

1 **Peer Review File**

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3 **Article information:** <http://dx.doi.org/10.21037/atm-20-4620>

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5 **Reviewer A**

6 **1* Reviewer A: Comments to the Author**

7 This is a well-performed systematic review and meta-analysis of outcomes following
8 carotid endarterectomy (CEA) and carotid artery stenting (CAS) in both symptomatic
9 and asymptomatic patients. The Introduction is well-structured, the search terms are
10 well-defined, the results are well-presented and the Discussion reviews nicely the
11 available literature.

12 I have 4 minor comments:

13 Answer: Many thanks for your careful review and positive comments. We had
14 reviewed your comments several times, and found that it was pretty meaningful and
15 helpful for our study. We had already recognized more investigation and revision
16 were needed for this issue. Meanwhile, we have revised the manuscript and have
17 responded, point by point, to the comments based on the comments and suggestions
18 of reviewers. Revised portions are marked in light grey in the paper.

19
20 **2* Reviewer A: Comments to the Author**

21 First of all, the manuscript requires some language polishing from a native English
22 speaker to correct a couple of grammatical errors.

23 Answer: Many thanks for your careful review and positive comments. We had already
24 recognized our grammar and punctuation issues and sent the article to a native
25 English speaker for modifying the grammar and punctuation. The language edit
26 certification is shown below:



Editing Certificate

This document certifies that the manuscript

Endarterectomy Versus Stenting for the Prevention of Periprocedural Stroke or Death in Patients with Symptomatic or Asymptomatic Carotid Stenosis: A Meta-Analysis of 10 Randomized Trials

prepared by the authors

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was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors at AJE.

This certificate was issued on **August 13, 2020** and may be verified on the [AJE website](https://aje.com) using the verification code **6BEF-04B5-FFCE-AA2B-0B78**.



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3* Reviewer A: Comments to the Author

Discussion lines 308 - 311: The threshold for intervention for combined death/stroke rates in symptomatic patients is not 7%, but 6%, i.e. it is <3% in asymptomatic and <6% in symptomatic patients.

Answer: Many thanks for your careful review and positive comments. We have revised it based on your suggestion. (Line300/Page12)

4* Reviewer A: Comments to the Author

it should be "a direct comparison between CEA and CAS for..." instead of "a direct comparison between CEA and CSA for..."

Answer: Many thanks for your careful review and positive comments. Thanks for remind us again, we have reviewed your comments several times and find that it

should be "a direct comparison between CEA and CAS for...". We have revised it.

(Line343- 345/Page13)

5* Reviewer A: Comments to the Author

The references need to be prepared according to the Journal's Instructions for Authors.

Answer: Many thanks for your careful review and positive comments. We have revised it and resubmit it to Annals of Translational Medicine now.

Reviewer B

1* Reviewer B: Comments to the Author

Well structured. Especially Table 2 is really concise and a great way to present the results in summary. However, a few comments should be addressed.

Stroke definitions are not discussed in three studies and this should be highlighted specifically in the limitations section.

Answer: Many thanks for your careful review, positive comments and affirming our research. According to your comments and suggestions, we have revised the manuscript and add it as our limitations. (Line341/Page14)

2* Reviewer B: Comments to the Author

Studies included range from 2001-2016, how do the authors adjust for the advance in techniques of CAS throughout these years. Did stroke risk change throughout these years?

Answer: Many thanks for your careful review, positive comments and affirming our research. I could not agree with you more that the advance in the techniques of CAS stroke risk change stroke risk a lot throughout these years. We acknowledge that this is a major limitation of this study, therefore, we describe it in the section of limitation, and we make an eTable5 to describe the techniques of CAS used in our included studies.

(Line332-337/Page13)

3* Reviewer B: Comments to the Author

Is it possible to perform a subgroup analysis for the studies reporting consistently high rates of EPDs utilization? This is a critical limitation since EPDs reduce stroke rates after CAS and different EPD use among the included studies might limit generalizability of the results of the current review.

