Subject: BMJ - Decision on Manuscript ID BMJ.2015.031222

Body: 25-Feb-2016

Dear Mr. Jaspers Focks

Manuscript ID BMJ.2015.031222 entitled "Polypharmacy and the effects of apixaban in patients with atrial fibrillation: insights from the ARISTOTLE trial"

Thank you for sending us your paper, manuscript # XXX entitled "YYY" We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Yours sincerely,

Georg Roeggla
groggla@bmj.com

https://mc.manuscriptcentral.com/bmj?URL_MASK=f8cdf64a5c2644a1b7b02a7093babd0d

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Manuscript meeting 25.02.2016

Elizabeth Loder (chair), Julie Morris (stats), Georg Roggla, Jose Merino, Anita Jain, Rubin Minhas, Jessamy Bagenal

Decision: ask for revision

The committee was interested in the topic of your research. The following concerns were mentioned:

- Do we understand correctly that this is a post-hoc analysis?
- The committee had concerns regarding the large number of post hoc papers following the ARISTOTLE trial.
- The committee question the use of no/medications as a proxy for comorbidities.
- Another issue is that bleeding risk can be estimated more directly, using HAS BLED, which includes the key risk markers.
- You make statements such as "Regarding intracranial bleeding, the benefit of apixaban remained consistent across tertiles" in the results section. We would prefer it you presented the data and left the interpretation for the discussion (the abstract also has multiple similar statements).
- Why were some patients taking so many medications? Was this because of significant comorbidities? Or does this may reflect prescription patterns?
- Patients in the US, for example, were taking more concomitant medications. Was this because they were sicker? Or because of lack of coordination among specialists? Is number of medications a marker for comorbidity?
- What medications were involved? Were there differences in medications between regions and patients? Were specific drug combinations deleterious?
- Please explain the clinical value for general readers in more detail.
- For p values above the conventional 0.05 cut-off there is little justification for quoting more than one decimal place.
- The committee thought the statistical analysis was appropriate and the conclusions justified.

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below. Please also respond to the additional comments by the committee.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

** Comments from the external peer reviewers**

Reviewer: 1

Recommendation:

Comments:

Drs Focks et al report on a sub-analysis of the Artistole trial with special reference in reference tot he polypharmacy used in older patient groups. This is a relevant topic with increasing importance with ageing of population. To get an objective information access tot he original patient charts/documentation is required.
Major comments:
1. Dividing of medication in quartiles is one possibility to assess the topic of the paper. However, interaction of medication between themselves and – more importantly – with Apixaban or Warfarin is not respected. This is a major drawback of the study and the results of the present4ed analysis are week if not misleading.
2. The decrease of the benefit of Apixaban over Warfarin by increase of medications. The contrary would have been expected because of the larger number of interaction of drugs with Warfarin compared to Apixaban. The conclusion does not take in account this results by just repeating the result and without giving an interpretation or hypothesis (see second to last sentence in Abstract) .
3. Tables 1 and 2 pool the data of the groups A and W. This is incorrect and all texts and tables and interpretations should be eliminated.
4. Table 3 and related text passages: the statement "that with increasing number of medications the effect of A over S reduces on bleeding event does not hold for all bleedings analysed: is holds for "major being" with p 0.0173 and for "major or clinically relevant non-major bleeding" with p 0.0475. For the other events this statement does not hold. Moreover, it is unclear, if "major bleeding" were counted twice for the two groups of bleeding. It would be clearer, if the second "major or clinically relevant non-major bleeding" would refer only to "clinically relevant non-major bleeding" (which is also in accordance with the literature).
5. What is the outcome on mortality?
Minor comments:
1. Figure 1 for supplementary
2. Many non-significant results. Shorten or add to supplementary
3. Table 1 A and 1 B: same as for Tables 1 and 2. Information misleading because treatment groups are pooled

Additional Questions:
Please enter your name: Harenberg

Job Title: emeritus Professor

Institution: University of Heidelberg

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: Yes

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: Sanofi-Aventis, BM-Pfizer, Bayer HeathCare, Daiichi-Sankyo

