Modelling and Simulation of the incidence of adverse events in clinical trials

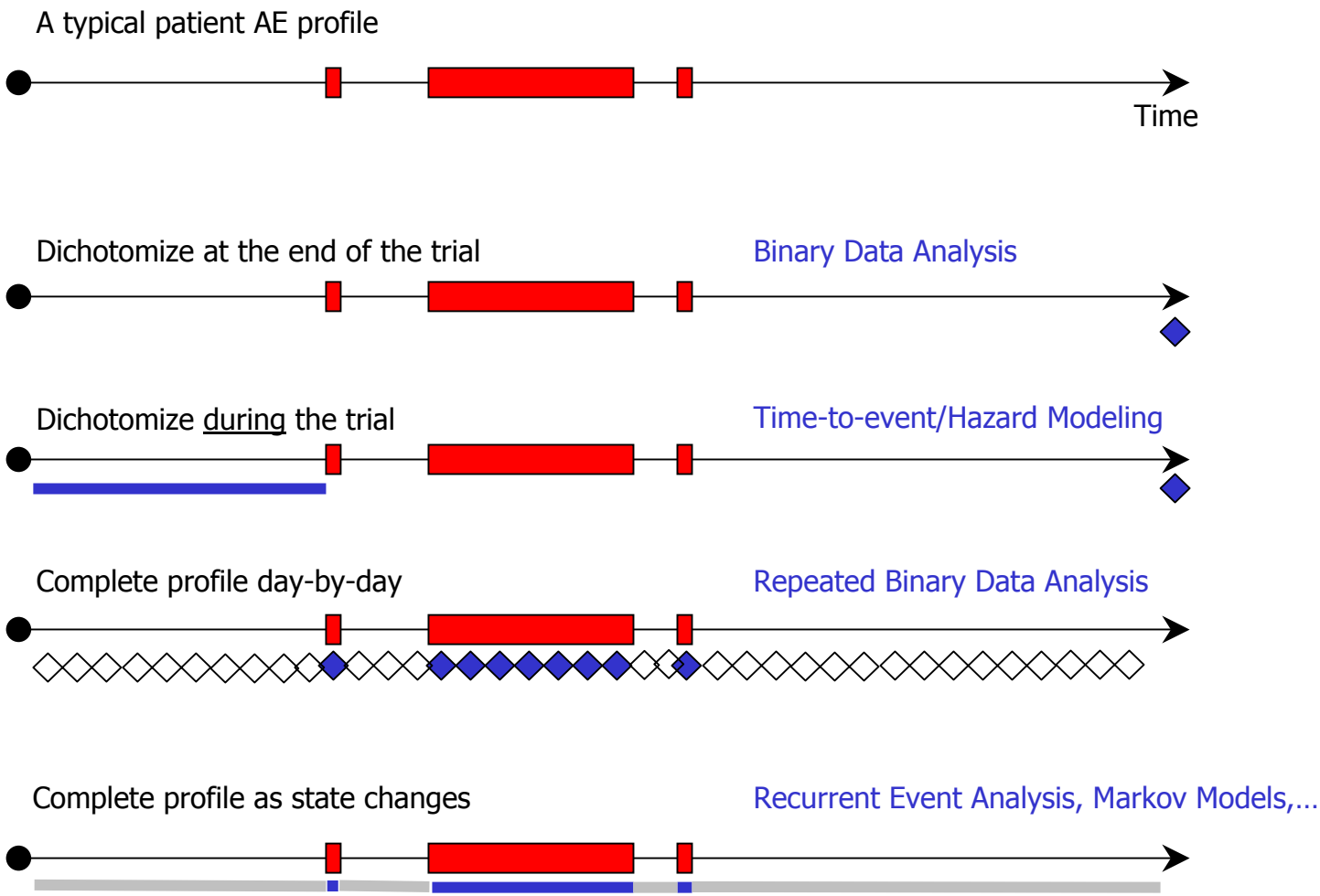
Filip De Ridder[1], An Vermeulen[2], Vladimir Piotrovskij[2]

[1]Biometrics & Clinical Informatics
[2]Global Clinical Pharmacokinetics & Clinical Pharmacology
Johnson & Johnson Pharmaceutical Research and Development
A division of Janssen Pharmaceutica N.V.
B-2340 Beerse, Belgium

Introduction

- Drug Y is an improved version of a marketed drug X
- A specific adverse event is related to supra-efficacious drug levels and is expected for drug Y as well.
- In planned clinical trials with drug Y, we want to control the incidence of the adverse event, to balance efficacy and safety
- PK/PD model using data of drug X (~2500 patients, 10 trials)
- Predict adverse event in clinical trials with Y (based on a pharmacokinetic and pharmacological rationale)

How to model adverse events?



