Rational and Safe Dosing

of Phenprocoumon

during Loading and Maintenance Phase

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Dedicated to Martin, Noah, Aaron & Samuel

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1 Abbreviations

ALAT	Alanin aminotransferase
AP	Alkaline phosphatase
BMI	Body-mass index
CALU	Calumenin
CI	Confidence interval
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CYP	Cytochrome P450 isoenzyme
eGFR	estimated glomerular filtration rate
EPHX	Microsomal epoxide hydrolase
FPH	Foederatio Pharmaceutica Helvetiae
F	Factor
GGCX	γ-glutamyl carboxylase
GI	gastrointestinal
INR	International normalized ratio
N	Number of cases
no.	Number
n.s.	not significant
NSAID	Nonsteroidal anti-inflammatory Drug
OA(s)	Oral anticoagulant(s)
OAC	Oral anticoagulation
OR	Odds ratio

p	Probability
PROC	Protein C
PTT	Partial thromboplastin time
Ref.	reference
SNP(s)	Single nucleotide polymorphism(s)
Tc	Thrombocyte
VKA(s)	Vitamin K antagonist(s)
VKOR	Vitamin-K-epoxide-reductase
VKORC1	Vitamin K reductase complex subunit 1
WHO	World Health Organisation

2 Introduction

Vitamin-K antagonists (VKAs) of the coumarin type are widely-used oral anticoagulants (OAs). They have proven to be highly effective antithrombotic drugs for the treatment or prevention of deep venous thrombosis, pulmonary embolism, and certain forms of ischaemic stroke. [1-3]

Adverse Effects of OAs

Beside these well-confirmed beneficial effects, OAs are associated with adverse effects, primarily the risk of bleeding. Anticoagulant-related bleeding is common and often serious. Indeed, OAs are the leading class of drug-associated adverse effects that result in hospitalization. [4-5] Every year, 10-17% of patients on anticoagulant therapy experience bleeding complications, and the incidence rate of serious bleeding (i.e. requiring hospitalization, blood transfusion and/or surgery) and fatal bleeding is 2-5 and 0.5-1 per 100 patient-years, respectively. [6-11]
In the United States, more than 30 million patients are treated with OAs and 29,000 visits caused by bleeding complications are observed each year. [12]
The anticoagulant warfarin represents the leading cause of lethal adverse drug reactions in the United States. [12] Major bleeding most often affects the gastrointestinal tract, soft tissues, and the urinary tract. Ansell et al. analysed 3,791 warfarin-treated patients from the National Registry of Atrial Fibrillation. They found that the rate of admissions for bleeding was 5.2 per 100 patient-years. Of these, 67.3% were gastrointestinal and 15.4% were intracranial hemorrhages; the overall 30-day mortality of patients admitted with major hemorrhage was 21.6%. [13]

Intensity of Anticoagulation

The international normalized ratio (INR) is used to measure the intensity of oral anticoagulation and should be maintained within a small therapeutic range usually between 2.0 to 3.0 for a long-term therapy. [14]

Figure 1 shows the conceptual model of the target INR with the best risk-benefit ratio. [8, 15-17]

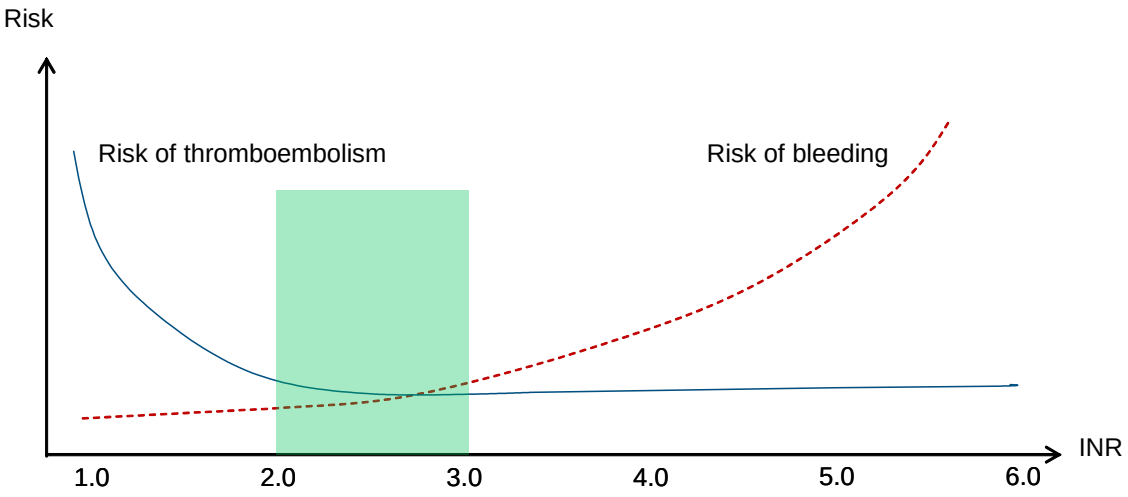

Figure 1: Conceptual model for the definition of an optimized range of the target-INR

The optimum range depends on two competing risks: the risk of thromboembolism and the risk of bleeding. Both risks vary with patient factors. These patient factors can shift one or both risk-curves, which necessitates an individualized definition of the optimum target-INR. Factors enhancing the risk of bleeding include advanced age, gender, co-morbidity, concurrent medication, interactions with food, lower body mass index and others. [7-8, 12, 18-20]

On the other hand, the risk of thromboembolism is enhanced in certain procoagulant states or in patients with certain mechanical valvular prostheses, where a higher intensity of OAC therapy may be required. [20] Finally, co-morbidity and medical interventions may both increase the risk of thrombosis and bleeding.

Nevertheless, it has always to be kept in mind that the INR is only a surrogate of the true intensity of anticoagulation. Especially during the first days of anticoagulation the INR only partly reflects the degree of protection from thromboembolism or the risk of bleeding because of the clotting factors' different half-lives. [16]

Even more importantly during the initial phase of treatment, bleeding complications or recurrent thrombosis caused by overanticoagulation or underanticoagulation can occur due to the large variability in the dose-response relationship and the narrow therapeutic range of coumarins. [18] These complications can lead to extended hospitalization.

Coumarin Derivatives

The coumarins most frequently used in humans are warfarin, acenocoumarol and phenprocoumon. Warfarin is the coumarin of first choice in the United States of America, the United Kingdom and many other countries around the world; acenocoumarol and phenprocoumon are frequently used in many European countries. In Switzerland, phenprocoumon is the drug of choice for long-term treatment and prevention of thromboembolic events.

The three coumarin derivatives mentioned above mainly differ in their half-life (cf. table 1). [21-22]

Table 1: Pharmacokinetic parameters of vitamin K antagonists [23-24]

Parameter	**Phenprocoumon**	**Acenocoumarol**	**Warfarin**
Volume of distribution [L/kg]	0.11 – 0.14	0.22 – 0.52	0.08 – 0.12
Protein binding [%]	> 99	> 98	> 99
Plasma concentration* [μmol/L]	1.5 – 15	0.03 – 0.3	1.5 – 8
Terminal elimination half-life [h]	S: 110 – 172 R: 110 – 156	S: 1.8 R: 6.6	S: 24 – 33 R: 35 – 58
Plasma clearance [L/h]	S: 0.045 – 0.055 R: 0.055 – 0.08	S: 28.5 R: 1.9	S: 0.10 – 1.0 R: 0.07 – 0.35
Elimination kinetics	First-order	Biphasic	First-order

* Refers to the total plasma concentration of bound and unbound racemic drug during therapeutic anticoagulation

Coumarins - Mechanism of Action

Coumarins work by decreasing the activation of vitamin-K-dependant clotting factors (II, VII, IX and X). Reduced vitamin K is needed for the carboxylation (activation) of these clotting factors. Coumarins inhibit vitamin-K-epoxide-reductase (VKOR), which recycles oxidized vitamin K (inactive) into reduced vitamin K (active). Vitamin K is thus a cofactor for the carboxylation of the vitamin K-dependent coagulation factors. These coagulation factors require γ-carboxylation by vitamin K for their biological activity. OAs inhibit vitamin-K-epoxide-reductase, resulting in insufficient generation of vitamin K hydroquinone to support full carboxylation and therefore full function of the vitamin K-dependent coagulation factors. [24-28]

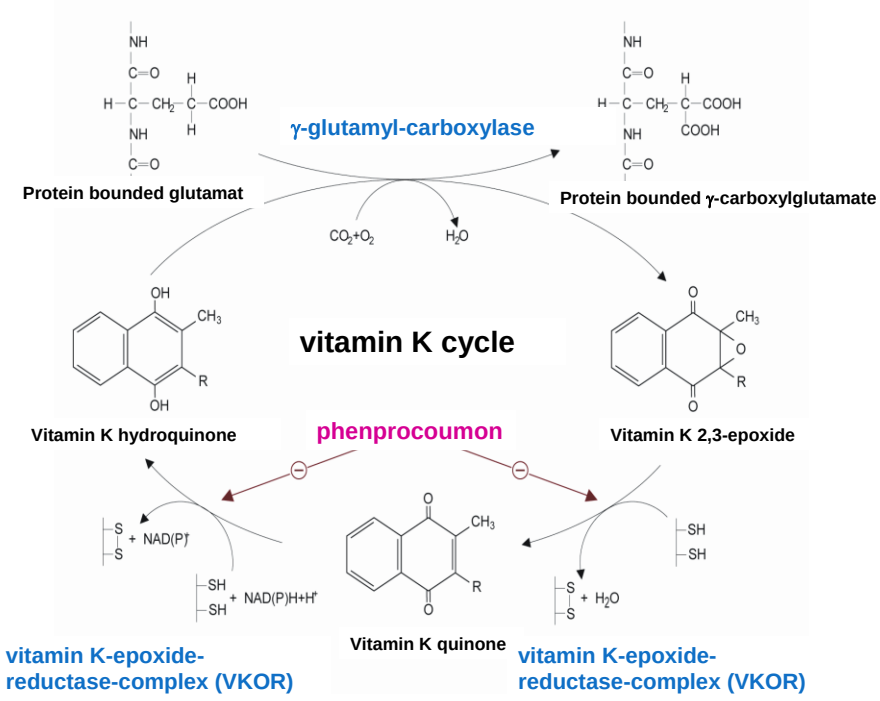

Figure 2: vitamin K cycle modified according to Wallin et al. [29]

This mechanism makes clear why the effect of coumarins is delayed. The latency period is 1-3 days because of the prolonged half-life of intact clotting factors. Only when the concentration of the clotting factors in the blood drops below a critical level, the reduced or missing regeneration in the liver becomes manifest.

Role of Vitamin K

Vitamin K is the family name for a number of fat-soluble compounds. They are synthesised by plants and bacteria. In plants the only important molecular form is phylloquinone (vitamin K_1). Bacteria synthesise a family of compounds called menaquinones (vitamin K_2). The highest concentrations of phylloquinone are found in green vegetables. Significant concentrations of menaquinones can be found in animal livers and in fermented foods, typically represented by cheese. [30]
The human intestinal microflora also synthesise large amounts of menaquinones. But the question whether the colonic microbiota provide a quantitatively significant source of menaquinones that can be absorbed and utilised has still not been satisfactorily answered. [26, 30]
Vitamin K_1 has an antidotal effect to vitamin-K antagonists. Schurgers et al. controlled vitamin K intake and increased content of dietary vitamin K weekly. The more the dose of vitamin K increases, the more the INR values decrease correspondingly. [31] When bleeding under OAC occurs, 5 – 10 (as antidot up to 20) milligrams of vitamin K_1 are given. [32-33] In contrast to the relatively slow onset (several days) of anticoagulation in acute inhibition of VKOR by coumarins, gamma carboxylation of inactive coagulation factors can be achieved within only a few hours if sufficient vitamin K is provided as an antidote even in the presence of high coumarin blood levels.

