Author’s response to reviews

Title: Standardized Warfarin Monitoring Decreases Adverse Drug Reactions

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Author's response to reviews:

January 22, 2019

Tovah Honor Aronin, Ph.D.
Editor-in-Chief, BMC Family Practice

Dear Dr. Aronin:

We are pleased to submit our revised manuscript entitled “Standardized Warfarin Monitoring Decreases Adverse Drug Reactions” (FAMP-D-18-00252) for publication in BMC Family Practice. Point-by-point responses to the comments are below. All changes are clearly marked in red within the manuscript.

We would like to take this opportunity to thank you and the reviewers for your meticulous work and valuable advice.
Technical Comment: Provide a Cover letter stating the intention of the article and the approval of all authors on submitting this manuscript to the journal.

Response to Technical Comment: We have included the following sentences in our Cover Letter: “The risk of adverse drug reactions (ADRs) associated with the anticoagulant warfarin poses a significant concern. We developed an anticoagulation task force at our Institution to decrease warfarin ADRs and to standardize warfarin monitoring and management. We present a 5-year (2013-2017) study of patients who were prescribed warfarin by their primary care provider (PCP) or cardiologist upon hospital discharge and in the ambulatory setting to determine the international normalized ratio (INR) within 5, 10, and 30 days after discharge, time in therapeutic range (TTR), and the number and total cost change of severe warfarin ADRs. The goals of our study were to decrease warfarin ADRs and to develop an anticoagulation task force aimed at educating PCPs and cardiologists about evidence-based guidelines for warfarin management, increasing the use of our Institution’s electronic warfarin module, and enhancing patient compliance with obtaining INR. All of the authors of this work have read and approve the final version of our manuscript and its submission to BMC Family Practice.”

Editor Comment: Under the heading “Ethics approval and consent to participate” in the Declarations, please include information on the consent to participate.

Response to Editor Comment: We have added the sentence “The patients in this study provided their written consent to participate” in the “Declarations” section.

Reviewer #1, Comment #1: This is an interesting study with some useful and informative data. Line 115. I am not sure why a Poisson generalised model was used to analyse time in therapeutic range. The authors need to justify this. Analysing the means using a weighted regression approach would seem more straightforward.

Response to Reviewer #1, Comment #1: We discussed the reviewer’s concern with the statistician who performed the statistical analysis on the data in this study. The statistician explained that the Poisson model is appropriate because even though TTR is measured as a proportion of time for each year represented in the table, those proportions arise from counted units of time as a fraction of the total amount of time being observed. The generalized Poisson
regression model is sufficiently robust to analyze such count data with differing reference frames (total time observed) per year. A weighted regression is not inappropriate and achieves essentially the same results. It analyzes a derived variable (the proportions themselves) rather than the direct data (unit counts and totals).

Reviewer #1, Comment #2: Lines 137-141. Because the sample sizes for cardiology and other specialities are so much smaller than for PCP the power to detect a trend is much less. Thus I am not sure it is that helpful to quote non significant results for the smaller groups.

Response to Reviewer #1, Comment #2: We discussed the reviewer’s concern with the statistician who performed the statistical analysis on the data in this study. The statistician stated that it would be more distracting to the reader to have the p-values from hypothesis tests for some classes of physicians and not others. The statistician recommended that we add a limitation in the “Discussion” section detailing that some of the tests, specifically those of the specialties, may not have been sufficiently powered to detect trends. We have followed the advice of the statistician and have added the following sentence in the “Discussion” section on Page 13, Lines 278-280: “Additionally, some of the statistical tests, in particular those for cardiology and the other medical specialties, may not have been sufficiently powered to detect trends due to the smaller number of patients.”

Reviewer #1, Comment #3: The improvements through the study are quite possibly due to the changes that have been instituted. However it could be that the non compliant unstable patients have been moved off warfarin onto other anticoagulants and that the improvements in for example, ADR rate are due to that. This possibility should be mentioned in the discussion.

Response to Reviewer #1, Comment #3: We have added the following sentence into our “Discussion” section on Page 12, Lines 254-256: “The decline in the ADR rate may also be due to noncompliant unstable patients who have discontinued warfarin and initiated DOACs or other anticoagulants.”

Reviewer #2, Comment #1: This paper reports the time trends of warfarin prescription at discharge from hospital and ADR to warfarin. The authors also had the objective to evaluate time in therapeutic range and the rate of use of an electronic health module to monitor warfarin treatment. Although not explicitly stated, from the analysis and discussion it appears that one of
the objectives was to evaluate whether the establishment of an anticoagulation task force had a positive effect on TTR and adverse drug reactions. This study has several major issues. The objectives should be restated clearly explaining if they also include the effect of the establishment of the anticoagulation task force.

