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)

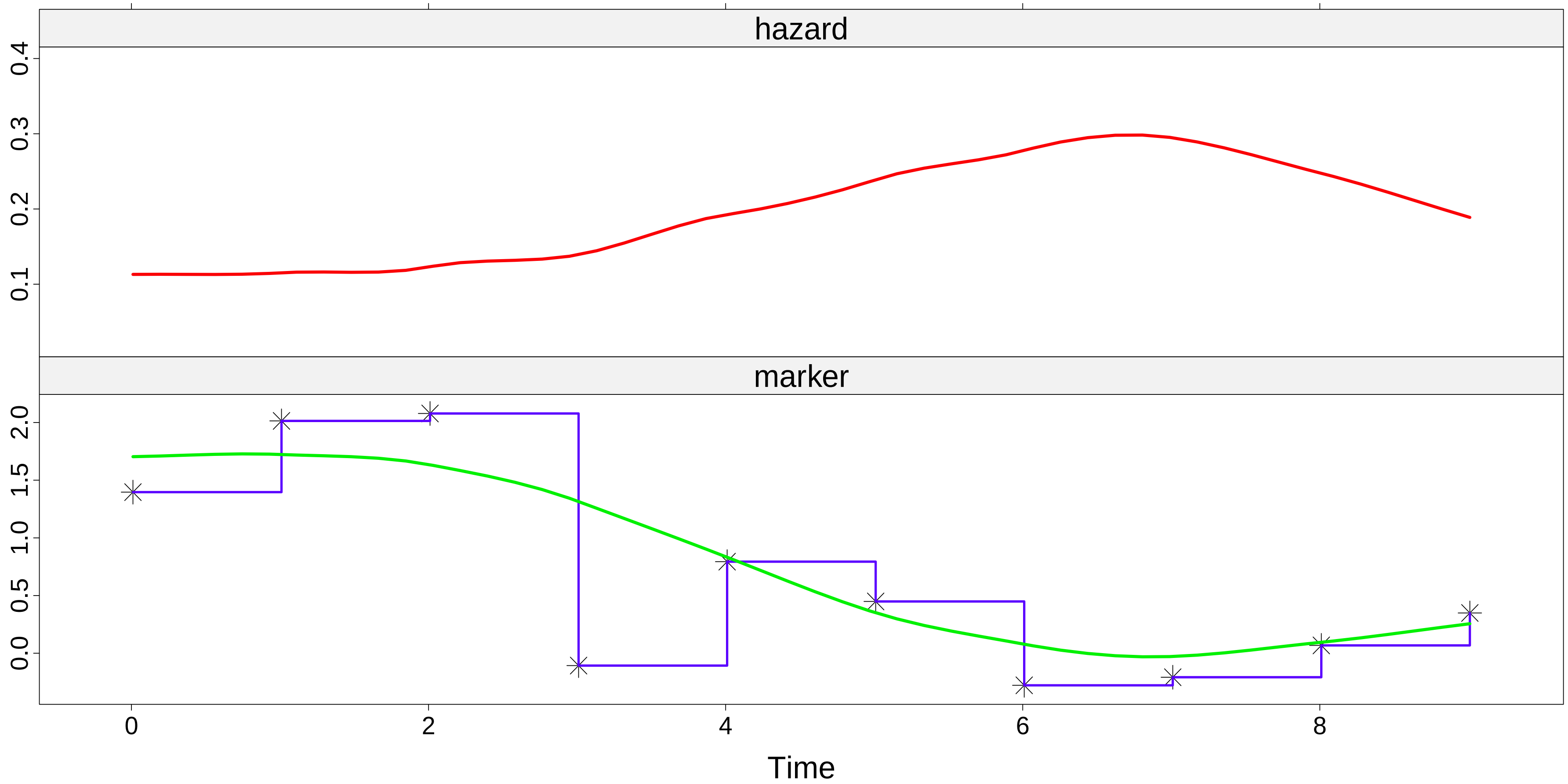
- **Goals of this talk**:
  - ▷ introduce joint models
  - ▷ dynamic predictions
  - ▷ optimal timing of next visit

