PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Safety and Efficacy of Transcarotid Artery Revascularisation Versus Carotid Endarterectomy: Protocol for a Systematic Review and Meta-analysis Study
AUTHORS	Bai, Xuesong; Zhang, Xiao; Yang, Wuyang; Wang, Tao; Wang, Yan; Feng, Yao; Yang, Kun; Wang, Xue; Ma, Yan; Jiao, Liqun

VERSION 1 – REVIEW

REVIEWER	Gert J de Borst UMC Utrecht the Netherlands
REVIEW RETURNED	19-Oct-2020

GENERAL COMMENTS	several reviews and meta-analyses have been published recently. The papers suggest an acceptable outcome for TCAR. however: - there is no direct comparison of TCAR versus CEA - there is no data on TCAR in RECENTLY symptomatic patients !! - there is no long term data on TCAR the literature is mosyly "produced" under supervision of the Silk Road medical company, and TCAR has been applied mostly in heterogenous small cohorts especially in asymptomatic patients. The authors spell out the potential advantages of TCAR whci indeed may be true. The authors however then should also spell out the disadvantages such as combined surgery with stenting (and thus loosing the general advantages of a pure endovascular solution); higher risk of CNP with TCAR versus TFCAS; anatomical restrictions for TCAR (approx one third would not be suitable to apply TCAR due to short thick necks; and the need for at least eight minutes flow reversal which for sure will not be tolerated by a part of the patients undergoing carotid revascularization. Please read and implement the recent paper by Coelho A et al in Stroke 2020 PMID 32811389. The critical appraisal points out the issues existing with TCAR these days! This paper should be integrated and included in the Discussion section. The authors refer to reference 8 and 12 for long term outcomes but these two papers did not study long term. In my view only the one year outcomes by Schermerhorn report on outcome beyond 30 days. There is noot yet any long term outcome available.

REVIEWER	Aram Baram University of Slemani

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REVIEW RETURNED	08-Nov-2020

GENERAL COMMENTS	Well organized paper needs minor linguistic revision.

REVIEWER	Rita Pavasini UO Cardiologia Azienda Ospedaliero Universitaria di Ferrara Ferrara Italy
REVIEW RETURNED	07-Jan-2021

GENERAL COMMENTS	This is a protocol for a meta-analysis. Firstly Authors give a number of identification for Prospero registration but I cannot find the protocol in Prospero. Is this a temporary number? Next considering that the meta-analysis has been already proposed to Prospero for registration of the protocol I cannot understand the need to publish another protocol for the same meta-analysis. It seems to be a duplicate. Next I have several concerns about methods: - The degree of I2 is not correct. Please see: BMJ 2003;327:557–560. - To perform meta-regression at least 10 studies are necessary. It is nor correct to choose a fixed or random effect on the base of heterogeneity. A random effect have to be used in case of studies with different characteristics (e.g. different follow-up, patients included, different treatment included). Please see: Cooper H, Hedges VL, Valentine JC. Handbook of Research Synthesis and Meta-Analysis. Second Edition. 2009 - Please define the subgroup analysis planned. - For publication bias please assess also: Egger's intercept and Begg and Mazumdar's text. - Considering that this are not case-control or cohort study I would suggest to use MINORS criteria and not Nos scale to assess quality in observational study included in this meta-analysis. - I would remove the empty flow diagram, it is a non-sense as well as the new-castle form empty.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Gert de Borst, Utrecht University

Comments to the Author:
Q: several reviews and meta-analyses have been published recently. The papers suggest an acceptable outcome for TCAR.
however:
- there is no direct comparison of TCAR versus CEA
- there is no data on TCAR in RECENTLY symptomatic patients !!
- there is no long term data on TCAR

the literature is mosyly "produced" under supervision of the Silk Road medical company, and TCAR has been applied mostly in heterogenous small cohorts especially in asymptomatic patients.

