MJ - Decision on Manuscript ID BMJ.2015.028062

Body: 23-Sep-2015

Dear Dr. Romley

Manuscript ID BMJ.2015.028062 entitled "Hypoglycemia associated with concurrent use of commonly used sulfonylureas and warfarin, an observational analysis"

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 athttp://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.

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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

Kristina Fišter
kfister@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'.

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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: Jose Merino (chair), Gary Collins (statistics advisor), editors - Elizabeth Loder, Alison Tonks, Georg Roggla, Tiago Villanueva, Wim Weber, Rubin Minhas, Kristina Fišter.

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:

* Many patients are prescribed warfarin because of atrial fibrillation. Many of these patients also take beta-blockers. Beta-blockers may mask the symptoms of hypoglycaemia. It is therefore quite possible that these patients had more severe hypoglycaemia in need of hospital admission than those who noticed hypoglycaemia early and could react themselves. Do you have any data on beta-blocker therapy?

* Have you identified all ED admissions, for example those due to falls?

* The study design in the title needs rephrasing. We weren't sure what 'observational analysis' was.

* Hospitalisation and ED visits seem rare, they only occurred in 0.01% and 0.04% of all person-quarters, but individuals could have more than one hospitalisation/visit - how many people did this affect, in this very large cohort?

* You don't seem to present any data on other diabetes medications used, and we also don't know whether sulphonylureas were being used in this population as first line. Some editors commented that gliclazide is used more often nowadays, rather than glipizide and glimepiride, but this may depend on the setting.

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

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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

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ID of ethics committee approval and name of the ethics committee/IRB; or a statement that approval was not required (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines) and a statement that participants gave informed consent before taking part

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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
The BMJ has partnered with the Dryad Digital Repository datadryad.org to make open deposition easy and to allow direct linkage by doi from the dataset to The BMJ article and back - we encourage authors to use this option
funding statement (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)
statement of the independence of researchers from funders (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)
for studies funded or sponsored by industry (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)
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:

General Comments:

This retrospective cohort analysis by Romley et al examines the following question: Is concomitant warfarin and sulfonylurea use associated with a higher incidence of hypoglycemic events in elderly patients? Their analysis utilizes pharmacy and medical claims submitted in 2006-2011 for diabetic Medicare patients (drawn from a 20% random sample of Medicare beneficiaries over the age of 65) who filled a prescription for a Sulfonylurea during this time (~466,000 patients). Approximately 15% of these patients (71,000 patients) also filled a prescription for Warfarin. They then compare rates of their primary outcome—ED visits or hospitalizations for hypoglycemia (defined by having hypoglycemia as primary billing diagnosis)—among patients on Sulfonylureas alone and Sulfonylureas and Warfarin. They present their outcomes in terms of rates of ED visits or hospitalizations per person quarter. They find that, while ED visits or hospitalizations for hypoglycemia are uncommon overall (.05% per person-quarter across entire population), they happen significantly more frequently in patients prescribed both Warfarin and Sulfonylureas than prescribed Warfarin alone. Equally if not more important, they find that they risk of a hypoglycemic event is greatest in the first three months following the initiation of Warfarin therapy. My overall impression is that this is a very strong paper on an important topic, and merits strong consideration for publication.

Major Strengths:

This paper has several strengths, including:

1) The relevance and importance of the question being studied: This question is a highly important one, as Warfarin and Sulfonylureas are among the most commonly prescribed medications in elderly populations. Moreover, and as the authors correctly point out, there is no empirical evidence to support claims that concomitant use of these two classes of drugs increases the risk of hypoglycemia. Indeed, as the authors also note, concerns about a potential interaction between Warfarin and Sulfonylureas stem actually stem from theories about Warfarin affects the metabolism and circulation of Sulfonylureas. To date, no empirical evidence exists to support this biologically plausible phenomenon. Given the potentially life threatening consequences of hypoglycemia, the results of this study could lead to meaningful improvements in the quality of care for the millions of people around the world who currently take, or will soon be started on, these agents.
2) The analytical methods are appropriate. The authors conduct multivariate regression analyses to control for several potential confounders. They also perform sensitivity analyses-including a well devised falsification analysis-which further support their findings and provide additional insight into the nature of the link between Sulfonylurea use, Warfarin use, and the risk of hypoglycemia.
3) The paper is well written, and the data is presented clearly and succinctly in the text and figures.