The aim of oral anticoagulation therapy is to achieve a balance between the degree of inhibition of the VKOR enzyme and the availability of reduced vitamin K that feeds into the vitamin K cycle and drives the synthesis of the clotting factors at a reduced rate. Ideally, to achieve stable anticoagulation with a constant daily dose of a VKA, the daily amounts of vitamin K available at the hepatic site of synthesis of the vitamin K-dependent clotting factors need to be kept constant as well. In reality this is difficult because the major dietary source, phylloquinone (vitamin K1), is present in different foods at very variable concentrations. Lubetsky et al. found in their study a range of daily vitamin K consumption of 17-974 μg which corresponds to a mean +/- SD of 248.3 ± 205 μg/day and a median of 179 μg/day. [34] Most surveys have shown that actual intakes of vitamin K in the USA and European populations vary widely between individuals but that the mean intakes are in the range of 60 – 200 μg/day. [35-36] Nevertheless, if dietary excesses are avoided, and given the relatively long half-lives of both vitamin K and VKAs, anticoagulation can usually be kept in a relatively narrow range in most individuals.

The best advice therefore is to continue normal dietary patterns and avoid gross daily fluctuations in intakes of vitamin K. There is limited quantitative information of dose-response relationships that are predictive of how changing dietary intakes of phylloquinone affect the pharmacodynamic response to OA. Schurgers et al. found that the threshold K_1 dose causing a statistically significant lowering of the INR was 150 μg/day. [31] In patients, the most informative study to date suggests that, on average, for every 100 μg increase in phylloquinone intake in the 4 days before the INR is measured the INR will fall by 0.2 units. [37]

Pharmacokinetics of Phenprocoumon

Phenprocoumon exists as optical isomers. It is a long-acting agent, with both the R- and the S-isomers having elimination half-lives of up to 5.5 days. S-phenprocoumon is 1.5-2.5 times more potent than R-phenprocoumon. Therefore, the S-enantiomer is predominantly responsible for the anticoagulant effect in phenprocoumon. [16, 24, 38]

Because of the long half-life phenprocoumon has the potential to sustain a stable anticoagulation. But it also takes more time to reach the steady state than shorter acting coumarins. That is why a loading dose of phenprocoumon is essential. Otherwise, it would take up to four weeks for an equal dose to reach the steady state.

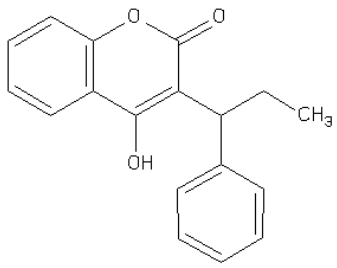

Figure 3: Structure of phenprocoumon [39]

Factors Influencing Pharmacokinetics and Pharmacodynamics of Phenprocoumon

The stability of anticoagulant therapy can be easily disturbed. Environmental factors such as drugs, diet, and various disease states can alter the pharmacokinetics of phenprocoumon. Drugs like cholestyramine can reduce the anticoagulant effect of phenprocoumon by reducing its absorption. The risk of overanticoagulation and underanticoagulation in patients taking VKAs is associated with drug – VKAs interactions. Some drugs potentiate the anticoagulant effect of phenprocoumon by inhibiting its clearance, whereas other drugs may inhibit the anticoagulant effect by enhancing its clearance. [12]

Drugs can also indirectly influence the pharmacodynamics of phenprocoumon by inhibiting the synthesis or by increasing the clearance of vitamin K-dependent coagulation factors or by interfering with other pathways of haemostasis. [16] Theoretically, antibiotics may augment the anticoagulant effect of phenprocoumon in patients by eliminating bacterial flora and aggravating vitamin K deficiency. [40]

Pharmacogenetic Influences

Other inter-individual variations such as pharmacogenetic predisposition can affect the amount of coumarin anticoagulants required. Therefore, pharmacogenetic plays an important role in safety and effectiveness of VKAs.

There are two key structures which may influence the concentration and/or the activity of phenprocoumon: The cytochromeP450 system (affecting pharmacokinetics) and vitamin K-epoxid reductase (affecting pharmacodynamics). [41-42]

Cytochrome P450 (CYP) is a group of hepatic microsomal enzymes which act as monooxygenases. Cytochromes transform lipophilic drugs into more hydrophilic metabolites which facilitates further elimination and renal excretion. The gene CYP2C9 encodes the enzyme CYP2C9, of which about 30 variant alleles have been described.

The gene VKORC1 encodes vitamin K-epoxid reductase (VKORC1), of which several variant alleles have been described. VKORC1 recycles vitamin K epoxide to vitamin K hydroquinone. Vitamin K hydroquinone is an essential cofactor for the maturation of the clotting factors II (prothrombin), VII, IX, and X. [16, 24, 43] Coumarin anticoagulant derivatives interrupt the vitamin K cycle by inhibiting VKORC1. (cf. figures 2, 4 and 5) [16, 24]

Nevertheless, phenprocoumon metabolism appears to be less influenced by the 2C9 genotypes when compared with other coumarin anticoagulants. [18, 41, 44] So, greater variability in dose requirement is observed by the VKORC1 genotype than by the CYP2C9 genotype. [45]

Beside these direct influences on the pharmacokinetics and pharmacodynamics of phenprocoumon, mutations of other genes coding for proteins involved in drug metabolism or in the coagulation cascade may have more indirect effects on the intensity of anticoagulation. Single nucleotide polymorphisms (SNPs) of calumenin (CALU), microsomal epoxide hydrolase 1 (EPHX1), factor VII (F7), γ-glutamyl carboxylase (GGCX) and protein C (PROC), are potential candidates and their ability to interfere with phenprocoumon action has previously been studied. [41]

Calumenin has been shown to inhibit the activity of VKOR und GGCX. [46]

EPHX1 is suspected to be a part of the vitamin K epoxide reductase complex. [47]

(cf. figure 4)

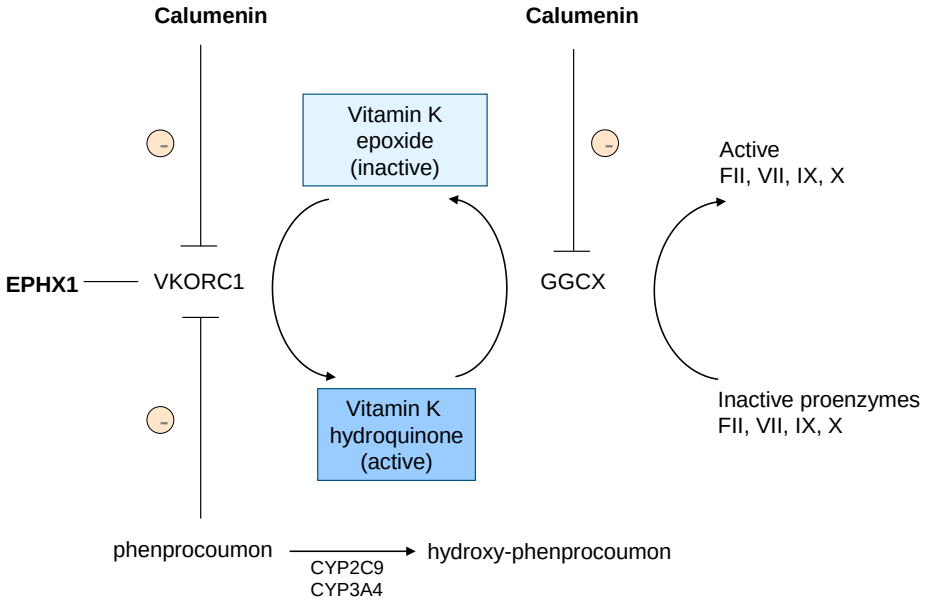

Figure 4: Interaction of phenprocoumon with the vitamin K-dependent γ-carboxylation system modified according to Luxemburg et al. [43]

Phenprocoumon is Highly Bound to Albumin

> 99% of phenprocoumon is bound to albumin (cf. table 1). Only the small (< 1%) unbound fraction of phenprocoumon is physiologically active and can be metabolized. Therefore, not only drug action but also drug elimination can be influenced by the serum concentration of binding proteins (mainly albumin). Since albumin is mainly intravascular the body-albumin content is determined by the product of albumin concentration and the plasma volume. This is sometimes referred to as “albumin space”. Plasma volume is essentially determined by body mass whereas many factors govern albumin concentration. Albumin synthesis is diminished in malnutrition or impaired liver function. However, albumin concentration can also be low in inflammatory states (acute-phase reaction) or in the presence of losses to the third space or the kidneys. In hypoalbuminaemia the initial loading dose of phenprocoumon is therefore expected to be lower due to the lower albumin space. On the other hand in patients with low serum albumin drug elimination is expected to be higher due to a higher fraction of unbound drug. Indeed, patients with liver cirrhosis and low serum albumin have a higher drug clearance than expected. [48-49] Several drugs can compete with the albumin binding of phenprocoumon. This is especially important at the onset of treatment with these drugs because even a small displacement of coumarins may substantially increase the biologically active unbound fraction.

Conceptual Model of Variable Phenprocoumon Dose Demands

As outlined above, coumarins not only have a narrow therapeutic range but patients treated with coumarins also show substantial interindividual variability in drug requirements.

Conceptually the factors controlling the variability of phenprocoumon requirement are summarized in figure 5. Some factors (e.g. age) have the potential to affect more than one pathway. The combined effects may be additive, subtractive, or even neutralizing.

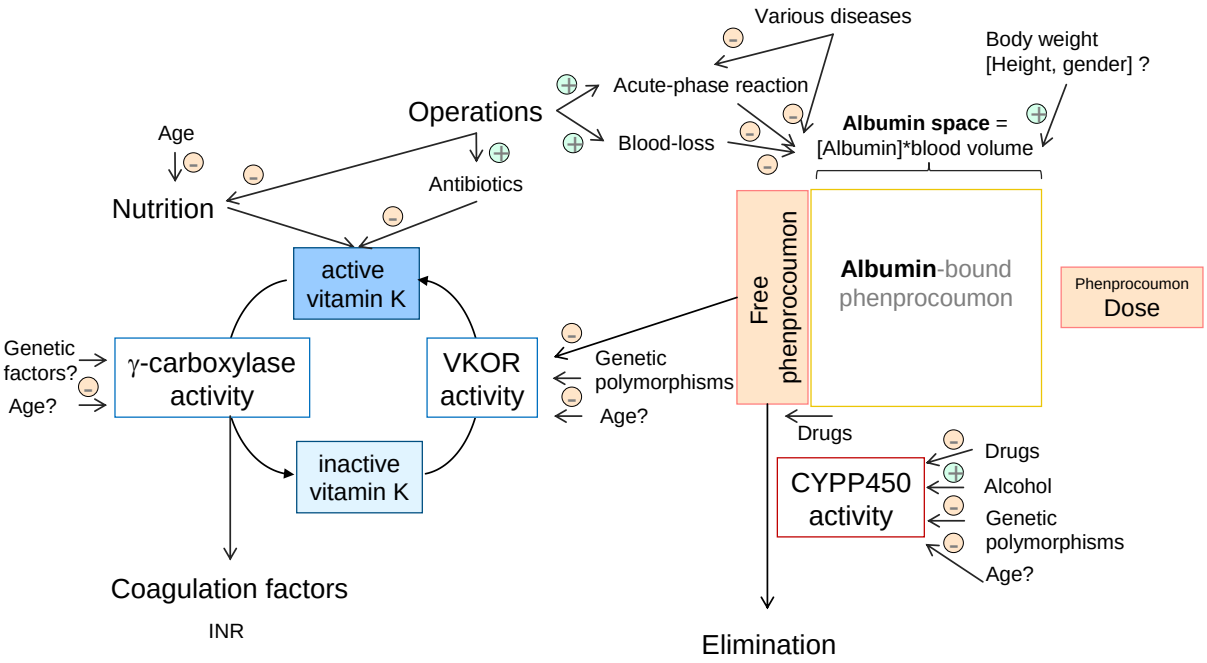

Figure 5: Conceptional model of the influencing factors during anticoagulation with coumarins

The incidences of both bleeding and thromboembolic events increase sharply with advanced age. [10, 50-51] Alcohol consumption, liver disease and other unknown factors also influence optimal daily dosages. Enzymatic induction due to long-term alcohol consumption may increase the clearance of phenprocoumon. [16, 48] Other inter-individual variations which affect the metabolism and thus the optimal daily dosages include pharmacogenetic predisposition (VKOR-, γ-carboxylase-activity) and weight. Indeed, Schwabedissen et al. found that the amount of phenprocoumon required during initiation of treatment was higher in obese patients. [52]

Several risk factors for overanticoagulation have been identified, such as advanced age, female gender, drug and dietary interactions, and previous bleeding. [12] But also the intensity of the anticoagulant effect achieved and the presence of serious comorbid diseases, particularly cerebrovascular, kidney, heart, and liver disease, and concurrent medication may be independent risk factors. [7]

Most of these factors mainly affect drug metabolism and thus the maintenance dose. During the initial rapid loading phase metabolism plays a minor role, whereas the volume of distribution is of primary interest. [52] Since coumarins are highly bound to albumin, the volume of distribution corresponds to the “albumin space”, i.e. blood volume multiplied by albumin concentration. Therefore, diverse factors may predict the loading dose as opposed to the maintenance dose of coumarins.