Response: Thank you so much for pointing these issues about TCAR. Indeed, most papers were "produced" under supervision of the Silk Road medical company. So, that may be the reason why TCAR is currently not widely used among countries compared with TFCAS. However, CEA has been the standard surgical therapy of treating carotid artery stenosis for decades, as well as TFCAS. There are many RCTs comparing the safety and efficacy between CEA and TFCAS, and both treatment modalities have been widely adopted around the world. The new treatment of modality of TCAR may provide new perspective of treating carotid artery stenosis and arouse the interest of investigating the true value of this modality, as many papers were published recently. It is undeniable there are some shortcomings of these studies related to TCAR. Many studies were heterogenous small cohorts, but there are some recent studies with very large sample size. (e.g. ML Schermerhorn et al, JAMA, 2020, PMID 31846015; Hanaa Dakour-Aridi, J Vasc Surg, 2020, PMID: 32035784). Also, most of the patients were asymptomatic patients, and only one third of the patients were symptomatic. We are not sure whether TCAR will so widely used that could replace TFCAS someday, or at least as a counterpart of TFCAS or CEA in some countries. But the comparison among different modalities is really intriguing, with the hope to benefit patients with carotid artery stenosis. It is true there were some meta-analysis published before, but some new studies have been recently published afterwards (eg. Schermerhorn ML PMID 33248241; Hanaa Dakour-Aridi, PMID: 32035784; Kashyap VS, PMID 32222590). To be more objective, we intended to make comparison between TCAR and CEA by recruiting studies using propensity-matched analysis. (e.g. Yee et al, PMID 32222590; Kashyap et al, PMID 30622007). Additionally, we would like to analyze the outcomes beyond 30 days after surgery (perhaps only 1-year outcome is accessible in published papers before our formal searching procedure). We don't know what the final results will be, because we are not allowed to do the final analysis in advance when drafting this protocol according to requirements from PROSPERO. We would like to provide new clinical evidence, to point out these shortcomings and to provide deeper insight for future researches through this systematic review and meta-analysis.

Q: The authors spell out the potential advantages of TCAR which indeed may be true. The authors however then should also spell out the disadvantages such as combined surgery with stenting (and thus loosing the general advantages of a pure endovascular solution); higher risk of CNP with TCAR versus TFCAS; anatomical restrictions for TCAR (approx one third would not be suitable to apply TCAR due to short thick necks; and the need for at least eight minutes flow reversal which for sure will not be tolerated by a part of the patients undergoing carotid revascularization.

> Please read and implement the recent paper by Coelho A et al in Stroke 2020 PMID 32811389. The critical appraisal points out the issues existing with TCAR these days! This paper should be integrated and included in the Discussion section.

Response: Thank you very much for further pointing out these shortcomings of TCAR. We were intended to write these shortcomings of TCAR in details in the "Discussion" section of our later formal manuscript after the final results. We have added a brief version in the Discussion section in this protocol. "It is worth noting that despite many proposed advantages compared with TFCAS, TCAR may also have inherent disadvantages, such as anatomical restrictions from short thick necks and the need for at least 8 minutes of flow reversal, which will not be tolerated by some patients undergoing carotid revascularization. Many studies were performed under the supervision of the Silk Road Medical company." **(Page 9 , line 23-30)** Also, we have added the reference you recommended after reviewing it. Thanks.

Q: The authors refer to reference 8 and 12 for long term outcomes but these two papers did not study long term. In my view only the one year outcomes by Schermerhorn report on outcome beyond 30 days. There is noot yet any long term outcome available.

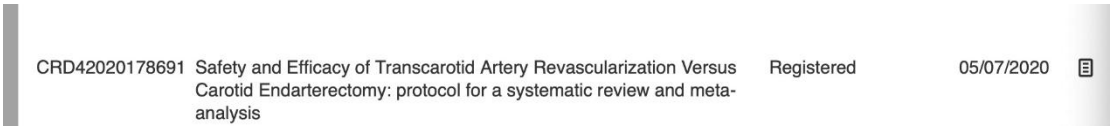
Response: Thank you for pointing out this issue. We have corrected our expression mistake as “Since the last meta-analysis, numerous new study outcomes beyond 30 days after surgery have been published, which warrant a repeat systematic review incorporating these results.” **(Page 4, line 54-58)** According to PROSPERO requirements, we cannot do the formal searching process when register this. But we agree with you long term results beyond 1 year may be lacking. We will check this during the search. We have also stated this issue in the “Discussion” section.

Reviewer: 2
Dr. Aram Baram, University of Sulaimani Faculty of Medical Sciences/School of Medicine

Comments to the Author:
Well organized paper needs minor linguistic revision.
Response: Really thanks for reviewing our article and giving us valuable advice. We have our paper language revised by Editage.