Response to Reviewer #2, Comment #1: We have detailed the objectives of our study at the end of the “Background” section on Pages 4-5, Lines 80-93: “An anticoagulation task force was established at our Institution in 2014 aimed at educating PCPs and cardiologists about evidence-based guidelines for warfarin management, increasing the use of our Institution’s electronic warfarin module, and enhancing patient compliance with obtaining INR. The primary objective of our study was to decrease the number of severe warfarin ADRs. Additional objectives included whether the establishment of the anticoagulation task force had a positive effect on TTR and severe ADRs. We hypothesized that the numerous strategies established by the anticoagulation task force such as providers using the electronic warfarin module and patients’ obtaining timely INRs and follow-up visits with their provider would positively impact our leading objective of reducing warfarin ADRs.

In the current study, we present our findings of the number of patients prescribed warfarin at hospital discharge and who obtained an INR within 5, 10, and 30 days of hospital discharge, the TTR, the number of patients treated with warfarin compared to other anticoagulant medications, the use of the electronic health module by PCPs and cardiologists, and the number and cost change of severe warfarin ADR events.”

Reviewer #2, Comment #2: The appropriateness of the study design depends on its objective, so at the moment I am unsure about this issue.

Response to Reviewer #2, Comment #2: We have provided a more detailed description of the objectives of our study at the end of the “Background” section and in the “Methods” section.

In the “Background” section on Pages 4-5, Lines 80-93, we added the following: “An anticoagulation task force was established at our Institution in 2014 aimed at educating PCPs and cardiologists about evidence-based guidelines for warfarin management, increasing the use of our Institution’s electronic warfarin module, and enhancing patient compliance with obtaining INR. The primary objective of our study was to decrease the number of severe warfarin ADRs. Additional objectives included whether the establishment of the anticoagulation task force had a positive effect on TTR and severe ADRs. We hypothesized that the numerous strategies established by the anticoagulation task force such as providers using the electronic warfarin
module and patients’ obtaining timely INRs and follow-up visits with their provider would positively impact our leading objective of reducing warfarin ADRs.

In the current study, we present our findings of the number of patients prescribed warfarin at hospital discharge and who obtained an INR within 5, 10, and 30 days of hospital discharge, the TTR, the number of patients treated with warfarin compared to other anticoagulant medications, the use of the electronic health module by PCPs and cardiologists, and the number and cost change of severe warfarin ADR events.”

In the “Methods” section on Pages 5-6, Lines 95-131, we added the following: “Under an institutional review board-approved protocol, our prospective study (January 1, 2013- December 31, 2017) investigated the number of severe warfarin ADRs after hospital discharge and the management of patients prescribed warfarin by approximately 200 PCPs and 48 cardiologists in an ambulatory setting at our Institution. Prior to the initiation of this study, our Institution observed that warfarin was the leading medication associated with ADRs. Our Institution defined a severe ADR as one in which the patient outcome is death, life-threatening (real risk of dying), hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or requiring intervention to prevent permanent impairment or damage. Patients who were solely evaluated in the Emergency Department (ED) and not admitted to the hospital did not experience a severe ADR. Established at our Institution in 2014, the anticoagulation task force aimed to improve adherence of evidence-based management guidelines established by the American College of Cardiology and to standardize monitoring and management of warfarin by implementing defined dosing algorithms and regulating treatment strategies with INRs with the goal of decreasing the number of warfarin ADRs (Table 1). The task force consisted of the following disciplines: ambulatory adult PCP, cardiology, adult hospitalists, clinical effectiveness engineers, and information technology, pharmacy, hospital, and ambulatory operations.

