Carotid Artery Stenting Versus Carotid Endarterectomy for Treatment of Asymptomatic Carotid Artery Stenosis
A Meta-Analysis Study
Guiyi Yuan, MD, Shuxian Zhou, MD, Wei Wu, MD, Yuling Zhang, MD, Juan Lei, MD and Boshui Huang, MD

Summary
Asymptomatic carotid stenosis is common and is associated with increased risk of stroke. The relative efficacy and safety of carotid endarterectomy (CEA) and carotid stenting (CAS) in patients with asymptomatic carotid stenosis remain unclear. Five studies that recruited patients with asymptomatic but significant carotid stenosis, who underwent CEA or CAS, were included in this systematic review and meta-analysis. The analyzed outcomes included risks of stroke, myocardial infarction (MI), and death. Risk ratio (RR) and 95% confidence interval (95% CI) were calculated and pooled for meta-analysis. Pooled analysis demonstrated that compared with CEA, CAS was associated with a decreased risk of MI (RR = 0.49, 95%CI = 0.26-0.91, \(P = 0.023\)) and slightly increased risk of stroke, although not significant (RR = 1.69, 95% CI = 0.97-2.92, \(P = 0.063\)). There was no difference in the death rates between the groups (RR = 0.60, 95% CI = 0.17-2.18, \(P = 0.436\)). In the subgroup analysis, CAS was associated with a decreased risk of MI in mixed patients (RR = 0.45, 95% CI = 0.26-0.78, \(P = 0.005\)), but not in asymptomatic patients (RR = 0.549, 95% CI = 0.26-1.17, \(P = 0.119\)). Compared with CAS, CEA was associated with decreased risk of perioperative stroke and increased risk of MI; it did not affect the risk of death in patients with asymptomatic carotid stenosis. In the subgroup analysis, the decreased risk of MI after CAS was significant only in the mixed patients group. CAS was associated with higher risk of stroke but lower risk of MI than those with CEA. Both procedures appeared equivalent in terms of the risk of death.

Key words: Prophylactic

Carotid artery stenosis refers to narrowing or blockage of the lumen of arteries due to intravascular plaque formation. Asymptomatic carotid artery stenosis is diagnosed in individuals without a history of ipsilateral carotid territory ischemic stroke or transient ischemic attack and without presentation of focal neurologic symptoms, such as amaurosis fugax, contralateral weakness, numbness of an extremity or face, dysarthria, or aphasia.\(^1,2\) With the aging of the general population and wide availability of noninvasive diagnostic modalities, asymptomatic carotid artery stenosis is increasingly detected in medical practice.\(^3\) This condition affects approximately 4.2% of the general population, and its prevalence increases with age.\(^4\) Asymptomatic carotid artery stenosis is an important health concern as significant/severe stenosis (50%-99%) is a strong risk factor for stroke.\(^5,6\) Many patients with carotid artery stenosis benefit from intensive medical treatment that includes high-dose statin drugs, blood pressure control, antiplatelet agents, optimal diabetes management, and other appropriate lifestyle changes.\(^7,8\) A recent report indicated that biological antioxidant potential was significantly associated with carotid artery intima-media thickness.\(^9\) Further, the osteoprotegerin level is significantly associated with endothelial function and may predict early carotid atherosclerosis in patients with coronary artery disease.\(^10\)

Despite advances in the medical management of asymptomatic carotid stenosis, patients with significant and severe (50%-99%) stenosis may require invasive treatment. Surgical treatment options include removal of the material inside the artery (carotid endarterectomy, CEA) or insertion of a supporting stent (carotid artery stenting, CAS). Based on several randomized clinical trials, current guidelines recommend prophylactic CEA in patients with > 70% stenosis given that the risk of perioperative stroke, myocardial infarction (MI), and death due to surgery is < 3%\(^10,12\). Comorbid conditions, life expectancy, and other individual factors should also be considered when selecting CEA for asymptomatic patients.\(^13\)

