Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Original article | Published 8 January 2013, doi:10.4414/smw.2013.13709
Cite this as: Swiss Med Wkly. 2013;143:w13709

Randomised trial of a clinical dosing algorithm to start anticoagulation with phenprocoumon

Angela Caduff Good[a], *Daniel Nobel*[b], *Stephan Krähenbühl*[c], *Christof Geisen*[d], *Samuel Henz*[e]

[a] Hospital Pharmacy, University Children's Hospital, Zurich, Switzerland
[b] Division of Cardiology, Cantonal Hospital, St. Gallen, Switzerland
[c] Clinical Pharmacology and Toxicology, University Hospital, Basel, Switzerland
[d] German Red Cross, Institute of Transfusion Medicine and Immunohaematology, University Hospital, Frankfurt, Germany
[e] Internal Medicine, Cantonal Hospital, St. Gallen, Switzerland

Summary

QUESTION UNDER STUDY: Prospective validation of two algorithms for the initiation of phenprocoumon treatment.

METHODS: Inpatients with new-onset anticoagulation were randomised 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 randomised 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.-1639 G>A was associated with lower loading doses whereas VKORC1:c.-1453 G>A needed higher doses. VKORC1:c.-1639 G>A was also associated with lower maintenance doses.

CONCLUSION: Both algorithms allow 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 use in polymorbid hospitalised 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*: randomised controlled trial; phenprocoumon; oral anticoagulation; coumarin; initiation of treatment; dosing; drug safety; hospital; pharmacogenetics; VKOR; loading dose; maintenance dose*

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 wide interindividual variation in 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 the prolonged time to reach therapeutic drug levels owing to the drug's long half-life (110–130 h) [4–6]. The following main causes contribute to interindividual variability in dose demands: differences in the volume of phenprocoumon distribution, 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. One main determinant of the loading dose is therefore total body albumin content, which has to be saturated during the loading phase.

In comparison, drug elimination by metabolising 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 metabolising enzymes, which may vary with age, drug interactions or genetic factors such as the CYP 450 genotype [7–11].

However, variable drug requirements can also be caused by differences in 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 activ-

ity of this enzyme [13–16]. Several other allelic variants of genes have been proposed as associated with either altered drug elimination or drug susceptibility [7, 13,16–23].

Given the complexity of these issues, inexperienced physicians often have difficulties in safely initiating treatment with phenprocoumon. A model for prediction of the loading dose with phenprocoumon is therefore desirable. Once a steady-state has been reached, future doses will be more easily predicted on basis of the response to past doses. In a retrospective study of 300 medical and orthopaedic inpatients we previously developed two dosing algorithms for 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, randomised 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, randomised, controlled study of two algorithms for 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 9,700-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 aged below 18, 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 randomised to one of three arms without stratification using a computer-based system integrated into 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 into arm C dosing was at the physicians' discretion. The algorithms have been described elsewhere [24]. In brief the dose-finding process used the same variables (except for amiodarone) as outlined in figure 1 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 one, 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 be trained in 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. Family physicians were also asked to obtain blood for genetic analyses. Unfortunately this blood was only provided for some half of patients. Genetic analyses were performed as previously described [16, 25]. For the duration of the patients' hospitalisation 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.

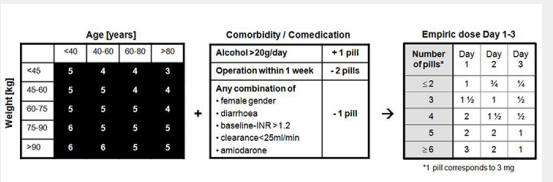


Figure 1

Revised dosing algorithm for day 1.

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, fall in haemoglobin by >20 g/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 metabolisation dur-

ing 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 in 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 approximately 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, diarrhoea, 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 biological 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 randomised to one of the management arms. An overview of the study protocol is presented in figure 2.

Due to slow recruitment, especially in orthopaedic patients (N = 110), more medical patients (N = 191) were included

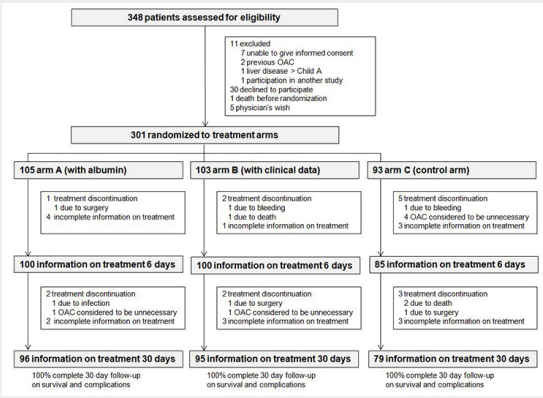
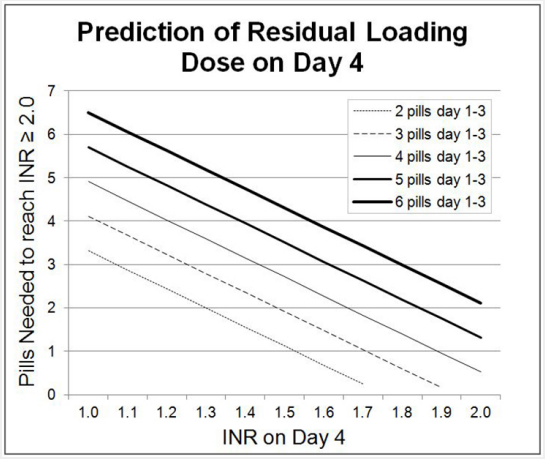


Figure 2

Overview of study protocol.



