Modelling in oral anticoagulation treatment

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PhD Thesis

Modelling in Oral Anticoagulation Treatment

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Abstract

An increasing number of people are prescribed blood thinning drugs as oral vitamin K antagonists (VKA). The drug is prescribed both prophylactic and therapeutically to a large group of patients at increased risk of thromboembolism. Optimal treatment with coumarins (i.e. warfarin) has been reported difficult mainly due to high inter- and intraindividual variability between patients' response to the required maintenance dose. Also dietary interaction from food containing vitamin K adds to difficulties in treatment with VKA, as vitamin K has an opposing effect of warfarin. Research has shown how involvement of patients in their VKA treatment improves the quality of the treatment; this is especially the case when patients are allowed to adjust medicine intake based upon International Normalized Ratio (INR). The treatment is a balance between avoiding adverse events as hemorrhages due to over-treatment and thromboembolisms due to under-treatment. The quality of the treatment may be further increased by introducing predictive models. Such models should account for variance in INR values and be able to aid patients in optimal dosing of warfarin by keeping the INR value at therapeutic level.

This PhD-project aims to develop predictive models that are able to account for inter- and intraindividual variability in patients' response to warfarin treatment. Furthermore, it has been hypothesized that including dietary information on vitamin K intake will increase precision of INR predictions. A novel compartment model of vitamin K has been developed and integrated into an already described model, which is able to predict INR values based upon warfarin intake. This study gave rise to exploration of other predictive factors that could potentially explain variations in INR values. Simple statistical techniques were applied to data from orally anticoagulated patients, and it was shown how temporal analysis of warfarin intake and vitamin K intake aid in explaining variance in INR values. The novel vitamin K model from the first study was refined in a third study to further investigate the importance of vitamin K when predicting INR values. A seemingly more accurate physiological model of vitamin K dynamics illustrated how vitamin K intake above or equal to recommended daily intake explains a large proportion of the INR prediction error. A fourth study was conducted with an attempt to develop a statistical model able to predict INR as well as predict a theoretical correct dose of warfarin intake to keep INR values at target level. In a fifth study, an analysis concerning variance in INR was conducted to explore the intrapatient variability in INR values. By comparing periods with equal intake of warfarin and vitamin K, and applying straightforward algebraic manipulation, measured INR values can be used in calculation of the intrapatient variability. This value can be regarded as a theoretical minimum of the prediction error when applying predictive models to this data.

All five studies contribute to the understanding of factors affecting variations in INR values. The thesis provides indication on the importance of including dietary vitamin K information in optimal oral VKA treatment. Further assessment of the proposed models should include trials to assess clinical outcome in patients treated with VKA in an out-patient setting.

Danish summary/Dansk resumé

Et stigende antal personer bliver ordineret blodfortyndende medicin så som peroral vitamin K antagonister (VKA). Medicinen ordineres både profylaktisk og terapeutisk til en stor gruppe af patienter med forhøjet risiko for embolisme. Optimal behandling med coumarin (f.eks. warfarin) har vist sig kompleks hovedsageligt grundet høj inter- og intraindividuel variation mellem patienternes respons til en givet vedligeholdelsesdosis. Interaktion med fødevarer, som indeholder vitamin K, har vist sig at tilføje til udfordringerne i behandling med VKA, da vitamin K har en modsatrettet effekt af warfarin. Forskning har vist, at kvaliteten af behandlingen øges, hvis patienterne tager aktiv del i behandlingen. Dette gælder især, når patienterne gives lov til at ændre medicinindtaget på baggrund af International Normalized Ratio (INR) værdier. Behandlingen er en balance mellem at undgå utilsigtede hændelser som indre blødninger grundet overbehandling, og at undgå thrombo-embolismer grundet utilstrækkelig behandling. Kvaliteten af behandlingen kan måske øges ved brug af prædiktive modeller. Sådanne modeller skal tage højde for varians i INR værdier og skal kunne hjælpe patienter i optimal dosering af warfarin; dette skal hjælpe til at holde INR værdierne i terapeutisk interval.

Dette ph.d. projekt har til formål at udvikle prædiktive modeller, som kan tage hensyn til inter- og intraindividuel variabilitet i patienternes respons til behandling med warfarin. Yderligere hypotiseres det, at ved inddragelse af information om vitamin K indtag, vil præcisionen af INR prædiktionerne øges. En kompartment model af vitamin K er blevet udviklet, og er integreret i en allerede beskrevet model, som kan forudsige INR værdier på baggrund af warfarin indtag. Denne undersøgelse gav anledning til en udforskning af andre prædiktive faktorer, som potentielt kunne forklare varians i INR værdier. Simple statistiske teknikker blev anvendt på data fra peroralt antikoagulerede patienter. Det blev vist hvordan analyse af den tidslige anskuelse af warfarin indtag og vitamin K indtag hjælper på forklaring af varians i INR værdier. For at få øget indsigt i vigtigheden af vitamin K når INR værdier prædikteres, blev modellen af vitamin K fra det første studie videreudviklet i et trejde studie. En tilsyneladende mere fysiologisk korrekt model af dynamikken for vitamin K viste hvordan vitamin K indtag, i niveau med dagligt anbefalet indtag, er istand til at forklare en stor andel af unøjagtigheden i INR prædiktionerne. Et fjerde studie blev udført i et forsøg på at udvikle en statistisk model, som kan forudsige såvel INR værdier og forudsige et teoretisk korrekt warfarin indtag, for at holde INR værdien i et terapeutisk niveau. I det femte studie blev der fortaget en analyse omhandlende varians i INR værdier for at udforske intrapatient variabiliteten. Ved sammeligning af perioder med ens indtag af warfarin og vitamin K, blev der, ved algebraisk manipulation, anvendt INR værdier i beregningen af intrapatient variabiliteten. Værdien fra denne beregning kan anses for at være et teoretisk minimum i prædiktionsfejlen, som fås ved anvendelsen af prædiktive modeller på disse data.

Alle fem studier bidrager til forståelse af faktorer, som kan relateres til variationer i INR værdier. Denne afhandling giver indikationer, af hvor vigtig vitamin K er, i optimal behandling med VKA. Yderligere vurderinger af de foreslåede modeller bør inkludere forsøg, som er struktureret til at vurdere de kliniske resultater ved brug af modellerne til patienter i VKA-behandling.

