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Regular Article

Improvement of anticoagulant treatment using a dynamic decision support algorithm
A Danish Cohort study

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ABSTRACT

Introduction: Warfarin is the most widely prescribed vitamin K antagonist and in the United States and Europe more than 10 million people are currently in long-term oral anticoagulant treatment. This study aims to retrospectively validate a dynamic statistical model providing dosage suggestions to patients in warfarin treatment.
Materials and methods: The model was validated on a cohort of 553 patients with a mean TTR of 83%. Patients in the cohort were self-monitoring and managed by a highly specialised anticoagulation clinic. The predictive model essentially consists of three parts handling INR history, warfarin dosage and biological noise, which allows for prediction of future INR values and optimal warfarin dose to stay on INR target. Further, the model is based on parameters initially being set to population values and gradually individualised during monitoring of patients.
Primary outcome: Time in therapeutic range was used as surrogate quality measure of the treatment, and model-suggested dosage of warfarin was used to assess the accuracy of the model performance.
Results: The accuracy of the model predictions measured as median absolute error was 0.53 mg/day (interquartile range from 0.25 to 1.0). The model performance was evaluated by the difference between observed and predicted warfarin intake in the preceding week of an INR measurement. In more than 70% of the cases where INR measurements were outside the therapeutic range, the model suggested a more reasonable dose than the observed intake.
Conclusion: Applying the proposed dosing algorithm can potentially further increase the time in INR target range beyond 83%.

Introduction

Warfarin is the most widely prescribed drug in oral anticoagulant treatment (OAT) and more than 6 million patients in Europe and approximately 4 million in the United States are currently living on long-term OAT [1,2]. The most common indications for warfarin treatment are atrial fibrillation (AF), deep venous thrombosis (DVT), pulmonary embolism (PE), post myocardial infarction (MI), and heart valve replacement. The treatment balances between avoiding thrombotic events and bleeding episodes.

Anticoagulant monitoring is done by measurement of the International Normalised Ratio (INR). The therapeutic range of INR is 2.0-3.0 or 2.5-3.5 for the majority of the underlying conditions mentioned above. Further, anticoagulation with vitamin K antagonists (VKA) is a complicated task due to food and drug interacting with the effect of VKA [3–5]. A noticeable *between* patients variation in response to warfarin entails individual dosing and frequent monitoring of the INR. The risk profile for patients undergoing VKA treatment is dependent on the time for which the INR value is within therapeutic range (TR) [6–9]. Time in therapeutic range (TTR) is often used as a quality marker of VKA management [7,10,11], and is recommended as an endpoint when analysing quality of anticoagulation management [12]. A recent study, however, shows that TTR is not the optimal predictor of mortality, stroke, bleeding and hospitalisation in atrial fibrillation patients receiving warfarin therapy [13].

Warfarin therapy is primarily monitored by laboratory determination of INR using plasma from venipuncture. Different settings of treatment management exists, including usual care provided by the general practitioner, hospital outpatient clinics, and highly specialised

Abbreviations: INR, international normalised ratio; OAT, oral anticoagulant treatment; AF, atrial fibrillation; DVT, deep venous thrombosis; PE, pulmonary embolism; MI, post myocardial infarction; VKA, vitamin K antagonists; TR, therapeutic range; TTR, Time in therapeutic range; PST, patient self-testing; PSM, patient self-management; MAE, median absolute error.

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anticoagulation clinics. However, some patients are eligible for patient self-testing (PST) or patient self-management (PSM) using portable point-of-care testing coagulometers and will benefit for this type of management [14,15]. A meta-analysis comparing PSM and PST with usual care proved a significant reduction in thromboembolic events, but neither a reduction in major haemorrhagic events nor reduction in death was shown [16]. Patients younger than age 55 and patients with mechanical heart valve replacement had the largest reduction in thrombotic events in the comparison (hazard ratio of 0.33 and 0.52, respectively).

Some PSM patients are using decision aiding electronic tools or online decision support systems that will provide an on-screen dosage advice [17,18]. These meta-analysis favours uses of such systems with an overall improvement across studies of 6% in time in therapeutic INR range. However, no significant difference was found between controls and patients using decision support systems when comparing the risk for major bleeding (risk of thrombotic events was not reported) [19]. A proportion of published warfarin prediction algorithms utilise pharmacogentic dose prediction [20–22]. While they have shown to perform better compared to physician managed warfarin dosing in predicting the initial optimal dose (often measured in the time to reach stable treatment), the genetic information does not persistently improve the warfarin treatment [23–26].

It may be important to consider the intention behind the use of decision aiding tools that includes a prediction model, and such underlying prediction model should perform well in at least two situations. First, the model should attempt to maintain a high TTR by providing a dose adjustment advice. This can only be investigated in a prospective study design. Second, the model should perform properly when a measured INR value is outside the INR target range, in the sense of providing a dose adjustment that will bring the future INR value(s) within the desired range. This can be investigated in a retrospective designed study. For the sake of patient's safety and prior to a randomized controlled trial, we propose to retrospectively validate such a model bearing in mind that OAT is a potential lethal treatment if inappropriate dosage is provided.