Recently, CAS has been proposed as an alternative to CEA. The advantages of CAS include mild sedation, absence of incision, low risk of cranial nerve palsy, and...
fewer cardiovascular complications. However, several studies have reported that CAS is associated with greater risk of stroke or death within 30 days of treatment than that with CEA. Conversely, a number of studies have shown that CAS might be equivalent to CEA, especially in patients younger than 70 years. Although uncertainty regarding the relative benefit of CAS over CEA in the management of asymptomatic carotid artery stenosis remains, the use of CAS has significantly increased from 2.8% of all carotid revascularization procedures in 1998 to 12.6% in 2008.

Because the annual risk of stroke for asymptomatic carotid stenosis is quite low (estimated to be approximately 2%), it is important to know whether prophylactic CEA or CAS actually benefits the patient in preventing adverse events. Therefore, the aim of our study was to systematically review the current evidence, comparing CAS with CEA for patients with significant carotid stenosis. The relative effectiveness and safety of these treatment strategies was determined using statistical meta-analysis techniques.

**Methods**

**Search strategy:** We followed the PRISMA guidelines for systematic review and meta-analysis of observational and diagnostic studies and searched the published literature using databases, such as MEDLINE, PubMed, Cochrane, Embase, and Google Scholar, up to March 21, 2016, with various combinations of the following keywords: carotid endarterectomy (CEA), carotid artery stenting (CAS), asymptomatic, carotid artery stenosis, and prophylactic. In addition, we manually searched references in relevant publications to identify other eligible trials. Specifically, we included randomized controlled trials (RCTs) that evaluated patients with asymptomatic but still significant carotid stenosis and who were scheduled to undergo CEA or CAS.

Nonrandomized studies, single-arm studies, case series, letters, comments, editorials, proceedings, personal communications, and studies conducted on patients with symptomatic carotid stenosis were excluded from the analysis.

**Study selection and data extraction:** Two independent reviewers extracted relevant clinical data, and a third reviewer was consulted in case of disagreements. We extracted data on study population (number, age, and gender of subjects in each group), study design, and major outcomes.

**Quality assessment:** The study quality was assessed using the Cochrane Risk of Bias Tool. The tool assesses risk of bias using 6 different criteria: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome), reporting bias (selective outcome reporting), and inclusion of intention-to-treat analysis (other bias). The quality assessment was performed by two independent reviewers, and a third reviewer was consulted if no consensus could be reached.

**Statistical analysis:** The primary outcomes were perioperative stroke, death, and MI. The risk ratio (RR) and 95% confidence interval (95% CI) were used as measures of the treatment effect of CAS compared with CEA. RR < 1 indicated that patients who underwent CAS had a lower risk of stroke, death, or MI than those who underwent CEA (favors CAS). RR > 1 indicated that patients who underwent CEA had a lower risk of stroke, death, or MI than those who underwent CAS (favors CEA). RR = 1 indicated that the risk of stroke, death, or MI was similar between CAS and CEA. Pooled estimates for RRs and differences in the means were calculated using the Der Simonian and Laird random-effects models. A two-sided P-value of < 0.05 was considered statistically significant.

The χ²-based test of homogeneity was performed, and the inconsistency index (I²) and Q statistics were determined. The I² statistic indicates the percentage of the observed between-study variability due to heterogeneity. If I² was > 50% or > 75%, the study was considered to be heterogeneous or highly heterogeneous, respectively. If I² was < 25%, the study was considered to be homogeneous.

Sensitivity analysis was performed using the leave-one-out approach. In addition, to identify whether patient characteristics affected the pooled estimates, subgroup analysis was performed according to whether or not asymptomatic patients were assessed in a study.

All statistical analyses were performed using the statistical software Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ).

