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Title: Report on predictions from first models

WP N° and Title: **WP9 – A next step into the future: Systems pharmacology and gene-drug-drug interactions**
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Comment: The work was initiated but not completely finalised at month 18. The delay has no consequence for the proceeding of the project.

Introduction

The main goal of the U-PGx consortium is to investigate, in a clinical study, a pre-emptive genotyping approach of a panel of important pharmacogenomic (PGx) variants as a new model of personalised medicine. The PGx variants and drugs to be studied are based on the Dutch Pharmacogenetics Working Group (DPWG) PGx-based therapeutic treatment recommendations.

The aim of WP9 is a next step into the future to improve the existing DPWG PGx guidelines by integrating knowledge of non-genetic factors based on a systems pharmacology approach. The two first objectives of WP9 are:

- 9.1: To develop pharmacometric models integrating PGx information with other sources of variability to predict expected effect for genetic variant groups on various outcomes.

- 9.2: To identify clinically relevant drug-drug interactions (DDI) as potential major confounder in the interventional pre-emptive U-PGx-trial.

In meeting these two objectives, one focus is the utilization of pharmacometric and systems pharmacology models for interpretation of the influence of PGx and non-genetic (e.g. demographics, interacting drugs, food intake etc.) factors on drug plasma concentrations as well as on biomarkers/clinical endpoints for safety and efficacy.

Deliverable D9.1 reported on the models that have been identified for potential further development. **The purpose of this deliverable** is to report on predictions from the first models developed, and includes description of development of and resulting predictions from one project (II) and description of another project not yet finalised (I):

- Project I) an irinotecan model
- Project II) a dabigatran model, which is a showcase illustrating the potential usage of the models

The research groups collaborating in WP9 are: i) Pharmacometrics Group, Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; ii) Clinical Pharmacy, Saarland University, Saarbrücken, Germany; iii) Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany/Department of Clinical Pharmacology, Institute of Experimental and Clinical Pharmacology and Toxicology, University Hospital, Tuebingen, Germany.

Project I: Irinotecan model

Background

Irinotecan is used in the treatment of various types of cancer, such as colon cancer and small cell lung cancer, usually in combination with other chemotherapy. Irinotecan is available as a solution for infusion and as concentrate for infusion solution in a liposomal formulation, and is delivered by intravenous infusion, typically over a period of 30 to 90 minutes. The normal dose in monotherapy is 350 mg/m^2, but varies with clinical indication and whether it is used in combination with other drugs.

Irinotecan is metabolized by carboxylesterase to its active metabolite SN-38, which in turn is conjugated by uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism (1, 2)**.** Irinotecan and SN-38 bind reversibly to the topoisomerase I-DNA complex, thereby inducing single-strand DNA lesions, which block the DNA replication fork and are responsible for the cytotoxicity. SN-38 is approximately 100 to 1000 times as potent as irinotecan (3).

Common side effects include diarrhoea, vomiting, bone marrow suppression, hair loss, shortness of breath, and fever, whereof neutropenia and delayed diarrhoea are the major and dose limiting adverse events (4). A reduction in the glucuronidation rate has been associated with irinotecan toxicity, and a prospective study showed that frequency of grade 4 neutropenia was statistically significantly higher I subject being UGT1A*28 homozygotes compared with UGT1A1*1 (5, 6).

Several population pharmacokinetic (PK) and exposure-response (ER) models for irinotecan and SN-38 are published. These models can be used to illustrate the influence of the PGx and non-genetic factors on safety endpoints.

Objectives

To perform simulations illustrating the influence of the PGx and non-genetic factors on two safety endpoints: myelosuppression and diarrhoea.

Methods

Population pharmacokinetic and exposure-response models

Two population PK models were selected to be used for the simulation of systemic exposure of irinotecan and SN-38, whereof one contained a PGx predictor (UGT1A1 polymorphism) for clearance of SN-38 (7, 8). For the simulation of longitudinal changes in neutrophil and leucocyte counts following irinotecan dosing, an ER model, developed by Friberg et al., was employed (9). The probability of a diarrhoea event and its severity as a function of irinotecan or SN-38 systemic exposure has been described by Xie et al (8), and this model was utilized for the simulations.

Model predictions

Model predictions will be performed following deterministic simulations (no variability included) for specific typical patients. Furthermore, stochastic simulations will be performed, putting emphasis on certain worst case scenarios and to illustrate the importance of PGx variability in comparison with overall explained and unexplained variability.

Results

To be reported in later deliverable.

Project II: Dabigatran project

Background

Dabigatran etexilate is an orally given prodrug and a potent, direct and competitive inhibitor of thrombin. It is sold under the brand name Pradaxa® and used in the prevention of strokes and systemic embolisms in patients without any heart valve issues. The drug is available as capsules with 75 mg, 110 mg and 150 mg dabigatran etexilate and typically dosed two times a day for stroke prevention. After absorption dabigatran etexilate is rapidly converted by different serum esterases into the active dabigatran (10) and afterwards mainly cleared primarily by kidney.

Dabigatran's PK features are influenced by polymorphisms concerning carboxylesterase 1 (CES1) as well as P-glycoprotein (Pgp), the latter effect due to that dabigatran etexilate is a Pgp substrate. Thus, Pgp inhibitors like verapamil or amiodarone can alter the systemic exposure of dabigatran.

