artery endarterectomy (CEA) is one of the primary revascularization strategies for treatment of symptomatic and asymptomatic carotid atherosclerotic disease.[1,2] Carotid artery stenting (CAS) has emerged as a less invasive, alternative revascularization approach to CEA.[3-5] Data from randomized controlled trials (RCTs) support that CAS is associated with a statistically significant higher risk of periprocedural stroke and a lower risk of myocardial infarction (MI).[6,7] The ultimate goal of carotid stenosis treatment is an extension of stroke-free survival along with maintenance of a high quality of life, which is particularly important in the elderly population.

The optimal revascularization approach for older adults (>80 years of age) is still unknown. A subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) showed that CEA may be safer in the elderly population when compared with CAS.[8-10] Furthermore, the same study highlighted that the effectiveness of CEA increases with patient age compared with CAS. From a technical standpoint, CAS can be more challenging to perform with complex aortic arch anatomy and supra-aortic trunk tortuosity, which is more prevalent in older adults. This in turn could lead to an increase in distal embolizations.[11] Nevertheless, RCTs are lacking and results from real-world studies comparing CEA with CAS in older adults are inconclusive across the literature.[12-14]

The aim of this meta-analysis is to systematically review studies comparing CEA with CAS for the elderly patient population (>80 years of age) and to synthesize the reported periprocedural outcomes.