Preface

This PhD-thesis presents the research and work done during my study period, August 2007 to August 2010. My affiliation during the PhD-study was the Medical Informatics Group, Department of Health Science and Technology, Aalborg University, Denmark. The title of the thesis is Modelling in Oral Anticoagulation Treatment.

The thesis is structured in three main sections: Introduction, Studies, and Discussion and conclusion. The Introduction section provides a general introduction to the field of oral anticoagulation treatment. Emphasis in this section is on what challenges are involved in the treatment and what approaches aim to counter these challenges. Furthermore, a short introduction to each of the five studies is given after stating the subject of the thesis. The Studies section presents the five studies that constitute this thesis. Each paper is presented in its original form, either as submitted or accepted paper. The Discussion and conclusion section gives a discussion of the presented work and how the different studies are related. Furthermore, the limitations of the work are discussed along with suggested future directions for research within this field; finally, a brief conclusion is given.

Acknowledgement

Through three years of intensive work, a number of people have contributed with their knowledge and support to my research and to my academic career.

I would like to thank my family and friends for their support and time to listen whenever my work posed challenges or excitements. Especially my girlfriend has been a constant support through academic difficulties and breakthroughs; she has brought me a positive spirit when most needed.

The staff at Medical Informatics Group deserves thank for being good colleagues and for letting me contribute to the research environment. Especially Louise Pape-Haugaard and Anne Randorff Rasmussen receive my thanks for keeping me good company at the office and providing a nice working atmosphere. Further, Louise has played an important role in my considerations regarding research and teaching, and she has always been challenging me as well as supporting me in difficult matters. She has provided just about the right amount of everything whenever needed.

My co-authors from Aalborg Hospital, Torben Bjerregaard Larsen, Lars Hvilsted Rasmussen, Anna-Marie Bloch Münster, and Søren Risom Kristensen, should receive a thank for important comments to the manuscripts. Further, the willingness to share their clinical experience and knowledge has contributed to the clinical relevance of the conducted studies.

Søren Lundbye-Christensen should receive a special thank for being a constant inspiration, and for showing me that difficult research can be fun. Our meetings through the last year have raised the level of the presented research as well as my personal understanding of statistics. His company and our friendship have been an invaluable contribution to my career.

A thank is given to my supervisor Ole K. Hejlesen. His ways of guiding me in academic matters have been motivating, encouraging, and supportive. Through two years of my master study and three years of PhD study, he has been a role-model in my career and he has made me constantly strive to perform my very best. He taught me his way of thinking science and for that I am in great debt!

Peter Brønnum Nielsen

Aalborg, August 30th 2010

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1. Introduction

Persons with an increased risk of thrombosis are in need of anticoagulation treatment. The medicine used is often a vitamin K antagonist (VKA) that extends the time it takes for the blood to clot, thereby reducing the risk of thrombosis. Oral anticoagulation treatment (OAT) has been used in a broad medical field with various underlying conditions for more than 60 years. The relation between blood clotting and coumarin derivates was established by Dam and Doisy who shared the Nobel Prize in 1943 for their work.[1,2] Their main discoveries were the postulation and prove of the existence of vitamin K (K for German Koagulation) and the description of structure of the vitamin. The fundamental physiological mechanism of affecting synthesis of certain coagulation factors was known, however, the biochemical description and understanding was yet to be established in the mid 70'ies.[3,4] As of today in Denmark more than 100.000[5] people are taking VKA, and in the United Kingdom the number is nearly one million people.[6]

1.1 Underlying conditions for OAT

OAT is a prophylaxis treatment commenced to prevent embolisms. Thromboembolisms can occur if an embolism is carried in the blood stream, from the site of formation of the clot, into the pulmonary artery or one of the main branches. Underlying clinical conditions increasing risk of unintended blood clotting in the blood stream can roughly be categorized into these main areas: Prosthetic heart valves, atria fibrillation, reduction of the risk of recurrent myocardial infarction, and deep venous thrombosis (DVT).

Thromboembolism remains a serious complication after heart valve replacement whether the prosthesis is a mechanical valve or a valve of bioprosthetic tissue. Relatively intensive anticoagulant treatment is recommended with mechanical valve replacement, and therapy is depending on valve type and position.[7] Bioprostheses do not always require OAT, but patients are often anticoagulated for a period of 3-6 months, and with less intensity compared to treatment of patients with mechanical heart valve replacement.[8,9] Atria fibrillation is one of the relatively new major patient groups who receive OAT to prevent formation of clots due to abnormal blood flow caused by the fibrillation.[10] Acute myocardial infarction and treatment with anticoagulants have been discussed since introduction of the treatment for this clinical condition. The prophylaxis treatment of this is often combined with aspirin.[11] Optimum treatment of DVT with OAT requires assessment of whether the thrombosis is proximal or distal. Further, it is important to know if the DVT is unprovoked (idiopathic).[12] Other areas where OAT is applied are post-surgery, e.g. knee or hip replacement, and hereditary diseases such as thrombophilia.

1.2 Physiology involved in OAT

Warfarin is the most widely used coumarin derivative, and throughout this thesis OAT and warfarin treatment will be used as synonyms.

Warfarin

Warfarin is a racemic mixture of two enantiomers: R-warfarin and S-warfarin, where the latter has been reported to have a 2-4 fold increased anticoagulant effect compared to R-warfarin.[13] Both

enantiomers are metabolized through the cytochrome P450 (CYP) enzyme group. S-warfarin is mainly affected by CYP2C9 while R-warfarin is metabolized through five sub-CYPs.[14] The drug is highly bound to albumin in the plasma and has a bioavailability close to 100%.[15,16] The drug acts by interfering with the vitamin K cycle, see Figure 1.