Overall, dabigatran's PK and ER, including relevant drug-gene interactions (DGI) due to CES1 and Pgp polymorphisms as well as potential DDIs due to concomitant use of other drugs, has been extensively investigated (11-17). Also, several models are developed describing different aspects of dabigatran's ER or clinical outcome (11-13, 16). For this reason, although dabigatran is not included in the PREPARE sub-study, it fits perfectly as an illustrative example of how pharmacokinetic knowledge can be used to predict possible worst-case scenarios and overcome dosing regimen issues.

Currently, no functional tool is available, which holds the capability to deliver all clinical relevant information in one engine. Furthermore, the mentioned models have complex structures and require special scientific and software skills to derive reasonable conclusions. Hence, there is currently no readily available way to use the models for calculating overall benefit-risk in a convenient and user-friendly way.

Objectives

For the above stated reasons, the following objectives evolved for project II:

- First, to develop a dabigatran ER online simulator, which combines the scope of in literature described dabigatran models with a user-friendly handling.

- Second, to implement a reproducible and easy-to-use documentation system for the ER online simulator.
- Third, to perform simulations illustrating the possibilities of the combined dabigatran ER online simulator.

Methods

Model parameters

All model parameters used for this project were extracted from literature. They were estimated based on analysis of the pivotal RE-LY trial (10) and various other clinical studies. As already stated, several relevant DGIs and DDIs concerning dabigatran are already described quantitatively (11, 12). Besides, covariate effects on dabigatran's PK due to demographic characteristics [2] has been investigated. Furthermore, with respect to ER, activated partial thromboplastin time (aPPT) as a biomarker (13) and patient's risk for having a major bleeding event or an ischemic stroke based on observed dabigatran plasma concentration trough values (16) are accessible through literature.

Dabigatran's PK is best described by a two compartment model with first-order absorption and elimination. Covariate effects and inter-individual variability (IIV) are included in the pharmacokinetic and aPPT models. Further information regarding the model structure, development and model evaluation can be found in the literature (11-13, 16, 18).

The net clinical benefit (NCB) can be calculated based on the risks for a major bleeding event and an ischemic stroke (18). Hence, minimizing NCB corresponds to a higher clinical benefit and thus, was used for a dose optimization procedure. For NCB calculation the risk for having an ischemic stroke event was weighted twice as high as having a major bleeding event.

Dabigatran exposure response online simulator development

For the online tool development, the R-Shiny environment was used (19). The R-Shiny environment enables statisticians and pharmacometricians to make their developed models easily deployable. For this purpose, models have to be re-coded in the R-Shiny language, which thereafter can be compiled to a platform independent html-page. Furthermore, interactive and responsible elements can be placed on the html-page, which gives clinicians the opportunity to simulate different therapy scenarios within minutes. Besides, report functionalities can be implemented to make a user controlled documentation possible.

The dabigatran ER online simulator was developed in a three-step approach. In a first step, all drug relevant structural models and model parameters were extracted from literature. In a second step, this information was re-coded in the R-Shiny environment. Finally, reasonable and responsive elements were added in a top-down approach. Thereby, a basic template-layout was developed.

Once this was accomplished, clinicians tested the beta-version and described further claims with regard to an ER online simulator for dabigatran. The described demands and

functionalities were implemented and subsequently re-evaluated. Model parameters included in the online dabigatran ER simulator were not further evaluated, given that information was extracted from published literature, as mentioned above.

Model simulations

With regard to covariate effects on dabigatran described in literature, countless combined scenarios are conceivable and could be simulated with the dabigatran ER online simulator (see Table 1 and Table 2 for overview of the covariates affecting PK or ER features). For this reason, only selected illustrative simulations were made, including investigating the effects of DDIs and DGIs on steady state systemic exposure, aPPT, risk for having a major bleeding or ischemic stroke event and NCB. The risk and NCB calculations were based on the simulated median dabigatran steady state plasma concentration-time trough value. Furthermore, a reference and two multivariate worst case scenarios were simulated and analysed. Differences between the reference and the worst case scenarios are summarized in Table 1. Also, calculations on the recommended dose adaption due to minimizing the NCB were performed.

DDI and DGI effects were analysed in a univariate way.

Finally, all covariate effects were compared to the results of the reference scenario simulation.

All simulations were performed with the statistical software R (V 3.4.2) embedded in RStudio (V 1.0.143). Model simulations were performed to simulate 1000 individuals for calculating the 90% confidence intervals and median values.

Table 1 Input parameter comparison for reference scenario and both worst case scenarios. Differences are marked with a red and bold text font.