It is the goal to reach a stable therapeutic level of anticoagulation in due time and with a minimum of complications. If anticoagulants are started with an anticipated maintenance dose, a steady-state will not be reached before 5 half-lives. This may be acceptable for coumarins with short half-lives but is not feasible in most cases for phenprocoumon. As the risk of anticoagulant-related complications is highest at the start of an OA therapy, the search for an algorithm for the initial phase of the phenprocoumon therapy is expected to contribute to drug safety.

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3 Aims of the Thesis

The general aim was to define one or more algorithms for the loading phase of phenprocoumon-treatment. These algorithms should be easily applicable in a clinical setting and help to improve the drug safety of phenprocoumon in the initial dose-finding process, which is presently largely empiric.

In the retrospective study, algorithms were to be established to predict the loading dose of phenprocoumon for a target-INR of 2.0 to 3.0 in medical and orthopaedic inpatients.

The prospective study was planned to validate and, if necessary, optimize these algorithms. Additionally, the predictive value of pharmacogenetic markers was to be studied.

4 Overall Summary of the Thesis

Phenprocoumon is the second most commonly used oral anticoagulant worldwide and the most common agent in many European countries including Switzerland. Given its long half-life of about one week, an initial loading-dose is generally applied. A high loading-dose is helpful to rapidly reach a therapeutic concentration but may be associated with an increased risk of bleeding if the effect overshoots.

Phenprocoumon has a narrow therapeutic range, and individual dose requirements are highly variable. In clinical practice the initial dose-finding process for phenprocoumon is largely empiric and often delegated to inexperienced staff members. Thus, both a prolonged loading phase and overshooting of anticoagulation is commonly observed.

Question under study

The general aim of the thesis was to define one or more algorithms for the loading phase of phenprocoumon-treatment. These algorithms should be easily applicable in a clinical setting and help to improve the drug safety of phenprocoumon especially during the initial dose-finding process.

Retrospective study

In a retrospective study, predictors of individual dosing needs for a target-INR of 2.0 to 3.0 in medical and orthopaedic inpatients were determined. Several significant predictors of the loading dose could be identified. Using these predictors two simple clinical algorithms for the initial dosing of phenprocoumon in medical and orthopaedic inpatients were developed. One algorithm contains clinical data and, additionally, serum albumin; the second algorithm contains clinical data only.

Prospective study

The aim of the prospective, randomized interventional study was to validate the efficacy and safety of the two previously proposed dosing algorithms for the initiation of oral anticoagulation with phenprocoumon. Additionally, the predictive value of pharmacogenetic markers was to be studied.

Both algorithms could be validated and were slightly optimized. They proved to be very safe and effective in hospitalized patients with a high rate of comorbidity. The algorithm using clinical data can be especially recommended due to its simplicity of use.

5 Methods, Results and Discussion

The content of this dissertation is based on the subject of two publications. Thus, the following pages contain these two papers, starting with the retrospective study and continuing with the prospective study.

A clinical Algorithm to Predict the Loading Dose of Phenprocoumon

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Introduction

In many countries phenprocoumon is predominantly used for oral anticoagulation. Given its long half-life of 110 - 130 h [1], an initial loading-dose is generally applied [2]. A high loading-dose is helpful to rapidly reach a therapeutic concentration but may be associated with an increased risk of bleeding if the effect overshoots. As other coumarins, phenprocoumon has a narrow therapeutic range and individual dose requirements are highly variable, but in contrast to Warfarin [3] no prediction rules for the initial loading phase are established. In clinical practice the initial dose-finding process for phenprocoumon is largely empiric. The goal of our study was to define readily available predictors of the loading dose of phenprocoumon for a target-INR of 2.0 to 3.0 in medical and orthopaedic inpatients.

Patients and methods

Patients

One year of consecutive inpatients of the medical department with new-onset oral anticoagulation and two years of patients undergoing hip or knee replacement surgery in the orthopaedic department of a 700-bed tertiary hospital in eastern Switzerland were retrospectively identified from electronic patient records. Clinical, drug and laboratory data were extracted by chart review and patient contact in case of missing data. Hospital food on average contained 185 μg/day of vitamin K. Patients were excluded if they had been under oral anticoagulation less than 6 weeks prior to the index hospitalisation or if they received vitamin K supplements within one week before anticoagulation was started or during the loading phase. Patients were also excluded if the information on dosing and the INR-values was incomplete before the first INR $\geq$ 2.0 was reached, if they had liver cirrhosis > Child grade A, or surgery during the loading phase with phenprocoumon. The study was approved by the institutional data protection board.

Predictors

Patient factors (age, gender, height, weight, active alcohol or substance abuse, current smoking, diabetes, congestive heart failure, COPD, cholestasis, active cancer, malabsorption, and liver cirrhosis), acute conditions within one week prior to onset of anticoagulation (surgery, diarrhoea, vomiting, fever, sepsis, type of diet, and fasting periods), the last available laboratory values (creatinine, bilirubin, albumin, ALAT, AP, CRP, PTT, and INR), and drugs used within 2 weeks of onset of treatment (antibiotics, heparins and other anticoagulants, inhibitors of platelet aggregation,

nonsteroidal anti-inflammatory drugs, corticosteroids, and inducers as well as inhibitors of Cytochrome P-450 3A4 or P-450 2C9) were assessed.

Outcome variables

The main outcome variable was the cumulative dose of phenprocoumon to reach the target INR of 2.0 to 3.0. This dose was corrected in case of overshooting (> 3.5) INR or prolonged (> 5 days) dosing to reach the target INR. Secondary outcome measures were predictors of overshooting (> 3.5) INR, and predictors of a dose < 25th percentile.

Statistics

Statistical calculations were performed using SAS 8.2 (SAS institute, Cary, NC, USA). Continuous data are presented as medians and interquartile range, and compared using Wilcoxon's test. Categorical variables are presented as percentages and compared using Fisher's exact test. Two models for the loading dose of phenprocoumon were developed. One model contained albumin whereas the second model was without albumin, since in clinical practice this variable is often unavailable at the time of drug prescription. Irrespective of their statistical significance, we then added significant predictors of overshooting INR (> 3.5) and / or of low dose demands (< 25th percentile) to the model for the loading dose of phenprocoumon. These predictors were derived by logistic regression.

Results

Baseline characteristics

During the period of observation, oral anticoagulation was started in 223 medical and 217 orthopaedic patients, all of whom were Caucasians. 71 medical and 69 orthopaedic patients were excluded, mainly due to prior treatment with oral anticoagulants. The baseline-data of the remaining 152 medical and 148 orthopaedic patients are summarized in Table 1.

Table 1: Baseline characteristics

Variable	Medical	Orthopaedic	p =
N	152	148	n.s.
Female sex	58 (38%)	89 (60%)	<0.0001
Age (years)	73 (61/80)	71 (62/77)	n.s.
Weight women (kg)	69 (60/76)	67 (60/79)	n.s.
Weight men (kg)	81 (70/90)	80 (70/92)	n.s.
BMI (kg/m^2)	27.2 (24/29)	27.0 (24/31)	n.s.
Co-morbidity			
Active cancer	20 (13%)	6 (4%)	0.007
Alcohol consumption > 2 drinks/day	9 (6%)	7 (5%)	n.s.
Cirrhosis Child A	0 (0%)	3 (2%)	n.s.
Clearance < 25 ml/min	7 (5%)	0 (0%)	0.01
Congestive heart failure	36 (24%)	0 (0%)	<0.0001
Current smoking	30 (20%)	31 (21%)	n.s.
Diabetes mellitus	21 (14%)	14 (9%)	n.s.
Diarrhoea within 1 week	17 (11%)	2 (1%)	<0.0005
Fever > 38 °C within 1 week	24 (16%)	9 (6%)	0.01
Laboratory values			
Albumin (g/l)	39 (35/41)	42 (40/43)	<0.0001
Clearance (ml/min)	70 (51/94)	69 (53/90)	n.s.
CRP	18 (5/65)	4 (3/7)	<0.0001
INR	1.0 (0.9/1.1)	1.0 (0.9/1.1)	n.s.

Drugs			
Antibiotics	47 (31%)	148 (100%)	<0.0001
NSAIDs	16 (11%)	132 (89%)	<0.0001
Cox-2 Inhibitors	9 (6%)	35 (24%)	<0.0001
Inducers of CYP450 2C9	9 (4%)	3 (3%)	n.s.
Inducers of CYP450 3A4	37 (24%)	29 (25%)	n.s.
Inhibitors of CYP450 2C9	59 (39%)	97 (85%)	<0.0001
Inhibitors of CYP450 3A4	84 (55%)	68 (60%)	n.s.

Data are presented as number of cases and % or median and interquartile range. N = Number of cases, BMI = Body-mass index, CRP = C-reactive protein, INR = International normalized ratio, NSAIDs = Nonsteroidal anti-inflammatory drugs.

Time-course of INR and phenprocoumon-dosing

The corrected cumulative dose until the first therapeutic INR was reached was overall (median [interquartile range]) 18.0 [14.75 - 24.0] mg. Orthopaedic patients needed substantially lower doses (15.75 [12.00 - 18.75] mg) than medical patients (21.0 [16.5 - 26.25] mg; p<0.0001).

Predictors of cumulative loading dose

The best model for the loading dose included weight, albumin, self-reported alcohol consumption exceeding 2 drinks/day, age over 60 years, and an operation within a week. This model explained 34% of the variance (R^2).

Predictors of overshooting INR and of phenprocoumon-needs < 25th percentile

After adjustment for age, weight, albumin, operation and alcohol consumption as well as the dose of phenprocoumon within the first three days, the following variables evolved as significant predictors of overshooting (> 3.5) INR: female gender (Odds ratio [OR] = 2.3; 95% Confidence interval [95%CI] = 1.1 - 4.7), creatinine clearance below 25 ml/min (OR = 6.6; 95%CI = 1.04 - 41) and diarrhoea (OR = 5.4; 95%CI = 1.7 - 17). Similarly, clearance below 25 ml/min (OR = 8; 95%CI = 1.5 - 44), diarrhoea

(OR = 3.8; 95%CI = 1.04 - 14), and higher initial INR (OR = 1.5; 95%CI = 1.08 - 2.0 for each 0.1 increase in INR) were significant predictors of a cumulative dose below the 25th percentile. For safety reasons the final model was extended by the above-mentioned factors associated with unusually low phenprocoumon demands or overshooting INR irrespective of their statistical significance.