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)

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

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)

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

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)

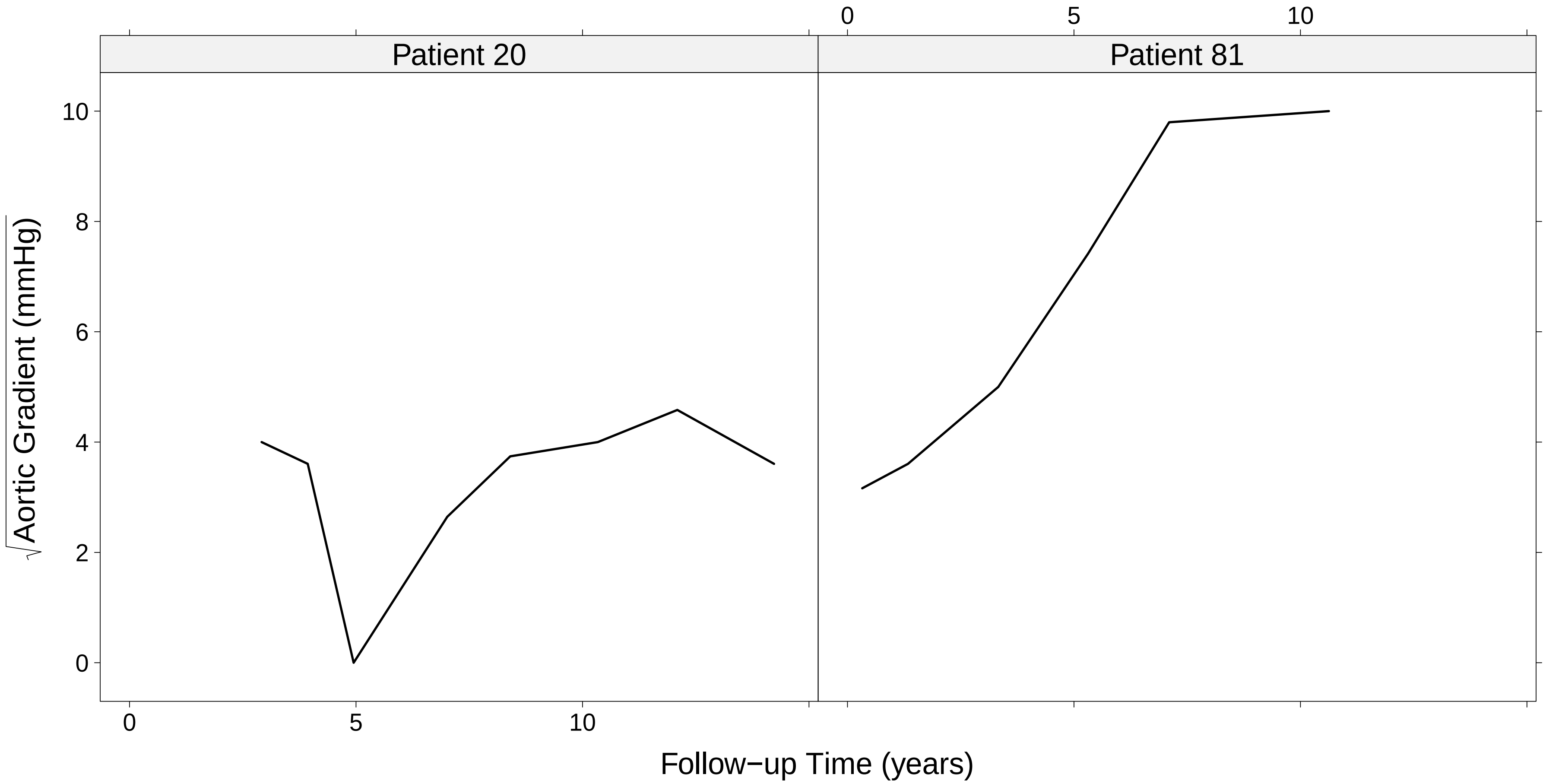
- Here we follow the Bayesian approach because it facilitates computations for our later developments. . .

