Iranian Journal of Pharmaceutical Research
Volume 23 · Issue 1 · e143898

OPEN PEER REVIEW

Cost-Effectiveness Analysis of Pharmacogenomics-Guided Versus Standard Dosing of Warfarin in Patients with Mechanical Prosthetic Heart Valve

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SUBMITTED	REVISED	ACCEPTED	DOI
12 Dec 2023	2 Mar 2024	8 Apr 2024	10.5812/ijpr-143898

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1 Original submission

1 comment · 21 Jan 2024

Associate Editor

MAJOR REVISION 21 Jan 2024

Dear Author(s)
Please consider the following comments on your submitted manuscript made by the reviewer(s).

1. It is recommended to include the comparator in the title.
2. It is highly recommended that authors adhere to the CHEERS guidelines when reporting the details of their study.
3. In the abstract section, the Methods part should start with the study type and the main analysis.
4. It is important to report the willingness-to-pay threshold in the Method section of the abstract.
5. In the abstract and main text, what is the meaning of "percentage of time" in the results of the one-way sensitivity analysis?
6. VKA should be written in full as Vitamin K Antagonist when it first appears in the text.
7. Please expand abbreviations only at their first appearance.
8. Authors should report any available guidelines, recommendations, or organizational approvals for pharmacogenomics-guided dosing of warfarin in patients with a mechanical prosthetic heart valve.
9. The decision model should start with the study characteristics, namely, the study type and study design.
10. Authors are requested to mention the rationale for setting the 1-year time horizon for the model.
11. Why did the authors rely on old evidence for clinical inputs when newer evidence is available?
12. It appears that the study's perspective may have been misstated according to the reported cost items.
13. In the results section, the authors should mention the statistical analysis they used to determine any differences in HRQOL between patient groups. They should also indicate whether or not this difference is statistically significant.
14. Authors should specify the exchange rate used for converting Iranian Rials (IRR) to United States Dollars (USD).
15. The authors seem to have directly used rates reported in clinical studies as probabilities in the study model. The authors are asked to clearly explain how they calculated the probabilities used in the model from these rates.
16. In the results section, the authors mentioned, "The model was not sensitive to the adverse events' disutilties and probabilities, while the PTTR of both groups had an influence on the cost-effectiveness because they increased the ICER by more than 20%." It would be appreciated if they could provide a reference for this definition.
17. In reporting the results of the one-way sensitivity analysis of the model, the term utility weight should be used instead of utility.
18. As the one-way sensitivity analysis of the model has shown, it is very important to find a statistically significant difference between the utility weights in the two compared arms. So, the authors are requested to consider this difference in the probabilistic analysis of the model.
19. In the results section, the authors are requested to mention the percentage of cost-effective results according to the IECR scatter plot of Probabilistic Sensitivity Analysis.
20. In the discussion section, the authors mentioned: "Although probabilistic sensitivity analysis showed the robustness of our model, the tornado sensitivity analysis demonstrated that the model is sensitive to the PTTR, the cost of pharmacogenetic test and the utility of standard dosing and pharmacogenetic-guided dosing group." This definition is misleading. They are asked to rephrase the sentence by reporting the percentage of cost-effectiveness in the PSA.

21. In the Tornado analysis (Figure 2), the variables should be sorted in the order of the sensitivity of the model to them from the highest to the lowest sensitivity.
Best regards,

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor-in-Chief,

I am writing to submit the revised manuscript entitled "Cost-Effectiveness Analysis of Pharmacogenomics-Guided versus Standard Dosing of Warfarin in Patients with Mechanical Prosthetic Heart Valve" for consideration for publication in the Iranian Journal of Pharmaceutical Research. I greatly appreciate the opportunity to revise and resubmit this manuscript following the valuable feedback provided by the reviewers.

In response to the reviewers' comments, I have carefully addressed each point raised and made significant revisions to enhance the quality and clarity of the manuscript. The comments and detailed responses are in next page. The edited parts in the manuscript are in yellow highlight. Overall, the most important revisions are:

1. Adding more detailed information following the CHEERS guideline suggestions.
2. Reporting suggestions of the CPIC guideline, related to pharmacogenomics-guided dosing of warfarin.
3. Giving more explanations about our decision model.
4. Reporting the P-value related to the difference between utilities of pharmacogenomics-guided and standard dosing group.
5. Resorting the parameters in the Tornado Diagram.

I believe that these revisions have strengthened the manuscript and have addressed the concerns raised during the review process. I am confident that the revised version makes a valuable contribution to the field of pharmaceutical research and aligns well with the scope and objectives of the Iranian Journal of Pharmaceutical Research.