In this study we aim to apply a developed dynamic statistical model for decision support [27] in a cohort of PSM patients treated in a highly specialised anticoagulation clinic.

Materials and methods

Population

Eligible patients were identified from the clinical database of the Thrombosis Research Clinic for PSM Oral Anticoagulation, Department of Cardiology, Aalborg University Hospital, Denmark. This centre includes a highly specialized anticoagulation clinic with approximately 850 patients who are trained in PSM OAT. The centre's functions are handled by specially trained nurses and specialists. The centre handles all matters relating to the patient's anticoagulant therapy including perioperative management when needed (regulation of INR, delivery of low molecular weight heparin, contact to other departments' etc.).

The patients are using an online dosage and decision support tool (AC Shared Care, ACURE, IBM, DK-8240 Risskov, Denmark), which provides dosage suggestions of warfarin for the following week based on the previous INR measurement. The dosage advice is given as a mean tablet (2.5 mg) intake per week, and subsequently calculated as a weekly pattern of daily dosage of warfarin. If an INR measurement typed into the system is not adequately close to or within the therapeutic range, a suggestion to contact the staff at the Thrombosis Research Clinic is given to the patient. The staff can order an instant dose change, e.g. double warfarin intake for a day or suspend the treatment for a day. These changes are registered in the clinical database as additions to the current intake of warfarin that day.

The data for the present study was acquired from January 2010 till December 2012 and consists of 837 patients assigned to PSM. Patients were excluded (N = 284) if the following criteria were met: less than 30 days of warfarin therapy or fewer than 4 INR measurements since onset of PSM (N = 38); registered with an event (thrombosis or minor/major bleeding) in the clinical database (N = 158); interval between INR measurements above 8 weeks (N = 87); no registered clinical information (N = 1). Data for each patient were then prepared to be applicable to the prediction model. The model required at least seven days of warfarin intake before the first INR measurement. Hence, the INR measurements that were performed within this period could not be included in the model and were removed accordingly.

Model description

The model is fully specified and discussed in details in [27], and is designed to handle time series of daily intake of warfarin and measured INR values. For a given patient, let T denote the target INR value, INR_t and INR_{t-1} be the measured INR value at a given day and the previous day (*INR history*), and w_{t-1} and w_{t-2} be the warfarin intake the previous day and the day before (*warfarin dosage*). Subjected to optimal dosing, the departure from target at a given day, apart from *biological noise*, is expected to be smaller than the departure the previous day. If the warfarin intake the previous day and the day before is higher than the optimal dose (to stay on target), the INR is expected to increase, and decrease if the warfarin intake is lower than the optimal dose. The day-to-day dynamics of warfarin and INR is modelled as

$$INR_t - T = \overbrace{\rho(INR_{t-1} - T)}^{INR\ history} + \overbrace{A(w_{t-1} + \lambda w_{t-2} - (1+\lambda)D_{t-1})}^{Warfarin\ dosage} + \overbrace{\varepsilon_t}^{Noise},$$

where ρ quantifies the day-to-day dynamics of INR, A is the sensitivity towards changes in warfarin intake, D is the idealised dose to maintain INR target, λ is a constant, and ε_t is a series of independent noise terms. The day-to-day dynamics of INR is quantified by the constant, ρ, between 0 and 1, leaving an auto-regressive structure of INR measurements when the patient is on optimal dosing. The sensitivity towards changes in warfarin intake, A, is an unknown patient specific parameter, negatively correlated to the dosage. This allows for modelling the individual INR change due to a unit change in warfarin, such that patients on a low warfarin dose are more likely to have a larger INR change compared to patients on a high dose. The idealised warfarin dose, D, is an unknown patient specific parameter. Over time D can exhibit small fluctuations reflecting changes in endogenous or exogenous factors. Warfarin affects INR_t through a between-day-profile of intake, $(w_{t-1} + \lambda w_{t-2})$, where λ is common to all patients. The noise sequence, ε_t, reflecting the biological noise has a patient specific standard deviation. Thus, the full specification of the model contains parameters describing population distributions.

Model based monitoring

When the model based monitoring of a patient is initiated all parameters are set to population values. Usually patients have a daily warfarin intake whereas INR measurements are less frequent. For each day predictions of INR, sensitivity and idealised dose are extrapolated from previous values. When an INR values becomes available the model parameters are updated. This so-called Kalman filter [28] offers recursive formulae for calculation of these updates, see details in [27]. Hereby the suggested dose at each time point is based on history of warfarin intake and INR measurements of the individual patient. Similarly, the individual sensitivity to changes in dose is updated. Hence the model adopts how the patient should be dosed aiming for a higher TTR.