

Getting a better description of treatment effects for time to event data using PKPD modelling I-32

Christian Bartels¹, Bruno Bieth¹, Thomas Dumortier¹, Xinting Wang², Jing Yu²

¹Novartis Pharma A.G., Basel, Switzerland; ²Novartis Institutes for BioMedical Research, Cambridge, MA, USA

Introduction

Exposure-response relations for time to event data are often analyzed with non-parametric (Kaplan Meier) or semi-parametric (Cox regression) methods. These methods have their limitations. Population pharmacokinetic–pharmacodynamic (PKPD) modelling can overcome some of the limitations.

Exposure-response analyses were done for the CANTOS trial (Ridker 2017). The CANTOS trial studied anti-inflammatory therapy with canakinumab for atherosclerotic disease, and involved 10,061 patients with previous myocardial infarction. The primary efficacy endpoint was nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death (MACE). The trial compared three doses of canakinumab (50 mg, 150 mg, and 300 mg, administered subcutaneously every 3 months) with placebo.

Objectives:

- Using data from the CANTOS trial (Ridker 2017), evaluate the potential of PKPD modeling in characterizing the exposure-response relationship for time to event data relative to simpler non-parametric or semi-parametric methods.
- Use the PKPD model to estimate the efficacy of the drug when all patients had strictly adhered to treatment, i.e., assess the treatment method effectiveness estimand (Sheiner and Rubin, 1995).
- Position the PKPD estimate of the method effectiveness within statistical causal inference framework (Robins, 2000; Daniel, 2018; Rogers, 2019).

Methods

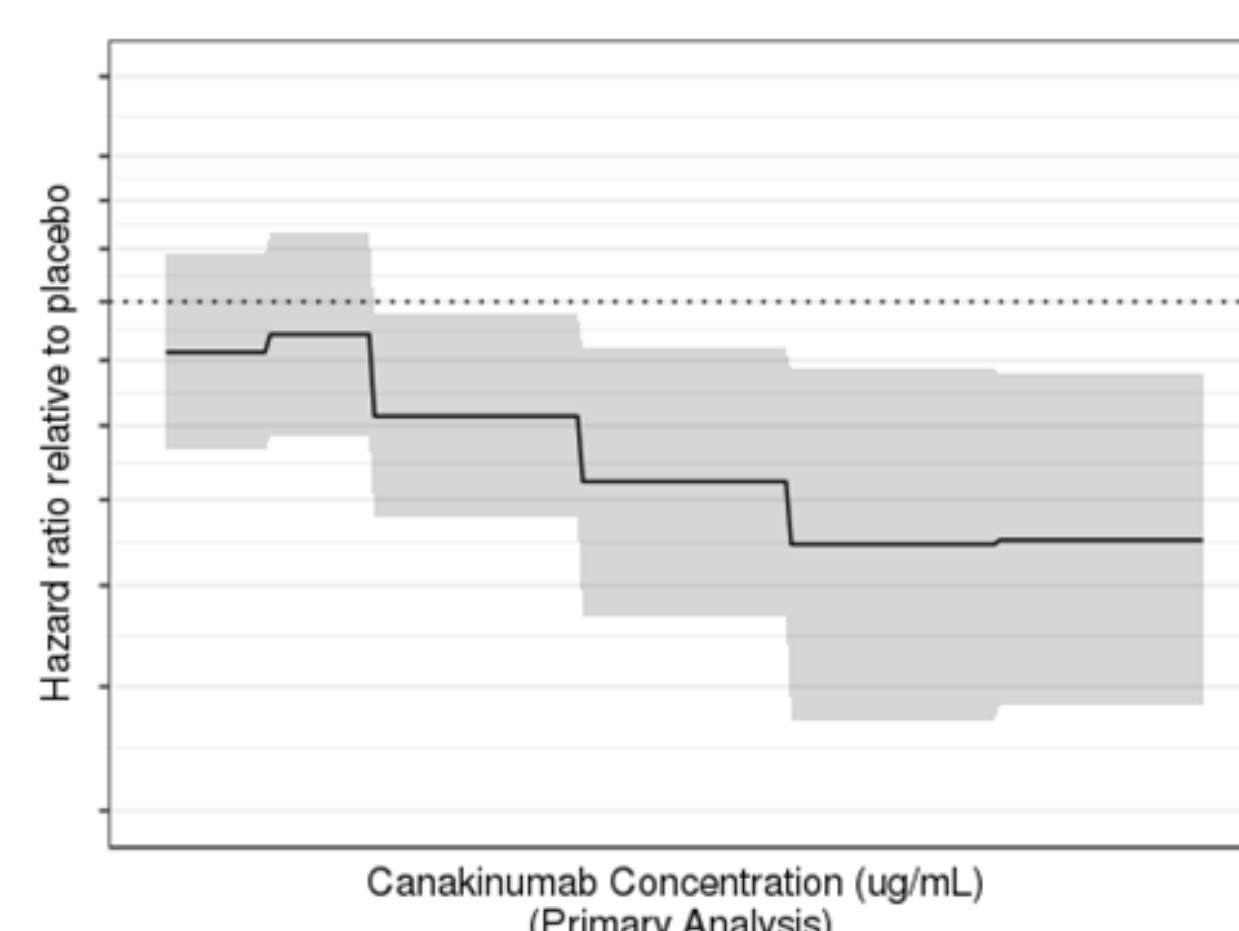
- The analyses extended from non-parametric Kaplan-Meier estimates, over semi-parametric proportional hazard methods (linear Cox regression) towards more detailed characterizations using full parametric non-linear population PKPD models for time to first MACE event. Standard model building strategies were used, and qualification included visual predictive checks
- Simulations based on the qualified model were used to assess method effectiveness.

