

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Quality Evaluation of Case Series Describing Four-Factor Prothrombin Complex Concentrate in Oral Factor Xa Inhibitor-Associated Bleeding: A Systematic Review
AUTHORS	Costa, Olivia; Baker, William; Roman-Morillo, Yuani; McNeil-Posey, Kelly; Lovelace, Belinda; White, Michael; Coleman, Craig

VERSION 1 – REVIEW

REVIEWER	Jing Tao Memorial Sloan Kettering Cancer Center, United States
REVIEW RETURNED	01-Jul-2020

GENERAL COMMENTS	Interesting review on the overall insufficient reporting of 4PCC use in FXai related bleeding that has now led to low to moderate recommendations for its use as a reversal agent. Can the authors provide information of 4PCC dosing. This may add strength to the argument that evidence is poor especially given the non-standardization of 4PCC dosing.
-------------------------	---

REVIEWER	Tyree Kiser, PharmD, FCCM, FCCP, BCPS University of Colorado Anschutz Medical Campus Aurora, Colorado USA Dr. Kiser's institution has received investigator initiated grant funding from CSL Behring and Portola Pharmaceuticals.
REVIEW RETURNED	10-Aug-2020

GENERAL COMMENTS	<p>The authors present a systematic review of data evaluating the use of 4F-PCC for DOAC reversal (anti-Xa specific agents). The methodology appears sound. The tool seems reasonable, even though not fully validated. A few specific comments from me:</p> <p>I don't have concerns about the design and methods used. However, I am not certain that conducting a systematic review on "case series" is very useful from a scientific standpoint. Methodology, reporting quality, and outcome definitions are going to be poor by definition. Space limits for these publications are usually limited by the category of journal submission and do not allow for elaborate data dumping into the manuscript. Data is going to be heterogeneous. Outcomes are usually adjudicated retrospectively with missing data. Any data from these case series, even when combined, are at best hypothesis generating for future well controlled studies. Maybe worth an expansion in the discussion.</p> <p>The oFXai abbreviation doesn't work very well with the font selected, because the I looks like a lower case I. Consider a</p>
-------------------------	--

	<p>different abbreviation. Maybe D-FXa-OAC; whatever you feel appropriate or the journal needs to use a different font so that the capital i is clear.</p> <p>I think table 1 can be an eTable, the impact factor and journal type is less important with a case series - most top tier journals will not even take case reports/series, so this finding is not super important as a first table.</p> <p>Although not your objective, I think that most people will read this title and be looking for the actual outcomes and results combined with visual forest plots, etc. to come to some conclusion regarding the effectiveness and safety of 4F-PCC. Consider adjusting the title to clearly state that this study only looks at the quality of evidence and not whether this medication is useful or safe for DOAC bleeding.</p> <p>As mentioned, the actual outcome data information is notably missing. Without it, I don't think that many readers will find this paper useful. They have already made up their minds about the quality of the evidence and whether they are willing to use 4F-PCC rather than andexanet alfa.</p>
--	---

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Jing Tao

Institution and Country: Memorial Sloan Kettering Cancer Center, United States

Please state any competing interests or state 'None declared': none

Please leave your comments for the authors below

Interesting review on the overall insufficient reporting of 4PCC use in FXai related bleeding that has now led to low to moderate recommendations for its use as a reversal agent.

Thank you.

Can the authors provide information of 4PCC dosing. This may add strength to the argument that evidence is poor especially given the non-standardization of 4PCC dosing.

We have now added data to the paper regarding 4F-PCC dosing. Of note, "The dose of 4F-PCC was reported in the majority of case series, however, the dosage was inconsistent between studies ranging from 25 to 50 U/kg."

Reviewer: 2

Reviewer Name: Tyree Kiser

Institution and Country: University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

Please state any competing interests or state 'None declared': Dr. Kiser's institution has received investigator initiated grant funding from CSL Behring and Portola Pharmaceuticals.

Please leave your comments for the authors below

The authors present a systematic review of data evaluating the use of 4F-PCC for DOAC reversal

(anti-Xa specific agents). The methodology appears sound. The tool seems reasonable, even though not fully validated.

Thank you for your positive review of the manuscript.

A few specific comments from me:

I don't have concerns about the design and methods used. However, I am not certain that conducting a systematic review on "case series" is very useful from a scientific standpoint. Methodology, reporting quality, and outcome definitions are going to be poor by definition. Space limits for these publications are usually limited by the category of journal submission and do not allow for elaborate data dumping into the manuscript. Data is going to be heterogeneous. Outcomes are usually adjudicated retrospectively with missing data. Any data from these case series, even when combined, are at best hypothesis generating for future well controlled studies. Maybe worth an expansion in the discussion.

We believe that within the general "family" of case series, there can be important difference in (relative) quality. Moreover, in the absence of study designs with greater internal validity, it is still valuable to detail the relative methodological and reporting quality. We have now added a sentence to the discussion to this affect: "This tool may be especially useful in the absence of study designs with greater internal validity in order to evaluate the relative quality amongst case series"

We have added text to the conclusion as recommended by the reviewer, stating: "Any data from these case series, are at best, hypothesis generating for future prospective, controlled studies."

The oFXaI abbreviation doesn't work very well with the font selected, because the I looks like a lower case l. Consider a different abbreviation. Maybe D-FXa-OAC; whatever you feel appropriate or the journal needs to use a different font so that the capital i is clear.

We have now changed the font from Corbel to Times New Roman to make the lettering clearer. We have also changed the wording from "oFXaI" to "oFXa inhibitor" throughout.

I think table 1 can be an eTable, the impact factor and journal type is less important with a case series - most top tier journals will not even take case reports/series, so this finding is not super important as a first table.

We have now moved table one to be eTable 1 and adjusted in-text reference to the table accordingly.

Although not your objective, I think that most people will read this title and be looking for the actual outcomes and results combined with visual forest plots, etc. to come to some conclusion regarding the effectiveness and safety of 4F-PCC. Consider adjusting the title to clearly state that this study only looks at the quality of evidence and not whether this medication is useful or safe for DOAC bleeding.

We have revised our title to "Quality Evaluation of Case Series Describing Four-Factor Prothrombin Complex Concentrate in Oral Factor Xa Inhibitor-Associated Bleeding: A Systematic Review" for clarity (but to also keep with from the PRISMA statement).

As mentioned, the actual outcome data information is notably missing. Without it, I don't think that many readers will find this paper useful. They have already made up their minds about the quality of the evidence and whether they are willing to use 4F-PCC rather than andexanet alfa.

The goal of this paper was to discuss the methodological quality/flaws associated with case series of 4FPCC to manage oFXa inhibitor associated bleeds. We feel the addition of outcomes data (of varying quality) to the paper would only be a distraction from our goal (a studies quality should be viewed blindly from its actual results/findings or bias in interpretation becomes more likely). Readers may or may not have made up their minds regarding the effectiveness of 4FPCC in this setting. This is intended to aid them in objectively assessing the available data.