PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	TIME IN THERAPEUTIC RANGE AND STABILITY OVER TIME FOR WARFARIN USERS IN CLINICAL PRACTICE: AN OBSERVATIONAL STUDY USING LINKED ROUTINELY COLLECTED HEALTH DATA
AUTHORS	Mcalister, Finlay Wiebe, Natasha Hemmelgarn, Brenda

VERSION 1 - REVIEW

REVIEWER	Adam Rose
REVIEW RETURNED	28-Mar-2017

GENERAL COMMENTS	I have previously reviewed this article in submission to another journal. I generally liked the paper then and I like it even more now, as the authors have addressed many of the comments I had before and also some comments from other reviewers. This is an effort to characterize the anticoagulation control over time of all the adults in Alberta with NVAF. In particular, the focus is on whether patients have sufficient INR monitoring, and of those who do, how many have good TTR in months 1-6, and of those who do, how many continue to have good TTR in months 7-12 and 13-18. The study is well done with appropriate analyses and statistics. The dataset is fitting for these questions and well used. The writing is clear and easy to follow. The conclusions are sound, well supported by the findings, and will be of clinical utility. The bottom line is that inadequate INR monitoring remains a big issue, and certainly some patients don't achieve good TTR, but there is a large and identifiable group who do well on warfarin and can continue it indefinitely. It occurs to me that a "voltage drop" model may be useful here as a way to describe the subsets of patients who don't make it to the next stage, i.e. enough INR monitoring, good TTR initially, good TTR subsequently. See https://www.ncbi.nlm.nih.gov/pubmed/25225140 or http://jamanetwork.com/journals/jama/fullarticle/185953 for examples of articles that describe similar phenomena of successively smaller groups of patients who make it to the next stage, and you are left with relatively few at the end with fully controlled BP for example. You don't have to do this, but it's a suggestion for how to frame the results. My one small critical comment is left over from my previous review and was not addressed. At the bottom of page 11, the authors say that "Our finding that patients with cirrhosis, cancer, alcohol misuse, and dementia were less likely to have INRs in target range is not surprising as all are factors known to negatively impact medication

	adherence..." This is not really true. Cirrhosis probably does not impact TTR through poorer adherence, but via a direct impact on the synthesis of clotting factors. Cancer probably has a dual effect that is both biological and adherence related, although it's questionable if you can call it a lack of adherence if the patient is just undergoing lots of procedures and thus interrupting therapy. Alcohol misuse similarly would have both biological and adherence-based effects on TTR. Dementia is probably solely mediated by adherence. To go on down the list, malnutrition is biological, fluctuating liver function is biological, etc. This is not a major point of the paper, but the way it's presented here is simplistic and incorrect. I suggest that the authors recognize that some of these may impact adherence (e.g. dementia) some may have mainly biological impact on TTR (e.g. cirrhosis) and some may have elements of both (e.g. alcohol misuse). No further suggestions for improvement. This is a very good effort and a nice addition to the literature.

REVIEWER	Peter Brønnum Nielsen
REVIEW RETURNED	18-May-2017

GENERAL COMMENTS	Dr McAlister and colleagues report on data from an administrative database in Alberta, Canada. They investigated TTR in atrial fibrillation patients receiving warfarin treatment for a minimum of 30 days. An association of 'good TTR' in a time-period of 1-6 months and 'good TTR' in the subsequent periods was observed. The manuscript concerns an important and contemporary research question in the era of NOACs being increasingly prescribed for stroke prophylaxis in atrial fibrillation patients. Major concerns: The Rosendaal TTR is a somewhat 'blind' measurement, as it does not provide information on time spent above or below designated therapeutic range. Also, the measure do not consider severe fluctuations as having a negative impact: Rather it will contribute 'good TTR' even for a patient with a pattern of INR measurement as (e.g.) INR 1.7 and the following INR value is 3.2, while the next is 1.7 again – clearly not a picture you would like to see as a clinician. This is the main limitation of the TTR method and one of the reason why other groups have suggested to not report 'good TTR' solely based on a single number. To accommodate this limitation of the selected method for reporting TTR, this reviewer suggest to tabulate information on frequency of INR values in periods; this would also allow for an evaluation of changes over time. Suggest to include i) TTR; ii) number of INR measurements and range; iii) proportion of readings above 3.0; iv) proportions of readings below 2.0; v) a measure of INR variability that could be either simple variance of INR measurements, or more sophisticated by Fihn et al [DOI: 10.1267/THRO03020260.], which include calculation of the log of the variance growth rate. Including this information would allow readers to more thoroughly understand the findings of this study. A second major concern is the risk of selection bias being present in the study due to the exclusion of patients with less than 30 days on anticoagulants (5824 patients). Thirty days is a relatively long period; within this timeframe, the treating physician may have opted to terminate the treatment – either due to non-compliance or by risk/benefit evaluation. From the author's research question it may