Parameter	Reference Values	Worst Case Scenario I Values	Worst Case Scenario II Values
Demographics			
Age	65	**72**	**85**
Sex	Male	**Female**	Male
Body Weight [kg]	80	**90**	**120**
Ethnicity	Caucasian	Caucasian	**Asian**
Creatinine Clearance [ml/min]	83	**40**	**60**
Haemoglobin Value [dL/g]	10	10	10
Co-Medication			
Amiodarone Comedication	False	False	**True**
Aspirin Comedication	False	False	**True**
Clopidogrel Comedication	False	**True**	False
Proton-Pump Inhibitor Comedication	False	False	**True**
Verapamil Comedication	False	**True**	False
Medical History			
Atrial Fibrillation	False	False	**True**
Coronary Artery Disease at Baseline	False	False	False
Diabetes Mellitus at Baseline	False	False	**True**
Heart Failure Classes II+III+IV	False	False	**True**
Prior Stroke	False	**True**	False
Pharmacogenetics			
ABCB1 SNP *rs4148738* (C>T)	Major Allele Homozygote	Major Allele Homozygote	**Minor Allele Homozygote**
CES1 SNP *rs2244613* (G>T)	Major Allele Homozygote	**Minor Allele Homozygote**	Major Allele Homozygote
CES1 SNP *rs8192935* (null>G)	Major Allele Homozygote	**Minor Allele Homozygote**	Major Allele Homozygote
Other			
Weighting Factor for Ischemic Stroke	2	2	2
Weighting Factor for Major Bleeding	1	1	1

Results

Dabigatran exposure response online simulator layout

The online dabigatran ER simulator is accessible
via www.dabigatran.modelingsimulation.de.

The final online tool layout consists of four main pages. The first page introduces the user as a "welcome" page in how to use the simulator. Page two and three are for "simulation" itself and "advanced settings", respectively. The last page was required as a legal notice disclaimer.

The simulation page consists of two separated parts. On the left side the user can specify all pharmacokinetic relevant parameters for two among themselves comparable patients. On the right side, the simulation results are displayed after pushing the button "start simulation". A list of all changeable input parameters included in the simulator and thereby influenced model parameters are listed in Table 2. Of particular interest are the integrated DDI and DGI partners including proton-pump-inhibitors, amiodarone, verapamil, aspirin and clopidogrel as potential hazardous comedications and CES1 SNP *rs2244613,* CES1 SNP *rs8192935* and ABCB1 SNP *rs4148738* as potentially problematic polymorphisms. Furthermore, the user is able to specify two more calculation options in the advanced settings page, where he can change the weight factors used in the NCB calculation.

Besides, a comment function enables the user to collect personal notes which will be transferred into the dynamic report together with all simulation results. This report can be exported *via* the "generate report" button and is accessible in three different formats pdf, html and word.

Simulation outputs displayed as in the report are exemplified in Figure 1 to Figure 5.

Table 2 Input parameters and thereby influenced model parameters.

Input parameter	Influenced model parameter
Demographics	
Age	• Clearance • Risk for having a major bleeding event • Risk for having an ischemic stroke event
Sex	• Clearance • Risk for having a major bleeding event
Body Weight [kg]	• Volume of distribution
Ethnicity	• Clearance
Creatinine Clearance [ml/min]	• Clearance
Haemoglobin Value [dL/g]	• Volume of distribution
Co-Medication	
Amiodarone Comedication	• Bioavailability
Aspirin Comedication	• Risk for having a major bleeding event
Clopidogrel Comedication	• Risk for having a major bleeding event
Proton-Pump Inhibitor Comedication	• Bioavailability
Verapamil Comedication	• Bioavailability
Medical History	
Atrial Fibrillation	• Activated partial thromboplastin time
Coronary Artery Disease at Baseline	• Risk for having a major bleeding event
Diabetes Mellitus at Baseline	• Risk for having a major bleeding event • Risk for having an ischemic stroke event
Heart Failure Classes II+III+IV	• Clearance • Activated partial thromboplastin time
Prior Stroke	• Risk for having an ischemic stroke event
Pharmacogenetics	
ABCB1 SNP *rs4148738* (C>T)	• Bioavailability
CES1 SNP *rs2244613* (G>T)	• Bioavailability
CES1 SNP *rs8192935* (null>G)	• Bioavailability
Other	
Factor 1 on Bioavailability	• Bioavailability
Factor 2 on Bioavailability	• Bioavailability
Factor Ischemic Stroke	• Net clinical benefit
Factor Major Bleeding	• Net clinical benefit

