

Personalized screening intervals for biomarkers using joint models for longitudinal and survival data

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1. Introduction

- Nowadays growing interest in tailoring medical decision making to individual patients
 - ▷ Personalized Medicine
 - ▷ Shared Decision Making

- This is of high relevance in various diseases
 - ▷ cancer research, cardiovascular diseases, HIV research, ...

Physicians are interested in accurate prognostic tools that will inform them about the future prospect of a patient in order to adjust medical care

1. Introduction (cont'd)

- Aortic Valve study: Patients who received a human tissue valve in the aortic position
 - ▷ data collected by Erasmus MC (from 1987 to 2008);
77 received sub-coronary implantation; 209 received root replacement

- Outcomes of interest:
 - ▷ death and re-operation → **composite event**
 - ▷ aortic gradient

1. Introduction (cont'd)

- General Questions:
 - ▷ Can we utilize available aortic gradient measurements to predict survival/re-operation?
 - ▷ **When to plan the next echo for a patient?**

1. Introduction (cont'd)

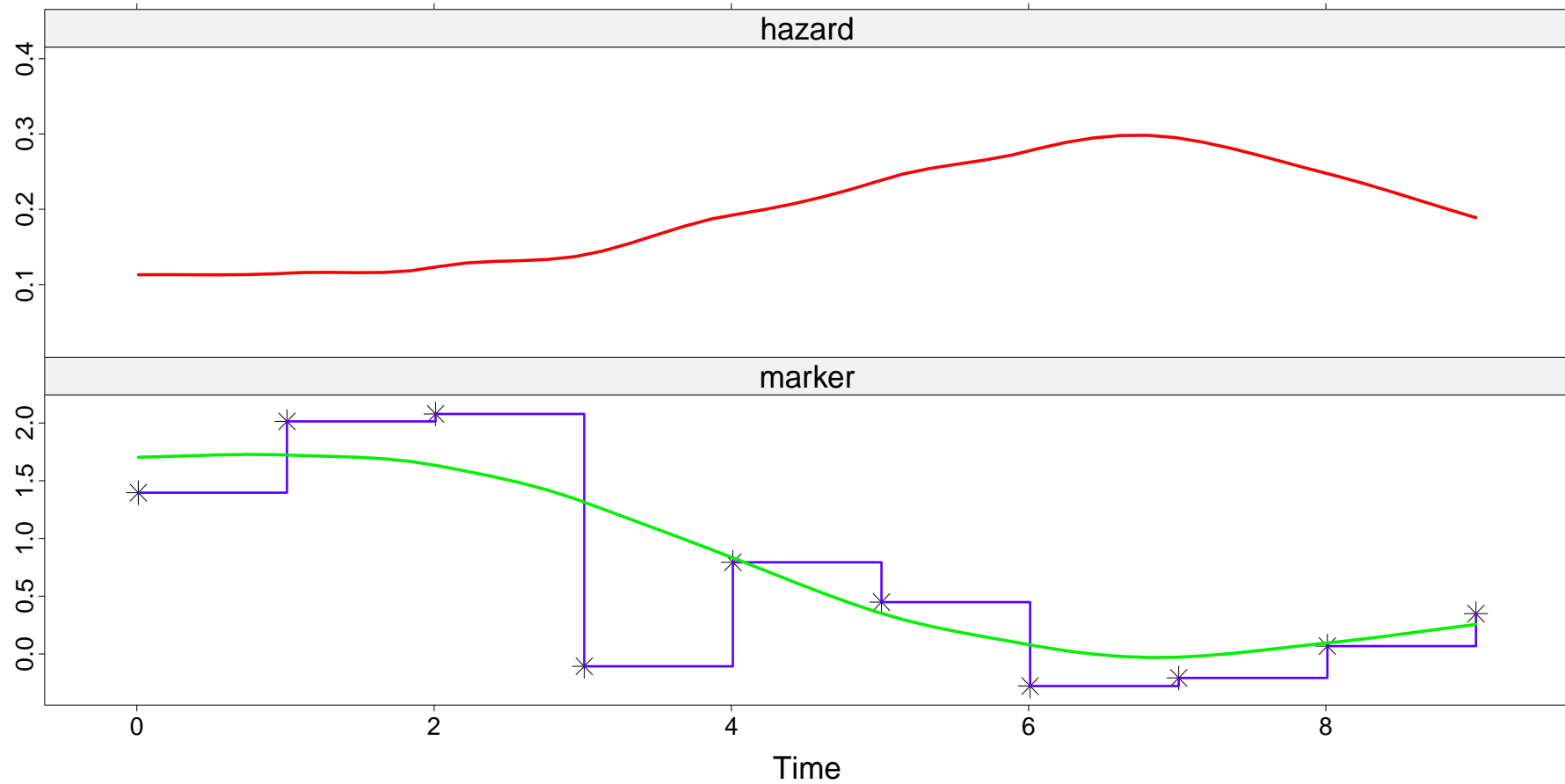
- **Goals of this talk:**
 - ▷ introduce joint models
 - ▷ dynamic predictions
 - ▷ optimal timing of next visit

2.1 Joint Modeling Framework

- To answer these questions we need to postulate a model that relates
 - ▷ the aortic gradient with
 - ▷ the time to death or re-operation

- Some notation
 - ▷ T_i^* : True time-to-death for patient i
 - ▷ T_i : Observed time-to-death for patient i
 - ▷ δ_i : Event indicator, i.e., equals 1 for true events
 - ▷ y_i : Longitudinal aortic gradient measurements

2.1 Joint Modeling Framework (cont'd)



2.1 Joint Modeling Framework (cont'd)

- We start with a standard joint model
 - ▷ Survival Part: Relative risk model

$$h_i(t \mid \mathcal{M}_i(t)) = h_0(t) \exp\{\gamma^\top w_i + \alpha m_i(t)\},$$

where

- * $m_i(t)$ = the *true & unobserved* value of aortic gradient at time t
- * $\mathcal{M}_i(t) = \{m_i(s), 0 \leq s < t\}$
- * α quantifies the effect of aortic gradient on the risk for death/re-operation
- * w_i baseline covariates

2.1 Joint Modeling Framework (cont'd)

- ▷ Longitudinal Part: Reconstruct $\mathcal{M}_i(t) = \{m_i(s), 0 \leq s < t\}$ using $y_i(t)$ and a mixed effects model (we focus on continuous markers)

$$\begin{aligned}
 y_i(t) &= m_i(t) + \varepsilon_i(t) \\
 &= x_i^\top(t)\beta + z_i^\top(t)b_i + \varepsilon_i(t), \quad \varepsilon_i(t) \sim \mathcal{N}(0, \sigma^2),
 \end{aligned}$$

where

- * $x_i(t)$ and β : Fixed-effects part
- * $z_i(t)$ and b_i : Random-effects part, $b_i \sim \mathcal{N}(0, D)$

2.1 Joint Modeling Framework (cont'd)

- The two processes are associated \Rightarrow define a model for their joint distribution
- Joint Models for such joint distributions are of the following form
(Tsiatis & Davidian, *Stat. Sinica*, 2004; Rizopoulos, CRC Press, 2012)

$$p(y_i, T_i, \delta_i) = \int p(y_i | b_i) \{h(T_i | b_i)^{\delta_i} S(T_i | b_i)\} p(b_i) db_i$$

where

- ▷ b_i a vector of random effects that explains the interdependencies
- ▷ $p(\cdot)$ density function; $S(\cdot)$ survival function

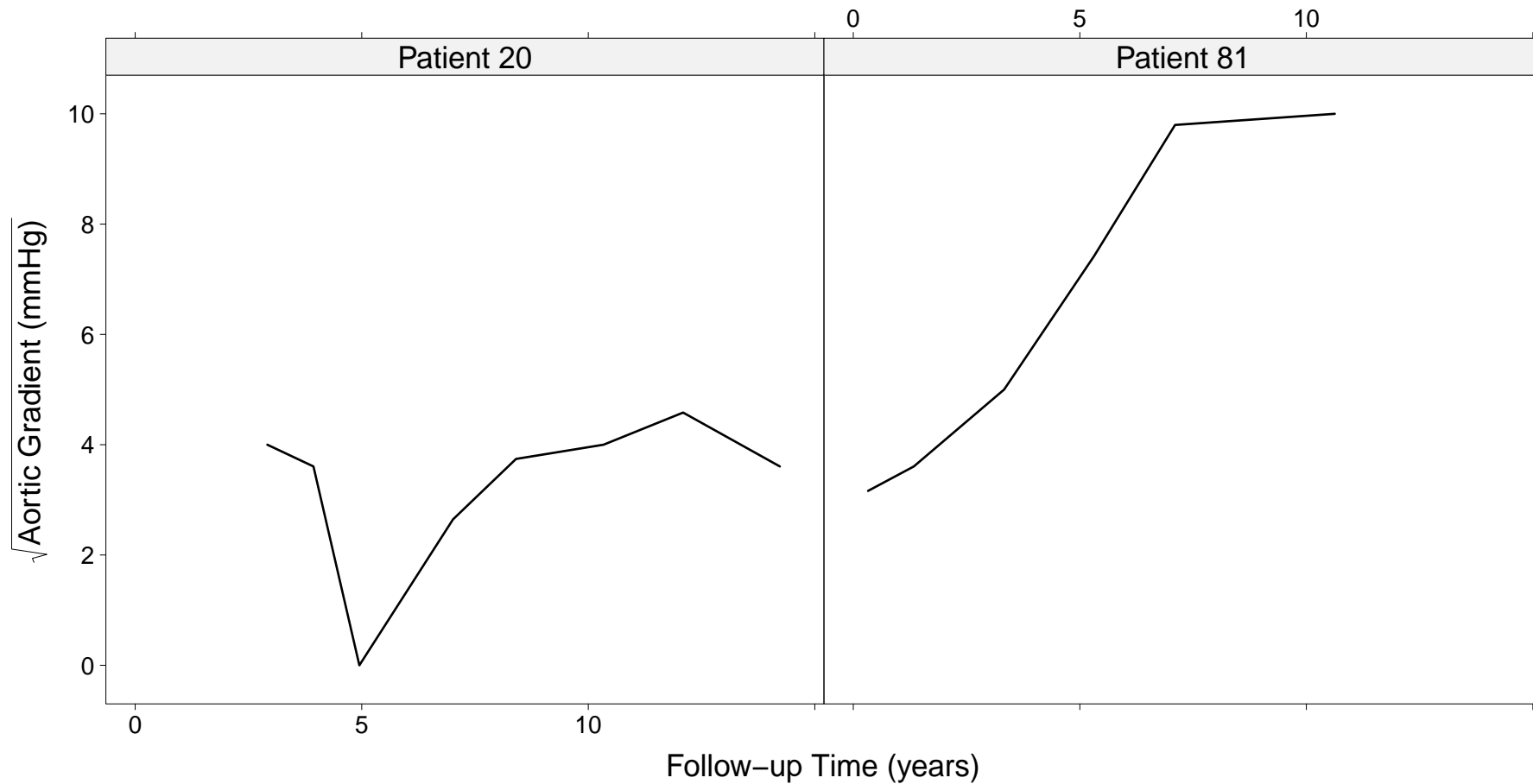
2.2 Estimation

- Joint models can be estimated with either Maximum Likelihood or Bayesian approaches (i.e., MCMC)
- Here we follow the Bayesian approach because it facilitates computations for our later developments. . .

