Reviewer’s report

Title: Optimal INR Level for Warfarin Therapy after Mechanical Mitral Valve Replacement

Version: 0 Date: 10 Jan 2019

Reviewer: Research Square

Reviewer's report:

"STATISTICAL REVIEWER ASSESSMENT:

Is the study design appropriate for the research question (considering whether the analyzed population accurately reflects the design and whether you see any problems with control/comparison groups, e.g., likely confounders)?
No - there are minor issues

Are methodologies adequate and well implemented (considering whether assumptions are addressed and whether analyses are robust)?
No - there are minor issues

Are the analyses adequately communicated (considering whether reporting details are adequate and whether figures and tables are well labeled and described)?
No - there are minor issues

Does the interpretation accurately reflect the analyses without overstatement (considering whether limitations/bias are acknowledged and whether accurate descriptors, e.g., 'significant', are used)?
No - there are minor issues

Could an appropriately REVISED version of this work represent a statistically sound contribution?
Probably - with minor revisions

STATISTICAL REVIEWER COMMENTS:

The findings of the study may help cardiovascular surgeons decide optimal INR range for warfarin dose optimization in patients undergoing prosthetic mitral valve replacement in the Thai population. Since warfarin is a narrow therapeutic index medicine and needs long-term therapy in patients undergoing prosthetic mitral valve replacement, findings of the present study would ultimately be beneficial for the target population.

The authors have studied the INR levels of 200 patients for 3.53±1.27 years with 707.81 patient-years. Application of patient-year concept is a good statistical and epidemiological interpretation in terms of descriptive statistic. This helped to depict the INR levels of the study population over a fairly long follow up period, i.e., 3.5 years (although it is not sufficiently long follow up period for patients taking
warfarin). They have shown their results in frequency and percentage form (i.e., applying descriptive statistics) in an illustrative manner and also shown p values in figures 1A, 1B, 1C, 1D, 2 and 3.

The authors have used a chi-square test to compare the incidence density of thromboembolic and bleeding complications, which seems an underutilization of better parametric alternative because chi square test better gives the association between two or among more than two variables; comparison of proportions and goodness of fit. Since the authors have studied INR values of more than 3.5 years' follow-up data, repeated measure ANOVA (if data were normally distributed) or Friedman's test (if data were not normally distributed) would be better inferential statistic of choice. Authors are suggested to check normality of their dataset with Kolmogorov Smirnov test and follow the above-mentioned suggestion.

REQUESTED REVISIONS:

ADDITIONAL REQUESTS/SUGGESTIONS:

General comments:
* Use proper subject-verb agreement with the term 'data' as it is plural term.
* Use 'who' with persons instead of 'that'.
* Follow citation within text properly such as in 'Marieke Torn, et al., 2009'.

Specific comments:
Abstract:
Results: Rewrite the sentence "Two hundred patients were included and followed over a period of 707.81 patient-years." The period was 3.53±1.27 years whereas 707.81 was patient-years.

Conclusion: It is not necessary to redefine 'optimal INR level' as it is already defined in Methods. This also applies to the Conclusion section in the main text.

Main text:
Methods:
* Mention study design properly; just mentioning data extracted retrospectively is not sufficient. However, it seems that the authors followed the time-series study as they took the follow-up data of 200 patients till 707 patient-years (i.e., more than 3.5 years' follow-up data). This has a significant impact on the choice of statistical test.
* Rewrite Methods section under various sub-headings such as study design, study area and site, study population and sample size calculation, ethics approval, study procedure, sampling technique, inclusion and exclusion criteria, data collection tool and data collection, reliability and validity, and statistical analysis although you have mentioned majority of sections (except data collection tool, reliability and validity and other) in the unstructured format.
* The authors have mentioned "Using a power of 90%, a type I error of 0.05, and a type II error of 0.10, a minimum sample size of 200 patients was calculated." Still, sample size calculation is not clear from the statement.
* The authors have mentioned "The incidence density of thromboembolic and bleeding complications was compared using chi-square test." Chi square test better gives the association between two or among more than two variables; comparison of proportions and goodness of fit. Since the authors have studied INR values of more than 3.5 years' follow-up data (although the frequency of follow ups are not clear from the text and that needs further elaboration), repeated measure ANOVA (if data were normally distributed) or Friedman's test (if data were not normally distributed) would be
better inferential statistic of choice. Chi square test seems an underutilization of better parametric alternative. Authors are suggested to check normality of their dataset with Kolmogorov Smirnov test and follow the above-mentioned suggestion.

Results:
* The authors have not shown the dose of warfarin being studied in the study sample.
* They have also not shown the frequency of INR level monitoring and frequency of warfarin optimization based on that.

Discussion:
* Rewrite the sentence "The study population of these studies were slightly difference than ours since they enrolled both mitral and aortic valve replacement especially ARENA study which enrolled aortic valve replacement in the majority" clearly.
* The sentence "As a result, our study may have lacked sufficient power to identify all significant associations" mentioned as the limitation seems controversial with the previous statement "Using a power of 90%, a type I error of 0.05, and a type II error of 0.10, a minimum sample size of 200 patients was calculated" mentioned in Methods section. Justify how can the power of 90% be insufficient?
* The authors have mentioned "Third, the patients enrolled in this study were from a single center." Are single-centric studies real limitations? Or are all multi-centric studies are free from such limitations?

Conclusion: Rewrite Conclusion section more specifically.
Figures 1A, 1B, 1C, 1D, 2 and 3: Show all p values in between each interval of INR."

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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