Pharm Res (2011) 28:1100–1111
DOI 10.1007/s11095-011-0369-x

RESEARCH PAPER

Development of a Bayesian Forecasting Method for Warfarin Dose Individualisation

Daniel F. B. Wright • Stephen B. Duffull

Received: 19 October 2010 / Accepted: 10 January 2011 / Published online: 8 February 2011

ABSTRACT

Purpose The aim of this study was to develop a Bayesian dose individualisation tool for warfarin. This was incorporated into the freely available software TCIWorks (www.tciworks.info) for use in the clinic.

Methods All pharmacokinetic and pharmacodynamic (PKPD) models for warfarin in the medical literature were identified and evaluated against two warfarin datasets. The model with the best external validity was used to develop an optimal design for Bayesian parameter control. The performance of this design was evaluated using simulation-estimation techniques. Finally, the model was implemented in TCIWorks.

Results A recently published warfarin KPD model was found to provide the best fit for the two external datasets. Optimal sampling days within the first 14 days of therapy were found to be days 3, 4, 5, 11, 12, 13 and 14. Simulations and parameter estimations suggested that the design will provide stable estimates of warfarin clearance and EC50. A single patient example showed the potential clinical utility of the method in TCIWorks.

Conclusions A Bayesian dose individualisation tool for warfarin was developed. Future research to assess the predictive performance of the tool in warfarin patients is required.

KEY WORDS anticoagulation · optimal design · population pharmacokinetic-pharmacodynamic modelling · therapeutic drug monitoring · warfarin

D. F. B. Wright (✉) · S. B. Duffull
School of Pharmacy, University of Otago
PO Box 56, Dunedin, New Zealand 9054
e-mail: dan.wright@otago.ac.nz

ABBREVIATIONS

BSV	between-subject variability
CL	clearance
CYP	cytochrome P450
diag	diagonal
EC50	the drug concentration at 1/2 of maximum effect
FIM	Fisher information matrix
INR	international normalised ratio
J	Jacobian matrix
KPD	kinetic-pharmacodynamic
MAP	maximum *a posterior*
MTT	mean transit time
PCA	prothrombin complex activity
PKPD	pharmacokinetic-pharmacodynamic
PT	prothrombin time
RSE	relative standard error
RUV	residual unexplained variability
SE	standard error
VKORC1	vitamin K epoxide reductase
VPC	visual predictive check (external [e] or internal [i])

INTRODUCTION

Warfarin is the most commonly prescribed oral anticoagulant worldwide. It is a difficult drug to dose accurately and reliably, with daily maintenance doses varying by ten-fold among patients (1). Dosing is further complicated by a narrow therapeutic range, which requires routine monitoring of warfarin response using the International Normalised Ratio (INR). If the INR falls below 2, the patient is at increased risk of clotting, while

INRs above 4.5 carry a significant risk of major bleeding events (2–7). In addition, there is a delay between a change in the dosing regimen and achievement of the steady state INR, which means that monitoring is often confounded by non-steady-state conditions. Not surprisingly, warfarin dose individualisation constitutes a major challenge for clinicians, with reports suggesting that patients achieve therapeutic INRs only 50–60% of the time (8–12).

Recent research has revealed that genetic differences in warfarin metabolism (via the drug metabolising enzyme CYP2C9) and the recycling of vitamin K (via vitamin K epoxide reductase (VKORC1)) are a significant source of dose variability (1,13–20). This has prompted a call for prospective genetic testing in newly initiated warfarin patients and has lead to the development of several genotype-guided dosing algorithms (1,15–17,19,20). While these algorithms incorporate all known phenotypic and genotypic influences on warfarin response, they currently only account for 50–60% of warfarin dose variability (13,17–19). Indeed, large improvements in the ability to predict future doses or in clinical endpoints, such as time within the therapeutic range, have not been consistently demonstrated using genotype-guided dosing compared to traditional methods (see Caraco *et al.* (16) *versus* Anderson *et al.* (20), for example). In addition, they require prior knowledge of the patient's genetic makeup, which is not routinely available in most clinical settings. Nevertheless, genotypic methods would be expected to provide a guide to the likely maintenance dose required for a patient.

The overarching motivation for this research is the belief that warfarin dose individualisation can be achieved by the application of Bayesian methodologies without the need for prospective genetic testing. This should require only routinely collected INR results. In general, Bayesian methodologies involve predictions of drug response (or plasma concentrations) in an individual patient, given knowledge of the underlying pharmacokinetic and pharmacodynamic (PKPD) model and parameter values from a prior population combined with response data from an individual patient (21). This means that as more response data becomes available, the posterior estimates of the parameters become more refined and specific to the individual patient (22). Armed with estimates of the individual patient parameters, future doses can be accurately predicted.

The aim of this study was to develop a Bayesian dose individualisation method based on INR. There were five specific objectives: (1) to identify PKPD models for warfarin from the literature, (2) to evaluate these models and determine the best overall model, (3) to develop an optimal design for Bayesian parameter control, (4) to assess this design using simulation-estimation techniques, and (5) to implement the model in TCIWorks (www.tciworks.info) with a single simulated case to show the practical translation of this work.

MATERIALS AND METHODS

Identifying PKPD Models for Warfarin

This research was conducted on the premise that published PKPD models for warfarin were intended by the authors to be used for predictions of anticoagulant response in new clinical settings. A literature review was conducted using Medline (1950–2010) and Embase (1947–2010) databases to identify all published PKPD models for warfarin. MESH terms (warfarin, anticoagulants, dose-response relationship, international normalised ratio, statistical models, biological models, population, algorithms, pharmacokinetics) and keywords (modelling, PKPD, pharmacodynamics) were used. Key review articles were identified and mined for further papers.

Models were included only if they provided sufficient details to enable simulations from the model.

Model Evaluation and Selection

Published models were evaluated using visual predictive checks (VPCs). Two types of VPCs are used in this work: (1) internal VPCs, where the predictions from the model were compared against the *index* data that was used to build the model (VPCi), and (2) external VPCs, where predictions from the model were compared to an external *test* dataset (VPCe). (See Duffull *et al.* (23) for a similar use of VPCs.)