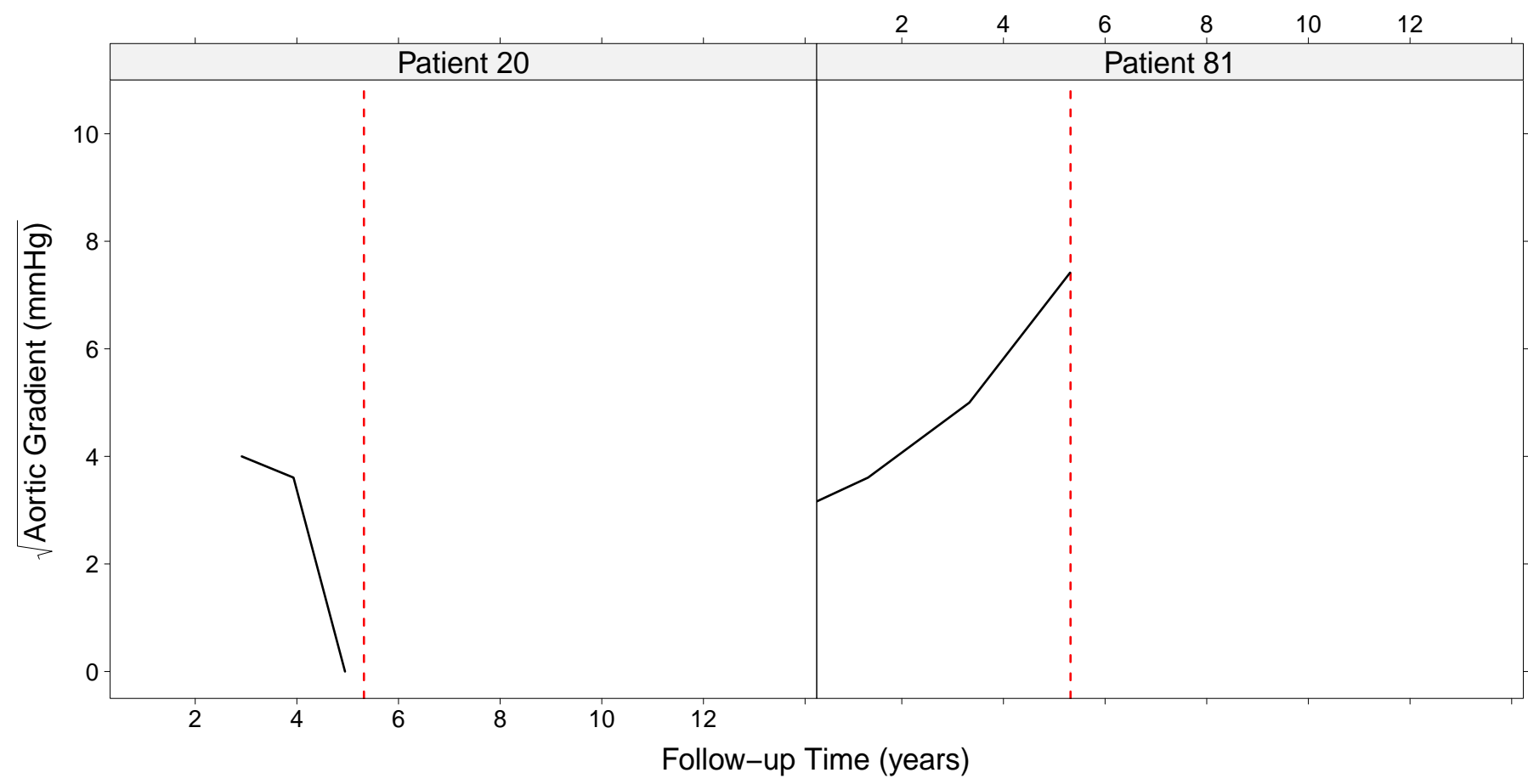
3.1 Prediction Survival – Definitions

- We are interested in predicting survival probabilities for a new patient j that has provided a set of aortic gradient measurements up to a specific time point t
- Example: We consider Patients 20 and 81 from the Aortic Valve dataset

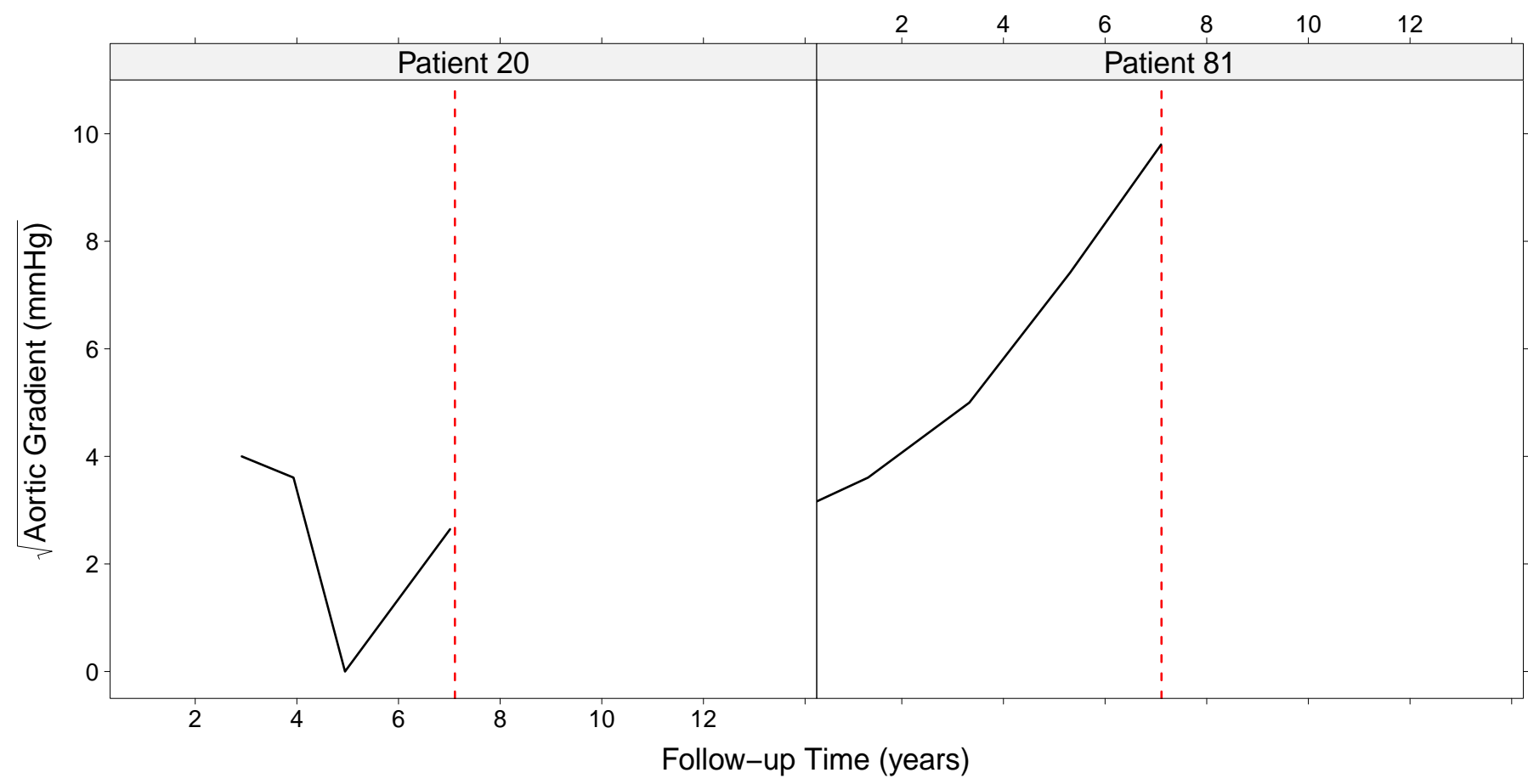
3.1 Prediction Survival – Definitions (cont'd)



3.1 Prediction Survival – Definitions (cont'd)



3.1 Prediction Survival – Definitions (cont'd)



3.1 Prediction Survival – Definitions (cont'd)

- What do we know for these patients?
 - ▷ a series of aortic gradient measurements
 - ▷ patient are event-free up to the last measurement
- **Dynamic Prediction** survival probabilities are dynamically updated as additional longitudinal information is recorded

3.1 Prediction Survival – Definitions (cont'd)

- Available info: A new subject j with longitudinal measurements up to t
 - ▷ $T_j^* > t$
 - ▷ $\mathcal{Y}_j(t) = \{y_j(t_{jl}); 0 \leq t_{jl} \leq t, l = 1, \dots, n_j\}$
 - ▷ \mathcal{D}_n sample on which the joint model was fitted

Basic tool: **Posterior Predictive Distribution**

$$p\{T_j^* \mid T_j^* > t, \mathcal{Y}_j(t), \mathcal{D}_n\}$$

3.2 Prediction Survival – Estimation

- Based on the fitted model we can estimate the conditional survival probabilities

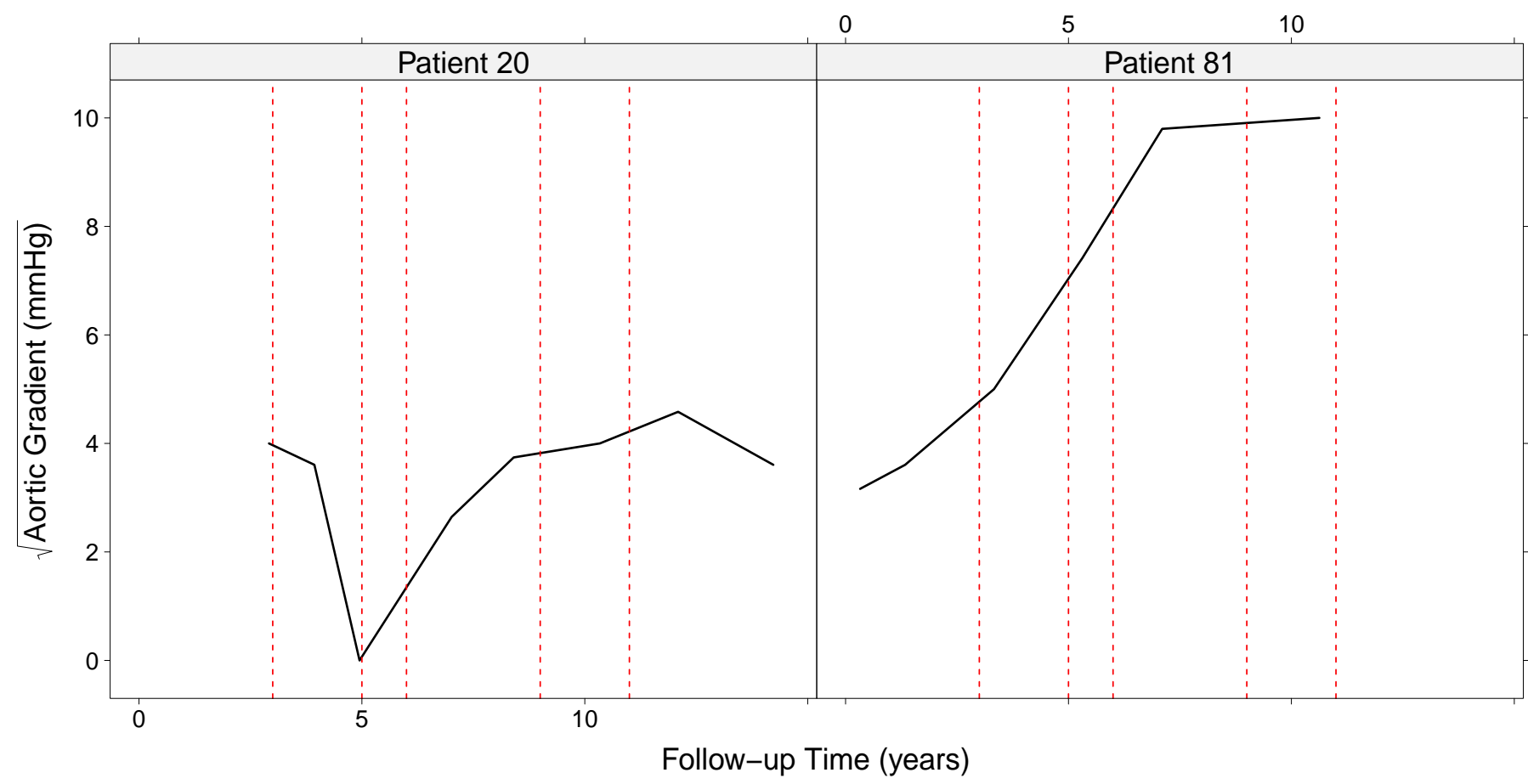
$$\pi_j(u | t) = \Pr\{T_j^* \geq u \mid T_j^* > t, \mathcal{Y}_j(t), \mathcal{D}_n\}, \quad u > t$$