3.1 Prediction Survival – Definitions

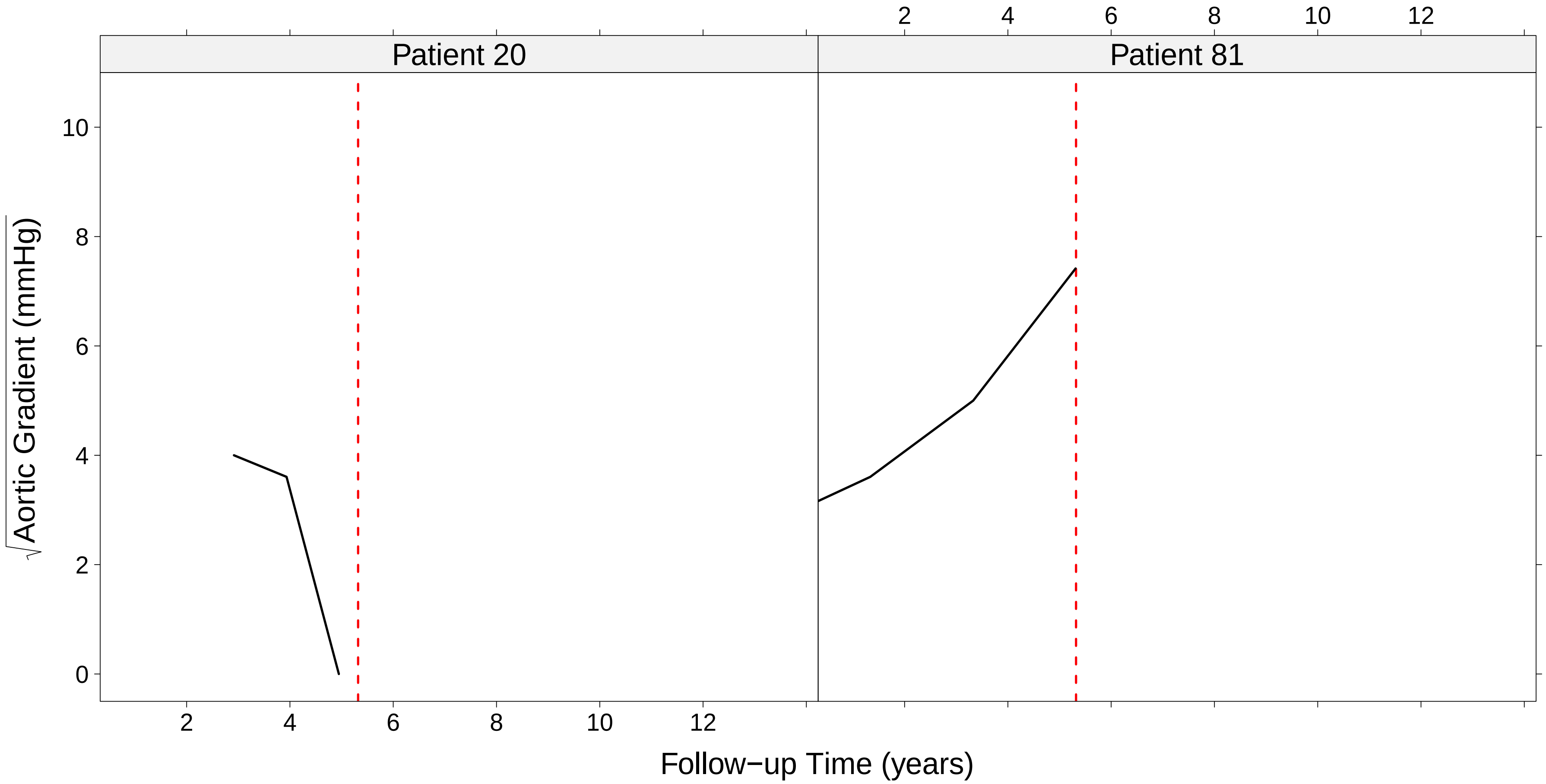
- We are interested in predicting survival probabilities for a new patient j that has provided a set of aortic gradient measurements up to a specific time point t

