Optimizing imatinib dosing in pulmonary arterial hypertension: a repeated time-to-event modeling approach to assess tolerability

M.M. Said[1,2,✉], R.B. de Mooij[1], J. Delgado San Martin[3], A.M.K. Rothman[4], S. Villar[5,6], J. Aman[7,8], EL.. Swart[1,2,9], R.A.A. Mathot[1], M.R. Wilkins[3], I.H. Bartelink[1,2]

Background

- Imatinib, a tyrosine kinase inhibitor, has been associated with severe adverse events and high rates of drug discontinuation in patients with pulmonary arterial hypertension (PAH). [1]
- Nasal spray study: no efficacy. [2] Oral still of interest but handling tolerance remains the main barrier.
- In the PIPAH study [3], patients received imatinib, with dosing guided by an adaptive Continuous Reassessment Method (CRM) design. Patients were treated with daily doses ranging from 100 to 400 mg over a 6-month period.

Aim

To characterize the relationship between imatinib exposure and adverse events in PAH patients by using a repeated time-to-event model to predict the risk and timing of adverse drug events

Results

- The log-logistic hazard function demonstrated the best predictive performance among the evaluated models.

$$h(t) = \frac{\lambda\gamma(\lambda t)^{\gamma-1}}{(1 + \lambda t^{\gamma})}$$

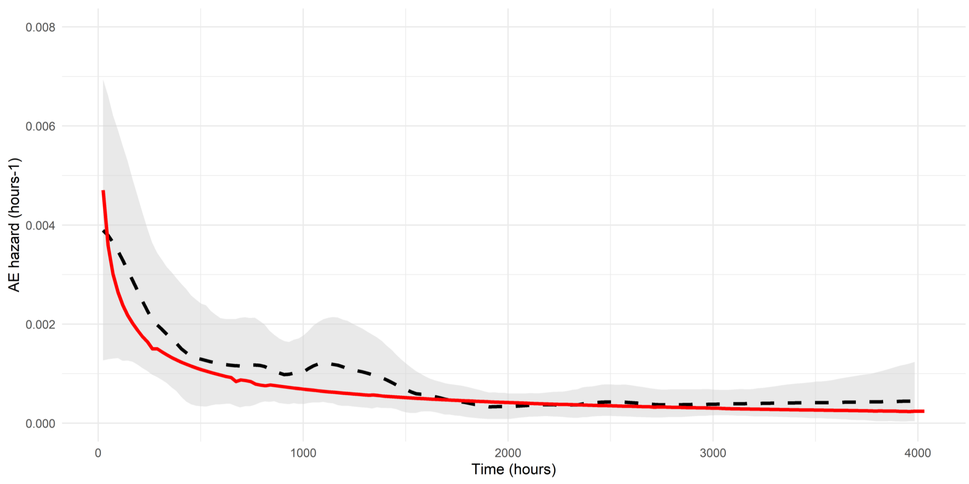


Figure 2. kbVHC of final model

- A sigmoid Emax covariate effect model with fixed Emax of 1 provided the most accurate hazard prediction.
- The model accurately predicted the time to the first adverse event; however, predictive accuracy decreased significantly for subsequent events, where the survival was underpredicted.

Parameter	Point estimate	RSE (%)	Shr. (%)
Structural model			
Lambda	0,0709	0	
Gamma	0,697	0	
Covariate model			
Emax	1 FIX		
EC50	75,7	0	
Hill	3,9	0	
Inter-individual variability			
Lambda	15,6	1	72
EC50	0,00941	17	100

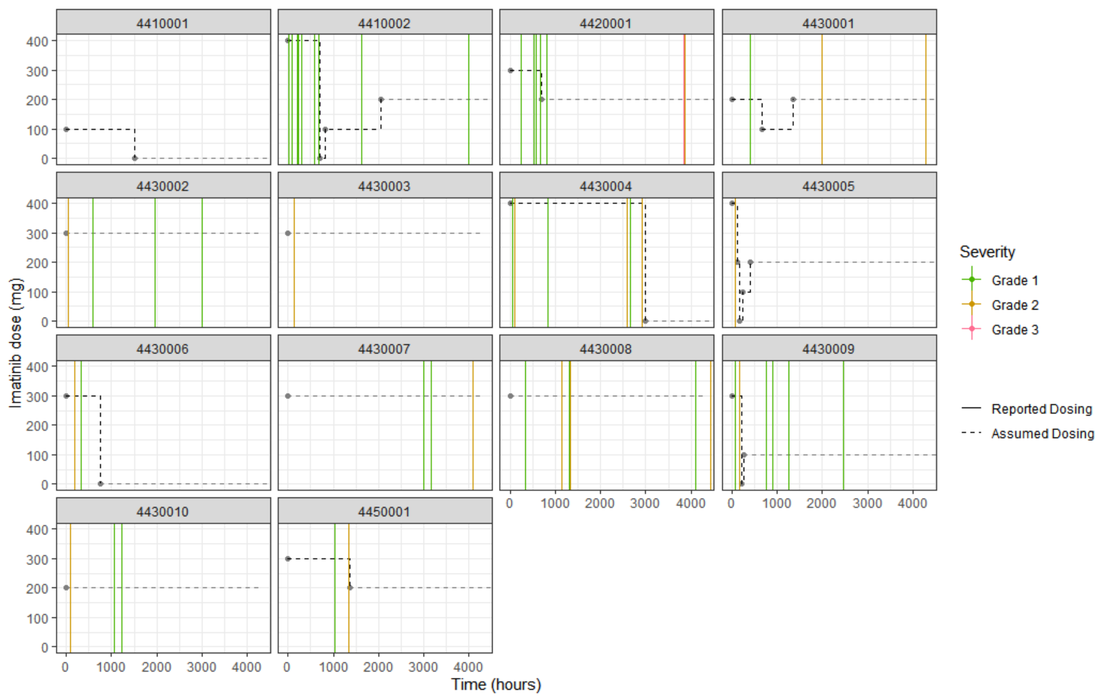
Table 1. Final model parameter estimates