- For more details check:
 - ▷ Proust-Lima and Taylor (2009, Biostatistics), Rizopoulos (2011, Biometrics), Taylor et al. (2013, Biometrics)

3.3 Prediction Survival – Illustration

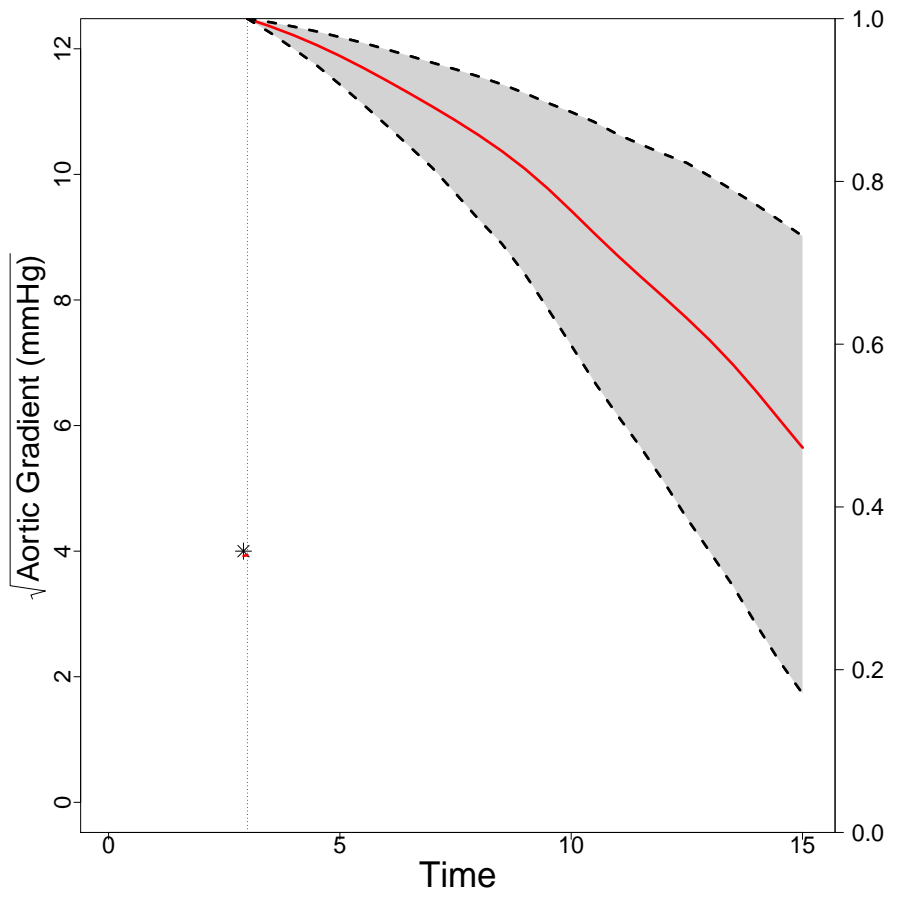
- Example: We fit a joint model to the Aortic Valve data
- Longitudinal submodel
 - ▷ fixed effects: natural cubic splines of time (d.f.= 3), operation type, and their interaction
 - ▷ random effects: Intercept, & natural cubic splines of time (d.f.= 3)
- Survival submodel
 - ▷ type of operation, age, sex + *underlying* aortic gradient level
 - ▷ log baseline hazard approximated using B-splines