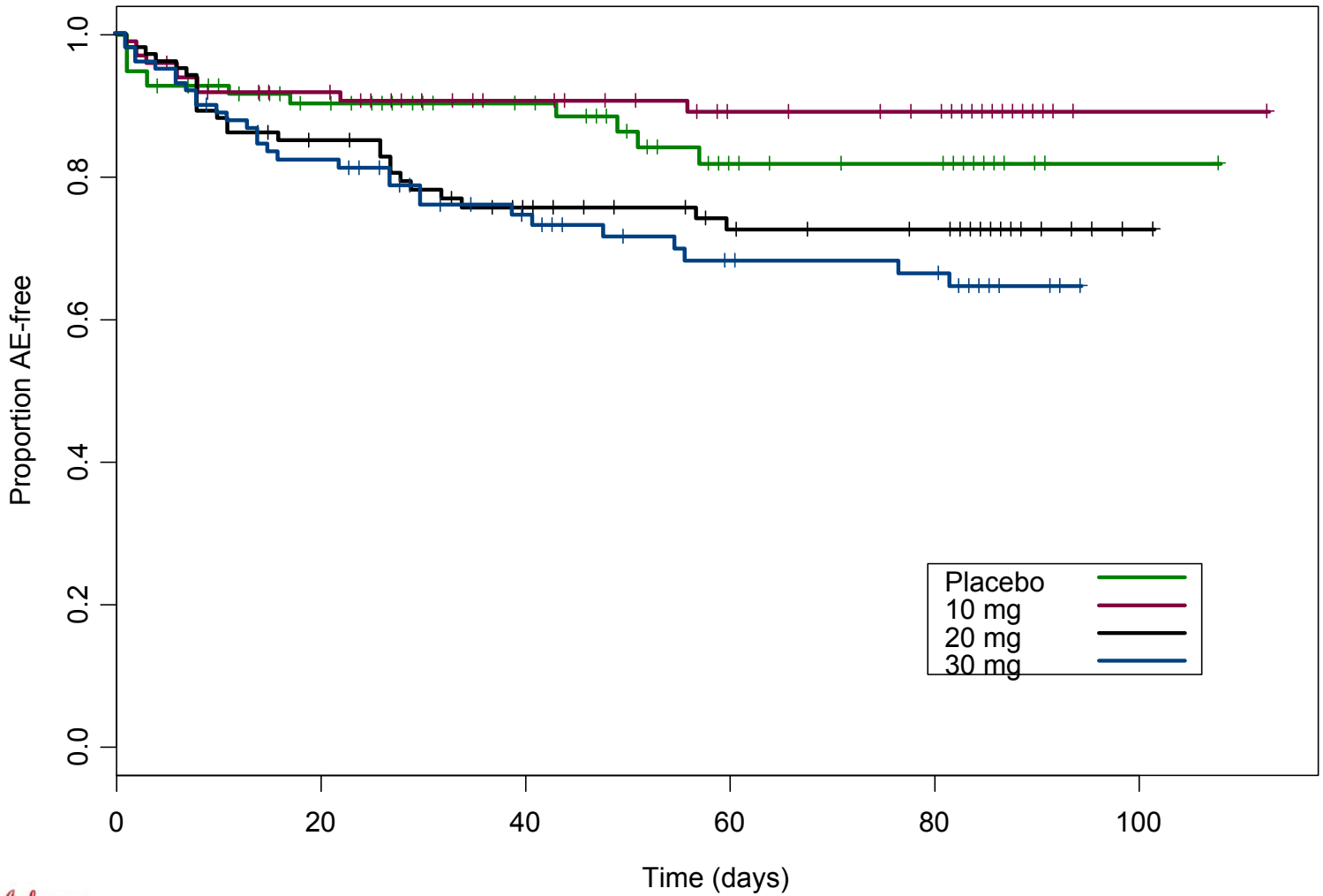
The Data of Drug X

- Double-blind placebo controlled trial with 3 doses

Treatment	N	Drop-out(%)	AE(%)
Placebo	98	67(68)	13(13)
10 mg	99	51(51)	10(10)
20 mg	103	54(51)	25(24)
30 mg	100	52(52)	29(29)

$$AE = \frac{\text{\# of patients with at least 1 AE-episode}}{\text{\# of patients randomized}}$$

Kaplan-Meier plot for time to first AE



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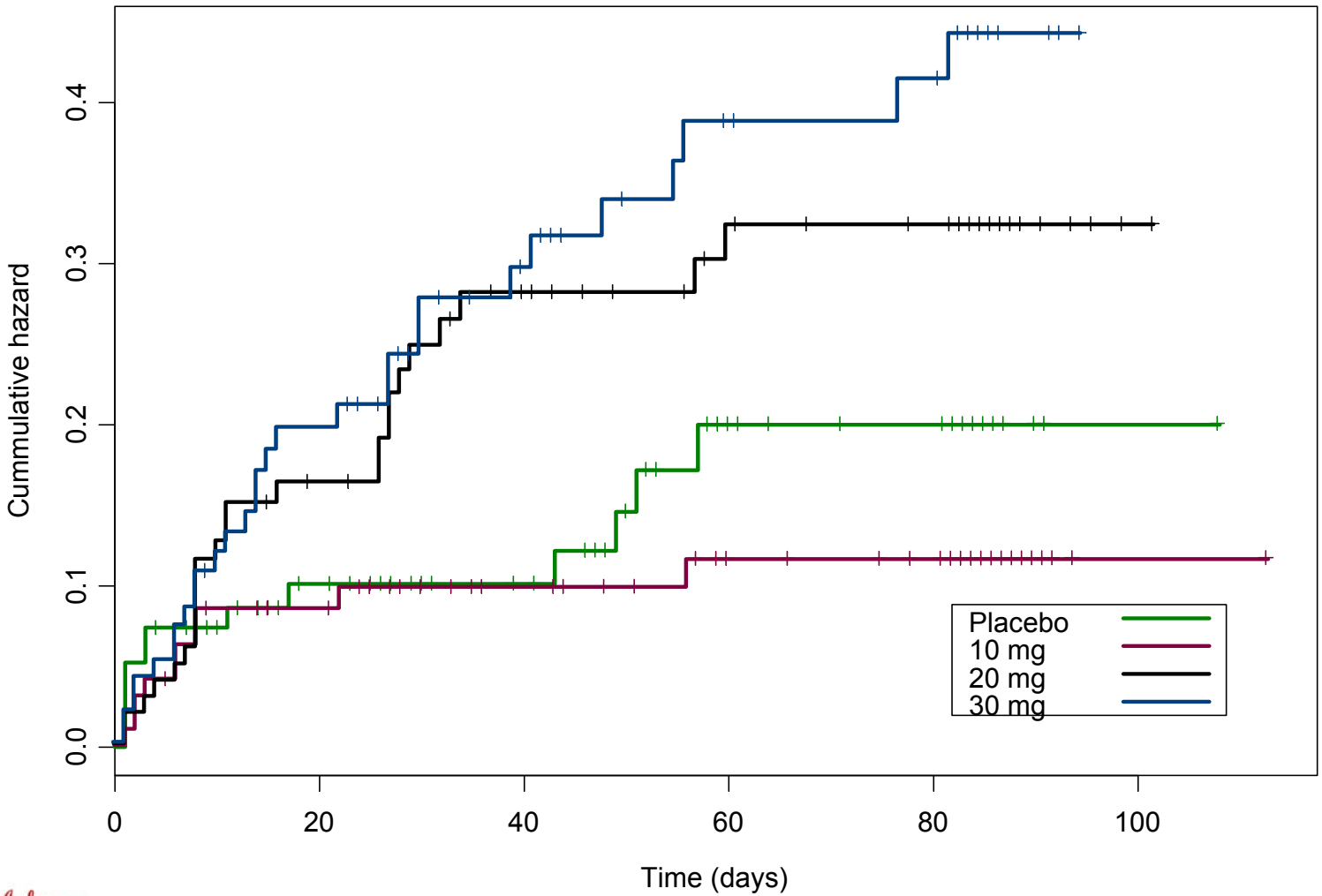
Cumulative hazard



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What measure of drug exposure?