Two datasets for external comparison were available. In the first dataset (O'Reilly data) (24,25), 32 healthy volunteers aged 21–63 years were given a single 1.5 mg/kg dose of racemic warfarin orally or by IV injection. Racemic warfarin plasma concentrations and prothrombin complex activity (PCA) were measured at 0, 0.5, 1, 1.5, 2, 3, 6, 9, 12, 24, 26, 48, 72, 96, 120 and 144 h after administration. In total, the dataset provided 251 plasma warfarin concentrations and 233 PCA measurements. The second dataset, from the University of Sydney (Sydney data) (26), included warfarin plasma concentrations for each enantiomer (R- and S- warfarin) and INR values for 12 healthy male volunteers, aged 18–34 years. Participants were given a single 25 mg dose of racemic warfarin, and blood samples were taken before (−48,−24 and 0 h) and at 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144 and 168 h after warfarin administration. INR values were converted to PCA using a rearrangement of a published conversion equation (27) (Eq. 1):

$$INR = \frac{a + (b^{*}PCA)}{PCA} \tag{1}$$

where $a=80.65$ and $b=0.18$.

All models were coded in MATLAB (2010a, the MathWorks, Inc). VPCs were constructed using 1000 simulations

under the design of the *index* and *test* dataset. The 10th, 50th, and 90th percentiles of the simulated data were compared to the same percentiles for the index and test data.

A population PKPD model was developed by the authors (Otago model) using the O'Reilly data (see Appendix 1). An internal VPC (VPCi) was produced for the O'Reilly data in order to provide a reference for the VPCes.

Weight-adjusted doses of racemic warfarin (1.5 mg/kg) used in the O'Reilly study were simulated by sampling from a vector of the original patient weights in the study population. Simulations evaluated against the Sydney dataset assumed a dose of 12.5 mg of S-warfarin. Simulated plasma concentrations were assumed to be racemic warfarin for comparisons with the O'Reilly data and S-warfarin for the Sydney data.

The final model selection was based on how well the model described the external datasets. Additional consideration was given to models developed using large and diverse population data. The goal was to select the model with the greatest chance of providing an unbiased prior model for TCIWorks, the Bayesian dose individualisation tool.

Optimised Designs for Bayesian Parameter Control

A KPD model from Hamberg *et al.* (28) was selected as the final warfarin model. Briefly, a KPD model is a simplified PKPD model, where the pharmacokinetic component is included implicitly rather than explicitly. No drug concentrations are measured, and parameter estimates (including PK parameters) are derived solely from the pharmacodynamic data (29). Details of the basic KPD model structure have been published elsewhere (28,29) so will not be reproduced in full here.

The KPD model was entered into MATLAB (2010a, the MathWorks, Inc). Optimal design calculations were performed at the population mean parameter values (see Table I) for a single 70-year-old patient given a 10 mg loading dose of racemic warfarin, followed by 13 days of 5 mg. Values for clearance and EC50 were assumed to be those associated with wild-type genotypes as per Hamberg *et al.* (28). No dosage adjustments were simulated during this exercise, as the goal was to evaluate the Bayesian algorithm with the optimal sampling for warfarin INR monitoring within the first 14 days of therapy. Baseline INR was fixed at 1, although this would not be a requirement in the clinic. Age was incorporated into the model as per Hamberg *et al.* (28,45):

$$CL_{si} = CL_{\theta}(1 + (-0.00571^{*}(AGE_i - 71))) \quad (2)$$

where CL_{si} is the individual estimate of clearance for *S*-warfarin, and CL_{θ} is the population mean value for *S*-warfarin clearance.

Using the KPD model, optimal sampling days for warfarin INR monitoring within the first 14 days of therapy were determined. To achieve this, a modified C-optimality criterion was used. The goal was to find sampling points for a single patient in which the sum of squared relative standard error (relative to each parameter value) for the maximum *a posteriori* (MAP) information matrix was minimised. The MAP information matrix was constructed in MATLAB and consisted of two components: the expectation of the Fisher information matrix of the data driven likelihood and the information matrix associated with the prior estimates of parameter values, weighted by between subject covariance ($\mathbf{\Omega}$). This joint information matrix simplifies to

$$FIM_{MAP} = \mathrm{J}\Sigma^{-1}\mathrm{J}' + \Omega^{-1} \quad (3)$$

where FIM_{MAP} is the MAP Fisher information matrix, J is a matrix of first partial derivatives of the model with respect to the parameters, such that

$$\mathcal{J} = \begin{bmatrix} \frac{\partial f(t_1)}{\partial \theta_1} & \cdots & \frac{\partial f(t_n)}{\partial \theta_1} \\ \vdots & \ddots & \vdots \\ \frac{\partial f(t_1)}{\partial \theta_n} & \cdots & \frac{\partial f(t_n)}{\partial \theta_n} \end{bmatrix} \quad (4)$$

Here we use $'$ to denote the transpose of the matrix. Σ is the covariance of the residual error and is given by $\Sigma = \sigma^2 \mathrm{I_n}$, where σ^2 is the residual variance and $\mathrm{I_n}$ an n x n identity matrix.

The standard error of the MAP information matrix (SE_{MAP}) is given by the square root of the diagonal of the inverse of the MAP information matrix (Eq. 5).

$$SE_{MAP} = \left(diag\left(FIM_{MAP^{\wedge}}{}^{-1}\right)\right)^{0.5} \quad (5)$$

The optimality criterion (Ψ_{RSE}) was given by the sum of relative standard error (Eq. 6) so that all parameters are weighted equally irrespective of their absolute value.

$$\Psi_{RSE} = \sum_{i=1}^{p} \frac{SE_{MAP_i}}{\theta_{POP_i}} \quad (6)$$

where SE_{MAPi} is the standard error of the MAP information matrix for the i^{th} parameter, θ_{POPi} is the population estimates for the ith parameter.

The optimality criterion was linked to an exchange algorithm for search across the design space (days for which INR is to be measured). In this algorithm, each element of the initial design vector was exchanged with a value from a grid of possible values. If the criterion value was improved, the new design was accepted. The design space was a unit grid over a period of 14 days. Three designs were considered, with 5, 7, and 9 sampling times during the first two weeks of therapy.

Table I Summary of the Four Published Warfarin Models Evaluated for This Research