3.3 Prediction Survival – Illustration (cont'd)

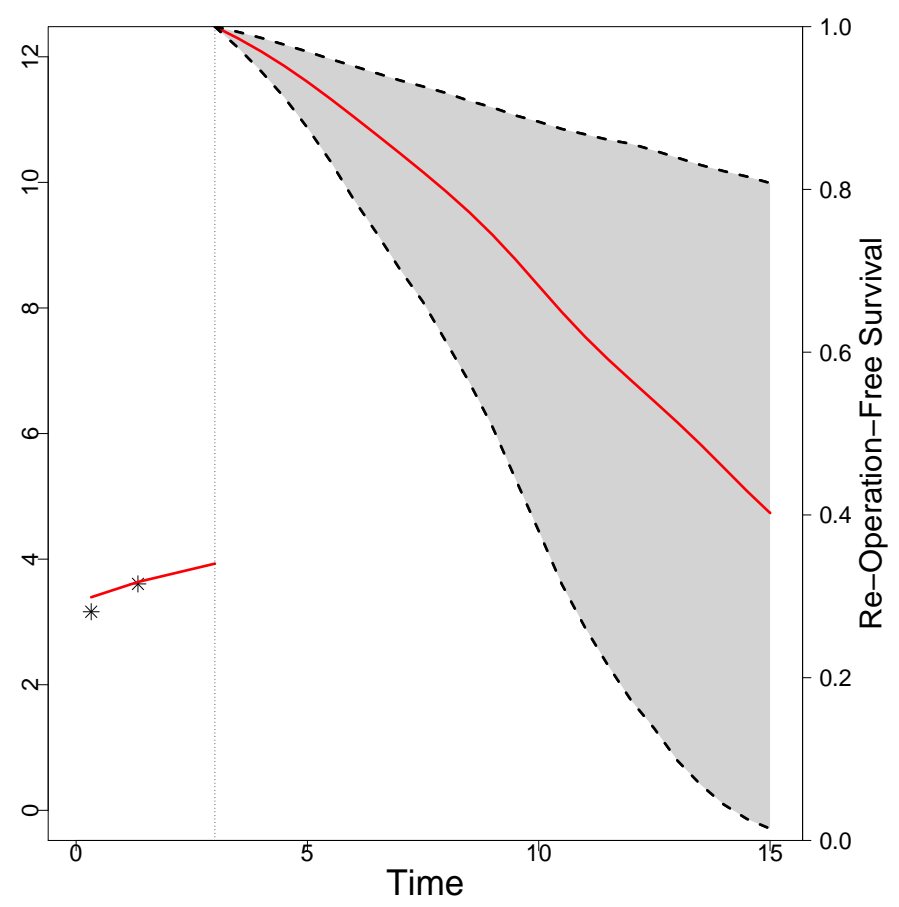


3.3 Prediction Survival – Illustration (cont'd)

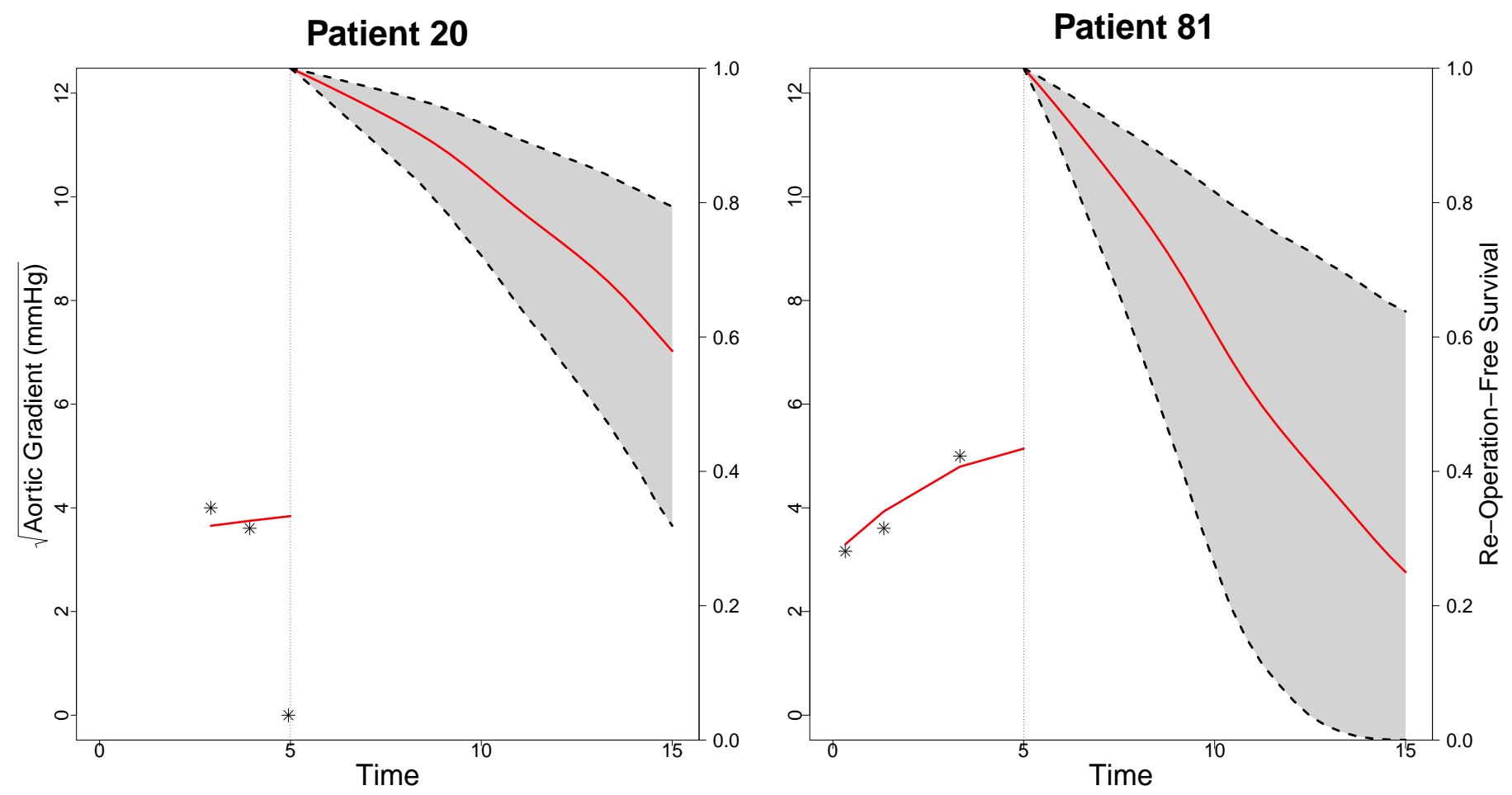
Patient 20



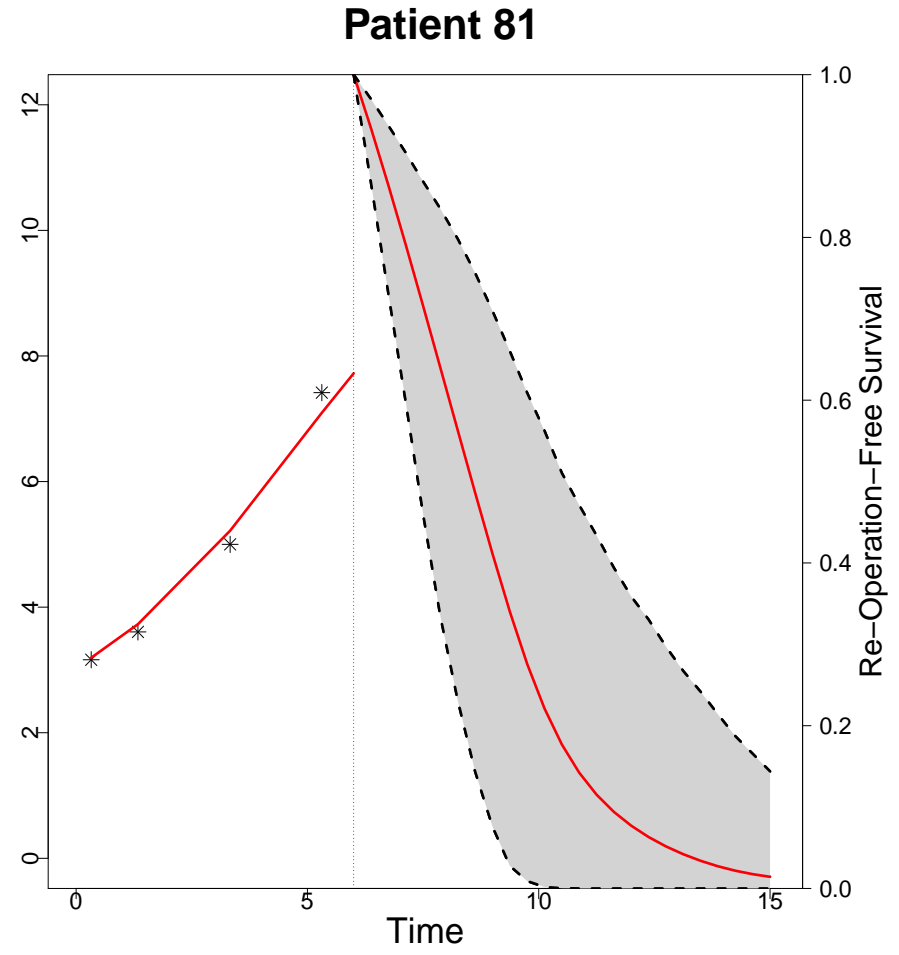
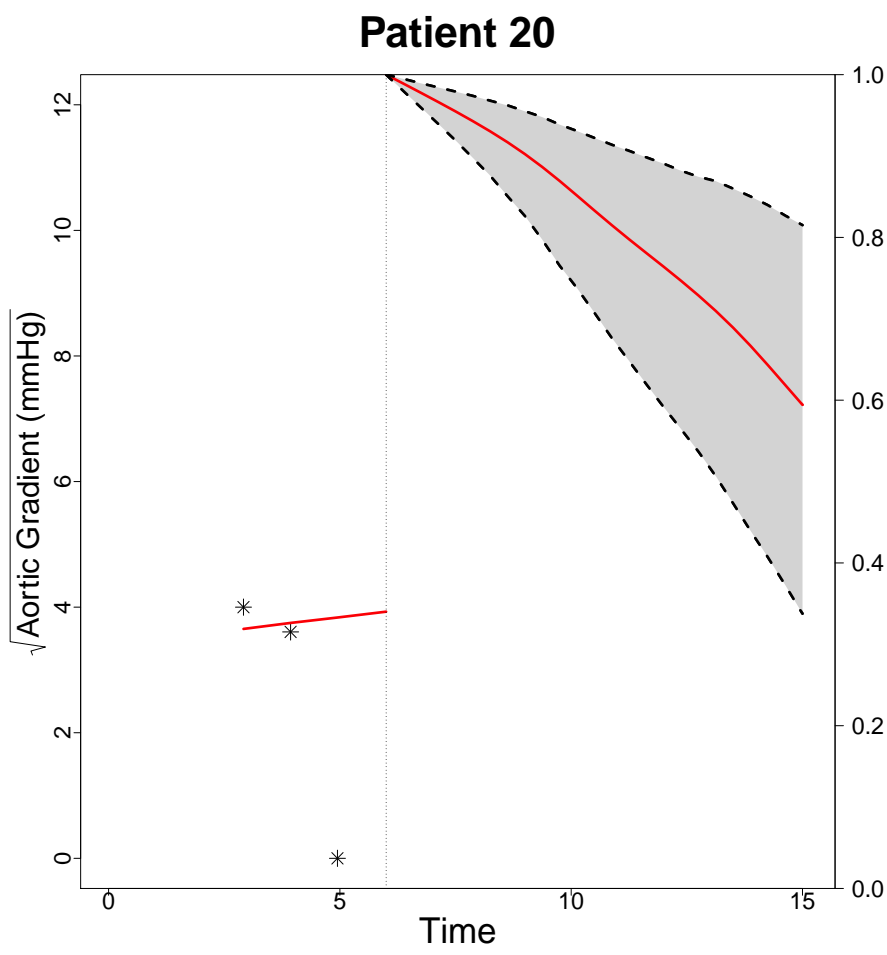
Patient 81