- No scientific rationale available
- As the adverse event develops over time, an integrated measure of long term exposure was chosen

Individual - Average Steady-State Concentration (Cav_i)

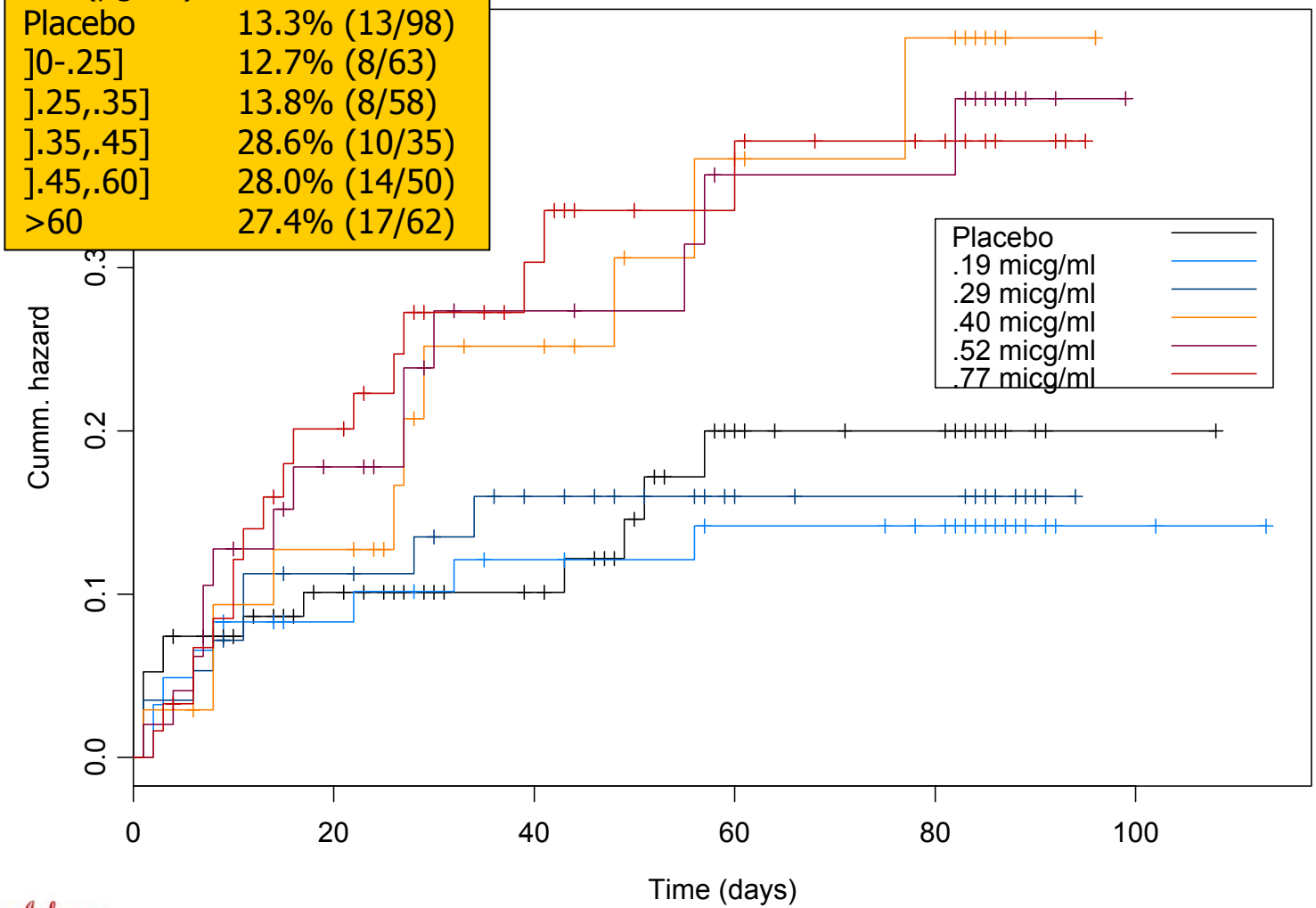
$$Cav_i = Dose/Cl_i/\tau$$

Bayesian Individual Predictions
Population PK model

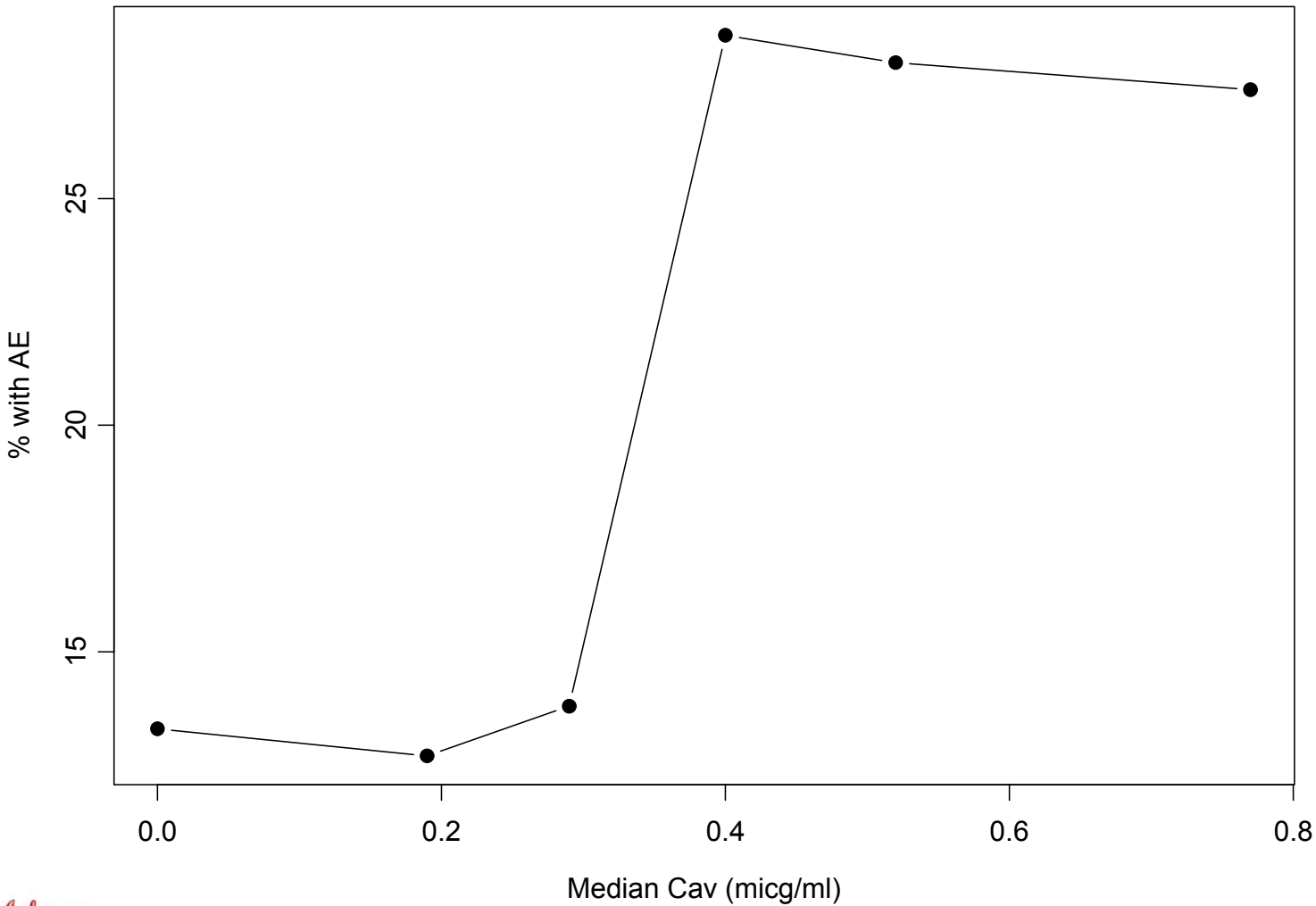
Cl_i : Individual Clearance
τ : Dosing interval