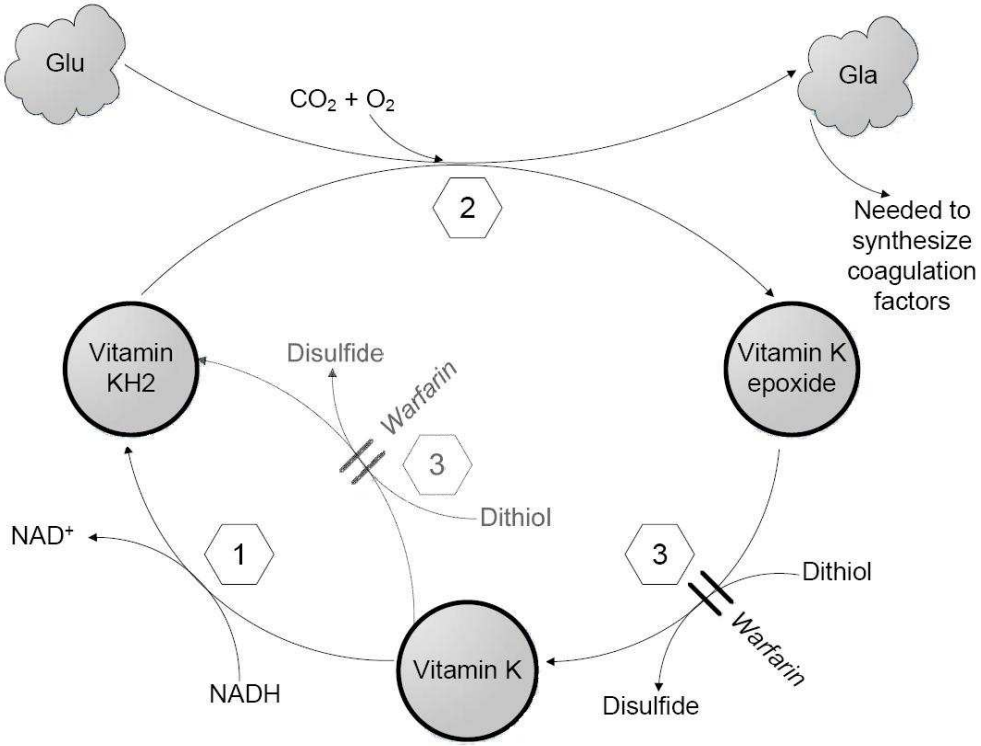

Figure 1: A diagram of the actions involved in the vitamin K cycle. Vitamin K is reduced either by a NADH dependent reductase activity, reaction ‹1›, or a reductase reaction dependent on the conversion of dithiol into disulfide, ‹3› (shaded). The carboxylation reaction, ‹2›, which converts glutamate residues (Glu) into gamma-carboxyglutamate residues (Gla), is driven by a vitamin hydroquinone (KH2) dependent carboxylase activity. This activity 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 vitamin K antagonists as warfarin, thus dietary vitamin K sources are necessary to maintain haemostasis.

Warfarin acts by a partly or complete block of two different steps in the vitamin K cycle. When vitamin K hydroquinone (VKH2) availability is decreased, the vitamin K-dependent carboxylation of glutamic acids is reduced. If this reaction is halted, only limited amount of vitamin K epoxide will be available for recycling of vitamin K by the enzyme Vitamin K epoxide reductase complex subunit 1 (VKORC1).[17] This leads to synthesis of proteins induced by vitamin K absence, i.e. coagulation factors missing a carbon chain and unable to function in the coagulation cascade.[18] Synthesis of functional vitamin K dependent coagulation factors now becomes dependent on new sources of vitamin K. Coagulation factor II (prothrombin), factor VII (stable factor), factor IX (anti haemophilic factor B), and factor X (Stuart-Prower factor) are all vitamin K dependent; besides these, protein C, protein S, and protein Z are proteins depending on vitamin K.

After warfarin treatment has been initiated, the first effects on INR values occur within two or three days.[19] Heparin is recommended to be concurrently administered due to the effect from warfarin

on all vitamin K depending proteins. Protein C and protein S are inhibiting activated factor VII in the coagulation cascade, and have a shorter half-life than most of the vitamin K dependent coagulation factors. If heparin is not administered, coagulation factors with longer half-life (relative to the regulative anticoagulant proteins C and S) could potentially exert a procoagulation effect. Heparin will add the anticoagulation effect needed before the warfarin effect reaches steady-state.[20]

Vitamin K

Two natural forms of vitamin K exists: phylloquinone often referred to as vitamin K_1, and menaquinones referred to as vitamin K_2. A third source of vitamin K is a synthetic precursor of vitamin K_2, called menadione or simply vitamin K_3. Vitamin K_1 is mainly found in leafy green vegetables, such as spinach, parsley, broccoli and kale.[21] Also beef and pork liver contain high amounts of vitamin K due to the fact that these animals feed on a diet rich in leafy greens. Internal production of vitamin K_2 is believed to involve the microflural population in the large intestine, and to be an important source of vitamin K.[22] The absorption of vitamin K is thought to be governed by the principles of fat-soluble vitamins including the need of bile salts, and appears mainly in the upper part of the small bovel.[18,23] The dietary intake of vitamin K is recommended to be approximately 1μg per kilogram body weight per day.[24]

1.3 Challenges involved in OAT

In spite of the well established evidence for warfarin treatment, under-utilization of the treatment has been shown in studies where more than half the eligible patients are not receiving treatment.[25,26] One of the main reasons for this is the fear of adverse events such as haemorrhagic. The OAT becomes a balance between avoiding the risk of bleeding complications, and not under treating the patient, which might lead to thrombotic events.