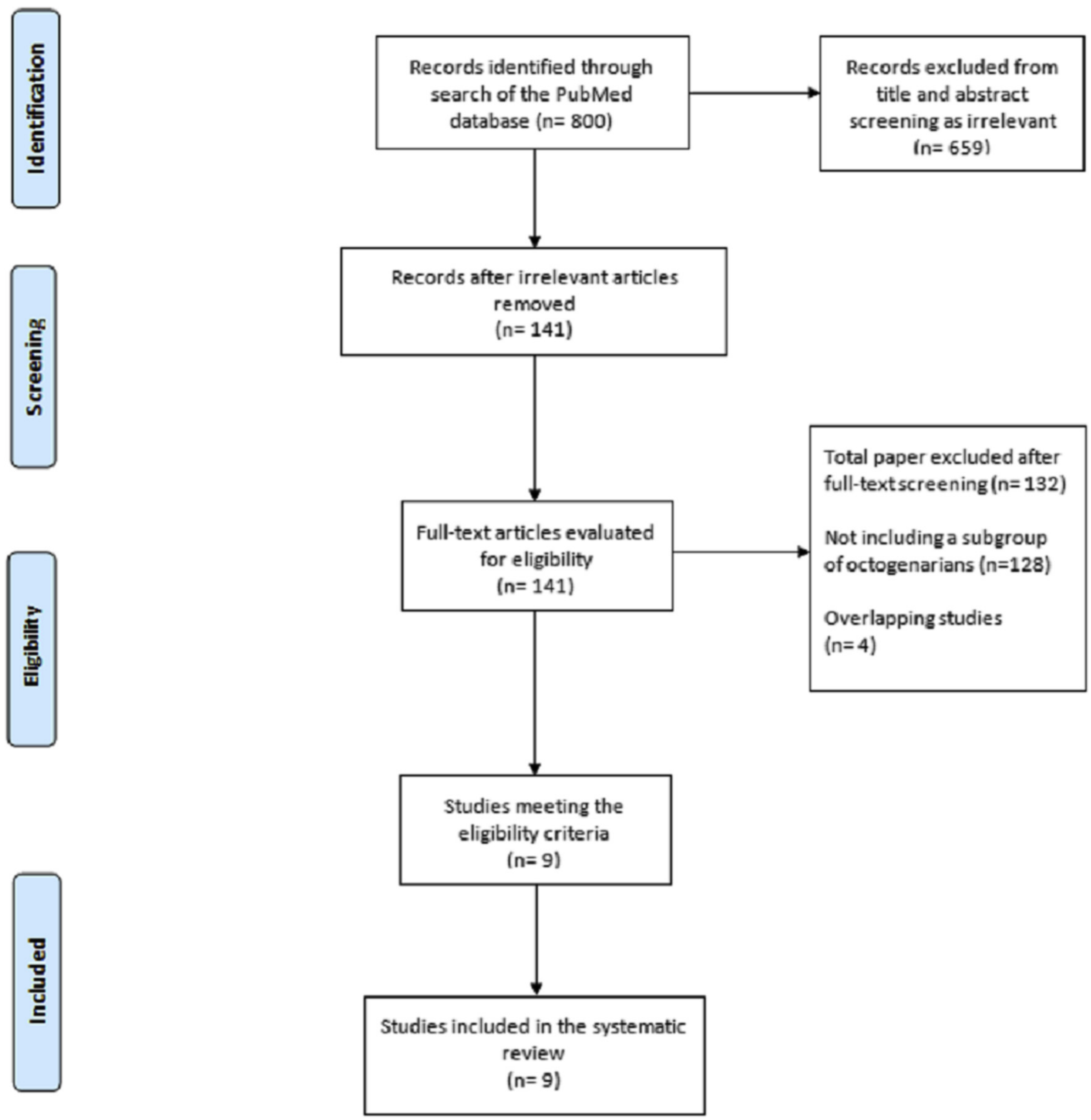

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses search flow diagram.

METHODS

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[15]

Search Strategy and Selection Criteria

Systematic searches were conducted in PubMed and Cochrane Central. The key words used for PubMed were “elderly,” “octogenarians,” “eighty,” “carotid,” “endarterectomy,” and “stenting.” The search was conducted by 1 of 2 independent investigators (P. T. and N. C.). Any disagreements or discrepancies were resolved by consensus. The references of the included studies were also manually reviewed to identify further eligible articles.

A study was included in this meta-analysis if it fulfilled 3 predefined criteria: 1) RCTs or prospective and retrospective observational analyses comparing CEA with CAS in octogenarians or older patients, 2) studies that reported quantitative data on clinical outcomes of interest, and 3) studies published up to May 2018. When duplicates were identified, the most recent analysis was included unless the earliest version reported more relevant outcomes.

Data Extraction and Outcomes

Two reviewers, blind to each other (P. T. and N. C.), independently extracted the relevant data from the eligible studies. Data extracted included the first author; title; date of publication; country of origin; number of patients; demographics; history of hypertension, diabetes mellitus, and

Table 1. Baseline Study and Patient Characteristics

Study	Country	Number of Patients	Number of Patients in CEA Group	Number of Patients in CAS Group.	Mean Age (years)	Male (%)	CEA Group: Sx Patients at Baseline (%)	CAS Group: Sx Patients at Baseline (%)	CAD (%)	HTN (%)	Diabetes (%)	Dyslipidemia (%)	SMK (%)
Rockman et al., 2003[21]	USA	224	161	63	NR	NR	NR	46.2	NR	NR	NR	NR	NR
Alvarez et al., 2008[12]	Spain	81	45	36	NR	82.7	44.4	30.5	32.1	76.5	32	38.2	6.1
Brown et al., 2008[18]	USA	24	9	15	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zarins et al., 2009[23]	USA	77	52	25	NR	NR	NR	NR	NR	NR	NR	NR	NR
De Rango et al., 2012[13]	Italy	348	186	162	82.3	78.2	53.2	43.2	31.3	82.2	14.7	27.3	NR
Vouyouka et al., 2012[14]	USA	4778	4302	476	NR	0	NR	NR	NR	NR	NR	NR	NR
Yoshida et al., 2014[22]	USA	211	164	47	NR	NR	36.5	48.9	NR	NR	NR	NR	NR
Miyawaki and Maeda, 2014[20]	Japan	46	34	12	NR	67.3	64.7	33.3	26.1	63	6.5	15.2	NR
Fantozzi et al., 2016[19]	Italy	166	44	122	86.9	56	13.6	27.5	NR	NR	NR	NR	NR

CEA, carotid artery endarterectomy; CAS, carotid artery stenting; Sx, symptomatic; CAD, coronary artery disease; HTN, hypertension; SMK, smoker; NR, not reported.

hypercholesterolemia; smoking status; coronary artery disease; previous stroke or transient ischemic attack (TIA); symptomatic status at baseline; type of arterial access; use of embolic protection devices in CAS; antiplatelet regimen; and type of anesthesia. All disagreements were resolved after discussion, and the final decision was reached by consensus with the addition of a third reviewer (S. G.). The primary end point was incidence of stroke within 30 days after the procedure. Stroke was consistently defined in the studies as any new neurologic deficit lasting >24 hours. Secondary outcomes were TIA, MI, death, and cranial nerve (CN) injury within 30 days.