Reference	Study details	Model	Parameter estimates	Variance estimates
Pitsui *et al.* 1993, 2003 (46,53)	• $n=5$, healthy volunteers. • Racemic warfarin 15 mg × 1 dose, then 13 days at sub-therapeutic doses	PK: 1 cpt bolus PD: modified sigmoid Imax	Vs = 11.3 l Ks = 0.027/h C50s = 0.298 mg/l Kd = 0.123/h Gamma = 1.66	BSV Vs = 0.0441 Ks = 0.0256 C50s = 0.2601 Kd = 0.0961 Gamma = 0.0529
Hamberg *et al.* 2007 (45)	• $n=150$ total. • Single dose: $n=57$ 10 mg with 3 samples at 12,36, 60 h • Chronic therapy: $n=93\times1$ sample 12–14 h after the dose	PK: 2 cpt w/FO absorption PD: inhibitory Emax with 2 parallel transit chains (6 and 1 compartments)	71 year old (CYP2C9 wild type) CLs = 0.314 l/h Vls = 13.8 l V2s = 6.59 l Ka = 2(/h) fixed Q = 0.131 l/h Emax = 1 (fixed) Gamma = 0.424 EC50(GG) = 4.61 mg/l EC50 (GA) = 3.02 mg/l EC50 (AA) = 2.20 mg/l MTT1 = 11.6 h MTT2 = 120 h Sigma = 3.61	BSV CLs = 0.0961 Vls = 0.0686 V2s = 0.982 EC50 = 0.167 MTT1 = 0.019 MTT2 = 1.04 RUV (additive) for INR 0.0325 RUV(additive) for S-warfarin 0.0908
Hamberg *et al.* 2010 (28)	• $n=196$ (model building) and $n=1426$ (WARG study) • Multidose and single dose data. • Age range 19–91	• KPD: Transit chain model, with two chains of three compartments each • Inhibitory Emax model for warfarin effect	CL/*1 allele = 0.174 l/h CL/*2 allele = 0.0879 l/h CL/*3 allele = 0.0422 l/h V = 14.3 l Ka = 2/h (fixed) Emax = 1 (fixed) Gamma = 1.15 EC50/G allele = 2.05 mg/l EC50/A allele = 0.96 mg/l MTT1 = 28.6 h MTT2 = 118.3 h	BSV CLs = 0.0894 V2s = 0.0538 EC50 = 0.1156 RUV (additive) for INR 0.04 RUV(additive) for S-warfarin 0.099
Yuen *et al.* 2010 (44)	• $n=16$, healthy male volunteers of Indian (8) and Chinese (8) descent • Aged 22–50 • Single dose 25 mg racemic warfarin with samples x 17 over 144 h	PK: 1 cpt with first order absorption PD: indirect-response, sigmoid (PCA)	CLs(*1/*1 t) = 0.276 l/h CLs(*2 or *3) = 0.18 l/h Vs = 10.6 l Ka = 0.402 l/h Kd = 0.0232 (l/h) Gamma = 2.83 EC50s(H7H7) = 0.479 mg/l EC50s(H1H7) = 0.288 mg/l EC50s(H1H1) = 0.206 mg/l	BSV CL = 0.011 Ka = 0.1318 EC50s(H7H7) = 0.0222 RUV(additive) for PCA 6.54 RUV for S-warfarin 0.1122

PK pharmacokinetic, *PD* pharmacodynamic, *cpt* compartment, *V* volume of distribution, *CL* clearance, *C50* and *EC50* the plasma concentration at which warfarin has 50% of full effect, *k* elimination rate constant, *Kd* elimination constant for PCA, *Ka* absorption rate constant, *BSV* between-subject variability, *RUV* random unexplained variability, *FO* first order, *Q* inter-compartmental clearance constant, *MMT* mean transit time

Design Performance (Simulation-Estimation)

The expected performance of the Bayesian dose individualisation method and the optimal sampling design was evaluated using a simulation-estimation exercise.

Simulation

One hundred virtual patients were simulated in MATLAB. For each virtual patient, a single set of "true" parameter values was simulated from a log normal distribution with a mean and variance derived from the published model. Seven parameters were simulated, including clearance, volume, Emax, gamma, EC50 and mean-transit times for transit chains 1 and 2, as per the published model (28). Patient age was included as a covariate on the clearance of *S*-warfarin (Eq. 2). The age for each patient was determined by randomly selecting from a vector of whole numbers matching the age range in the original study cohort. Adjustments were also made for latent genetic covariates on parameter values for clearance and EC50 during the

simulation phase (but not during parameter estimation below) to account for differences associated with CYP2C9 and VKORC1 polymorphisms. In each case, a vector of adjusted mean population parameter values associated with specific genetic polymorphism was sampled in proportion to their expected occurrence in the prior population (data taken from Hamberg *et al.* (28)). Baseline INR was fixed at 1, since no estimate of the population variance associated with baseline INR was available.

Estimation

For each virtual patient,

1. Initial estimates for the individual parameter values were set to the population mean values (clearance and EC50 were assigned values associated with wild-type genotypes for CYP2C9 and VKORC1, respectively. (Table I). From here, a search for the individual maximum *a posteriori* (MAP) values was conducted using a simulated annealing algorithm (30). The MAP estimator is given by

$$\hat{\Phi}_\theta = \arg\min_{\vec{\theta}} \left[\left(\vec{y} - f\left(t,\vec{\theta}\right)\right) \Sigma^{-1} \left(\vec{y} - f\left(t,\vec{\theta}\right)\right)' + \left(\vec{\theta} - \vec{\mu}_\theta\right) \Omega^{-1} \left(\vec{\theta} - \vec{\mu}_\theta\right)' \right] \quad (7)$$

   where Φ is the criterion for the MAP estimator, y is the observed INR value (calculated from the "true" parameter values with associated error), θ is the updated posterior parameter value, μ is the population mean value for the parameter and $f(t,\theta)$ is the updated predicted value for INR conditioned on the "new" estimates of the parameters. Parameter values for V, emax, gamma, MTT1 and MTT2 were fixed at the population mean value for the simulated annealing algorithm. The purpose of this was to reduce computational time and to allow the algorithm to search exclusively for MAP estimates of CL and EC50.
2. Each virtual patient was then followed for a period of 14 days. Patient data in the form of INR was made available as per the optimal, or a previously determined, empirical design. As new data was made available, the MAP was minimised to provide updated posterior estimates of the parameters.
3. Each iteration of the overall simulation algorithm was defined as each updated posterior estimate. Hence, if there were seven INR values available over the duration of treatment, then the overall simulation algorithm would have seven iterations. At each iteration the updated MAP parameter estimates are compared to the true parameter values for that virtual patient.

MAP Estimate Comparisons

The final MAP parameter estimates were compared to the "true" parameter values (see above) using relative error. For each iteration, relative error was calculated using the following equation:

$$\text{Relative error} = \frac{\theta_{\text{MAP}_{jk}} - \theta_{TRUE_j}}{\theta_{TRUE_j}} \quad (8)$$

where θ_{MAP} is the MAP parameter estimate for the jth patient at iteration k, and θ_{TRUE} is the simulated "true" parameter estimate for the jth patient.

Application in TCIWorks

The final KPD model was entered into TCIWorks, a freely available Bayesian dose optimisation software (www.tciworks.info) developed by one of the authors (SBD) in conjunction with colleagues at the University of Queensland. The software uses the Target Concentration Intervention (TCI) approach to dose individualisation, which is a patient-focused modification of Therapeutic Drug Monitoring (TDM) (31).