I would like to express my sincere gratitude to the reviewers for their constructive feedback, which has undoubtedly improved the quality of the manuscript. Their insights have been instrumental in shaping this revised version.

Thank you for considering this revised manuscript for publication in your esteemed journal. I am confident that it will make a valuable addition to the scientific literature and contribute to advancing research in the field of pharmaceuticals.

Please do not hesitate to contact me if you require any further information or have any additional questions regarding the manuscript.

Sincerely,

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Tehran University of Medical Sciences, Tehran, Iran

Comments and Responses

1. **It is recommended to include the comparator in the title.**

   Thank you for the valuable comment. The comparator was included in the title: "versus Standard Dosing"

2. **It is highly recommended that authors be adhere to the CHEERS guidelines when reporting the details of their study.**

   Your comment is highly appreciated. We considered suggestions of CHEERS guideline and edited the manuscript.

CHEERS guideline	Added parts in the manuscript (yellow highlight)
Background and Objectives (mentioning practical relevance of the study for decision making in policy or practice.)	In Iran, like other developing countries healthcare budgets are limited. Therefore, it is vitally important to find evidence to help decision makers direct resources to most beneficial interventions. To guide resource allocation, this economic evaluation was conducted to assess…
Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	For the base-case analysis, a hypothetical cohort of 1000 Iranian patients aged 18 or above that have recently undergone MPHV surgery with no contraindications to warfarin administration entered the model.
Perspective (State the perspective(s) adopted by the study and why chosen.)	Additionally, since there were limitations to calculate indirect medical costs and have an accurate estimate of these costs, this study has a healthcare sector perspective and only direct medical costs are considered
Rationale and description of model (if modelling is used, describe in detail and why used.)	Since a limited time frame was considered, we developed a decision tree model in MS Excel 2022.
conclusion	We deleted this part as it was not suggested by CHEERS guideline

3. In the abstract section, the Methods part should start with the study type and the main analysis.

Thank you for your insightful suggestion. We edited the Methods part; here is the edited part: " In this economic evaluation study, a cost-effectiveness analysis was conducted to compare pharmacogenomics-guided versus standard warfarin dosing".

4. It is important to report the willingness-to-pay threshold in the Method section of the abstract.

Thanks to your informative comment, we edited the Methods part, and added the pharmacoeconomic threshold: "The considered pharmacoeconomic threshold for medical intervention in Iran's healthcare system was 1500 $."

5. In the abstract and main text, what is the mean of "percentage of time" in the results of one-way sensitivity analysis?

This is a very important question. We added this explanation to the Method part: "The estimated percentage of time in the therapeutic range (PTTR) of INR has become a widely applied measure of the quality of vitamin K antagonist anticoagulation (1). A considerable number of prospective clinical trials, which were usually designed to assess the effect of genotype-based dosing on warfarin anticoagulation control, considered PTTR as the primary outcome (2-4)." The PTTR was an input parameter of our model. To investigate the sensitivity of the results to variations of this parameter, we conducted a deterministic sensitivity analysis and reported it in the Results part.

6. VKA should be written in full as Vitamin K Antagonist when it first appears in the text.

We appreciate your insightful comment in this matter. We wrote Vitamin K Antagonist instead of VKA as it was only mentioned once in the paper.

7. Please make abbreviations expand only at the first appearance.

We are thankful for this valuable suggestion and we edited the manuscript accordingly.

8. Authors should report any available guidelines, recommendations, or organizational approvals for pharmacogenomics-guided dosing of warfarin in patients with mechanical prosthetic heart valve.

Your informative comment is highly appreciated. We added CIPIC guideline suggestions to Introduction part: "Furthermore, the Clinical Pharmacogenetics Implementation Consortium (CPIC) has developed guidelines on new developments in the field of PGx-guided dosing of warfarin to help clinicians utilize genetic test results to optimize warfarin therapy. This guideline has assigned a CPIC level of "1A" to warfarin/CYP2C9 and warfarin/VKOR1, suggesting that genetic information about the mentioned genes should be considered in warfarin dosing."

9. The decision model should start with study characters, namely, the study type and study design.

Considering your insightful suggestion, we edited the Decision Model part as you suggested: "In this study we conducted a cost-utility analysis to…"

10. Authors are requested to mention the rationality of setting the 1-year time horizon for the model.

Thank you for the valuable comment. We considered 1-year time horizon for some reasons similar to other studies. We described the reasons below and added it to the discussion part.