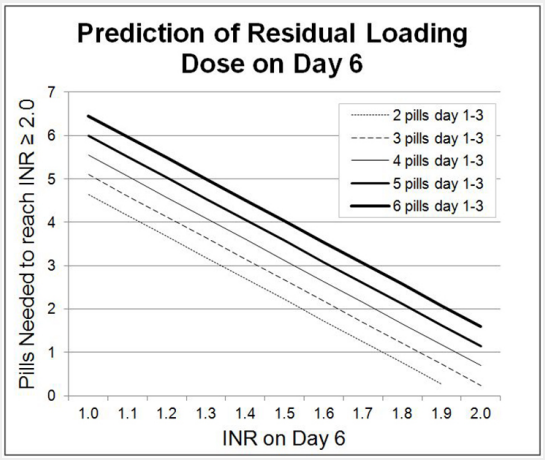


Figure 3

Prediction of residual loading dose on days 4 and 6.

and enrolment was stopped prematurely. The baseline characteristics were evenly distributed in all arms, as outlined in table 1.

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-day bleeding rate (minor and major) was 0%, 1.9% and 5.4% respectively (p = 0.06), and 30-day 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 1–3 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).

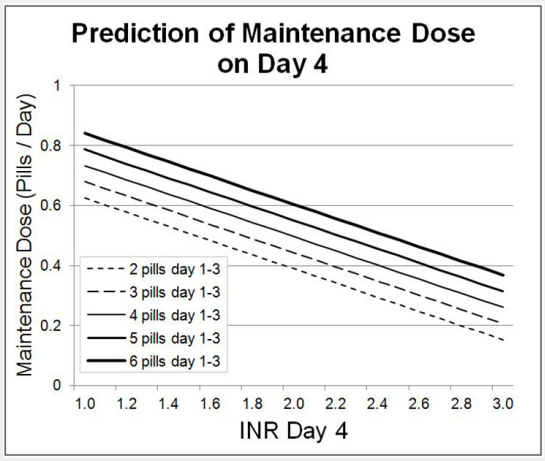


Figure 4

Prediction of maintenance dose on days 4 and 6.

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.

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 towards a higher loading dose could be observed (table 2).

Genetic predictors of the loading dose and the maintenance dose

The influence of genetic predictors on dose demands could be evaluated only 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.1238 G>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 (table 3).

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 (diarrhoea, 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 (tables 4 and 5).

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 (tables 6 and 7).

Dose estimation as a dynamic process

Dose estimation is a multistep dynamic process in clinical practice. Static models to predict dose-demands can therefore be helpful in cautiously starting anticoagulation, but with each INR measurement the biological 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 defining the starting dose (i.e. the "row" in the table of the algorithms), we used this starting dose in subsequent models 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 (fig. 3). In contrast, both the starting dose and the INR were significant predictors of the maintenance dose at both time points (fig. 4).

Revised algorithm

Based on these findings three changes were made to the previous algorithm: (1.) amiodarone was added to the dose-reduction scheme for days 1–3, (2.) the correction dose according to the INR on day 4 was slightly modified for the lower dose groups and (3.) 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 (figs. 1 and and 5).

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 patients to be classified 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 pro-

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 >20 g/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
Diarrhoea	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.

posed dosing regimens. A few patients showed moderate overshooting of INR-values owing to a too high correction dose for days 4 and 5 in the groups in which low initial dosing requirement was predicted. 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 the 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]. In consequence we propose including amiodarone in the revised algorithm and slightly modifying the correction dose on day four.

Nevertheless, the control arm, in which dosing was at the discretion of the hospital residents, performed similarly to 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 arms A and B). Yet these differences did not quite reach statistical significance, possibly due to the insufficient power of the study. It could therefore be assumed that dosing algorithms for phenprocoumon are unnecessary or even useless. However, it must be borne in mind that the study physicians were specially trained in optimal dosing and management of phenprocoumon at the 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. With the advent of newer anticoagulants experience with phenprocoumon will decrease despite a subgroup of patients who may still need the drug. We therefore conclude that both algorithms are safe and effective in a broad spectrum of hospitalised patients, including patients in the postoperative setting, and since the proposed algorithms performed at least as well as specially 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 must be taken. In contrast, algorithm B, which performed as 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 due to its ease of use.

