

Title: Comparative Efficacy and Safety of Adenosine and Regadenoson for Assessment of Fractional Flow Reserve: A Systematic Review and Meta-Analysis

Reviewers' comments:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Dear authors, Dear authors, The paper represents the results of the systematic review and meta-analysis focused on comparative efficacy and safety of adenosine and regadenoson for assessment of fractional flow reserve. The article is written with the good English-speaking adduction of the arguments. The article is sufficiently novel and very interesting to warrant publication. All the key elements are presented and described clearly. The most discussable options in the article are:

Author Response: We appreciate the comments.

Questions:

1. Would you please kindly correct all your typos and grammar errors throughout the manuscript.

Author Response: We appreciate the reviewer's suggestion. We have thoroughly reviewed the manuscript for any grammatical errors.

2. The objective of the meta-analysis is missing at the end of Introduction.

Author Response: We appreciate the comment. We have now amended the introduction to further clarify the objective of this study.

Introduction, page 5, line 69

Herein, we systematically reviewed published literature comparing the efficacy of regadenoson to adenosine for achieving maximal hyperemia, the correlation in FFR measurements, and the adverse effects to ascertain the safer and more cost-effective hyperemic agent.

3. The statistical power must be clearly provided.

Author Response: We appreciate the reviewer's comment. In our investigation, we conducted extensive sensitivity analyses where exclusionary analysis based on study characteristics yielded similar results.

Power calculation is of importance if results show that a moderator is not associated with an effect, however, in our study, significant p-values and cumulative correlation coefficient negate the need for power analysis.

4. The bias should be characterized

Author Response: We appreciate the comment. We have further elaborated potential bias in our study.

Results, page 7, line 132

Pooled odds for any adverse effect were significantly higher for patients after administration of adenosine, than after receiving regadenoson (OR 2.39, 95% CI 1.22 – 4.67; $p=0.01$) (Figure 3B). There was no evident heterogeneity among included studies with I^2 estimated at 0%. There was no evidence of dissemination bias on visual inspection of the funnel plot and Begg's test.

Limitations and Strengths, page 11, line 223

Lastly, in an attempt to conduct the analysis in consistency with PRISMA guidelines, this study may be subject to publication bias (30). Inherently however, our investigation had limited risk of residual bias since all included studies had a prospective design with patients receiving both hyperemic agents.

Re-reviewers' comments:

Questions:

Dear authors, Thank you for your substantial efforts to improve the article.

Author Response: Thanks for your comments.

Editors' comments:

(1) Science editor:

1 Scientific quality: The manuscript describes a meta-analysis of the comparative efficacy and safety of adenosine and regadenoson for assessment of fractional flow reserve. The topic is

within the scope of the WJC. (1) Classification: Grade B; (2) Summary of the Peer-Review Report: The paper represents the results of the systematic review and meta-analysis focused on comparative efficacy and safety of adenosine and regadenoson for assessment of fractional flow reserve. The questions raised by the reviewers should be answered; (3) Format: There are 2 tables and 3 figures; (4) References: A total of 30 references are cited, including 1 reference published in the last 3 years; (5) Self-cited references: There is no self-cited reference; and (6) References recommendations: The authors have the right to refuse to cite improper references recommended by the peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately.

2 Language evaluation: Classification: Grade B.

3 Academic norms and rules: The authors provided the Biostatistics Review Certificate. No academic misconduct was found in the Bing search.

4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJC.

5 Issues raised:

1. The "Author Contributions" section is missing. Please provide the author contributions;

Author Response: We have now added the author contributions to the manuscript.

Author Contributions, page 2, line 18

Gauravpal Singh Gill and Akshaya Gadre independently conducted literature search for studies to be included in the final analysis. All authors discussed disagreement in included studies. Gauravpal Singh Gill prepared the first manuscript draft, tables and figures, conducted statistical analysis, and contributed to major revision. Akshaya Gadre contributed to revisions. Arun Kanmanthareddy conceptualized the study, performed statistical analysis, supervised methodology, made substantial changes to the manuscript, and contributed to major revision

2. The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor

Author Response: Original figure documents have now been attached. PowerPoint files with editable text have been added.

3. PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout

Author Response: We have now added the PMID and the DOI to reference list. All authors in the reference have now been listed as well.

4. The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text.

Author Response: Article highlight section has now been added

Highlights, page 17

- *There is excellent correlation between FFR calculations using adenosine, and an alternate hyperemic agent, regadenoson.*
- *Time to FFR period is shorter with regadenoson by 34 seconds*
- *Odds of adverse effects are higher with adenosine, although effects are transient with both agents*

6 Re-Review: Required.

7 Recommendation: Conditional acceptance.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Cardiology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

Author Response: PowerPoint file with decomposable figures has been added

Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden.

Author Response: We have reformatted tables 1 and 2 per three-line format.

The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Author Response: Tables 1 and 2 have been updated per journal recommendations.