Looking behind the curtain of PLATO: the impact of regulatory agency reviews and the clinical study report on risk of bias assessments

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Background

- Clinical study reports (CSRs) are extensive documents that manufacturers include in their submission to regulatory agencies for the market approval of their drugs.
- Examples of past studies that found differences between CSRs and published articles include Restoring Study 329 and the Cochrane neuraminidase inhibitors review by Jefferson *et al*.
- Following the approval of new drugs, regulatory agencies such as Health Canada, the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA) may provide a summary of their review on their website.
- A comparison of the regulatory agency reviews, the CSR and the published trial using the Cochrane Risk of Bias (ROB) tool to assess for internal validity has not been done in the past.

Objective

- To compare a published trial (ticagrelor versus clopidogrel in patients with acute coronary syndromes; PLATO) to its CSR and to assessments by regulatory agencies using the Cochrane Risk of Bias (ROB) tool.

Methods – Figure 1: Data extraction process

Data source and order of data extraction

PLATO (including its appendix and published protocol)

Health Canada's Summary Basis of Decision (SBD)

FDA's Medical Review

EMA's Public Assessment Report (PAR) of ticagrelor 90 mg

CSR and selected appendix as provided by EMA

Data Extraction:
Applying the Cochrane ROB tool across 7 domains and 9 pre-specified outcomes of interest by two reviewers

Data Reconciliation:
Disagreements resolved by a third reviewer

Data Analysis:
Descriptive analysis of the impact of each reviewed document on ROB assessments

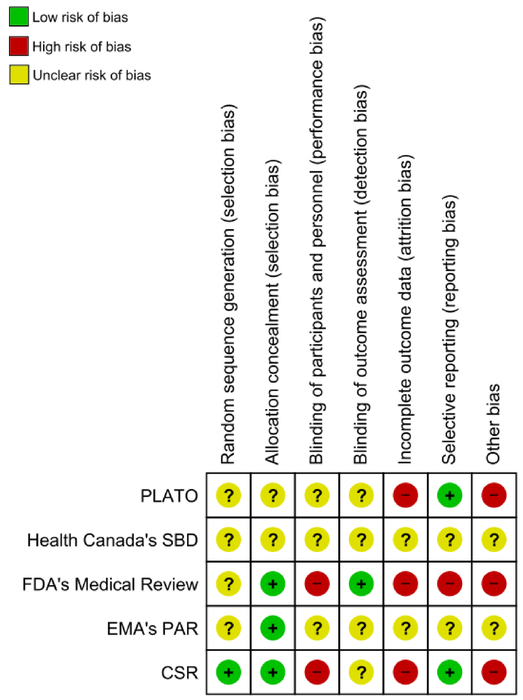

Table 1: Risk of bias assessments

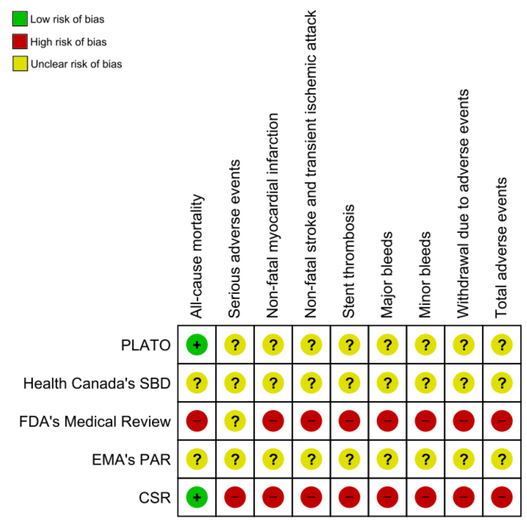

Table 2: Risk of bias assessments of outcomes

Results

Comparisons of ROB classifications (Table 1):

- Of the four unclear ROB assessments based on the published trial:
  - Health Canada's SBD: none were reclassified to low or high risk.
  - FDA's Medical Review: two were reclassified as low ROB and one reclassified as high ROB. Selective reporting was reclassified from low ROB to high ROB.
  - EMA's PAR: one was reclassified as low ROB.
  - CSR: two were reclassified as low ROB, one reclassified as high ROB.

Narrative summary of findings:

- FDA's Medical review provided extensive examples of:
  - Unblinding
  - Transcription and data collection error
  - Lack of submission of some data for adjudication
  - Methodological flaws in data collection for non-procedural bleeding events
- From the CSR, we noted that 19% of patients had missing data which led to a high ROB assessment for all outcomes with the exception of all-cause mortality.
- Noteworthy differences between the FDA review and the CSR:
  - Random sequence generation: The CSR described how the randomization codes were generated which was not described in the FDA review.
  - Selective reporting: FDA review noted inappropriate omission of certain outcomes based on clinical report forms. This could not be recognized from the CSR body which did not include these forms.

Limitations

- Assessments made were based on the CSR body and parts of Appendix 12.1.1 – Protocol and Protocol Amendments due to EMA's time constraint in providing all appendix material.
- Inexperience in assessing the CSR body which contained 419 pages.

Conclusions

- The published PLATO article may be an incomplete representation of the trial.
- While the CSR body and the FDA Medical review offered more information to allow for most ROB assessments, the FDA Medical review identified methodological limitations of PLATO which were not included in the CSR body.