Risk of Bias Assessment

Risk of bias was assessed by 2 investigators (P. T. and N. C.) with the ROBINS-I tool for nonrandomized studies.[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. Discrepancies in quality assessment were resolved via consensus.

Statistical Synthesis and Analysis

Odds ratios (ORs) 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 with the Higgins I^2 statistic.[17] I^2 >50% indicated significant heterogeneity.[17] Forest plots were used to graphically display the effect size in each study and the pooled estimates. Meta-regression analysis was conducted to adjust for the ratio of symptomatic carotid stenosis in the study groups as a study level covariate. $P < 0.05$ was considered significant. STATA 14.1 (StataCorp LLC, College Station, Texas, USA) was used as statistical software.

RESULTS

Search Results

The initial literature search yielded 800 potentially relevant records after duplicates were removed. After screening titles and abstracts, 141 articles were retrieved

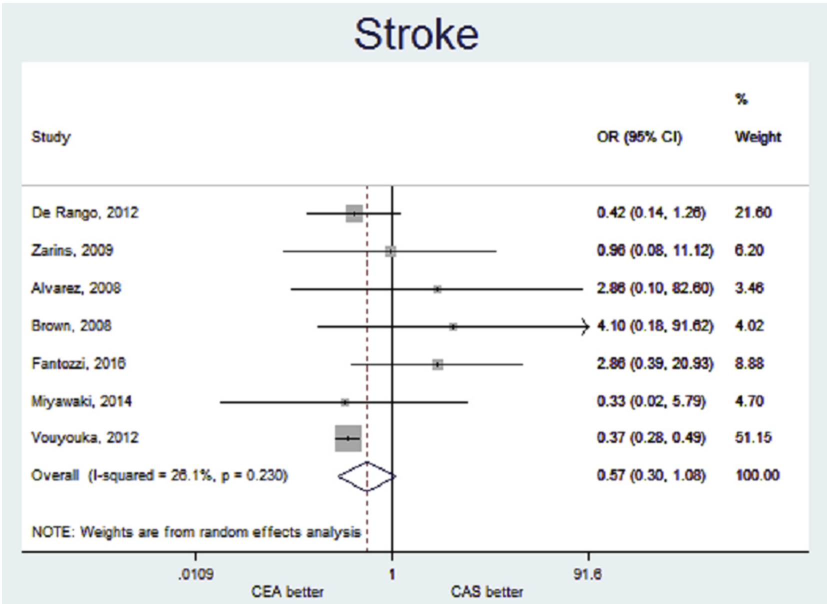

Figure 2. Forest plot comparing stroke between patients in the carotid artery endarterectomy and carotid artery stenting groups. CAS, carotid artery stenting; CEA, carotid artery endarterectomy; CI, confidence interval; OR, odds ratio.

for full-text evaluation. Nine studies met the predetermined eligibility criteria and were included in the meta-analysis as shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (Figure 1).

Characteristics of the Included Studies

All 9 studies were real-world studies and comprised a total of 5955 patients.[12-14,18-23] None of the included studies had a serious risk of bias (Supplementary Table S1). Detailed patient and study characteristics are illustrated in Table 1. An embolic protection device was consistently used in all studies with the exception of 2 cohorts. These 2 studies reported partial use of an embolic protection device in the enrolled patients (73.7% and 98% in the CAS group).[18,19] CAS was performed through the transfemoral approach in all studies except for Alvarez et al.,[12] which used the transcervical approach, and Fantozzi et al.,[19] which included the transfemoral, transcervical, and transradial approach interchangeably. The CEA procedure was performed under general or local anesthesia; CAS was performed under local anesthesia.