Reviewer: 3
Dr. Rita Pavasini, Azienda Ospedaliero-Universitaria S. Anna

Comments to the Author:
This is a protocol for a meta-analysis. Firstly Authors give a number of identification for Prospero registration but I cannot find the protocol in Prospero. Is this a temporary number? Next considering that the meta-analysis has been already proposed to Prospero for registration of the protocol I cannot understand the need to publish another protocol for the same meta-analysis. It seems to be a duplicate. Next I have several concerns about methods:
Response: Thank you for your comments. Basically, when performing meta-analysis, it is encouraged to perform protocol first. Like clinical trials, we are encouraged to register in the relative journals before start. On the one hand, people can know some area are studied by other researcher, on the other hand, this protocol can regulate the performance of researcher during this study. And from the protocol published in the BMJ OPEN, we find many had PROSPERO registration number. Registration on PROSPERO is like the first step to confirm the feasibility of research, then we write the formal protocol which is more concrete and comprehensive. The registered information of this review on Prospero registration is illustrated by the following image.



CRD42020178691	Safety and Efficacy of Transcarotid Artery Revascularization Versus Carotid Endarterectomy: protocol for a systematic review and meta-analysis	Registered	05/07/2020

Comment: The degree of I2 is not correct. Please see: BMJ 2003;327:557–560.
Response: Thanks for your valuable advice. We have re-checked and revised the degree of I2 based on the above article of BMJ, and the revised draft is as follows:
“We will assign the degree of low, moderate and high heterogeneity to the I^2statistic of 25%, 50%, and 75%.” **(Page 8, line 5-6)**

Comment: To perform meta-regression at least 10 studies are necessary. It is nor correct to choose a fixed or random effect on the base of heterogeneity. A random effect have to be used in case of studies with different characteristics (e.g. different follow-up, patients

included, different treatment included). Please see: Cooper H, Hedges VL, Valentine JC. Handbook of Research Synthesis and Meta-Analysis. Second Edition. 2009
Response: Thanks for your valuable suggestion. We have corrected the section of meta-regression according your advice, and the revised draft is as follows:
"Meta-regression analysis will be performed on the condition that there are at least 10 included studies." **(Page 8, line 42-43)**
In addition, we have corrected the use of random effect model according to Handbook of Research Synthesis and Meta-Analysis, and the revised draft is as follows:
"If the included studies are associated with different characteristics, such as differences in included patients, treatment, and follow-up, a random-effects model will be used. In contrast, a fixed effect model will be performed." **(Page 8, line 25-27)**

Comment: Please define the subgroup analysis planned.
Response: Thanks for your valuable advice. We have defined the subgroup analysis panned, and the revised draft is as follows:
"If there is moderate to substantial heterogeneity (I^2>50%) and sufficient studies (at least 10), subgroup analyses will be performed to examine the potential sources of heterogeneity, which will include characteristics of the patients, treatments, and clinical outcomes. For instance, one can expect a difference between symptomatic and asymptomatic participants, and we will therefore divide them into two groups and analyse the safety and efficacy outcomes of either group of participants." **(Page 8, line 31-39)**

Comment: For publication bias please assess also: Egger's intercept and Begg and Mazumdar's text.
Response: Thanks for your valuable suggestion. We have added Egger's intercept and Begg and Mazumdar's text in the section of publication bias assessment, the revised draft is as follows:
"In addition, Egger's intercept and Begg and Mazumdar's text will also be used to assess publication bias." **(Page 8, line 54-55)**

Comment: Considering that this are not case-control or cohort study I would suggest to use MINORS criteria and not Nos scale to assess quality in observational study included in this meta-analysis.
Response: Thanks for your valuable suggestion. We have changed MINORS criteria to assess quality for observational study. The revised draft is as follows:
"Cochrane Collaboration criteria and Methodological Index for Non-randomised Studies criteria will be performed to assess the bias risk of RCTs and observational studies, respectively.**" (Page 7, line 44-47)**

Comment: I would remove the empty flow diagram, it is a non-sense as well as the new-castle form empty.
Response: Thanks for your valuable advice. We have removed the empty flow diagram.

VERSION 2 – REVIEW

REVIEWER	Rita Pavasini UO Cardiologia Azienda Ospedaliero Universitaria di Ferrara Ferrara Italy
REVIEW RETURNED	10-Feb-2021

GENERAL COMMENTS	The author replied to all my questions. I have no other questions.