Dear Dr. Abraham:

Manuscript ID BMJ.2014.023104.R1 entitled "Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban and warfarin" which you submitted to BMJ,

Thank you for sending us this paper and giving us the chance to consider your work, which we enjoyed reading.

Decision: We are pleased to say that we would like to publish it in the BMJ as long you are willing and able to revise it as we suggest below: we are provisionally offering acceptance but will make the final decision when we see the revised version.

In addition to responding to the comments of our statistician in entirety, it would be helpful to know if there was any overlap in included patients between the database used in this study and other available databases. Are the databases exclusive of one another?

Deadline: Because we are trying to facilitate timely publication of manuscripts submitted to BMJ, your revised manuscript should be submitted by one month from todays date. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

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Yours sincerely,

Rebecca Burch, MD
Associate Editor, The BMJ
rburch@bmj.com,

Reviewer: 1

Recommendation:

Comments:
Stats Report:

This manuscript uses medical and pharmacy administrative claims from a large database to evaluate the risk of gastrointestinal bleeding found in new cases of individuals taking dabigatran and rivaroxaban comparing against those found in new cases of people taking warfarin. As there are important differences in the characteristics of the individuals in each of these groups, the authors use Propensity scores to obtain matched (1:1) samples between intervention and control. The authors present results separately for the group with and without Atrial fibrillation and find little difference overall but significant interactions with age suggest that recommendations for treatment need to take Age into consideration.

After reviewing the authors’ replies to the reviewers of the original manuscript, I believe many of the queries have been solved but unfortunately not all. These are summarized below:

Main points:

Information in the Abstract – The data source quoted here, although not incorrect, is misleading. The total population on which this analysis was based on is less than 20k individuals for each comparison. Please correct/clarify. The “Main Outcomes” talk
about incidence rates and Cox proportional hazard ratios. However, the “Results” only provide crude incidence rates of two of the groups (not for Warfarin) and no HRs. Please give incidence rates for all groups with confidence intervals (not currently provided) as well as the HRs (with CIs) for the main comparisons – Total bleeding by NOAC by AF/Non_AF. I assume that the age interaction was part of the primary objective and hence at least the most relevant HRs (e.g. for age 75+) should also appear in the Results so that the current “Conclusion” is adequately supported.

No inclusion of mortality/effectiveness data: - A major issue arising from the Introduction is that, within RCTs, evidence of equivalence in efficacy with extra rates of adverse events has been identified. The manuscript presents evidence that in “real life” there is no evidence of extra adverse events. However, the same analysis could (should?) be done to determine if in “real life” equivalence of effect (in stroke and systolic embolism) is found. From the data reported, although the authors do not have access to mortality data, they appear to have access to stroke (as an event). Presenting if the finding of equivalence in effect on stroke prevention in the present data is maintained would therefore help to interpret the findings in light of the evidence obtained from RCTs.

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Additional Questions:
Please enter your name: Rafael Perera

Job Title: Professor of Medical Statistics

Institution: University of Oxford

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No
Fees for consulting?: No

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If you have any competing interests (please see BMJ policy) please declare them here: I have carried out (NIHR, UK) funded research on the efficacy of self-monitoring in Patients using OAT (mainly warfarin) and I am a co-author on several Systematic Reviews on this subject.

First, however, please read these four important points about sending your revised paper back to us:

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IMPORTANT
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d. Please include these items in the revised manuscript to comply with BMJ style:

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structured abstract including 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 study registration number and name of register – in the last line of the structured abstract.

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

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.

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/

Summary statistics to clarify your message. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

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)

For a cohort study:
- Absolute event rates over time (eg 10 years) among exposed and non-exposed groups
- RRR (relative risk reduction)

For a case control study:
- OR (odds ratio) for strength of association between exposure and outcome

For a study of a diagnostic test:
- Sensitivity and specificity
- PPV and NPV (positive and negative predictive values)

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

Discussion

Please write the discussion section of your paper in a structured way, to minimise the risk of careful explanation giving way to polemic. Please follow this structure:
- Statement of principal findings of the study
- Strengths and weaknesses of the study
- Strengths and weaknesses in relation to other studies, discussing important differences in results and what your study adds. Whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses (eg Cochrane reviews)
- Meaning of the study: possible explanations and implications for clinicians and policymakers and other researchers; how your study could promote better decisions
- Unanswered questions and future research

Footnotes and statements

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

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for studies that are relevant to patients we expect authors to report in their articles the extent of their study’s patient-centredness, as highlighted by these questions: did you involve patients/service users/carers/lay people in the design of this study? Please state whether you did, and give details (Methods section) was the development and/or selection of outcome measures informed by patients’ priorities and experiences? Please give details (Methods section) were patients/service users/carers/lay people involved in developing plans for
participant recruitment and study conduct? If so, please specify how (Methods section)
how you planned to disseminate the results of the study to participants? If so how
will this be done? (Describe in brief footnote)
for articles reporting randomised controlled trials: did you assess the burden of the
intervention on patients’ quality of life and health? If so, what evaluation method did
you use, and what did you find? (Methods and Results sections)

Reviewer: 1

Recommendation:

Comments:

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Please enter your name: Rafael Perera

Job Title: Professor of Medical Statistics

Institution: University of Oxford

Reimbursement for attending a symposium?: No

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A fee for organising education?: No

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Funds for a member of staff?: No

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END

Date Sent: 24-Feb-2015