Results

Non-parametric and semi-parametric linear analyses

- Kaplan-Meier estimates for groups of patients stratified by exposure suggest dependence of survival on exposure
- Cox regression
 - Provides clear evidence for exposure-response
 - Gives initial characterization of the shape of the exposure-response

Figure 1. Steady state exposure versus hazard



Direct PKPD Model: plasma concentration drives log-hazard

- Longitudinal description of response
- Quantifies non-linear exposure-response relationship, including estimates of EC50 and Emax
- Improved correction for covariates, including non-linear terms
- Model diagnostics qualified the model for simulations

Figure 2. Time dependent plasma concentration drives hazard

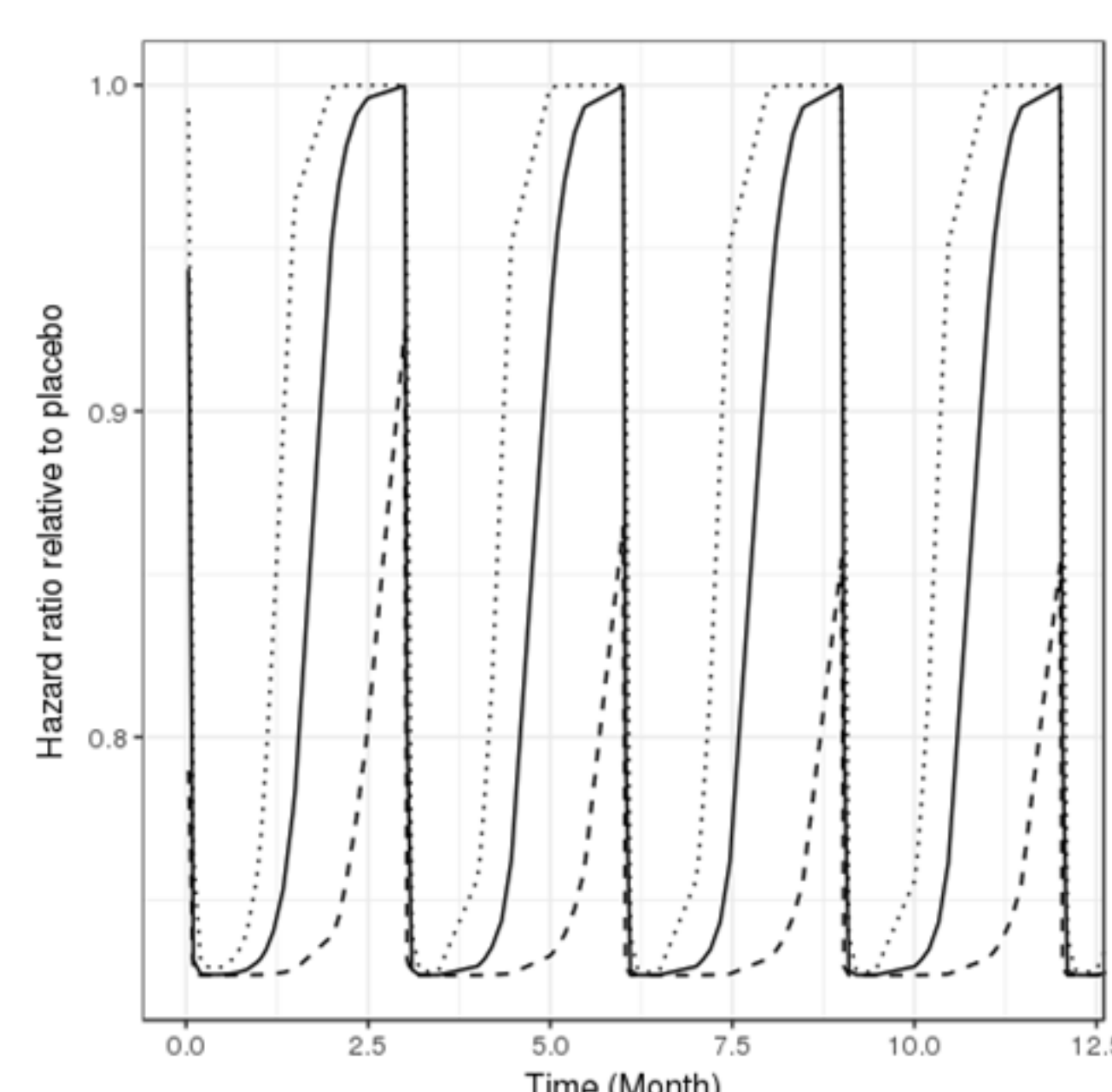
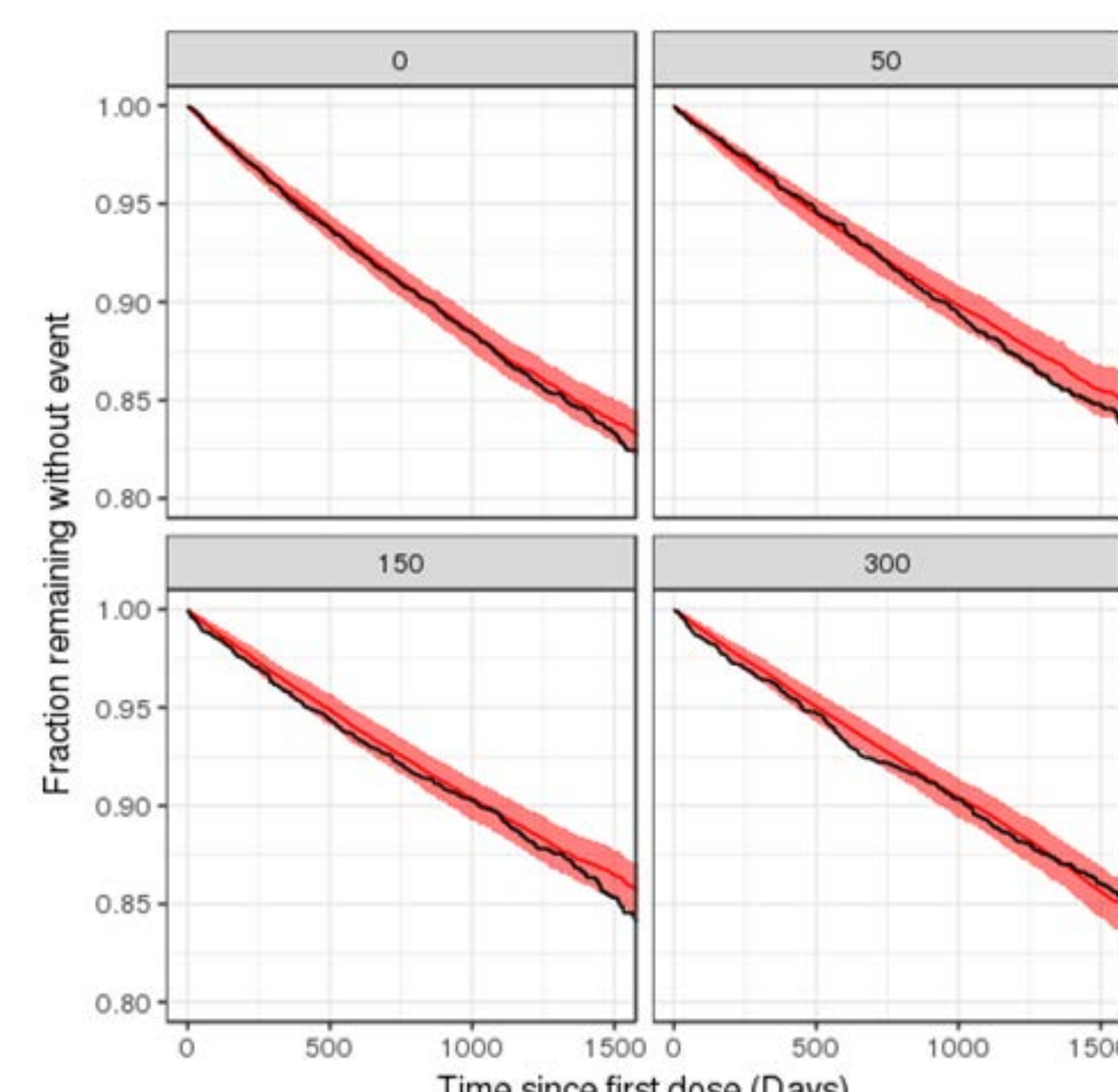