Cumulative hazard x Exposure

Cav(μg/ml)	**Incidence**
Placebo	13.3% (13/98)
]0-.25]	12.7% (8/63)
].25,.35]	13.8% (8/58)
].35,.45]	28.6% (10/35)
].45,.60]	28.0% (14/50)
>60	27.4% (17/62)



Incidence of AE x Exposure



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Modeling the AE risk

$$\log \lambda(t, c_i) = f(t) + g(t, c_i)$$

t : time since trial start

c_i : individual average steady state concentration

Time dependency

$$f(t) = \beta_0 + \beta_1 t$$

Drug effect - logistic

$$g(c_i) = \frac{\theta_1}{1 + \exp\left(\frac{\theta_2 - c_i}{\theta_3}\right)}$$

θ_1 : maximal effect

θ_2 : EC50

θ_3 : scale parameter (steepness)

Drug effect - threshold

$$g(c_i) = I(c_i > \theta_1) \cdot \theta_2$$

θ_1 : threshold for risk increase

θ_2 : log risk increase

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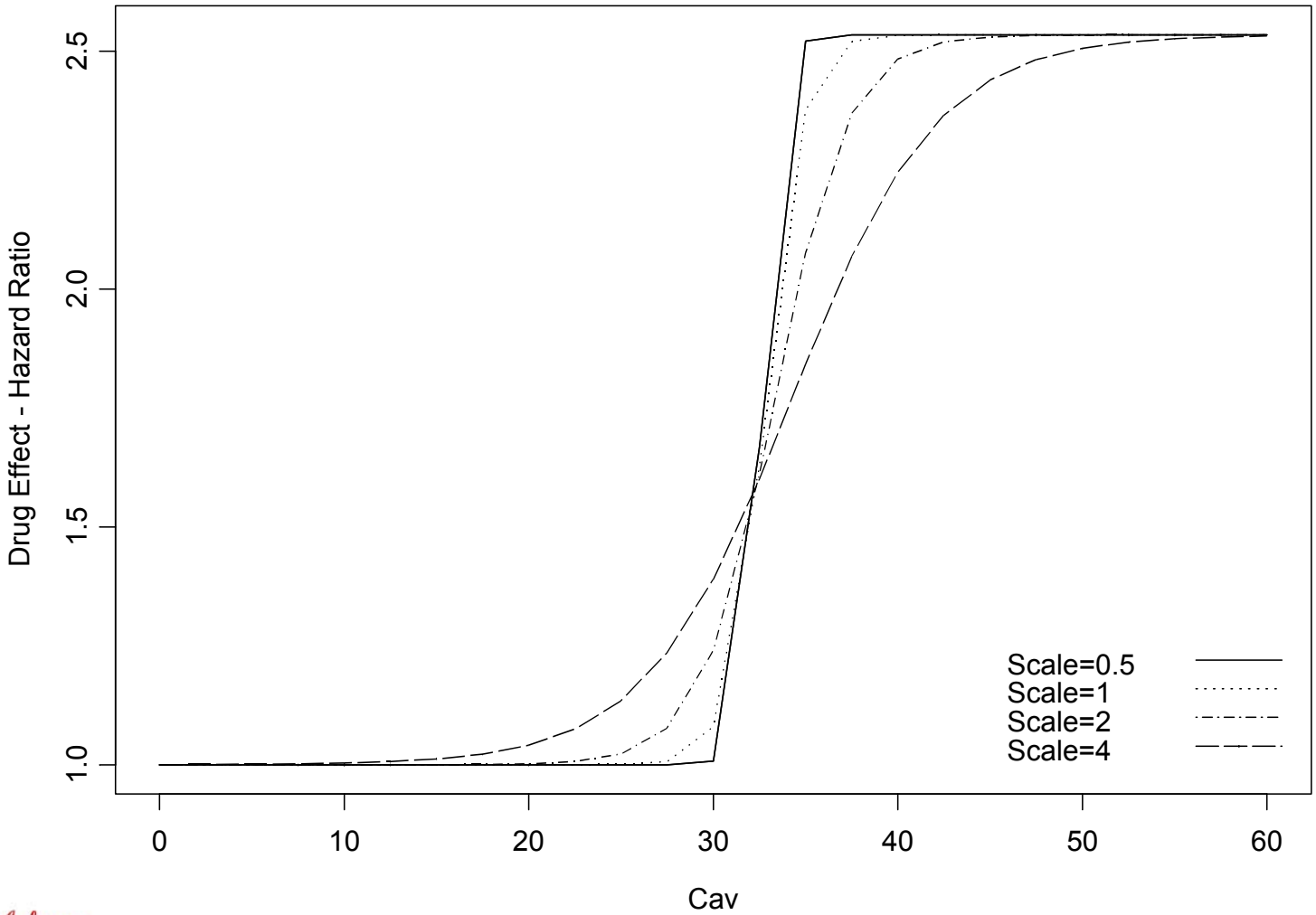
Functional form for various θ_3