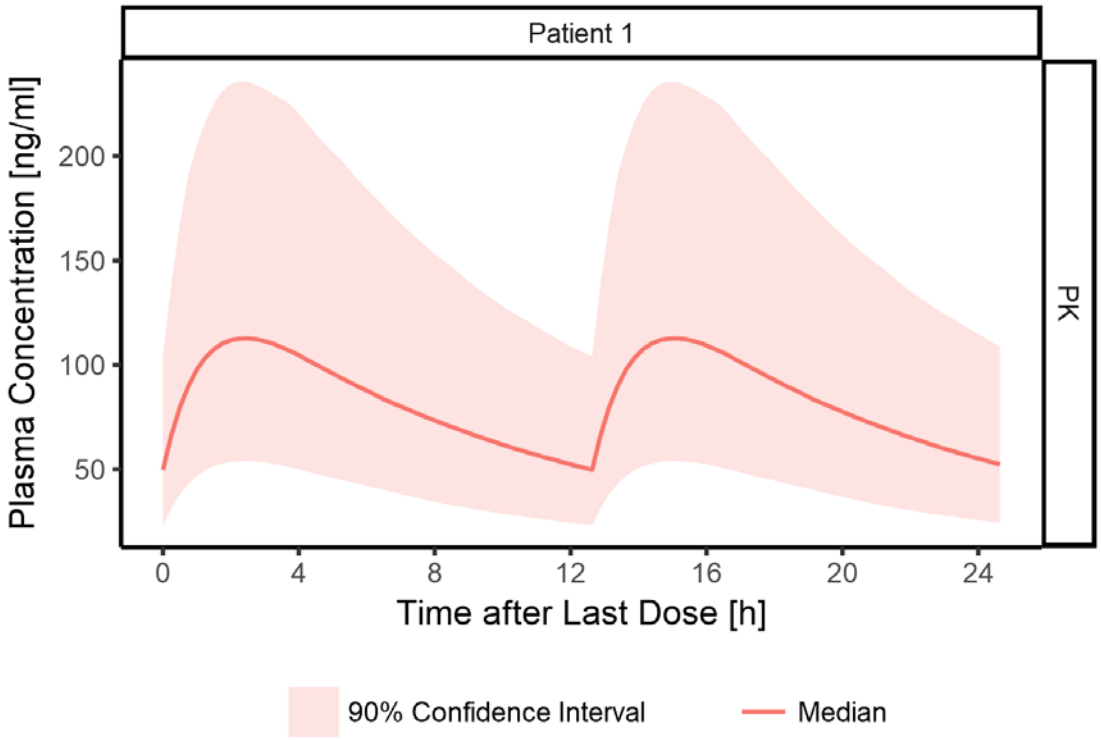

Figure 1 Dabigatran steady-state plasma concentration for the reference scenario and a given dose of 110 mg dabigatran etexilate.

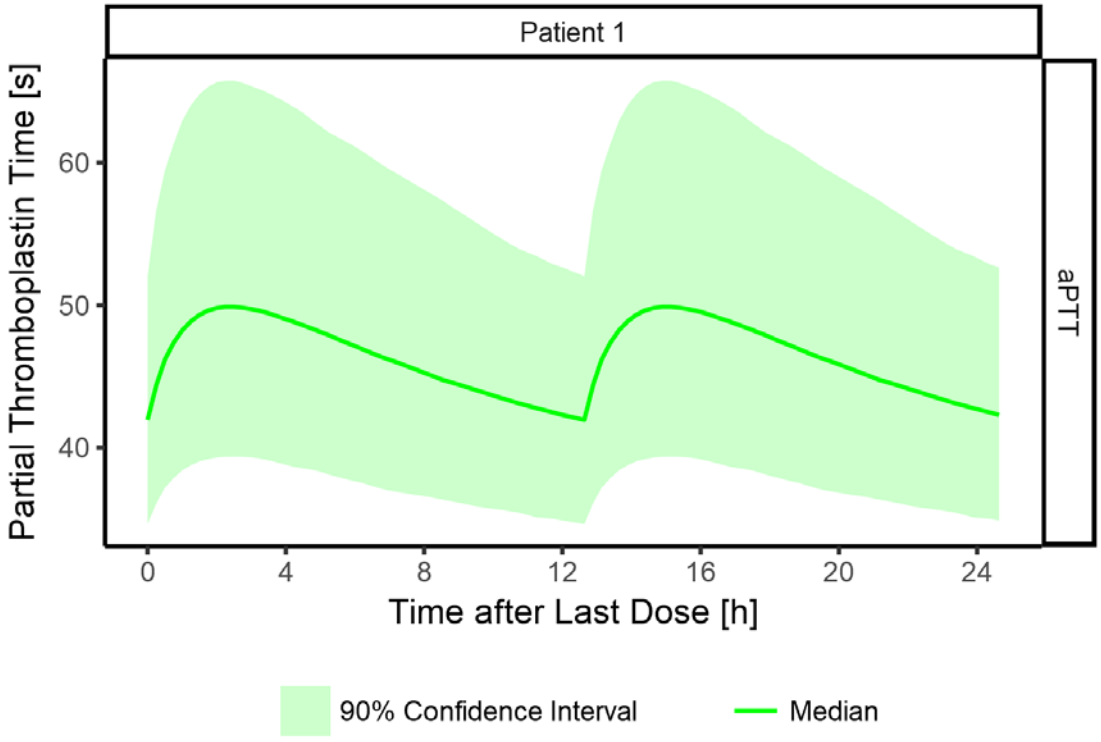

Figure 2 Dabigatran aPPT biomarker response for the reference scenario and a given dose of 110 mg dabigatran etexilate.

