Reviewer's report

Title: Meta-analysis and meta-regression analysis of the associations between sex and the operative outcomes of carotid endarterectomy

Version: 3 Date: 1 April 2015

Reviewer: Michael Behnes

Reviewer's report:

The reviewer congratulates the authors to their effort of analyzing the gender differences during CEA by a comprehensive meta-analysis of the literature between 1980-2015.

Unfortunately, the authors chose to present their data in a very confusing manner.

Sometimes (abstract and introduction) they state that they only analysed case series or databases (meaning registries??), sometimes they talk about RCTs.

The authors present a bouquet of statistical approaches together with a more confusing and not straight forwarded kind of non-hierarchic data presentation. The reviewer misses a clear structure with clear and redundant headings (both in methods and results). The authors decided to jump from one aspect to another one, making it pretty difficult to follow their thoughts.

The reviewers respects the power of the authors datasets and encourages them to rewrite their manuscript taking into account the above and below described aspects and encourages them to apply the following critiques to almost every passage of their manuscript.

Their aim needs to be clear and hierarchical and utmost precise with short sentences, explanations (where useful), and clear redundant/structured headings (both equal in methods and results) to guarantee a much better readability and understanding in every passage of the manuscript (abstract, introduction, methods, results, discussion).

Was a statistician involved in the analysis? If so please include him either in the co-authors or acknowledgement as this improves the trust of your work.

In principal over the decades 1980 and 2015 optimal medical treatment has been changed tremendously (e.g. statins). Please discuss this change according to possible gender differences/effects in studies of different time points. Please rebuttal to the fact that analysing the studies e.g. decade-wise (e.g. 1980-1990, 1990-2000, 2000-2015) or any other kind of separation would be more useful.

Major revisions are required.

---
Specific Comments:

Please delete the use of "We" throughout the manuscript. Be neutral in wording. Better use: it was investigated, this study analysed...

Abstract:

Line 4: Please be more precise and correct to:
"Subgroup analyses from RCTs of CEA for both .... suggest less benefits in women compared to men due partly to higher age-independent peri-operative risk."

Line 6: The second sentence is not logic; please correct/replace by:
"However, a meta-analysis of case series and databases focussing on CEA-related gender differences has never been investigated."

Line 9: "We performed a systematic review of all publications reporting data on the association between sex and procedural risk of stroke and/or death following CEA from 1980 to 2015."

Is this true? didn’t the authors only included/analyse case series and databases, or did you review "all available publications" including RCTs? Please be precise, which kind of studies were included, please state here already. Please don’t use WE performed... be neutral and professional, stating "A systematic review of all.... was investigated".

Please add to abstracts methods the main parts of statistical assessment:
e.g. overall meta-analysis and specific sensitivity analysis... Mantel Haenszel method, Peto method for ORs, random effects model, intention to treat analysis, heterogeneity and bias (I2 stats, egger test).

Line 14: "..., the incidence of stroke and death in the male and female groups differed significantly (Peto OR, 1.162; 95% CI, 1.067-1.266; P=.001)." Please re-formulate this sentence precisely towards the gender group revealing the worse outcome (women or men?).

Line 17: "Whereas in sensitivity analyses the meta-analysis of case series with gender aspects as a secondary outcome showed a significantly increased risk for 30-day stroke and death in women compared to men 19 (Peto OR, 1.390; 95% CI, 1.148-1.684; P=.001), meta-analysis of databases (Peto OR, 20 1.025; 95% CI, 0.958-1.097; P=ß.474) and case series with gender related outcomes as a primary aim (Peto OR, 1.202; 95% CI, 0.925-1.561; P=0.168) demonstrated no increase in operative risk of stroke and death in women compared to men."

This is a much too long sentence for an abstract, please interrupt and make different sentences starting with concise adverbs, such as whereas/in
Abstract Line 26: "The effects of sex on the operative risk of CEA in published case series, and database analyses are not consistent with those observed in the RCTs. These results do not support the generalizability of the analyses of the overall effects of CEA from the 27 unselected study data to routine clinical practice."

The conclusion is much too complicated: please shorten and be precise (e.g.):

Metanlyses of case series and databases dealing with CEA reveal inconsistent results regarding gender differences related to CEA-procedure and should not be transferred into clinical practice.

---

Introduction:

Line 55: "...we performed a systematic review of all surgical case-series...."

What about databases?

Please list the number and kind of publications being used for the meta-analysis in the last frame of figure 1: Total number 58: n=xy case series; n=xy RCTs, n=xy databases.

Please always use clear headings/terms, which will be repeated everytime (such as case series, databases, RCTs) and make it easier to the reader to follow your presentation.

---

Statistical methods:

The formulation and style of the methods section is quite confusing. Please be extremely short and precise, and only if useful please explain shortly the advantage/indication of the tests being used. Please include a reference referring to each main statistical test, where each method has been explained and evaluated. The authors strongly need to reformulate this complete paragraph.

Please make clear paragraphs for the statistical methods being used to analyse the individual aspects. Currently its one long paragraph covering every aspect in a melting pot...

As an advice, adjust to the order in which your analyses have been undertaken, please be systematic: e.g. 1) overall analyses, 2) in depth/sensitivity etc, 3) proof of bias, 4) etc.... This methodological hierarchical steps need to afterwards transferred and recognized (by the same headings) in the results section, were the specific results are then presented clearly.

Please reformulate this important part of your manuscript (use clear and traceable headings and terms), as it will lead to support the power of your data presentation and understanding.

Please also shorten this part and be precise. Avoid "We", who else should have
done it???

Examples:
"We used the Peto method for odds ratios (ORs) [18, 19]. The Peto OR is viewed as the most optimal approach when there are relatively few events in individual trials."
The second sentence is inadequate, a better, easy and more precise formulation would be:
"We used the Peto method.... (ref 18/19) for studies with few events."

"Summary estimates of Peto ORs were obtained with a random effects model. A random-effects model was used, owing to the variability in baseline characteristics in each paper."
Better wording would be:
"To counterbalance random effects of the different studies, such as variabilities of baseline characteristics, the summary estimates of Peto ORs was applied."

---

Results:

Table 1:
The formatting of table 1 is pretty bad, the margin areas cannot be seen and are cut, thousands of numbers are too small, unreadable, and placed with even greater spaces in between. Please urgently renew this table, that it becomes readable and understandable.

What kind of publications do the 58 analyzed articles consist of: how many case series, RCTs, databases, registries???
please include this into the results beginning and figure 1 (see above).

Why did the authors chose to suddenly analyse studies after 2004 separately, no description is given in the methods...

Accordingly, subgroup analyses regarding CAD, DM, AHT, PAD are not mentioned in the methods section.

It might make sense to include further frames after the last of figure 1 dividing those 58 articles according to analysed outcomes: e.g. 30 day stroke (n=xx case series, etc), 30 day stroke rate (n=xxx...) and so one... Please adjust.

Presentation of results should accord to a clear hierarchical structure and should be in line to the structure of the revised statistical methods section! (see above).

The terms "primary aim" and "secondary aim" suddenly occur in the results section and have never been explained before.

The results are not presented in a concise manner, delete passage of minor
value. Please adjust to all above stated remarks and facilitate data presentation.

----

After a major revision, which is strongly recommended, a second revision will more focus on the scientific content.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.