Clinical Research in Cardiology (2019) 108:212–217
https://doi.org/10.1007/s00392-018-1345-9

ORIGINAL PAPER

A prospective, multi-center cohort study: investigating the ability of warfarin-treated patients to predict their INR

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Received: 23 April 2018 / Accepted: 24 July 2018 / Published online: 8 August 2018

Abstract

Background In practice, warfarin-treated patients may share insight regarding their international normalized ratio (INR) value before it is measured. The accuracy and potential utility of these predictions have not been evaluated.

Objective To (1) test how accurately patients can predict their INR; (2) identify demographic factors associated with their ability to predict their INR accurately; and (3) identify demographic factors associated with the patient's INR being in the therapeutic range.

Methods A prospective, multi-center cohort study enrolled patients from eight anticoagulation clinics in Iowa. Inclusion criteria were: age ≥ 18 years, warfarin use ≥ 60 days, INR goal of 2.0–3.0, and expected warfarin use > 6 months. Subjects completed a data collection form during enrollment and before each INR measurement. Data included demographics, a set of medication taking beliefs and practices, self-reported adherence, past INR values, INR prediction and reason(s) for the prediction.

Results There were 87 subjects enrolled with 372 INR measurements. The mean (SD) number of INRs per subject was 4.3 (1.8). Thirty percent of subjects reported they could tell when their INR is out of goal range. Patients predicted that 90.5% of their INRs would be within goal range, although only 65.5% of INRs were therapeutic. Patients correctly predicted a low INR as low or high INR as high in only 9.4% of out of range instances. A set of demographic characteristics and medication beliefs were not associated with prediction accuracy or percentage of INR measurements in range (PINRR). Most patients did not give a reason for their predicted result. For those that did, the most common factor was perceived stability at current dose.

Conclusion While some patients believed they could predict when their INR was out of range, only few were able to do so. Most patients assumed a therapeutic INR and missed when their INR was high or low. Patients should be advised against modifying their warfarin dose without consulting the provider that manages their therapy.

Trial registration ClinicalTrials.gov number, NCT 02764112.

Keywords Warfarin · Patients · Treatment adherence · International normalized ratio

Views expressed in the following article are those of the author(s) and not an official position of institutions involved in this study.

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Introduction

In the US, more than 30 million outpatient prescriptions for warfarin are dispensed annually [1], and it is estimated that more than 2 million patients start warfarin each year [2]. Warfarin is a challenging medication to manage because of a wide variation in how patients respond to dosing, the drug's narrow therapeutic window, variable adherence, and various dietary, medication, disease, and other factors that can influence the pharmacokinetics of the drug [3–5]. There also are genetic factors (CYP2C9 and VKORC1 polymorphisms) which affect warfarin pharmacokinetics and pharmacodynamics [3]. The FDA approved new labeling in 2007 for warfarin that explains the impact genetic differences can have in the way people respond to warfarin [2]. These factors necessitate regular monitoring using the international normalized ratio (INR) laboratory test.

INR monitoring and warfarin dose adjustment are important for both efficacy and safety reasons. Patients that spend more time in therapeutic range is directly related to improved clinical outcomes with warfarin [6]. Studies suggest a time in therapeutic range (TTR) of 58% or greater for warfarin is necessary to ensure that patients will experience benefit relative to antiplatelet therapy alone for patients with atrial fibrillation [6]. Elevated INRs place patients at risk for hemorrhagic events, especially as the INR rises above 5.0 [7].

Cost also is a concern with warfarin therapy. While warfarin tablets are inexpensive, the annual costs associated with monitoring range from $291–943 per patient in 2011 US dollars [8]. Current guidelines suggest INR monitoring frequency of up to 12 weeks in patients with stable INRs over the previous 3 months [9]. Patients and providers may be more willing to exercise this extended monitoring schedule if patients could identify changes that would warrant an ad hoc INR check. For example, if a patient had been eating more leafy green vegetables or drinking more alcohol, they could alert the provider that a between-interval INR check is warranted. Communicating these changes could potentially decrease costs and empower patients to take a greater role in their care and monitoring [10, 11]. Such an arrangement, however, would be premature without evidence that patients can predict an out of range INR.