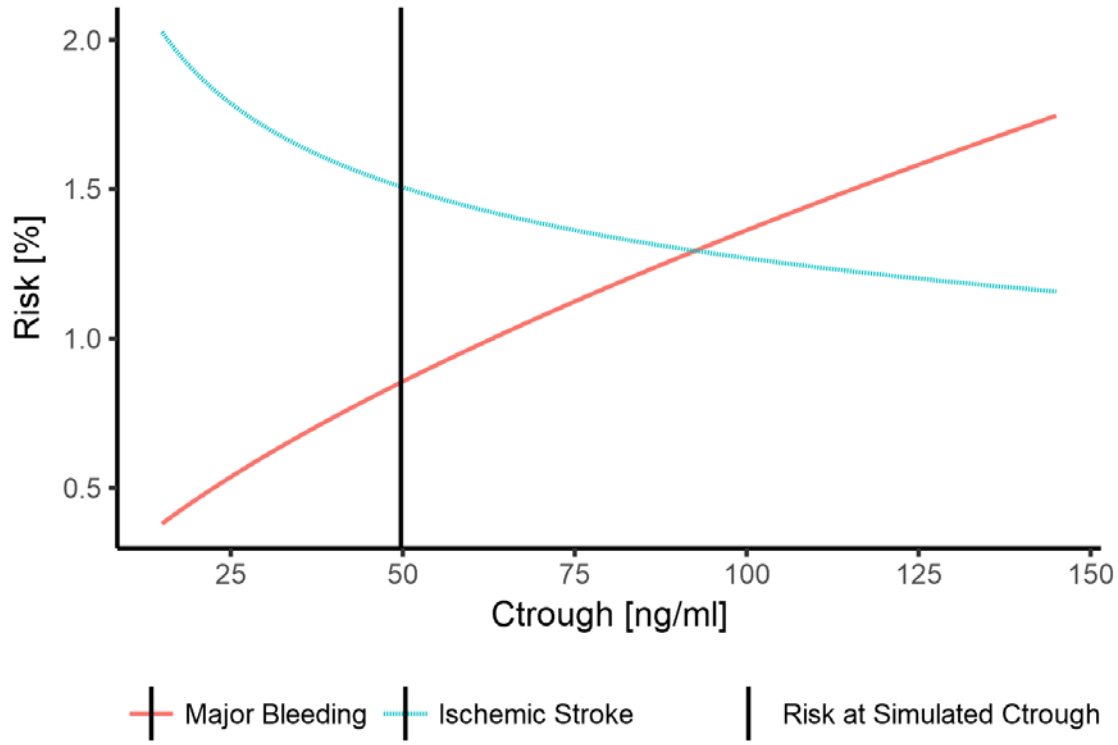

Figure 3 Risk of having a major bleeding event or an ischemic stroke event for versus dabigatran plasma concentration trough values.

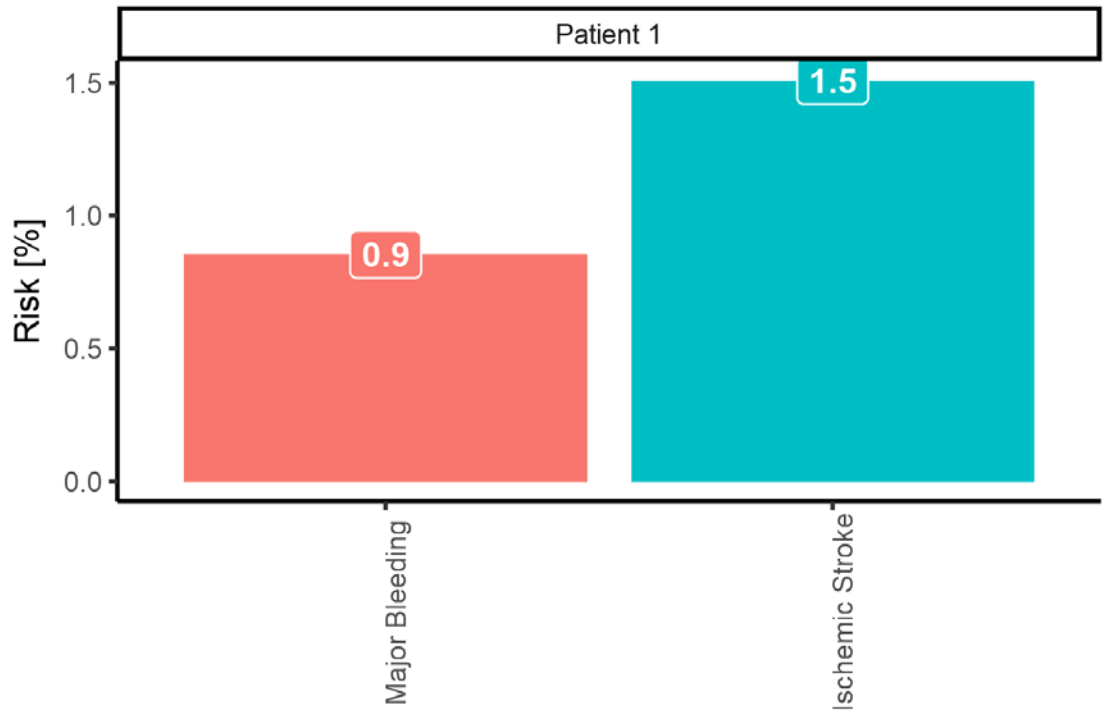

Figure 4 Risk of having a major bleeding event or an ischemic stroke event for the reference scenario and a given dose of 110 mg dabigatran etexilate.

