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Dr. Kristina Fišter
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The BMJ
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Dear Dr. Fišter:

We are pleased to resubmit a revised version of our manuscript "Serious hypoglycemic events associated with concurrent use of commonly used sulfonylureas and warfarin, a retrospective cohort analysis" to The BMJ. This manuscript's ID is BMJ.2015.028062.

We very much appreciated the concerns raised by the referees and are grateful for the opportunity to respond. We believe that our quite extensive responses to the referees have strengthened the paper, and we hope that you agree.

We have included below a point-by-point response to the comments made by the manuscript committee and the two referees who reviewed our manuscript, with their comments in italics.

Thank you again for considering our work for publication in The BMJ. If we can provide any further information or clarification, please do not hesitate to contact us.

Sincerely,
Anne Peters

Manuscript Committee

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?*

Thank you for this hypothesis. We have added an analysis in which the effect of concurrent warfarin use is distinguished according to concurrent use of a beta blocker (again measured by a prescription fill within the calendar quarter.) The odds ratio on the warfarin effect is higher with beta blocker use than without – 1.29 versus 1.20 – as our revised Figure 2 shows. However, we are unable to distinguish these odds ratios. The confidence interval with concurrent beta blocker use is wide. This imprecision is perhaps due to the fact that concurrent use of warfarin and beta blockers represents a fraction of a fraction of our sample of person-quarters with glipizide / glimepiride use (10% of observations have warfarin use, and 17% of these observations have beta blocker use.)

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

This is an important question, and it led to new insights.

While we have used a validated approach from the literature to identify hypoglycemia in claims data, falls are an important consequence of hypoglycemia, and could be a proxy for undiagnosed hypoglycemia.[1] We have thus performed a new analysis of this outcome, following an approach used in prior research on the relationship between hypoglycemia and fall-related fractures in Medicare claims (the algorithm identifies fracture sites likely to be related to falls, such as hip, and rules out causes other than falls using external injury codes.) As shown in a new figure (Figure 5), the odds ratio for fall-related fractures was 1.47, and highly significant.

Note that our algorithms allow both outcomes (hypoglycemia and fall-related fractures) to be identified in the same encounter. A supplemental analysis reported in the appendix shows that the relationship of concurrent warfarin use with fall-related fractures persists when we exclude person-quarters with hypoglycemia.

Altered consciousness / mental status can also be a consequence of hypoglycemia.[2,3] Discussions with ED physicians at our affiliated academic medical center underscored the importance of this effect. We have therefore analyzed this outcome, and found an odds ratio of 1.22 (95% CI 1.16 - 1.29) for altered consciousness / mental status. Additional detail on these outcomes is reported in a new Appendix Table 5.

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

Thank you for noting this issue. We have replaced "observational status" in the manuscript title with "retrospective cohort analysis." Given the inclusion of fall-related fractures and altered consciousness / mental status, we have also revised the title to refer to "serious hypoglycemic events."

** 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?*

As we now note in the Results section (p. 13 of the tracked-changes version of the revised manuscript), there were 2111 individuals in our 20% sample of Medicare beneficiaries with a hypoglycemia ED visit or hospitalization, with 78 individuals experiencing multiple events.

For the secondary outcome of fall-related fractures, there were 24678 person-quarters with an ED visit or hospitalization, experienced by 22078 individuals.

** 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.*

Gliclazide has not been approved for marketing in the United States.[4] It is worth noting that the drugs of primary interest in this study, glipizide and glimepiride, are marketed widely throughout the world.[5,6]

As to other diabetes medications, we interpreted this comment (and those from the first reviewer) in two ways. Each interpretation led to further analysis.

First, it is possible that patients who need warfarin also have more severe diabetes, so that the measured effect of warfarin use is confounded. To address this concern, we have done a supplemental analysis that included concurrent use of a variety of diabetes medications (including insulin, thiazolidinediones, metformin and meglitinides) in response to a reviewer's comment. The utilization of these medications is described in a new Appendix Table 3; metformin is first-line under the treatment guidelines[7], and is commonly used with glipizide / glimepiride. As shown in our revised Figure 3, the odds ratio is almost identical – and remains significantly greater than one – when we control for the use of these other medications.