	not be feasible to explore the reason for this short duration of treatment, but this should indeed be included as a limitation of the study. Third, the dichotomous stratification of TTR (above or below 65%) is arbitrary; disregarding the landmark NOAC trials instituted this threshold. It would be more appropriate to make e.g. 'poor TTR' (<65%), 'proper TTR' (65-80%), and 'excellent TTR' (>80%). This would allow readers to understand if TTR deteriorates or improves in this population over time. Minor comments: Page 8, line 32. Why were all INR values excluded +/- one week after hospital visit? The arguments provided is not entirely convincing. I would suggest this is a sensitivity analysis. Page 8, line 46. How was stop of treatment defined? Table 1: Cancer patients contribute around 12,000 patients. Should cancer patients be investigated separately, recognizing the higher likelihood of surgery and concomitant medical treatment that may influence decisions on warfarin treatment? The manuscript disposition could be increased by proof reading and grammar checks.

REVIEWER	Brian Cryder
REVIEW RETURNED	23-May-2017

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. First, the research question is excellent and represents a common dilemma facing clinicians in choosing oral anticoagulant therapies, especially with greater use and familiarity of IIa and Xa inhibiting medications. Abstract: seems to be a balanced overview of the manuscript Introduction: Presents a fair and evidence based set up to the research question. Appropriate literature support provided. Methods: well described procedure from a database that seems to be ideal for the type of information collected. Results: Findings were presented in clear manner, with wording complementing the tables/figures. Discussion: Seems relevant to findings of study and well connected to the clinical issue being addressed. While I would like to be able to highlight areas to improve in this manuscript, I found it very balanced with what appears to be valid statistical analysis. I have no significant critiques to address in this work. These results could be impactful to clinicians using anticoagulant medications. Well done.

VERSION 1 – AUTHOR RESPONSE

Dear Dr. Bedi,

Manuscript ID bmjopen-2017-016980 entitled "TIME IN THERAPEUTIC RANGE AND STABILITY OVER TIME FOR WARFARIN USERS IN CLINICAL PRACTICE: AN OBSERVATIONAL STUDY USING LINKED ROUTINELY COLLECTED HEALTH DATA"

Thank you for your e-mail of May 24 and the opportunity to revise/resubmit our manuscript. We also thank the reviewers for their helpful reviewer comments. We have tracked textual changes in the manuscript and highlight changes below. Of note, when we updated our database to include more recent laboratory data we discovered a coding error in the datafile we had been using before. Thus, several all of our n's statistics have changed in the revised manuscript – these numeric revisions have not been tracked. While The correction of that error has not substantially changed our finding that a substantial proportion of warfarin-treated patients were inadequately monitored in the first 6 months (40% in prior version, 30% in this version), but it did substantially alter our results with respect to stability of INRs over time (reducing the proportion of patients treated with warfarin exhibiting stable INRs over time from >80% to 57%). We apologize for this error in our original datafile coding. We have double and triple-checked the datafiles this time and are comfortable these results are correct.

Editorial Requirements:

- Please revise your title to state the research question, study design, and setting (location). This is the preferred format for the journal.

Reply: Done.

