Author’s response to reviews

Title: Direct oral anticoagulants in treatment of cerebral venous thrombosis: a systematic review protocol

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Author’s response to reviews:

SYSTEMATIC REVIEW PROTOCOL FOR DOAC USE IN CVT REVIEWER COMMENTS

Reviewer 1:

Thank you for your comments, we have made the following alterations:

Comment: 1.Background: page 4

Rationale:

For the adults with symptomatic CVT, the initial anticoagulation therapy is with subcutaneous low molecular weight heparin (LMWH) or intravenous heparin. After the acute phase of CVT, anticoagulation with vitamin K antagonist, warfarin recommended. The authors should mention this current treatment approach in their manuscript and clarify whether they are investigating the use of DOAC's in Acute CVT or post-acute phase, i.e., for long term CVT?

Response:

1. Background: the purpose of this review is to collate published patients who were treated with DOAC at any point during their CVT, acute and in the long-term phases. We have included this clarification to page 4 and included your suggestion to add details on current treatment recommendations to the rationale.
Comment: 2. Methods: Page 5

- Studies to be included must be written in either English or French? Why is this a criterion? Any reason the authors don't want to add Chinese, Japanese, Spanish and other major language studies in the review.

- Under information sources, authors need to update the manuscript to include the end of search date from September 2017 to current time (December 2018/January 2019).

Response: 2. We initially considered studies to be available in English or French due to our authors’ language proficiencies, but have revised to include studies in any language. We have also updated the beginning and end-dates of the search strategy to include the estimated date of acceptance of this protocol (Feb 2019)

Comment 3. Discussion:

The authors of the ongoing RCT (RE-SPECT CVT) from Europe (ClinicalTrials.gov number: NCT02913326) comparing dabigatran with dose-adjusted warfarin in 120 patients with CVT or dural sinus thrombosis for the prevention of recurrent venous thrombotic event are about to publish results by the end of this year, (1). Given the timing, do authors plan to include this RCT in their systematic review?

References:


Response: 3. Thank you for the suggestion. We are aware this trial will be published imminently and given the timing of our review we do plan on including the results from RE-SPECT CVT and have added a statement to our discussion to indicate this.

Reviewer #2:

Thank you for the review suggestions. We have clarified the aim and methods of our systematic review.

Comment: WHY?
The aim of the study is not clear. From the abstract it seems that the aim was to collect evidence of reported safety and efficacy of DOAC. One would expect that these evidence would be used for guidelines. From the introduction it seems that data would be used for standardising dosage etc. for prospective trial. From the method section it seems that data will be used for designing future studies, this sounds more like methodological designing (line 159). I don't see how all these information would help in designing future studies, as the main problem is the recruitment due to the rarity of the CVT.

In the introduction Heparin or VKA were also mentioned in details, and one would expect that these treatment modalities would also be compared.

Response:

- Specifically, the purpose is to review any patients that have been published being treated for CVT with DOAC, not to suggest standardized dosing. We do hope our results will help inform the design of future phase 3 trials, but the point on recruitment is well-taken. We have made edits to the sections highlighted by the reviewer in order to have a consistent objective statement throughout the manuscript: “This systematic review will collate evidence of reported safety and efficacy of direct oral anticoagulant therapy in cerebral venous thrombosis.”

- Our aim is not specifically to compare the efficacy of heparins or VKA with each other, nor with DOACS, as the majority of papers would likely be retrospective, case studies and series, it is instead to describe the literature for any use of DOAC in CVT and summarize safety concerns, and any efficacy data available. We hope that this will both assist with planning future RCTs, since if there are safety signals or efficacy metrics that are more useful than others, capturing that data on patients with this rare disease is important, as well as to provide clinicians a summary of the literature.

Comment: HOW?

The language restriction is a major limitation. The authors should include all relevant papers. Even other language papers do have an abstract and/or title in English.

DOAC was introduced in 2010. Why do the authors include papers from 1946? And why are papers from 2018 not included?

Which of the prisma checklist would be used?

Important details in the method sections are missing. E.g. inclusion criteria, outcomes, tools for bias, data synthesis. This is my major concern. It does not seems that the authors do have a plan in details.

Response:
- We have amended our study to include all languages as well as re-defined the search strategy to have more updated years of search: to February 2019.

- The methods section indicates PRISMA-P for the protocol and PRISMA checklist elements are all to be included, specifically

Line 98-106 (eligibility, inclusion / exclusion criteria)

Line 143-149 (outcome data)

Line 151-159 (risk of Bias)

- Please see Appendix 2 in the manuscript which has a copy of the PRISMA-P checklist and indicate line-numbers for all important details required for the Methods section, we have reviewed to ensure they have been included and are clarified.

Reviewer 3:

Comments:

I don't think that the protocol of systematic review would add much benefit on current ongoing trial to the level of practice changes. We have many meta-analyses that provide the safety/efficacy of DOACs over warfarin in particular population not included in the very first randomized trial release in early 2000.

Response:

Thank you for the review, we appreciate your concern regarding the utility of a protocol paper of a systematic review on DOAC treatment of CVT. It is true that randomized clinical trials are underway and our aim is to include the papers in the systematic review (the first will be published imminently), which would be helpful in making a strong argument, perhaps to the level of practice change. Furthermore we agree that there are excellent meta-analyses comparing DOACS to warfarin, however since CVT is so rare, as you acknowledge, specified summary of the evidence on this disease population being treated with CVT does not exist, hence guidelines have not recommended using DOAC to treat CVT, and therefore we aim to provide clinicians a summary of the available evidence (granted most reports would be of low level of evidence), so that they may make a more informed decision as to why the guidelines are hesitant at recommending DOACS that have some advantages compared to warfarin. We feel developing a sound protocol prior to performing such a systematic review is a necessary first step to collating such evidence.
Reviewer #4:

Comments:

There are misused and misspelled words as below:

1. "high level studies" should be "high-level studies"

2. "Comparison of the Efficacy of Rivroxaban to Coumadin (Warfarin)" Rivroxaban is misspelled

3. "who was treated with a direct oral anticoagulant" "was" should be "were" because subject for this sentence are "patients"

Response:

Thank you kindly for the reviews,

1. Correction made

2. The Clinical Trials Identifier spelt “Rivroxaban” this way, we acknowledge it is misspelled but cannot correct as this is the official title published online.

3. Correction made