Polymorphisms of genes involved in vitamin K metabolism further improve prediction of the loading dose in our models. In multivariable models *VKORC1*:-c.1639 G>A was a potent predictor of lower loading doses, which is in line with previous studies [13, 16, 33, 34]. In contrast *VKORC1*:c.-1453 G>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 addition of the two genetic tests. Therefore, if genetic tests are 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 safely be 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 four, 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 biological re-

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
Diarrhoea	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 higher)	–	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 phenprocoumon; eGFR = estimated glomerular filtration rate.

sponse 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. Hence 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 into an evidence-based dosing decision.

Conclusions

We are able to demonstrate that both algorithms are associated with safe and effective anticoagulation in a broad spectrum of hospitalised patients including postoperative states. The two algorithms were equally effective but the

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
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 phenprocoumon; eGFR = estimated glomerular filtration rate.

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

algorithm without serum albumin is easier to apply. Although the proposed algorithms did not perform better than specially trained physicians, they may be of particular value for less experienced physicians. We propose to include amiodarone in the dose estimation for days 1–3 and to slightly modify the correction algorithm for days 4 and 6.

Limitations

The present study included only 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.

Acknowledgement: The authors thank Wolfgang Korte from the Institute for Clinical Chemistry and Haematology, Cantonal Hospital, St. Gallen, Switzerland for helpful discussions. We further thank our colleagues in the St. Gallen Cantonal Hospital for their help with patient recruitment and data collection.
Trial registration number: NCT00586287.
Funding / potential competing interests: This study was in part supported by grants of AstraZeneca and Pfizer. These companies had neither a role in the study design, in the analysis of data nor the writing process.

Correspondence: *Samuel Henz M.D., MPH, Cantonal Hospital St. Gallen, Rorschacherstrasse 95, CH-9000 St. Gallen, Switzerland,* samuel.henz[at]kssg.ch

References

1 Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med. 1999;131(7):492–501.

2 Hirsh J, Dalen J, Anderson DR, Poller L, Bussey H, Ansell J, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest. 2001;119(1 Suppl):8–21S.

3 Stein PD, Alpert JS, Bussey HI, Dalen JE, Turpie AG. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. Chest. 2001;119(1 Suppl):220S–7S.

4 Ufer M. Comparative pharmacokinetics of vitamin K antagonists: warfarin, phenprocoumon and acenocoumarol. Clin Pharmacokinet. 2005;44(12):1227–46.

5 Hemker HC, Frank HL. The mechanism of action of oral anticoagulants and its consequences for the practice of oral anticoagulation. Haemostasis. 1985;15(4):263–70.

6 Kelly JG, O'Malley K. Clinical pharmacokinetics of oral anticoagulants. Clin Pharmacokinet. 1979;4(1):1–15.

7 Beinema M, Brouwers JR, Schalekamp T, Wilffert B. Pharmacogenetic differences between warfarin, acenocoumarol and phenprocoumon. Thromb Haemost. 2008;100(6):1052–7.

8 Becquemont L. Evidence for a pharmacogenetic adapted dose of oral anticoagulant in routine medical practice. Eur J Clin Pharmacol. 2008;64(10):953–60.

9 Meyer zu Schwabedissen C, Mevissen V, Schmitz F, Woodruff S, Langebartels G, Rau T, et al. Obesity is associated with a slower response to initial phenprocoumon therapy whereas CYP2C9 genotypes are not. Eur J Clin Pharmacol. 2006;62(9):713–20.

10 Tanaka E. In vivo age-related changes in hepatic drug-oxidizing capacity in humans. J Clin Pharm Ther. 1998;23(4):247–55.

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.-1639 G>A AA GA	–3.50 –0.72	–4.87 to –2.14 –1.84 to 0.39	<0.0001 0.2
VKORC1:c.-1453 G>A GA	3.50	1.29 to 5.71	0.002

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.-1639 G>A AA GA	–0.20 –0.10	–0.30 to –0.10 –0.17 to –0.02	0.0002 0.01

11 Sotaniemi EA, Arranto AJ, Pelkonen O, Pasanen M. Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. Clin Pharmacol Ther. 1997;61(3):331–9.

12 Oldenburg J, Watzka M, Rost S, Muller CR. VKORC1: molecular target of coumarins. J Thromb Haemost. 2007;5(Suppl 1):1–6.

13 Luxembourg B, Schneider K, Sittinger K, Toennes SW, Seifried E, Lindhoff-Last E, et al. Impact of pharmacokinetic (CYP2C9) and pharmacodynamic (VKORC1, F7, GGCX, CALU, EPHX1) gene variants on the initiation and maintenance phases of phenprocoumon therapy. Thromb Haemost. 2011;105(1):169–80.

14 Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):160S–98S.