Reviewer 1 Comments:

I have previously reviewed this article in submission to another journal. I generally liked the paper then and I like it even more now, as the authors have addressed many of the comments I had before and also some comments from other reviewers.

This is an effort to characterize the anticoagulation control over time of all the adults in Alberta with NVAF. In particular, the focus is on whether patients have sufficient INR monitoring, and of those who do, how many have good TTR in months 1-6, and of those who do, how many continue to have good TTR in months 7-12 and 13-18. The study is well done with appropriate analyses and statistics. The dataset is fitting for these questions and well used. The writing is clear and easy to follow. The conclusions are sound, well supported by the findings, and will be of clinical utility. The bottom line is that inadequate INR monitoring remains a big issue, and certainly some patients don't achieve good TTR, but there is a large and identifiable group who do well on warfarin and can continue it indefinitely.

Reply: Thank you for the kind words and the helpful suggestions you made for previous iterations of this manuscript. As described above, we discovered a coding error in our original datafile when updating the laboratory data for this revision and while correction of that error has not substantially changed our finding that a substantial proportion of warfarin-treated patients were inadequately monitored in the first 6 months (40% in prior version, 30% after correction), it did substantially alter our results with respect to stability of INRs over time (reducing the proportion of patients treated with warfarin exhibiting stable INRs over time from >80% to 57%). We have corrected the associated text in the Discussion section accordingly and apologize for not catching this error sooner.

It occurs to me that a "voltage drop" model may be useful here as a way to describe the subsets of patients who don't make it to the next stage, i.e. enough INR monitoring, good TTR initially, good TTR subsequently. See https://www.ncbi.nlm.nih.gov/pubmed/25225140 or http://jamanetwork.com/journals/jama/fullarticle/185953 for examples of articles that describe similar phenomena of successively smaller groups of patients who make it to the next stage, and you are left with relatively few at the end with fully controlled BP for example. You don't have to do this, but it's a suggestion for how to frame the results.

Reply: We modified figure 1 as suggested to improve our clarity of presentation. Of note, we did not track that as a change in the manuscript and just provide the new version.

My one small critical comment is left over from my previous review and was not addressed. At the bottom of page 11, the authors say that "Our finding that patients with cirrhosis, cancer, alcohol misuse, and dementia were less likely to have INRs in target range is not surprising as all are factors known to negatively impact medication adherence..." This is not really true. Cirrhosis probably does not impact TTR through poorer adherence, but via a direct impact on the synthesis of clotting factors. Cancer probably has a dual effect that is both biological and adherence related, although it's

questionable if you can call it a lack of adherence if the patient is just undergoing lots of procedures and thus interrupting therapy. Alcohol misuse similarly would have both biological and adherence-based effects on TTR. Dementia is probably solely mediated by adherence. To go on down the list, malnutrition is biological, fluctuating liver function is biological, etc. This is not a major point of the paper, but the way it's presented here is simplistic and incorrect. I suggest that the authors recognize that some of these may impact adherence (e.g. dementia) some may have mainly biological impact on TTR (e.g. cirrhosis) and some may have elements of both (e.g. alcohol misuse).

Reply: Good points, and we have modified the manuscript text as suggested (para 1 on page 12).

Reviewer 2 Comments:

Major concerns:

The Rosendaal TTR is a somewhat 'blind' measurement, as it does not provide information on time spent above or below designated therapeutic range. Also, the measure do not consider severe fluctuations as having a negative impact: Rather it will contribute 'good TTR' even for a patient with a pattern of INR measurement as (e.g.) INR 1.7 and the following INR value is 3.2, while the next is 1.7 again – clearly not a picture you would like to see as a clinician. This is the main limitation of the TTR method and one of the reason why other groups have suggested to not report 'good TTR' solely based on a single number. To accommodate this limitation of the selected method for reporting TTR, this reviewer suggest to tabulate information on frequency of INR values in periods; this would also allow for an evaluation of changes over time. Suggest to include i) TTR; ii) number of INR measurements and range; iii) proportion of readings above 3.0; iv) proportions of readings below 2.0; v) a measure of INR variability that could be either simple variance of INR measurements, or more sophisticated by Fihn et al [DOI: 10.1267/THRO03020260.], which include calculation of the log of the variance growth rate. Including this information would allow readers to more thoroughly understand the findings of this study.