Albumin measurements are often unavailable when the first three doses of phenprocoumon are prescribed. Higher age correlates with lower albumin and is a significant predictor risk of overshooting INR. We therefore substituted age for albumin in this situation. This model had an explanatory power of 33% (Table 2).

Table 2: Two models to predict the total loading dose (mg* for 5 days)

Variable	Model using Albumin		Model using Age	
	Effect	p =	Effect	p =
Intercept of regression model	6.7	–	17.0	–
Weight (per kg)	0.12	<0.0001	0.12	<0.0001
Albumin (per g)	0.20	0.02	–	–
Age (per year)	–	–	–0.07	0.007
Age > 60 years	–1.6	0.05	–	–
Alcohol > 20 g / d	2.7	0.05	3.5	0.02
Operation	–6.2	<0.0001	–5.6	<0.0001

Predictors of the corrected cumulative loading dose (on average 5 days) of phenprocoumon. The first model needs a recent albumin value, the second model assumes that no albumin value is available. Both models are adjusted for gender, first INR, creatinine-clearance, and diarrhoea.
n.s. = Not significant, p = Probability, INR = International normalized ratio.

* 1 pill of phenprocoumon corresponds to 3 mg.

Most clinicians prescribe the first three doses of phenprocoumon empirically and adjust the further doses according to an INR measured on day four.

In line with this clinical habit we propose two algorithms for the empiric dose-estimation: 70% of the predicted loading dose is prescribed within the first three days and a standardized dose-escalation scheme is provided for the subsequent days according to the INR value on day four. This dosing algorithm has not yet been prospectively validated. (Figs. 1 – 3)

Albumin (g/l)

Weight (kg)	< 20	21 - 30	30 - 40	> 40
< 45	3	4	4	5
45 – 60	4	4	5	5
60 – 75	4	5	5	5
75 – 90	5	5	5	6
> 90	5	5	6	6

+

Correction for comorbidity

Alcohol > 20 g/day	**+ 1 pill**
Operation within 1 week	**– 2 pills**
Any combination of - age > 60 - female sex - diarrhoea - baseline-INR > 1.2 - clearance < 25 ml/min	**– 1 pill**

Figure 1: Number of pills* for the first three days if albumin is available. To obtain the empiric dose for the first three days the number of pills is determined on the left hand side at the intersection of the patient's albumin and weight. This dose is further adjusted in the presence of comorbidity or female gender. This dose is then subdivided according to the nomogram in Fig. 3.

* 1 pill of phenprocoumon corresponds to 3 mg.

Age (years)

Weight (kg)	< 40	40 - 60	60 - 80	> 80
< 45	5	4	4	3
45 – 60	5	5	4	4
60 – 75	5	5	5	4
75 – 90	6	5	5	5
> 90	6	6	5	5

+

Correction for comorbidity

Alcohol > 20 g/day	**+ 1 pill**
Operation within 1 week	**– 2 pills**
Any combination of - female sex - diarrhoea - baseline-INR > 1.2 - clearance < 25 ml/min	**– 1 pill**

Figure 2: Number of pills* for the first three days if albumin is not available. To obtain the empiric dose for the first three days the number of pills is determined on the left hand side at the intersection of the patient's age and weight. This dose is further adjusted in the presence of comorbidity or female gender. This dose is then subdivided according to the nomogram in Fig. 3.

* 1 pill of phenprocoumon corresponds to 3 mg.

Number of pills	Empiric dose			INR after 3 doses							
				< 1.5		1.5 – 2.0		2.1 – 3.5		> 3.5	
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 4	Day 5	Day 4	Day 5	Day 4	Day 5
≤ 2.0	1	¾	¼	2	1	½	¼	0	¼	0	0
3.0	1 ½	1	½	2	1	½	½	0	¼	0	0
4.0	2	1½	½	2	2	¾	¾	¼	¼	0	0
5.0	2	2	1	2	2	¾	1	¼	¼	0	0
≥ 6.0	3	2	1	2	2	1	1	¼	¼	0	0

Figure 3: Nomogram for empiric initial dosing of phenprocoumon. The number of pills derived from Figs. 1 or 2 corresponds to the number in the leftmost column. All doses for a given patient are obtained from this specific row. The empiric doses for day 1 to day 3 are first prescribed and the INR is determined after three doses. The dosing for days 4 and 5 is then guided by the result of this INR.

* 1 pill of phenprocoumon corresponds to 3 mg.

Discussion

The loading-dose of coumarins has two main components: the saturation of the volume of distribution and the ongoing elimination during the loading period. Given the long elimination half-life of phenprocoumon of roughly one week, the loading-dose is mainly dependent on the volume of distribution, which is 0.15 to 0.2 l/kg. Since 99% of phenprocoumon is bound to albumin [4] the volume of distribution correlates with plasma albumin concentration and plasma volume, which again depends on body weight. Indeed, albumin concentration and body weight resulted as the main predictors of the loading dose in our model. Our findings parallel those of others [5], who derived dosing algorithms for warfarin including weight and albumin. In contrast to warfarin, phenprocoumon-clearance is less affected by genetic polymorphisms of CYP450 [6]. Indeed, no significant effect of inducers or inhibitors of CYP450 2C9 or 3A4 was found. 16 patients, however, who habitually consumed more than 20 g alcohol (2 drinks) per day prior to hospital admission on average had a 3 mg higher demand of phenprocoumon. Induction of the cytochrome-P450 system is the most likely reason for this effect. This hypothesis is in line with data from Penning-van Beest and co-workers, who identified a decrease in alcohol intake as an important risk factor for overanticoagulation [7].

Orthopaedic patients needed substantially lower doses of phenprocoumon than medical patients. The most obvious explanation is a lower albumin concentration in orthopaedic patients due to perioperative blood loss, and an operation-induced acute-phase reaction. In most orthopaedic patients albumin was only determined at hospital admission, i.e. one day before surgery.

Orthopaedic patients also more commonly took NSAIDs or Cox-2 inhibitors, which can compete with albumin-binding sites.

Finally, perioperative fasting and perioperative antibiotic prophylaxis may have decreased the intake of vitamin K or its production by intestinal bacteria [8].

Older age, female gender, diarrhoea, higher baseline INR, and low creatinine-clearance were independent predictors of lower phenprocoumon-needs or overshooting INR. Caloric intake decreases with older age and with it the intake of vitamin K. Moreover, drug metabolism decreases with age [4]. Women have a lower plasma-volume than men of similar weight due to a different body composition. Patients with diarrhoea often eat less due to nausea, and the production of vitamin K by intestinal bacteria and its resorption may be reduced due to accelerated intestinal transport. Higher baseline INR can indicate malnutrition, impaired liver function, or a coagulation disorder and thus warrants careful dosing of coumarins. Persons with impaired kidney function often show a reduced caloric intake and with it a reduced intake of vitamin K. Furthermore, a higher fraction of coumarins remains unbound to albumin in kidney disease since uraemic toxins compete with it at the same binding site [9].

Study limitations

The present study only included hospitalised patients, which limits its generalizability. In clinical experience outpatients tend to need higher doses than inpatients. An algorithm derived from our data is therefore likely to predict somewhat conservative doses for outpatients. In our analysis we also did not test for polymorphisms of CYP450 2C9 or the VKORC1 gene, which are responsible for substantial variations in dose requirements [10]. Genetic profiling may become more widely available in the future but it is expensive and – especially in an ambulatory setting – the result will not arrive in due time to influence the first prescription of coumarins. Oral anticoagulation will therefore still often be initiated empirically with dose-adjustment according to INR-values.

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Randomized Trial of a Clinical Dosing Algorithm to Start Anticoagulation with Phenprocoumon

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Summary

Question under study

Prospective validation of two algorithms for the initiation of phenprocoumon treatment

Methods

Inpatients with new-onset anticoagulation were randomized to one of two computer assisted dosing algorithms, or to a control arm. The primary outcome measure was the time to achieve therapeutic anticoagulation without overshooting (INR > 4.0 within 10 days). Secondary outcomes included overshooting INR-values, death, or bleeding within 30 days. In addition, predictors of the dosing algorithms for the loading dose and the maintenance dose including genetic parameters were reassessed.

Results

105 patients were randomized to arm A, 103 to arm B, and 93 to the control arm. Arms A and B needed a median of 7 days to reach a therapeutic INR, arm C 6 days (p=0.5). Overshooting INR was observed in 3.8%, 1.9% and 4.3% respectively (p=0.6). Bleeding was found in 0%, 1.9%, and 5.4% (p=0.06) and 30-day mortality was 0%, 1%, and 2.2% respectively (p=0.2). *VKORC1*:c.-1639G>A was associated with lower loading doses whereas *VKORC1*:c.-1453G>A needed higher doses. *VKORC1*:c.-1639G>A was also associated with lower maintenance doses.

Conclusion

Both algorithms allow a safe initial dosing of phenprocoumon but they are not superior to anticoagulation by trained physicians. Dosing aids for coumarins with readily available clinical parameters may nevertheless be helpful for the use in polymorbid hospitalized patients. Clinical data and the INR-response to treatment provides powerful information and delaying initiation of anticoagulation while awaiting genetic tests is not expected to increase drug safety.

Key words

randomized controlled trial; phenprocoumon; oral anticoagulation; coumarin; initiation of treatment; dosing; drug safety; hospital; pharmacogenetics; VKOR; loading dose, maintenance dose

ClinicalTrials.gov registration number: NCT00586287

Introduction

Coumarin derivatives are still the drugs of choice for long-term treatment and prevention of thromboembolic events because they are cheap and highly effective for the treatment and prevention of deep venous thrombosis, pulmonary embolism, and embolic stroke. [1-3] In many European countries phenprocoumon is the predominantly used anticoagulant. The management of anticoagulation with phenprocoumon is challenging because of its narrow therapeutic range and large interindividual variation of dose demands. In addition, the onset of action is typically delayed due to the long half-life of the intact coagulation factors in the circulation. Unless an initial loading dose is given, the onset of action is further delayed due to a prolonged time to reach therapeutic drug levels owing to the long half-life (110 - 130 h) of the drug. [4-6] The following main causes contribute to interindividual variability in dose demands: differences in the volume of distribution of phenprocoumon, differences in drug metabolism and differences in the concentrations of reduced (active) vitamin K.

More than 99% of phenprocoumon is bound to serum albumin and only unbound coumarins contribute to the anticoagulant effect. Therefore, one main determinant of the loading dose is the total body albumin content, which has to be saturated during the loading phase

In comparison, drug elimination by metabolizing enzymes is the main determinant of the maintenance dose because during steady state conditions the maintenance dose has to equal drug elimination.

Drug elimination depends on the activity of the metabolizing enzymes which can vary with age, drug interactions or genetic factors as the CYP 450 genotype. [7-11] However, variable drug requirements can also be caused by differences of drug susceptibility at the site of action. One central pharmacodynamic factor for coumarins is the availability of reduced vitamin K which depends on diet but also on the activity of vitamin K epoxide reductase complex 1 (VKORC1). [12] Single-nucleotide polymorphisms (SNPs) of this gene have been shown to reduce the activity of this enzyme. [13-16] Several other allelic variants of genes have been proposed to be associated with either altered drug elimination or drug susceptibility. [7, 13, 16-23] Given the complexity of these issues, inexperienced physicians often have difficulties to safely initiate treatment with phenprocoumon. A model to predict the loading dose with phenprocoumon is therefore desirable. Once a steady-state has been reached, future doses will be more easily predicted based on the response to past doses. In a retrospective study of 300 medical and orthopaedic inpatients we previously developed two dosing algorithms for the initiation of anticoagulation with phenprocoumon based on clinical predictors such as age, body weight, and readily available laboratory values. [24] The aim of this prospective, randomized interventional study was to validate the efficacy and safety of the two dosing algorithms compared to “conventional dosing” by staff physicians in medical and orthopaedic inpatients. Further aims were to improve these algorithms and to assess the additional predictive value of genetic markers.

