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Data Mining to Assess Variations in Oral Anticoagulant Treatment

Peter Brønnum Nielsen[a], Søren Lundbye-Christensen[b], Torben Bjerregaard Larsen[b], Lars Hvilsted Rasmussen[b], Søren Risom Kristensen[bc], Anna-Marie Münster[bc], Ole K. Hejlesen[ad]

[a] *Medical Informatics Group, Department of Health Science and Technology, Aalborg University, Denmark*
[b] *Department of Cardiology, Center for Cardiovascular Research, Aalborg Hospital, Århus University Hospital, Denmark*
[c] *Department of Clinical Biochemistry, Center for Cardiovascular Research, Aalborg Hospital, Århus University Hospital, Denmark*
[d] *Institute of Health Science, University of Agder, Norway*

Abstract

Variations in International Normalized Ratio's (INR) are closely related to bleeding and thrombosis incidents in patients on oral anticoagulation treatment. This study investigates predictive factors that affect INR values. Data sampled with relatively high frequency allows for detection of local INR variations, and hence also allows detection and evaluation of predictive factors where time is taken into consideration. Univariate linear regression was applied and different models were reduced into a final predictive model. F-tests were utilized to test whether or not a model reduction would benefit INR predictions, in terms of decreasing observed variance. In addition to an INR submodel, the final model includes individual interaction from the last three days change in mean warfarin intake and three days change in mean vitamin K intake. Prediction residual error was mainly reduced by the INR submodel, while the warfarin model and the vitamin K submodel did not benefit predictions to same extend compared to the INR submodel. However, more studies on the temporal aspects of the effect of warfarin seem to be relevant.

Keywords:

Anticoagulation, Linear regression model, Time series model, Vitamin K, Prediction model.

Introduction

Oral vitamin K antagonists such as warfarin and other coumarin derivatives are prescribed to an increasing number of patients enrolled for lifelong therapy with underlying disorders such as heart valve replacement, atria fibrillation and venous thromboembolism. Despite well-described clinical benefits, use of warfarin is known to be associated with adverse effects, in particular haemorrhage, if too much warfarin is given. The dosage of oral anticoagulation agents should be based on minimizing both the risk of thrombotic events and the risk of bleeding [1].

Three different types of patient management exist. One is "usual-care" where patients visit the hospital-based or the GP every 4-6 weeks to have a blood sample taken to have the so-called International Normalized Ratio (INR) measured. The INR represents a patient's coagulation time compared to a normal healthy individual. An INR value of 1 is normal and, for example, a measured INR value of 2 means that blood coagulation takes twice as long compared to the normal coagulation. In the "usual-care" warfarin dosage is recommended by the doctor based on current and historic INR values. Some patients are able to take part in the management of oral anticoagulation treatment (OAT) by handling a Point-of-Care (PoC) device and measure INR values themselves. Patients assigned to "self-testing" will report this INR value to a responsible clinician who prescribes the dose of warfarin. Patients educated in "self-management" will both handle INR measurement by a PoC device, and are allowed within a preset range to change warfarin dosage. In the latter two mentioned groups, measurements of INR values are most frequent: once every week or two.