Answer: Many thanks for your careful review and positive comments. We also think that EPDs could reduce stroke rates after CAS. At the beginning of this study, we would like to perform a subgroup according to the EPDs utilization, however, most of included studies did not describe the EPDs utilization. Although some studies describe the EPDs utilization, the usage rates of EDP are different. We give up performing this subgroup analysis.

Meanwhile, we also think that this is the limitation of our study, therefore, we describe it in the section of limitation. (Line332-337/Page13)

4* Reviewer B: Comments to the Author

Please elaborate on preoperative statin use in Table 1, unless it is not available from the included studies.

Answer: Many thanks for your careful review, positive comments and affirming our research. As we all know, statin is a conventional drug for carotid stenosis, we have reviewed our included studies several times, and demonstrate most of included studies report perioperative use of antiplatelet therapy without describing statin. We provide a supplementary table with intervention of antiplatelet therapy in eTable5.

5* Reviewer B: Comments to the Author

Please elaborate on definitions of hypotension/ bradykardia among the included studies. Maybe you can add a column in one of the supplemental tables.

Answer: Many thanks for your careful review, positive comments and affirming our research. In this study, three articles reported the number of bradycardia or hypotension and data pooled by a fixed-effect model ($I^2 = 0\%$, $P = 0.408$) to reveal that the CEA group was associated with a low rate of bradycardia or hypotension compared to the CAS group ($RR = 0.105$, $P < 0.001$).

Currently, hypotension is defined as mean arterial pressure < 60 mm Hg, bradycardia was defined as $> 50\%$ reduction in heart rate compared with the pre-treatment value. But none of the three studies reported their specific definitions.

6* Reviewer B: Comments to the Author

It would be interesting to compare the two techniques regarding postoperative MI (Myocardial Infarction) as well. Please elaborate why this outcome was beyond the scope of this meta-analysis.

Answer: Many thanks for your careful review, positive comments and affirming our research. We also think that comparing the two techniques regarding postoperative MI would be more interesting. In this study, we aimed to compare periprocedural stroke or death of patients with symptomatic or asymptomatic carotid artery stenosis (CS) treated with CEA or CAS. The endpoints associated with the stroke or death were included, and the stroke were divided into several kinds. Therefore, the endpoint of postoperative MI was deleted in this study.

In the symptomatic group, three literature provided the numbers of MI in patients. No significant heterogeneity was found. ($P = 0.557$, $I^2 = 0.0\%$). The results show that the CEA was associated with a higher rate of MI compared to the CAS group [$RR = 2.496$, $95\%CI (1.119, 5.566)$, $P = 0.025$].

121 In the asymptomatic group, three literature provided the number of MI. The result
122 show 1004 cases in the experimental group, 1751 cases in the control group. No
123 significant heterogeneity was observed. ($I^2 = 0\%$, $P = 0.668$). The incidence of MI
124 between the experimental and control group was not statistically significant.
125 [RD=0.005, 95%CI (-0.003, 0.013), P= 0.191].

126 Thanks for reminding us again. We have added it back into our study. Revised
127 portions are marked in light grey in paper. (Line45-46/Page2; Line222-223/Page9;
128 Line238/ Page10)

130 7* Reviewer B: Comments to the Author

131 It would be interesting to synthesize HRs reported in the included studies regarding
132 the composite outcome of death or any stroke and then conduct a metaregression
133 analysis in case of Follow up inconsistencies among the included studies.

134 Answer: Many thanks for your careful review, positive comments and affirming our
135 research. Initially, we planned to compare the results at different follow-up times, but
136 their follow-up was different. Therefore, in this study, we aimed to compare 30-days
137 stroke or death of patients with symptomatic or asymptomatic carotid artery stenosis
138 (CS) treated with CEA or CAS.

139 With regard to a Hazard ratio analysis regarding the composite outcome of death or
140 any stroke. We are unable to performed it owing to lacking of data. Meanwhile, we
141 wrote two letters to the author, but did not get the original data.