Author’s response to reviews

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

Authors:

Itthidet Kamthornthanakarn (dr.itthi@hotmail.com)
Rungroj Krittayaphong (rungroj.kri@mahidol.ac.th)

Version: 2 Date: 15 Mar 2019

Author’s response to reviews:

Response to comments from reviewers and editors
BCAR-D-18-00341R1
Optimal INR Level for Warfarin Therapy after Prosthetic Mitral Valve Replacement
Itthidet Kamthornthanakarn, MD; Rungroj Krittayaphong, M.D.
BMC Cardiovascular Disorders

STATISTICAL REVIEWER COMMENTS:

The authors have addressed most of the concerns raised previously.

The authors have applied patient-year concept which is a good statistical and epidemiological interpretation in terms of descriptive statistic. They have also mentioned the application of chi square test (although underutilized) and have also applied descriptive statistics such as frequency distribution and percentage.

Concerns about probable application of repeated measure ANOVA (if data were normally distributed) or Friedman's test (if data were not normally distributed) has not been addressed. Status of normality of their dataset has not been mentioned yet. Other comments have been given with this peer review.

REQUESTED REVISIONS:
General comments:
* Still not addressed
* Use proper subject-verb agreement with the term 'data' as it is plural term.

Response:
We made correction as suggested throughout the manuscript.

* Use 'who' with persons instead of 'that'.
Response:
We made correction as suggested throughout the manuscript.

* Follow citation within text properly such as in 'Marieke Torn, et al., 2009'.

Response:
We made correction as suggested throughout the manuscript.

Specific comments:
Methods:
* Study design is still not mentioned clearly.

Response:
We added the statement ‘This is a retrospective cohort study design.’ In the abstract (page 2 line 6) and in the methods section (page 4 line 1).

* Still, sample size calculation is not clear.

Response:
We explained the sample size calculation in more details as follows:
We calculated sample size based on the results of a previous publication by Marieke Torn, et al., 2009. They reported the incidence of thromboembolic and bleeding events in the <2, 2.0-2.4, 2.5-2.9, 3.0-3.4, 3.5-4.5, and >4.5 INR groups to be 0.319, 0.067, 0.02, 0.025, 0.033, and 0.247, respectively. We calculated sample size by G group Chi-square test comparing proportions in C Categories formula by nQuery program (Statistical Solutions Ltd, Cork, Ireland). From the estimation of proportion of patients in each INR group, we calculates the ratio of n/n1 assuming that n1 which is the number of patients in the group with the lowest INR (INR <2) = 1. The calculated ratio of n for the 6 INR groups were 1: 6: 4.2: 4: 4: and 0.8. The average proportion of thromboembolism and bleeding outcome from the calculation was 0.062 and variance of proportion was 0.005. By using the proportion of outcome at 0.062, variance of 0.005, with the power of 90% (a type II error of 0.10), a type I error of 0.05, The sample size of all groups was 192 patients. We then proposed the total sample size of 200 patients. (page 4, line 9-21)

* Concerns about probable application of repeated measure ANOVA (if data were normally distributed) or Friedman's test (if data were not normally distributed) has not been addressed. Status of normality of their dataset has not been mentioned yet.

Response:
We added the following statement in the statistical section.
Kolmogorov Smirnov test was used to test the normality of the data distribution. All continuous variables inn this study such as age, LVEF, LA volume, LA diameter, and INR were normally distributed.(page 7, line 4-6)
Concerning the comparing repeated measure INR data, since the number of INR tests during follow-up of the study population varied, it may not be suitable to use repeated measure ANOVA to run the analysis. For repeated measure ANOVA analysis, the number of repeated measure data should be the same to prevent excluding patients’ data from analysis. Linear mixed model (fixed effect) is the preferred test to compare the repeated measurement INR levels related outcome measures at time.
Limitations of the study:
* The statement about power analysis has been hidden.

Response:
We added the following statement in the limitation of study paragraph.
Second, the size of the study population was relatively small. Although we ran power analysis to calculate sample size needed for the primary objective of this study, we felt that the number of patients of 200 is relatively small. Further study with a larger number of study population may be needed to confirm the results of this study. (page 11, line 7-10)

* Limitation about single-centric or multi-centric studies has been omitted."

Response:
We added the following statement in the limitation of study paragraph.
Third, the patients enrolled in this study were from a single center. The nature of hospital and medical practice may be different. Also our center is Thailand’s largest tertiary referral hospital, which means that we are often referred patients with complicated and intransigent conditions. As such, it is possible that our findings may not be generalizable to patients with the same condition in other settings. (page 11, line 10-14)

We thank all the comments. We believe that the revised manuscript is suitable for publication in BMC Cardiovascular disorders.