International Normalized Ratio

The quality of OAT is often assessed by measuring the International Normalized Ratio (INR), which provides a standard for comparing blood coagulation tests. The INR is calculated based on Prothrombin Time (PT) as follows:

$$INR = (\text{patient PT} / \text{mean normal PT})^{ISI}$$

where ISI is an international sensitivity index of the responsiveness of thromboplastin, which is used as reactant in the PT measurement. PT is obtained by measuring the time it takes for the blood to clot after adding thromboplastin. The recommended INR target value is diagnosis dependent; e.g. atria fibrillation has a target INR of 2.5, while mechanic heart valve replacement often requires a slight higher target INR of 3.0 or 3.5. Instead of a specific value of the INR target a therapeutic window is utilized and regarded as adequate treatment with OAT; e.g. atria fibrillation has a therapeutic window of INR between 2 and 3.[8] Further quality assessment of the treatment involves calculation of Time (spent) in Therapeutic Range (TTR), which uses consecutive INR measurements to establish a percentage based number indicating the duration where INR values are

within the preset window.[27] Studies indicate that both in clinical trials and routine settings optimizing OAT to increase TTR is still a complicated task.[28,29]

Flensted and colleagues investigated the variation in consecutive INR values, with an attempt to eliminate external sources of variation (vitamin K intake, drug interactions, alcohol consumption, etc.).[30-32] One of the main research goals was to quantify random fluctuations in INR measurements. Fluctuations could be due to "spontaneous variation" or reflect clinical relevant change in coagulation. If random fluctuations were accounted for between two consecutive INR measurements, the difference between these measurements could be of sub-clinical interest. They proposed a novel method that quantifies critical difference between two INR measurements. A retrospective test of this method revealed a "ping-pong" effect, where changes in dose of coumarin were made based on INR measurements outside therapeutic window, but without critical difference compared to the last measurement; this causes oscillating INR values. Further elaboration of their model lead to quantification of critical difference on the INR scale taking INR target into consideration: with target INR at 2.5 the difference between two measurements of clinical interest is 0.7, and for target INR at 3.5, the clinical critical difference is 1. In summary, the work from Flensted and colleagues indirectly proved the fact that there is a lack of a simple relationship between a dose of VKA and the therapeutic effect.

Genetic variations

Mutations in the gene coding for warfarin metabolism enzymes have been shown to alter the response to warfarin treatment, thus increasing inter-individual INR variation. Some of the best documented wild types of CYP2C9*1 is CYP2C9*2 and CYP2C9*3.[33] These mutations are associated with an impaired ability to metabolize warfarin, hence prolonging warfarin half-life and leading to reduced warfarin requirements. Screening for gene-mutations before initiating warfarin treatment is an ongoing discussion, but the relation between the mutations and higher risk of bleeding has been established.[34,35] The VKORC1 enzyme is the target for warfarin's inhibitory effect on the vitamin K cycle. Mutations in this gene have shown to account for some of the difficulties to maintain INR at target level.[36] Whereas of three well-described wild types of CYP2C9, there is a higher degree of diversity in mutations on VKOR1C; some leads to warfarin resistance, while others lead to reduced VKOR activity.[37] Fifty percent of the inter-individual variation on warfarin response is believed to be directly accounted for by the pharmacokinetic variants (CYP2C9) and pharmacodynamic variants (VKORC1).[38,39] A population based model of different types of genetic mutations and warfarin treatment showed the effect of different combination of wild type alleles. The model showed how equal dose of warfarin could potential lead to an INR value of 2 in one patient, and an INR value above 6 in another patient solely depending on gene mutations.[40]

Dietary vitamin K

OAT can be affected by numerous environmental factors that can alter warfarin kinetics and dynamics.[41] Vitamin K dietary intake is one of these factors, which may alter the response to warfarin treatment. New external sources of vitamin K will increase the production of functional coagulation factors depending on vitamin K. The clinical relevance of changes in vitamin K has

been discussed, and it has been shown how patients with poor dietary intake of vitamin K often has less stable control of anticoagulation.[42] It has been suggested to provide these unstable anticoagulated patients with oral vitamin K supplementation; however unrecognized intake of such can lead to warfarin resistance.[43] Other studies reported that steady-state warfarin treatment was not affected by dietary vitamin K intake.[44,45] However, Khan and colleagues suggested that their findings, of vitamin K having no effect in their regression model, could be related to the fact that warfarin dosage had already been adjusted to control for individual vitamin K status. Further, they only involved patients whose dose of warfarin remained constant. Variations in vitamin K might be greater in patients who do not receive an optimized warfarin dose that remains constant. Although Loebstein and colleagues reported vitamin K as negligible; a recently published review by the same research group acknowledges that vitamin K plays an important role in maintaining therapeutic stability.[46] The magnitude of clinically relevant change in dietary vitamin K intake has been reported to be above 100μg/day.[47-50] A prospective study established proof of the clinical relevance of vitamin K as a major independent factor that interferes with OAT stability [51], and de Assis and colleagues established a dietary vitamin K strategy to improve OAT.[52] This approach has, however, been questioned, and suggested to be most effective for those who are under-anticoagulated and only consume small amounts of vitamin K rich foods.[53] Still, it remains clear that patients who have poorly controlled OAT will benefit from a diet with controlled vitamin K content.[54]

1.4 Approaches to counter challenges in OAT

Approaches to improve OAT include (among others) development of new antithrombotic drugs, use of different types of management of the treatment, and use of computer software that can aid in dose adjustment.

Through the last decade researchers have been working on development of a new type of antithrombotic drug, which could eliminate or minimize the difficulties in warfarin treatment: the relatively narrow therapeutic window, large inter-individual dose response, drug-to-drug interactions, and the need for close monitoring that is associated with the fear of adverse events of over-treatment. Direct thrombin inhibitors are a newly developed class of anticoagulants that acts by directly inhibiting activated clotting factor II. Another type of newly developed drug class is direct clotting factor X inhibitors.[55,56] Both drug classes can be given in a fixed dose and does not require routine monitoring. Large-scale randomized controlled trials have been conducted with different types of commercially available analogues, and the usage has been explored in different clinical conditions.[57-64] A discussion of whether or not these new drugs will completely replace the use of warfarin is beyond the scope of this thesis. However, the topic is an ongoing discussion in the literature.[65-68]

Types of OAT management

In general three different types of OAT management exist.[69] One is “routine-care” where patients visit the hospital-based anticoagulation clinic or General Practitioner (GP) every 4-6 weeks to have the INR value measured. Some patients can take part in the management of OAT by handling a coagulometer as a Point-of-Care device and measure INR values themselves. Patients assigned to

"self-testing" (PST) will report this INR value to a responsible clinician who decides on dosage adjustment of warfarin. Patients educated in "self-management" (PSM) will both handle INR measurement, and are allowed within a preset range to change warfarin dosage. In the latter two groups, measurements of INR values are most frequent: once every week or two.