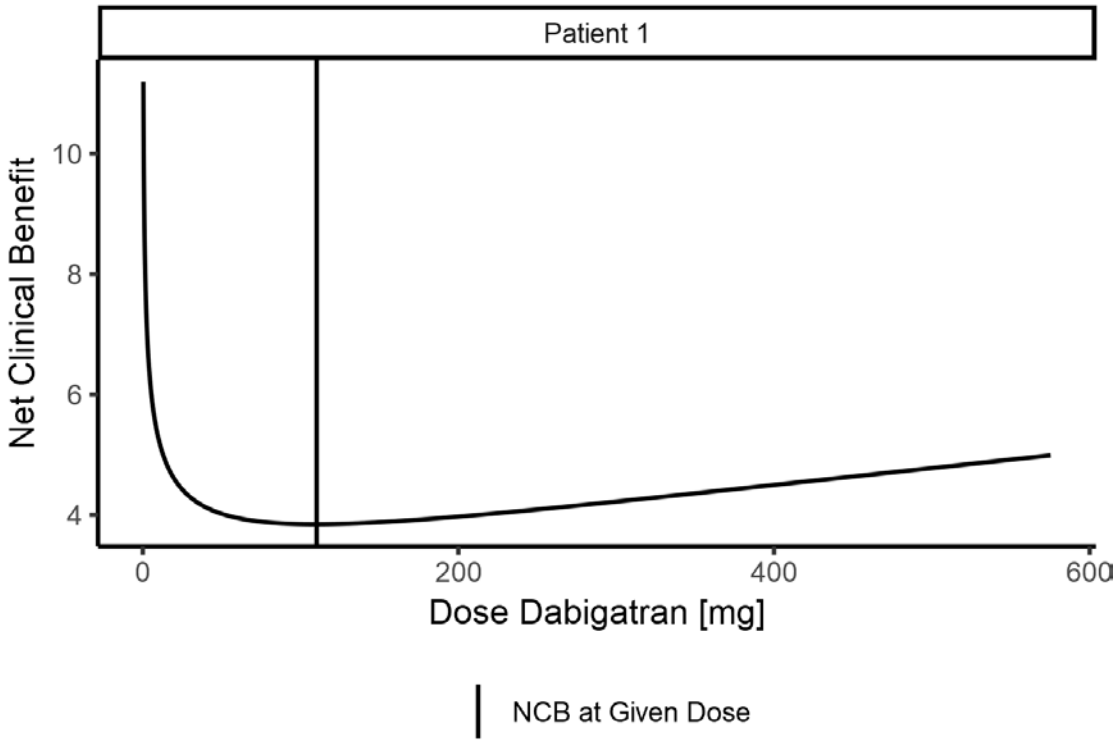

Figure 5 NCB for the reference scenario with regard to different dabigatran doses.

Model simulations

Overall, users of the final dabigatran ER simulator are capable to simulate over 300 categorical covariate combination effects and countless possible continuous covariate effects. Hence, as mentioned before, only a limited number of simulations including a reference scenario, univariate DDI and DGI effects and multivariate two worst case scenarios were performed. The reference scenario outputs are summarized in Table 3.

Table 3 Parameter outputs for the reference scenario.

Parameter	P5	Median	P95
Ctrough [ng/ml]	23.770	49.005	105.397
aPPT at Ctrough [s]	34.740	41.992	53.014
Risk Major Bleeding [%]	-	0.845	-
Risk Ischemic Stroke [%]	-	1.514	-
NCB	-	3.872	-
Optimal Dose [mg]	-	110.000	-

Univariate impact of DGI and DDI on model simulations

DDI and DGI effect results are visualized in Figure 6.

Univariate comparison of possible DGIs revealed that ABCB1 SNP *rs4148738* has the strongest effect on dabigatran's steady state plasma trough concentration (+25%), aPPT (+4%) and risk of having a major bleeding event (16%). Risk of having an ischemic stroke event is equally (5%) decreased and increased by CES1 SNP *rs8192935* and ABCB1 SNP

rs4148738, respectively. NCB changes for all DGIs +/- |1%|. Furthermore, for all DGIs the recommended dose adaption compared to reference is≤ |1%|.

Comparison of the simulated DDI effects reveals that dabigatran steady state plasma trough concentration, aPPT and risk for having an ischemic stroke is most significantly changed by verapamil comedication (+21%, +4% and -5% respectively). Although, clopidogrel has the strongest effect on the risk for having a major bleeding event (+58%), NCB is equally increased by clopidogrel and aspirin (+12%). Furthermore, dose adaptions under aspirin or clopidogrel comedication recommend a 39% reduction for aspirin and 38% dose reduction for clopidogrel.

Multivariate impact of two different worst case scenarios on model simulations

Both worst case scenarios effect results are shown in Figure 7.
Worst case scenario I reflects an elderly, female patient with prior stroke, severe reduced creatinine clearance, on concomitant clopidogrel and verapamil treatment and being homozygote for the minor allele for both CES1 polymorphisms (Table 1). This resulted in increased dabigatran's steady state plasma trough concentration by 174%, aPPT by 24%, risk of having a major bleeding event by 517%, risk of having an ischemic stroke by 64% and the NCB by 163%. Hence, a dose reduction by 73% would be recommended. Worst case scenario II described an elderly, Asian patient with atrial fibrillation, diabetes mellitus and heart failure, a moderate reduced creatinine clearance on concomitant amiodarone, aspirin and proton-pump inhibitor treatment and being homozygote for the minor allele for Pgp polymorphism (Table 1). This scenario influenced all model results even stronger than scenario I. Hereby, dabigatran's steady state plasma trough concentration was increased by 269%, aPPT by 44%, risk for having a major bleeding event by 1428%, risk for having an ischemic stroke by 51% and the NCB by 351%. For worst case scenarios II the recommended dose reduction was 89%.