Reply: As per the reviewer suggestion, we have included this new table in the manuscript as Table 4:

Table 4. INR control in those with at least 3 INRs and TTR ≥65% in months 1-6 (N=16,639)

	Months 1-6	Months 7-12	Months 13-18
INR counts	9 (3,80)	7 (0,70)	7 (0,84)
>3.0, %	0.0 (0.0,35.0)	5.9 (0.0,100.0)	0.0 (0.0,100.0)
<2.0, %	12.5 (0.0,35.0)	13.0 (0.0,100.0)	12.5 (0.0,100.0)
INR SD	0.41 (0.00,3.26)	0.46 (0.00,5.70)	0.45 (0.00,5.66)
Median TTR, % (Range)	77.8 (65.0,100.0)	66.7 (0,100.0)	62.5 (0.0,100.0)

A second major concern is the risk of selection bias being present in the study due to the exclusion of patients with less than 30 days on anticoagulants (5824 patients). Thirty days is a relatively long period; within this timeframe, the treating physician may have opted to terminate the treatment – either due to non-compliance or by risk/benefit evaluation. From the author's research question it may not be feasible to explore the reason for this short duration of treatment, but this should indeed be included as a limitation of the study.

Reply: As per the reviewer suggestion, we have included two sentences in the Limitations section about this – bottom of page 13.

Third, the dichotomous stratification of TTR (above or below 65%) is arbitrary; disregarding the landmark NOAC trials instituted this threshold. It would be more appropriate to make e.g. 'poor TTR' (<65%), 'proper TTR' (65-80%), and 'excellent TTR' (>80%). This would allow readers to understand if TTR deteriorates or improves in this population over time.

Reply: As per the reviewer suggestion, we have included a new Figure 3.

Minor comments:

Page 8, line 32. Why were all INR values excluded +/- one week after hospital visit? The arguments provided is not entirely convincing. I would suggest this is a sensitivity analysis.

Reply: We have clarified that we meant INR values within one week of a hospitalization – we believe this accounts for the impact of acute illnesses or having therapy stopped for surgical procedures.

Page 8, line 46. How was stop of treatment defined?

Reply: If the patient's prior prescription expired and they had not had a new prescription dispensed we defined that as stopping treatment. We did not have information on actual patient consumption of pills, just dispensation records from pharmacies and we have acknowledged this in the Limitations section on page 13 (third point).

Table 1: Cancer patients contribute around 12,000 patients. Should cancer patients be investigated separately, recognizing the higher likelihood of surgery and concomitant medical treatment that may influence decisions on warfarin treatment?

Reply: We elected not to sub-divide our results by comorbidities as we wanted to focus on the overall message for this paper. We

have included some discussion of the negative impact of all co-morbidities on INR control in the revised manuscript (second para of the Results section and first para of the Discussion section).

Reviewer 3 Comments:

Thank you for the opportunity to review this manuscript. First, the research question is excellent and represents a common dilemma facing clinicians in choosing oral anticoagulant therapies, especially with greater use and familiarity of IIa and Xa inhibiting medications. I found it very balanced with what appears to be valid statistical analysis. I have no significant critiques to address in this work. These results could be impactful to clinicians using anticoagulant medications. Well done.

Reply: Thank you for the kind words.

All of my co-authors are aware that I am submitting the revised manuscript and have approved the submitted version. Thank you for your continued consideration of our manuscript.

Sincerely,

Finlay McAlister on behalf of all co-authors

VERSION 2 – REVIEW

REVIEWER	Adam Rose
REVIEW RETURNED	23-Jun-2017

GENERAL COMMENTS	The revision is acceptable. I congratulate the authors on their fine contribution

REVIEWER	Peter Brønnum Nielsen
REVIEW RETURNED	03-Jul-2017

GENERAL COMMENTS	The authors have replied sufficiently to all my raised concerns - thank you.