Studies have compared how well OAT is controlled when the treatment is managed by the primary physician and when the treatment is managed by a specialized anticoagulant management service: Compared to routine-care managed by the GP, management handled by the specialized clinic was shown to reduces complication rates for more than 50% of the cases, and achieves higher TTR.[70,71] A large randomized controlled trial comparing specialized anticoagulant management service and treatment by the GP did, however, fail to show a significant difference in TTR between the two types of management.[72]

PST and PSM are recommended as effective alternative treatment models compared to routine-care. Heneghan and colleagues conducted a meta-analysis and pooled estimates from 14 randomized controlled trials of PST.[73] They reported significant lower rate of thrombotic events and lower mortality in PSM compared to PST. However, this type of management was noted not to be suited for every patient, and patients should be carefully identified and educated in PSM.[26,74,75]

Decision support systems

Computer programs with algorithms capable of predicting the next warfarin dose (or response to a future warfarin dose), can potentially aid poorly controlled dose management in OAT. Such systems are based on different approaches ranging from strict expert-based algorithms, population-based pharmacokinetic/pharmacodynamic (PK/PD) models, and rigid mathematical methods such as regression modelling. Bayesian parameter optimization methods are common techniques in the latter two approaches, and are meant to account for inter- and intraindividual response to VKA.[76]

Through the past 25 years computerized decision support systems (CDSS) have been available to assist clinicians in OAT. Some of the first studies have shown that such systems can be at least as effective as experienced physicians with regard to dose adjustment.[77-79] In a large scale multicenter randomized trial Poller and colleagues showed the effective use of the computer program DAWN AC.[80] The computer program gave significantly better INR control compared to physician management. Another approach by Manotti and colleagues using the software program PARMA (later PARMA 5) achieved similar results as the DAWN AC study; even though they obtained a slight higher TTR.[81,82] Poller and colleagues conducted yet another multicentre randomized study comparing the use of DAWN AC and PARMA 5 in different countries.[83] This proved that computer-assisted dosage could be both safe and effective. However, the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) do not directly recommend use of CDSS, and the guidelines state that it should be based on physician preferences.[13]

Modelling in OAT

The CDSS used in OAT could be based on PK/PD models that account for warfarin metabolism and warfarin's effect on vitamin K dependent coagulation factors. Such models can be useful for

estimating inaccessible pharmacodynamic parameters, which may be useful in determining the pharmacological action on each individual coagulation factor. An excellent review in the field of modelling in OAT has been published by N.H.G. Holford.[84] His review and the work by L. B. Sheiner have partly set the stage for PK/PD models developed throughout the years in the field of OAT.[85] One of their important contributions was the link between levels of clotting factor and PT or INR, which was established by a theoretical compound referred to as Prothrombine Complex Activity (PCA). This made it possible to link the fairly accurate kinetics of warfarin and the coagulation factors with the clinical tests, and hence made it possible to develop models that could be used in a clinical setting. Ovesen and colleagues conducted a small study including 35 patients, and showed that using techniques for predicting warfarin dose was significantly better than empirically dosing.[86]

Some of the very early CDSS were only sporadically tested, but the result from modelling physiology involved in OAT was promising.[87] Abbrecht and colleagues developed a model that is able to predict PCA. It was retrospectively evaluated and marked as a good representation of the involved physiological system. Prospective evaluation of the model proved a slightly worse performance in terms of days to reach therapeutic PCA intervals when compared to the control group.[88] Wiegman & Vossepoel described the use of a compartment modelling to develop a dose-response model of warfarin, which was able to predict coagulation time. At that time it was successfully used for the majority of the patients in a Dutch specialized anticoagulant management service.[89] Svec and colleagues published a PK/PD model using a Bayesian forecasting technique to predict the prothrombin ratio based on population based parameters. By adapting these parameters by feedback from five prothrombin ratio measurements, they almost doubled the accuracy of the predictions giving a Root Mean Square (RMS) error of 0.219.[90] Boyle and colleagues achieved a prediction error of the same level as Svec and colleagues, using a Bayesian regression model (named WarfCalc), and also required five measurements to achieve the reported results.[91] A large variety of models, with different modelling approaches for predicting warfarin treatment, have been described and evaluated.[92-105]

Vadher and colleagues developed a compartment model that is able to predict warfarin dosage based on INR predictions; this approach was evaluated in a randomised controlled trial with 148 patients requiring initiation of warfarin treatment.[106,107] The model is comprised of four compartment models that handles coagulation factor II, VII and X, and plasma warfarin. The INR value is calculated based on a fraction of the mentioned coagulation factor, which (in modelling context) is not affected by warfarin intake. The model was incorporated into a CDSS and proved to lower the median time to achieve a stable dose of warfarin (7 days), compared to trainee doctors (9days).

Pasterkamp and colleagues developed a simplified model (named TRODIS) based on the structure proposed by Holford.[108] The model calculates a maintenance dose of warfarin, based on an individual sensitivity parameter, to keep a patient on INR target. The proposed dosages from the model were initially evaluated by two “dosing experts” in three levels: in 91.8% of the cases (of 194 proposals) they were ranked as “good”. A more solid evaluation of the model was conducted in a

double-blinded, randomized controlled trial in 712 patients where a new algorithm (named ICAD) was introduced. The ICAD algorithm allowed for continuous adjustment of the sensitivity parameter over time, and proved to be significantly better than the original TRODIS model.[109]

2. Aim of PhD-thesis

The focus of this PhD-thesis is an assessment of the effect of predictive factors than can influence INR values. From the previous chapter, it is evident that such factor is dietary vitamin K, which however, has not been utilized in a modelling context. The objective of the work presented in this thesis is therefore to explore the usage of vitamin K in modelling in OAT and to reveal the magnitude of the effect from vitamin K on INR values, in order to explain some of the variation in INR values.

2.1 Studies employed in the PhD-thesis

The first novel attempt, of using vitamin K in a model predicting INR values, was based on the model described and tested by Vadher and colleagues.[107] Their model has been expanded with a one-compartment model, which handles both pharmacokinetic and pharmacodynamic aspects of vitamin K from dietary intake. The model is able to predict INR values seven days into the future, and handles patient sensitivity to warfarin individually. This is done by a warfarin sensitivity parameter, which is continuously updated each time the model is presented to an INR value. This is presented in the paper "*Assessing Importance of Dietary Data in Anticoagulation Treatment*".