To illustrate the potential usefulness of the TCIWorks method in the clinic, INR response data from a single patient was simulated in MATLAB. The virtual patient was a 70-year-old female with CYP2C9 *1/*1 genotype and VKORC1 A/A genotype given a typical induction regimen of 3 mg racemic warfarin for five days. Simulations were conducted at the population mean parameter values. The resulting INR response data was entered into TCIWorks and the dose and INR predicted for days 1 to 5.

RESULTS

Published PKPD Models

A total of eighteen population PKPD models for warfarin were identified in the medical literature, dating back to 1969. Several were developed using simple linear or log-linear direct effects pharmacodynamic models for the warfarin dose-

response relationship and were not included in this research (see (32–38)). Of the remaining models, six did not include adequate details of parameter estimates or error models to enable simulation (e.g. (39–43)). The remaining four models (28,44–46) were included in this research. Details of these models are presented in Table I.

Model Evaluation and Selection

External visual predictive checks (VPCes) for each model compared to the O'Reilly and Sydney data are presented in Figs. 1 and 2. Internal and external visual predictive checks for the Otago model are also included in Figs. 1 and 2, respectively, though details of the model itself are presented in Appendix 1. None of the published models predicted the O'Reilly dataset well, with the exception of the Hamberg *et al.* 2010 model (Fig. 1b). Three of the four models (as well as the Otago model) under-predicted anticoagulant response when compared to the Sydney data. This will be discussed below. The Pitsui model, by contrast, over-predicted PCA in the first 48 h after dosing (Figs. 1d and 2d).

On balance, the Hamberg *et al.* 2010 provided a reasonable fit for both datasets, bearing in mind that the Otago model was developed from the O'Reilly data (note that Fig. 1a represents a VPCi, not a VPCe). The model parameters and error values were also estimated from a large and diverse (n=1426) population.

Optimised Designs for Bayesian Parameter Control

The optimal sampling days for a single 70-year-old patient given a 10 mg loading dose of racemic warfarin, followed by 13 days of 5 mg were found to be days 3, 4, 5 13 and 14 (5 samples); 3, 4, 5, 11, 12 13 and 14 (7 samples); and 3, 4, 5, 9,10,11, 12 13, 14 (9 samples). Relative standard errors (RSE) for clearance and EC50, which represents the precision of these parameter estimates, are presented in Table II. RSE improved, compared to the prior values, with the addition of five and seven observed INR values, but no further improvements were noted with nine samples. The seven-sample design was selected as the optimal design.

Design Performance (Simulation-Estimation)

The results of the simulation-estimation exercise to assess the performance of the seven-sample design are shown in Fig. 3. Only clearance (CL) and EC50 were estimated, as these were considered the most important parameters for dose individualisation. For both EC50 and CL, the initial bias reduced when more data became available. In addition, the relative error decreased with the addition of more data for EC50. This was not evident for CL, suggesting shrinkage towards the prior mean. The relative error values for CL and EC50 were stable between 1 and −1, indicating precise MAP parameter estimates.

Application in TCIWorks

The TCIWorks output screen is presented in Fig. 4. The INR results based on the prior parameter values, which do not account for genetic polymorphisms, are much lower than the observed INR data for a simulated patient with an A/A VKORC1 genotype. The predicted (individualised) values for clearance and EC50 were 0.378 l/h and 2.08 mg/l, compared to the simulated ("true") values of 0.348 l/h and 1.92 mg/l, respectively. The reduced EC50 value predicted by TCIWorks reflects the A/A genotype for the simulated patient.

DISCUSSION

There is a large body of literature dedicated to improving INR control through the individualisation of warfarin dosing. Three principle methods have been developed: dose refinement tools, dosing algorithms based on prior patient demographics, and Bayesian methods.

Dose refinement tools have been found to improve INR control compared to empirical (trial-and-error) methods (47–49). However, many of these tools function by simply fine-tuning the warfarin dose in proportional increments depending on how far the measured INR is from the target. They are, therefore, of questionable value for predicting doses in newly initiated patients or in those not at steady-state (e.g. recent dose adjustment or initiation of an interacting drug). It has been suggested that their benefit may derive largely from the standardisation of empirical warfarin dose adjustment amongst physicians (11,20). In addition, unlike Bayesian methods, dose refinement tools are based only on warfarin response data and, hence, do not take into account the underlying pharmacokinetic and pharmacodynamic factors which make the patient an individual.

Several methods for predicting warfarin dose *a priori* have also been suggested. These include traditional warfarin nomograms, as well as clinical and genotype-guided algorithms (as discussed above). While these provide broad suggestions for initial dosing based on patient characteristics such as age (50) or genetic information (1,15–17,19,20),

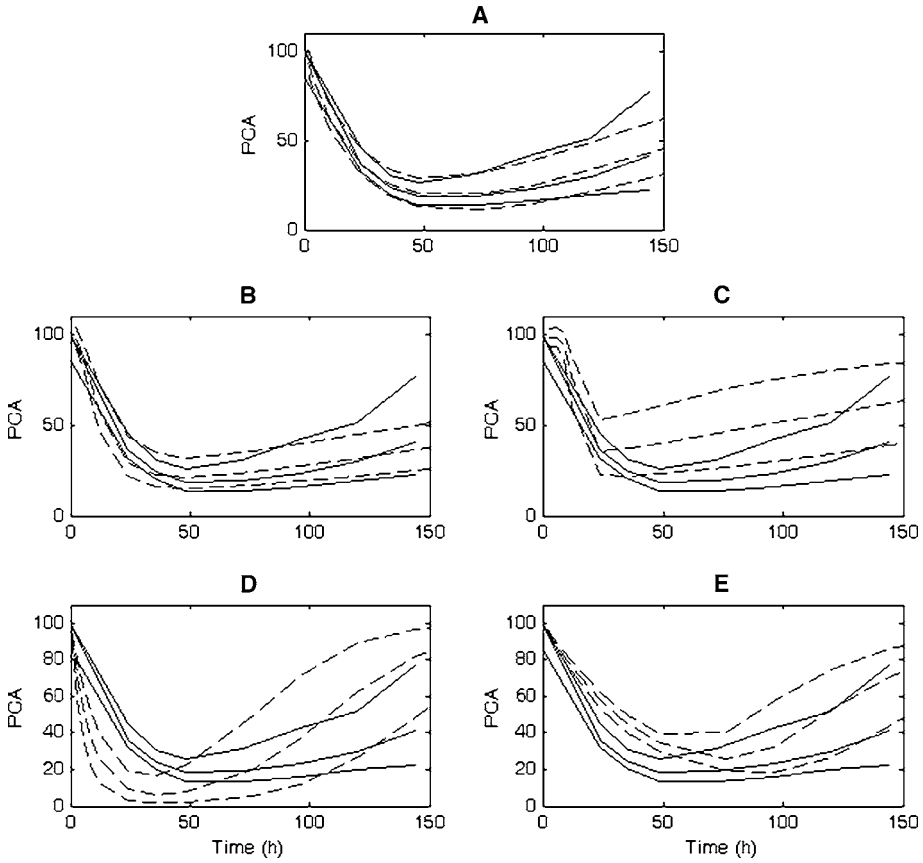

Fig. 1 Visual predictive checks for simulated data from the models (dashed lines) against the O'Reilly data (solid line). Models: (**A**) Otago model (Appendix 1), (**B**) Hamberg *et al.* 2010 (28), (**C**) Hamberg *et al.* 2007 (45), (**D**) Pitsui *et al.* 1993, 2003 (46,53), (**E**) Yuen *et al.* 2010 (44). Note that A is a VPCi, while the others are VPCes.

they provide no guidance for dose adjustment once INR values become available.