**Results**

**Basic characteristics of included studies:** Using the keyword-based search, we initially identified 51 articles. Of these, 14 were non-RCTs, 14 assessed different interventions, 6 were single-arm studies, one was a review, one analyzed only the cost-effectiveness, 3 were duplicate studies, 3 reported the study protocol, and 2 did not provide an outcome of interest; therefore, these studies were excluded from the analysis. Thus, we could identify 5 eligible publications. The flow chart describing the selection of trials for the analysis is presented in Figure 1.

The studies recruited a total of 4414 patients: 2581 in the CAS group and 1833 in the CES group. The mean age ranged from 66.6 to 72.5 years in the CAS group and 64.0 to 72.6 years in the CEA group. All basic characteristics of selected studies are summarized in Table I. Detailed clinical characteristics of included patients, including treatment protocols, are listed in the Supplemental Table.

**Comparison of treatment effects of CAS and CEA on stroke rate:** A total of 3 studies reported complete data for stroke rates in the CAS and CEA groups and were included in the meta-analysis. There was no evidence of heterogeneity among the studies (I² value = 0%, df = 2, P = 0.761). The combined effect indicated that patients treated with CAS might have a higher risk of stroke than those treated with CEA; however, the results did not reach statistical significance (RR = 1.69, 95% CI = 0.97-2.92, P = 0.063) (Figure 2A).

**Comparison of treatment effects of CAS and CEA on MI rate:** A total of 4 RCTs reported complete data on MI
Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Table 1. Summary of Basic Characteristics of Selected Studies

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Study design</th>
<th>Intervention</th>
<th>Patient number (Total: 4414)</th>
<th>Asymptomatic (%)</th>
<th>Male (%)</th>
<th>Mean age (years)</th>
<th>Smoking (%)</th>
<th>Follow-up time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenfield (2016)</td>
<td>RCT</td>
<td>CAS</td>
<td>1089</td>
<td>100.0%</td>
<td>61.2%</td>
<td>67.7</td>
<td>24.4%</td>
<td>5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CEA</td>
<td>364</td>
<td></td>
<td>56.9%</td>
<td>67.9</td>
<td>19.5%</td>
<td></td>
</tr>
<tr>
<td>Brott (2010)</td>
<td>RCT</td>
<td>CAS</td>
<td>1262</td>
<td>47.1%</td>
<td>63.9%</td>
<td>68.9</td>
<td>26.4%</td>
<td>4 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CEA</td>
<td>1240</td>
<td>47.3%</td>
<td>66.4%</td>
<td>69.2</td>
<td>26.1%</td>
<td></td>
</tr>
<tr>
<td>Liu (2009)</td>
<td>RCT</td>
<td>CAS</td>
<td>20</td>
<td>30.0%</td>
<td>75.0%</td>
<td>66.8</td>
<td>65.0%</td>
<td>18 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CEA</td>
<td>20</td>
<td>25.0%</td>
<td>85.0%</td>
<td>64.0</td>
<td>60.0%</td>
<td></td>
</tr>
<tr>
<td>Brooks (2004)</td>
<td>RCT</td>
<td>CAS</td>
<td>43</td>
<td>100.0%</td>
<td>NA</td>
<td>66.6</td>
<td>4000.0%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CEA</td>
<td>42</td>
<td></td>
<td></td>
<td>69.9</td>
<td>3700.0%</td>
<td></td>
</tr>
<tr>
<td>Yadav (2004)</td>
<td>RCT</td>
<td>CAS</td>
<td>167</td>
<td>70.1%</td>
<td>66.9%</td>
<td>72.5</td>
<td>16.9%</td>
<td>1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CEA</td>
<td>167</td>
<td>72.3%</td>
<td>67.1%</td>
<td>72.6</td>
<td>16.4%</td>
<td></td>
</tr>
</tbody>
</table>

CAS indicates carotid stenting; CEA, carotid endarterectomy; RCT, randomized controlled trial; and NA, not available

rates in the CAS and CEA groups and were included in the meta-analysis. There was no heterogeneity among the studies (I2 value = 0%, df = 3, \( P = 0.967 \)). The overall analysis showed that patients who underwent CAS had a lower risk of MI than those who underwent CEA (RR = 0.49, 95% CI = 0.26-0.91, \( P = 0.023 \)) (Figure 2B).