Further investigation of factors that potentially could affect INR variations was carried out by using simple statistical models. Data sampled with high frequency (once per day) was used to detect local (or short-term) variations in consecutive INR measurements. This allows for detection of predictive factors affecting INR variations, where time has been taking into consideration. A number of univariate linear regression models were employed, and F-tests were applied to remove models that would not benefit in decreasing observed variance on INR values. This study is presented in the paper "*Data Mining to Assess Variations in Oral Anticoagulation Treatment*".

Another investigation using the previously described compartment model was performed to evaluate the impact of dietary vitamin K intake. Inspired by the results using the statistical regression model, the compartment model was slightly refined to account for effects from vitamin K during a longer period of time. To further assess the importance of dietary vitamin K, the model was evaluated both on data where patients have consumed recommended daily requirement of vitamin K and on data where patients consumed vitamin K above this recommendation. This is presented in the paper "*Model based prediction of INR utilizing vitamin K information*".

A seemingly very different modelling approach was made to investigate the possibility of not only predicting INR values, but also predicting a theoretical correct dose of warfarin to keep an individual patient on a specific target INR value. The developed model is set on state-space form and is using Kalman filtering technique to update parameters used in the prediction of INR values

and theoretical correct warfarin. The model is presented in the paper "*A Dynamic Prediction Model for Anticoagulation Therapy*".

A fifth study was conducted to assess the intrapatient variability in INR values. Intrapatient variability can be used to give a theoretical quantification of the lowest achievable prediction error for e.g. metabolic models. Matching pairs of shorter periods of data (three days) with identical warfarin intake and vitamin K intake was used to estimate the intrapatient variability in the data used throughout the work that comprises this thesis. The analysis is presented in the paper "*Estimation of Intra-patient Variation in Clinical International Normalized Ratio (INR) Data Used to Evaluate a Predictive Model in Oral Anticoagulation Treatment*".

3. Studies

This chapter of the thesis presents the scientific work. Each section corresponds to a study and a paper. The papers are provided in the original form, both accepted for publication and submitted for publication. Statuses of the papers of September 2010 are:

- Assessing Importance of Dietary Data in Anticoagulation Treatment: ***Published*** *in Studies in Health Technology and Informatics*
- Data Mining to Assess Variations in Oral Anticoagulation Treatment: ***Accepted for publication*** *on MEDINFO 2010 – 13th World Congress on Medical and Health Informatics*
- Model based prediction of INR utilizing vitamin K information: ***Submitted*** *to Journal of Thrombosis and Haemostasis*
- A Dynamic Prediction Model for Anticoagulation Therapy: ***Submitted*** *to Computer Methods and Programs in Biomedicine*
- Estimation of Intrapatient Variation in Clinical International Normalized Ratio (INR) Data Used to Evaluate a Predictive Model in Oral Anticoagulation Treatment: ***Submitted*** *to Clinical Chemistry*

Each of the papers will in the following sections have its individual list of reference in the end of the publication.

4. Discussion and conclusion

For more than 50 years VKA has been prescribed in prophylactic and therapeutic treatment to people with an increased risk of thrombosis.[6,13] The main physiological process involved in OAT with warfarin is the vitamin K cycle.[16] Warfarin interferes with two different steps in the biochemical process of recycling vitamin K.[17,19] If vitamin K supplies are halted, the liver cannot produce functional vitamin K dependent clotting factors. This leads to impaired haemostasis and the time it takes for the blood to form a clot is prolonged. Vitamin K is found in different types of food, e.g. leafy green vegetables.[21] If adequate amounts of vitamin K are consumed by patients in warfarin treatment, this will mediate changes in INR values as new sources of vitamin K are available to the liver.[46,47,50] Optimal treatment with warfarin has been shown difficult due to inter- and intraindividual response to the treatment.[31,40] One of the main causes of this is related to the variation in enzyme alleles leading to differences in the metabolism of warfarin and recycling of vitamin K.[31,39,40] Patients assigned to PSM have shown to benefit from this type of management.[110] Some of these patients use CDSS that can aid them in warfarin dosing to keep their INR value at target level. Large randomized controlled clinical trials have shown how the use of CDSS can lead to higher TTR when compared to conventional management.[81-83] The models used in CDSS in OAT have been refined through the past 25 years.[111] A large proportion of these systems are based on PK/PD models that are modelling the physiology related to the treatment.[84,89,90] Two studies have evaluated two different models used to provide initial and maintenance doses of warfarin. It was shown how the results using the models were comparable to the results in the control groups where trainee doctors were giving dosage advice.[106,109]

The work described in this thesis investigates the use of different modelling approaches to examine factors affecting variation in INR values. The thesis further aims to add to the knowledge regarding the relevance of using dietary information on vitamin K when predicting INR values.

In the first study, a novel model of the impact of dietary vitamin K on INR values was proposed. The model was based on the model of Vadher and colleagues [107], which was evaluated in warfarin initiation. Even though our model can be used to predict warfarin initiation dose and maintenance dose, this was not tested in the study as the scope was to assess the importance of vitamin K when predicting INR values. The model was evaluated on data from five patients in OAT assigned to PSM. The study indicated a potential benefit from including vitamin K when predicting INR values. However due to the limited number of patients, the strength of vitamin K as a predictor of INR values remained unclear from this study. Furthermore, other factors of potential importance were not considered.

In the second study, a wider approach to assess potential parameters that explain INR variation was taken. Of special interest were temporal relations between warfarin and vitamin K intake and INR measurements. Data from 18 patients in OAT were used to evaluate a set of different univariate linear regression models. Due to warfarin pharmacokinetic parameters (with a half-life of approximately 36 hours) it was chosen to include four days of past intake in the study to explain INR variation; the same period was chosen for past vitamin K intake. Therefore, the initial

regression model included INR values and warfarin and vitamin K intake from the past four days (i.e. all 3 types of data from day -4 to -1). This model was then successively reduced by using F-test statistics to determine whether or not each parameter contributed in explaining INR variation (at day zero). The final model for predicting INR on day zero used the following input: INR from day -1 (lag 1 INR); deviation in warfarin intake on day -1 relative to the mean warfarin intake in the past 4 days; deviation in vitamin K intake on day -2 relative to the mean vitamin K intake in the past 4 days.