- 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)



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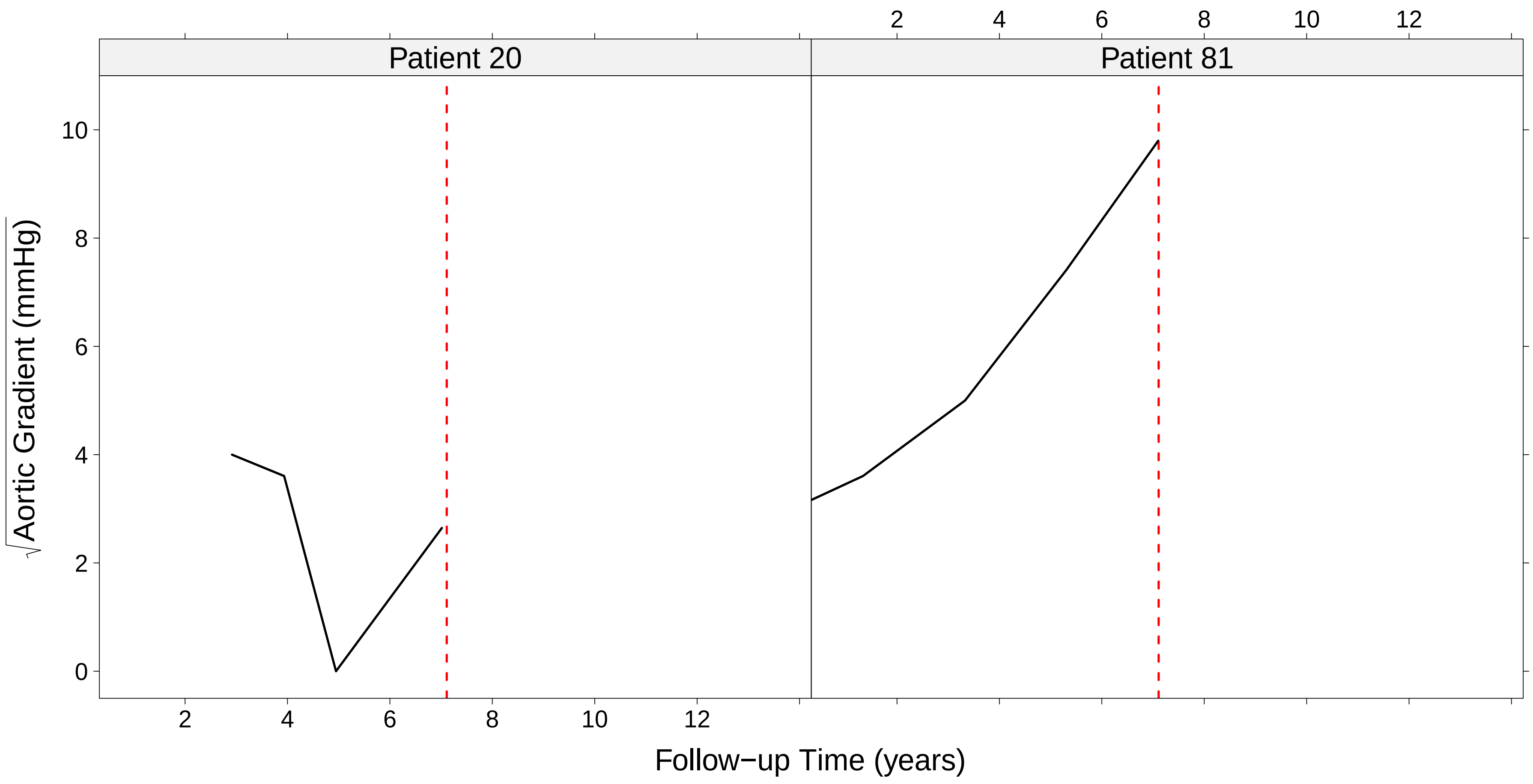


