

Peer-Review Record

The association between warfarin usage and international normalized ratio increase: systematic analysis of FDA Adverse Event Reporting System (FAERS)

J Cardiovasc Aging 2023;3:33. <http://dx.doi.org/10.20517/jca.2023.33>

by Robert Morris, Megan Todd, Nicole Zapata Aponte, Milagros Salcedo, Matthew Bruckner, Alfredo Suarez Garcia, Rachel Webb, Kun Bu, Weiru Han, Feng Cheng

Received: 14 Sep 2023 | **First Decision:** 28 Sep 2023 | **Revised:** 29 Sep 2023 | **Accepted:** 10 Oct 2023 | **Published:** 17 Oct 2023

Academic Editor: Ali J. Marian

Reviewer 1: Anonymous

Reviewer 2: Anonymous

Round 1

Reviewer 1 Report

This is a clinically relevant and important study and particularly important in the elderly as the risk of increased INR and bleeding as well as DDI are much higher in this age population. The reviewer suggests minor revisions and adding more data, if available, as follows:

Please add N (the number of cases) to the relevant information in the abstract (how many people were studied, how many and what % had increased INR or developed some of the adverse events mentioned).

If the information is available, please add the magnitude of the changes, for example how much drop in the Hg (mean or median and SD or SE).

Please define “lift” in the abstract to give it a meaning when referring to the strength of drug -drug interaction. Same for ROR.

Please revise conclusion in the abstract as it states the obvious that “Patients prescribed warfarin were at greater risk of reporting increase INR.” You may wish to state that warfarin use and increased INR were associated with (list the side effects) and the risk was more common in the elderly. The reviewer suggests keeping the last sentence of the conclusion.

If data are available, the reviewer suggests adding data on frequency of bleed, sites of bleed

(GI, CNS, GU, etc.), blood transfusion and clinical outcomes related to bleeding.

Compliance data if available would be valuable.

The reviewer suggests removing the formula how INR is calculated, as it is rather a common knowledge.

Please discuss under-reporting as a confounder, if that is a concern, as in the clinical setting often increased INR is not reported to the FDA.

Regarding the temporal distribution of increased INR reports, it would be informative to complement the data with the use of warfarin during the reported period (increased INR reports is less perhaps because of less use of warfarin).

Association rule mining abbreviation should be inserted on line 126 (first use) rather than in the discussion section.

No need to define hematuria as blood in the urine for the JCA audience.

Authors' Response

This is a clinically relevant and important study and particularly important in the elderly as the risk of increased INR and bleeding as well as DDI are much higher in this age population. The reviewer suggests minor revisions and adding more data, if available, as follows:

1. Please add N (the number of cases) to the relevant information in the abstract (how many people were studied, how many and what % had increased INR or developed some of the adverse events mentioned).

[Answer: Thank you for the suggestion! We clarified the sample sizes and lift values for the top adverse events mentioned in the abstract.](#)

2. If the information is available, please add the magnitude of the changes, for example how much drop in the Hg (mean or median and SD or SE).

[Answer: This is a great suggestion! Unfortunately, FAERS only contains adverse events and indications for use. The closest thing to change magnitude would be the severity of the elevated INR i.e., did it require hospitalization, did it lead to death, etc... but there is no standard or input for the exact INR change in these individuals. This would be great information to have!](#)

3. Please define "lift" in the abstract to give it a meaning when referring to the strength of drug-drug interaction. Same for ROR.

Answer: Thank you for the suggestion. We added details explaining the relevance of these terms in the abstract section.

4. Please revise conclusion in the abstract as it states the obvious that “Patients prescribed warfarin were at greater risk of reporting increase INR.” You may wish to state that warfarin use and increased INR were associated with (list the side effects) and the risk was more common in the elderly. The reviewer suggests keeping the last sentence of the conclusion.

Answer: Thank you for the suggestion! We modified the conclusion portion of the abstract to better reflect the most salient findings.

5. If data are available, the reviewer suggests adding data on frequency of bleed, sites of bleed (GI, CNS, GU, etc.), blood transfusion and clinical outcomes related to bleeding.

Answer: Thank you for the great suggestion!. FAERS uses a standardized set of terms to describe bleeding events. In Table 1, we listed the 15 most commonly reported ADEs for warfarin users and frequencies for these common ADEs.. Many of the top ADEs were directly or indirectly related to bleeding such as general hemorrhaging (n = 5794), GI hemorrhaging (n = 5397), epistaxis (n = 3023), and hematuria (n = 2693). In addition, common reported side effects such as anemia and decreased hemoglobin are frequently associated with blood loss, particularly in the GI tract, and other symptoms such as contusions and dizziness may also be a consequence of severe bleeding events. FAERS does not contain data on whether or not blood transfusions were required. We included several additional sentences concerning this in the results section.

6. Compliance data if available would be valuable.

Answer: This is another great suggestion! Like information concerning specific clinical outcomes and specific measurement changes, compliance data is absent from FAERS case reports. We agree that this information would greatly improve the FAERS database!

7. The reviewer suggests removing the formula how INR is calculated, as it is rather a common knowledge.

Answer: Thank you for the suggestion. We removed the INR formula as per your suggestion.

8. Please discuss under-reporting as a confounder, if that is a concern, as in the clinical setting often increased INR is not reported to the FDA.

Answer: This is an excellent point! In general, under-reporting is a major concern for these types of observational studies. For warfarin, however, we feel that the effects of this type of bias would be considerably smaller since INR evaluation is a frequent and required part of check ups for patients taking warfarin. Because of this emphasis and the frequency in which this is monitored, we believe that the effects of under-reporting should be rather

minimal. We added additional information in the discussion section concerning this possible issue.

9. Regarding the temporal distribution of increased INR reports, it would be informative to complement the data with the use of warfarin during the reported period (increased INR reports is less perhaps because of less use of warfarin).

Answer: This is a great point! One of the largest possible explanations for this is the emergence of direct oral anticoagulants (DOACs) as an alternative to warfarin for anticoagulation therapy. The first approved DOAC, dabigatran in 2010 and the subsequent approval of two additional drugs in this class, edoxaban and betrixaban, in 2015 and 2017 respectively provided new options for the treatment for thromboembolic events that were generally viewed as safer with regards to the risk of stroke and all-cause mortality. In addition, essentially all Medicare Prescription Coverage Plans by the end of 2017 covered the costs of at least 1 DOAC drug and pushes made by several advisory committees/boards in the field further shifted focus towards DOACs. We added this additional information into the discussion section.

10. Association rule mining abbreviation should be inserted on line 126 (first use) rather than in the discussion section.

Answer: Thank you for pointing this out. We made the correction in the manuscript.

11. No need to define hematuria as blood in the urine for the JCA audience.

Answer: Thank you for pointing this out. We removed the hematuria definition from the manuscript.

Reviewer 2 Report

I do think it is a good job.

Authors' Response

Thanks!