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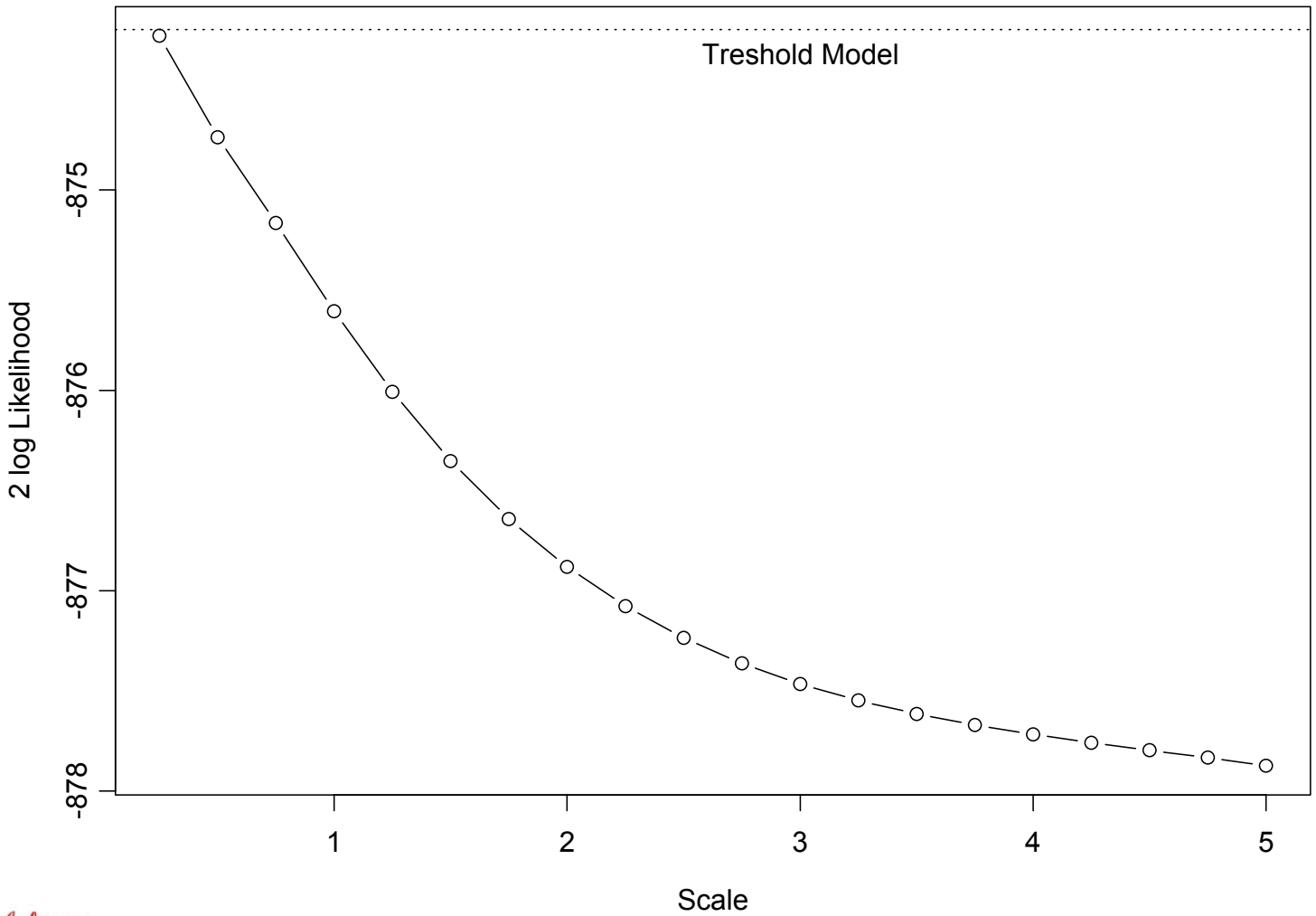
Likelihood profile for θ_3



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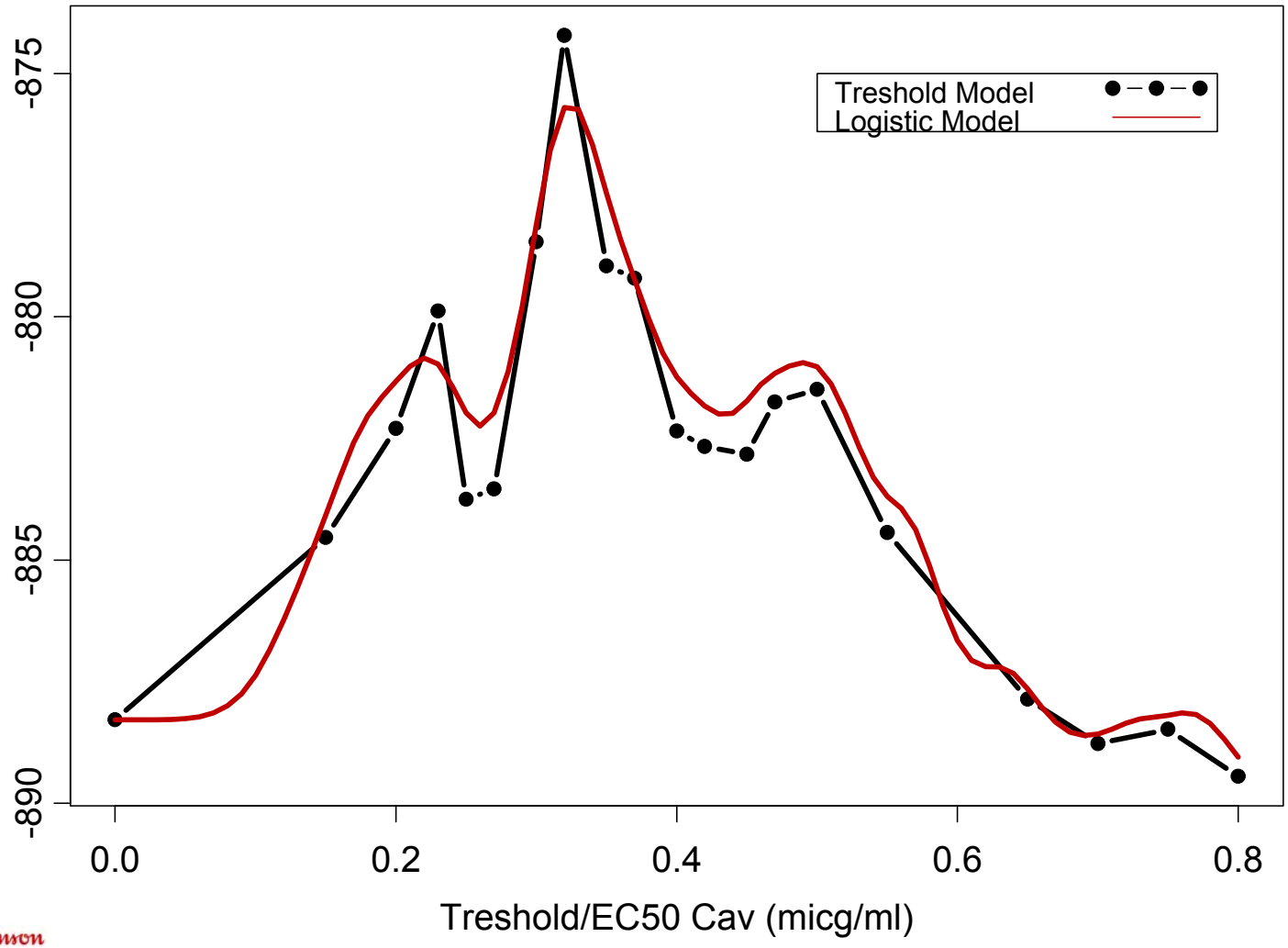
Threshold versus logistic model (θ_3=1)