15 Arnold ML, Grond-Ginsbach C, Kloss M, Di Mascio MT, Veltkamp R, Ringleb P, et al. Pharmacogenetic testing for guiding de novo phenprocoumon therapy in stroke patients. Cerebrovasc Dis. 2009;28(5):468–71.

16 Geisen C, Luxembourg B, Watzka M, Toennes SW, Sittinger K, Marinova M, et al. Prediction of phenprocoumon maintenance dose and phenprocoumon plasma concentration by genetic and non-genetic parameters. Eur J Clin Pharmacol. 2011;67(4):371–81.

17 Yin T, Miyata T. Warfarin dose and the pharmacogenomics of CYP2C9 and VKORC1 – rationale and perspectives. Thromb Res. 2007;120(1):1–10.

18 Schalekamp T, Brasse BP, Roijers JF, van Meegen E, van der Meer FJ, van Wijk EM, et al. VKORC1 and CYP2C9 genotypes and phenprocoumon anticoagulation status: interaction between both genotypes affects dose requirement. Clin Pharmacol Ther. 2007;81(2):185–93.

19 Visser LE, van Vliet M, van Schaik RHN, Kasbergen AAH, De Smet PAGM, Vulto AG, et al. The risk of overanticoagulation in patients with cytochrome P450CYP2C9*2 or CYP2C9*3 alleles on acenocoumarol or phenprocoumon. Pharmacogenetics. 2004;14(1):27–33.

20 Rieder MJ, Reiner AP, Gage BF, Nickerson DA, Eby CS, McLeod HL, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med. 2005;352(22):2285–93.

21 Schwarz UI, Ritchie MD, Bradford Y, Li C, Dudek SM, Frye-Anderson A, et al. Genetic determinants of response to warfarin during initial anticoagulation. N Engl J Med. 2008;358(10):999–1008.

22 Schalekamp T, Oosterhof M, van Meegen E, van Der Meer FJ, Conemans J, Hermans M, et al. Effects of cytochrome P450 2C9 polymorphisms on phenprocoumon anticoagulation status. Clin Pharmacol Ther. 2004;76(5):409–17.

23 Werner D, Werner U, Wuerfel A, Grosch A, Lestin HG, Eschenhagen T, et al. Pharmacogenetic characteristics of patients with complicated phenprocoumon dosing. Eur J Clin Pharmacol. 2009;65(8):783–8.

24 Good AC, Henz S. A clinical algorithm to predict the loading dose of phenprocoumon. Thromb Res. 2007;120(6):921–5.

25 Geisen C, Watzka M, Sittinger K, Steffens M, Daugela L, Seifried E, et al. VKORC1 haplotypes and their impact on the inter-individual and inter-ethnical variability of oral anticoagulation. Thromb Haemost. 2005;94(4):773–9.

26 Anderson JL, Horne BD, Stevens SM, Grove AS, Barton S, Nicholas ZP, et al. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. Circulation. 2007;116(22):2563–70.

27 Gage BF, Eby C, Johnson JA, Deych E, Rieder MJ, Ridker PM, et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. Clin Pharmacol Ther. 2008;84(3):326–31.

28 Gong IY, Tirona RG, Schwarz UI, Crown N, Dresser GK, Larue S, et al. Prospective evaluation of a pharmacogenetics-guided warfarin loading and maintenance dose regimen for initiation of therapy. Blood. 2011;118(11):3163–71.

29 Caraco Y, Blotnick S, Muszkat M. CYP2C9 genotype-guided warfarin prescribing enhances the efficacy and safety of anticoagulation: a prospective randomized controlled study. Clin Pharmacol Ther. 2008;83(3):460–70.

30 International Warfarin Pharmacogenetics C, Klein TE, Altman RB, Eriksson N, Gage BF, Kimmel SE, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med. 2009;360(8):753–64.

31 Millican EA, Lenzini PA, Milligan PE, Grosso L, Eby C, Deych E, et al. Genetic-based dosing in orthopedic patients beginning warfarin therapy. Blood. 2007;110(5):1511–5.

32 Milligan G, Gage, Eby, Gatchel, Deych, King. WARFARINDOSING. Oct 30, 2011 [cited 2012]; Available from: http://www.warfarindosing.org/Source/Home.aspx.

33 Qazim B, Stollberger C, Krugluger W, Dossenbach-Glaninger A, Finsterer J. Dependency of phenprocoumon dosage on polymorphisms in the VKORC1 and CYP2C9 genes. J Thromb Thrombolysis. 2009;28(2):211–4.