Patients have reported various symptoms which they associate with symptoms of low INR, high INR or both. Some of these feelings/symptoms include fatigue, cold intolerance, headache, and dizziness [12, 13]. To our knowledge, it has not been studied whether patients have insight into their INR result. Patient beliefs about medicines also have not been examined in relation to the patient's PINRR.

Objectives

To (1) test how accurately patients can predict their INR and whether they are in therapeutic range; (2) identify demographic factors associated with their ability to predict their INR accurately; and (3) identify demographic factors associated with the patient's INR being in the therapeutic range.

Methods

This prospective, multi-center cohort study was coordinated by Northeast Iowa Family Practice Center in Waterloo, Iowa and received IRB approval from Wheaton Franciscan Healthcare Institutional Review Board in October 2015 (ClinicalTrials.gov number, NCT 02764112). Additional anticoagulation clinics were recruited via email correspondences with details and discussion occurring over conference calls.

Eight anticoagulation clinics across the state of Iowa participated in this study. Patients were recruited between November 2015 and April 2016 if they met the following inclusion criteria: age $\geq$ 18 years, warfarin use $\geq$ 60 days, INR goal of 2.0–3.0, and expected warfarin use > 6 months. Patients were excluded if they: utilized a home point-of-care INR monitoring device, had an INR range of 2.5–3.5 or a therapeutic range smaller than 1.0 INR unit, held a medical diagnosis of dementia or were receiving pharmacologic therapy indicated to treat Alzheimer's dementia, or were a resident of a long-term care facility. Eligible patients filled out informed consent forms at the time of their enrollment.

Subjects completed a data collection form during enrollment and prior to each INR measurement. INR measurement at each study site was obtained with the Coaguchek XS® point-of-care coagulometer (Roche Diagnostics). Data collected at enrollment included demographics, a set of medication taking beliefs and practices, and self-reported adherence. Site staff also abstracted the past ten INR values from the patient's electronic medical record. For each encounter, the data collection forms included the following items for each patient: the patient's INR prediction, answers to a set of questions to identify potential influences on INRs, and responses to a set of reasons why they guessed the INR value they predicted. For both sets, patients could check as many items as applied, or none at all. All INR measurements were intended to be consecutive measurements in each patient, however, this was not verified.

Each patient was assigned a unique identifier, so that the follow-up surveys could be matched to the initial

intake survey. Surveys completed at other sites were faxed or scanned and sent to the main study site. Surveys were entered into a Microsoft Excel spreadsheet (Redmond, WA) and imported into IBM SPSS v.24 (Armonk, NY) for analysis.

Descriptive statistics were calculated for demographics and other self-reported items. Three items based on the Merck Adherence Estimator®[1] were coded based on a published scoring algorithm to estimate the risk of non-adherence [14]. The Merck Adherence Estimator® was used with permission and Merck Sharp and Dohme own the copyrights as well as trademarks, so they are not reproduced within this manuscript.

PINNR was calculated by dividing the number of visits where the patient's INR was between 2.0 and 3.0 by their total number of INR values. PINNR was used as a dependent variable in multiple linear regression analyses and in an ANOVA comparing Adherence Estimator® risk level with PINNR ≥ 70 and < 70. While TTR is the established measure of anticoagulation quality in clinical trials, it is seldom used in clinical practice due to its tedious calculation which requires interpolation of INR values between measurements [15]. The PINNR is a user-friendly alternative which has high sensitivity and positive predictive value in predicting TTR [16].

Results

Table 1 reviews patient characteristics at the time of enrollment into the study. Of the 87 patients enrolled, 47 (54%) were female. The mean duration of warfarin use was 7.4 (SD 6.6) years. A large majority (82.8%) reported using an adherence aid such as a weekly medication planner. The mean number of weeks in which patients were at their current warfarin dose before starting the study was 15.2 ± 22.5. There were 26 patients (30.2%) at enrollment who had therapeutic INRs in $> 80\%$ of their most recent INRs (up to 10) (Table 1). Overall, the average historical PINRR was 64.4%, and the average PINRR for the 371 study encounters was 65.5%.