"We considered a 1-year time horizon for our model, similar to previous studies (5, 6). for some reasons. Firstly, studies have shown that the first postoperative year is marked by the highest incidence of thrombosis, which decreases in the following years. So, the incidence of side effects is highest at the first year after surgery (7, 8). Secondly, thanks to consultation with clinicians, we were informed that patients suffer the most from warfarin's side effects during the first year after mechanical heart valve surgery. Because they are not familiar with warfarin and INR. Thirdly, during the first year, they are recovering from the surgery. Because of this, they are more prone to warfarin side effects. Lastly, we consulted with a genetic specialist and were informed that taking genetic tests has an impact on dosing if it is taken as soon as possible before starting warfarin. In this way, physicians will be capable of recognizing sensitive patients before dosing. But, if the patient takes genetic test sometime after initiating warfarin, it will not be as impactful. Because during the 6 months after surgery, physicians could identify sensitive patients by checking their INR test records or because of the side effects like bleeding that they experience. Considering this, one year after surgery, warfarin therapy in both groups is the same."

11. Why did authors rely on old evidence for clinical inputs when newer evidence is available?

We did a systematic search to find evidence on the input parameters of our model and we selected the evidence that best suited our model and study. Since new evidence was not available for some of the input parameters, we used older evidence.

12. It appears that the study's perspective may have been misstated according to the reported cost items.

Thank you for the valuable comment. This study had a healthcare system perspective. Therefore, we only calculated the direct medical costs including: the cost of INR tests, clinical visits for INR monitoring, hospitalization due to side effects of warfarin, and management of side effects related to warfarin.

13. In the results section, the authors should mention the statistical analysis they used to determine any differences in HRQOL between patient groups. They should also indicate whether or not this difference is statistically significant.

We conducted a Paired t-test, which showed that the difference between the utility weights for standard dosing and genotype-guided dosing is statistically significant (P-value<0.0001). we mentioned this in the manuscript. In Methods: "after measuring utility weights, we conducted a paired t-test to evaluate the significance of difference between utility weights." In Results: " Additionally, results of paired t-test showed that the difference between the utility weights is significant (P-value<0.0001)."

14. Authors should specify the exchange rate used for converting Iranian Rials (IRR) to the United States Dollars (USD).

Taking this insightful comment into account, we added the exchange rate to the Methods part: "All costs were converted from Iranian Rials (IRR) to 2022 US Dollars (USD) with the exchange rate of 279655 IRR."

15. The authors seem to have directly used rates reported in clinical studies as probabilities in the study model. The authors are asked to clearly explain how they calculated the probabilities used in the model from these rates.

We appreciate your comment regarding the probability parameters. We did not use rates as an input parameter. We checked all the references we used, and made sure that the input parameters were not rates.

16. In the results section, the authors mentioned, "The model was not sensitive to the adverse events' disutilties and probabilities, while the PTTR of both groups had an influence on the cost-effectiveness because they increased the ICER by more than 20%." It would be appreciated if they could provide a reference for this definition.

We are thankful for this important comment. In addition to considering our model sensitive to those parameters that change the result of the study from not cost-effective to cost-effective, we considered our model sensitive to the parameters that the changes in their value result in more than 20% change in the ICER. To put it in other words, we considered 20% change in ICER as a threshold and reported the parameters that change the ICER more than this threshold.

17. In reporting the results of the one-way sensitivity analysis of the model, the term utility weight should be used instead of utility.

Thank you for the valuable comment. We edited the manuscript as you suggested.

18. As the one-way sensitivity analysis of the model has shown, it is very important to find a statistically significant difference between the utility weights in the two compared arms. So, the authors are requested to consider this difference in the probabilistic analysis of the model.

Taking this important comment into account, we conducted a Paired t-test, which showed that the difference between the utility weights is statistically significant (P-value<0.0001). We have considered changes in the utility weights of both groups in probabilistic sensitivity analysis.

19. In the results section, the authors are requested to mention the percentage of cost-effective results according to the IECR scatter plot of Probabilistic Sensitivity Analysis.

Your comment is highly appreciated. We added the percentage of cost-effectiveness as you suggested.