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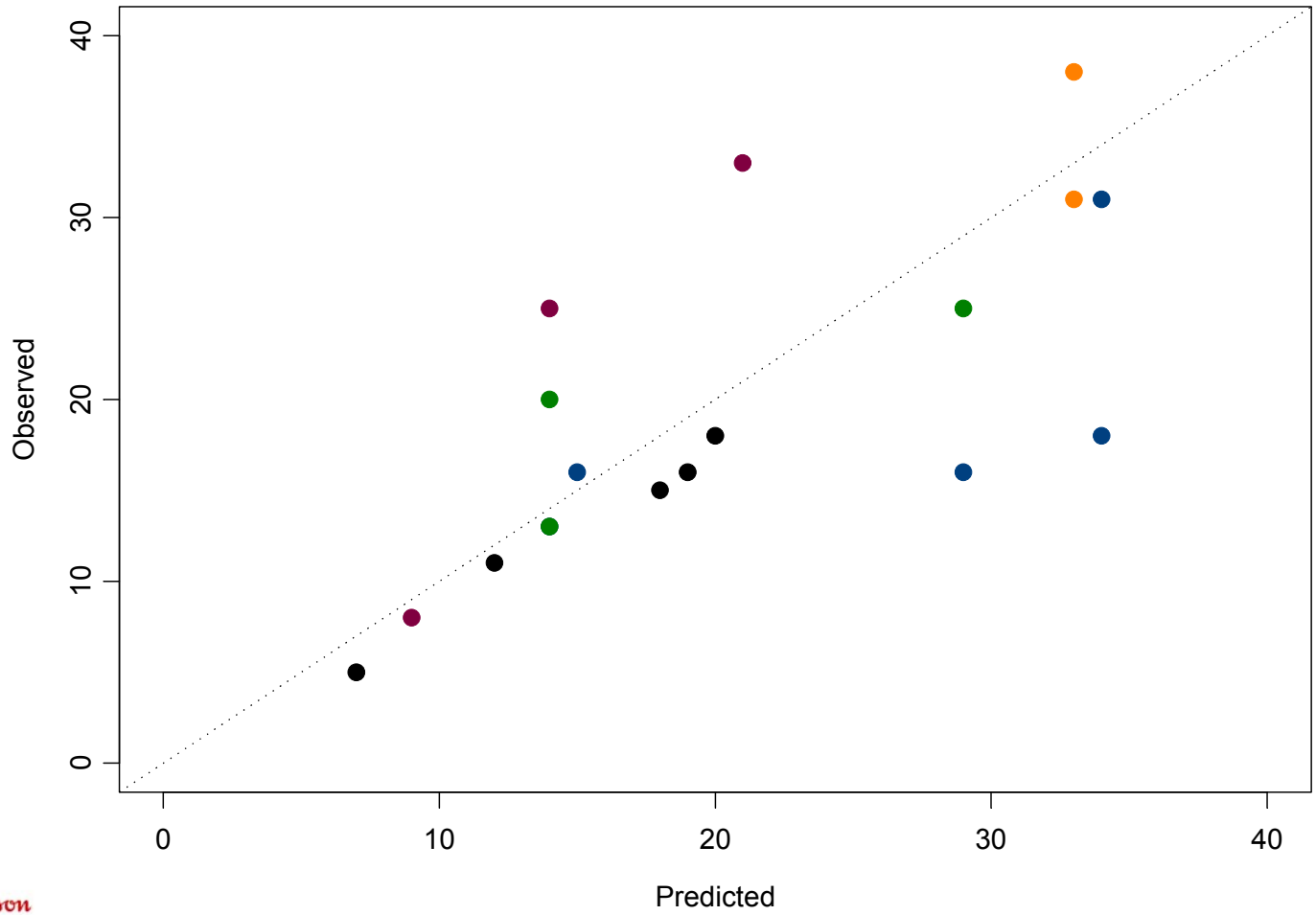
Implementation in SAS 8.2

```
id time cav event;
1    1      12   0
1    2      12   0
1    3      12   0

…

1   60      12   0 = censored at Day 60
2    1      65   0
2    2      65   0
2    3      65   1 = has AE at Day 3

…
```

```
proc nlmixed;
parms a=-4  b=-0.04 emax=1 ec50=3 scale=4;
loghaz=a+b*time+emax/(1+exp(ec50-cav)/scale);
p=exp(loghaz);
model event~binomial(1,p);

run;
```

Model Validation

AE incidence (%) in 5 independent clinical trials with drug X (total ±2000 pat.). Each point is a different dose, each color a different trial