The warfarin data were evaluated over 5 years: (1) baseline - prior to the anticoagulation task force (1/1/2013- 12/31/2013) and (2) 1- 4 years later (1/1/2014-12/31/2017). Numerous measures were implemented at our Institution following the initiation of the task force (Table 2). The electronic warfarin module is a template build software that utilizes the electronic medical record software application Epic which may be accessed by treating physicians at all times. Prior to anticoagulation task force, providers monitored their patients’ INRs without the use of the warfarin module in Epic. The electronic warfarin module adds and archives lab results, displays data trends, and offers standardized recommendations and guidelines regarding the appropriate management of warfarin. By educating providers about the warfarin module and incorporating this module in their daily practice, it was easier and more reliable to monitor INRs. Additionally, providers were able to observe trends in relation to the module usage, TTRs, and patients treated with warfarin. Special attention focused on dramatic changes in a patient’s INR
results, necessitating more frequent PCP visits. Following the initiation of the task force, PCPs were educated about numerous topics, including (1) a video and link informing PCPs about how to use the electronic warfarin module, specifically, how to monitor their patients’ INRs to ensure that they remain in the TTR, (2) a hyperlink on Epic indicating the appropriate warfarin dosing protocols as established by the American College of Cardiology, and (3) how to educate their patients about warfarin use, particularly how to contact their PCPs for the medication. Furthermore, a visual calendar and after-visit summary permits patients to view their previous INR values, upcoming appointments, and warfarin dosing.”

Reviewer #2, Comment #3: The current description of the methods do not allow to express a judgement about the conduction of the study, with special regard to evaluation of ADRs.

Response to Reviewer #2, Comment #3: We significantly revised the “Methods” section on Pages 5-6, Lines 95-131 to clarify the conduction of the study, including an evaluation of severe ADRs: “Under an institutional review board-approved protocol, our prospective study (January 1, 2013 - December 31, 2017) investigated the number of severe warfarin ADRs after hospital discharge and the management of patients prescribed warfarin by approximately 200 PCPs and 48 cardiologists in an ambulatory setting at our Institution. Prior to the initiation of this study, our Institution observed that warfarin was the leading medication associated with ADRs. Our Institution defined a severe ADR as one in which the patient outcome is death, life-threatening (real risk of dying), hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or requiring intervention to prevent permanent impairment or damage. Patients who were solely evaluated in the Emergency Department (ED) and not admitted to the hospital did not experience a severe ADR. Established at our Institution in 2014, the anticoagulation task force aimed to improve adherence of evidence-based management guidelines established by the American College of Cardiology and to standardize monitoring and management of warfarin by implementing defined dosing algorithms and regulating treatment strategies with INRs with the goal of decreasing the number of warfarin ADRs (Table 1). The task force consisted of the following disciplines: ambulatory adult PCP, cardiology, adult hospitalists, clinical effectiveness engineers, and information technology, pharmacy, hospital, and ambulatory operations.

The warfarin data were evaluated over 5 years: (1) baseline - prior to the anticoagulation task force (1/1/2013 - 12/31/2013) and (2) 1-4 years later (1/1/2014-12/31/2017). Numerous measures were implemented at our Institution following the initiation of the task force (Table 2). The electronic warfarin module is a template build software that utilizes the electronic medical record software application Epic which may be accessed by treating physicians at all times. Prior to anticoagulation task force, providers monitored their patients’ INRs without the use of
the warfarin module in Epic. The electronic warfarin module adds and archives lab results, displays data trends, and offers standardized recommendations and guidelines regarding the appropriate management of warfarin. By educating providers about the warfarin module and incorporating this module in their daily practice, it was easier and more reliable to monitor INRs. Additionally, providers were able to observe trends in relation to the module usage, TTRs, and patients treated with warfarin. Special attention focused on dramatic changes in a patient’s INR results, necessitating more frequent PCP visits. Following the initiation of the task force, PCPs were educated about numerous topics, including (1) a video and link informing PCPs about how to use the electronic warfarin module, specifically, how to monitor their patients’ INRs to ensure that they remain in the TTR, (2) a hyperlink on Epic indicating the appropriate warfarin dosing protocols as established by the American College of Cardiology, and (3) how to educate their patients about warfarin use, particularly how to contact their PCPs for the medication. Furthermore, a visual calendar and after-visit summary permits patients to view their previous INR values, upcoming appointments, and warfarin dosing.”

Reviewer #2, Comment #4: I am unsure about the use of a Poisson model to analyse TTR, the authors should provide the rationale for this choice.

Response to Reviewer 2, Comment #4: We discussed the reviewer’s concern with the statistician who performed the statistical analysis on the data in this study. The statistician explained that the Poisson model is appropriate because even though TTR is measured as a proportion of time for each year represented in the table, those proportions arise from counted units of time as a fraction of the total amount of time being observed. The generalized Poisson regression model is sufficiently robust to analyze such count data with differing reference frames (total time observed) per year.