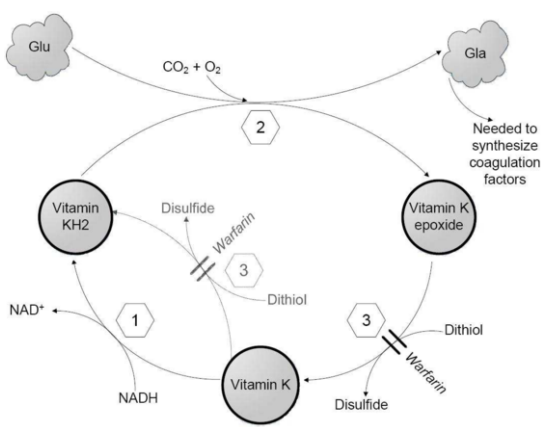

Figure 1- Vitamin K is reduced either by a NADH dependent reductase activity reaction ‹1› or a reductase reaction dependent on the conversion of dithiol into disulfide ‹3› (shaded). The carboxylation reaction ‹2›, which converts Glu (glutamate residues) into Gla (gamma-carboxyglutamate residues, aka Gla-residues), is driven by a vitamin KH2 dependent carboxylase activity, which simultaneously converts vitamin KH2 into vitamin K epoxide. The last step in the vitamin K cycle reaction ‹3› is a reductase of vitamin K epoxide dependent on conversion of dithiol into disulfide. The two reactions indicated by ‹3› are inhibited by anticoagulants as warfarin, thus dietary vitamin K sources are necessary to maintain haemostasis. Adopted from [7].

Maintaining patients within the desired therapeutic range presents a challenge due to at least three factors: (1) a target INR value restricted by a relatively narrow therapeutic range; (2) an interindividual variation of the effect of oral vitamin K antagonists, and (3) changes in dietary intake of vitamin K.[2-4] A change of 0.7 INR in two consecutive measurements has been shown to be clinically relevant for OAT.[5]

Fluctuations in vitamin K intake through dietary sources have shown clinical relevance, and must be regarded as a major independent factor that interferes with anticoagulation stability.[6] Based on known physiology the interactions between INR, warfarin, and vitamin K are well described; an overview is provided in Figure 1.

Since they are based on accessibility of Gla-residues the amount of functional vitamin K dependent coagulation factors will decrease if warfarin is administrated; this leads to an increase in INR value.

Disregarding the complexity of the vitamin K cycle, a novel approach to describe the course of action of INR values is proposed in Equation (1), where INR_t denotes the INR measurement at time t.

$$INR_t = \alpha(INR_{history}) + \beta(Warfarin_{history}) + \gamma(Vitamin\ K_{history}) \quad (1)$$

where α, β and γ are arbitrary coefficients. Due to the slow-acting physiological systems involved, one must take time into consideration, e.g. warfarin has a half-life of 36 hours. Warfarin and vitamin K interaction will have carryover effect from previous intake(s), affecting the current INR value. Being able to take into account such different predictive over-coagulating and under-coagulating factors could potentially decrease bleeding risk or decrease risk of thrombosis in patients assigned to an outpatient setting of OAT.

The purpose of this analysis is to utilize quality data to assess interactions between current and previous INR values, warfarin administration changes, and changes in dietary vitamin K intake. Such interactions might reveal important predictive factors for variation in INR values.

Methods

We have built models predicting the current INR value from available information. This is performed in three steps:

- Information on previous INR measurements
- Additional information on warfarin intake
- Additional information on vitamin K intake

The first model provides information on the serial correlation structure of individuals that are well regulated with respect to warfarin and vitamin K intake. Having established a prediction model solely based on historic INR values, the inclusion of warfarin intake in such a model provides information on the time-span of the effect from warfarin on INR. Further, it will provide information on between-subject variation of sensitivity to warfarin treatment. Finally by also including vitamin K intake in the model, it is possible to assess the time-span of the effect from vitamin K. Again, the between-subject variation of sensitivity can be assessed. The analysis also provides empirical knowledge to judge to which amount these three predictive variables reduce the unexplained variation.

Materials

All patients included in this study referred to Medicinsk Ambulatorium, Brædstrup Sygehus. Approval from the Danish Data Protection Agency was obtained prior to onset of the data acquisition program. Clinicians at the facility enrolled suitable patients to be included in a data collection protocol, and the study was conducted in the period from June 2008 to February 2009. Patients were asked to fill out a daily scheme for a one month period. Schemes included information (among others) on INR value, diet, and warfarin intake. Data were entered into Microsoft Excel ®. Nutrition data was evaluated to calculate vitamin K content. The vitamin K assessments were performed by using the USDA National Nutrient Database for Standard Reference.