A majority of patients (60.5%) said they disagreed, either mostly or completely, that they were able to tell if their INR is out of range before having it checked (Table 2). Most patients (81.6%) responded that they were convinced of the importance of their warfarin therapy. Financial burden from out of pocket expenses and worrying about warfarin doing more harm than good were not concerns for very many patients (2.3% each).

By the end of the study period, 371 INR predictions met the inclusion criteria and were analyzed. Of all measurements, 68.8% of predicted INRs were within 0.5 INR units of the observed INR value (256/372) and 91.4% of predicted INRs were within 1.0 INR units of the observed INR value (340/372). In total, 90.6% (336/371) of INR predictions were for an INR between 2.0 and 3.0, but only 65.5% (243/371) of INRs fell in this range (Table 3). When comparing the predicted INR and the measured INR, 63.3% (235/371) of the predictions matched the range of the measured INR. The most common match was for the therapeutic range of 2.0–3.0, but there were a small number of correct predictions for INRs < 2.0 and > 3.0 (Table 3).

At each visit, patients were asked if they had experienced any variety of different potential influences on their INR within the past 2 weeks (Table 4). The most common reported factor was a change in other medications (16.9%) followed by feeling sick and missed doses of warfarin (11.3 and 9.1%, respectively). About a third of patients (37.3%) reported one or more of these changes and 62.7% reported no changes. Before each INR check, the patient predicted their INR and was asked what made them guess that value. The mean INR predicted was 2.440 (SD 0.412). The most common reasons for their prediction (Table 5) were stable at their current dose (34.7%), change in diet (9.9%) and self-adjusting warfarin dose (8.3%). Seventy-one percent of forms had at least one reason supporting their guess, and 29.0% listed no reasons.

Several associations were tested, although none were statistically significant. There was no association between patients stating they can tell when their INR is out of range and their prediction accuracy ($p = 0.813$) or PINRR (0.394). There also was no association between having an Adherence Estimator® result suggesting a potential adherence problem and PINRR ($p = 0.613$).

Discussion

This study shows patients taking warfarin were not able to accurately predict their INR or whether or not they were in therapeutic range. The accuracy of patients predicting their INR is poor, as patients generally assumed a therapeutic value for their INR. The prediction of a therapeutic INR may be a result of the patient being previously stable on their dose of warfarin. There is some evidence, however, that having a history of a stable INR is not predictive of future INR stability [17]. In patients with a stable INR ($> 80\%$ of INRs in therapeutic range) for 6 months, less than 40% continued to remain stable over the next 6 months [17]. Our findings, combined with that from Pokorney et al., reiterate

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Table 1 Patient characteristics

Characteristic	Study group ($N=87$) no. (%)
Age (years)	Mean = 73.1 SD = 12.6
Female	47 (54.0)
Education	
Low level of schooling	4 (4.6)
High school graduate	44 (50.6)
College graduate	33 (37.9)
Post-graduate	6 (6.9)
Alcohol drinks per week ($N=85$)	
<1	64 (75.3)
1–2	11 (12.9)
>2	10 (11.8)
Arranges medications at home	
Self	79 (90.8)
Other	8 (9.2)
Missed doses of warfarin in past month	
0	68 (78.2)
1	14 (16.1)
2–4	5 (5.7)
Uses calendar or pillbox	72 (82.8)
Takes daily multivitamin	37 (42.5)
Takes antiplatelet	28 (32.2)
Warfarin indication	
Atrial fibrillation	63 (72.4)
DVT/PE	20 (23.0)
Other	4 (4.6)
Duration of warfarin use (years)	Mean = 7.4 (SD = 6.6)
History of serious bleeding event	9 (10.3)
Weekly warfarin dose (mg)	Mean = 33.4 (SD = 14.8)
Recent INRs in therapeutic range, no. (%)[a] ($N=86$; mean = 64.4%)	
20–40%	12 (14.0)
50–70%	48 (55.8)
80–100%	26 (30.2)
No. of INRs performed while in study per subject	Mean = 4.3 (SD = 1.8)

[a]Percent of 10 most recent INR values within therapeutic range

Table 2 Results from Merck Adherence Estimator®

Question	Agree completely/mostly	Agree somewhat/disagree somewhat	Disagree mostly/completely
Medication importance item	71	14	2
Medication concern item	2	12	73
Medication cost item	2	4	81
Responses condensed from a 6-point Likert scale based on scoring algorithm			
I usually can tell if my INR is out of range before I have it checked	14	16	46

the complexity of managing warfarin therapy and maintaining a therapeutic INR.