Second, we interpreted this comment to suggest that we investigate whether concurrent use of warfarin and other diabetes medications is also associated with hypoglycemia. Warfarin is known to interact with a number of foods, and could lead to dietary changes which make hypoglycemia more (or less) likely. Metformin and thiazolidinediones are low-risk for hypoglycemia [7], and so an apparent interaction of these medications with warfarin would suggest that our primary finding reflects something other than a true interaction between warfarin and glipizide / glimepiride. We have therefore performed a new analysis of the adjusted risk of hypoglycemia in person-quarters with metformin and thiazolidinedione fills, according to concurrent use of warfarin. As shown in a new figure (Figure 4), the odds ratios for warfarin use were not significantly different from one. Insulin and glyburide (another second-generation sulfonylurea) do entail substantial risk of hypoglycemia.[7] However, we do not find a warfarin effect for these medications. (Additional detail on these analyses is reported in a new Appendix Table 4.) Altogether, these null findings for a variety of diabetes medications other than glipizide / glimepiride suggest that warfarin interacts specifically with these agents.

References

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Referee 1

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.

We thank the reviewer for the very thoughtful and constructive review of our work.

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.

We are gratified that the review views this work as important, the methods as appropriate, and the findings as plausible.

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.

This was a good suggestion. In a new Appendix Table 3, we now report the utilization of insulin, thiazolidinediones, meglitinides, and metformin during a person-quarter with a glipizide / glimepiride fill, overall and according to warfarin use.

In addition, as suggested by the reviewer, we have done a new analysis that included concurrent use of a variety of warfarin and other diabetes medications, including insulin, thiazolidinediones, meglitinides and metformin. As shown in our revised Figure 3, the odds ratio is almost identical – and remains significantly greater than one – when we control for the use of these other diabetes medications.

We also explored the issue of aspirin. Its utilization is not captured reliability in the Part D prescription drug claims, because it is frequently over the counter. In our claims, it was used in 1.20% of person-quarters with a glipizide / glimepiride fill. To carefully address the issue, we repeated the analysis adjusting for use of other medications to include aspirin. The odds ratios on concurrent use of warfarin and glipizide / glimepiride were virtually identical, 1.206627 versus 1.209425.

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.

Thank you for the very helpful suggestion. We now report absolute risk in the Results section, and have included the relevant portion below for your convenience. Please note that at the editor's suggestion, we now also consider additional hypoglycemia-related outcomes, including fall-related fractures.

> "Use of warfarin with glipizide / glimepiride was associated with other hypoglycemia-related diagnoses. For fall-related fractures, hospitalization and ED visits were more common in person-quarters in which warfarin was used compared to quarters in which it was not (3919/416479, or 0.941%, hospitalizations for hypoglycemia in person-quarters with warfarin use versus 20759/3938939, or 0.529% (**Appendix Table 5**). In multivariable analysis (**Figure 5**), the adjusted OR was 1.47 (95% CI 1.41-1.54). For altered consciousness / mental status, the adjusted OR was 1.22 (95% CI 1.16-1.29). Results were similar when person-quarters with a hypoglycemia hospitalization or ED visit were excluded, as shown in **Appendix Figure 1**.
>
> In absolute terms, the probability of the combined outcome of hospitalization or ED visit for a fall-related fracture is predicted to increase with concurrent warfarin use from 0.318% to 0.467% per quarter (these calculations are described in **Appendix Note 1**). For hypoglycemia and altered consciousness / mental status, the risk per quarter increases by 0.002% and 0.038%, respectively. For any of the three diagnoses, the adjusted OR of a hospitalization or ED visit with concurrent use of warfarin and glipizide / glimepiride was 1.38 (95% CI 1.33-1.42) (**Figure 5**)."

The calculation of these statistics is described in a new **Appendix Note 1.**

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?