Periprocedural Outcomes (30 days): CEA versus CAS

Stroke occurred in 5.8% (n = 257/4415) and 10.5% (n = 81/767) in the CEA and CAS groups, respectively. However, this difference did not reach statistical significance (OR, 0.57; 95% CI, 0.30–1.08; $I^2 = 26.1\%$) (Figure 2). The cumulative risk of TIA was 0% (n = 0/98) and 4.2% (n = 7/166) in the CEA and CAS groups, respectively, without statistically significant differences (OR, 0.28; 95% CI, 0.03–2.52; $I^2 = 0\%$) (Figure 3). MI occurred in 1.1% (n = 4/357) of patients in the CEA group and 0.5% (n = 2/355) of patients in the CAS group, demonstrating a similar risk between the 2 revascularization approaches (OR, 1.67; 95% CI, 0.37–7.46; $I^2 = 0\%$) (Figure 4). The risk of periprocedural mortality was similar between the CEA and CAS groups (CEA: 1.5% [n = 8/523]; CAS: 0.9% [n = 4/431]; OR, 1.41; 95% CI, 0.43–4.58; $I^2 = 0\%$) (Figure 5). Finally, no differences were identified in terms of CN injury (CEA: 5.8% [n = 3/51]; CAS: 0% [n = 0/51]; OR, 4.74; 95% CI, 0.5–44.98; $I^2 = 0\%$) (Figure 6).

Meta-Regression Analysis

Meta-regression analysis did not point to a modifying effect of symptomatic carotid stenosis on periprocedural stroke rates (coefficient: −0.65; 95% CI, −5.57 to 4.25; P = 0.63) (Supplementary Figure S1).

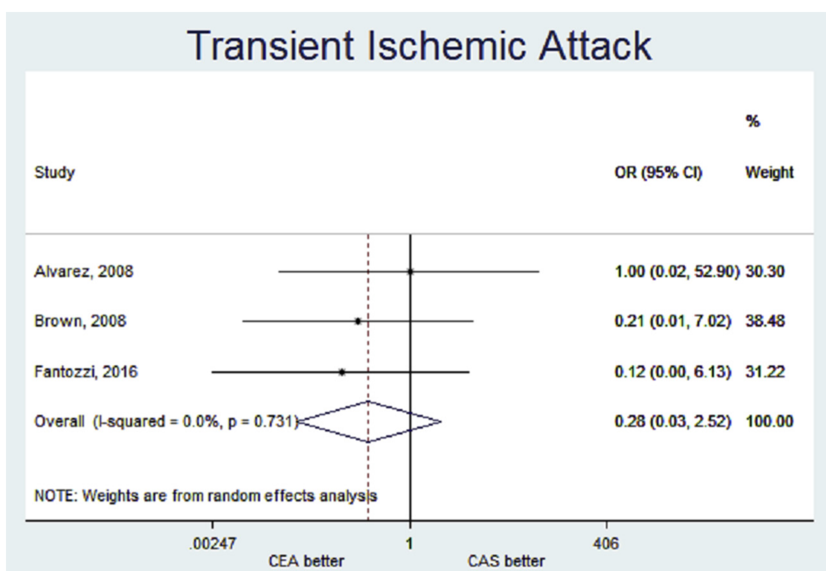

Figure 3. Forest plot comparing transient ischemic attack between patients in the carotid artery endarterectomy and carotid artery stenting groups. CAS, carotid artery stenting; CEA, carotid artery endarterectomy; CI, confidence interval; OR, odds ratio.