Bayesian methodologies have not been extensively applied to warfarin dose individualisation (see (40,46) for examples), and few appear to have been developed into tools for use in the clinic. One exception is a Bayesian forecaster developed in the 1980s (37) which is still available on the internet (51). This tool is underpinned by a log-linear model for warfarin dose-response (34) which assumes a linear relationship between the log of warfarin plasma concentration and anticoagulation effect.

Simulations from the published warfarin PKPD models reviewed in this paper showed a propensity to under-predict anticoagulant effect when compared to the external datasets (see Figs. 1 and 2). This was also evident with the Otago model (Fig. 2a) and has been reported by Hamberg *et al.* (52) when evaluating their model against external data. The exception was the model from Pitsui *et al.* (46,53) (Figs. 1d and 2d), which tended to over-predict effect in the initial 48 h after the dose. These differences may relate to differences in how anticoagulant response was measured across studies (e.g. PT (prothrombin time), INR, or PCA). This raises two important problems, which represent limitations for this research. First, systematic differences in the measurement of anticoagulant effect between different labs exist (54) despite improved standardisation with the introduction of the INR in the 1980s. This appears to be a particular problem between labs using the so-called Owren method for PT determination (e.g. Scandinavian countries) and those using the Quick method (54). Second, in our research, INR measurements from the Sydney dataset had to be converted to PCA to allow comparisons with the published models. The equation used (Eq. 1) is of unknown provenance, and it is unclear whether it has been evaluated in terms of accuracy and precision. A further limitation of this research was the use of external data collected from healthy, young volunteers to evaluate the models. The individuals in the two external datasets do not necessarily represent the typical population of patients who would be expected to receive warfarin, and, therefore, the observed anticoagulant effect may be biased. Indeed, this may have contributed to differences between the anticoagulant effect predicted by the published models and the observed effect in the external datasets noted in Figs. 1 and 2.

To our knowledge, this is the first published research to explore the application of optimal design methodologies to warfarin dose individualisation. Our findings suggest that a cluster of INR samples in the first few days of therapy,

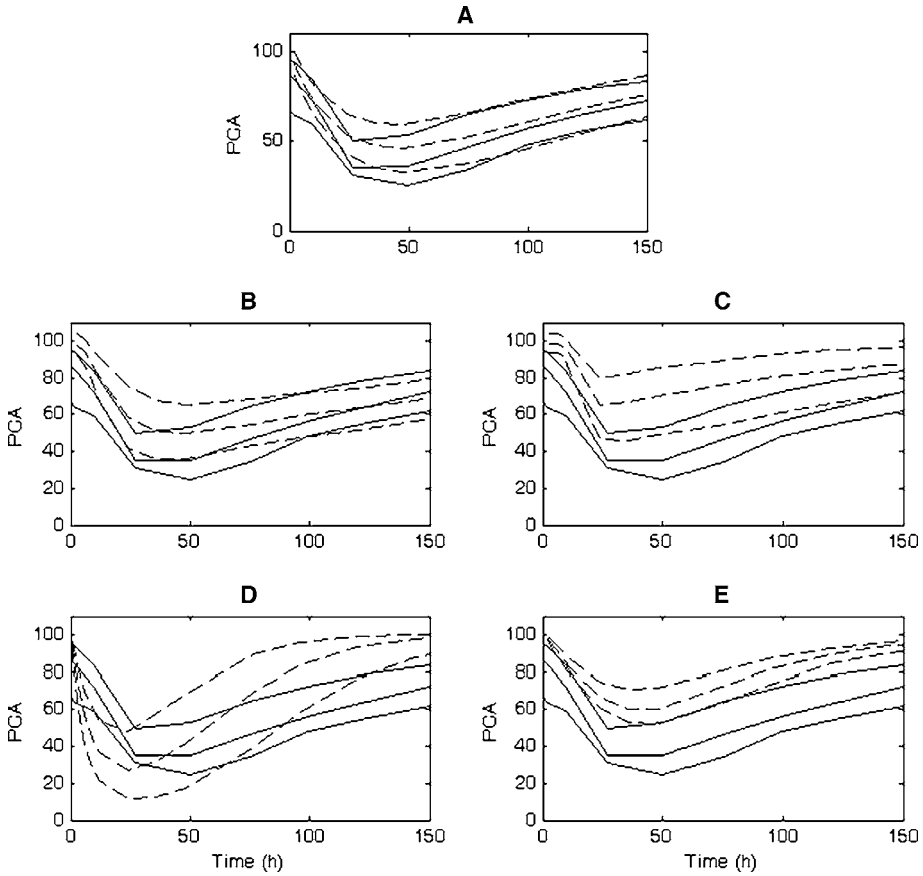

Fig. 2 External visual predictive checks (VPCe) of simulated data from the models (dashed line) against the Sydney data (solid line). Models: (**A**) Otago model (Appendix 1), (**B**) Hamberg *et al.* 2010 (28), (**C**) Hamberg *et al.* 2007 (45), (**D**) Pitsui *et al.* 1993, 2003 (46,53), (**E**) Yuen *et al.* 2010 (44).

followed by another cluster in a week's time, will optimise the estimates of parameter values and, hence, enable accurate dose prediction in many patients within the setting of Bayesian dose individualisation. The utility of this finding in clinical practice is unclear. For example, our method did not find any optimal INR sampling points in the first two days of therapy because the baseline INR was fixed at 1. In clinical practice, a baseline INR is almost always recommended.