Comparison of treatment effects of CAS and CEA on death rate: A total of 3 RCTs reported complete data for death rates in the CAS and CEA groups and were included in the meta-analysis. There was no evidence of heterogeneity among the studies (I2 value = 0%, df = 2).
2, \( P = 0.531 \)). The overall analysis did not reveal a significant difference in the mortality rate between CAS and CEA (RR = 0.60, 95% CI = 0.17-2.18, \( P = 0.436 \)) (Figure 2C).

**Sensitivity analysis:** Sensitivity analysis was performed using the leave-one-out approach (Figure 3). The direction and magnitude of combined estimates did not vary markedly with the removal of individual studies, indicating that the data was not over influenced by individual studies, thereby indicating the robustness of this meta-analysis. However, the combined results of stroke became significant after removal of the study by Yadav, et al.\(^{29}\) (Figure 3A). After the removal of studies by Brott, et al. or Yadav, et al.\(^{29,29}\) the difference in the MI rate between CAS and CEA was not significant (Figure 3B).

**Subgroup analysis:** Subgroup analysis was performed according to whether the studies recruited only asymptomatic or both asymptomatic and symptomatic patients (mixed patients).

Regardless of patient characteristics (i.e., asymptomatic or mixed), patients in the CAS group had a higher risk of stroke than those in the CEA group (asymptomatic: RR = 1.88, 95% CI = 1.01-3.51, \( P = 0.048 \); mixed: RR = 1.161, 95% CI = 0.37-3.69, \( P = 0.800 \)). CAS was not associated with reduced risk of MI in studies that recruited only asymptomatic patients (RR = 0.55, 95% CI = 0.26-1.17, \( P = 0.119 \)) as well as those assessing both symptomatic and asymptomatic patients (RR = 0.39, 95% CI = 0.14-1.14, \( P = 0.085 \)). There was no difference in the risk of death between patients in the CAS and CEA.
A Stroke

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics with study removed</th>
<th>Risk ratio and 95% CI with study removed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk ratio</td>
<td>Lower limit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenfield (2016)</td>
<td>1.537</td>
<td>0.777</td>
</tr>
<tr>
<td>Brott (2010)</td>
<td>1.615</td>
<td>0.782</td>
</tr>
<tr>
<td>Yadav (2004)</td>
<td>1.880</td>
<td>1.006</td>
</tr>
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</table>

B Myocardial infarction

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics with study removed</th>
<th>Risk ratio and 95% CI with study removed</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Risk ratio</td>
<td>Lower limit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenfield (2016)</td>
<td>0.474</td>
<td>0.237</td>
</tr>
<tr>
<td>Brott (2010)</td>
<td>0.446</td>
<td>0.192</td>
</tr>
<tr>
<td>Liu (2009)</td>
<td>0.495</td>
<td>0.264</td>
</tr>
<tr>
<td>Yadav (2004)</td>
<td>0.537</td>
<td>0.257</td>
</tr>
</tbody>
</table>

C Death

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics with study removed</th>
<th>Risk ratio and 95% CI with study removed</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Risk ratio</td>
<td>Lower limit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosenfield (2016)</td>
<td>0.725</td>
<td>0.162</td>
</tr>
<tr>
<td>Liu (2009)</td>
<td>0.433</td>
<td>0.105</td>
</tr>
<tr>
<td>Yadav (2004)</td>
<td>0.845</td>
<td>0.101</td>
</tr>
</tbody>
</table>

Figure 3. Sensitivity analysis for the treatment effects of CEA versus CAS on stroke (A), mortality (B), and MI (C). The 95%CI indicates lower and upper limits.