Data Analysis

A retrospective statistical evaluation of variability in INR values was performed. The current INR value is predicted from previous values in a regression model, and hence the approach is auto-regressive time series modelling. However, as the data is characterized by being shorter time series from a number of independent individuals, the statistical methods applied are mainly univariate linear regression analyses rather than the classic approach developed by Box and Jenkins [8].

Prediction model based on previous INR values

Prediction of the current INR value at time *t* for the *i*th subject is given in Equation (2).

$$INR_{i,t} = \alpha_{i1}\, INR_{i,t-1} + \alpha_{i,2}\, INR_{i,t-2} + ... + \alpha_{tv}\, INR_{i,t-n} + \varepsilon_{i,t}, \quad (2)$$

where the lag time is n, $\alpha_{i,k}$ are weights in a weighted average of previous INR values, and $\varepsilon_{i,t}$ is the residual uncertainty (prediction error). We assume that $\varepsilon_{i,t} \sim N(0,\sigma^2)$. It should be noted that in this model we assume variation between individuals in weights. Reductions of this model could be:

I. Reducing the lag time of influence
II. Reducing the interindividual variation

Reductions in lag time must be performed in descending order, and likewise, reductions in interindividual variation should be done in descending order of lag time.

Prediction model based on previous INR values and changes in warfarin intake

The preceding model is now expanded by adding intake of warfarin. Assume that an individual is in steady state and dependence of previous INR values is described by $\alpha(INR_{history})$. In this case changes in warfarin dose will affect the prediction of INR. The absolute change in warfarin intake from previous days is, however, not a sophisticated way of modelling the effect from warfarin. This is mainly due to the nature of warfarin administration: the advised dosage pattern of warfarin is rarely fixed in terms of tablets per day. A normal pattern could be; 2, 2, 3, 2, 2, 3, 2 tablets per day for one week. If the absolute change in previous warfarin intake is modelled as change

from one day to another, the effect from previous changes would be negated due to this pattern of changes (i.e. positive change always followed by a negative change and vice versa). Hence, it is decided to model changes in warfarin intake based on the difference from the mean intake of the last day's change as in Equation (3).

$$INR_{i,t} = \alpha(INR_{history}) + \beta_{i,1}\,\Delta W_{i,t-1} + \ldots + \beta_{n,1}\,\Delta W_{i,t-n} + \varepsilon_{i,t}, \quad (3)$$

where $\Delta W_{i,t-1} = W_{i,t} - W_{i,t-1}$ is the change in warfarin intake compared to change in mean warfarin intake from t days. Again we model potential between-subject variations in sensitivity toward vitamin K antagonist treatment.

Vitamin K based model

Expanding the model to incorporate intake of vitamin K is done similar to the intake of warfarin, see Equation (4).

$$INR_{i,t} = \alpha(INR_{history}) + \beta_i(W_{history}) + \gamma_{i,1}\,\Delta K_{i,t-1} + \ldots + \gamma_{n,1}\,\Delta K_{i,t-n} + \varepsilon_{i,t} \quad (4)$$

where $\Delta K_{i,t-1} = K_{i,t} - K_{i,t-1}$ is the current change in vitamin K intake compared to mean intake from t days. The reduction of this model follows the same rules as the previous model. However, the reduction in interindividual variation may be performed in two steps; 1) reduction in weights modelling potential between-subject variation, and 2) reduction to weights specific to a grouping into individuals who take, and who do not take supplementary vitamins including vitamin K. The latter approach is based on Schurgers et al. who reported a threshold of 150µg/day of vitamin K supplements for having a clinically relevant effect. [9] For this reason, the vitamin K model was tested with two types of interaction: vitamin K supplements interaction and interindividual interaction.

Results

A total of 30 patients accepted to be contacted, six declined to participate. Out of the 24 patients going into the study, 18 patients completed the data collection protocol (Table 1), equivalent to a 25% dropout rate.