Patients and Methods

This was a single-centre, randomized, and controlled study of two algorithms for the initiation of phenprocoumon. All medical inpatients irrespective of the indication for anticoagulation and patients undergoing hip or knee replacement surgery of the orthopaedic department of the St. Gallen Cantonal hospital, a 700-bed tertiary care hospital in eastern Switzerland, with new-onset oral anticoagulation were eligible for participation in the study. Recruitment took place between January 2007 and December 2009. Patients were excluded if they had been under oral anticoagulation less than 6 weeks prior to the index hospitalisation or if they received vitamin K supplements within one week before anticoagulation was started. Patients were also excluded if they were younger than 18 years, pregnant, unwilling or unable to give informed consent, had liver cirrhosis other than Child grade A, contraindications to anticoagulation, or insufficient communication skills in German, French, Italian, or English. The study was approved by the institutional review board.

Patients were automatically randomized to one of three arms without stratification using a computer-based system integrated in the clinical information system Phoenix(R) (Parametrix, Lachen Switzerland). In arm A phenprocoumon was dosed using the algorithm based on albumin and clinical data, in arm B using the algorithm based on clinical data only, and in arm C dosing was at the discretion of the physicians. The algorithms have been described elsewhere. [24] In brief the dose-finding process was made using the same variables (except for amiodarone) as outlined in figure 4 of the present article for arm B. The algorithm for arm A was identical to arm B except for the categorical use of albumin instead of age in the left-hand table and an additional dose-reduction for age > 60 in the ‘comorbidity’-list.

For arms A and B, the computer program provided doses for three days on day 1, and when the INR of day 4 was entered, the system provided doses for the next two days. The review board requested that all participating physicians were trained about best practice of anticoagulation. Furthermore, patients with concomitant anti-platelet treatment (mainly aspirin and/or clopidogrel) and patients within one week after orthopaedic operations were only allowed to receive a cumulative maximum dose of 3 pills (3 mg per pill) during the first 3 days due to safety concerns. Clinical, drug and laboratory data were extracted by chart review. After 30 days patients were contacted and asked to provide a copy of the anticoagulation booklets (doses and INR). If the booklets were not available from patients, their physicians were contacted and asked to provide information on clinical course and INR values. Treating physicians were also asked to obtain blood for genetic analyses. Unfortunately this blood was only provided for about half of the patients. Genetic analyses were performed as previously described. [16, 25] As long as the patients were hospitalized, INR was measured from citrate plasma using the thromboplastin reagent Recombiplastin 1 (Axon Lab AG, Baden, Switzerland) on the automated coagulation analyzer ACLTOP 700 LAS (Axon Lab AG, Baden, Switzerland). After discharge INR-measurements were usually performed by family physicians.

Outcome parameters

Outcome parameters were assessed by chart review. The primary outcome measure of the prospective study was the time to achieve therapeutic anticoagulation (loading phase) without consecutive overshooting of INR. Secondary outcomes included overshooting INR-values, death, or bleeding within 30 days. The duration of the *loading phase* was defined as the number of days to reach the first INR > 1.9. *Bleeding* during anticoagulation was the main adverse outcome variable. Major bleeding was defined as death due to bleeding, intracranial haemorrhage, need for (re-)operation, drop of haemoglobin by > 20g/l and/or the need for blood transfusions. All other bleeding episodes were considered to be minor. *Overshooting of INR* attributed to the loading dose was defined as an INR > 4.0 within 3 days after the loading phase.

In addition, predictors of the dosing algorithms for the loading dose and the maintenance dose including genetic parameters were reassessed. Since we intended both a safe and a rapid loading phase, the goal was to achieve therapeutic INR values within about one week without overshooting. We therefore had to estimate the ideal *individual loading dose*, which would result in a therapeutic INR if it was given within 6 days in the same patient in a similar situation. If a therapeutic INR was reached by this time, the observed cumulative dose directly equalled the individual loading dose. If the loading phase was prolonged or if overshooting of INR was observed, the observed cumulative dose had to be corrected for drug metabolization during this prolonged period or overdosing as previously described. [24]

The *individual maintenance dose* was defined as the average daily dose in a stable phase of therapeutic anticoagulation after the loading phase.

Statistics

In our retrospective study 58% of patients reached therapeutic INR levels without overshooting or complications within one week. In order to detect a 15% change of this endpoint with a power of 80% a sample size of 155 patients for each study arm was determined. Categorical variables are expressed as absolute numbers, rates or percentages and compared using Fisher's exact tests. Continuous variables with approximate normal distributions are expressed as means and standard deviation and compared using Student's t-Tests or ANOVA (if more than two groups were compared). If normality was questionable, they are presented as medians and interquartile range and compared using Wilcoxon's Rank-Sum Tests or Kruskal-Wallis Tests respectively. Missing information for genetics and doses were considered to be missing at random. This assumption was corroborated by a comparison of loading doses and maintenance doses between patients with and without genetic variables which yielded no statistical differences. The models from our derivation algorithms were repeated by linear regression and assessed for their explanatory power using the adjusted R2. New parsimonious models both for the individual loading dose and the individual maintenance dose were derived separately with and without genetic information using a backward selection method. Additional models using the predicted dose for the first three days and the most recent available INR were further built for days 4 and 6 in order to define the residual dose demands at these time points. INR measurements and phenprocoumon doses were used as time-dependent variables.

All other variables (age, gender, height, weight, active alcohol abuse, current smoking, diabetes, congestive heart failure, COPD, cholestasis, active cancer, malabsorption, vomiting, diarrhea, and liver cirrhosis, albumin, creatinine, genetic information, and comedication (antibiotics, platelet inhibitors, corticosteroids, amiodarone, as well as inducers and inhibitors of the cytochrome P450 3A4 and/or 2C9 within two weeks before the onset of anticoagulation)) were considered to be time-constant. Statistical calculations were performed using SAS 9.2 (SAS Institute, Cary, NC, USA). All significance-tests were two-sided with a p-value < 0.05 indicating statistical significance.

Derivation of the revised dosing algorithm

To avoid overdosing a conservative algorithm was chosen. Therefore, the dose for the first three days aimed at the 10th percentile of the loading doses for each group, and subsequent dosing steps aimed at the 25th percentile of the residual dose-distribution at the respective time point. This approach was chosen because on day one the predictive power of the model was still low and thus the unexplained variation of loading doses was still broad. At each subsequent dosing step the biologic response of the INR to phenprocoumon could be incorporated into the models which substantially improved the prediction and reduced the residual variability of the remaining dose-demands.

Results

Inclusion was attempted in 348 patients, and 301 patients were randomized to one of the management arms. An overview of the study protocol is presented in fig. 1.

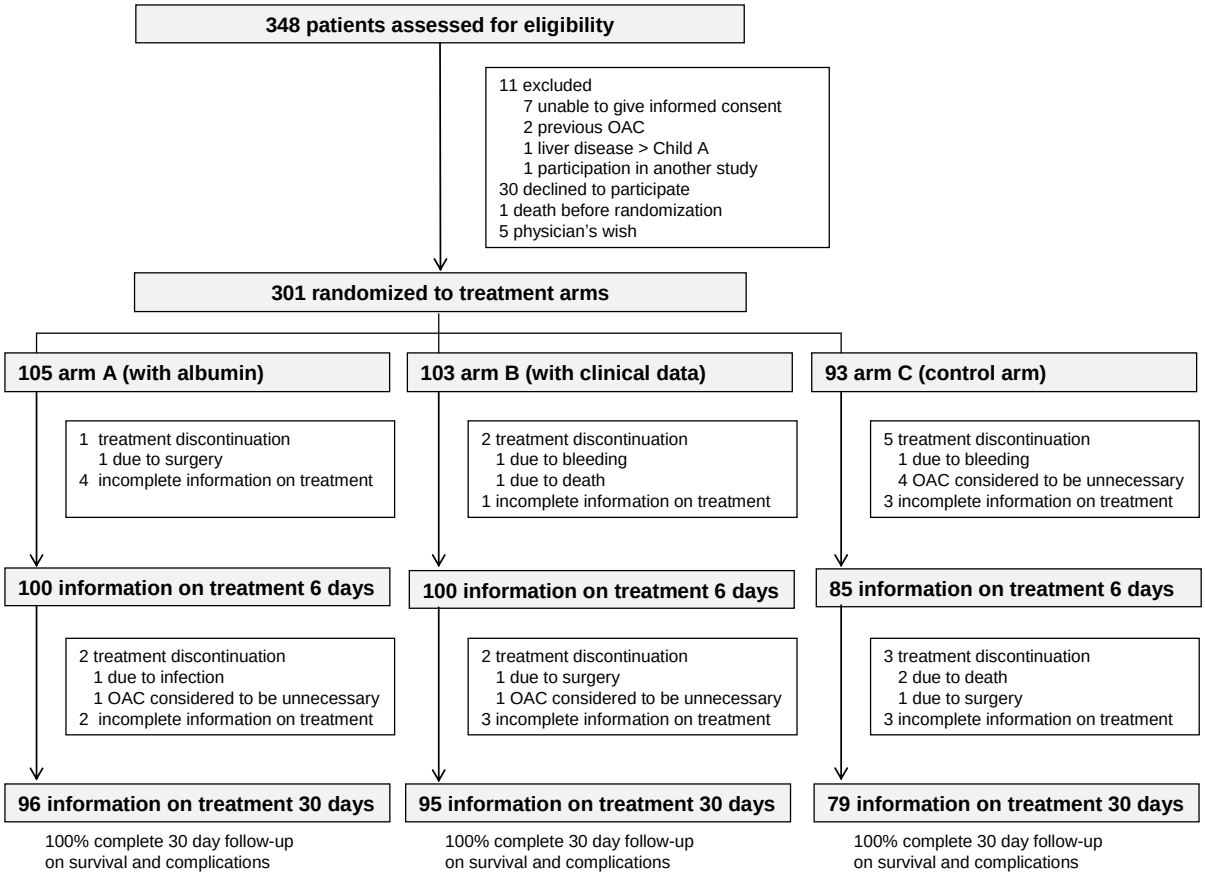

Figure 1: Overview of the study protocol

Due to slow recruitment especially in orthopaedic patients (N=110) more medical patients (N=191) were included and enrolment was stopped prematurely. The baseline characteristics were evenly distributed in all arms as outlined in table 1.