Table II. Subgroup Analysis for Treatment Effects of CAS Versus CEA on Stroke, Death, and MI according to Patient Characteristics

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Subgroup</th>
<th>Number of studies</th>
<th>Heterogeneity</th>
<th>Risk ratio</th>
<th>Pooled results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>F</td>
<td>P</td>
<td>Pooled results</td>
</tr>
<tr>
<td>Stroke</td>
<td>Asymptomatic</td>
<td>2</td>
<td>0%</td>
<td>0.860</td>
<td>1.880</td>
</tr>
<tr>
<td>MI</td>
<td>Asymptomatic</td>
<td>2</td>
<td>0%</td>
<td>0.982</td>
<td>1.161</td>
</tr>
<tr>
<td>Death</td>
<td>Asymptomatic</td>
<td>1</td>
<td>0%</td>
<td>0.969</td>
<td>0.390</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
<td>1</td>
<td>NA</td>
<td>0.333</td>
<td>0.725</td>
</tr>
</tbody>
</table>

NA indicates not assessed

The results are shown in Figure 4. All the included studies had random sequence generation and low risk of attrition and reporting biases. Two studies had allocation concealment and 3 had intention-to-treat analysis. However, the risk of performance bias was high, possibly related to the groups (asymptomatic: RR = 0.33, 95% CI = 0.02-4.73, P = 0.417; mixed: RR = 0.73, 95% CI = 0.16-3.25, P = 0.675) (Table II).

Quality assessment: The quality of the included studies was assessed using the Cochrane Risk of Bias Tool, and the included studies had random sequence generation and low risk of attrition and reporting biases. Two studies had allocation concealment and 3 had intention-to-treat analysis. However, the risk of performance bias was high, possibly related to the
difficulty in blinding due to the characteristics of interventions. Overall, the included studies were of fair quality.

**Discussion**

Carotid artery stenosis is an important cause of stroke-related mortality and morbidity, and is a significant public health concern. Moderate-to-severe carotid artery stenosis may require surgical treatment. The current standard for invasive treatment is CEA. CAS, a technique introduced into clinical practice within the last two decades, has been proposed as a valuable alternative to CEA. Although a number of studies have addressed the effectiveness of these treatment modalities, uncertainties about the relative benefits of CAS over CEA for patients with carotid artery stenosis persist. Since the publication of the latest meta-analysis on the topic, the data from two large, multicenter, randomized trials [Asymptomatic Carotid
Trial (ACT I) and Carotid Revascularization Endarterectomy versus Stenting Trial] comparing early and late outcomes after CAS and CEA have been published. We pooled the results of these two most recent trials and earlier eligible studies and used meta-analysis techniques to compare CAS and CEA in terms of perioperative outcomes, including stroke, MI, and death. To improve the reliability of the results, we included only RCTs, thus avoiding the biases associated with analysis of prospective or retrospective studies.

Our results suggest that CAS may lower the risk of MI for patients with carotid artery stenosis, and is associated with a slightly higher risk of stroke, although not statistically significant. The underlying etiology of this phenomenon is not completely understood but may be related to clotting around the stent or the shearing force of red cells moving through the stent. We did not observe any differences in the risk of death between the two procedures. In addition, we performed subgroup analysis comparing procedural outcomes in asymptomatic and mixed patients (asymptomatic and symptomatic patients) and found that CAS had a higher risk of stroke than CEA in both the asymptomatic and mixed patient groups. We observed a clear benefit in the rate of MI in patients treated with CAS in the mixed patient group, but no significant difference in the MI rate was found in asymptomatic patients. In addition, we did not observe any differences in the risk of death between the two procedures in the subgroup analysis. Recently, Rosenfield, et al. reported a similar cumulative 5-year rate of stroke-free survival of 93.1% in the CAS group compared with 94.7% in the CEA group. Furthermore, no significant differences in the rate of nonprocedure-related stroke, all stroke, and survival were observed between the two groups.

