

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Direct oral anticoagulants in treatment of cerebral venous thrombosis: systematic review
AUTHORS	Bose, Gauruv; Graveline, Justin; Yogendrakumar, Vignan; Shorr, Risa; Fergusson, Dean; Le Gal, Gregoire; Coutinho, Jonathan; Mendonca, Marcelo; Viana-Baptista, Miguel; Nagel, Simon; Dowlatshahi, Dar

VERSION 1 – REVIEW

REVIEWER	Benjamin Tan Singapore
REVIEW RETURNED	03-Jun-2020

GENERAL COMMENTS	<p>This is a timely systematic review performed by the authors and adds to the existing evidence in an evolving field.</p> <p>Major comments:</p> <ul style="list-style-type: none">• When evaluating the outcome of mRS in the results, the authors need to report consistently when the mRS was assessed in the relevant study• In the discussion, the authors should discuss how DOAC anticoagulation compares with current treatment guidelines in terms of efficacy• The authors should make an attempt to do a comparison between specific DOACs, especially since the authors stated above that the results are largely from Dabigatran, followed by Rivaroxaban• A main limitation of this report is that it does not have a comparative arm in standard anticoagulation. This should be stated explicitly in the limitations• In the discussion, the authors should compare how their current report adds value or differs from a recently published systematic review: Lee GK, et al. Comparing the efficacy and safety of direct oral anticoagulants with vitamin K antagonist in cerebral venous thrombosis. Journal of thrombosis and thrombolysis. 2020 Apr 11.
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REVIEWER	Gili Kenet Sheba Medical Center, Twel Hashomer, Israel
REVIEW RETURNED	14-Jul-2020

GENERAL COMMENTS	<p>CSVT is a rare disease that may result in severe morbidity and current use of DOAC among patients is still limited. This systematic review addresses all studies with available follow up results , using dabigatran (93 patients) , rivaroxaban (n=85) or apixaban (n=10 patients) and providing data of safety and refficacy. Authors acknowledge the linitations of their review and the paper is well written.</p>
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	<p>Some issue deserve attention :</p> <p>1- Authors are advised to carefully look into studies included/ excluded as some are missing from their list...please update and include as it fits criteria....examples: Direct oral anticoagulants in the treatment of cerebral venous sinus thrombosis: a single institution's experience. Rusin G, Wypasek E, Papuga-Szela E, Żuk J, Undas A. <i>Neurol Neurochir Pol.</i> 2019;53(5):384-387. doi: 10.5603/PJNNS.a2019.0037. Epub 2019 Aug 27. There is also at least one case report of Edoxaban care (not sure if this is an English paper)</p> <p>2- While discussing the relevant DOAC studies it would be nice if authors could state the exact length of follow up and estimate the rate of outcomes/ complications per patient years follow up (of course limitations of lumping up studies should be acknowledged)</p> <p>3-Authors mention Einstein- JR study- kindly briefly discuss the different nature and history of pediatric CSVT (mostly triggered by trauma or infection)- therefore unsure if results could be elaborated upon</p> <p>4- references appear twice and are numbered rather than named as recommended by BJH, please reformat them</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Benjamin Tan

Institution and Country: Singapore

Competing interests 1: None declared

Comments to the Author

This is a timely systematic review performed by the authors and adds to the existing evidence in an evolving field.

Major comments:

- When evaluating the outcome of mRS in the results, the authors need to report consistently when the mRS was assessed in the relevant study

Response: Thank you for the suggestion, we have reviewed the results section to include mRS, when reported by the study, as well as relevant statistics (risk ratio)

- In the discussion, the authors should discuss how DOAC anticoagulation compares with current treatment guidelines in terms of efficacy

Response: we have included section headers to the discussion, one of which is on DOAC compared to current treatment in terms of efficacy and safety

- The authors should make an attempt to do a comparison between specific DOACs, especially since the authors stated above that the results are largely from Dabigatran, followed by Rivaroxaban
- Response: We have created a specific discussion section to elaborate on the differences, and limitations, of the study outcomes of each DOAC compared with each other.

- A main limitation of this report is that it does not have a comparative arm in standard anticoagulation. This should be stated explicitly in the limitations

Response: We updated the literature search as requested and given new data we were able to include data of a comparison with standard therapy when available, however since no comparison between DOACs was possible we have outlined this explicitly as a main limitation.

- In the discussion, the authors should compare how their current report adds value or differs from a recently published systematic review: Lee GK, et al. Comparing the efficacy and safety of direct oral anticoagulants with vitamin K antagonist in cerebral venous thrombosis. *Journal of thrombosis and*

thrombolysis. 2020 Apr 11.

Response: We have reviewed the suggested new publication of DOACs compared to vitamin K antagonist and in a new section of a discussion "Direct oral anticoagulants versus standard of care" we have compared the findings and note that our search is updated with two new cohorts, as well as we were able to contact authors for patient level data. The purpose of our review was to report the various DOACs compared with each other for CVT and have created an additional specific discussion section on this.