Table 1: Baseline characteristics

	Arm A	Arm B	Control arm
N	105	103	93
Age (years)	64.8 +/-15.7	68.1 +/-14.3	65.9 +/- 16.7
Female gender	54 (51.4%)	57 (55.3%)	48 (51.6%)
Weight (kg)	77.6 +/- 16.7	80.2 +/- 21.9	78.5 +/- 17.9
Orthopaedics	39 (37.1%)	43 (41.7%)	28 (30.1%)
Internal Medicine	66 (62.9%)	60 (58.3%)	65 (69.9%)
Operation within 7 days	39 (37.1%)	45 (43.7%)	29 (31.2%)
Alcohol > 20g/day	9 (8.6%)	7 (6.8%)	11 (11.8%)
eGFR (ml/min)	82.6 +/- 34.4	82.1 +/- 42.4	80.1 +/- 38.8
Diarrhea	9 (8.9%)	6 (5.8%)	7 (7.5%)
INR before start	1.0 +/-0.10	1.0 +/- 0.09	1.0 +/- 0.08
Albumin (g/l)	34.8 +/- 6.5	33.4 +/- 5.8	33.8 +/- 6.0
Tc-aggregation Inhibitors	29 (27.6%)	32 (31.1%)	28 (30.1%)
Amiodarone	6 (5.7%)	3 (2.9%)	4 (4.3%)
CYP450-2C9 Inhibitors	28 (26.7%)	22 (21.45)	29 (31.2%)
CYP450 2C9 Inducers	1 (0.95%)	3 (2.9%)	5 (5.4%)
CYP450-3A4 Inhibitors	23 (21.9%)	17 (16.5%)	21 (22.6%)
CYP450-3A4 Inducers	30 (28.6%)	31 (30.1%)	23 (24.7%)

Data are presented as numbers of cases and percent (%) within each arm or mean and standard deviation. N = number of cases, INR = international normalized ratio, eGFR = estimated glomerular filtration rate, CYP450 = cytochrome P450, arm A = arm using clinical predictors and albumin, arm B = arm with clinical predictors only.

Performance of the algorithms

The median (interquartile range) time to reach a therapeutic INR was 7 (5/11) days in arm A, 7 (5/12) days in arm B and 6 (3/12) days in the control arm (p=0.5). Overshooting INR due to an excessive loading dose (i.e. INR > 4.0 within 10 days after the start of treatment) was observed in 3.8% in arm A, 1.9% in arm B and 4.3% of patients in the control arm (p=0.6). No episode of these overshooting INRs was associated with complications. 30-days bleeding rate (minor and major) was 0%, 1.9% and 5.4% respectively (p=0.06), and 30-days mortality was 0% in arm A, 1% in arm B and 2.2% in the control arm (p=0.2).

The reasons for death were congestive heart failure in a 91-year-old male in arm B, and in group C paraneoplastic pulmonary embolism in a 63-year-old male and retroperitoneal bleeding in a 72-year-old female. This retroperitoneal bleeding occurred with an INR of only 2.2 and without previous overshooting and was the only episode of major bleeding in the entire study within 30 days.

The detailed analysis of the episodes with overshooting INR showed that in only one patient (with a max. INR of 4.1) the initial dose for day 1 to 3 provided by the algorithm was responsible for overshooting. This patient was later shown to be homozygous for the *VKORC1*:c.-1639 G>A variant. In contrast, overshooting could be attributed to the correction dose for days 4 and 5 provided by the algorithm in 5 episodes. All these episodes occurred in patients who had had a low-dose prediction (2 to 4 pills) for days 1 to 3. In addition, 5 patients with overshooting INR were exposed to amiodarone. In multivariate models amiodarone was consistently but not statistically significantly associated with a lower loading dose (-0.35 pills; to convert pills to mg multiply by 3).

Clinical predictors of the loading dose and the maintenance dose

The mean (+/-SD) loading dose was 8.2 (+/- 3.8) pills in medical patients and 7.1 (+/- 3.4) pills in orthopaedic patients (p=0.04). In univariate analysis higher age, lower weight, female gender, a recent operation, low albumin, higher initial INR, and impaired kidney function were significant predictors of lower loading doses. The predictors of the maintenance dose were almost identical to the predictors of the loading dose with the exception of albumin, which did not reach statistical significance. On the other hand alcohol abuse was associated with a significantly higher maintenance dose whereas only a trend for a higher loading dose could be observed.

Approximate position of table 2 (cf. p. 65)

Genetic predictors of the loading dose and the maintenance dose

The influence of genetic predictors on dose demands could only be evaluated in a subset of 143 patients. VKORC1:c.-1639 G>A was associated with significantly lower dose demands both for the loading dose and the maintenance dose. Heterozygous patients showed about 50% of the effect of homozygous persons. A polymorphism of the factor VII-gene F7:c.1238G>A was associated with a similar absolute reduction of the loading dose in homozygous persons as the above mentioned VKORC1 polymorphism but was only present in the homozygous form in 4 patients which may explain the marginal statistical significance (p=0.05). In contrast, the polymorphism VCORC1:c.-1453 G>A was associated with significantly higher loading dose demands.

Approximate position of table 3 (cf. p. 66/67)

Multivariate Models

In multivariate analysis including clinical parameters only, age, weight, first INR and recent operations proved to be strong independent predictors of the loading dose. In contrast, neither serum albumin nor the remaining predictors included in the algorithms (diarrhea, female gender, kidney function) significantly improved the model. With the exception of gender the effect size of these factors was comparable to the derivation cohort, which suggests that the power may have been insufficient to corroborate a true effect. When genetic tests were added, both the VKORC1:c.-1639 G>A (associated with lower loading doses) and the VKORC1:c.-1453 G>A variants (associated with higher loading doses) proved to be additional significant predictors of the loading dose. The explanatory power of the model (adjusted R2) increased from 19% to 37% after the addition of genetic tests.

Table 4: Multivariate predictors of loading dose (clinical predictors only)

Factor	Effect on Loading Dose (pills)	95% CI	p=
Intercept	12.60		
Age (per 10 years older)	-0.38	-0.73 to -0.05	0.03
Weight (per 10 kg higher)	0.72	0.45 to 0.98	<0.0001
INR before start (per 0.1 higher)	-0.69	-1.19 to -0.19	0.008
Recent operation	-1.93	-2.93 to -0.92	0.0002

Table 5: Multivariate predictors of loading dose including genetic tests

Factor		Effect on Loading Dose (pills)	95% CI	p=
Intercept		12.29		
Age (per 10 years older)		-0.42	-0.78 to -0.05	0.02
Weight (per 10 kg higher)		0.66	0.37 to 0.94	<0.0001
INR before start (per 0.1 higher)		-0.54	-1.09 to 0.02	0.06
Recent operation		-1.28	-2.32 to -0.25	0.02
VKORC1:c.-1639G>A	AA	-3.50	-4.87 to -2.14	<0.0001
	GA	-0.72	-1.84 to 0.39	0.2
VKORC1:c.-1453G>A	GA	3.50	1.29 to 5.71	0.002

Higher age and lower weight were also independent predictors of a lower maintenance dose. The strongest predictor was, however, the number of pills needed to reach the first therapeutic INR. Among the genetic tests only the *VKORC1*:c.-1639 G>A polymorphism proved to be an additional significant predictor of lower maintenance doses. Yet the explanatory power of the model only increased from 55% to 57% when this genetic test was added.

Table 6: Multivariate predictors of maintenance dose (clinical predictors only)

Factor	Effect on Maintenance Dose (pills)	95% CI	p=
Intercept	0.343		
Age (per 10 years older)	-0.040	-0.06 to -0.02	<0.0001
Weight (per 10 kg higher)	0.037	0.02 to 0.05	<0.0001
Pills needed to reach first INR ≥ 2.0	0.024	0.02 to 0.03	<0.0001

Table 7: Multivariate predictors of maintenance dose including genetic tests

Factor	Effect on Maintenance Dose (pills)	95% CI	p=
Intercept	0.28		
Age (per 10 years older)	-0.04	-0.07 to -0.02	0.001
Weight (per 10 kg higher)	0.07	0.05 to 0.09	<0.0001
Pills needed to reach first INR ≥ 2.0	0.015	0.01 to 0.02	<0.0001
VKORC1:c.-1639G>A AA GA	-0.20 -0.10	-0.30 to -0.10 -0.17 to -0.02	0.0002 0.01

Dose estimation as a dynamic process

Dose estimation is a multistep dynamic process in clinical practice. Therefore, static models to predict dose-demands can be helpful to cautiously start anticoagulation but with each INR measurement the biologic response to the administered doses provides strong additional information on future responses. Phenprocoumon is typically started with a prescription for the first three days followed by INR-measurement and re-prescription every two to three days until the individual maintenance dose is found and controlling intervals can be prolonged. We therefore computed models for the remaining loading dose and the maintenance dose for days 4 and 6. Age and weight, the cumulative applied dose and the INR at each respective time point allowed gradually more precise dose estimations. Given that all these factors already contributed to define the starting dose (i.e. the “row” in the table of the algorithms) we used this starting dose in subsequent models in order to simplify the correction algorithms. On day 4 both the starting dose and the INR were strong individual predictors of the residual loading dose demand. On day 6 only the INR remained a significant predictor of the residual loading dose in the subset of patients who had not yet reached a therapeutic INR (see figures 2 and 3).

In contrast, both the starting dose and the INR were significant predictors of the maintenance dose at both time points (see figures 2 and 3).

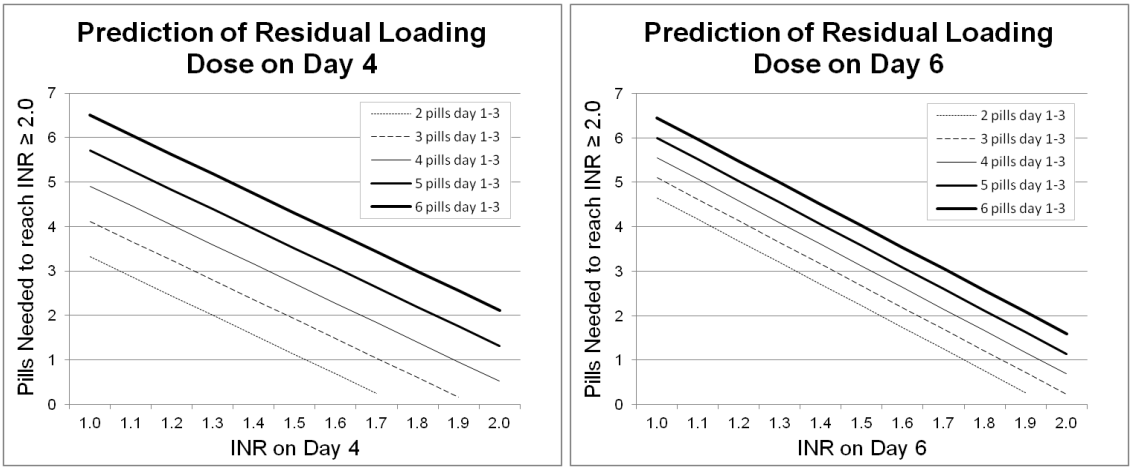

Figure 2: Prediction of the residual loading dose on days 4 and 6

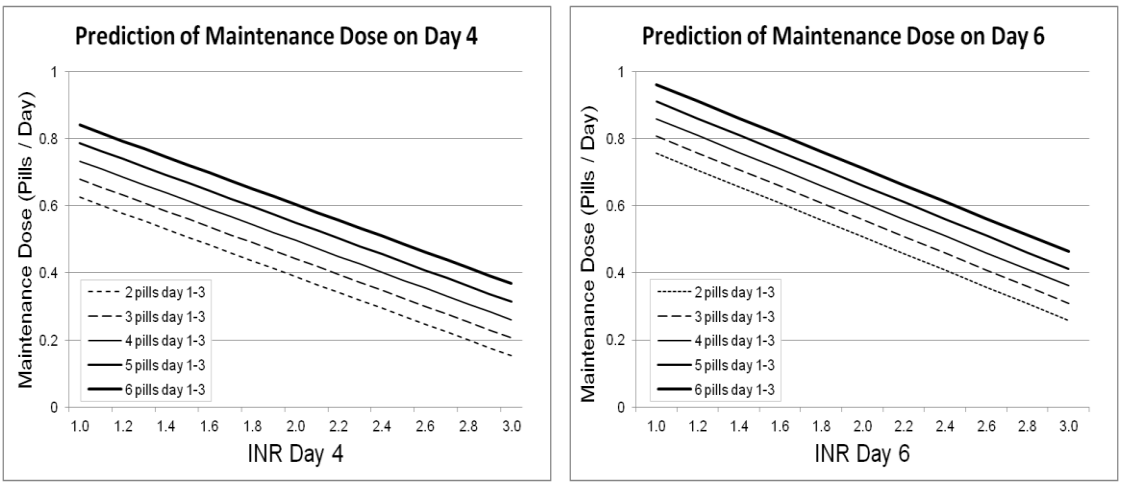

Figure 3: Prediction of the maintenance dose on days 4 and 6

Revised algorithm

Based on these findings three changes were made to the previous algorithm: i) amiodarone was added to the dose-reduction scheme for days 1 to 3, ii) the correction dose according to the INR on day 4 was slightly modified for the lower dose groups and iii) since the predicted residual doses and the maintenance doses on days 4 and 6 were very similar the dosing table for day 4 was extended to be valid on day 6. As outlined in the methods section these algorithms do not attempt to predict the most likely average dose but aim at a slightly lower dose and a stepwise approach to the individual dose without overshooting (see figures 4 and 5).