34 Gage BF. Pharmacogenetics-based coumarin therapy. Hematology Am Soc Hematol Educ Program. 2006:467–73.

Figures (large format)

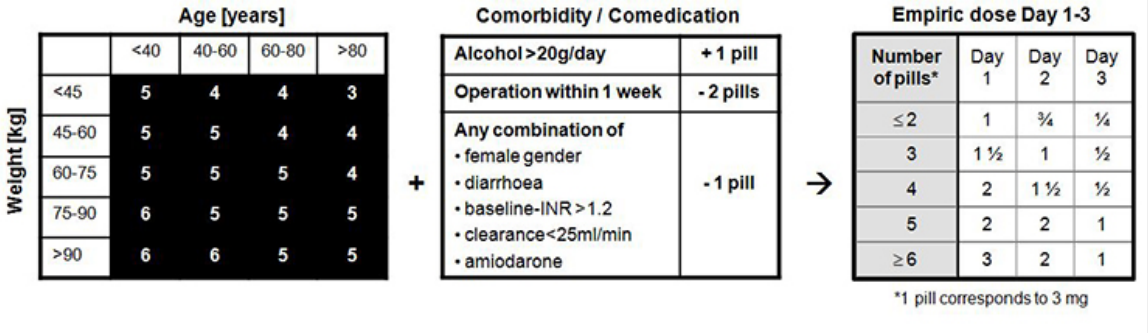


Figure 1

Box Plot showing the absolute error in estimating GFR (inulin clearence as the gold standard). CYSA, BTPA, CKCA, MDRDA, ALMA = absolute error in estimating the GFR using algorithms based respectively on Cystatin C; Beta-trace protein, creatinine and anthropometric values (Cockcroft); creatinine and anthropometric values (MDRD), creatinine, anthropometric values and appendicular lean mass (approximating muscle mass) measured by bioimpedance.

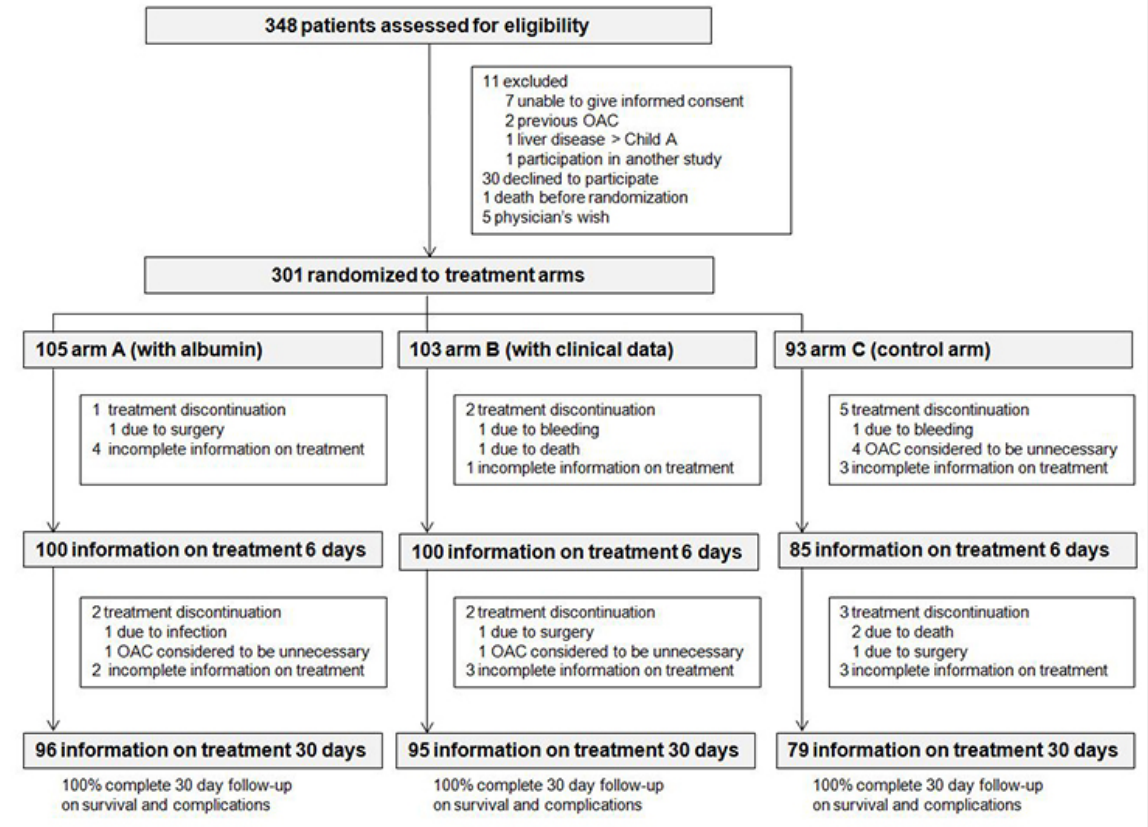


Figure 2

Overview of study protocol.