3.3 Prediction Survival – Illustration (cont'd)

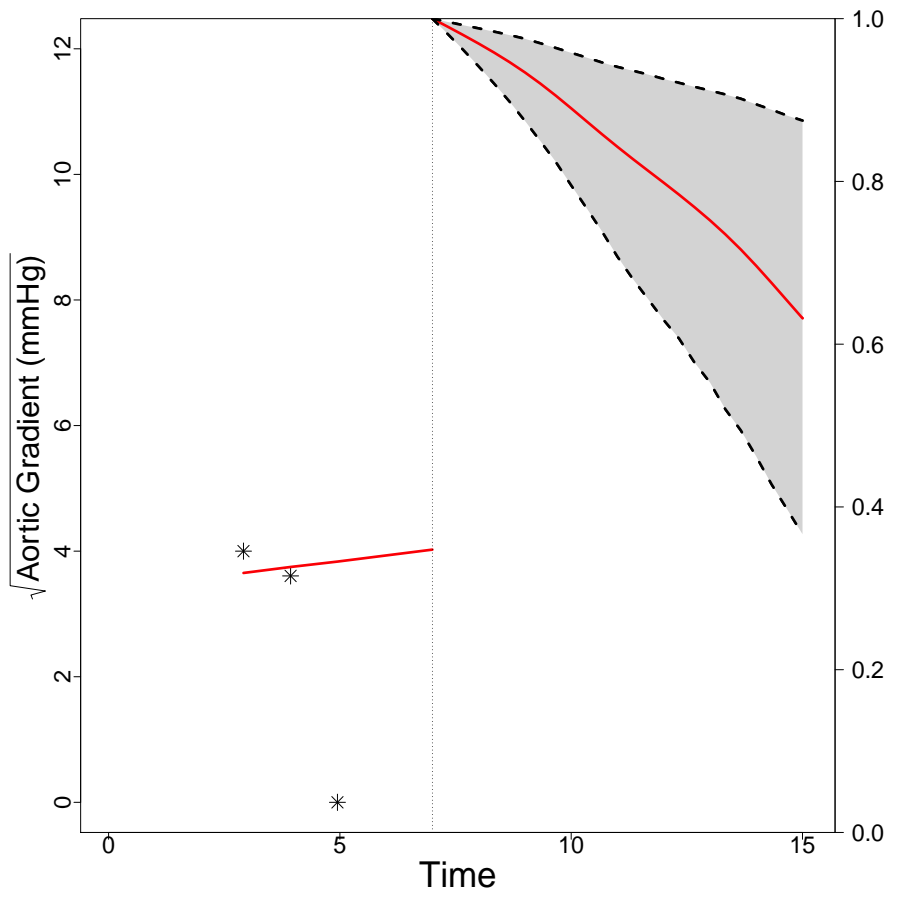


3.3 Prediction Survival – Illustration (cont'd)

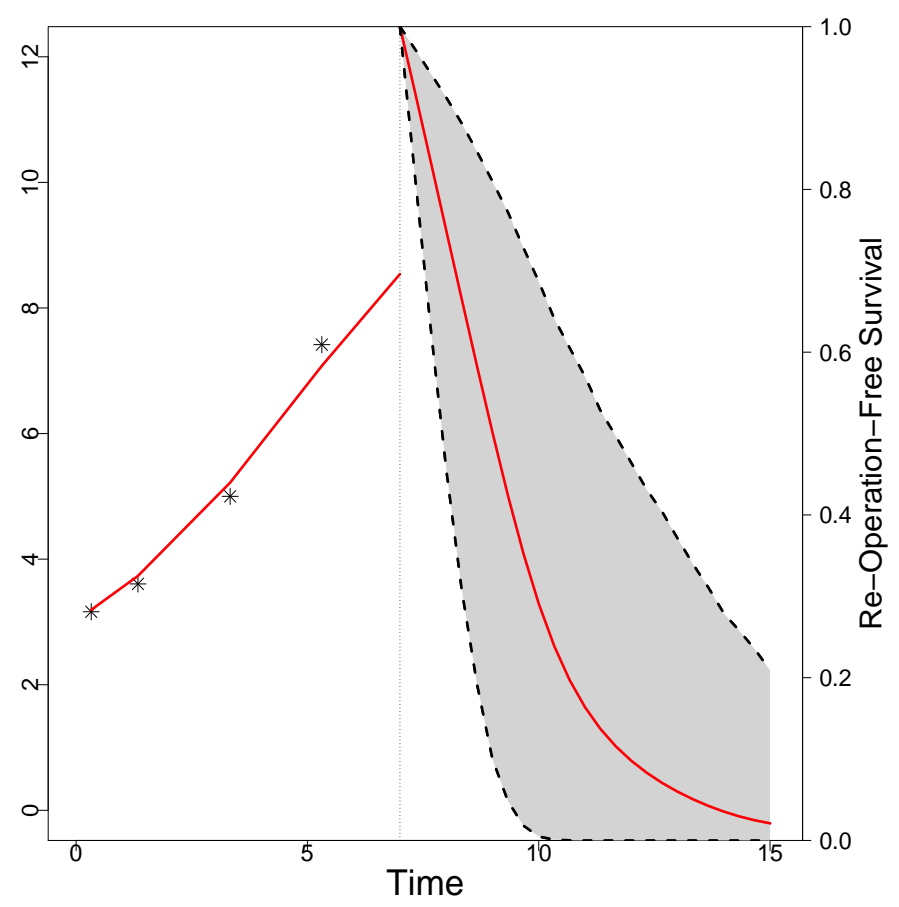


3.3 Prediction Survival – Illustration (cont'd)

Patient 20

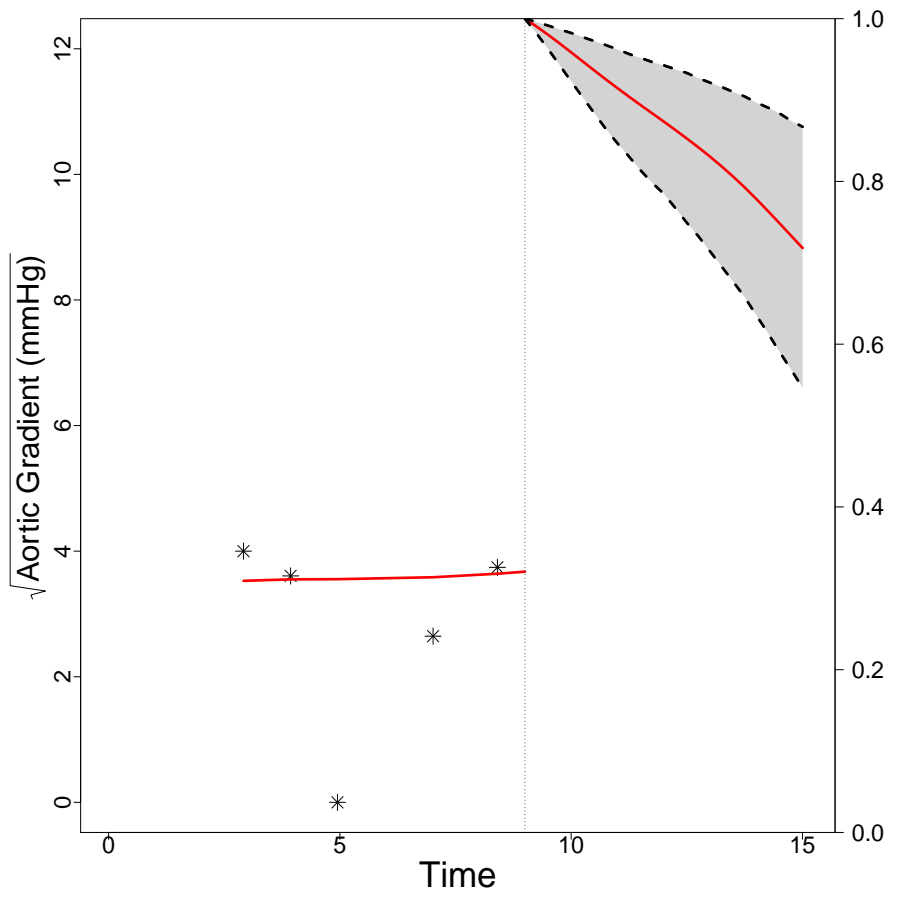


Patient 81

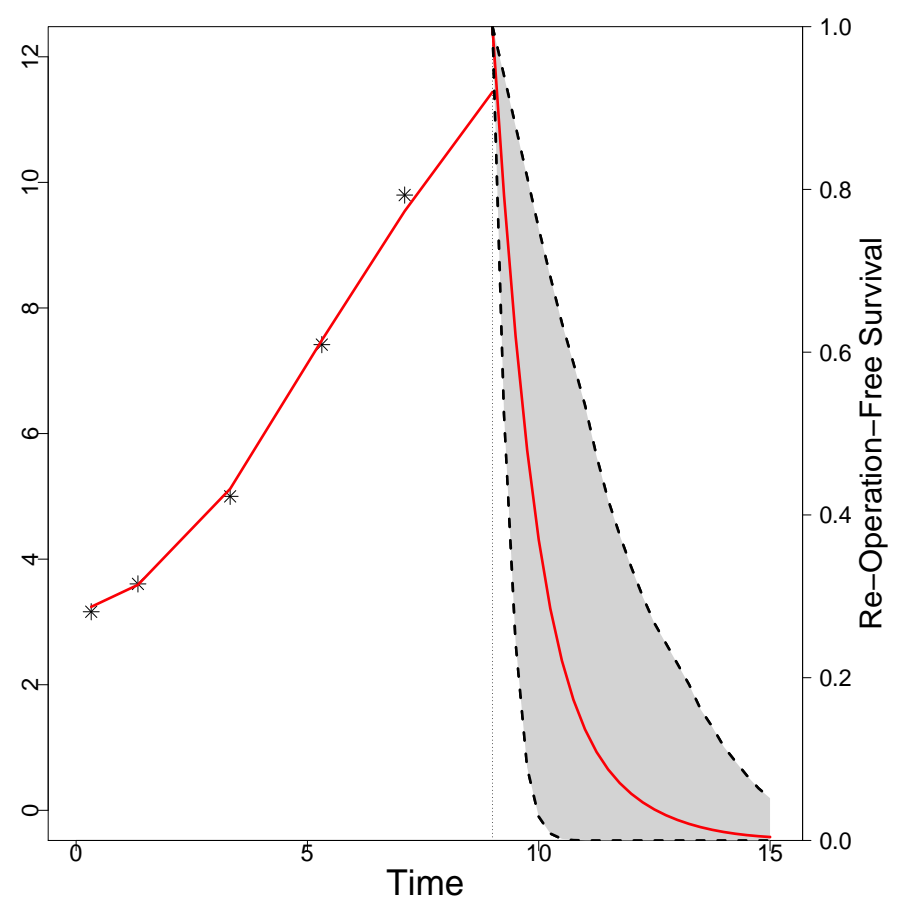


3.3 Prediction Survival – Illustration (cont'd)

Patient 20

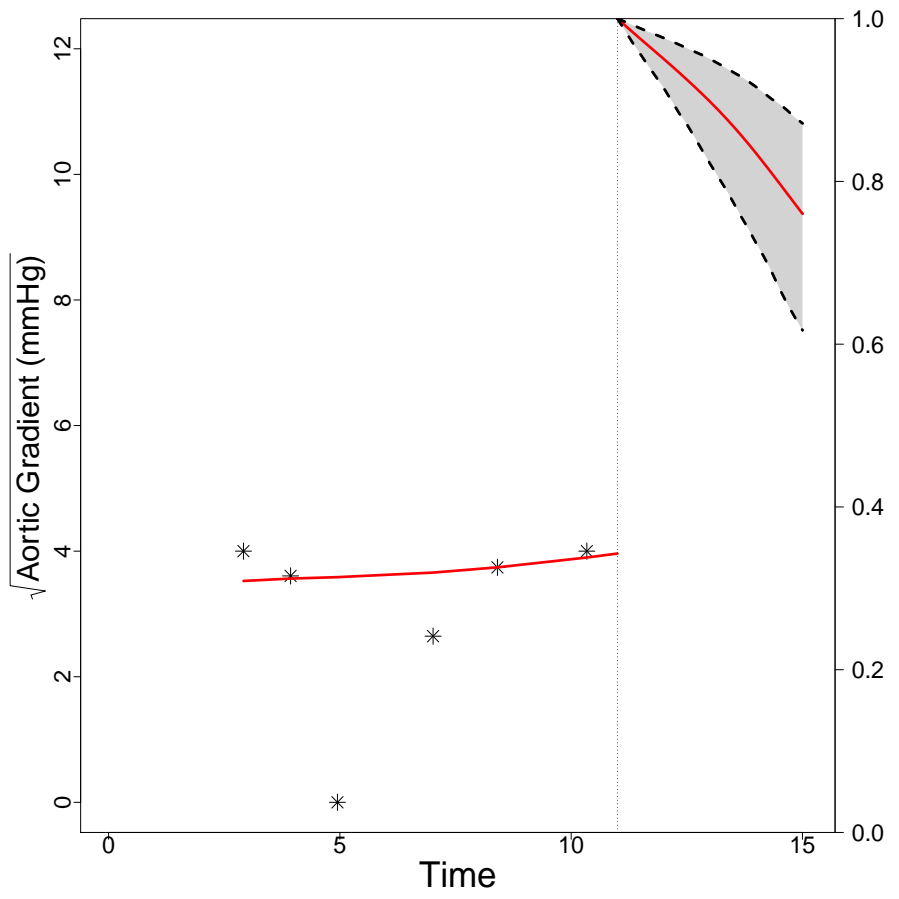


Patient 81

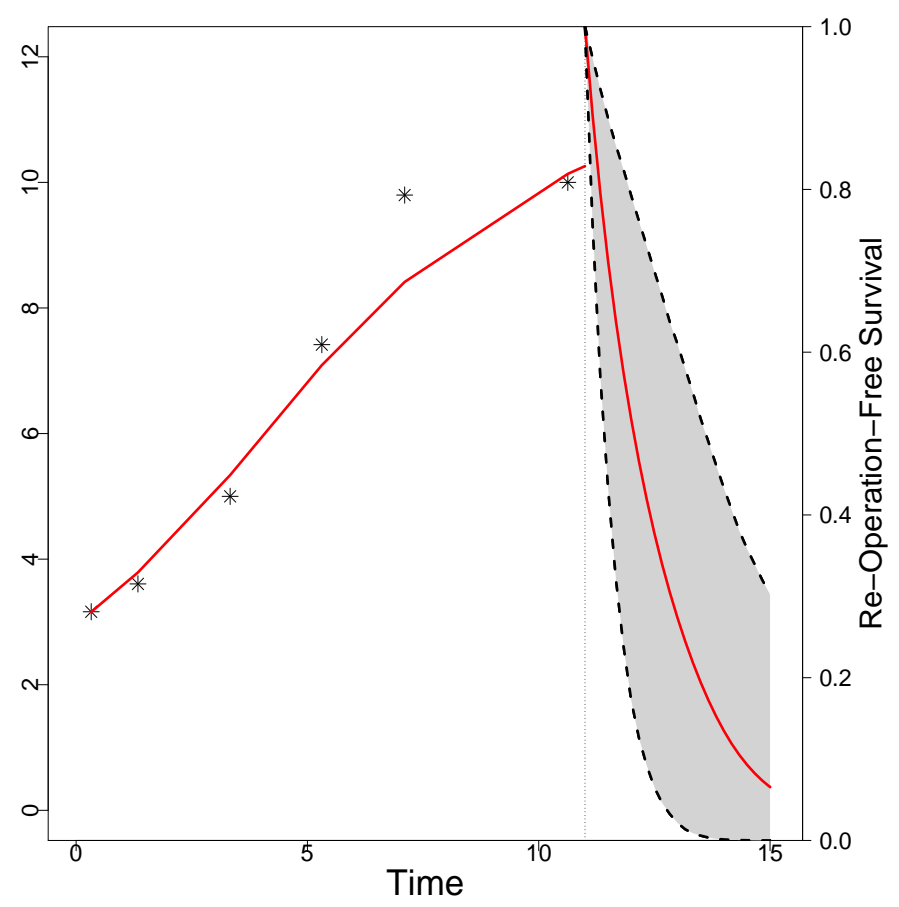


3.3 Prediction Survival – Illustration (cont'd)

Patient 20



Patient 81



4.1 Next Visit Time – Set up

- **Question 2:**

- ▷ When the patient should come for the next visit?

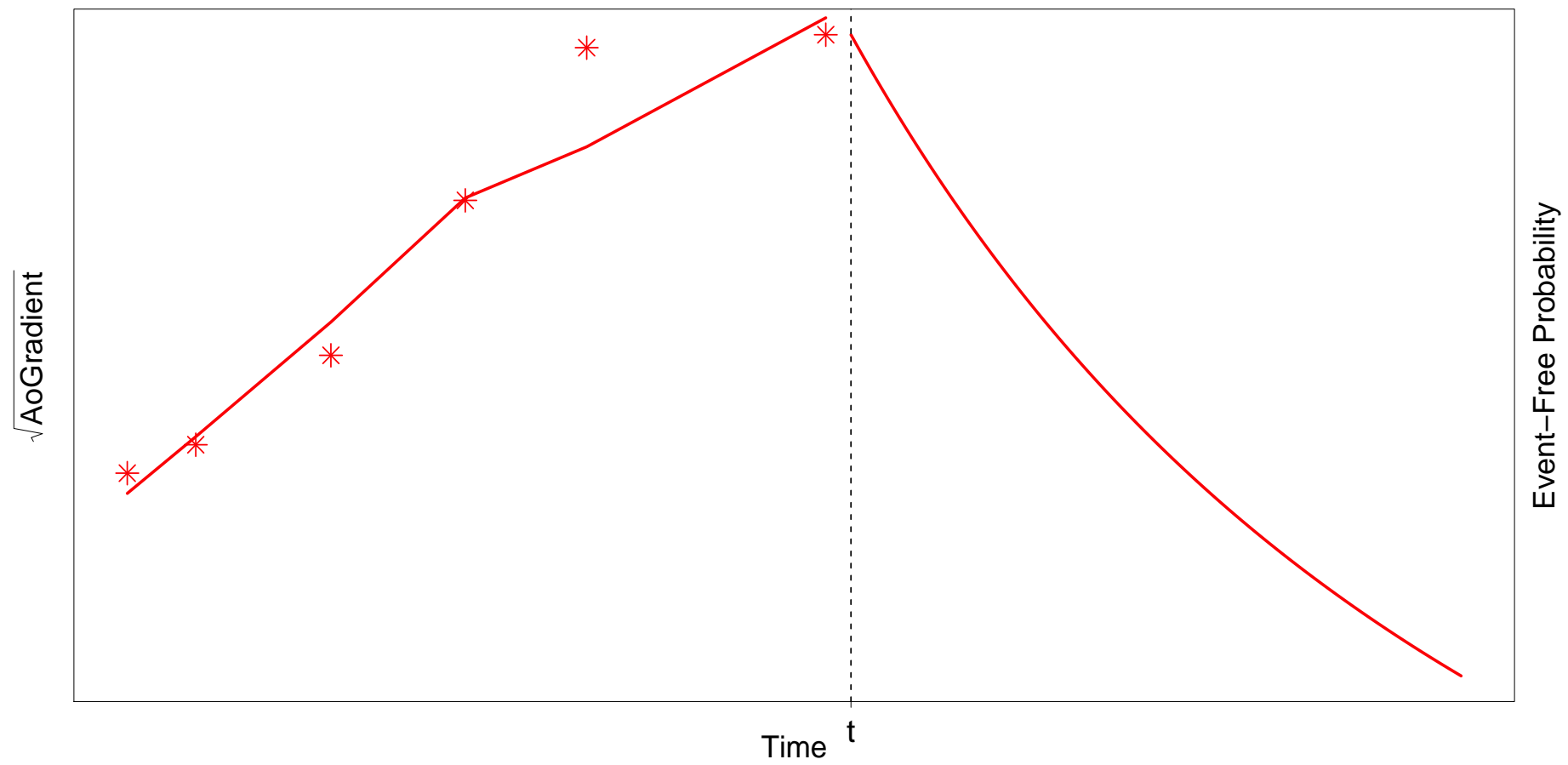
4.1 Next Visit Time – Set up (cont'd)

This is a difficult question!