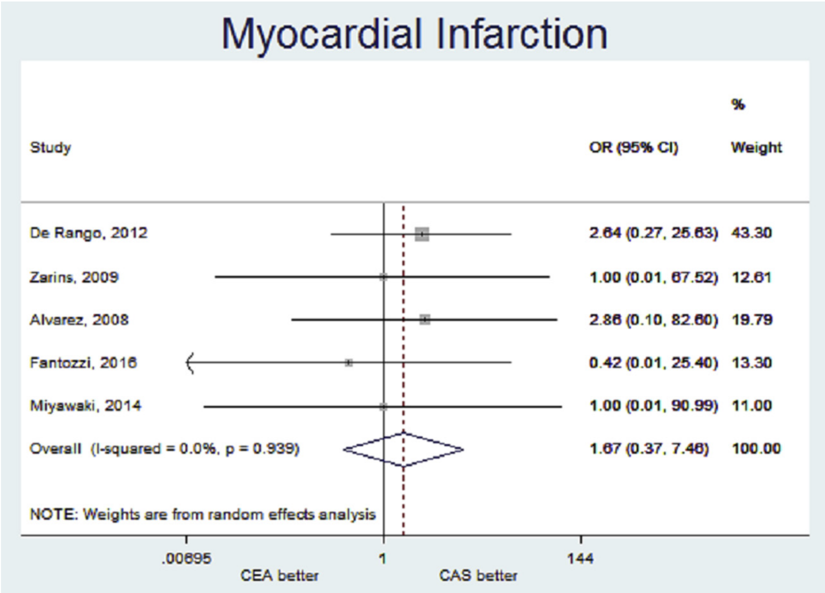

Figure 4. Forest plot comparing myocardial infarction between patients in the carotid artery endarterectomy and carotid artery stenting groups. CAS, carotid artery stenting; CEA, carotid artery endarterectomy; CI, confidence interval; OR, odds ratio.

Subgroup Analysis of Stroke: CEA versus Protected Transfemoral CAS

A separate analysis of stroke conducted by including only studies that exclusively used the transfemoral approach in CAS cases with distal or proximal protection showed that elderly patients who had CEA were at a statistically significant lower risk of 30-day stroke (OR, 0.38; 95% CI, 0.29–0.50; $I^2 = 0\%$) (Figure 7).

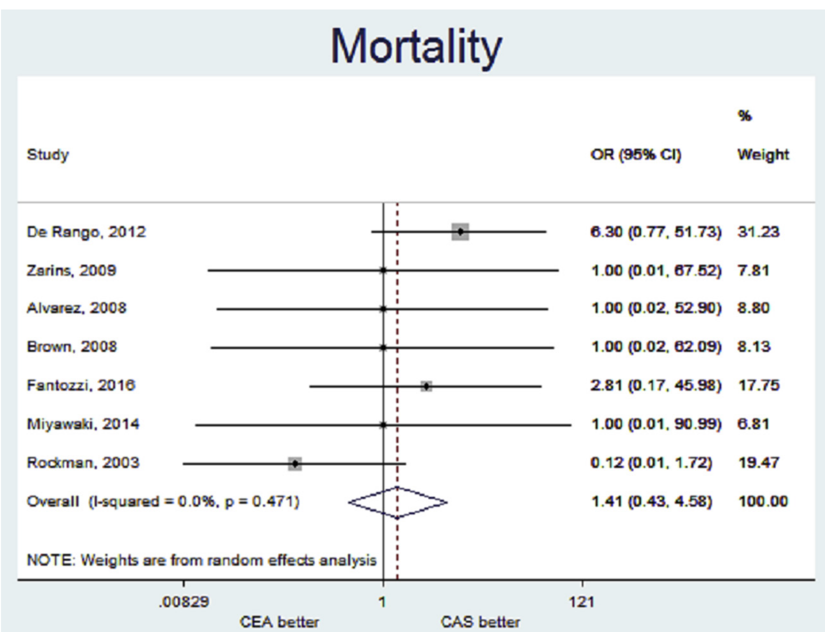

Figure 5. Forest plot comparing mortality between patients in the carotid artery endarterectomy and carotid artery stenting groups. CAS, carotid artery stenting; CEA, carotid artery endarterectomy; CI, confidence interval; OR, odds ratio.

DISCUSSION

This meta-analysis compared periprocedural (30-day) adverse event rates between elderly patients (>80 years of age) who had CEA with CAS for carotid artery stenosis. Overall, this study supports that CEA and CAS are similarly safe without any statistically significant differences in terms of 30-day stroke, TIA, MI, mortality, and CN injury. However, in the sensitivity analysis of CEA versus transfemoral CAS with distal or proximal protection, elderly patients in the CEA group were at a statistically significant lower risk of 30-day stroke.