Table II Relative Standard Errors for Clearance and EC50 for 3 INR Sampling Designs

Parameters	Relative standard error (%)			
	Prior	5 INRs	7 INRs	9 INRs
CL (l/kg)	122	43	28	27
EC50 (mg/l)	83	37	25	25

CL clearance, *EC50* the plasma concentration at which warfarin has 50% of full effect, Relative standard error = SEj/θj*100

For a warfarin dose individualisation tool to be useful clinically, it should be freely accessible and account for the underlying pharmacokinetic and pharmacodynamic factors that make each patient an individual. Ideally, this would be accomplished without the need for additional genetic testing. This research has laid the foundations for such a method. Unlike many dose individualisation tools developed for warfarin, our method has used a prior model developed from a large and diverse population. The TCIWorks tool with the warfarin model can be downloaded from www.tciworks.info.

CONCLUSION

This paper has described the development of a Bayesian dose individualisation tool for warfarin. This included the evaluation of five population models for the dose response relationship of warfarin, development and assessment of an optimal design for Bayesian parameter estimation, and illustration of a single patient example in TCIWorks.

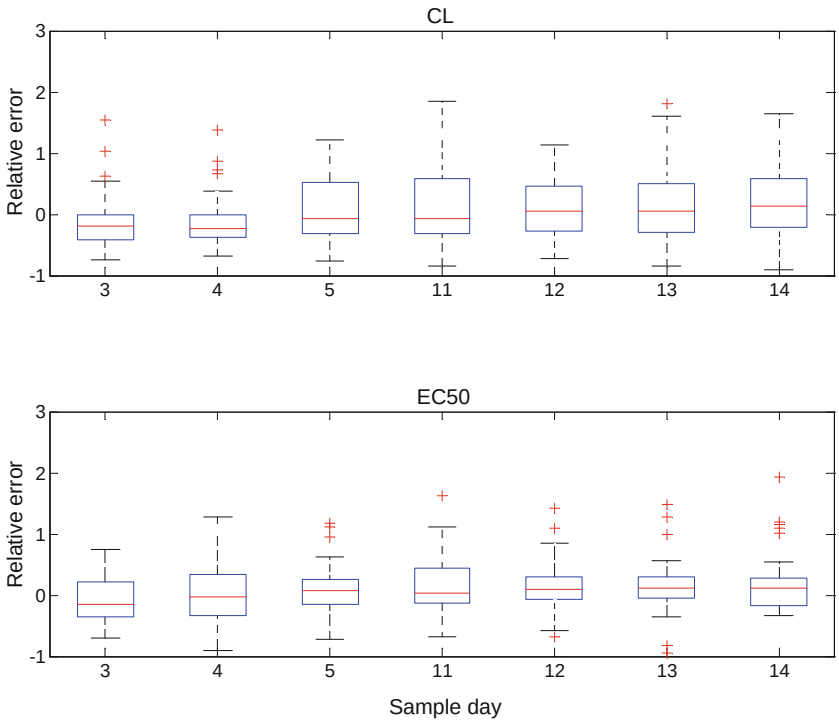

Fig. 3 Relative error for estimations of clearance and EC50 from the simulation-estimation exercise.

Future research to assess the predictive performance of the tool in warfarin patients is required.

ACKNOWLEDGMENTS

The authors wish to thank Professor Andrew McLachlan, Faculty of Pharmacy, University of Sydney, Australia, for access to the warfarin data set for external model evaluation. We thank Anna-Karin Hamberg, Faculty of Pharmacy, Uppsala University, Uppsala, Sweden, for assistance with the published KPD warfarin model. At the time of writing, Dan Wright was the recipient of a University of Otago Postgraduate Scholarship.

APPENDIX 1: THE OTAGO WARFARIN PKPD MODEL

Methods

PKPD Modelling

A warfarin PKPD model was developed using data from the O'Reilly dataset. Population PK analysis was carried out with NONMEM VI using the first-order conditional estimation with interaction (FOCEI). One- and two-compartment pharmacokinetic models with first-order absorption were fitted to the warfarin concentration data. An absorption lag

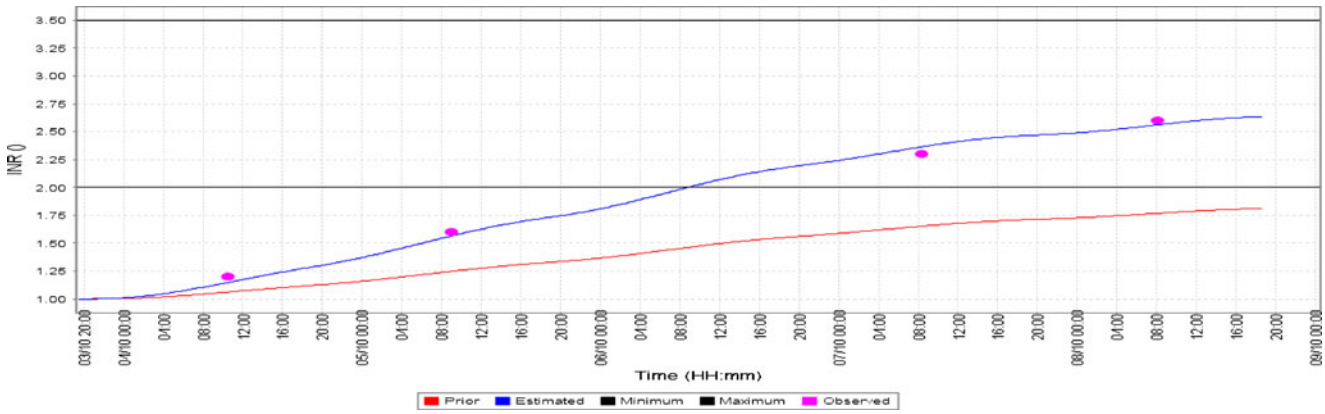

Fig. 4 Screen-shot from TCIWorks for a simulated patient with CYP2C9 *1/*1 and VKORC1 A/A genotypes. The blue (upper) line represents the estimated INR, the red (lower) line the prior predictions, and the pink dots the simulated (i.e. "real") INR values.

time (tlag) was also considered to help describe the apparent absorption delay of warfarin. Total body weight, sex and age were considered as covariates. These were retained in the model if inclusion decreased the objective function value by 3.84 or more (χ^2, $p \leq 0.05$, d.f. = 1). Model discrimination and covariate inclusion were also assessed using graphical goodness-of-fit analysis. The between-subject variability was assumed to be log-normally distributed, with a mean of zero and a variance of ω^2. Residual error was modelled using a combined additive and proportional error model.

Once the best PK model had been identified, a simultaneous PKPD model was developed. Graphical inspection of a PCA *versus* time plot overlayed on a concentration *versus* time plot suggested a considerable delay between warfarin response and dose. Therefore, only delayed effects models, such as effect compartment and inhibitory turnover (Imax) models, were considered. Candidate PKPD models were evaluated by comparison of the objective function values and by visual inspection of visual predictive checks (VPCs).