4) The authors' finding that the risk of hypoglycemia increases in the first few months following initiation of Warfarin is not only important clinically, but also further strengthens the overall plausibility of their findings (e.g. it makes sense). If the risk of hypoglycemia with concomitant use of Warfarin and Sulfonylureas is influenced by Warfarin dosing, then we would expect that this risk is highest when patients are taking higher doses of Warfarin. As it turns out, Warfarin doses are often highest, and INR values most labile, immediately following initiation of Warfarin therapy, as the Warfarin dose is titrated to achieve a consistent, therapeutic INR. Indeed, Warfarin therapy is often initiated at daily doses of 5-10 mg in order to reduce the amount of time needed to achieve a therapeutic INR. However, the elderly often require lower than normal doses of warfarin to achieve and maintain a therapeutic INR. Thus, the daily doses of Warfarin taken by elderly patients shortly after initiation of Warfarin therapy are very likely to be the highest daily doses that they will ever take. Consequently, if Warfarin dose is positively associated with the risk of hypoglycemia, we would expect the risk of hypoglycemia to be highest at, or shortly after, the initiation of Warfarin therapy. Second, if the risk of hypoglycemia due to concomitant use of Warfarin and Sulfonylureas is unrelated to Warfarin dosing, but merely due to concomitant exposure to both agents, we'd still expect the risk of hypoglycemia to be highest soon after a patient starts to use both medications together.

Suggestions for Improvement

1) The authors do not state whether or not they collected information about, and controlled for, use of a few important medications which can also increase the risk of hypoglycemia when used with sulfonylureas. These agents include:
a. Other Oral Hypoglycemics, particularly Thiazolidinediones and Meglitinides (e.g. Repaglinide), and (to a lesser extent) Metformin;
b. Insulin therapy; and

c. Aspirin
If possible, the authors should provide some basic descriptive and comparative data on rates of use of these agents in their cohort. Ideally, they should also control for oral hypoglycemic and insulin use in their regression analyses.

2) The authors present their results in a fashion which is customary for this type of analysis (e.g. in terms of likelihood of an event per person quarter or person year). They might also want to consider describing/presenting these data in a manner that makes it easier for clinicians to quickly interpret the practical meaning of their findings, and incorporate them into their clinical practice. For example, the authors could consider calculating, and reporting, one or more of the following pieces of data:
a. The absolute increase in yearly risk of an ED visit or hospitalization for hypoglycemia in patients on both a Sulfonylurea and Warfarin compared to a Sulfonylurea alone; and/or
b. The absolute increase in risk of an ED visit or hospitalization for hypoglycemia in the first three months after starting Warfarin therapy.
3) The authors might consider devoting some additional space in their discussion to addressing the implications of what appears to be an increased risk of hypoglycemia during the first three months following initiation of Warfarin therapy. More specifically, are there any additional implications of this finding for patient safety efforts to reduce adverse drug events? And are the rates of events high enough to justify closer monitoring of patients already on Sulfonylureas when they are starting Warfarin? How do rates of hypoglycemia in patients on a combination of Sulfonylureas and Warfarin compare to rates of other important, and drug-drug interactions that clinicians commonly worry about, and attempt to avoid?

Additional Questions:
Please enter your name: Daniel M. Blumenthal

Job Title: Clinical Cardiology Fellow

Institution: Massachusetts General Hospital

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:

Reviewer: 2

Recommendation:

Comments:
Impression:

This is a well written using administrative insurance claims data to address an important issue: whether the use of warfarin is associated with an increase in ED visits and hospitalizations for hypoglycemia among patients using sulfonylureas. Although there have been some reports that the use of warfarin/sulfonylureas is associated with an increased risk for hypoglycemia, this paper provides the first large-scale study establishing such a risk. Although observational studies are always subject to the usual caveats, the authors include robust sensitivity analyses—such as the use of fixed effects models and falsification analyses—to address these potential limitations. As the paper uses robust analytic methods to address a question with important consequences, I am enthusiastic about its publication subject to the comments below.

Major comments:
1) The authors used the chronic conditions warehouse to identify diabetic patients and to provide risk adjustment. Although the chronic conditions warehouse has been validated and used for many studies, it does have its limitations (See http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3975984/

and http://www.ncbi.nlm.nih.gov/pubmed/21649659). I think it would be helpful to assess the robustness of these results to alternative methods of identifying diabetics/risk adjusting, such as the use of Medicare's Hierarchical Condition Category system, which is also used by CMS for risk adjustment.
2) The elevated risk of hypoglycemia when warfarin is started is particularly relevant to clinical practice. For new enrollees, the first period with a sulfonylurea fill in the Part D claims may also be the first period with a warfarin fill. However, both drugs could have been used prior to Part D enrollment. To address this concern, I would encourage the authors not to treat such cases as warfarin starts, and to acknowledge the (minor) limitation that pre-enrollment utilization is unmeasured.
3) The falsification analysis clearly relies on the assumption that there are no interactions between statins and sulfonylureas; it's probably worth doing a bit more to document this lack of interaction; for example consider the following paper:
http://www.ncbi.nlm.nih.gov/pubmed/24548191

Minor Comments:

1) I'm sure that the authors took care to address this issue, but some of the sulfonylureas are provided in formulation that contain another drug (e.g., glipizide/metformin). Did the authors exclude such combinations?
2) More a topic for another paper, but do sulfonylureas affect warfarin/INR? If so, I would discuss this in the introduction.

Respectfully Submitted,

Eric C Sun

Additional Questions:
Please enter your name: Eric Sun

Job Title: Instructor

Institution: Stanford University

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

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END

Date Sent: 23-Sep-2015