Reviewer #2, Comment #5: The interpretation of these data should take into account information from other sources. The lack of a control group, if relevant (see above), should be acknowledged. If the objective is just to describe changes in warfarin prescription, ADR, and TTR, then this should be made clear, and confusion about the effect of the adoption of a software and education strategy should be avoided; furthermore, comparison with statistics from other sources should be provide. If the objective is to describe the changes observed in relation to the implementation of the above-mentioned measures, then the lack of a control group is a major issue that should be acknowledged in the limitation.
Response to Reviewer #2, Comment #5: We have detailed the objectives of our study at the end of the “Background” section on Pages 4-5, Lines 80-93: “An anticoagulation task force was established at our Institution in 2014 aimed at educating PCPs and cardiologists about evidence-based guidelines for warfarin management, increasing the use of our Institution’s electronic warfarin module, and enhancing patient compliance with obtaining INR. The primary objective of our study was to decrease the number of severe warfarin ADRs. Additional objectives included whether the establishment of the anticoagulation task force had a positive effect on TTR and severe ADRs. We hypothesized that the numerous strategies established by the anticoagulation task force such as providers using the electronic warfarin module and patients’ obtaining timely INRs and follow-up visits with their provider would positively impact our leading objective of reducing warfarin ADRs.

In the current study, we present our findings of the number of patients prescribed warfarin at hospital discharge and who obtained an INR within 5, 10, and 30 days of hospital discharge, the TTR, the number of patients treated with warfarin compared to other anticoagulant medications, the use of the electronic health module by PCPs and cardiologists, and the number and cost change of severe warfarin ADR events.”

We have also added the following paragraph to the “Discussion” section on Pages 10-11, Lines 214-225 in response to the reviewer’s request for information from other sources: “While predictors of warfarin-associated adverse events have been reported in hospitalized patients [29-32], a paucity of studies addressed attempts to reduce warfarin ADRs in an outpatient setting [33, 34]. Salinero and Hyman reported a model of reducing warfarin ADRs with a nurse led anticoagulation clinic in South Miami, Florida [34]. An interdisciplinary team with physicians, nurses, and nurse practitioners was established in response to the increased number of hospital admissions for warfarin toxicity. Physicians referred their warfarin patients to the anticoagulation clinic with evidence-based clinical warfarin management, replete with dosing adjustments and follow-up intervals. Following the implementation of the anticoagulation clinic, the number of hospital admissions related to warfarin ADRs decreased from 27 in 2006 to 9 in 2015. The goal of reducing warfarin ADRs was accomplished in both Salinero and Hyman’s work and the present study, specifically, through an anticoagulation clinic in the former and an electronic warfarin module in ours.”

We have also added the following sentence in the “Discussion” section on Page 13, Lines 281-288: “As the objective of our study was to observe the changes in relation to the implementation of the various measures aimed at decreasing warfarin ADRs, we did not have a control group. While the lack of a control group was a limitation in the present study, we believed that our efforts would be valuable for the entire population. Therefore, we wanted to implement the
constructive strategies throughout our Institution for all patients treated with warfarin instead of withholding positive modifications from certain members of our community. Thus, we are unable to demonstrate the differences between the group which benefitted from alterations incorporated by the anticoagulation task force and a control group.”

Reviewer #2, Comment #6: The methods do not allow a complete understanding of the data. More information is needed about the software and the education program. More importantly, more information is needed about ADR: how were they established? What was the likelihood that a patient with a warfarin-related ADR was referred to another hospital and thus missed from this study?

Response to Reviewer #2, Comment #6: We have added the following paragraph in the “Methods” section on Pages 5-6, Lines 112-131 to provide further details about the software and the education program for providers, as follows: “The warfarin data were evaluated over 5 years: (1) baseline - prior to the anticoagulation task force (1/1/2013- 12/31/2013) and (2) 1- 4 years later (1/1/2014-12/31/2017). Numerous measures were implemented at our Institution following the initiation of the task force (Table 2). The electronic warfarin module is a template build software that utilizes the electronic medical record software application Epic which may be accessed by treating physicians at all times. Prior to anticoagulation task force, providers monitored their patients’ INRs without the use of the warfarin module in Epic. The electronic warfarin module adds and archives lab results, displays data trends, and offers standardized recommendations and guidelines regarding the appropriate management of warfarin. By educating providers about the warfarin module and incorporating this module in their daily practice, it was easier and more reliable to monitor INRs. Additionally, providers were able to observe trends in relation to the module usage, TTRs, and patients treated with warfarin. Special attention focused on dramatic changes in a patient’s INR results, necessitating more frequent PCP visits. Following the initiation of the task force, PCPs were educated about numerous topics, including (1) a video and link informing PCPs about how to use the electronic warfarin module, specifically, how to monitor their patients’ INRs to ensure that they remain in the TTR, (2) a hyperlink on Epic indicating the appropriate warfarin dosing protocols as established by the American College of Cardiology, and (3) how to educate their patients about warfarin use, particularly how to contact their PCPs for the medication. Furthermore, a visual calendar and after-visit summary permits patients to view their previous INR values, upcoming appointments, and warfarin dosing.”