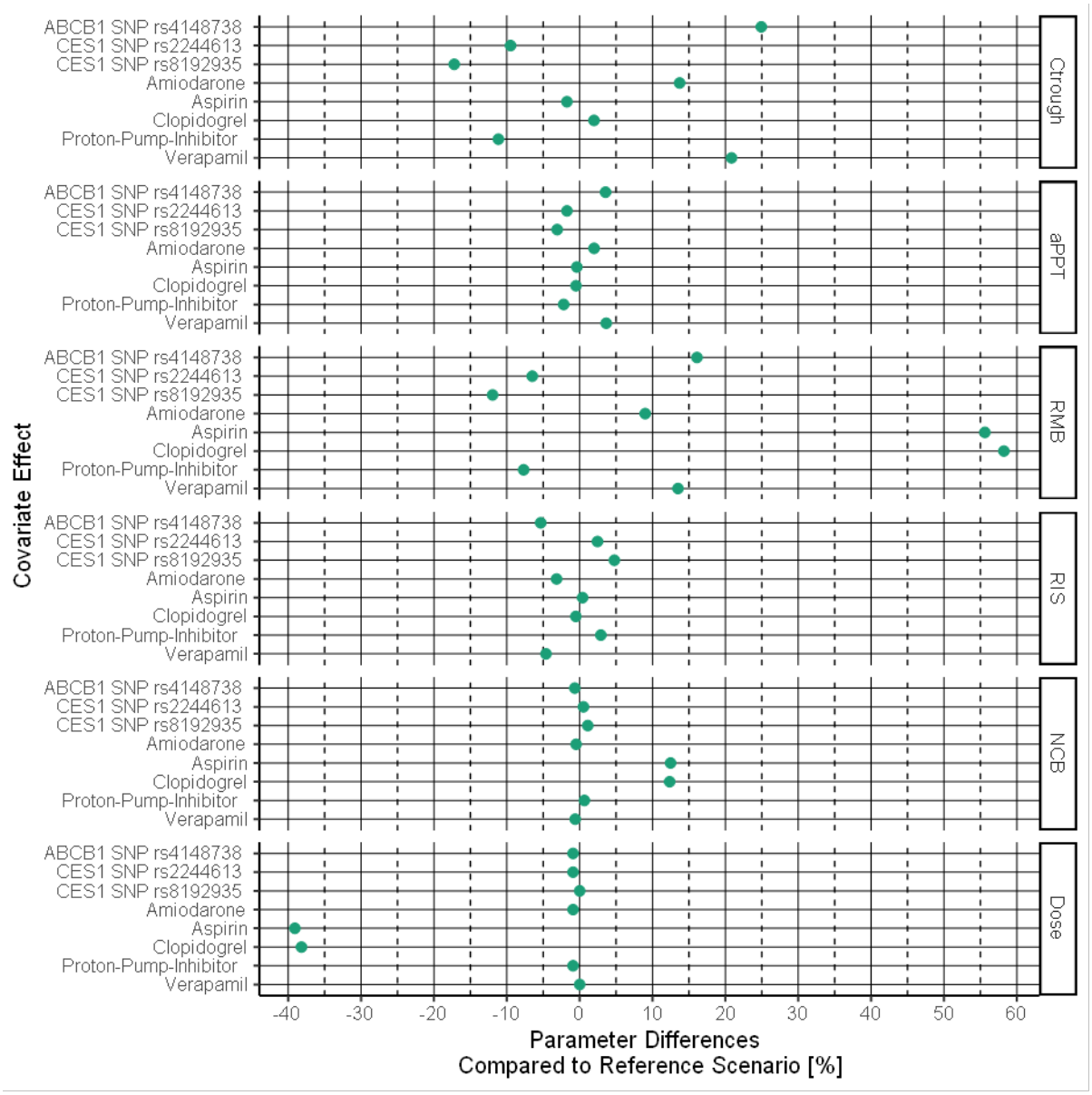

Figure 6 Comparison of univariate DGI and DDI covariate effects on plasma through concentration (Ctrough), partial thromboplastin time at Ctrough (aPPT), risk of having a major bleeding event (RMB), risk of having an ischemic stroke event (RIS), net clinical benefit (NCB) and recommended dose adaption compared to reference scenario simulation.