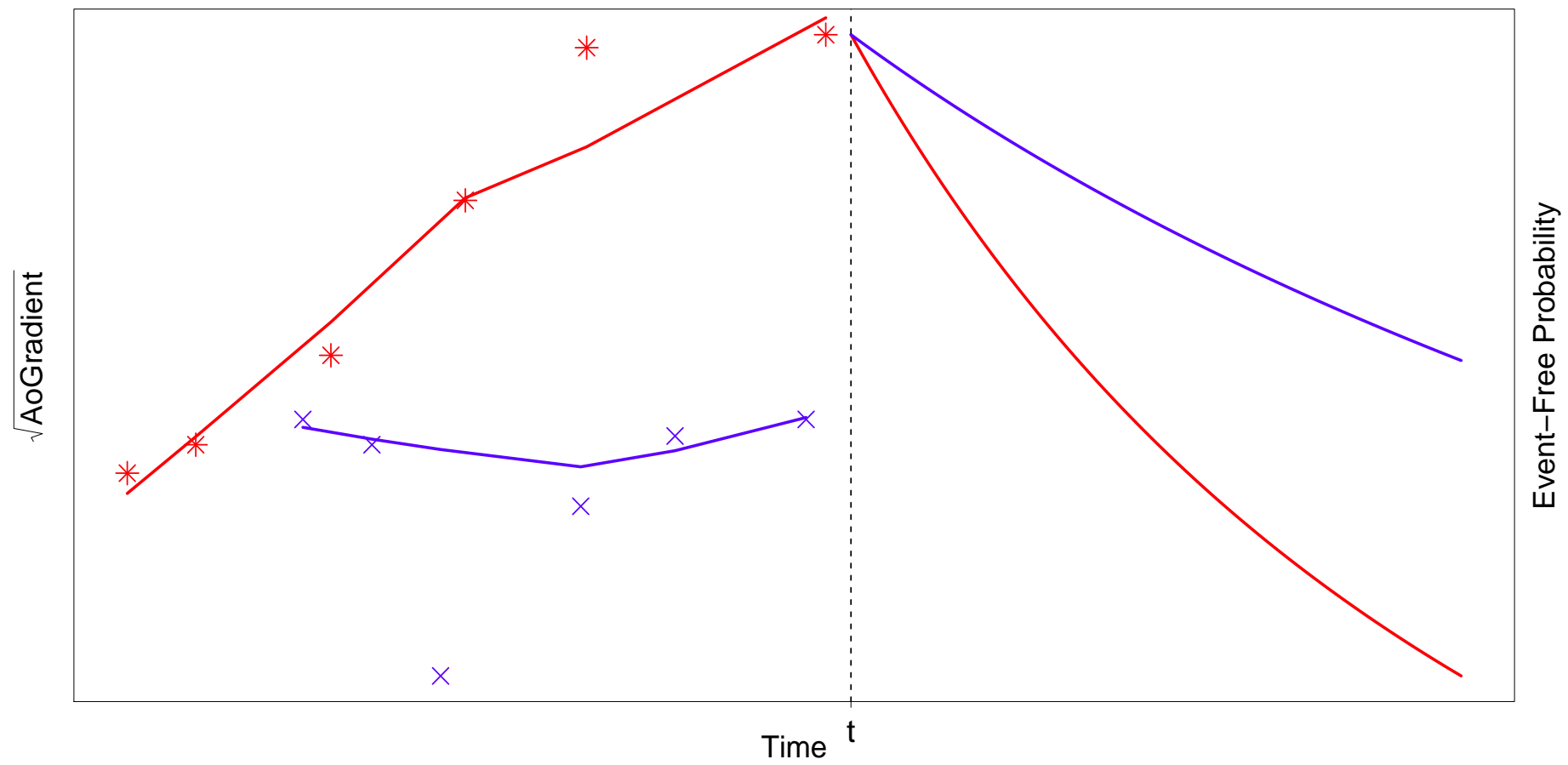
- Many parameters that affect it
 - ▷ which model to use?
 - ▷ what criterion to use?
 - ▷ change in treatment?
 - ▷ ...

We will work under the following setting ⇒

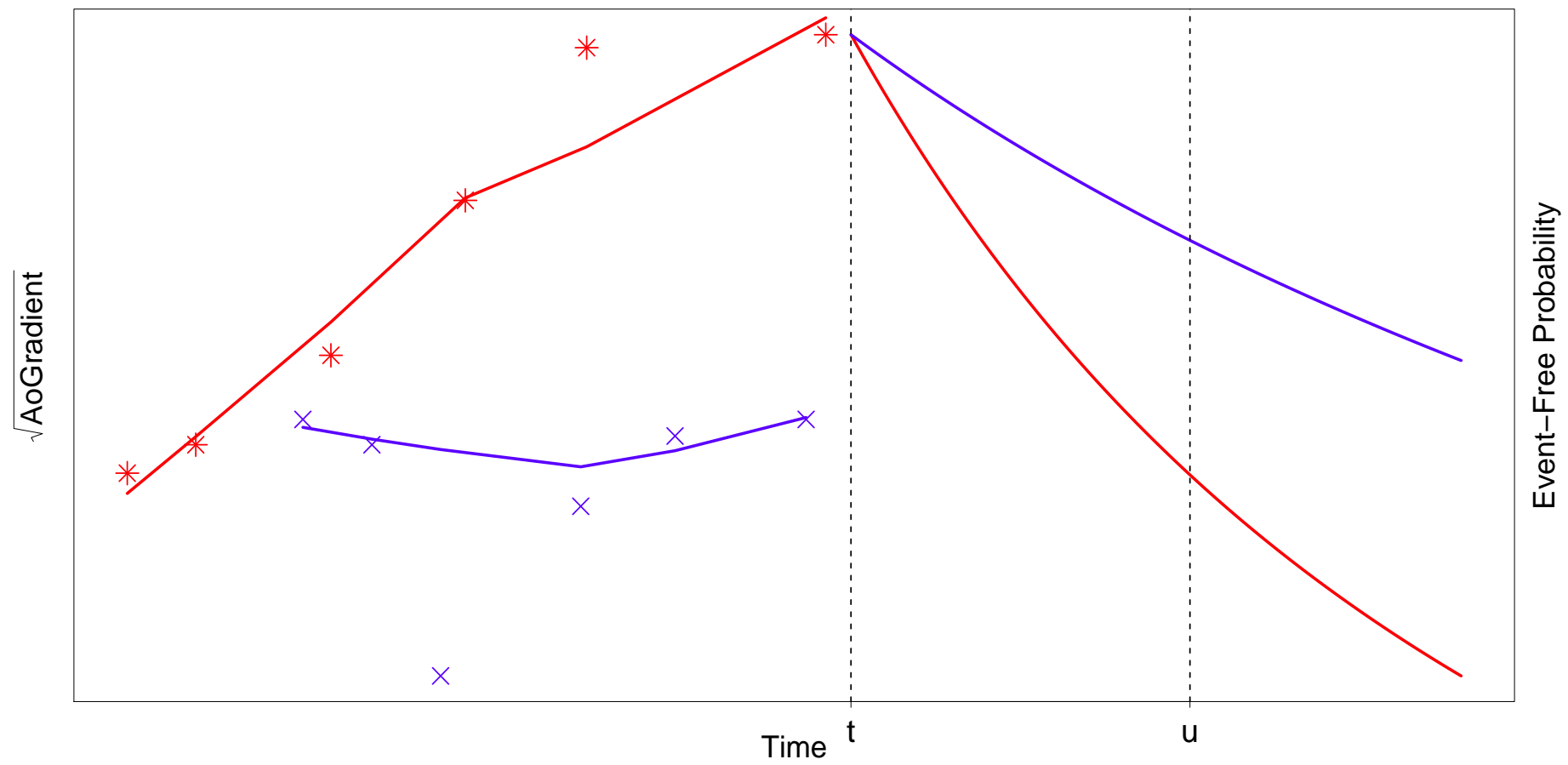
4.1 Next Visit Time – Set up(cont'd)



4.1 Next Visit Time – Set up(cont'd)



4.1 Next Visit Time – Set up(cont'd)



4.2 Next Visit Time – Timing

- Let $y_j(u)$ denote the future longitudinal measurement $u > t$
- We would like to select the optimal u such that:
 - ▷ patient still event-free up to u
 - ▷ maximize the information by measuring $y_j(u)$ at u

4.2 Next Visit Time – Timing (cont'd)

- Utility function

$$U(u | t) = E \left\{ \underbrace{\lambda_1 \log \frac{p(T_j^* | T_j^* > u, \{\mathcal{Y}_j(t), y_j(u)\}, \mathcal{D}_n)}{p\{T_j^* | T_j^* > u, \mathcal{Y}_j(t), \mathcal{D}_n\}}}_{\text{First term}} + \underbrace{\lambda_2 I(T_j^* > u)}_{\text{Second term}} \right\}$$

First term

Second term

expectation wrt joint predictive distribution $[T_j^*, y_j(u) | T_j^* > t, \mathcal{Y}_j(t), \mathcal{D}_n]$

- ▷ **First term:** expected Kullback-Leibler divergence of posterior predictive distributions with and without $y_j(u)$
- ▷ **Second term:** ‘cost’ of waiting up to $u \Rightarrow$ increase the risk

4.2 Next Visit Time – Timing (cont'd)

- Nonnegative constants λ_1 and λ_2 weigh the cost of waiting as opposed to the information gain
 - ▷ **elicitation in practice difficult** \Rightarrow trading information units with probabilities
- How to get around it?