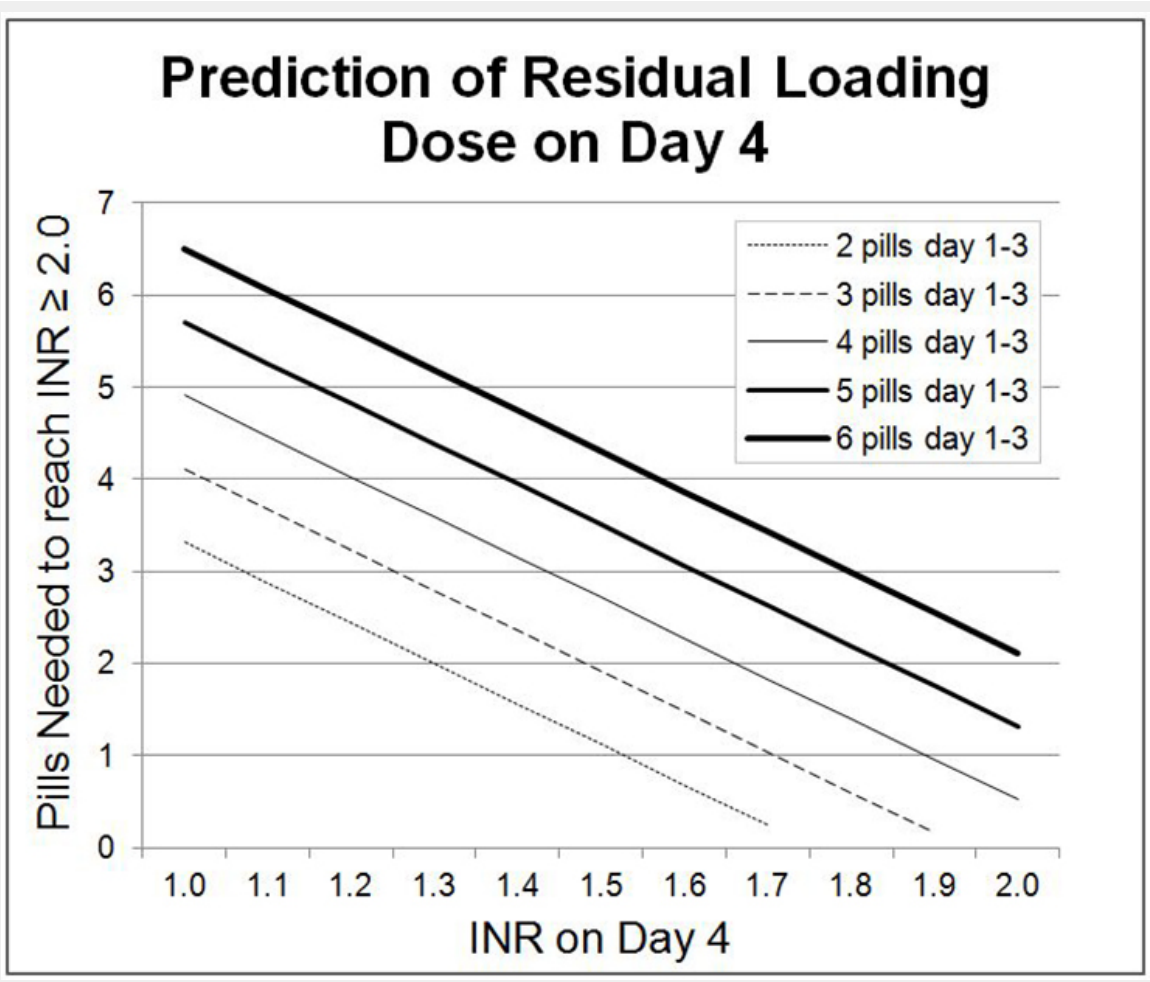


Figure 3

Prediction of residual loading dose on days 4 and 6.