3.1 Prediction Survival – Definitions (cont'd)

- 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
  - ▷ $T_j^* > t$
  - ▷ $\mathcal{Y}_j(t) = \{y_j(t_{jl}); 0 \leq t_{jl} \leq t, l = 1, \ldots, n_j\}$
  - ▷ $\mathcal{D}_n$ 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

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

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

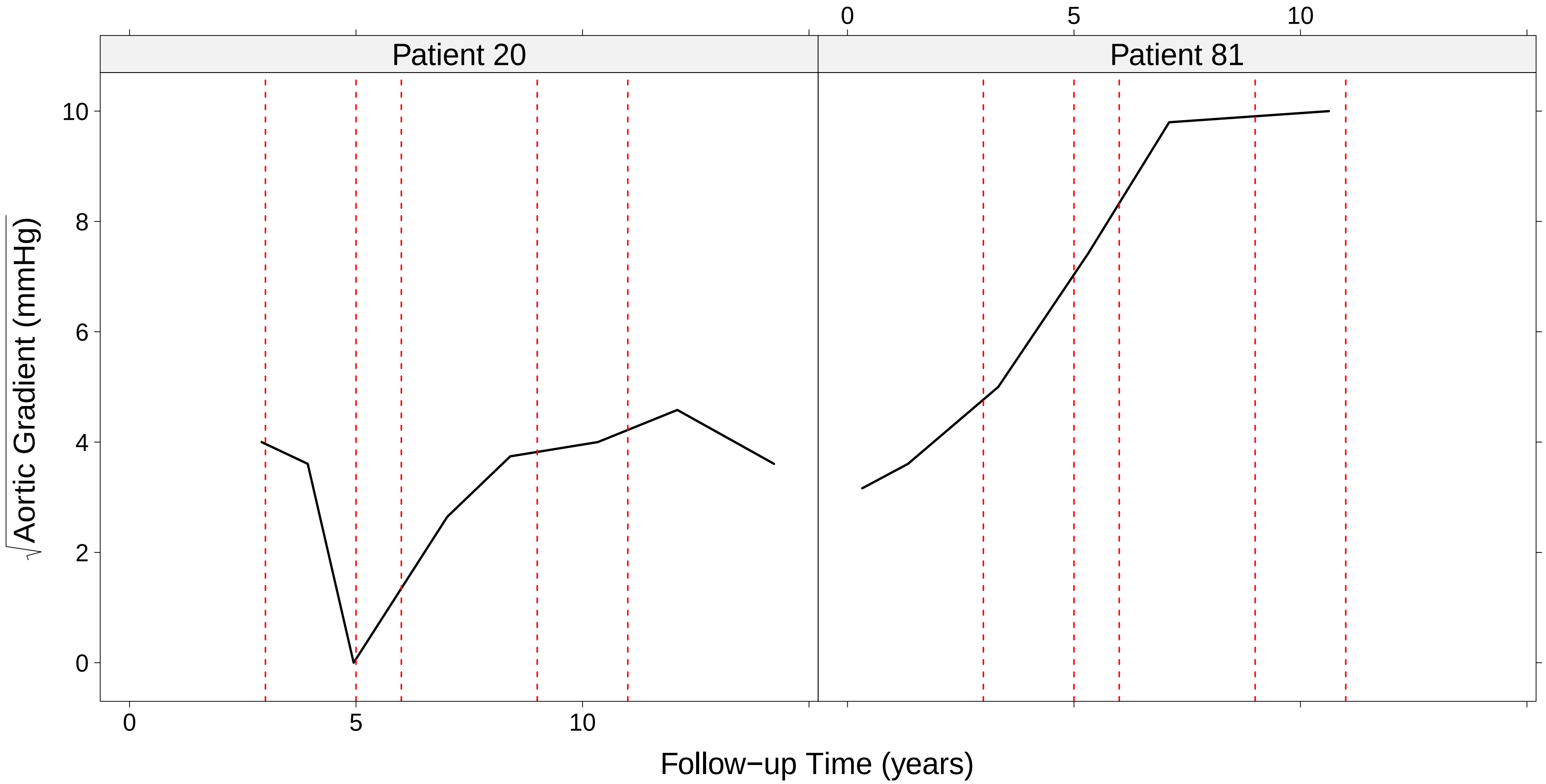
3.3 Prediction Survival – Illustration

- 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)