The reviewer makes an excellent suggestion. Within the Discussion section, we have put our findings in context, and include the relevant section for your convenience:

> "Existing evidence on the incidence of adverse drug events offers perspective on our results. For example, Gurwitz and colleagues analyzed Medicare managed care beneficiaries treated at a multispecialty group practice in 1999-2000[1], and found a rate of 8.0 events per thousand person-years which were serious to fatal (including fall with fracture), and preventable (having been caused by an error or otherwise avoidable.) More recently, Budnitz and colleagues estimated that unintentional medication overdoses, adverse effects at recommended doses, and allergic reactions led to 265,802 hospitalizations and ED visits among older U.S. residents in 2010, implying a rate of 6.6 events per thousand person-years.[2] Among elderly Medicare beneficiaries using glipizide / glimepiride, our analysis indicates that the concurrent use of warfarin is associated with approximately 8.8 adverse events per thousand person- years, in terms of hospitalization or an ED visit for hypoglycemia, fall-related fracture or altered consciousness / mental status."

Furthermore, to enhance the clinical relevance of our study, we have elaborated on the critical role of pharmacovigilance, and include the revised section below, putting key additions in **bold**:

> "Our study suggests a role for increased pharmacovigilance in individuals receiving both warfarin and the sulfonylureas glipizide or glimepiride. In its development of ambulatory care medication quality measures, the National Quality Forum (NQF) has endorsed a warfarin-specific measure that requires INR testing within 3 to 7 days of initiating anti-infective agents to lower the risk of major bleeding.[3] NQF has also endorsed a measure of the rate of severe hypoglycemia following administration of glipizide, glimepiride and other anti-diabetic medications within a hospital.[3] **Such measures may be expanded to include glycemic monitoring**

among patients on glipizide or glimepiride who initiate warfarin in an ambulatory setting. A workgroup of the American Diabetes Association and American Endocrine Society has emphasized the importance of clinical surveillance and glucose monitoring, and noted that older individuals are particularly vulnerable to harm from hypoglycemia.

Medication therapy management (MTM) services may play an important role in monitoring patients concurrently using glipizide or glimepiride and warfarin.[4-6] MTM services focus on the evaluation and assessment of a patient's entire medication regimen. Within Medicare Part D prescription drug plans, certain enrollees with multiple chronic conditions are entitled to MTM services from a health care professional.[7] The American Pharmacists Association recommends that MTM services be considered for any individual with actual or potential medication-related problems, regardless of the number of medications, specific disease states, or health plan coverage.[8] **It is noteworthy that warfarin treatment guidelines have called for lower initial dosing among individuals age 75 or older, in order to mitigate bleeding risk[9]; our findings suggest that lower dosing may also be appropriate for individuals age 65-74 who initiate warfarin while treating diabetes with glipizide / glimepiride.**"

References

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Referee 2

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.

We appreciate the reviewer's kind words and thoughtful comments.

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.

This is a good suggestion. As described in the Methods section (p. 10 of the tracked-changes version of the revised manuscript), we have performed a new analysis that uses HCC scores to measure health status. As shown in our revised Figure 3, the odds ratio for concurrent warfarin use is similar, and remains significantly greater than one.

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.

At the reviewer's suggestion, our analysis of first versus subsequent use now excludes the first quarter in which an individual appears in the data whenever there was a warfarin fill in the quarter. As shown in our revised Figure 2, the odds ratio for first warfarin use is now 2.47 (95% CI 1.77 - 3.45.) We have noted the limitation about pre-enrollment utilization in the discussion (p. 17.)

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

Thank you for this suggestion. We now note the lack of an interaction between statins and sulfonylureas in the Methods section (p. 11.)

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?

Thank you for noting this issue. As we have clarified in the Methods section (p. 8), regimens combining glipizide / glimepiride with other agents are included in the analysis. We identified these cases by searching for the drug names of interest within the full generic names. Please note further that we have performed a new analysis that adjusted for use of other diabetes medications, including metformin. As our revised Figure 3 shows, the odds ratio for warfarin use is almost identical to the baseline analysis.

2) More a topic for another paper, but do sulfonylureas affect warfarin/INR? If so, I would discuss this in the introduction.

Motivated by the reviewer's comment, we have determined that a clinical drug reference indicates that glyburide, another second-generation sulfonylurea, may increase the risk of bleeding with warfarin. We now note this interaction in the introduction (p. 4.)