Reviewer: 2

Recommendation:

Comments:
This is another post-hoc analysis of the ARISTOTLE trial, a phase III trial that investigated apixaban vs. warfarin for stroke prevention in atrial fibrillation (AF). Here, the authors aimed at analyzing the effect of polypharmacy on risk of stroke and bleeding. In detail, the authors analyzed the correlation of the "crude" number of concomitant medications with clinical outcomes.
The results of the analysis are not unexpected, as both ischemic and bleeding complications occurred more often in patients treated with a higher number of concomitant medications. The efficacy results seem to be similar to result of the original publication of the ARISTOTLE trial, while bleeding complication were similar for apixaban and warfarin with increasing number of co-medications.

Here are my specific comments:
Was this analysis predefined in the study protocol of ARISTOTLE?
The number of co-medications seem to be a surrogate for co-morbidities/frailty, and risk scores for stroke and/or bleeding. Explanation of the added value of this particular analysis would be important.
The definition of polypharmacy and classification based on the crude number of concomitant medications is

somehow arbitrary:
It would be interesting to have detailed information of the medications (class of drugs, reason of prescription, etc.).
Also analysis according co-medications that inhibit p-glycoprotein and/or the CYP-syestem would be clinically useful - instead categorizing patients according to the "crude" number of co-medications.
One limitation is that only the baseline number of co-medications was analyzed, changes during follow-up might be relevant. However, this is a clinical trial setting and I do not expect a relevant effect of changes during follow-up on the effects of anticoagulation on stroke prevention and bleeding.

Additional Questions:
Please enter your name: Cihan Ay

Job Title: MD

Institution: Medical University of Vienna

Reimbursement for attending a symposium?: No

A fee for speaking?: Yes

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: Yes

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

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Deadline: Your revised manuscript should be returned within one month.

How to submit your revised article: Log into http://mc.manuscriptcentral.com/bmj and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

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When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision. Please include these items in the revised manuscript to comply with BMJ style (see: http://www.bmj.com/about-bmj/resources-authors/article-submission/article-requirements and http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists).

Items to include with your revision (see http://www.bmj.com/about-bmj/resources-authors/article-types/research):

1. What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

2. Name of the ethics committee or IRB, ID# of the approval, and a statement that participants gave informed consent before taking part. If ethics committee approval was not required, please state so clearly and explain the reasons why (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines.)

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9. Funding statement and statement of the independence of researchers from funders (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements).

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11. Please ensure the paper complies with The BMJ's style, as detailed below:

a. Title: this should include the study design eg "systematic review and meta-analysis."

b. Abstract: Please include a structured abstract with key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research). For every clinical trial - and for any other registered study- the last line of the abstract must list the study registration number and the name of the register.

c. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.

d. Methods: For an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found.

e. Results: Please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

i. For a clinical trial: Absolute event rates among experimental and control groups; RRR (relative risk reduction); NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000.)
ii. For a cohort study: Absolute event rates over time (eg 10 years) among exposed and non-exposed groups; RRR (relative risk reduction.)
iii. For a case control study:OR (odds ratio) for strength of association between exposure and outcome.
iv. For a study of a diagnostic test: Sensitivity and specificity; PPV and NPV (positive and negative predictive values.)
v. For a systematic review and/or meta-analysis: Point estimates and confidence intervals for the main results; one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used. For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

f. Discussion: To minimise the risk of careful explanation giving way to polemic, please write the discussion section of your paper in a structured way. Please follow this structure: i) statement of principal findings of the study; ii) strengths and weaknesses of the study; iii) strengths and weaknesses in relation to other studies, discussing important differences in results; iv) what your study adds (whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses); v) meaning of the study, including possible explanations and implications for clinicians and policymakers and other researchers; vi) how your study could promote better decisions; vi) unanswered questions and future research

g. Footnotes and statements

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Date Sent: 25-Feb-2016