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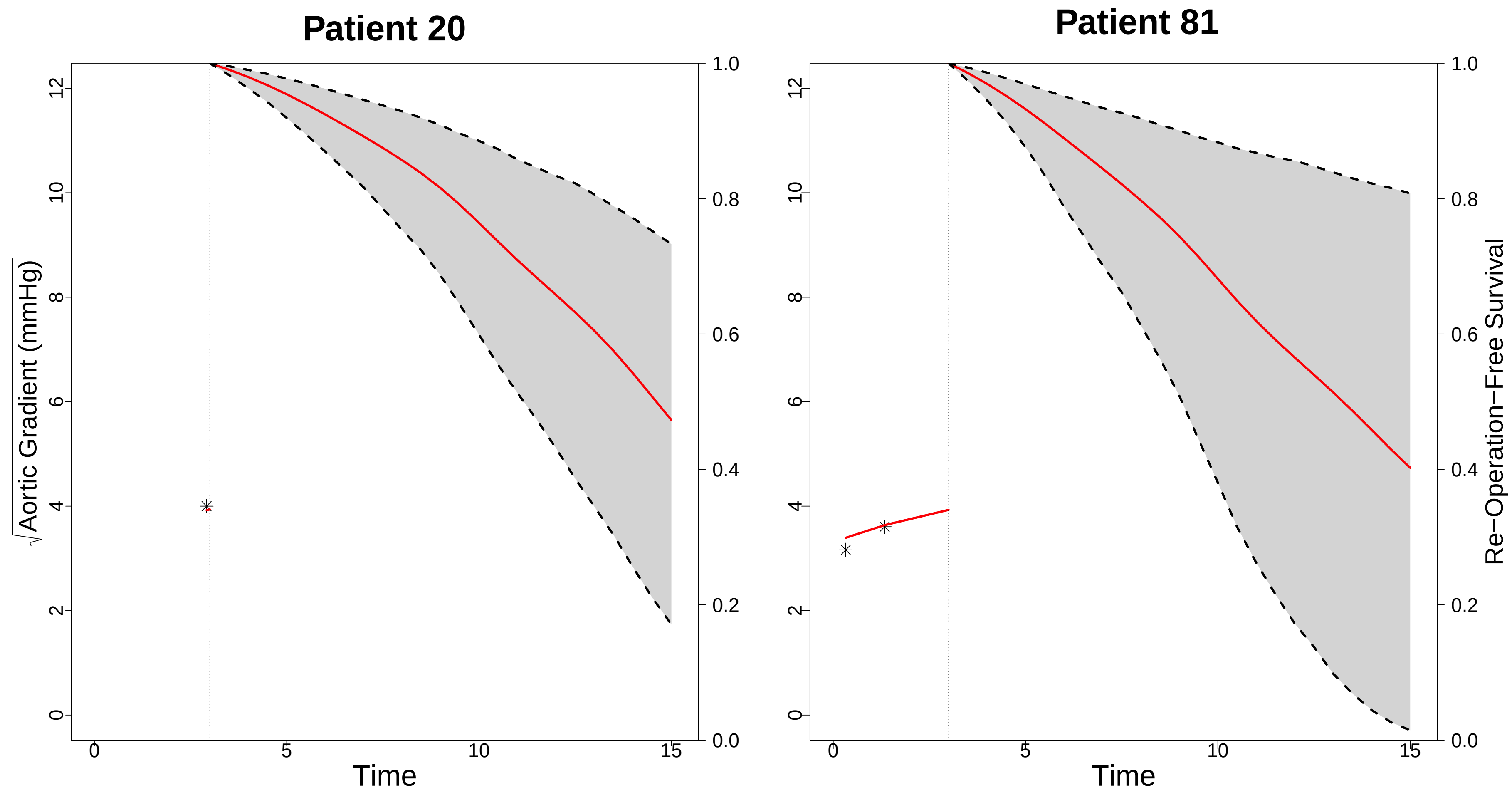