Methods

- A previously developed population pharmacokinetic (PK) model was used to predict the individual daily exposure of total and unbound imatinib.
- Patient reported adverse event were collected during the PIPAH study and graded based on severity.
- Model evaluation was conducted using kernel-based Visual Hazard Comparisons (kbVHC) and a Visual Predictive Check (VPC) to assess predictive performance and model adequacy.

Figure 1. Overview of number of adverse events (table) and of each patient

Category	Count (%)	Grade 1	Grade 2	Grade 3
Cardiac	7 (14.6)	5	2	
Dermatological	4 (8.3)	3	1	
Gastrointestinal	15 (31.2)	13	2	
Hematological	8 (16.7)	4	4	
Musculoskeletal	1 (2.1)		1	
Neurological	10 (20.8)	6	4	
Ophthalmological	1 (2.1)	1		
Respiratory	2 (4.2)		1	1
Total	48 (100)	32	15	1



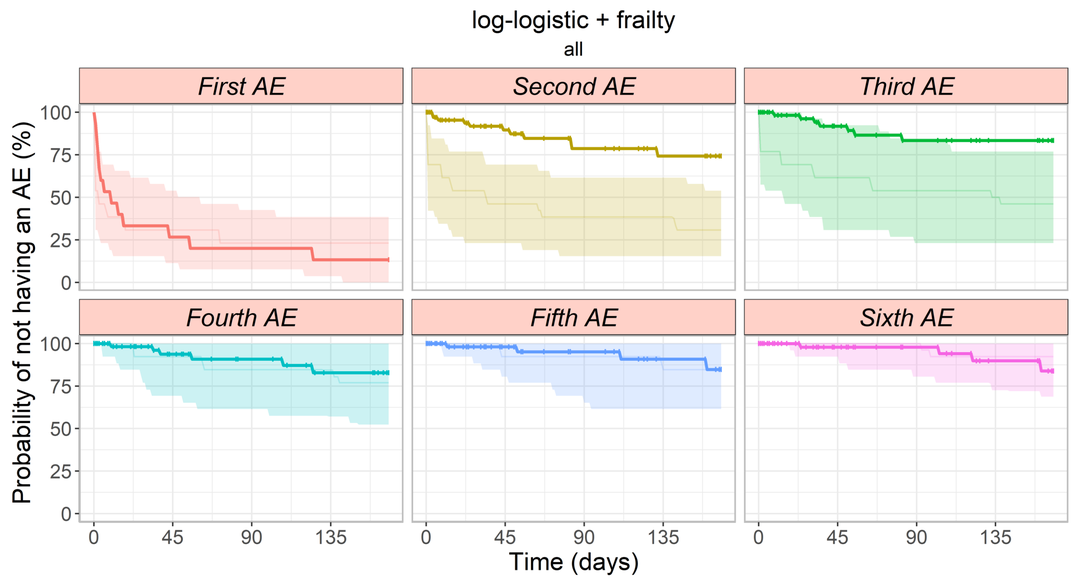


Figure 3. VPC of time to n events.

Conclusion

The RTTE model reliably predicts the timing of the first adverse event but is less accurate for subsequent events, indicating limitations in modeling recurrent AEs. Additional data are needed to improve these predictions. Overall, the findings highlight the model's potential for early AE risk assessment and the need to better capture repeated event dynamics for clinical decisions.

Affiliations:
[1] Department of Pharmacy and Clinical Pharmacology, Amsterdam UMC, location VUmc, Amsterdam, The Netherlands;
[2] Cancer Center Amsterdam, Amsterdam, The Netherlands;
[3] Imperial College London, Hammersmith Hospital
[4] Department of Infection, Immunity and Cardiovascular Disease, The Medical School Sheffield
[5] MRC Biostatistics Unit, University of Cambridge, UK.
[6] Papworth Trials Unit Collaboration, Royal Papworth Hospital NHS Foundation Trust, Cambridge, UK
[7] Department of Pulmonary Medicine, Amsterdam UMC, location VUmc, Amsterdam, The Netherlands;
[8] Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands
[9] Amsterdam Institute for Infection and Immunity, Amsterdam, The Netherlands.

References:
1. Hoeper, M. M. *et al.* Imatinib Mesylate as Add-on Therapy for Pulmonary Arterial Hypertension. *Circulation* **127**, 1128–1138 (2013)
2. Aerovate Therapeutics Announces 24-Week Topline Results from the Phase 2b Portion of IMPAHCT Evaluating AV-101 for the Treatment of PAH | Aerovate Therapeutics, Inc. (n.d.). Aerovate Therapeutics, Inc. https://ir.aerovatetx.com/news-releases/news-release-details/aerovate-therapeutics-announces-24-week-topline-results-phase-2b
3. Wilkins, M. R. *et al.* Positioning imatinibfor pulmonary arterial hypertension: A phase I/II design comprising dosefinding and single-arm efficacy. *Pulmonary Circulation***11**, 1–12 (2021)