Equivalence between compound and constrained optimal designs

4.2 Next Visit Time – Timing (cont'd)

- It can be shown that
 - ▷ for any λ_1 and λ_2 ,
 - ▷ there exists a constant $\kappa \in [0, 1]$ for which

$$\operatorname{argmax}_u \mathbf{U}(u \mid t) \iff \operatorname{argmax}_u E \left\{ \log \frac{p(T_j^* \mid T_j^* > u, \{\mathcal{Y}_j(t), y_j(u)\}, \mathcal{D}_n)}{p\{T_j^* \mid T_j^* > u, \mathcal{Y}_j(t), \mathcal{D}_n\}} \right\}$$

subject to the constraint $\pi_j(u \mid t) \geq \kappa$

4.2 Next Visit Time – Timing (cont'd)

- Elicitation of κ is relatively easier
 - ▷ Chosen by the physician
 - ▷ Determined using ROC analysis

- Estimation is achieved using a Monte Carlo scheme
 - ▷ more details in Rizopoulos et al. (2015)

4.3 Next Visit Time – Example

- **Example:** We illustrate how for Patient 81 we have seen before
 - ▷ The threshold for the constraint is set to

$$\pi_j(u | t) \geq \kappa = 0.8$$

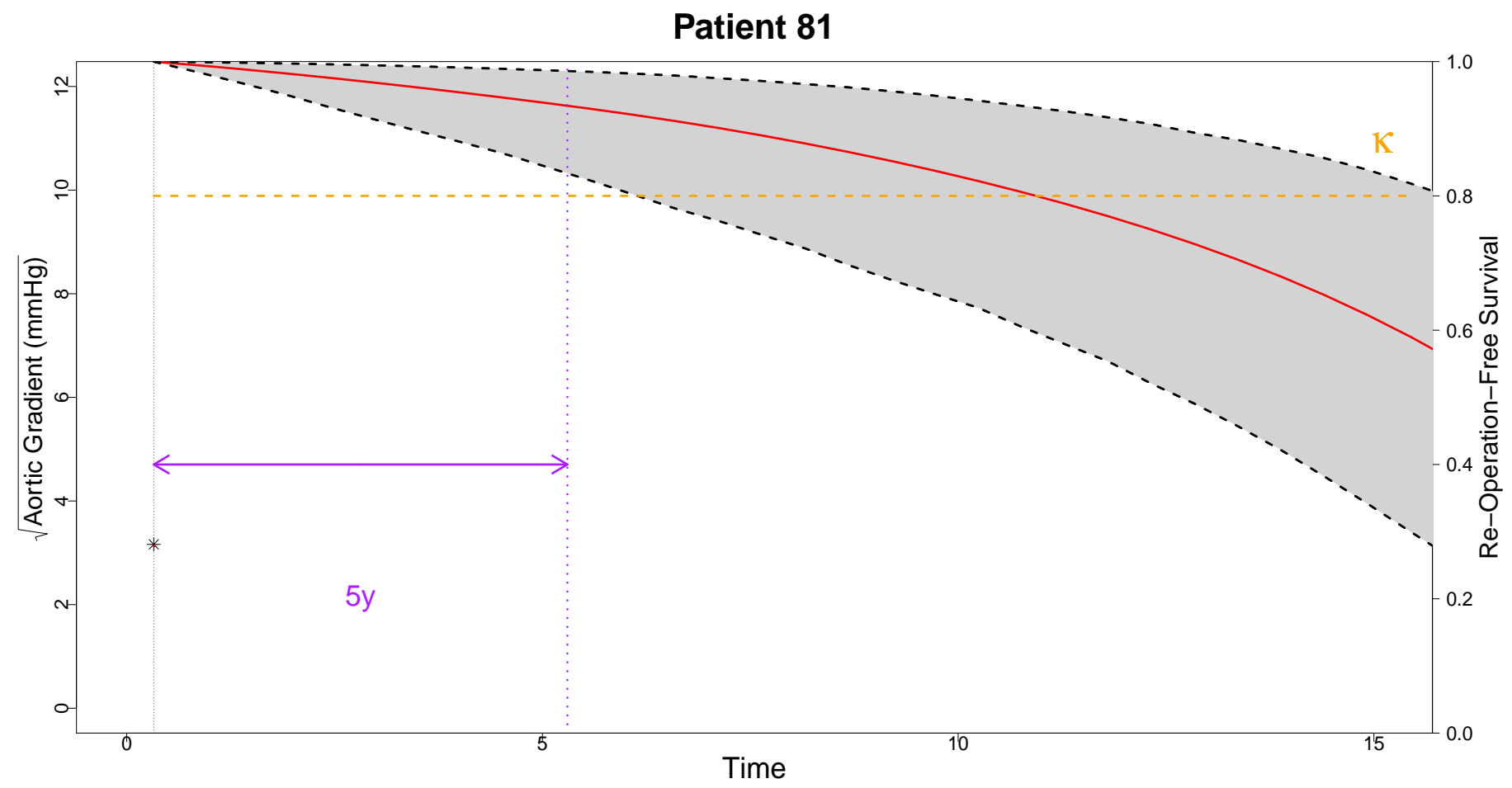
- ▷ After each visit we calculate the optimal timing for the next one using

$$\operatorname{argmax}_u \text{EKL}(u | t) \quad \text{where } u \in (t, t^{up}]$$

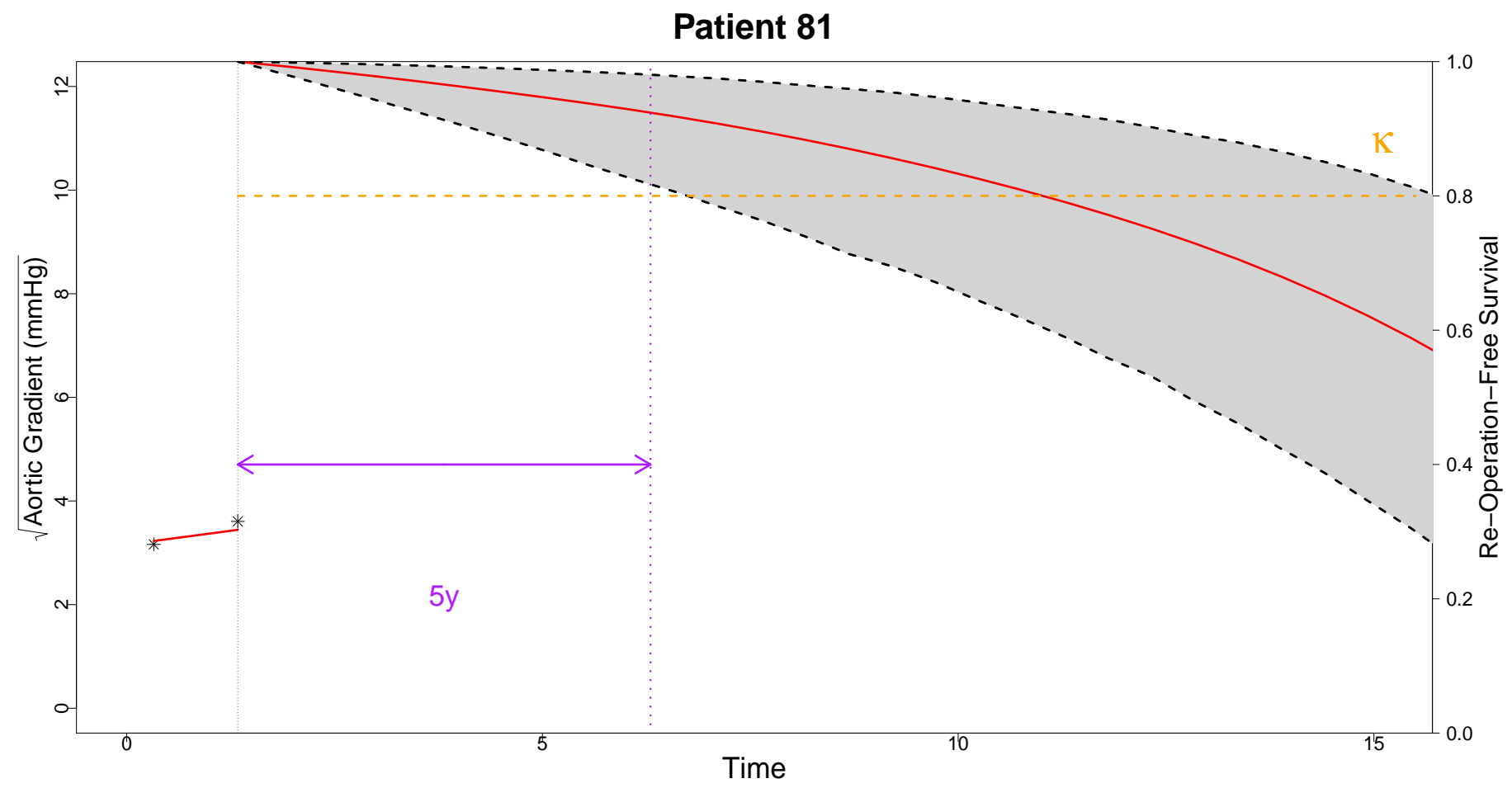
and

$$t^{up} = \min\{5, u : \pi_j(u | t) = 0.8\}$$

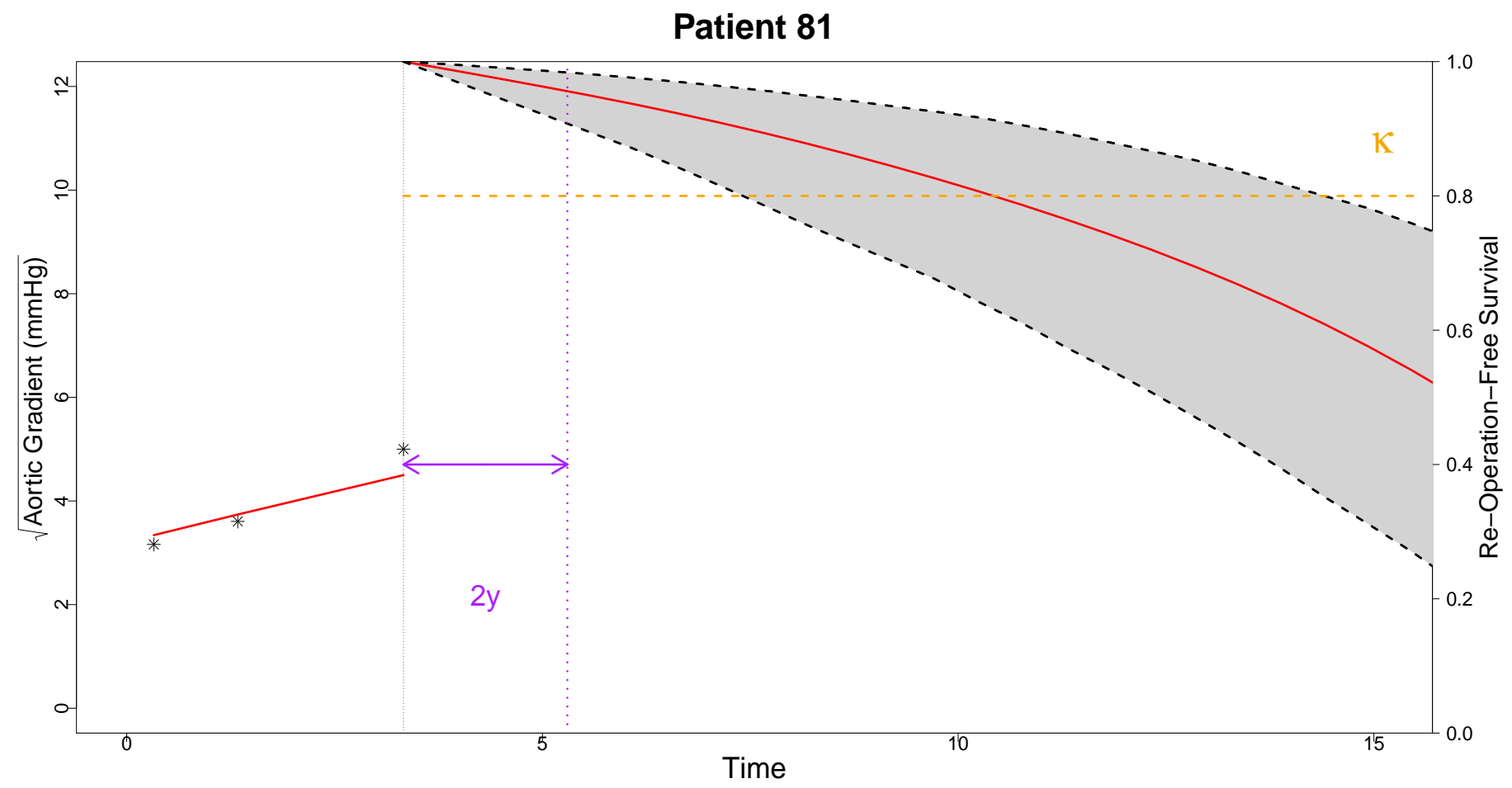
4.3 Next Visit Time – Example (cont'd)