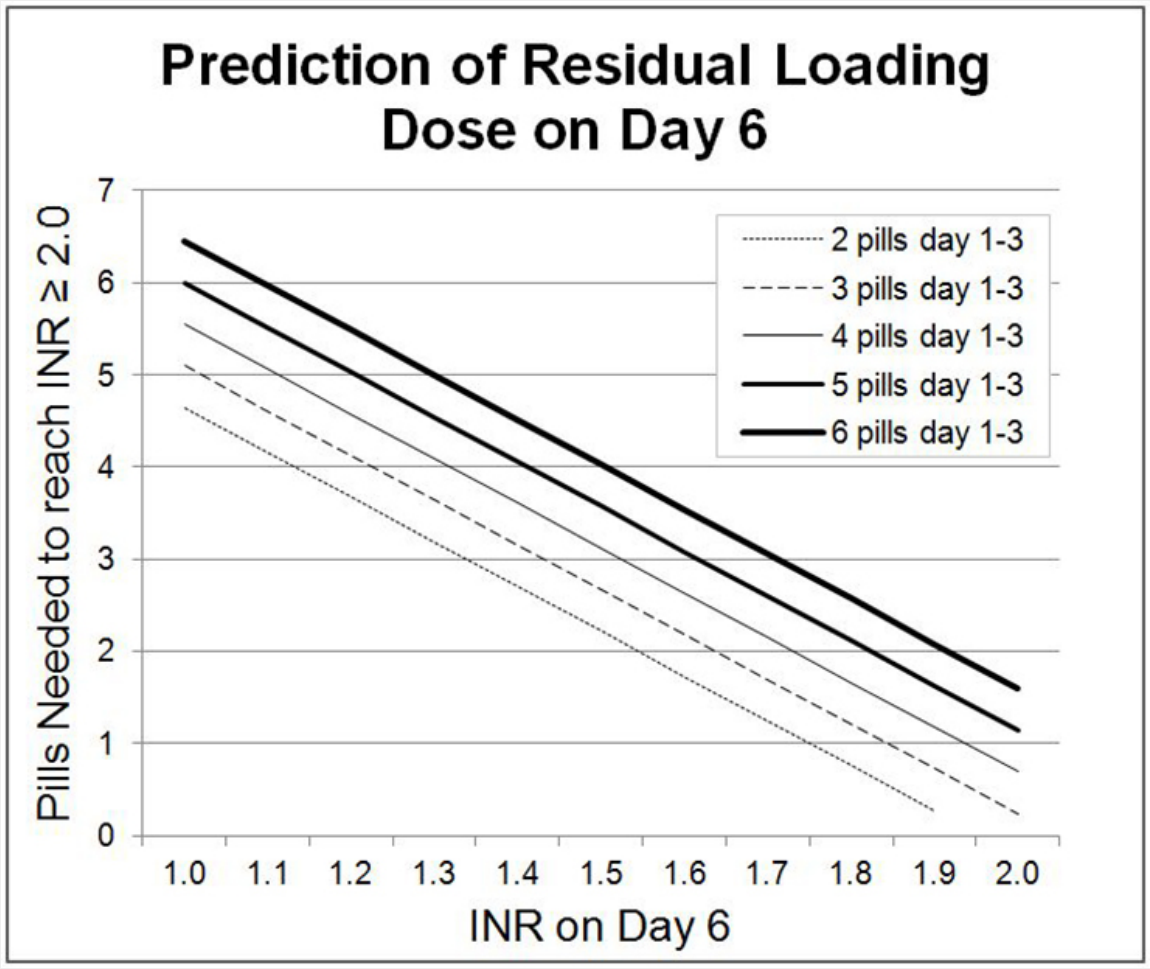


Figure 3

Prediction of residual loading dose on days 4 and 6.