Internal and External Model Evaluation

The model was evaluated by simulating 1000 patients under the model and plotting the 10th, 50th, and 90th percentiles of the simulated PCA values. This was compared to the same percentiles from the O'Reilly dataset (VPCi) and the University of Sydney (VPCe).

Results

PKPD Modelling (The Otago Model)

Parameter and error model estimates for the final PKPD model are presented in Table III. A one-compartment pharmacokinetic model with first-order absorption and tlag provided the best fit for the data. Visual inspection of covariate plots suggested a relationship between CL, V and weight. A model for weight, standardised to 70 kg, was applied to clearance and volume. An allometric scaling function was also applied to clearance. The final model for clearance is given by

$$CL = \theta_{CL} * \left(\frac{wt}{70}\right)^{0.75} \quad (1)$$

and for volume by

$$V = \theta_V * \left(\frac{wt}{70}\right) \quad (2)$$

An inhibitory turnover model provided the best fit for the pharmacodynamic (PCA) data (see Eq. 3).

$$\frac{dPCA}{t} = (Rate_{in} * IC) - k_{out} * PCA$$
$$IC = 1 - \frac{(IMAX * C_p)}{(EC50 - C_p)} \quad (3)$$

Table III Warfarin PKPD Parameter Estimates for the final Otago Model

Parameter	Estimate	Between subject variability (CV%)
CL (L/hr)	0.135	26
V (L)	8.06	14
Ka (/hr)	1.19	73
tlag (hr)	0.814	59
Baseline PCA (%)	96.4	5.4
Imax	1.06	0.156
IC50 (mg/L)	1.49	40
Kout (/hr)	0.0491	11
Proportional error	0.00683	
Additive error (mg/L)	0.0934	
Additive error for PCA (%)	13.6	

CV coefficient of variation, *CL* clearance, *V* volume of distribution, *Ka* absorption rate constant, *tlag* absorption time lag, *PCA* prothrombin complex activity, *Imax* maximum inhibition, *IC50* concentration at 1/2 Imax, *Kout* prothrombin complex elimination rate constant

where $Rate_{in}$ is the zero-order production rate for PCA, K_{out} is PCA elimination rate constant, Imax is the maximum inhibition of PCA, Cp is the plasma concentration (of warfarin), and EC50 is warfarin plasma concentration at 1/2 Imax.

Internal and External Evaluation of the Otago Model

An internal visual predictive check (VPCi) for warfarin response compared to the O'Reilly dataset is presented in the main body of the text (Fig. 1a). The plot suggests good model performance. An external evaluation (VPCe) of the model against the Sydney dataset is presented in the main body of the text (Fig. 2a). The model appears to underpredict anticoagulant response somewhat. This is discussed further in the main body of the paper.

REFERENCES

1. The International Warfarin Pharmacogenetics Consortium. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med. 2009;360(8):753–64.
2. Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research Group. Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity. Lancet. 1994;343(8896):499–503.
3. The Stroke Prevention in Atrial Fibrillation Investigators. Bleeding during antithrombotic therapy in patients with atrial fibrillation. Arch Intern Med. 1996;156(4):409–16.
4. Jones M, McEwan P, Morgan CL, Peters JR, Goodfellow J, Currie CJ. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of treatment with warfarin in patients with non-valvar atrial fibrillation: a record linkage study in a large British population. Heart. 2005;91(4):472–7.

5. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation. 2007;115(21):2689–96.
6. Oake N, Fergusson DA, Forster AJ, van Walraven C. Frequency of adverse events in patients with poor anticoagulation: a meta-analysis. Can Med Assoc J. 2007;176(11):1589–94.
7. Oake N, Jennings A, Forster AJ, Fergusson D, Doucette S, van Walraven C. Anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: a systematic review and meta-analysis. Can Med Assoc J. 2008;179(3):235–44.
8. Tan ES, Bonnett TJ, Abdelhafiz AH. Delayed discharges due to initiation of warfarin in atrial fibrillation: a prospective audit. Am J Ger Pharmacol. 2007;5(3):232–5.
9. The Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin *versus* low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. Lancet. 1996;348(9028):633–8.
10. van Walraven C, Jennings A, Oake N, Fergusson D, Forster AJ. Effect of study setting on anticoagulation control. Chest. 2006;129 (5):1155–66.
11. Rose AJ, Ozonoff A, Berlowitz DR, Henault LE, Hylek EM. Warfarin dose management affects INR control. J Thromb Haemost. 2009;7(1):94–101.
12. Kalra L, Yu G, Perez I, Lakhani A, Donaldson N. Prospective cohort study to determine if trial efficacy of anticoagulation for stroke prevention in atrial fibrillation translates into clinical effectiveness. BMJ. 2000;320(7244):1236–9.
13. 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.
14. Wadelius M, Pirmohamed M. Pharmacogenetics of warfarin: current status and future challenges. Pharmacogenom J. 2007;7 (2):99–111.
15. McMillin GA, Melis R, Wilson A, Strong MB, Wanner NA, Vinik RG, *et al.* Gene-based warfarin dosing compared with standard of care practices in an orthopedic surgery population: a prospective, parallel cohort study. Ther Drug Monit. 2010;32(3):338–45.
16. 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. 2007;83(3):460–70.
17. Wadelius M, Chen LY, Lindh JD, Eriksson N, Ghori MJR, Bumpstead S, *et al.* The largest prospective warfarin-treated cohort supports genetic forecasting. Blood. 2009;113(4):784–92.
18. Sconce EA, Khan TI, Wynne HA, Avery P, Monkhouse L, King BP, *et al.* The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. Blood. 2005;106(7):2329–33.
19. Lenzini P, Wadelius M, Kimmel S, Anderson JL, Jorgensen AL, Pirmohamed M, *et al.* Integration of genetic, clinical, and inr data to refine warfarin dosing. Clin Pharmacol Ther. 2010;87 (5):572–8.
20. 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.
21. Sheiner LB, Beal S, Rosenberg B, Marathe VV. Forecasting individual pharmacokinetics. Clin Pharmacol Ther. 1979;26 (3):294–305.
22. Sheiner LB, Beal SL. Bayesian individualization of pharmacokinetics: simple implementation and comparison with non-Bayesian methods. J Pharm Sci. 1982;71(12):1344–8.
23. Duffull SB, Chadaud S, Nony P, Laveille C, Girard P, Aarons L. A pharmacokinetic simulation model for ivabradine in healthy volunteers. Eur J Pharm Sci. 2000;10(4):285–94.
24. O'Reilly RA, Aggeler PM, Leong LS. Studies on the coumadin anticoagulant drugs: the pharmacodynamics of warfarin in man. J Clin Invest. 1963;42:1542–51.
25. O'Reilly RA, Aggeler PM. Studies on coumarin anticoagulant drugs. Initiation of warfarin therapy without a loading dose. Circulation. 1968;38(1):169–77.
26. Mohammed Abdul M, Jiang X, Williams K, Day R, Roufogalis B, Liauw W, *et al.* Pharmacodynamic interaction of warfarin with cranberry but not with garlic in healthy subjects. Br J Pharmacol. 2008;154:1691–700.
27. Jiang XM, Blair EYL, McLachlan AJ. Investigation of the effects of herbal medicines on warfarin response in healthy subjects: a population pharmacokinetic-pharmacodynamic modeling approach. J Clin Pharmacol. 2006;46(11):1370–8.
28. Hamberg AK, Wadelius M, Lindh JD, Dahl ML, Padrini R, Deloukas P, *et al.* A pharmacometric model describing the relationship between warfarin dose and INR response with respect to variations in CYP2C9, VKORC1, and age. Clin Pharmacol Ther. 2010;87(6):727–34.
29. Jacqmin P, Snoeck E, van Schaick E, Gieschke R, Pillai P, Steimer J, *et al.* Modellling response time profile in the absence of drug concentrations: definition and performance evaluation of the K-PD model. J Pharmacokinet Pharmacodyn. 2007;34 (1):57–85.
30. Duffull SB, Retout S, Mentre F. The use of simulated annealing for finding optimal population designs. Comput Methods Programs Biomed. 2002;69(1):25–35.
31. Holford NH. Target concentration intervention: beyond Y2K. Br J Clin Pharmacol. 2001;52 Suppl 1:55S–9.
32. Sheiner LB. Computer-aided long-term anticoagulation therapy. Comput Biomed Res. 1969;2(6):507–18.
33. Nagashima R, O'Reilly RA, Levy G. Kinetics of pharmacologic effects in man: the anticoagulant action of warfarin. Clin Pharmacol Ther. 1969;10(1):22–35.
34. Theofanous TG, Barile RG. Multiple-dose kinetics of oral anticoagulants: methods of analysis and optimized dosing. J Pharm Sci. 1973;62(2):261–6.
35. Wiegman H, Vossepoel AM. A computer program for long term anticoagulation control. Comput Programs Biomed. 1977;7 (2):71–84.
36. Wingard Jr LB, O'Reilly RA, Levy G. Pharmacokinetics of warfarin enantiomers: a search for intrasubject correlations. Clin Pharmacol Ther. 1978;23(2):212–7.
37. Svec JM, Coleman RW, Mungall DR, Ludden TM. Bayesian pharmacokinetic/pharmacodynamic forecasting of prothrombin response to warfarin therapy: preliminary evaluation. Ther Drug Monit. 1985;7(2):174–80.
38. Murray B, Coleman R, McWaters D, Ludden T, Mungall D. Pharmacodynamics of warfarin at steady state. Ther Drug Monit. 1987;9(1):1–5.
39. Powers WF, Abbrecht PH, Covell DG. Systems and microcomputer approach to anticoagulant therapy. IEEE Trans Biomed Eng. 1980;27(9):520–3.
40. Vadher B, Patterson DLH, Leaning M. Prediction of the international normalized ratio and maintenance dose during the initiation of warfarin therapy. Br J Clin Pharmacol. 1999;48(1):63–70.
41. Abbrecht PH, O'Leary TJ, Behrendt DM. Evaluation of a computer-assisted method for individualized anticoagulation: retrospective and prospective studies with a pharmacodynamic model. Clin Pharmacol Ther. 1982;32(1):129–36.
42. Chan E, O'Reilly R, Rowland M. Stereochemical aspects of warfarin in man: a combined pharmacokinetic-pharmacodynamic model. Br J Clin Pharmacol. 1984;19:545P.

43. Holford NH. Rational warfarin dosing: a pharmacokinetic-pharmacodynamic analysis. Clin Pharmacol Ther [abstract]. 1986;39:199.
44. Yuen E, Gueorguieva I, Wise S, Soon D, Aarons L. Ethnic differences in the population pharmacokinetics and pharmacodynamics of warfarin. J Pharmacokinet Pharmacodyn. 2010;37(1):3–24.
45. Hamberg AK, Dahl ML, Barban M, Scordo MG, Wadelius M, Pengo V, *et al.* A PK-PD model for predicting the impact of age, CYP2C9, and VKORC1 genotype on individualization of warfarin therapy. Clin Pharmacol Ther. 2007;81(4):529–38.
46. Pitsiu M, Parker EM, Aarons L, Rowland M. A Bayesian method based on clotting factor activity for the prediction of maintenance warfarin dosage regimens. Ther Drug Monit. 2003;25(1):36–40.
47. Manotti C, Moia M, Palareti G, Pengo V, Ria L, Dettori AG. Effect of computer-aided management on the quality of treatment in anticoagulated patients: a prospective, randomized, multicenter trial of APROAT (Automated PRogram for Oral Anticoagulant Treatment). Haematologica. 2001;86(10):1060–70.
48. Poller L, Shiach CR, MacCallum PK, Johansen AM, Munster AM, Magalhaes A, *et al.* Multicentre randomised study of computerised anticoagulant dosage. Lancet. 1998;352(9139):1505–9.
49. Ryan PJ, Gilbert M, Rose PE. Computer control of anticoagulant dose for therapeutic management. Br Med J. 1989;299 (6709):1207–9.
50. Roberts GW, Helboe T, Nielsen CBM, Gallus AS, Jensen I, Cosh DG, *et al.* Assessment of an age-adjusted warfarin initiation protocol. Ann Pharmacother. 2003;37(6):799–803.
51. Lee J, Lin T. Warfdocs for web version 1.0 Copyright © 2006 Regents of the University of California; 2006 [cited 2010 July 5 2010]; [website]]. Available from: warfdocs.ucdavis.edu.
52. Hamberg AK, Wadelius M, Pirmohamed M, Jonsson EN. Internal and external evaluation of a pharmacometric model for warfarin using prediction corrected visual predicitive check (PC-VPC). Population Approach Group Europe. Nineteenth meeting June 8–11 2010. http://www.page-meeting.org/pdf_assets/2122-Poster_PAGE2010_published.pdf; Berlin, Germany2010.
53. Pitsiu M, Parker EM, Aarons L, Rowland M. Population pharmacokinetics and pharmacodynamics of warfarin in healthy-young adults. Eur J Pharm Sci. 1993;1(3):151–7.
54. Horsti J, Uppa H, Vilpo JA. Poor agreement among prothrombin time international normalized ratio methods: comparison of seven commercial reagents. Clin Chem. 2005; 51(3):553–60.