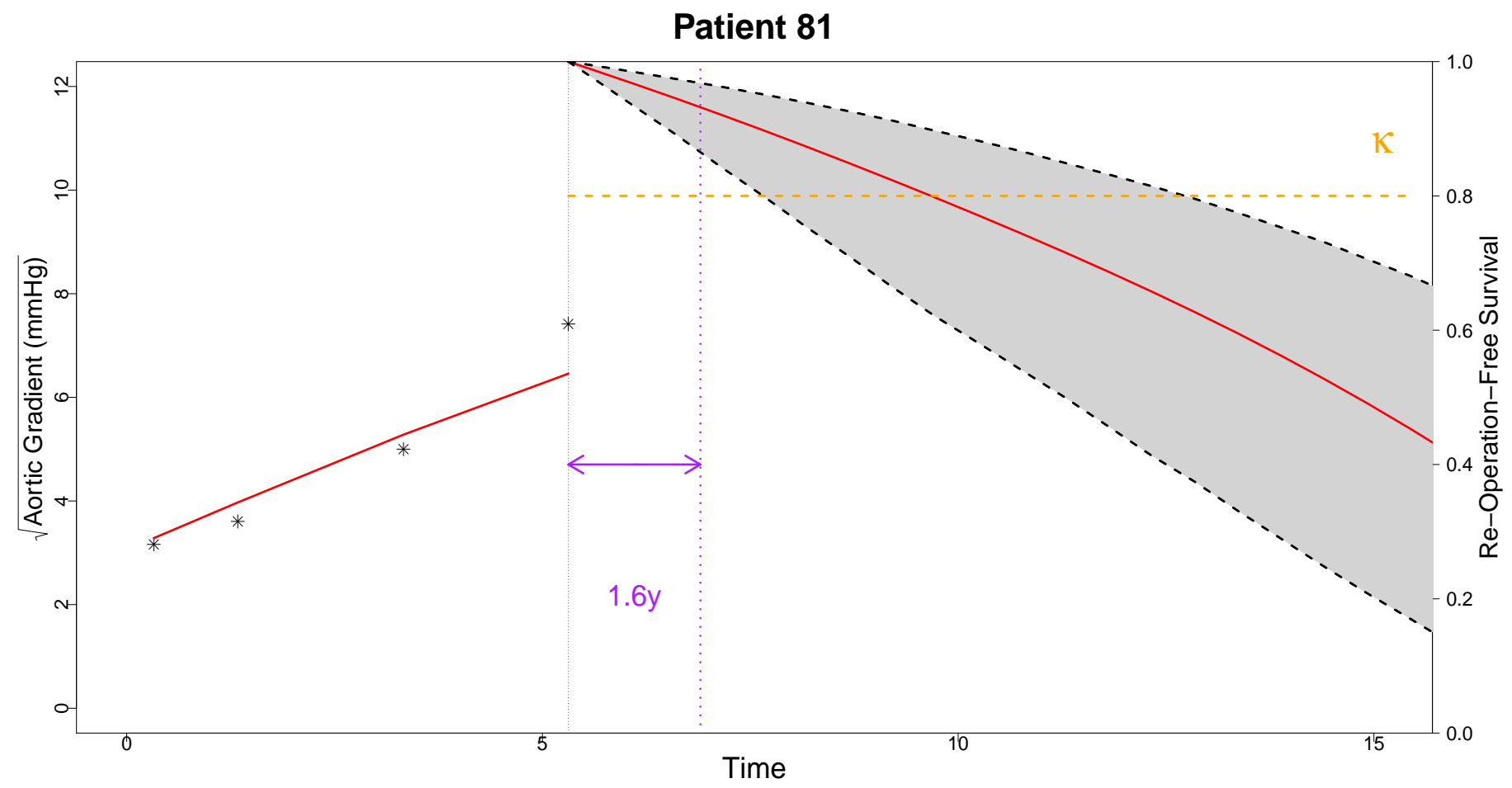
4.3 Next Visit Time – Example (cont'd)



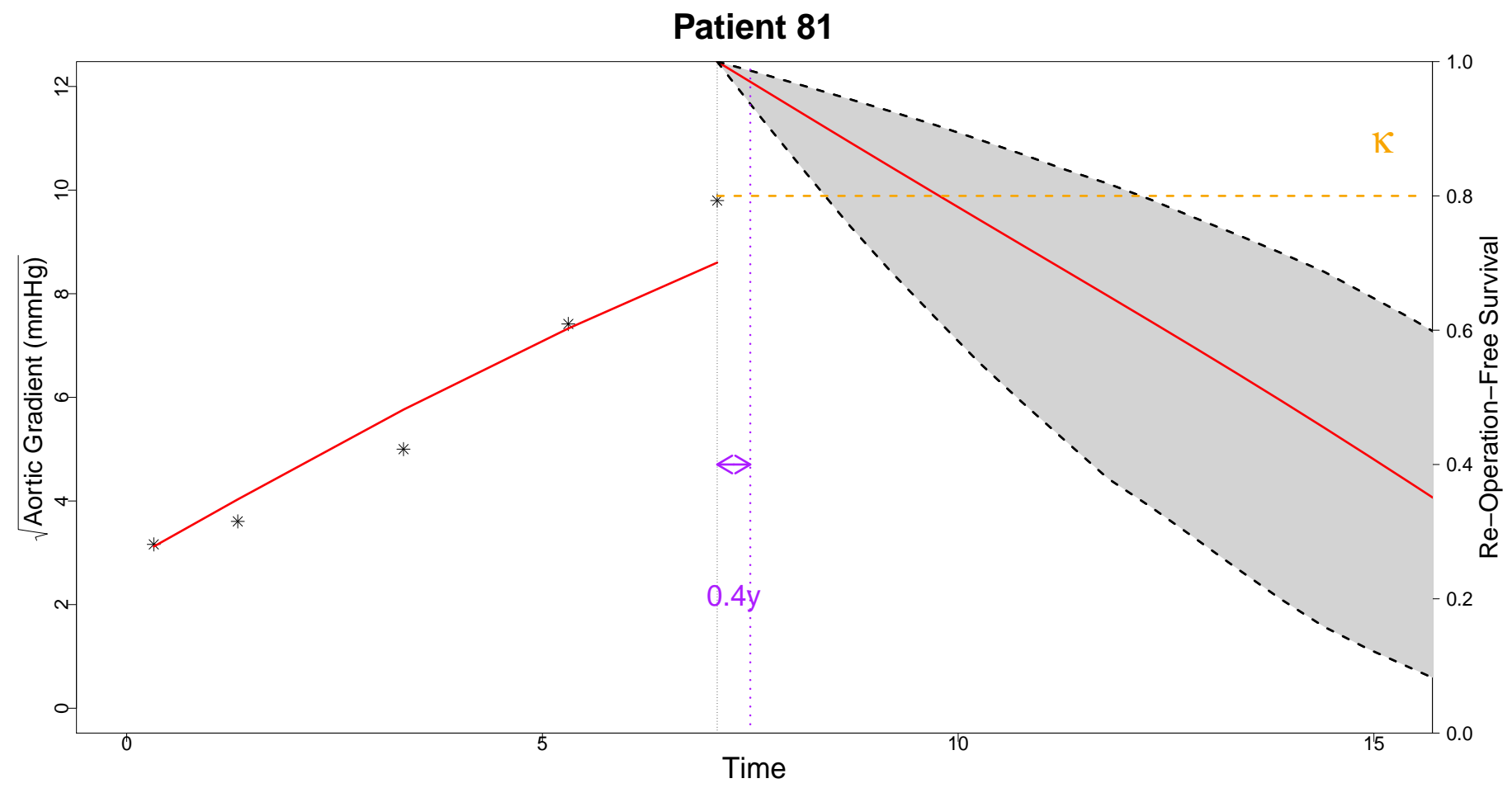
4.3 Next Visit Time – Example (cont'd)



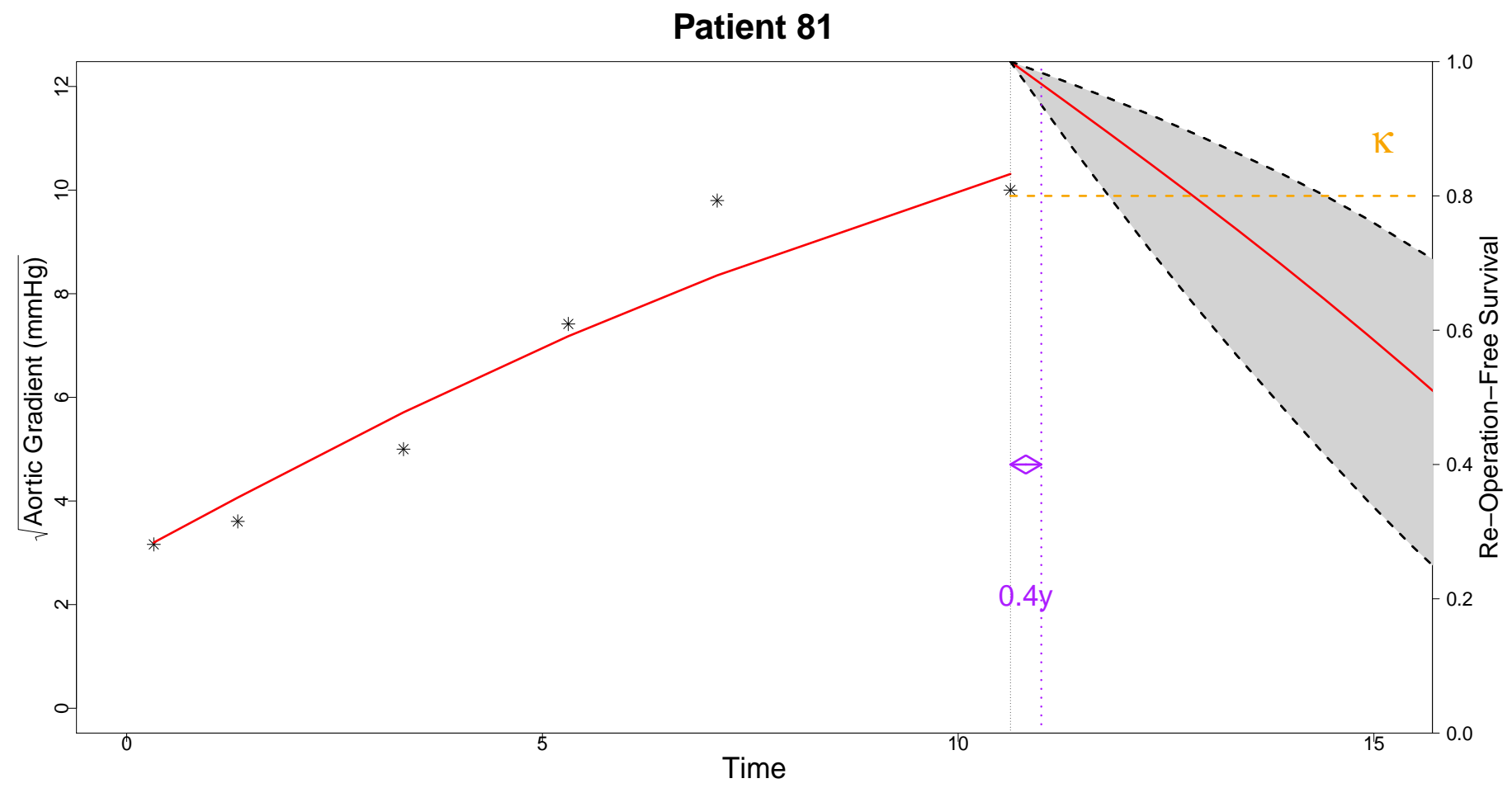
4.3 Next Visit Time – Example (cont'd)



4.3 Next Visit Time – Example (cont'd)



4.3 Next Visit Time – Example (cont'd)



5. Software

- Software: R package **JMbayes** freely available via <http://cran.r-project.org/package=JMbayes>
 - ▷ it can fit a variety of joint models + many other features
 - ▷ relevant to this talk: `cvDCL()` and `dynInfo()`

GUI interface for dynamic predictions using package
shiny

Thank you for your attention!