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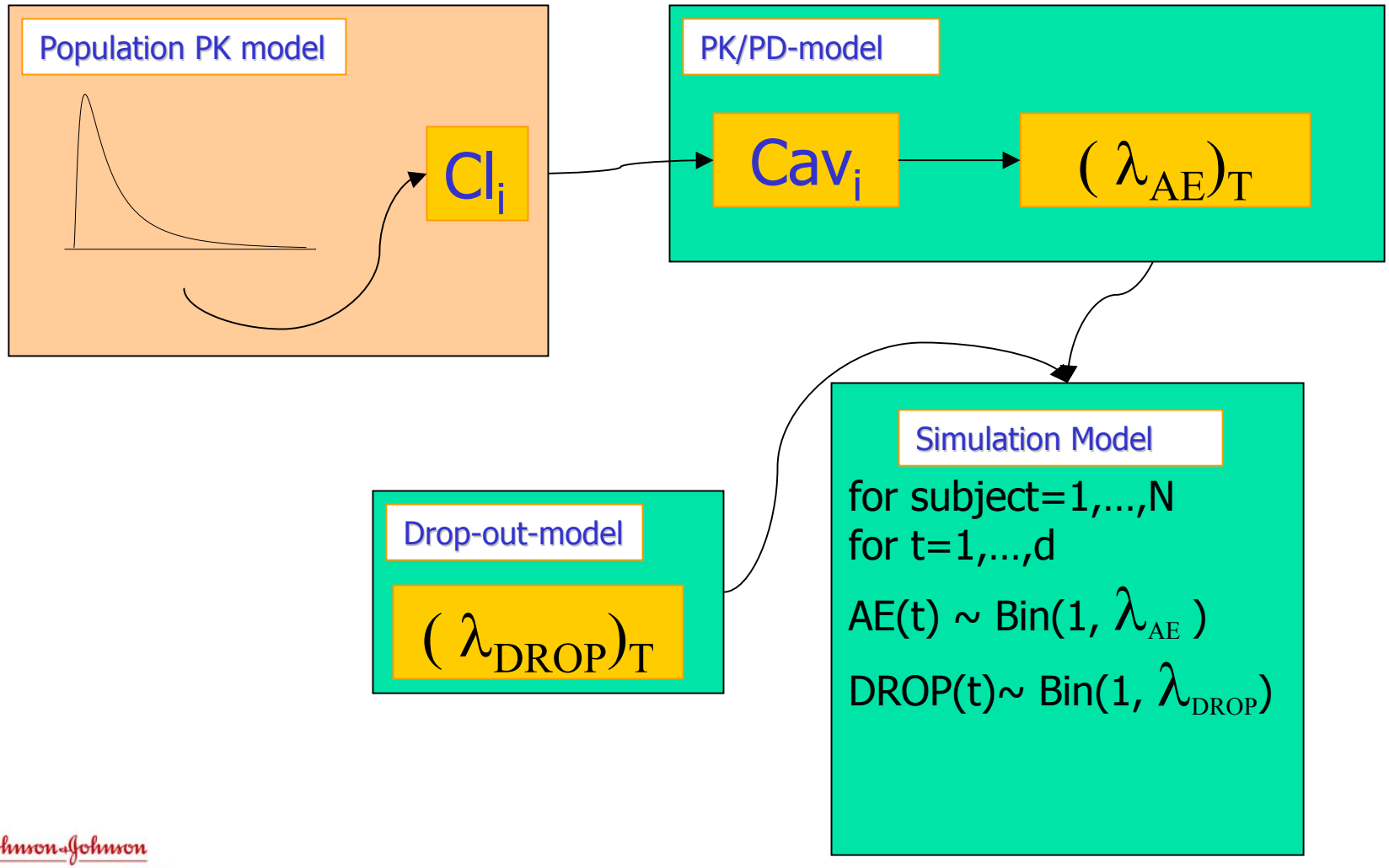
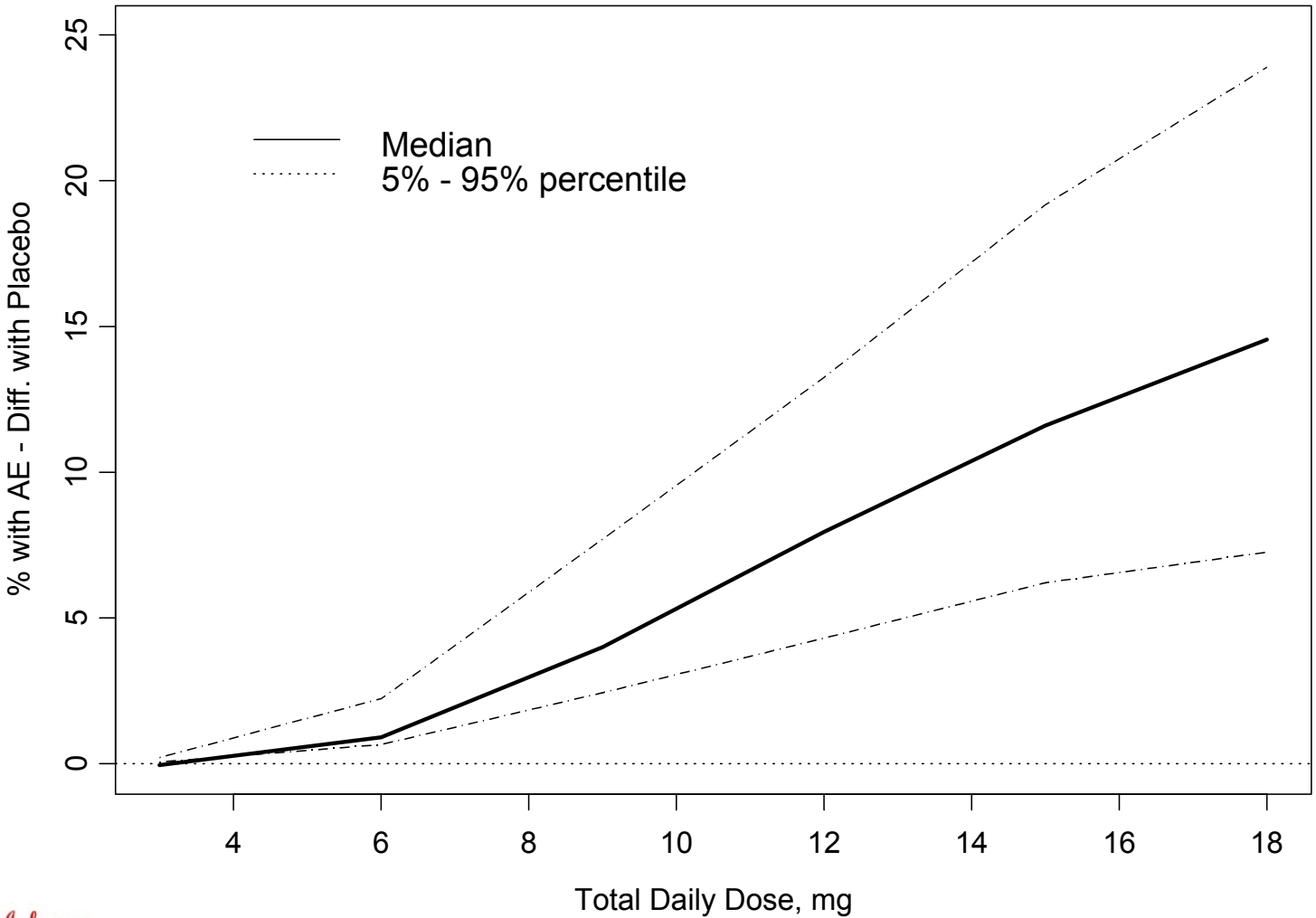
Clinical Trial Simulation for Drug Y