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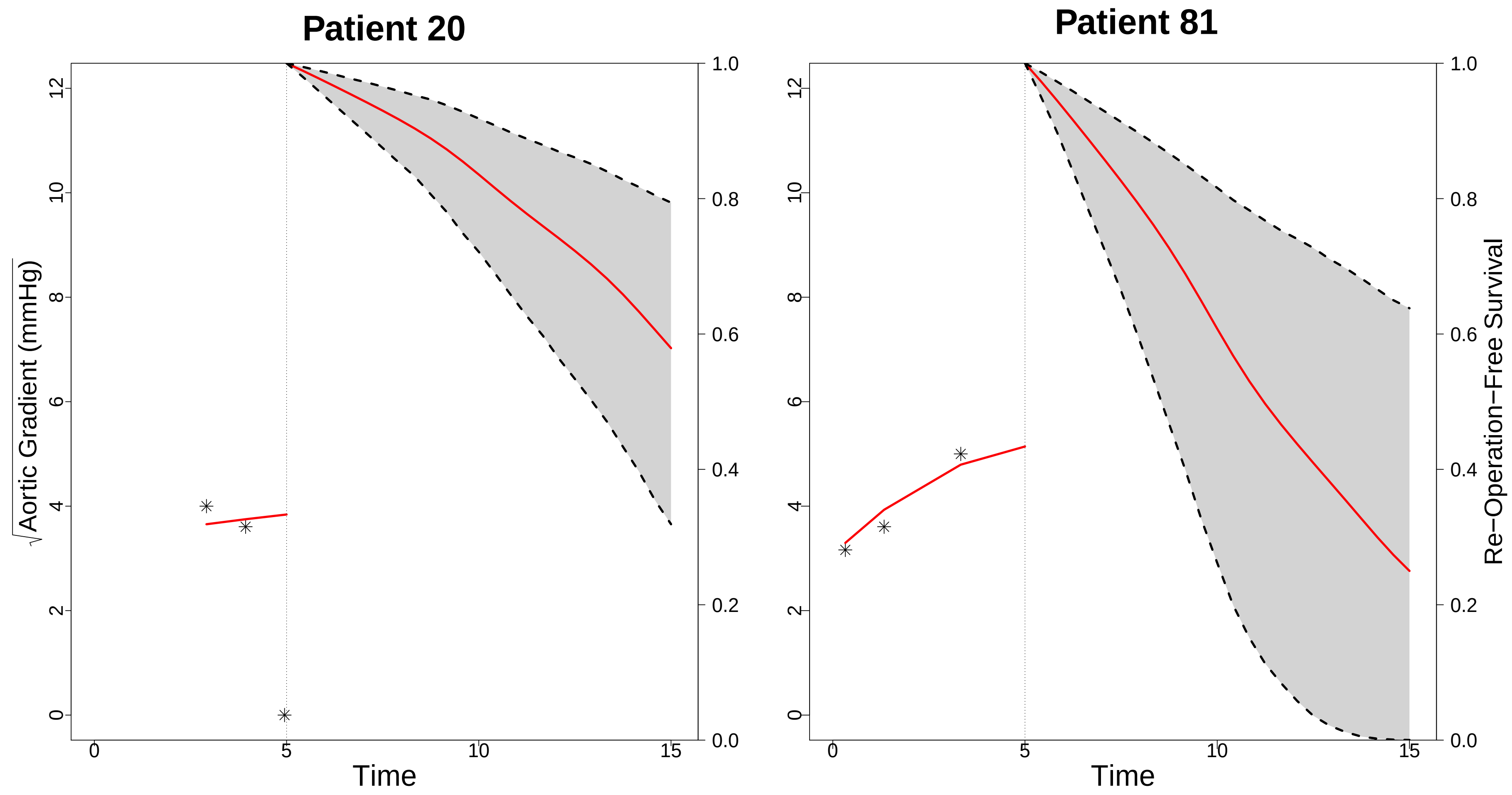