Stroke is a primary complication in carotid revascularization procedures and can cause significant long-term morbidity. It is very important to identify specific patient populations where CEA or CAS is safer to perform and could potentially diminish the incidence of periprocedural adverse events including stroke.[24,25] Specifically, CREST reported a 12% periprocedural risk of stroke in octogenarians compared with 3% in younger patients.[26] Of note, calcific atherosclerosis is more prevalent in the octogenarian population and can be a source of thromboembolic stroke.[27] In theory, transfemoral CAS can be more challenging and risky to perform than CEA in the presence of tortuous anatomy. Catheter interaction with aortic arch atherosclerotic disease can cause stroke because of distal embolizations.[27] Preprocedural arch evaluation with noninvasive imaging could help stratify the risk of embolization before patients undergo carotid revascularization. Data from this study show a 30-day stroke rate of 5.7% and 10.5% in patients who underwent CEA and CAS, respectively. Even though the difference in the cumulative risk of stroke between the 2 groups did not reach statistical significance, it is possible that the current analysis was underpowered to detect it.

Our overall analysis included studies that used the transcervical approach for CAS. In theory, transcervical access in CAS could reduce strokes related to catheter manipulation in the aortic arch and

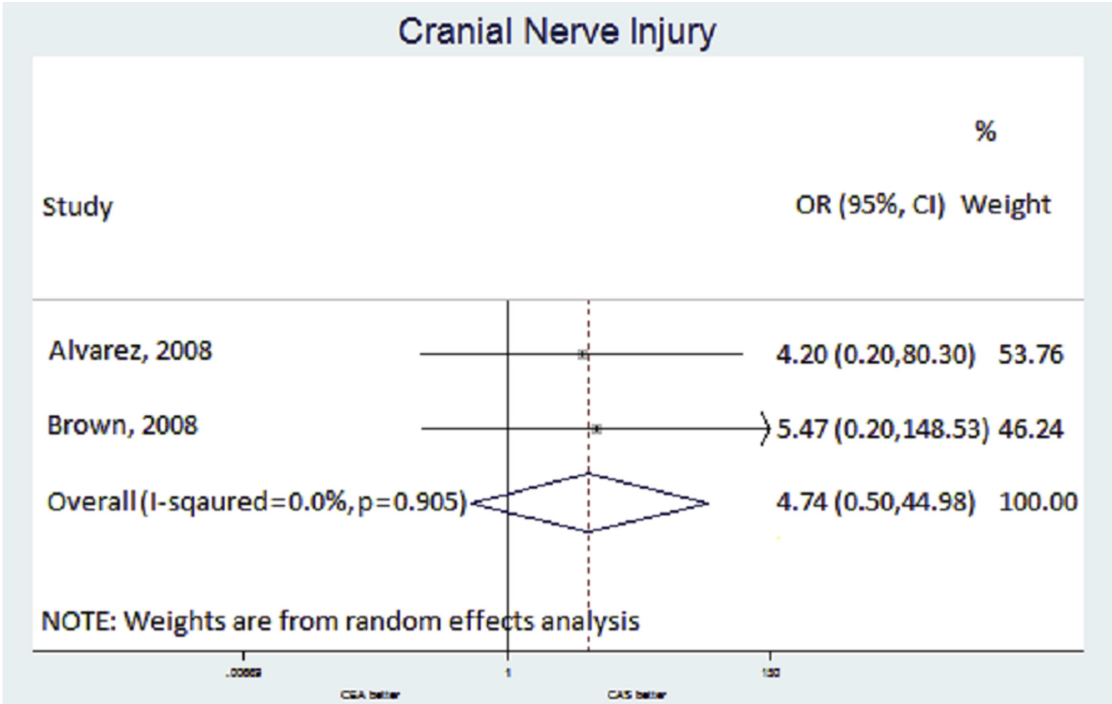

Figure 6. Forest plot comparing cranial nerve injury between patients in the carotid artery endarterectomy and carotid artery stenting groups. CAS, carotid artery stenting; CEA, carotid artery endarterectomy; CI, confidence interval; OR, odds ratio.