Figure 3. Visual predictive checks



Causal inference to estimate method effectiveness

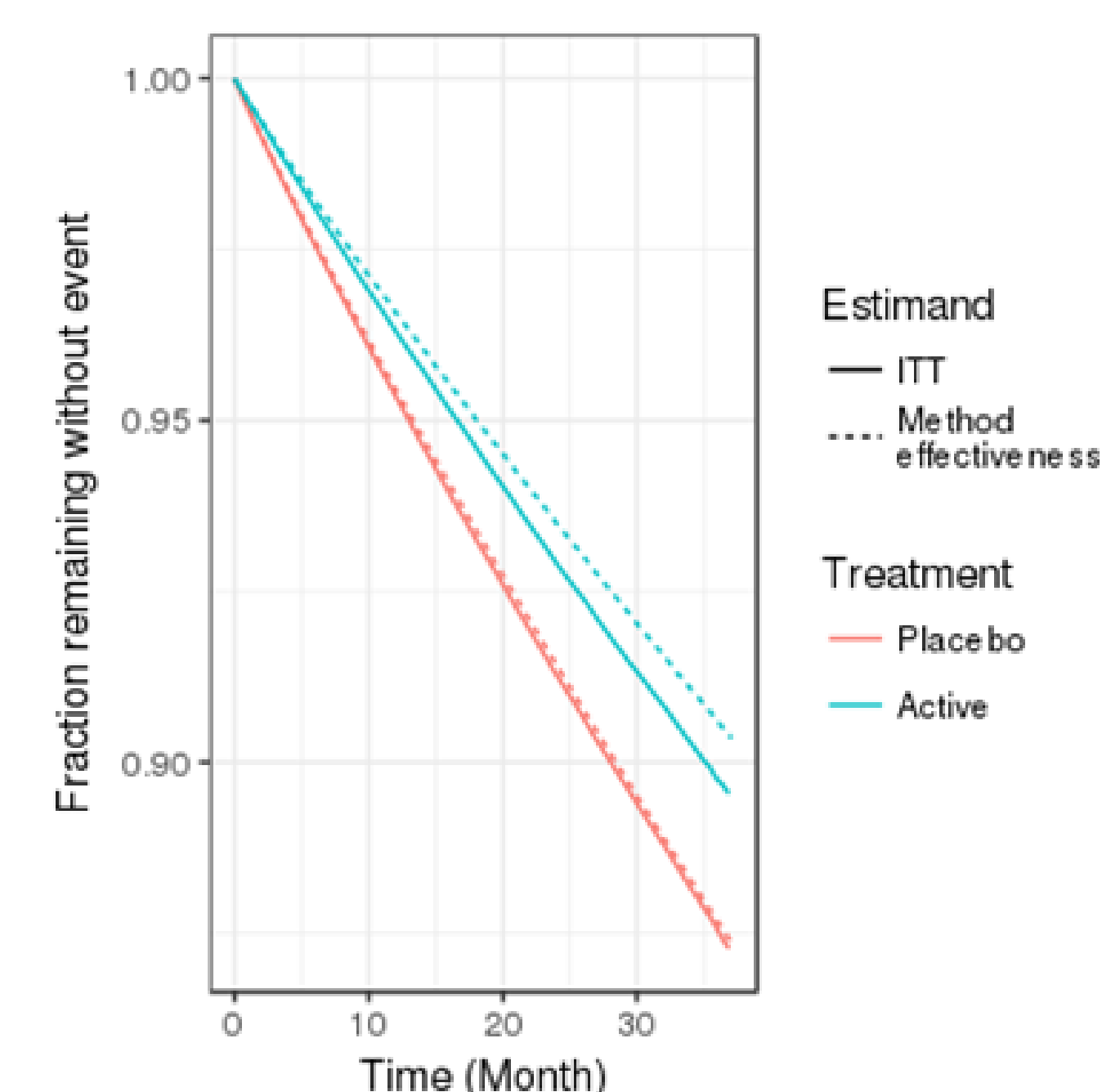
- Method effectiveness estimand (Sheiner and Rubin, 1995): efficacy of the prescribed treatment method, i.e., efficacy that would be observed, if all patients adhere to the prescribed treatment
- Estimates of method effectiveness are often of interest, however they are not easy to be obtained
- PKPD modeling and simulations corresponds to the g-computation approach used for statistical causal inference and may be used to estimate method effectiveness (Rogers 2019; Daniel 2018, Snowden 2011); steps are:
 - Fit regression model, e.g., non-linear PKPD model
 - Simulate (counterfactual) outcomes of interest for patients of interest, e.g., for each patient probability of not having an event when receiving one of the treatments as prescribed
 - Summarize simulated outcomes, e.g., fraction of population remaining without events

- In CANTOS patients were dosed every three months; some patients missed some doses or discontinued dosing

- PKPD model was used to simulate patients under different regimens
 - Method effectiveness: assuming regular dosing every three months
 - ITT: use dosing records from the study

- Finding: If taken as prescribed, hazard ratio of active relative to placebo improves by ~0.05 compared to result from ITT analysis

Figure 4. Method effectiveness



- The obtained estimates of method effectiveness are valid if (1) the model conditions on all confounders of the exposure-response relationship (i.e., no observed or unobserved confounders left not accounted for; Robins, 2000), and (2) model diagnostics have been used to qualify the model for simulations ...

Conclusions:

- Standard descriptions of time to event data using semi-parametric (Cox regression) models might be enough to characterize exposure response in most cases.
- Describing data in a more detailed longitudinal manner using parametric PKPD methods gives additional insights into shape of the exposure response, describes the progression of the clinical endpoints over time, and it enables simulations.
- Simulations from the PKPD model adjusted for confounders correspond to g-computations and can provide valid statistical causal inference estimates of method effectiveness.

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