Results from model reductions are reported in three steps:

- Reduction of lags on previous INR measurements and individual interaction
- Reduction from INR model including reduction from information on warfarin intake and individual interaction
- Reduction from INR model and warfarin model including reduction from information on vitamin K intake and individual interaction as well as vitamin K supplement interaction

A lag of four days, meaning four historic values relative to the current INR value was selected as appropriate, taking the amount of data per individual into account.

Table 1- Outline of 18 patients receiving warfarin

Characteristics	Number (%) or Mean ± SD
Age (years)	56 ± 15
Females	8 (44%)
Days in study	27 ± 1.78
INR value	2.5 ± 0.5
Warfarin intake [mg/day]	6 ± 2.5
Vitamin K intake [µg/day]	59 ± 105
Patients on daily vitamin K supplement	7 (39%)
Indication for OAT	
Heart valve replacement	9 (50%)
Deep venous thrombosis	3 (16%)
Atria fibrillation	4 (22%)
Coronary prosthesis	1 (6%)
Thromboembolism	1 (6%)

Analysis of INR model

The initial model holds both the main effect from INR with four lags and the interaction effect from INR and the individual with four lags. The interindividual variation between patients is not significant (p = 0.99), and only lag 1 is significant, lag 2 to lag 4 having a p-value > 0.87. The final INR model applied in the next step, where warfarin will be included is given in Equation (5).

$$INR_{i,t} = \alpha\, INR_{i,t-1} + \varepsilon_{i,t}, \quad (5)$$

with the within-individual Standard Deviation (SD) = 0.25 and α=0.99. The regression parameter does not differ significantly from 1 (p = 0.96), and hence the model describes the within-individual variation in INR by independent increments with a day-to-day SD of 0.25. Likewise, α is set to 1.

Analysis of INR and warfarin model

The first noticeable result is the importance of individual interaction with a p-value <0.00005; hence further testing will be including interaction from individuals. The warfarin model is deduced from successively testing the difference in warfarin intake from the last two, three or four days mean warfarin intake. The final INR and warfarin model is provided in Equation (6).

$$INR_{i,t} = INR_{i,t-1} + \beta_i\,\Delta W_{i,t-1} + \varepsilon_{i,t}, \quad (6)$$

with a SD = 0.54 and average value β = 0.52.

Analysis of INR, warfarin and vitamin K model

The addition of vitamin K information to the model and results for reduction of INR variation are described in the following. As no interactions from vitamin K supplement will

benefit the model (p = 0.1182), further testing of model reduction related to vitamin K information will be done without vitamin K supplement.

Reduction of lags on mean intake of vitamin K is done successively by removing one lag of the time, starting from fourth lag. There is no clear indication of a beneficial model provided by this reduction method. However, utilizing lag two including interindividual interaction will be a beneficial model compared to the full interaction one, with a successive p-value from F-test between the two of p=0.8338. Hence, the final model will be as in equation (7).

$$INR_{i,t} = INR_{i,t-1} + \beta_i \Delta W_{i,t-1} + \gamma_i \Delta K_{i,t-2} + \varepsilon_{i,t}, \quad (7)$$

with a SD = 0.22, average values $\beta_i = 0.51$ and $\gamma_i = -8.16*10^{-4}$.

Model control

The serial correlation structure of the model was checked by Durbin-Watson statistic (D-W = 2.074) and autocorrelation plots of residuals indicating mutually independent residuals. Hence, it is concluded that the suggested correlation structure is adequate. However, negative lag 1 autocorrelation suggest a possible improvement by adding white noise on top of independent INR increments. The normality assumption was checked by visual inspection of QQ-plots of residuals and found adequate. Variance homogeneity was assessed by scatter-plots of residuals versus fitted values, and no indication of heterogeneity was found.

Relative benefit of each independent variable

Significance tests between different models have shown what will benefit reduction of variance in INR predictions. By assessing the relative magnitude of each independent variable, it is revealed how much variance each variable explains. Each contribution to residual error reduction relative to total variation on INR is given in the following list:

- Contribution from the INR model 95.7%
- Contribution from adding the warfarin model 15.6%
- Contribution from adding vitamin K model 7.5%

Discussion

This paper reports the outcome of utilizing univariate linear regression models on quality OAT data.