In the third study, the physiological model (developed in the first study) was refined in accordance with the results from the second study. A data set was divided into a training set used to estimate the model parameters, and a test set that was used to evaluate the INR predictions from the model. The results showed how the average INR prediction error can be significantly reduced by using a model including vitamin K information. Not surprisingly, the effect of including vitamin K information was found to be largest in data containing relatively large vitamin K consumption (on or above recommended daily requirements).

In the fourth study, a quite different type of prediction model was developed; a state space model using an extended Kalman filter to optimize parameters each time the model was presented to a new INR value. The algorithm takes warfarin intake and INR measurements as input, and based on these, the model performs INR predictions and suggests a theoretical correct dose of warfarin to maintain an individual target INR. When no INR measurements are available as input, the model expands the confidence limits of the INR prediction.

A fifth study was conducted in order to assess intrapatient variability in INR values. In data from 18 patients in warfarin treatment, matching pairs of shorter periods of data, with identical warfarin intake and vitamin K intake, were identified. Under the assumption of independence between the two periods in a pair, the pair of INR values on the last day in the two periods was used to calculate the intrapatient variability. The study illustrated how the intrapatient variability can be compared with the RMS prediction error when using a model to predict INR values.

4.1 Comparison of the models

The presented studies of modelling in OAT are based on data from the same data collection protocol. This provides an opportunity to compare the outcome of each study. Table 1 summarizes the results comparing the average Root Mean Square (RMS) error of the predicted INR values for the three models when predicting one day into the future.

Study	Without warfarin information	With warfarin and vitamin K information	Number of patients in the test
Model 1 (section 3.1)	0.235	0.210	5
Model 3 (section 3.3)	0.264	0.291	13
Model 4 (section 3.4)	0.266	Not available	18

Table 1: Summary of the predictive performance of the three predictive models expressed as average Root Mean Square INR prediction errors.

The size of the data material varies between the three studies, which adds to the difficulties when comparing the RMS errors. Furthermore, the number of measurements used to adjust the models is different: for example Model 1 uses five INR measurements to estimate the warfarin sensitivity (*warfsens*) before making the predictions. Model 4 does initially only use one INR measurement to produce predictions, and therefore the initial confidence limits of the INR prediction are wide, as the parameters are not (yet) adapted to each individual. As more measurements are added the quality increases. In the study on Model 4, all 18 patients are used both for developing the model and for testing the model, whereas in the study on Model 3, the first 5 patients are used to develop the model and the remaining 13 patients are used to test it. Even though this theoretically might favour the test results for Model 4, the consequences of the differences in test design are expected to be very small. It can be argued from Table 1 that the models perform equally well when predicting INR values a single day into the future.

Adding vitamin K information reduces one day prediction RMS errors in Model 1 but increases the error in Model 3. It should be noted, though, that for predictions 7 days into the future, both Model 1 and Model 3 have a lower prediction error when including vitamin K information. The effect of adding dietary vitamin K information to Model 4 still remains to be assessed. Model 4, in its current form, generates a suggested dose of warfarin and predicts INR for the following day. Model 1 and Model 3 are not limited to an INR prediction once a day: the implemented compartment models generate a prediction of INR values each hour. Even though the performance of Model 1 and Model 3 is only evaluated against measured INR values once a day, visual inspection of the INR predictions between INR measurements appear to be in accordance with the expected physiological behaviour. Figure 2 shows the level of each of the three modelled coagulation factors in a simulation during the warfarin initiation phase.

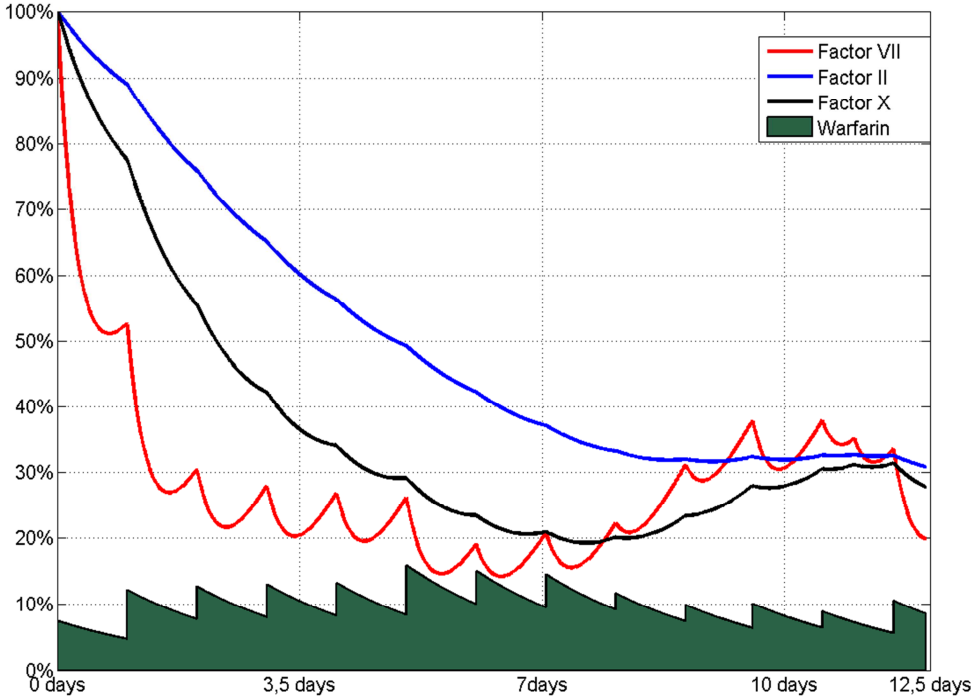

Figure 2: A simulation of the development of three coagulation factors during the initiation of warfarin treatment using Model 3. The concentration in the warfarin compartment is illustrated by the green area (using an arbitrary scale); the daily intake of warfarin being in the range of 2.5mg to 5mg (corresponding to the vertical steps of the green area). The three curves, depicting each coagulation factor, are showing the proportion of each of the functional coagulation factors in the model. From the slope and shape of the curves, the importance of the half-life of each of the factors becomes evident. Factor VII has a relatively short half-life (3-6 hours), while Factor II has a relatively long half-life (60 hours). The proportions of functional coagulation factors are the basis for the INR calculation in Model 1 and 3.