Age [years]

Weight [kg]	<40	40-60	60-80	>80
<45	5	4	4	3
45-60	5	5	4	4
60-75	5	5	5	4
75-90	6	5	5	5
>90	6	6	5	5

+

Comorbidity / Comedication

Alcohol >20g/day	+ 1 pill
Operation within 1 week	- 2 pills
Any combination of • female gender • diarrhoea • baseline-INR >1.2 • clearance<25ml/min • amiodarone	- 1 pill

→

Empiric dose Day 1-3

Number of pills*	Day 1	Day 2	Day 3
≤2	1	¾	¼
3	1 ½	1	½
4	2	1 ½	½
5	2	2	1
≥6	3	2	1

*1 pill corresponds to 3 mg

Figure 4: Revised dosing algorithm for day 1

Number of pills Day 1-3	INR Day 4 or Day 6											
	<1.2		1.2 – 1.4		1.5 – 1.7		1.8 – 2.0		2.1 – 3.0		>3.0*	
	This Day	Next Day	This Day	Next Day	This Day	Next Day	This Day	Next Day	This Day	Next Day	This Day	Next Day
≤2	1 ½	1	1 ½	½	¾	½	½	¼	0	¼	0	0
3	2	1	1 ½	1	1	½	½	½	¼	¼	0	0
4	2	1 ½	2	1	1	¾	¾	½	½	¼	0	0
5	2	2	2	1 ½	1	1	1	½	½	½	0	0
≥6	3	2	2	2	2	½	1	¾	¾	½	0	0

*INR>5.0: consider vitamin K

Figure 5: Revised dosing algorithm for days 4 and 6

Table 2: Univariate clinical predictors of loading dose and maintenance dose

Factor	N	Effect on Loading Dose (pills)	95% CI	p=	Effect on Maintenance Dose (pills/day)	95% CI	p=
Age (per 10 years older)	-	-0.45	-0.8 to -0.1	0.01	-0.07	-0.1 to -0.04	<0.0001
Weight (per 10 kg higher)	-	0.29	0.04 to 0.5	<0.0001	0.06	0.04 to 0.08	<0.0001
Female gender	159 (53%)	-1.53	-2.6 to -0.5	0.003	-0.14	-0.2 to -0.1	0.0002
Recent operation	112 (37%)	-1.26	-2.3 to -0.2	0.02	0.08	0.0 to 0.2	0.06
Alcohol (per 10 g more/day)	-	0.29	-0.02 to 0.6	0.08	0.03	0.0 to 0.05	0.04
Diarrhea	22 (7%)	-0.92	-2.7 to 0.8	0.3	-0.13	-0.3 to 0.0	0.5
Vomiting	18 (6%)	-0.99	-3.1 to 1.1	0.3	-0.12	-0.3 to 0.04	0.4
COPD	14 (5%)	0.63	-1.7 to 3.0	0.6	-0.05	-0.2 to 0.1	0.6
Diabetes	39 (13%)	0.55	-0.9 to 2.0	0.5	0.02	-0.1 to 0.1	0.7
Cholestasis	29 (10%)	-0.72	-2.4 to 0.9	0.3	-0.09	-0.2 to 0.03	0.2
Active tumor	28 (9%)	-0.62	-2.3 to 1.1	0.5	-0.08	-0.2 to 0.05	0.2
Smoking	25 (8%)	0.82	-1.5 to 3.2	0.5	0.1	-0.1 to 0.3	0.3
Albumin (per 10 g/L higher)	-	1.39	0.6 to 2.2	0.0015	0.04	-0.03 to 1.0	0.2
eGFR (per 10 ml/min	-	0.28	0.1 to 0.4	0.0002	0.04	0.03 to 0.05	<0.0001
Initial INR (per 0.1 higher)	-	-0.69	-1.3 to -0.1	0.02	-0.05	-0.9 to -0.01	0.03
Amiodarone	13 (4%)	-0.47	-2.9 to 2.0	0.7	-0.15	-0.33 to 0.03	0.1
Corticosteroids	35 (12%)	-0.07	-1.6 to 1.5	1.0	-0.03	-0.1 to 0.1	0.6
Tc-aggregation inhibitors	96 (32%)	-0.42	-1.5 to 0.7	0.4	-0.05	-0.2 to 0.1	0.2

1 pill corresponds to 3 mg of phenprocoumon; eGFR: estimated glomerular filtration rate.

Table 3: Univariate genetic predictors of loading dose and maintenance dose

Gene-Locus	Geno-type	N	Effect on Loading Dose (pills)	95% CI	p=	Effect on Maintenance Dose (pills/day)	95% CI	p=
VKORC1:c.-1639 G>A	GG	53	Ref.	-	-	Ref.	-	-
	GA	62	-1.75	-3.0 to -0.5	0.006	-0.15	-0.3 to -0.05	0.004
	AA	28	-4.86	-6.4 to -3.3	<0.0001	-0.33	-0.5 to -0.2	<0.0001
VKORC1:c.-1453 G>A	GG	136	Ref.	-	-	Ref.	-	-
	GA	7	5.31	2.6 to 8.0	0.0002	0.2	-0.02 to 0.4	0.08
	AA	0	-	-	-	-	-	-
CYP2C9:c.430 C>T	CC	107	Ref.	-	-	Ref.	-	-
	CT	35	-0.25	-1.7 to 1.2	0.7	-0.11	-0.7 to 0.5	0.7
	TT	1	6.2	-1.2 to 13.5	0.1	-0.11	-0.7 to 0.5	0.3
CYP2C9:c.1075 A>C	AA	127	Ref.	-	-	Ref.	-	-
	AC	16	-0.4	-2.4 to 1.6	0.7	-0.06	-0.2 to 0.1	0.4
	CC	0	-	-	-	-	-	-
GGCX:c.214+597 G>A	GG	59	Ref.	-	-	Ref.	-	-
	GA	55	-0.46	-1.8 to 0.9	0.5	-0.06	-0.2 to 0.04	0.2
	AA	26	-1.25	-2.9 to 0.5	0.2	-0.07	-0.2 to 0.06	0.3
CYP4F2:c.1297 G>A	GG	66	Ref.	-	-	Ref.	-	-
	GA	57	0.86	-0.5 to 2.2	0.2	0.03	-0.07 to 0.1	0.5
	AA	20	0.93	-0.9 to 2.8	0.3	0.04	-0.1 to 0.2	0.6

1 pill corresponds to 3 mg of phenprocoumon; Ref.: reference

Table 3: Univariate genetic predictors of loading dose and maintenance dose

Gene-Locus	Geno-type	N	Effect on Loading Dose (pills)	95% CI	p=	Effect on Maintenance Dose (pills/day)	95% CI	p=
CALU:c.*4 A>G	AA	47	Ref.	-	-	Ref.	-	-
	AG	65	0.20	-1.2 to 1.6	0.8	-0.01	-0.1 to 0.1	0.9
	GG	31	-0.58	-2.3 to 1.1	0.5	0.05	-0.1 to 0.2	0.5
EPHX1:c.337 T>C	TT	65	Ref.	-	-	Ref.	-	-
	TC	68	-0.64	-1.9 to 0.6	0.3	-0.09	-0.3 to 0.1	0.4
	CC	10	-1.10	-3.6 to 1.4	0.4	-0.03	-0.1 to 0.1	0.6
PROC:c.-228 C>T	CC	53	Ref.	-	-	Ref.	-	-
	CT	72	-0.13	-1.5 to 1.2	0.8	-0.04	-0.2 to 0.1	0.4
	TT	18	-0.84	-2.9 to 1.2	0.4	-0.06	-0.2 to 0.1	0.4
PROC:c.-215 G>A	GG	23	Ref.	-	-	Ref.	-	-
	GA	74	-0.55	-2.4 to 1.2	0.5	-0.04	-0.2 to 0.1	0.6
	AA	46	-0.35	-2.2 to 1.5	0.7	-0.02	-0.2 to 0.1	0.8
F7:c.-402 G>A	GG	87	Ref.	-	-	Ref.	-	-
	GA	53	1.15	-0.1 to 2.4	0.08	0.03	-0.1 to 0.1	0.5
	AA	3	-0.77	-5.1 to 3.5	0.7	-0.08	-0.4 to 0.3	0.6
F7:c.-401 G>T	GG	103	Ref.	-	-	Ref.	-	-
	GT	36	-0.52	-2.0 to 0.9	0.5	-0.01	-0.1 to 0.1	0.8
	TT	4	-2.00	-5.8 to 1.8	0.3	-0.07	-0.4 to 0.2	0.7
F7:c.1238 G>A	GG	109	Ref.	-	-	Ref.	-	-
	GA	30	-0.58	-2.1 to 0.9	0.5	-0.05	-0.2 to 0.1	0.4
	AA	4	-3.69	-7.4 to 0.03	0.05	-0.26	-0.6 to 0.04	0.09

1 pill corresponds to 3 mg of phenprocoumon; Ref.: reference

Discussion

The main goal of this study was to test the effectiveness of two different dosing algorithms for the loading phase of phenprocoumon. Indeed both algorithms allowed classifying patients into groups with low, intermediate or high phenprocoumon demand on the basis of readily available parameters such as age, weight, a recent operation, or the last INR measurement. Both algorithms were safe and no major complication could be attributed to the proposed dosing regimens. A few patients showed a moderate overshooting of INR-values owing to a too high correction dose for days 4 and 5 in the groups which were predicted to require low initial dosing. Importantly, patients who showed early overshooting of the INR were often exposed to amiodarone. In multivariate models amiodarone was associated with lower loading doses; however, this was not statistically significant, presumably due to insufficient power of this small subgroup. Amiodarone is associated with lower coumarin demands due to its inhibition of CYP450 3A4 and 2C9. Accordingly, it is also included in dosing algorithms for warfarin. [26-32] As a consequence, we propose to include amiodarone into the revised algorithm and to make a slight modification of the correction dose on day 4.

Nevertheless, the control arm, in which dosing was at the discretion of the hospital residents, performed similarly well as the two algorithmic arms. 30-day mortality was 2.2% in the control arm (as opposed to 0% and 1% in arms A and B, respectively) and the 30-day bleeding-rate was 5.4% in the control arm (as opposed to 0% and 1.9% in arm A and B). Yet these differences did not quite reach statistical significance possibly due to insufficient power of the study.

It could therefore be assumed that dosing algorithms for phenprocoumon are unnecessary or even useless. However, it has to be kept in mind that the study physicians were especially trained on optimal dosing and management of phenprocoumon on request of the institutional review board. The control arm may therefore have performed worse without training. Indeed in our retrospective study [24] in the same hospital and with an equivalent patient population we found substantially higher rates of overshooting INRs and complications especially in orthopaedic patients. In the advent of newer anticoagulants the experience with phenprocoumon will decrease despite a subgroup of patients who may still need the drug. Therefore, we conclude that both algorithms are safe and effective in a broad spectrum of hospitalized patients including patients in the postoperative setting and since the proposed algorithms performed at least as well as especially trained physicians, they may be of particular value for less experienced physicians.