Notable, although our results provided general guidance regarding the treatment of patients with carotid artery stenosis, the decision to perform the prophylactic surgical procedure depends on an individual’s risk assessment for future cerebrovascular events. Furthermore, in patients that are likely to benefit from the surgical procedure, individual anatomical and clinical characteristics (e.g., sex, age, degree of plaque calcification, cardiac disease, kidney disease, complex aortic arch, carotid bifurcation above C-2, and tandem stenosis) can influence the choice between CEA and CAS. In addition, it was reported that medical treatment is an important option for asymptomatic carotid artery stenosis compared with the surgical group, which included either CAS or CEA. Because we observed a lower risk of stroke with CEA than with CAS, it would be meaningful to compare CEA with medical treatment in future studies.

Overall, our analysis was in agreement with the results of prior meta-analysis studies that focused on symptomatic or mixed patients. In a recent meta-analysis, Guay reported that compared with CAS, CEA decreases the risk of stroke at 30 days, increases the risk of MI, and does not affect the risk of death. Similarly, Murad, et al. and Bonati, et al. reported that the risk of stroke within 30 days of intervention was slightly lower in the CEA group than in the CAS group.

In contrast to other studies, Bonati, et al. reported that CAS was associated with increased risk of periprocedural death and concluded that CAS should be avoided among individuals aged > 70 years. The data were insufficient to determine the safety and potential efficacy of CAS in younger patients. The differences in the death rates observed by Bonati, et al. can be due to significant differences in the clinical characteristics of recruited patients. Other potential sources of variability are the differences in the skills of the physicians performing the procedures. Increasing numbers of highly trained physicians as well as advancements in stenting technology may contribute to decreased rates of complications with CAS in more recent trials compared with older trials.

This meta-analysis should be interpreted in the context of several limitations. First, there were only a small number of available studies. We could identify only 5 trials that met our inclusion criteria. Out these, not all reported the outcomes of interest, which particularly limited the validity of the subgroup analysis. In addition, for the subgroup analysis, we could not divide the patients into asymptomatic and symptomatic groups due to the limitation of the reported data. Moreover, quality assessment results showed that there was generally a high risk of performance bias in the included randomized trials. This may be explained by the nature of surgical interventions that cannot be double-blinded. Furthermore, the differences in medication, especially after the procedure, their dosages and durations, and differences in the types of stents could also have confounded the present results.

Due to limited data, we could not assess the relative benefits of CAS and CEA in different patient groups (e.g., patients with different degrees of stenosis, complex carotid anatomy, or other clinical symptoms). Subgroup analysis
of these parameters can address individual risk assessment and help to identify the minimum degree of stenosis that requires surgical intervention. Future large RCTs assessing the abovementioned parameters are warranted to address these questions.

Conclusions

In our study, we assessed the perioperative risks of stroke, death, and MI in patients with carotid artery stenosis who underwent CAS or CEA. Our results suggested that CAS is associated with significantly lower risk of MI and a slightly higher risk of stroke than those with CEA. Both procedures seemed equivalent in terms of the risk of death. In the subgroup analysis, decreased risk of MI after CAS was significant only in the mixed patient group but not in the asymptomatic patient group, whereas the risk of stroke after CAS remained higher in both the mixed and asymptomatic groups. Our results questioned the clinical value of CAS in prophylactic settings and reinforced the notion that individual risks of patients with asymptomatic carotid artery stenosis should be carefully evaluated prior to selecting the prophylactic procedure.

Disclosures

Conflicts of interest: The authors declare that they have no conflict of interest.

Ethical approval: Meta-analyses do not involve human subjects and do not require IRB review [J Grad Med Educ 2011; 3(1): 5-6].

References


Supplemental Files
Supplemental Table
Please see supplemental files; https://doi.org/10.1536/ihj.17-312