Dear Dr. Prieto-Alhambra

Thank you for sending us your revised manuscript. Our statistical editor has reviewed it and provided a stats report as below. We hope very much that you will be willing and able to provide a point-to-point response and revise your paper accordingly.

When you return your revised manuscript, please note that The BMJ requires an ORCID ID for corresponding authors of all research articles. If you do not have an ORCID ID, registration is free and takes a matter of seconds.

Yours sincerely,

Di Wang
Clinical Editor, the BMJ

T: 010 6410 0685
E: dwang@bmj.com
W: bmj.com/company
dwang@bmj.com

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** Comments from the external peer reviewers**

Reviewer: 1

Recommendation:

Comments:

The comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with different COVID-19 vaccines: an international network cohort study from five European countries and the US

Stats Report:

The authors present an international study based on multiple cohorts, mainly obtained through electronic health records, from the UK, France, Germany, Spain, the Netherlands, and the US, to carry out a comparison of the risk of thrombosis following different types of COVID-19 vaccines (ChAdOx1, BNT162b2, Janssen, and mRNA). They have used multiple state of the art approaches aiming to minimise the potential bias that arises from the use of observational data when carrying out comparative effectiveness. In particular, they use L1 regularised logistic regression to carry out their PS matching, they ensure power in each cohort to carry out a valid comparison (including only results that are based on more than one cohort), and finally they use negative controls to further validate and calibrate their
effect estimates. These are all useful and valid approaches, nevertheless, their conclusions do not appear to be based on this strategy. In particular, their conclusions regarding Janssen (Ad26.COV2.S) are based on results from a single cohort that did not appear to provide adequate negative controls (based on their own analysis strategy and results presented in Table 5). Hence, the manuscript requires some critical adjustments/clarifications before publication in the BMJ could be recommended.

Major issues:

The following statement: ‘Our international analysis allowed us to analyse both adenovirus-based vaccines to confirm TTS as a potential class effect.’, is misleading as none of your estimates for the Janssen vs. other comparison is significant for this outcome based on the uncalibrated analyses (the calibrated analyses do not pass the authors’ own requirements set). The same applies for the effect for this outcome on ChAdOx1 vs. BNT162b2. Again, this is only reported in one database. The Results need to be re-written based on this and this will also affect the main conclusions (including Abstract) and the ‘What this study adds’.

Reference 31, Tian et al, presents a simulation study comparing L1 regularized logistic regression vs. high-dimensional propensity score (hdPS) and find that in some scenarios L1 outperforms hdPS. This is not the same as saying that this approach will be better than any situation where the covariates to be included in the PS are identified (by experts or otherwise). Please correct this mention in the Methods section as this could generate incorrect analyses going forward. The lack of some important confounders in some of the datasets is still a major limitation. This will need acknowledging in the Discussion. The use of negative control outcomes and their role here to identify potential unmeasured confounding is therefore particularly relevant, and so are the calibrated estimates presented (hence the reason for the Janssen results being particularly problematic).

As there are no results reported for the LPD France and US Hospital CDM, it would be worth mentioning this in the Results as it currently gives the wrong impression that the conclusions are based on all countries/datasets. Similarly, need to decide if the fact that calibration was not possible in the IPCI and Germany DA means it should also be included in the results. It seems to me that the results really rest on the data from UK, Spain and one US database.

In the Comparative safety section, the authors write ‘Seven outcomes were estimated in more than one database, and therefore included in meta-analyses.’ However, in Figure 2, there are 11 outcomes for the Janssen COVID-19 comparison. In Table 5, there does appear to be only 7 outcomes for the Janssen COVID-19 comparison with 2 or more studies reporting but this does not correspond to Figure 2.

Regarding this last point, in Table 5, there is a mention that only the ChAdOx1 vs. BNT162b2 comparison met your criteria for minimising bias (1st dose and 2nd dose too). I imagine this is the reason only these are included in the Results section. If that is the case, all the other results for the other comparisons, should only be included as supplementary material and not in the main Results.

Figure 2: What is presented in the second column? Is this the I2? Please label. In the same Figure, please include the studies reporting on these outcomes. This could be as a simple label for each comparison.

Minor issues:

Do the IQVIA hospital charge (US) and the US Open Claims datasets have some overlap or are they completely separate populations? If there is overlap, this might have generated
some bias (even if the Open Claims dataset analysed was only a 20% sample of the total).
If there is substantial overlap, one alternative is to do a sensitivity analysis excluding one
of the US databases (this is not an issue as this is not included in any analysis but would
be useful to have a comment in the Discussion).

Please check definition in sensitivity analysis. Likely there is a typo (before OR after?): “1.
Requiring the concurrent thrombocytopenia happened within 5 days before of after the
thromboembolic event after vaccination.”

Additional Questions:
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If you have any competing interests please declare them here: One member of my team has received funding to carry out a similar analysis for the AZ vaccine using EHRs from General Practice in the UK.

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