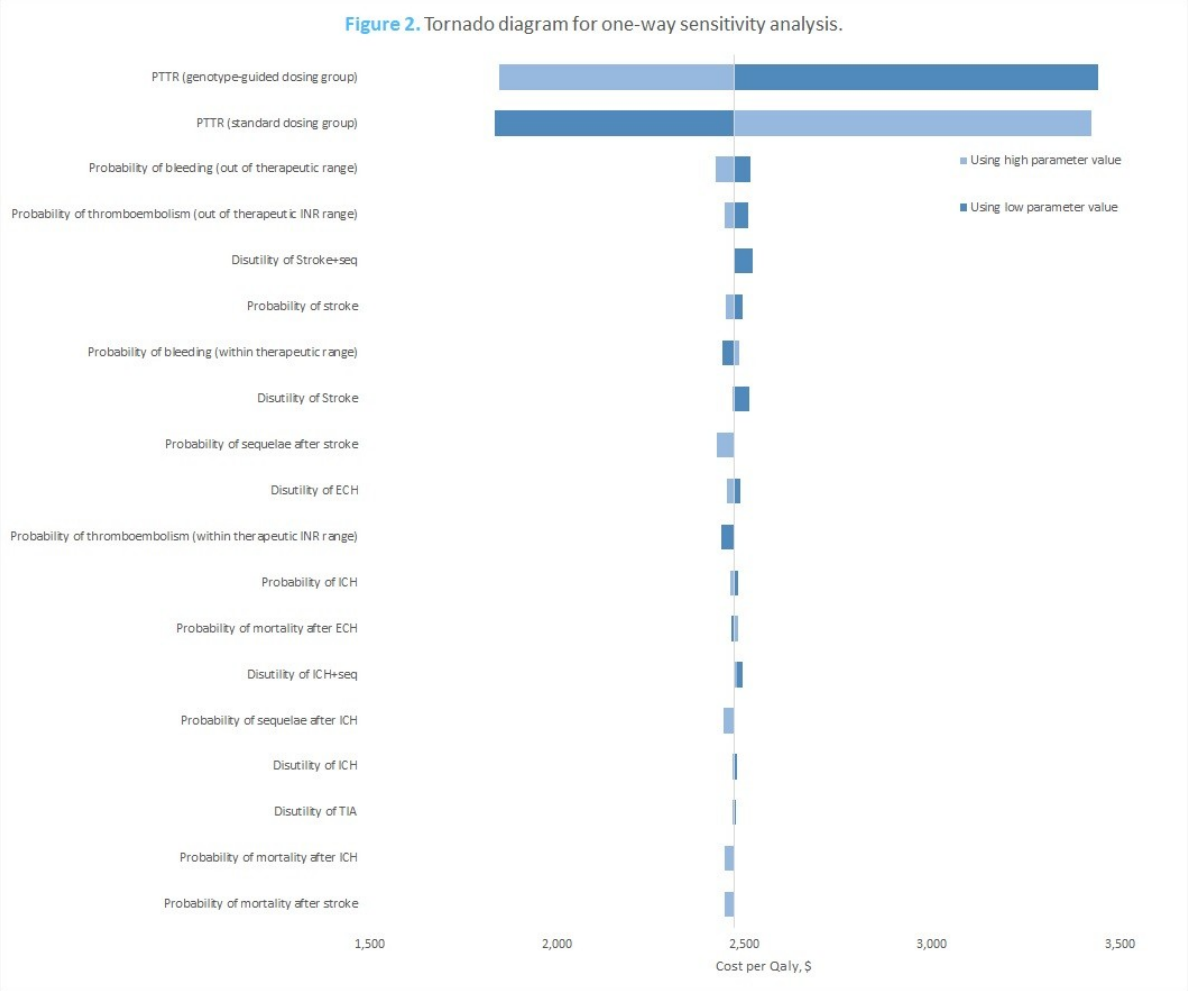
20. In the discussion section, the authors mentioned: "Although probabilistic sensitivity analysis showed the robustness of our model, the tornado sensitivity analysis demonstrated that the model is sensitive to the PTTR, the cost of pharmacogenetic test and the utility of standard dosing and pharmacogenetic-guided dosing group.". This definition is misleading. They are asked to rephrase the sentence by reporting the percentage of cost-effectiveness in the PSA.

In consideration of your insightful comment, we edited the mentioned part in Discussion: "Although in 86.1% of probabilistic sensitivity analysis simulations showed that PGx-guided dosing is not cost-effective and the model is robust, the deterministic sensitivity analysis

demonstrated that the model is sensitive to the PTTR, the cost of pharmacogenetic test and the utility of standard dosing and pharmacogenetic-guided dosing group."

21. In the Tornado analysis (Figure 2), the variables should be sorted in the order of the sensitivity of the model to them from the highest to the lowest sensitivity.

In consideration of your valuable comment, we changed the order as you suggested.



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2 Revision 1

1 comment · 7 Apr 2024

Associate Editor

ACCEPT 7 Apr 2024

All the comments have been addressed, and it is accepted.