The data is characterized by a close recording in terms of interval between observations; however the dataset is small in terms of number of individuals. The advantage is that it is possible to model and study the day-to-day dynamics of INR, warfarin and vitamin K. The disadvantage is that the group is small and selected. Hence, only qualitative and not quantitative results generalize to a larger population.

The model analysis directs the potential monitor/decision support system towards a state space model [10]. One virtue of the state space approach is that it is modular and flexible. It is possible to model the dynamics of a recommended dose of warfarin, the actual warfarin intake, intake of vitamin K and the INR level, true as well as measured. By use of the Kalman filter [11] it is possible to make inference on the recommended warfarin dose (in order to keep INR within the therapeutic interval) and to predict future INR values. This approach has been used to monitor pregnancy [12] and monitor post-surgical cancer patients [13]. By using the state space approach, it will be possible to suggest an optimal dose of warfarin given past values of INR, warfarin and vitamin K. Also the suggested dose can be adjusted for expected future intake of vitamin K.

The results from warfarin modelling showed the importance of individual interactions. This is in accordance with the fact that sensitivity to warfarin therapy often is associated with an interindividual dosage. In addition it was shown how the current warfarin intake was not a significant predictor for the current INR, while information from past days intake was able to explain INR variation. This is good in accordance with the pharmacological properties of warfarin that has a half-life of 36 hours in the plasma, and for this reason have a long-lasting effect on INR values. To further elaborate the utilized approach, one might include screening for polymorphisms of the enzyme (CYP2C9) involved in warfarin metabolism. Genetic variants in CYP2C9*2 and CYP2C9*3 have been shown to require lower maintenance dose of warfarin. In addition, patients with these variations are associated with an increased risk of over-anticoagulation.[2] Further, warfarin dosage variation is closely related to CYP2C9 and vitamin K epoxide reductase complex subunit 1 (VKORC1) and account for up to 30% of the variability in warfarin dose among European-Americans, and 10% variability among African-Americans.[16] Currently, screening for CYP2C9 variants before initiating coagulation therapy is an ongoing discussion in the literature, as this may allow clinicians to develop even more individual dosing protocols to reduce the risk of adverse drug effects.

While one could be tempted to neglect both the warfarin and the vitamin K model, the frequency of INR measurement from each individual must be taken into consideration. These patients are trained to aim for a target INR value by adjusting their dose of warfarin. In a regular setting, INR measurements would be done once a week and not every day. This additional information by more frequent measurements has earlier been reported to be related to an increase in Time in Therapeutic Range (TTR). [14] This will directly raise the contribution from the INR model to explain variance on the behalf of the other models. The indeed small contribution to explain variance from vitamin K model is also associated with the amount of intake. As vitamin K is found in a limited diversity of food, the daily intake is associated with large variations. Mean intake is 59.26µg/day with a SD of 104.62 µg. These large day-to-day variations in vitamin K intake may partly be the explanation of the low contribution from this model in terms of explaining variance in INR values.

In contrast to the findings in the present study, a recent study based on a physiological model of the vitamin K cycle, and tested on 157 days of data from 5 patients, has indicated that, for days with a high dietary intake of vitamin K, adding information on dietary vitamin K seems to significantly improve the accuracy of INR predictions [15]. Other studies have also shown a much larger effect of vitamin K intake than what can

be deduced from the 7.5% contribution from the vitamin K model in the present study [3, 6].

While it from a clinical point of view is to be expected that information on the intake of the anticoagulation drug, warfarin, is important in order to predict future INR values, more studies on the temporal aspects of the effect of the drug seems to be relevant. Furthermore, the vitamin K intake has to be further studied in order to assess its importance.

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Correspondence to:
Peter Brønnum Nielsen
Department of Health Science and Technology
Aalborg University
Fredrik Bajers Vej 7, D1-210
9220 Aalborg
Denmark
E-mail: pbn@hst.aau.dk