Algorithm A contains serum albumin as a major predictor which is not always available when the first dosing decision has to be made. In contrast, algorithm B, which performed equally well as algorithm A, contains mainly clinical data and in the multivariate analysis albumin was no longer an independent predictor of both the loading and the maintenance dose. Therefore, algorithm B seems to be preferable because of its ease of use.

Polymorphisms of genes involved in vitamin K metabolism further improve the prediction of the loading dose in our models. In multivariable models *VKORC1*:-c.1639G>A was a potent predictor of lower loading doses, which is in line with previous studies. [13, 16, 33-34]

In contrast, *VKORC1*:c.-1453G>A predicted higher loading doses. This is the first study to demonstrate a significant effect of this relatively rare polymorphism. Both polymorphisms are located in the promotor region of the VKORC1-gene, which suggests that these effects are mediated by altered gene expression. The explanatory power (adjusted R^2) of the baseline model for the loading dose substantially increased from 19% to 37% after the addition of the two genetic tests. Therefore, if genetic tests were available on the first day, they could accelerate the dose-finding process. Yet genetic information is rarely available before the start of treatment and we could demonstrate that treatment can nevertheless be safely started using our algorithm. Therefore, delaying treatment while awaiting the result of a genetic test is not warranted. However, genetic information is more likely to be available on day 4, when the second dose decision is usually made. Yet, on day 4, the clinical model (including a recent INR) could already explain 55% of the variance and the addition of genetic tests only improved the model prediction to 57%. In other words the biologic response of the INR to the first three doses comprises powerful dynamic information on individual dose demands, and the additional static information provided by genetic tests is almost negligible once treatment has been started. Therefore, instead of adding costs and complexity by additional tests, the management of anticoagulation can be improved to a greater extent, if the information included in the INR response to treatment at each time-point and in each subgroup of patients is integrated in an evidence-based dosing decision.

Conclusions

We could demonstrate that both algorithms are associated with safe and effective anticoagulation in a broad spectrum of hospitalized patients including postoperative states. Both algorithms were equally effective but the algorithm without serum albumin is easier to apply. Although the proposed algorithms did not perform better than especially trained physicians, they may be of particular value for less experienced physicians. We propose to include amiodarone into the dose estimation for days 1 to 3 and to slightly modify the correction algorithm for days 4 and 6.

Limitations

The present study only included hospitalised patients of predominantly Caucasian origin which limits the generalisability to outpatients and other racial groups. However, due to the higher prevalence of disease in inpatients it is unlikely that the algorithms would result in overdosing in outpatients. We propose to use the revised correction algorithm for day 4 also on day 6 although it has not yet been prospectively validated. However, dose-demands for the same INR were consistently slightly higher on day 6 than on day 4, which makes overdosing very unlikely. A larger study sample could have improved the power to detect group differences. This holds especially true for genetic predictors which were only available in about half of the patients.

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6 Conclusions

Clinical management of anticoagulation with coumarins is difficult, as a target range has to be achieved by drugs with a narrow therapeutic range and high intra-individual and inter-individual variability in pharmacokinetic and pharmacodynamic responses. The importance of maintaining coumarin users within the therapeutic range is driven by the aim of preventing thromboembolic events and by the necessity to minimize the risk of serious bleeding, the main manifestation of coumarin toxicity.

In hospitalized patients this problem is even more acute because:

i) these patients have a higher burden of disease than outpatients, which is likely to broaden the range of dose requirements,

ii) they are also more often exposed to comedication and nutritional changes, which increases the risk of interactions or of low vitamin-K levels,

iii) they undergo invasive procedures more often, which is expected to increase the complication rate,

iv) less time is available to observe responses, and

v) many decisions are made by inexperienced staff members.

In order to provide an applicable tool to guide the dosing of coumarins, readily available information is required.

The general aim of the thesis was to define dosing algorithms for phenprocoumon which can easily be implemented in clinical practice. These algorithms should help to improve the drug safety of phenprocoumon in the initial dose-finding process which was until now largely empiric.

Retrospective study

In our retrospective study we could identify individual predictors of the loading dose from which we developed two clinical algorithms for the initial dosing of phenprocoumon in medical and orthopaedic inpatients. One algorithm contains clinical data and additionally serum albumin; the second algorithm contains clinical data only. The algorithm containing albumin performed slightly better in the retrospective analysis but it is less practical to apply because albumin is not always available when the first dosing decision (usually for days 1 to 3) has to be made.

Prospective study

In our prospective study both algorithms could be validated and were slightly optimized. Both algorithms proved to be very safe and essentially equivalent. The algorithm using clinical data only is preferable simply because it is easier to apply than the algorithm also using albumin. The institutional Review Board demanded a special training for study physicians. This introduced an inevitable source of bias into the study design. Presumably as a consequence of this training the algorithms proved not to be superior to dosing by the specially trained study physicians in a control arm. Although the data are not directly comparable, these results are in strong contrast to the result of our observational data in the retrospective study,

where we found a much higher rate of overshooting INR values and bleeding complications.

In summary, both algorithms are safe and effective in hospitalized patients with a high rate of comorbidity. The algorithm using clinical data can be especially recommended due to its simplicity of use.

As an extension of these studies which had the principal aim of defining a loading dose and a focus on the first six days of treatment, we additionally derived precise dosing information even for extended loading periods and an algorithm for the maintenance dose. In a nested sample of these patients we further assessed the additional predictive value of pharmacogenetic markers both for the loading dose and the maintenance dose.

We chose a stepwise, conservative approach to find the target-INR without significant overanticoagulation. Even in the absence of information on genetic polymorphisms or previous dose demands, each patient can be reliably allocated to a stratum of low, intermediate or high drug demand by using readily available clinical information. This allows the a priori stratification of the dose for the first three days. Later on, the INR-response to this semi-empiric dose is a very potent predictor of future dose demands. A minimal response predicts much higher dose demands to reach a therapeutic level of anticoagulation whereas a steep rise of the INR indicates minimal residual dose demands. Similarly, the INR-response to subsequent doses becomes the main determinant of the maintenance dose.

Although these findings seem to be rather trivial, the strength of our studies lies in the structured approach and the provision of a simple and effective tool for inexperienced physicians.

Genetic Testing

The availability of genotypic information prior to administration of the first OA dose is not feasible for most patients at the moment. Genetic profiling may become more widely available in the future but it is expensive and – especially in an ambulatory setting – the result will not arrive in due time to influence the first prescription of coumarins. Even if genetic testing is ordered, oral anticoagulation will therefore often be initiated empirically with dose-adjustment according to INR-values. Delaying initiation of OA therapy is not an option as this is likely to delay discharge, prolong the use of heparins in ambulatory patients and increase healthcare costs. Pharmacoeconomic evaluations of pharmacogenetic testing suggest that genotype-guided dosing for Warfarin therapy is not cost-effective. [1-2] This was the main factor for holding back a general recommendation of genetic screening for patients on anticoagulant therapy.

We and others [3-9] could confirm that genetic variants are also significantly associated with phenprocoumon dose demands both during the loading and the maintenance phase. As outlined above, genetic information would ideally be most helpful at the time of the first dosing decision. At later time points the value of genetic information is rapidly compensated by functional information provided by the response of the INR to dosing.

Indeed, in our nested study with genetic markers the explanatory effect of these markers waned in multivariate analysis.

However, if genetic information were available right at the beginning, it could substantially add to the dose prediction. The genes of one human being do not change during a lifetime, therefore genetic analysis theoretically only needs to be done once. We were able to demonstrate that even with the absence of genetic tests, dosing is safe with the use of a standardized approach. If our algorithm is used, pharmacogenetic testing before initiating coumarin oral anticoagulants may thus accelerate the time to reach the therapeutic goal.

Limitations of the Retrospective and Prospective Study

The present studies only included hospitalised patients of predominantly Caucasian origin, which limits their generalizability to outpatients and other racial groups. However, due to the higher prevalence of disease in inpatients it is unlikely that the algorithms would result in overdosing in outpatients who are generally less vulnerable.

Our prospective study was limited to the loading phase. Further studies are needed to validate the proposed dosing algorithms during the maintenance phase.

Recommendations

We strongly recommend using an evidence-based approach to coumarin dosing. Due to its simplicity our proposed algorithm can easily be used as a paper-based decision support tool. It could further be integrated in a computer program or as a hand-held version. Similar programs are available for warfarin on www.warfarindosing.org. [10] In hospitals the most efficient mode would be to integrate the algorithm into the electronic patient record because relevant covariates as gender, age, weight, comedication and laboratory values could automatically be included and transformed to an electronic prescription.

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7 Publications

Caduff A, Gempeler-Messina P, Dubied A. Monitoring of a psycho-geriatric nursing home and a psychiatric clinic by the Hospital Pharmacy. An analysis of the current situation. GSASA News 2002;16,2:45/46. [Abstract in German]

Gräflein C, Caduff A, Mühlebach S. Pharmaceutical Safety of Organic Phosphates for Neonatal Parenteral Nutrition. Clinical Nutrition 2002;21 Suppl 1:82. [Abstract]

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8 Poster Presentations

Postgraduate Education in Hospital Pharmacy FPH. Basel, Switzerland, November 15 – 16, 2001. Caduff A, Gempeler-Messina P, Dubied A. Monitoring of a psycho-geriatric nursing home and a psychiatric clinic by the Hospital Pharmacy. An analysis of the current situation. [in German]

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3. Jahrestagung Schweizerische Arbeitsgemeinschaft Perinatale Pharmakologie (SAPP). Zurich, Dezember 09, 2010. A. Caduff Good, C. Balmer, M. I. Hug, P. Vonbach. Obstructed nasal breathing after propranolol intake in infants.

16th Congress of the European Association of Hospital Pharmacists. Vienna, Austria, March 30 – April 1, 2011. A. Caduff Good, C. Balmer, M. Hug, P. Vonbach. Obstructed nasal breathing after propranolol intake in infants.

GSASA – pharmaSuisse 2011 Kongress. 1. Schweizerischer Apothekerkongress. Interlaken, Switzerland, November 30 – December 1, 2011. A. Caduff Good, C. Balmer, M. Hug, P. Vonbach. Obstructed nasal breathing after propranolol intake in infants.

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56. Jahrestagung der Gesellschaft für Thrombose- und Hämostaseforschung (GTH). St. Gallen, Switzerland, February 1 – 4, 2012. A. Caduff Good, D. Nobel, W. Korte, C. Geisen, S. Henz. Prediction of phenprocoumon loading dose and maintenance dose by genetic and non-genetic parameters.

9 Oral Presentations

FPH-Prüfungsvortrag, Universität Bern. Bern, November 20, 2003. Qualitätssicherung der postoperativen Schmerztherapie durch Patienten- und Mitarbeiterbefragungen.

Journal Club, Spitalapotheke, Kantonsspital Basel. Basel, January 15, 2004. Qualitätssicherung der postoperativen Schmerztherapie durch Patienten- und Mitarbeiterbefragungen.

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Teachingwoche Kinderspital Zürich. December 6, 2011. Fallbeispiel – 4 für alle Fälle.

10 Congress Participations

Kongress der Gesellschaft Schweizerischer Amts- und Spitalapotheker. St. Gallen, November 13 - 14, 2003.

9th Congress of the European Association of Hospital Pharmacists. Sevilla, Spain, March 17 - 19, 2004.

73. Jahresversammlung der Schweizerischen Gesellschaft für Innere Medizin. Basel, May 25 - 27, 2005.

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