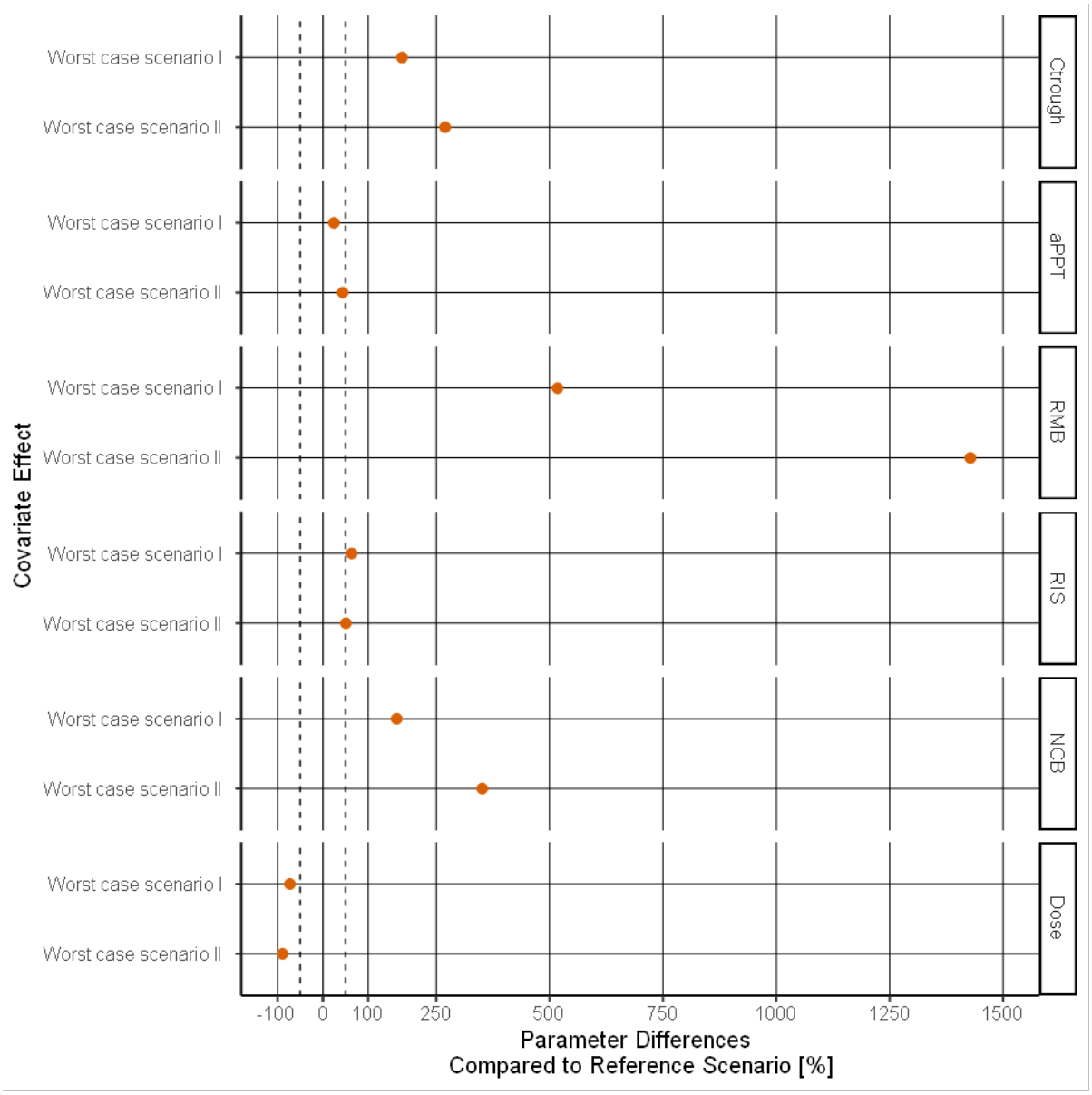

Figure 7 Comparison of multivariate two worst case scenario effects on plasma through concentration (Ctrough), partial thromboplastin time at Ctrough (aPPT), risk of having a major bleeding event (RMB), risk of having an ischemic stroke event (RIS), net clinical benefit (NCB) and recommended dose adaption compared to reference scenario simulation.

Discussion

The newly developed dabigatran ER online simulator enables clinicians to predict and compare dabigatran's ER behaviour based on individual patient's characteristics. The information utilized by the simulator are dosing information, demographics, medical history, comedication and patient's pharmacogenetics. Simulation results include dabigatran plasma concentration-time profiles, aPPT as a biomarker response, risks of having a major bleeding event or an ischemic stroke event, the NCB and last but not least an adapted optimal dose. Therefore, it holds the capability for a truly individualized pharmacotherapy including patient-related knowledge about DDIs, DGIs and a several other relevant covariates. Hence, the dabigatran ER simulator can help to reduce the risk of having a major bleeding event or an ischemic stroke dramatically, by using an optimized dose for each patient. On the other hand, the realisation of dose optimization for dabigatran is limited r, since dabigatran is currently only available as undividable capsules of 75 mg, 110 mg or 150 mg. However, a conceivable approach to enable dose individualisation would be development of a liquid formulation. Also, a changed dose regimen would be a possible way to adapt dabigatran's exposure and to enhance the clinical outcome. Nevertheless, it has to be noted that the benefit of such dose optimizations is still not validated for dabigatran. Hence, further clinical studies have to be performed to investigate the influence of using dose optimization tools like the newly developed dabigatran ER online simulator. At the moment, dose adaptions apart the licensed doses always result in an off label use and are thus, not recommended. Besides, further model improvements are conceivable including dabigatran clearance under dialysis and individual estimated pharmacokinetic parameters based on patient's dabigatran plasma concentration samples. Both would enhance the models scope and would make it more valuable for the usage in a real live clinical setting.

Nevertheless, the developed dabigatran ER online simulator is a unique showcase on how ER knowledge can be used to find the patient's best dose and to individualize pharmacotherapy.

Conclusion

A dabigatran ER online simulator was successfully developed, which holds the capability to predict the patient's individual therapy outcome and outputs an optimized dose recommendation in a convenient and user-friendly way. Although the usage in clinical practice has to be further evaluated it serves as an excellent example how pharmacotherapy could be improved by pharmacometric modelling.

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