Dear Dr. Abraham

Manuscript ID BMJ.2014.023104 entitled "Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban and warfarin"

Thank you for sending us this paper, which we were pleased to have the chance to consider and enjoyed reading. 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. This is 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 committee meeting, so that we will be in a better position to understand your study and to decide whether The BMJ is the right journal for it.

Many thanks again. We look forward to seeing your revised article within a month and, we hope, to reaching a decision.

**THE REPORT FROM THE MANUSCRIPT COMMITTEE MEETING, REVIEWERS’ REPORTS, AND THE BMJ’S GENERAL REQUIREMENTS FOR RESEARCH PAPERS ARE AVAILABLE AT THE END OF THIS LETTER.**

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

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

2. Online and print publication: All original research in The BMJ is published with open access. The full text online version of your article, if accepted after revision, will be the indexed citable version (full details are at http://resources.bmj.com/bmj/about-bmj/the-bmjs-publishing-model), while the print and iPad BMJ will carry an abridged version of your article, usually a few weeks afterwards. This abridged version of the article is essentially an evidence abstract called BMJ pico, which we would like you to write using a template and then email it to papersadmin@bmj.com (there are more details below on how to write this using a template). Publication of research on bmj.com is definitive and is not simply interim “epublication ahead of print”, so if you do not wish to abridge your article using BMJ pico, you will be able to opt for online only publication. Please let us know if you would prefer this option. If/when your article is accepted we will invite you to submit a video abstract, lasting no longer than 4 minutes, and based on the information in your paper’s BMJ pico evidence abstract. The content and focus of the video must relate directly to the study that has been accepted for publication by The BMJ, and should not stray beyond the data.

3. Open access publication fee: The BMJ is committed to keeping research articles Open Access (with Creative Commons licences and deposit of the full text content in PubMedCentral as well as fully Open Access on bmj.com). To support this we are now asking all authors to pay an Open Access fee of £3000 on acceptance of their paper. If we accept your article we will ask you to pay the Open Access publication fee; we do have a waiver policy for authors who cannot pay. Consideration of your paper is not related to whether you can or cannot pay the fee (the editors will be unaware of this), and you need do nothing now.

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You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) and Committee in the space provided. You can use this space to document any changes you make to the original manuscript and to explain your responses. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Yours sincerely

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

As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation ‘Revised Manuscript Marked copy’.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

INFORMATION ON REVISING THE CONTENT AND FORMAT OF YOUR ARTICLE

**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.

Members of the committee were:
Elizabeth Loder (chair), Tiago Villaneuva, Emma Parish, Jose Merino, Georg Roeggla, Rebecca Burch, Wim Weber, Raphael Peralta (statistican).

Decision: request revisions

Detailed comments from the meeting:
First and foremost, 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 these additional comments by the committee:
Decision: Major revision (Put points).

*Editors felt that this was a very clinically relevant research question.

*We would like the authors to clarify if there are other databases that capture similar information, whether there is any overlap between the databases, and why this particular one was chosen.
*Several authors noted that the doses of medications used in this study are not available in Europe. The authors might want to comment on how this affects generalizability.

*We had the following statistical comments:

The propensity scoring seems to have been well done, although there seem to have been some residual differences in the non atrial fibrillation group.

There are differences between the results of this paper and prior RCTs. We would be interested to see if the results of this paper change after the reviewers' concerns are taken into account. These include questions about how data were collected, and which individuals were included in the datasets, how exposure was defined.

**IMPORTANT**

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.

a. In your response to the reviewers and committee please provide, point by point, your replies to the comments made by the reviewers and the editors, and please explain how you have dealt with them in the paper. It may not be possible to respond in detail to all these points in the paper itself, so please do so in the box provided.

b. If your article is accepted it will then be edited, proofed, and - after your approval - published on bmj.com with open access. This open access Online First article will not be a pre-print. It will represent the full, citable, publication of that article. The citation will be year, volume, elocator (a unique identifier for that article): eg BMJ 2008;337:a145 — and this is what will appear immediately in Medline, PubMed, and other bibliographical indexes. We will give this citation in print and online, and you will need to use it when you cite your article.

c. Please write an abridged version of the article for the print and iPad BMJ using the appropriate BMJ pico template for your study's design. Please be reassured that it doesn't take long to complete this. When your BMJ pico is ready please email it to papersadmin@bmjgroup.com. The templates for you to download are at http://resources.bmj.com/bmj/authors/bmj-pico.

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

**Title:** this should include the study design eg “systematic review and meta-analysis”

**Abstract**

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)

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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a statement that any identifiable patients have provided their signed consent to publication. Please submit, as a supplemental file, the signed BMJ patient consent form giving consent to publication in The BMJ of any information about identifiable individual patients. Publication of any personal information about a patient in The BMJ, for example in a case report or clinical photograph, will normally require the signed consent of the patient.

