

Nieuwegein, April 4, 2023

Dear prof. dr. A.S. Tarnawski,

We would like to thank you and the reviewers for the valuable time and considerate feedback on our manuscript **“Current opinions on the use of therapeutic anticoagulation for splanchnic vein thrombosis in acute pancreatitis: a survey and case-vignette study in the Netherlands”**. We highly value the comments and questions and feel that these have improved our manuscript. We have uploaded the revised manuscript using track changes and hereby provide a detailed point by point response.

We thank you for your kind consideration.

Yours sincerely, on behalf of all authors,

Noor J. Sissingh, *MD*

J. Sven D. Mieog, *MD, PhD*

Dutch Pancreatitis Study Group – St. Antonius Hospital

Koekoekslaan 1, 3420 EM Nieuwegein, The Netherlands, Tel: +31 88 320 7053; Fax: +31 88 3207070

Revisions

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: I review the article titled "Therapeutic anticoagulation for splanchnic vein thrombosis in acute pancreatitis: a national survey and case-vignette study". In this study, the authors present the results of a nationwide survey of pancreatologist about the anticoagulation use in splanchnic vein thrombosis in acute pancreatitis patients, they also included case studies and related questions.

- 1 Title. Does the title reflect the main subject/hypothesis of the manuscript? - I think the title could be changed to reflect the aim of the study or the conclusion, right now it is not so definite. E.g. Use of anticoagulation for splanchnic vein thrombosis in AP..., or Therapeutic anticoagulation with LWMH is preferred in splanchnic vein thrombosis in AP... Consider changing it.
- 2 Abstract. Does the abstract summarize and reflect the work described in the manuscript? It is well written and contains the relevant points.
- 3 Key Words. Do the key words reflect the focus of the manuscript? Yes, they are ok.
- 4 Background. Does the manuscript adequately describe the background, present status and significance of the study? - Length and content is adequate.
- 5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? YES. - DPSG and DPCG abbreviations should be mentioned first in brackets after the organization names. - statistical analysis: IBM SPSS should be cited in longer form as recommended here: <https://www.ibm.com/support/pages/how-cite-ibm-spss-statistics-or-earlier-versions-spss>
- 6 Results. Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field? The results are presented clearly, the tables are well structured and easily followed.
- 7 Discussion. Does the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practice sufficiently? - The discussion section is clearly presented and appropriate.
- 8 Illustrations and tables. Are the figures, diagrams, and tables sufficient, good quality and appropriately illustrative, with labeling of figures using arrows, asterisks, etc, and are the legends adequate and accurately reflective of the images/illustrations shown? - Figures and tables are ok.
- 9 Biostatistics. Does the manuscript meet the requirements of biostatistics? Simple descriptive statistics were used which is appropriate for this survey.
- 10 Units. Does the manuscript meet the requirements of use of SI units? Ok.
- 11 References. Does the manuscript appropriately cite the latest, important and authoritative references in the Introduction and Discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references? They referenced their previous meta-analysis of the same topic which is important.
- 12 Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate? I suggest checking the manuscript for some typos (e.g. noncirrothic) British and American English

should not be mixed (e.g. oesophageal vs. summarized) The overall English language quality is good.

13 Research methods and reporting. Authors should have prepared their manuscripts according to BPG's standards for manuscript type and the appropriate topically-relevant category, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. For (6) Letters to the Editor, the author(s) should have prepared the manuscript according to the appropriate research methods and reporting. Letters to the Editor will be critically evaluated and only letters with new important original or complementary information should be considered for publication. A Letter to the Editor that only recapitulates information published in the article(s) and states that more studies are needed is not acceptable? STROBE is not recommended in this study type to my knowlegde.

14 Ethics statements. For all manuscripts involving human studies and/or animal experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. Did the manuscript meet the requirements of ethics? Ethical review was waived and it is appropriate in this study type.

Response to Reviewer #1:

We thank the reviewer for the critical assessment of our manuscript. A point-by-point response is given for comment 1, 5 and 12. Regarding the other comments, we thank the reviewer for his or her compliments.

Response to comment 1. We agree with the reviewer's suggestion to change the title and have changed it into: Current opinions on the use of therapeutic anticoagulation for splanchnic vein thrombosis in acute pancreatitis: a survey and case-vignette study in the Netherlands.