Incidence of AE in the population

Simulation of 2000 patients/dose, no drop-out, 8-week trial



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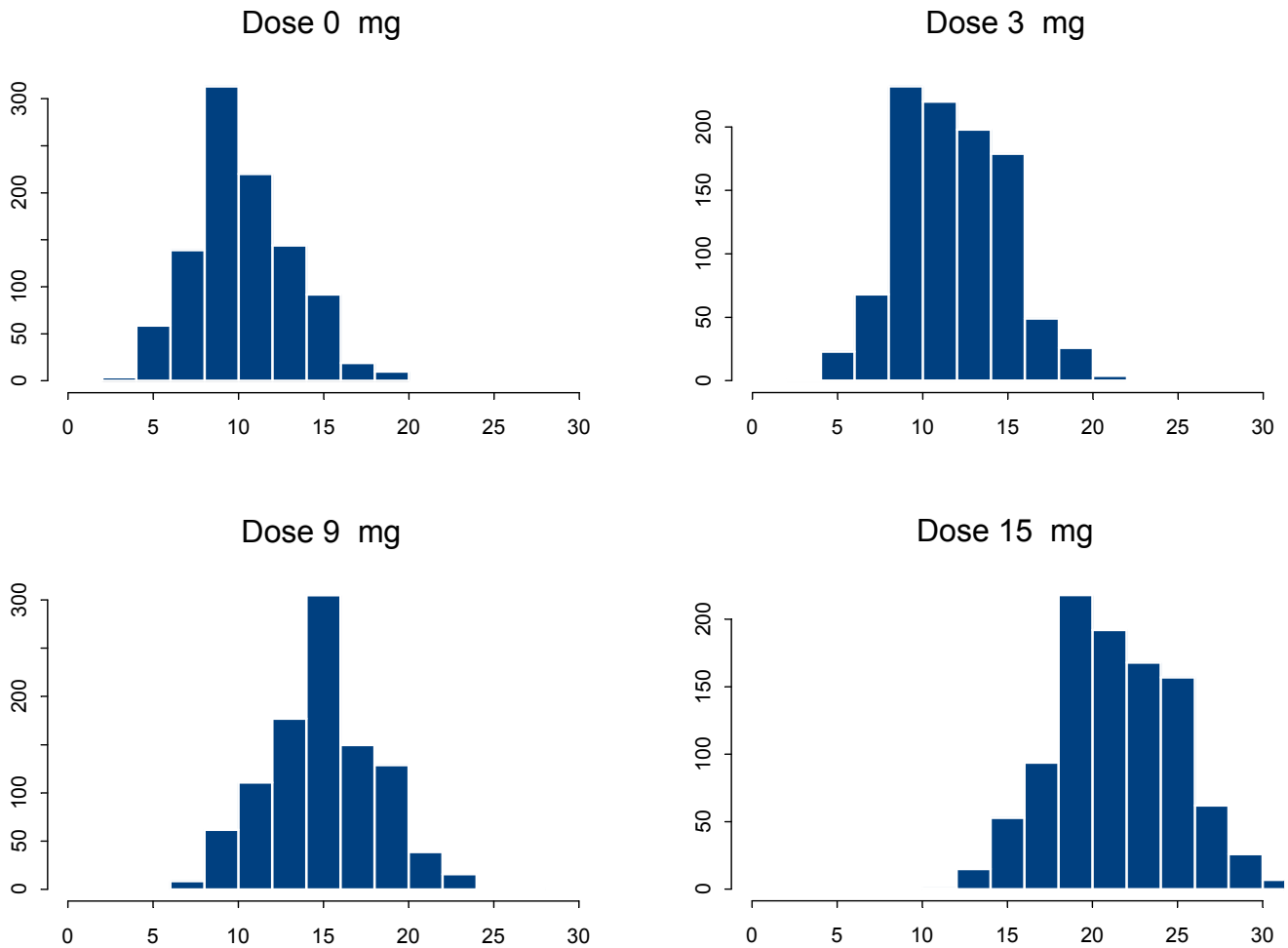
AE Incidence (%) in planned trials

Simulation of 1000 trials, 100 patients/dose, drop-out, 8-weeks



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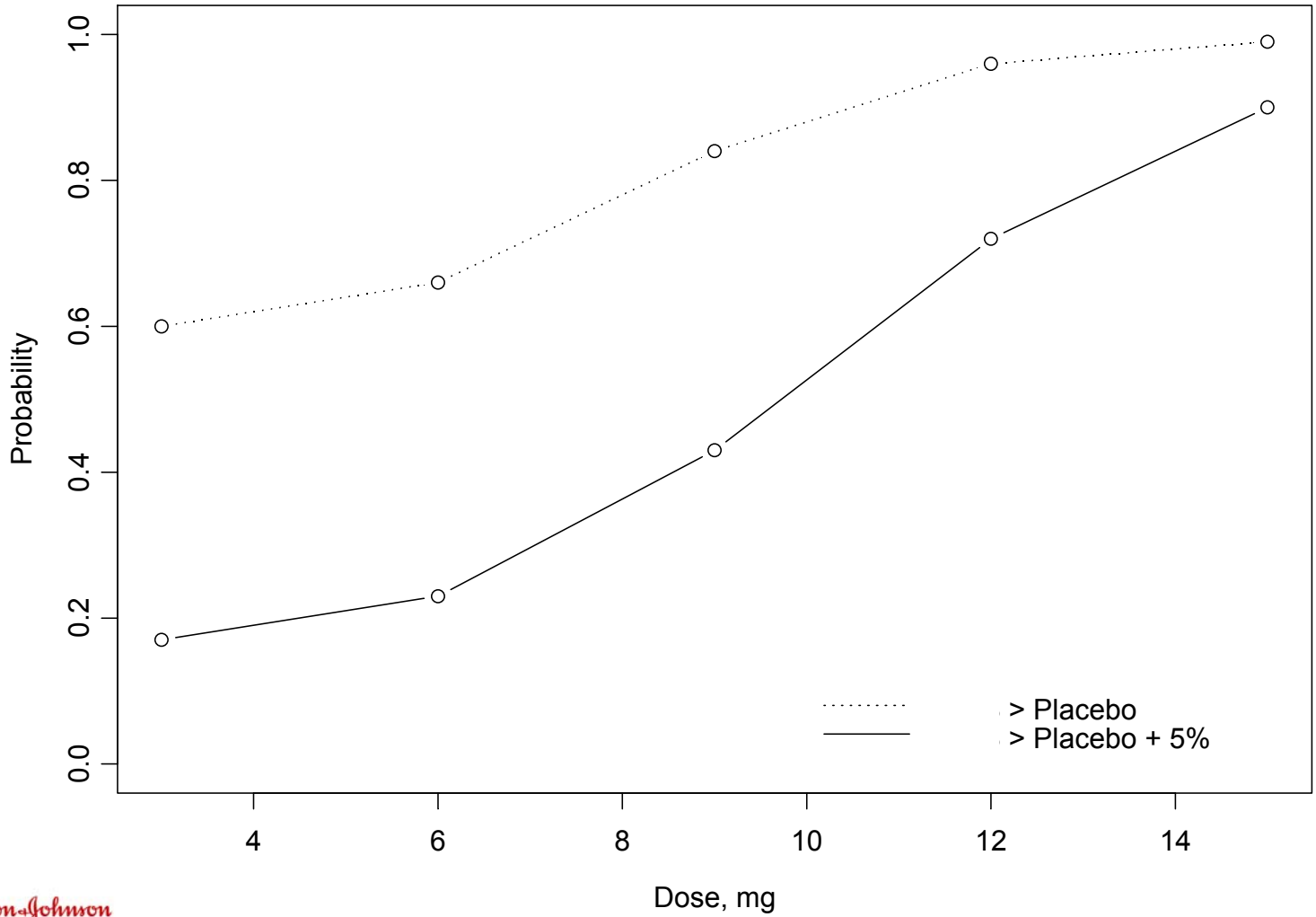

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Conclusions

- Hazard modeling is a flexible tool to model the occurrence of side effects in clinical trials
- In the example presented here, the risk for a specific adverse event showed a steep (~on/off) relation with the patient-specific average steady state concentration
- Modeling allowed synthesis of data of a large number of studies of a marketed drug
- Clinical Trial Simulation allowed to study what can be expected in planned clinical trials, and optimize the dose range to study.