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signed patient consent form(s), if the article gives enough personal information about any patient(s): this sometimes occurs even in research papers - for example in a table giving demographic and clinical information about a small subgroup in a trial or observational study, or in quotes/tables in a qualitative study - (see http://resources.bmj.com/bmj/authors/editorial-policies/copy_of_patient-confidentiality)

a data sharing statement declaring what further information and data you are willing to make available, over and above the results reported in the paper. Suggested wording: "Data sharing: technical appendix, statistical code, and dataset [state whether any patient level data have been anonymised] are available at this repository or website OR from the corresponding author at " . If there are no such further data available, please use this wording: "Data sharing: no additional data available". For papers reporting the main results of trials of drugs or devices we require that the authors state, at a minimum, that the relevant anonymised patient level data are available on reasonable request from the authors

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a statement describing the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication

assurance, in the cover letter, that a clinical trial funded by a pharmaceutical or other commercial company follows the guidelines on good publication practice (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)

inclusion in the list of contributors the name(s) any professional medical writer(s), specifying in the formal funding statement for the article who paid the writer. Writers and authors must have access to relevant data while writing articles.

Patient centred research

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)

have you planned to disseminate the results of the study to participants? If so how will this be done? (Describe in brief footnote)

are patients thanked in the contributorship statement or acknowledgements?

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)

REFEREES COMMENTS
Reviewer: 1

Recommendation:

Comments:
This manuscript provides useful, real-world information about a common concern with the use of the target-specific oral anticoagulant agents. Thus, it may be of interest to the readership of BMJ. However, I do have a variety of questions regarding the analyses and their interpretation that should be addressed prior to recommending acceptance.

1) Introduction: Consider using an alternative term to NOAC, since these agents are no longer “novel”. Perhaps something like “target-specific oral anticoagulants (TSOACs)”. Also, either mention all of the available agents in the 1st paragraph (vs only dabi & riva), or just mention the drug classes as a whole.
2) Methods, Variables of Interest: Why were inducers/inhibitors of warfarin specifically mentioned, but not agents interacting with either dabigatran or rivaroxaban? Also, consider using the more universally recommended CHADS2-VASc stroke risk score rather than the outdated CHADS2.
3) Results: I am not clear on why so many differences remained different between groups (particularly in the rivaroxaban non-AF patients) following propensity-score matching. Did the model that was used for matching not fit the data appropriately? Please provide the model diagnostics to support/refute this. Were too few variables used to match?
4) Results, Table 3: How do you explain why the hazard of GI bleeds was higher in the non-AF group with dabigatran vs. warfarin? This was not addressed anywhere in the discussion. While not statistically significant, the results are trending opposite of the AF cohort. Why might this be?
5) Results: When discussing the results of the rivaroxaban analyses, please keep wording consistent. Stating that there were numerically, albeit not statistically significantly, fewer events with riva vs. warf in the AF-cohort, while saying “similar rates of GIB when compared to warfarin” in the non-AF cohort is inconsistent. The non-AF cohort had confidence intervals much closer to statistical significance than the AF cohort.
6) Discussion: In the first paragraph, why was only the AF findings mentioned, and the non-AF findings ignored?
7) Discussion, Interpretation of Findings: When discussing the differences in age between your cohort & the clinical trials, you seem to suggest that the difference of 4 years in mean age could explain the differences in GIB rates. Please substantiate how this magnitude of age difference relates to significant GIB rates.
8) Discussion: Is there a mechanistic rationale for why one might expect differences in upper vs. lower GIB rates with these agents?
9) Figures 2 & 3: Consider adding the p-value for each comparison at the various timepoints to allow for easier interpretation of the data within the figures (same for those in the appendix).

Additional Questions:
Please enter your name: William L. Baker

Job Title: Assistant Professor

Institution: University of Connecticut School of Pharmacy

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?: No
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:

Reviewer: 2

Recommendation:

Comments:

Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin.

This paper used administrative data for more than 100 million private insured or Medicare advantage patients in the US to investigate the risk of gastrointestinal (GI) bleeding associated with dabigatran or rivaroxaban versus warfarin.

The study incorporated data from November 1, 2010 through December 2013. Patients were included if they had a new prescription for one of the study anticoagulants (with no anticoagulant use in the prior 12 months). The analysis was not limited to patients with atrial fibrillation, although analysis was conducted separately for patients with atrial fibrillation and patients using anticoagulants for a different indication. The authors created propensity-matched samples based on patient characteristics at the time of anticoagulant initiation. Overall, results indicated a significantly lower rate of GI hemorrhage with dabigatran compared to warfarin, but no difference in GI hemorrhage between rivarixaban and warfarin. These results reflect propensity matched patients with atrial fibrillation. Among patients without atrial fibrillation, differences in GI bleeding rates were not statistically significant. However, analysis by age found that the relative likelihood of GI bleed associated with dabigatran increased with age, so that dabigatran was associated with significantly more bleeding events than warfarin among patients age 75 years or older. This was true for patients with AFib and other patients.