The proportion of functional coagulation factors in warfarin treatment illustrated in Figure 2 is in accordance with other studies.[112,113] Even though Model 4 might also have been implemented allowing for e.g. hourly INR predictions, it was, however, chosen not to attempt to model physiology. One could argue that how this model behaves between INR measurements is - in a strict sense - not interesting for this particular type of model.

Model 4 has the ability to directly provide a suggested warfarin dose to keep the INR value at target. This functionality could also be added to Model 1 and Model 3 by implementing an iterative algorithm suggesting the optimal warfarin dose: the dose that by using the model is predicted to lead to the best possible future INR values. Doing this, Model 1 and Model 3 could be used as an inference engine in a decision support tool for warfarin dosage adjustment. The warfarin adjustment can also be done manually illustrating the expected INR values after changes suggested by patients or clinicians.

As described in the fifth paper, the data used throughout the thesis have an intrapatient variability of 0.46 if warfarin is considered as the dominant external source of variation, and an intrapatient variability of 0.36 if both warfarin and vitamin K intake are included in the calculation. Under the assumption of independence in the calculation, the intrapatient variability is the theoretical minimum for the RMS prediction error and it can therefore be used as a benchmark. It can be seen that the

average RMS error for the one day predictions, listed in Table 1, are all significantly lower than the intrapatient variability. This can be explained by a relatively high correlation between data from two consecutive days. In fact, the results described in the fifth paper seem to indicate that INR measurements are not independent for a period of at least 3-4 days. This is however, in good accordance with action profiles for warfarin and vitamin K: For example if the warfarin intake, which usually is taken in the morning by a particular patient, is shifted to the evening, this will not only influence the next day's INR measurements but will have an effect on several days of INR measurement. Likewise, a vitamin K rich meal will influence INR measurements for more than one day. Other unknown factors may contribute to the correlation between consecutive days: changes in warfarin sensitivity, exercise, alcohol intake etc. At present, only Model 1 and 3 can predict more than one day into the future. The difference between the intrapatient variability and the RMS prediction error of Model 1 and Model 3 after 7 days seems to be around 0.1. This indicates that the model prediction error for these models is close to the theoretical minimum.

4.2 Limitations

The data used in all the studies were collected based upon a standardized diary for daily collection of OAT data. The content of vitamin K in the diet was not accurately measured, but was estimated based upon diet notes in the diary. From the notes, the "USDA National Nutrient Database for Standard Reference edition 16"[114] was used to estimate vitamin K in the diet. This method may introduce a bias. The patients estimated the amount of each type of food, and wrote notes like "half a plate of salad". From this type of information it is not possible to obtain the exact amount of vitamin K in the diet. To counter this, one might request the patients to weigh each type of food in each meal, and for example give an accurate description of the type of salad: "80 grams of iceberg lettuce". However, it is believed that this approach would be an extra burden on the patients substantially increasing the dropout rate.

Since the patients enrolled in the data collection measured the INR value once a day, the data available in the studies cannot be regarded as representative of "normal" OAT data. If patients were not enrolled in this study, a weekly INR measurement would have been recommended to this type of patients. A high frequency of INR measurements has been shown to increase the time in therapeutic range (TTR) and to benefit the quality of the treatment.[7,115] Hence, the data used in the studies show well-regulated anticoagulated patients; which is also evident from a high average TTR of 81.2%. It is unknown if the proposed prediction models would perform differently if presented to a set of data from less well-regulated patients. The studies assessing the quality of the models use a retrospective approach, and they have to be followed by proper prospectively designed studies to assess the impact on clinical outcome when using the models to adjust the warfarin dosage.

4.3 Future directions

Future work should aim to further explore the impact of vitamin K information when predicting INR values. Temporal aspects of the physiology could be of interest: what is the duration of the effect of a change in vitamin K intake on INR values? Furthermore, what is the threshold of the amount of vitamin K intake that can induce a clinically important change in INR values? Such

studies could add to the knowledge regarding the usefulness of vitamin K information when predicting INR values. An important question to answer is whether patients will benefit from taking into account the intake of vitamin K when making decisions on warfarin dosing in OAT. Prospective intervention studies should be carried out to assess the causal relation between the vitamin K intake and the need for warfarin adjustment in OAT.

The proposed models should be evaluated on datasets from a broad range of patients in OAT. The thesis has illustrated how the models perform when using a dataset of high quality in terms of frequency of measurements, which only allows for conclusions regarding this type of patients: The conclusions cannot be extended to the broad range of patients. This would require a much larger dataset including all types of patients. It might therefore, be relevant to perform another retrospectively designed study using a large dataset with a broad population of patients in OAT. An interesting dataset might be collected from patients that follow the normal treatment pattern of patients assigned to PSM who often measure INR approximately once a week.

To assess whether the proposed models can improve the outcome of OAT, e.g. measured as increased TTR, prospective clinical studies should be conducted. This would require further system development in order to implement the models in a CDSS to make it possible for clinicians and/or patients to operate the models. The study design should be a randomized controlled trial and it might include patients assigned to PSM letting the intervention group use a model based CDSS.

4.4 Conclusion

This PhD thesis describes two quite different predictive modelling approaches in OAT, with and without the use of vitamin K information. Evaluation results are compared with an estimate of the intrapatient variability.

Three of the five papers describe the development of models capable of predicting future INR values. Two models are using compartment modelling techniques and are using INR values to estimate an individual warfarin sensitivity parameter. The third predictive model is based on statistical techniques and is able to give a suggestion on a theoretically correct warfarin dose for keeping the INR at a designated target. One of the papers in this thesis analyses various factors that may explain INR variations. The last paper describes a method for estimating the intrapatient variability, which can be used as a benchmark when evaluating the predictive power in predictive models.

Through this dissertation, the relevance of further studies on the temporal relation between vitamin K and OAT has been emphasized. Studies assessing the clinical outcome of using the proposed predictive models in a decision support system still need to be carried out.

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