Self-reported ability to identify out of range INR values was not associated with improved accuracy of INR prediction. Interestingly, there was no evidence of a Hawthorne effect as patients spent the same amount of time in therapeutic range for offering their INR predictions as in the pre-study period. There is no evidence that engaging

Table 3 Accuracy of patient INR predictions ($N=371$)

	Measured INR < 2.0	Measured INR 2.0–3.0	Measured INR > 3.0	Total predicted INRs
Predicted INR < 2.0	8	8	1	17
Predicted INR 2.0–3.0	71	223	42	336
Predicted INR > 3.0	2	12	4	18
Total measured INRs	81	243	47	371

Table 4 Patient-reported changes within 2 weeks prior to INR ($N=373$)

Question[a]	Number "yes" (%)
Missed dose(s) of warfarin	34 (9.1)
Felt sick	42 (11.3)
Change in other medications	63 (16.9)
Change in diet	29 (7.8)
Change in alcohol intake	7 (1.9)
Forms with 1 or more changes	139 (37.3%)
Forms with nothing checked	234 (62.7%)

[a]Could check more than one option or none at all

Table 5 Responses to "What made you guess this value today?" ($N=373$)

Responses[a]	Yes (%)
Missed doses	20 (5.4)
I adjusted my warfarin dose	31 (8.3)
I recently felt sick	16 (4.3)
Change in other medications	22 (5.9)
Change in diet	37 (9.9)
Change in alcohol intake	4 (1.1)
Stable at current dose	129 (34.7)
Other recent experience	30 (8.1)
Other—warfarin dose adjusted at last visit	15 (4.0)
Forms with 1 or more reasons checked	265 (71.0%)
Forms with nothing checked	108 (29.0%)

[a]Could check more than one option or none at all

patients in INR prediction as a regular practice improves their PINRR.

Other studies have shown a variety of ways to help increase the time a patient's INR is therapeutic. These include interventions targeted at improving medication adherence, such as thorough education and organization aids like pillboxes [18, 19]. Such supports may especially be beneficial for patients with low health literacy as non-adherence can have a significant impact on warfarin effectiveness [20]. There also is evidence that patients using an anticoagulation clinic may spend more time in therapeutic range than patients managed by other arrangements [21]. Similarly, patients who have their INR monitored more frequently appear to spend more time within the therapeutic range [19]. However, more frequent INR testing increases costs associated with more frequent monitoring [22].

Initial education for patients starting warfarin may include stressing the importance of warfarin, how to manage risks, dietary strategies related to vitamin K, and alcohol moderation. In this study, patients reported changing their warfarin dose in 8.3% INR follow-ups. This number, while small as a percent, may still be meaningful given the millions of patients on warfarin and the narrow therapeutic range of the drug. It may be beneficial to routinely discuss that INR values fluctuate and can be difficult to predict, therefore, patients should avoid making changes without obtaining an INR test and discussing the results with the provider managing their warfarin therapy, even if they have feelings or symptoms that they perceive to be indicative of an out of range INR. The only actionable INR measure remains the INR, not intuitions or predictions.

Limitations

While all sites were trained on the study protocol using a guide, there may have been variability in the way pharmacists at different sites phrased questions to patients. Also, there were no means to verify adherence with dispensing data. Warfarin therapy can take up to 6 months to reach a stable INR in some patients [20] and no adjustments were made based on treatment duration. As a result, some patients who had a lower PINRR may have been relatively newer to warfarin therapy. Lastly, the Adherence Estimator® has not been validated for predicting adherence specifically for warfarin therapy.

Conclusions

Patients rarely predicted an out of range INR and patients generally assumed a therapeutic value. Self-reported ability to identify out of range INR values is not associated with improved accuracy of INR prediction. It may be advisable to warn patients against altering their warfarin dose based on feelings or intuitions about their INR.

Acknowledgements The authors would like to acknowledge statistical support from Brahmendra Viyyuri.

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