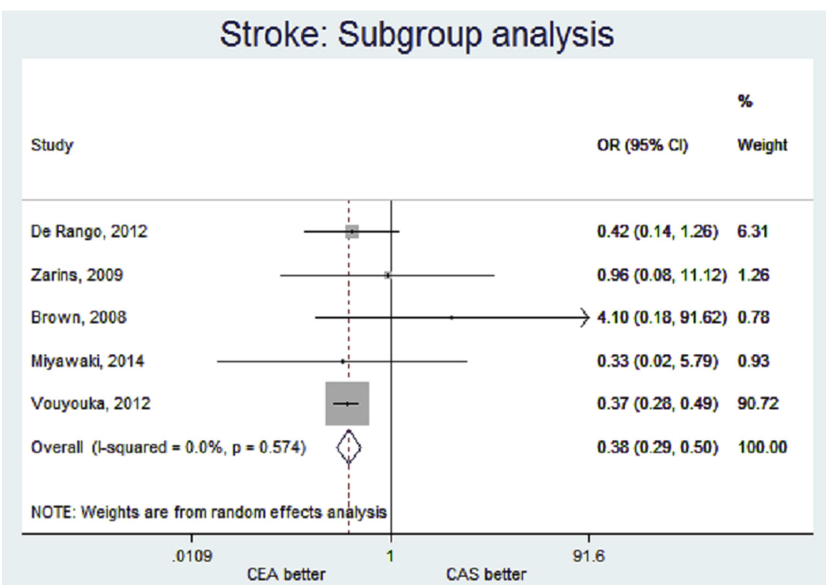

Figure 7. Forest plot comparing stroke between patients in the carotid artery endarterectomy and transfemoral protected carotid artery stenting groups. CAS, carotid artery stenting; CEA, carotid artery endarterectomy; CI, confidence interval; OR, odds ratio.

trunk.[27] Based on this rationale and the fact that the transcervical approach is less commonly used, we performed a subgroup analysis by excluding all studies that used the transcervical approach. Interestingly, our results demonstrated that the transfemoral CAS was associated with a statistically significant higher risk of 30-day stroke in older adults compared with CEA. CREST included only patients who had transfemoral CAS; in contrast, the study by Alvarez et al.[12] showed that periprocedural stroke rates in octogenarians were comparable with those of younger patients when CAS was performed through the transcervical approach. Therefore, this meta-analysis suggests that CEA can mitigate the risk of stroke in octogenarians compared with transfemoral CAS. However, no direct comparisons could be made between CEA and the transcervical CAS. Future comparative studies are warranted to investigate whether the transcervical approach in CAS can diminish the risk of stroke compared with CEA not only in older adults but also in the general population.

The cumulative risk of 30-day MI was 1.1% in the CEA group and 0.5% in the CAS group; however, this difference did not reach statistical significance. In contrast, several RCTs have shown that CAS is associated with a statistically significant lower risk of MI in the general population.[7] It is possible that the current analysis was underpowered to detect a real difference in the MI rate. Future prospective studies would shed light on whether the revascularization strategy can affect the risk of MI in older adults. Notably, periprocedural TIA and death were similar between the 2 groups, which are in accordance with results from RCTs in the general population.[6,28] CAS has been demonstrated to have a lower risk of CN injury compared with CEA in comparative studies.[25,29] In our analysis, only 2 papers reported the 30-day rate of CN injuries in the CEA and CAS groups, and that could be the reason why statistical significance was not reached. However, this could be a future area of investigation.