Response to comment 5. We thank the reviewer for pointing this out. We now present the spelled-out version and the abbreviation of DPSG and DPCG upon first use (page 6). We have also inserted the SPSS citation following the recommendations of IBM (page 8).

Response to comment 12. We thank the reviewer for the grammatical correction and have changed noncirrothic into noncirrhotic (page 13). As suggested, we have also screened our manuscript for consistent use of British English spelling, and if necessary, rewritten the text (e.g. necrotizing into necrotising - page 7, randomized into randomised – page 13).

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: This article is well written article which indicate that therapeutic anticoagulation for splanchnic vein thrombosis seem to be recommended by the pancreatologists through a national survey and case-vignette study. Since the recent result of meta analysis and guideline did not support, many cases were benefit from the anticoagulation therapy. "a deeper understanding of the pathophysiology and natural course of splanchnic vein thrombosis secondary to acute pancreatitis would allow us to clarify the therapeutic role of anticoagulation." Expect the data analysis, expert consensus maybe a good guide to the clinic and basic research.

Response to Reviewer #2:

We thank the Reviewer for these compliments, and we highly value the time spent reviewing our manuscript.

Reviewer #3:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors:

1. "This proportion of untreated patients is substantially higher.." If the study was targeting the reasons for lesser usage, the questionnaire could have addressed the same
2. "Based on the available literature, it remains unclear whether therapeutic anticoagulation is associated with higher rates of bleeding". The statement is negated by the ref(no 18 -"therapeutic anticoagulation resulted in recanalization of the involved vessels without significantly increasing the risk of bleeding complications")
3. The possible risks / complications could have been quantified to assess the rationale behind the "nonprescribing trend"
4. The legend description could include more details as in the manuscript
5. Factors like ICU stay / comorbidities with potential influence on the decision making could have been explored

Response to Reviewer #3:

We highly value the useful contribution of the reviewer, which has led to considerable improvements of our manuscript.

Response to comment 1 and 3. We agree with the reviewer that more information about the 'nonprescribing trend' would have been relevant. We have therefore addressed this as a limitation in the discussion section of our revised manuscript (page 15):

"Finally, the rationale behind the 'nonprescribing trend' was not assessed adequately, which could be a focus for future research."

Response to comment 2. Thank you for the opportunity to clarify this statement. Indeed, this meta-analysis (ref. no. 18)¹ reported no association between therapeutic anticoagulation and bleeding. However, we respectfully point out that these results are based on low quality data, as we previously described in our meta-analysis². Both meta-analyses conducted a comparable literature search until December 2020 and consequently included a similar set of retrospective cohort studies, which were of limited quality. For this reason, we believe that the current available literature could not provide such objective conclusions yet.

Response to comment 4. According to the suggestion of the reviewer, we provided additional details in the figure legend (page 26).

Response to comment 5. We thank the reviewer for this valuable comment as we agree that both patient and disease-related factors may have an impact on decision-making. We have chosen to leave out specifics regarding the current condition of the patient to not further complicate the conjugative analysis of the case-vignette study, thereby focussing on the impact of pancreatitis-specific conditions on the use of therapeutic anticoagulation. We have revised our discussion section to put more emphasis to this limitation (page 15):

“Second, the clinical presentation of SVT is very heterogeneous, as well as the patient characteristics and clinical disease course among acute pancreatitis patients, which influences current decision making.”

References

2. Chandan S, Buddam A, Khan SR, Mohan BP, Ramai D, Bilal M, Dhindsa B, Bhogal N, Kassab LL, Goyal H, Perisetti A, Facciorusso A, Adler DG. Use of therapeutic anticoagulation in splanchnic vein thrombosis associated with acute pancreatitis: a systematic review and meta-analysis. *Ann Gastroenterol*. 2021 Nov-Dec;34(6):862-871.
1. Sissingh NJ, Groen JV, Koole D, Klok FA, Boekestijn B, Bollen TL, van Santvoort HC, Verdonk RC, Bonsing BA, van Eijck CHJ, van Hooft JE, Mieog JSD; Dutch Pancreatitis Study Group. Therapeutic anticoagulation for splanchnic vein thrombosis in acute pancreatitis: A systematic review and meta-analysis. *Pancreatology*. 2022 Mar;22(2):235-243.