To address the reviewer’s concern about patients who may have a warfarin-related ADR who were referred to another hospital, we have added the following sentence in the “Discussion”
section on Page 12, Lines 256-259: “Some patients who experienced a warfarin-related ADR may have been referred to another facility outside of our Institution, and we were unable to capture the number of patients who may have done so. Therefore, these patients would have been missed from our study.”

Reviewer #2, Comment #7: The statement that warfarin is the most commonly used anticoagulant for thrombosis and pulmonary embolism is probably true, but the references supporting it are a bit dated and many of them are about indication, not prevalence of use. Of note, the most recent reference is from 2012, that is just after the approval of DOAC. The authors should acknowledge that the epidemiology of anticoagulants prescription is rapidly changing. Indeed, the results of this paper show that in 2017 warfarin accounted for less than 50% of prescriptions.

Response to Reviewer #2, Comment #7: We added the following sentences into the first paragraph of the “Background” section on Page 3, Lines 53-63 with newer references and a brief discussion about the benefits of DOACs, as follows: “The epidemiology of anticoagulant prescriptions has been rapidly changing over the past decade. Warfarin, a vitamin K antagonist, has historically been the most frequently used oral anticoagulant in the world for patients with venous thrombosis, pulmonary embolism, atrial fibrillation, prosthetic heart valves, recurrent myocardial infarction, and stroke [1-7]. Thromboembolic disorders contribute prevention in atrial fibrillation and atrial flutter. The direct oral anticoagulants (DOACs) have a lower incidence of major bleeding than warfarin, minor drug and food interactions, rapid onset and offset, short half-life, and stable pharmacokinetics eliminating the need for regular monitoring and dose adjustment [8, 9]. It has been reported that the prevalence of warfarin use decreased from 69.8% in 2008 to 42.2% in 2014 paralleled with an increase in the DOAC rivaroxaban from 1.3% in 2010 to 12.1% in 2011 [1].”

We have also added the following sentences into our Discussion on Pages 11-12, Lines 241-248: “Over this 5-year period, the number of patients prescribed warfarin at hospital discharge decreased, from a total of 925 at baseline in 2013 to 665 in 2017. Furthermore, the proportion of warfarin prescriptions out all anticoagulants decreased over the 5 years, from 72.2% to 42.1% (p<0.001). We attribute the decreased percentage to a trend for patients to initiate safer DOACs that did not require retrieval of INRs. The increased number of patients was most likely due to the larger patient population treated at our Institution over the course of our study. Furthermore, a large population of patients continued to consume warfarin primarily due to the lower cost of this medication.”
Reviewer #2, Comment #8: Poisson regression was used to analyze TTR. This variable is supposed to be numerical, while Poisson distribution is used for count data. The authors should report the rationale for this choice.

Response to Reviewer #2, Comment #8: We discussed the reviewer’s concern with the statistician who performed the statistical analysis on the data in this study. The statistician explained that the Poisson model is appropriate because even though TTR is measured as a proportion of time for each year represented in the table, those proportions arise from counted units of time as a fraction of the total amount of time being observed. The generalized Poisson regression model is sufficiently robust to analyze such count data with differing reference frames (total time observed) per year.

Reviewer #2, Comment #9: Some statements in the discussion are confusing. For example, at page 10 the authors state that "... the proportion of warfarin prescriptions [...] decreased over the 5 years". Soon after, however, they state that "the number of patients treated with warfarin in our study remained constant". Please explain.

Response to Reviewer #2, Comment #9: We have elucidated the reviewer’s concern in the “Discussion” section on Pages 11-12, Lines 241-248: “Over this 5-year period, the number of patients prescribed warfarin at hospital discharge decreased, from a total of 925 at baseline in 2013 to 665 in 2017. Furthermore, the proportion of warfarin prescriptions out all anticoagulants decreased over the 5 years, from 72.2% to 42.1% (p<0.001). We attribute the decreased percentage to a trend for patients to initiate safer DOACs that did not require retrieval of INRs. The increased number of patients was most likely due to the larger patient population treated at our Institution over the course of our study. Furthermore, a large population of patients continued to consume warfarin primarily due to the lower cost of this medication.”