It is worth highlighting that this is a meta-analysis of periprocedural (30-day) adverse event rates. Unfortunately, long-term outcomes including stroke-free survival and restenosis rates were not uniformly available among the included studies; these outcomes in older adults are another area ripe for investigation. In addition, it remains important to identify patient characteristics, anatomic factors, and comorbidities that could potentially worsen prognosis after CEA or CAS. For instance, preliminary reports have suggested that women and asymptomatic octogenarians may not benefit from invasive carotid interventions.[13] Finally, it is relatively common that elderly patients who undergo carotid revascularization with CEA or CAS have not yet failed standard medical care including antiplatelets, statins, and antihypertensives[13,30]; therefore, a comparison between carotid interventions and best medical care in older adults may be the most important end point to settle. Our analysis revealed a high risk of stroke for either CAS or CEA (10.5% vs. 5.7%, respectively) in older adults, again supporting the idea that no intervention at all may be the safest path. We think an accurate risk stratification algorithm developed with further studies would help identify patient subgroups that would benefit more from carotid revascularization procedures with low periprocedural hazards and high stroke-free survival rates.

Limitations

Our results should be interpreted in the context of several limitations. First, the retrospective design and nonblinded nature of the included studies could potentially introduce selection bias in this meta-analysis. Second, because of unavailability of patient-level data, it was not feasible to adjust for specific comorbidities which may have affected the outcomes. Finally, different operators and centers created heterogeneity in our pooled results.

CONCLUSIONS

This study shows that CEA is associated with a statistically significant lower risk of 30-day stroke compared with transfemoral CAS with distal or proximal protection in the elderly population. No differences were noted in the rates of periprocedural TIA, MI, death, and CN injury.

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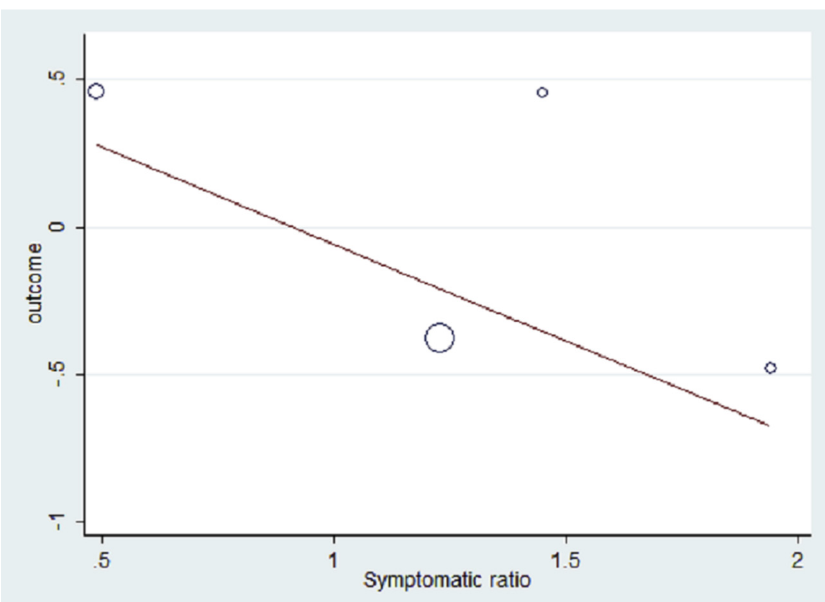
APPENDIX

Supplementary Table S1. Risk of Bias Assessment for Observational Studies (ROBINS-I Tool)

Study	Confounding	Selection	Measurement of Interventions	Deviations from Intended Interventions	Missing Data	Measurement of Data	Selection of the Reported Result
Rockman et al., 2003[21]	Moderate	Low	Moderate	Low	Low	Low	Low
Alvarez et al., 2008[12]	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Low
Brown et al., 2008[18]	Moderate	Moderate	Low	Moderate	Moderate	Low	Low
Zarins et al., 2009[23]	Moderate	Low	Moderate	Low	Moderate	Low	Low
De Rango et al., 2012[13]	Moderate	Low	Low	Low	Low	Low	Low
Vouyouka et al., 2012[14]	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate
Yoshida et al., 2014[22]	Moderate	Low	Low	Low	Low	Low	Moderate
Miyawaki and Maeda, 2014[20]	Moderate	Low	Low	Low	Low	Low	Low
Fantozzi et al., 2016[19]	Moderate	Moderate	Low	Low	Moderate	Moderate	Low



Supplementary Figure S1. Bubble plot showing the modifying effect of symptomatic status on the outcome of stroke.

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