In general I thought the methodological approach was appropriate for the observational data. However, there were a number of analytical details that were either not addressed in the analysis or not described well in the manuscript. Specific comments follow.

Methods:

Regarding the definition of the outcome: The authors never state whether they included GI Hemorrhage on inpatient claims only, or inpatient and outpatient (and whether they included all GI hemorrhage diagnoses, or only those appearing in the primary position on claims).

Definition of anticoagulant use: How were different dosages handled (e.g., 150 mg and 75 mg for dabigatran). Did the study include 75 mg dabigatran as well as 150 mg? Given the relatively infrequent use of 75 mg dabigatran, presenting results for 150 mg only is perhaps more relevant, or at least presenting results for 150 and 75 mg separately. Similary, what about dosing for rivaroxaban?

Censoring events: How did the analysis deal with death? This is never discussed in the description of analysis, but if death occurs at different rates in patients receiving a novel oral anticoagulant versus warfarin (as was found in the Re-LY trial), the likelihood of observing a GI bleeding event will be impacted. One option is to censor patients at the time of death. Of course, this can be problematic because ideally, with Cox regression models, the reason for censoring should be unrelated to the patient’s health status.

In addition, if I understand correctly, use of the index anticoagulant was considered continuous until one of the following events occurred: a gap of 30 days, a prescription...
was provided for another anticoagulant, disenrollment from the healthcare plan, or
the absence of a new prescription 45 days after the last medication prescription fill. It
is never stated clearly in the text, but I believe these events were treated as
censoring events in the analysis. If this is correct please clarify in the text. If not
correct, describe how these events were handled in the analysis. (In a related issue, if
medication cessation was treated as a censoring event, it would be very useful to also
include a sensitivity analysis based on 'intent to treat' analysis, in which patients are
assumed to continue the index medication until end of follow-up or GI bleed. Given
that several publications from the RE-LY and ROCKET-AF data used 'intent to treat',
this facilitates direct comparison to published results of clinical trials).

Regarding the non-Afib patients: It would be nice to see a more complete description
of these patients (i.e., a description of other indications for which dabigatran,
rivaroxaban, and warfarin are approved and/or used).

Presentation of results:

In the first sentence of results, the authors indicate that they included patients who
were continuously enrolled between November 2010 and September 2013. Although it
is not stated, I assume that an exception to the criteria of 'continuous enrollment’ is
made for patients who died during the observation period? Also, the authors state
that ‘four percent were excluded due to medication switch prior to the termination of
their last medication fill’. This is confusing, and is related to my previous comment
regarding the lack of clarity about how medication cessation was treated in the
analysis. Were patients who switched anticoagulants excluded altogether (and if so, why?),
or was termination of the index anticoagulant treated as a censoring event
(whether or not a different anticoagulant was prescribed)?

The tables showing matched and unmatched patient characteristics take up a lot of
space and present too many numbers to absorb. Also, assessing the success of the
matching algorithm using p-values is not always informative because the sample size
is substantially smaller in the matched sample, potential impacting the statistical
significance. I recommend presenting baseline characteristics in two tables: the first
showing unmatched characteristics of Afib patients taking warfarin, dabigatran, and
rivaroxaban, and the second showing unmatched characteristics of non-Afib patients
taking warfarin, dabigatran, and rivaroxaban. The authors can then demonstrate the
success of their matching algorithm using two graphs of standardized differences
before and after matching (one graph for Afib patients taking rivaroxaban, dabigatran,
or warfarin, and the other for non-Afib patients). [See example graph in: Austin PC.
“Balance diagnostics for comparing the distribution of baseline covariates between
treatment groups in propensity-score matched samples” Statistics in Medicine,

I would prefer to see more detail provided regarding results by age. Rather than
presenting overall results for all ages in the tables (e.g., Table 3), I would like to see
the tables show bleeding rates and hazard ratios for patients <75, and patients >=75.
I find the survival graphs difficult to compare to other literature previously published
regarding bleeding rates in old and young patients, and to place in context of what we
already know about GI bleeding with rivaroxaban or dabigatran.

Discussion:
I would like to see more comparison in the discussion section to previous
investigations of differences in GI bleeding rates by age, and how the current study
adds to that literature. (for example, Eikelboom et al investigated rates of major
bleeding by age using RE-LY data [Eikelboom et al, Circulation 2011]).

Additional Questions:
Please enter your name: Mary S. Vaughan Sarrazin

Job Title: Associate Professor, Research
Institution: University of Iowa

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?: No

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: none

END