Reviewer: 2

Reviewer Name: Gili Kenet

Institution and Country: Sheba Medical Center, Twel Hashomer, Israel

Competing interests : None

Comments to the Author

CSVT is a rare disease that may result in severe morbidity and current use of DOAC among patients is still limited. This systematic review addresses all studies with available follow up results, using dabigatran (93 patients) , rivaroxaban (n=85) or apixaban (n=10 patients) and providing data of safety and efficacy. Authors acknowledge the limitations of their review and the paper is well written.

Some issue deserve attention:

1- Authors are advised to carefully look into studies included/ excluded as some are missing from their list...please update and include as it fits criteria....examples: Direct oral anticoagulants in the treatment of cerebral venous sinus thrombosis: a single institution's experience. Rusin G, Wypasek E, Papuga-Szela E, Żuk J, Undas A. *Neurol Neurochir Pol.* 2019;53(5):384-387. doi: 10.5603/PJNNS.a2019.0037. Epub 2019 Aug 27. There is also at least one case report of Edoxaban care (not sure if this is an English paper)

Response: The search date is now updated to Nov. 18, 2020, and an additional 11 studies were added, including 5 edoxaban reports and the case series by Rusin et al you reference

2- While discussing the relevant DOAC studies it would be nice if authors could state the exact length of follow up and estimate the rate of outcomes/ complications per patient years follow up (of course limitations of lumping up studies should be acknowledged)

Response: This is an excellent point and major limitation of including all reported studies, the follow-up duration is not explicitly stated in the articles. We have updated our Table 2 to include the treatment duration, beyond this information if a specific study did outline the follow-up duration or at least the duration from treatment to event (death, ICH, end of follow-up) we included this information.

3-Authors mention Einsten- JR study- kindly briefly discuss the different nature and history of pediatric CSVT (mostly triggered by trauma or infection)- therefore unsure if results could be elaborated upon

Response: We have included more information on this recently published study, outlining that they did not conduct subgroup outcome assessment for CVT so direct conclusions could not be drawn.

4- references appear twice and are numbered rather than named as recommended by BJH, please reformat them

Response: We have reviewed the BMJ Open journal guidelines and re-formatted the citations

FORMATTING AMENDMENTS

Required amendments will be listed here; please include these changes in your revised version:

- Please spell out acronyms when first mentioned (ICH).

Response: We have reviewed the paper for acronyms and spelled out at first instance (ICH, RCT)

- Please include any relevant statistical results in the abstract results section.

Response: We have updated the search, as such there are relevant statistical results that can be drawn and hence abstract is updated.

- Please revise your Strengths and Limitations section to include limitations which relate specifically to the methods in your study.

Response: We have taken out the general statements and results of our Summary section and only included specifics of the Methods.

- Please explain why a meta-analysis was not conducted here

Response: Since no comparison studies of CVST between different DOACs has been performed, studies are heterogenous and for the most part retrospective, a formal meta-analysis comparing DOACs was not possible. However, we have revised the literature review to include a comparison against standard treatment (LMWH, UFH or warfarin) and could perform meta-analysis on this. We also describe the overall differences between the published reports of each DOAC in the discussion.

- Along with your revised manuscript, please include a copy of the SwiM checklist indicating the page/line numbers of your manuscript where the relevant information can be found (<https://www.equator-network.org/reporting-guidelines/synthesis-without-meta-analysis-swim-in-systematic-reviews-reporting-guideline/>).

Response: We have updated the PRISMA checklist given the updated search strategy and included the SWIM guidelines and checklist, updating the methods as needed.

- Side headings in the Discussion would help guide the reader

Response: As requested we have included discussion headers. Due to the updated search and analysis, as well as the request to comment on the recently published study by Lee et al, we have reformatted the discussion. The sections are "Outcomes of DOAC compared with standard therapy, Comparison between different DOAC, Limitations, Unanswered questions and future research".

Further Questions from the Editors:

- Search is old (Sept 2019) Can you update it?

Response: We have updated the search to the revision date – Nov 18, 2020.

- In the text please explain what the scores in an mRS mean.

Response: In the methods, subsection Data Items (page 6 p1), we have outlined the key segments of the mRS as well as included an original citation, as well as included mRS definition beside the relevant text (p8 & p11).

- Numbers in the headers of Table 2 don't add up to n=188

Response: We have updated the search and thus revised table two, the total now adds up to the new n=273 for DOAC patients, and n=315 for standard therapy patients.

VERSION 2 – REVIEW

REVIEWER	Benjamin Tan National University of Singapore, Singapore
REVIEW RETURNED	09-Dec-2020

GENERAL COMMENTS	The authors have made significant improvements to the manuscript.
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REVIEWER	Gili and Gabriel Kenet Sheba medical center, Tel Hashomer, ISRAEL
REVIEW RETURNED	24-Dec-2020

GENERAL COMMENTS	Well revised!
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