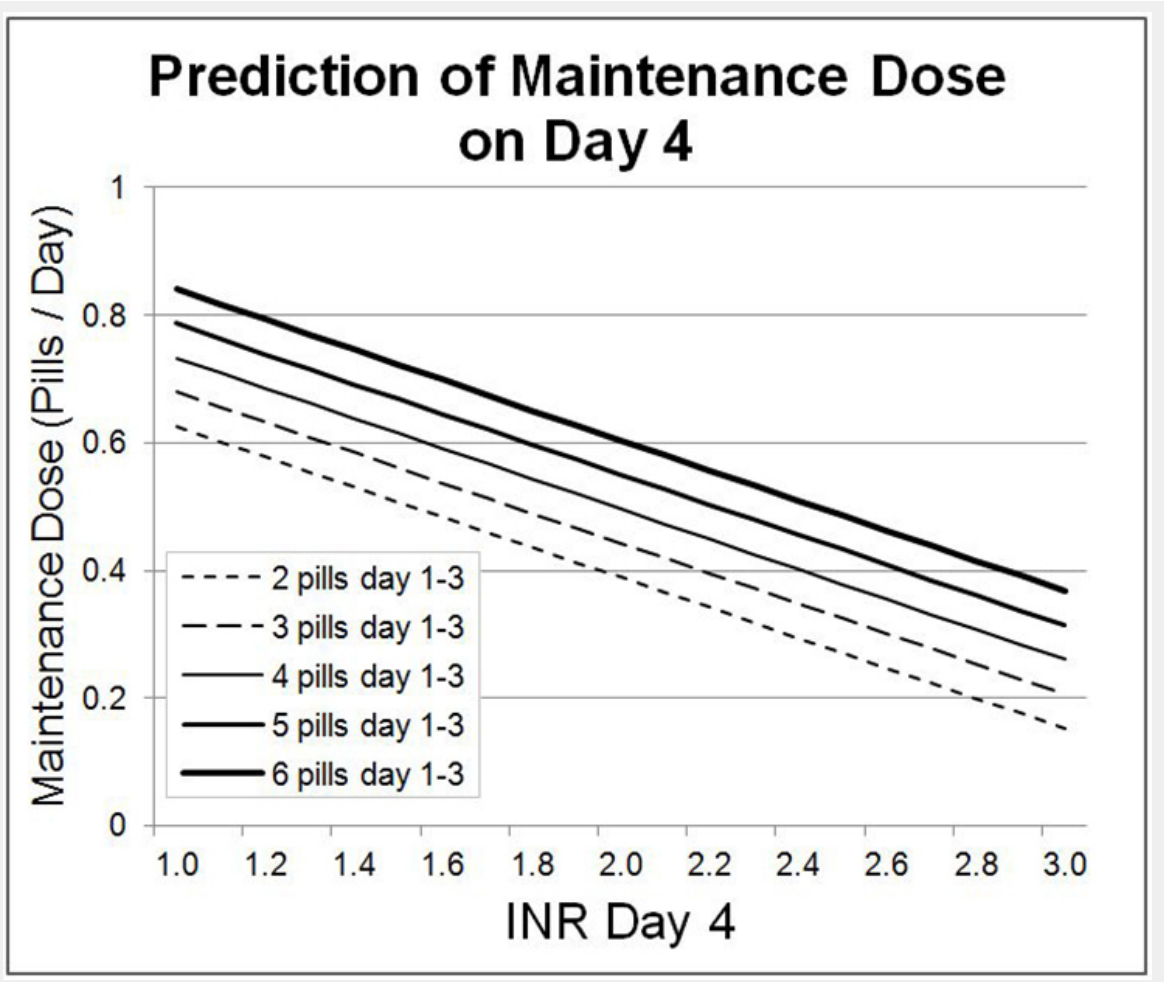


Figure 4

Prediction of maintenance dose on days 4 and 6

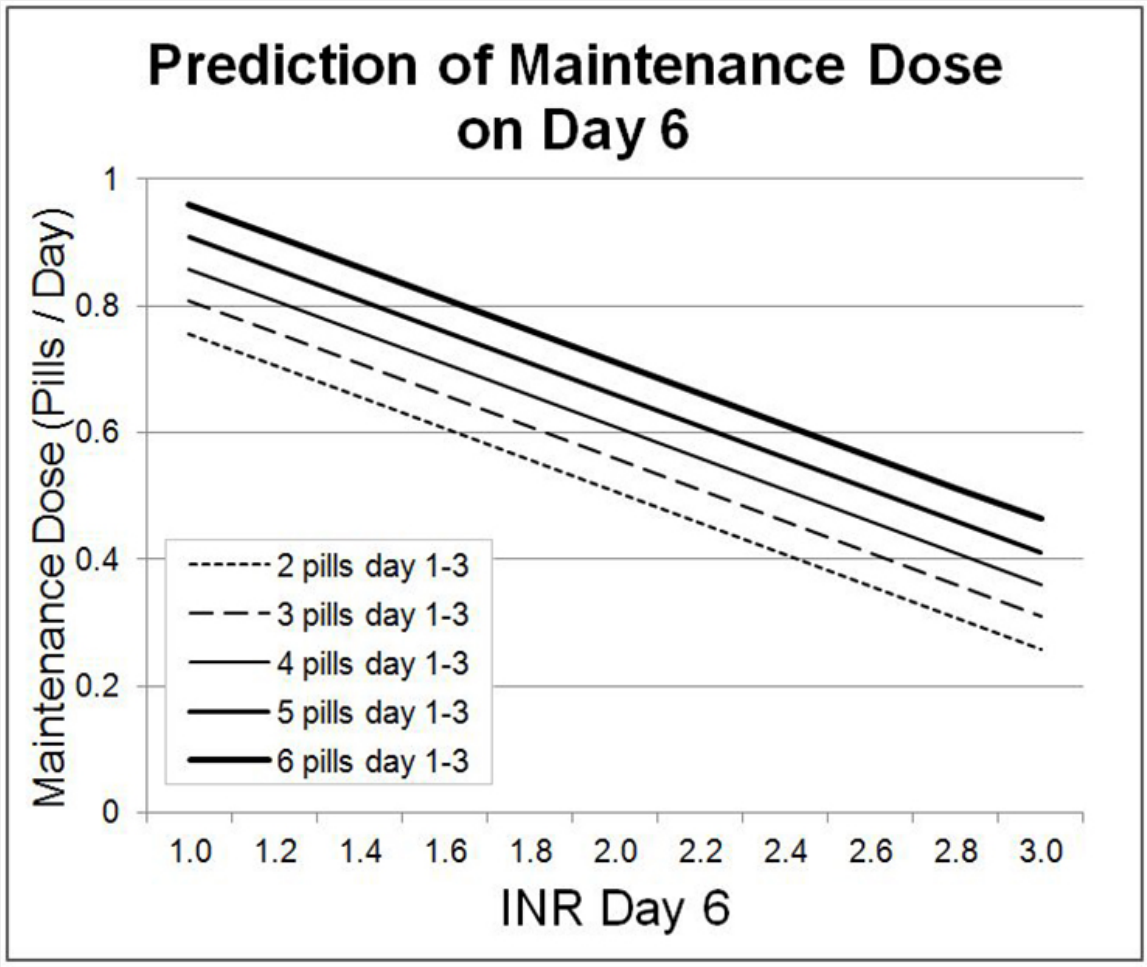


Figure 4

Prediction of maintenance dose on days 4 and 6

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.