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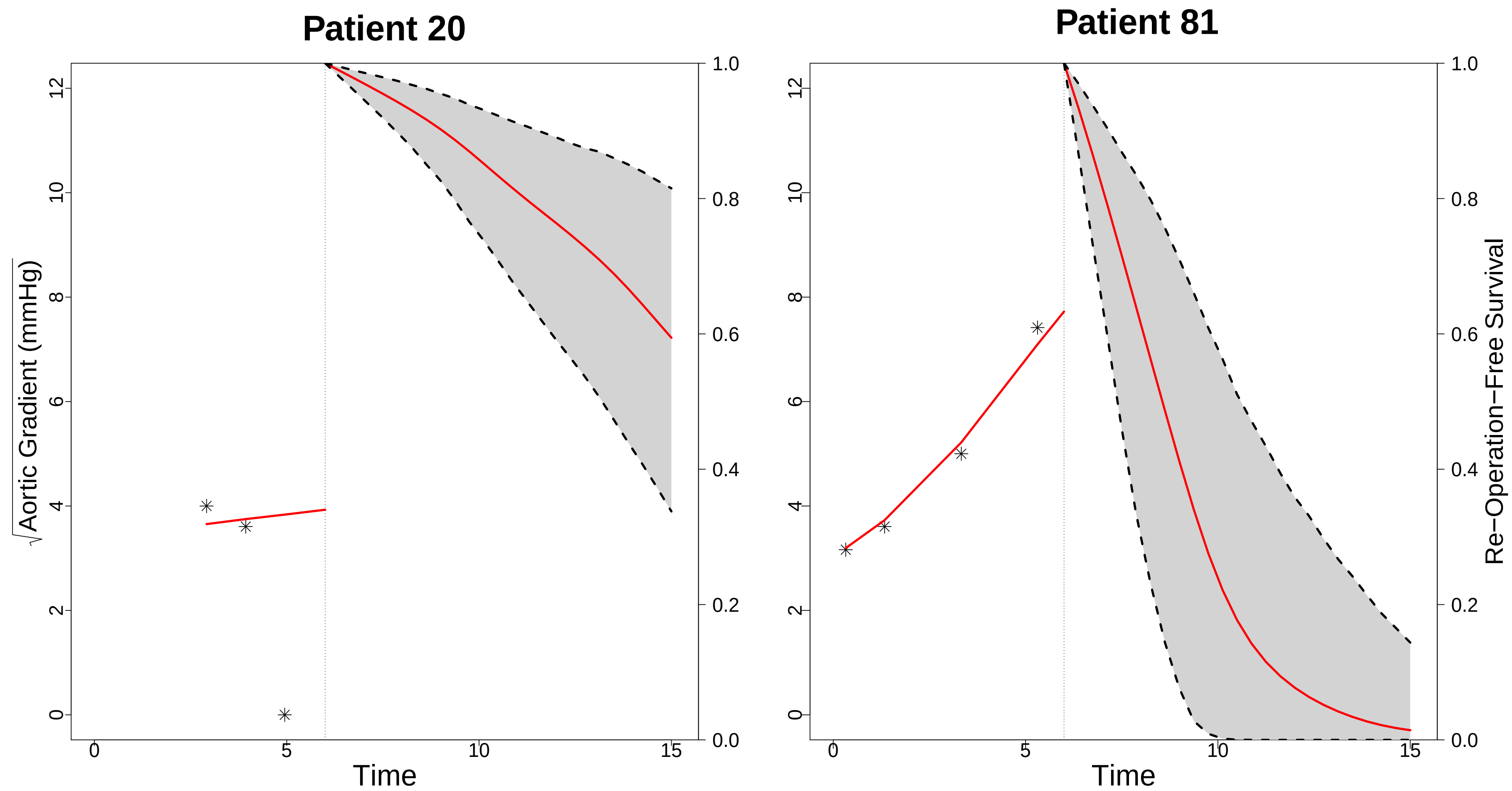

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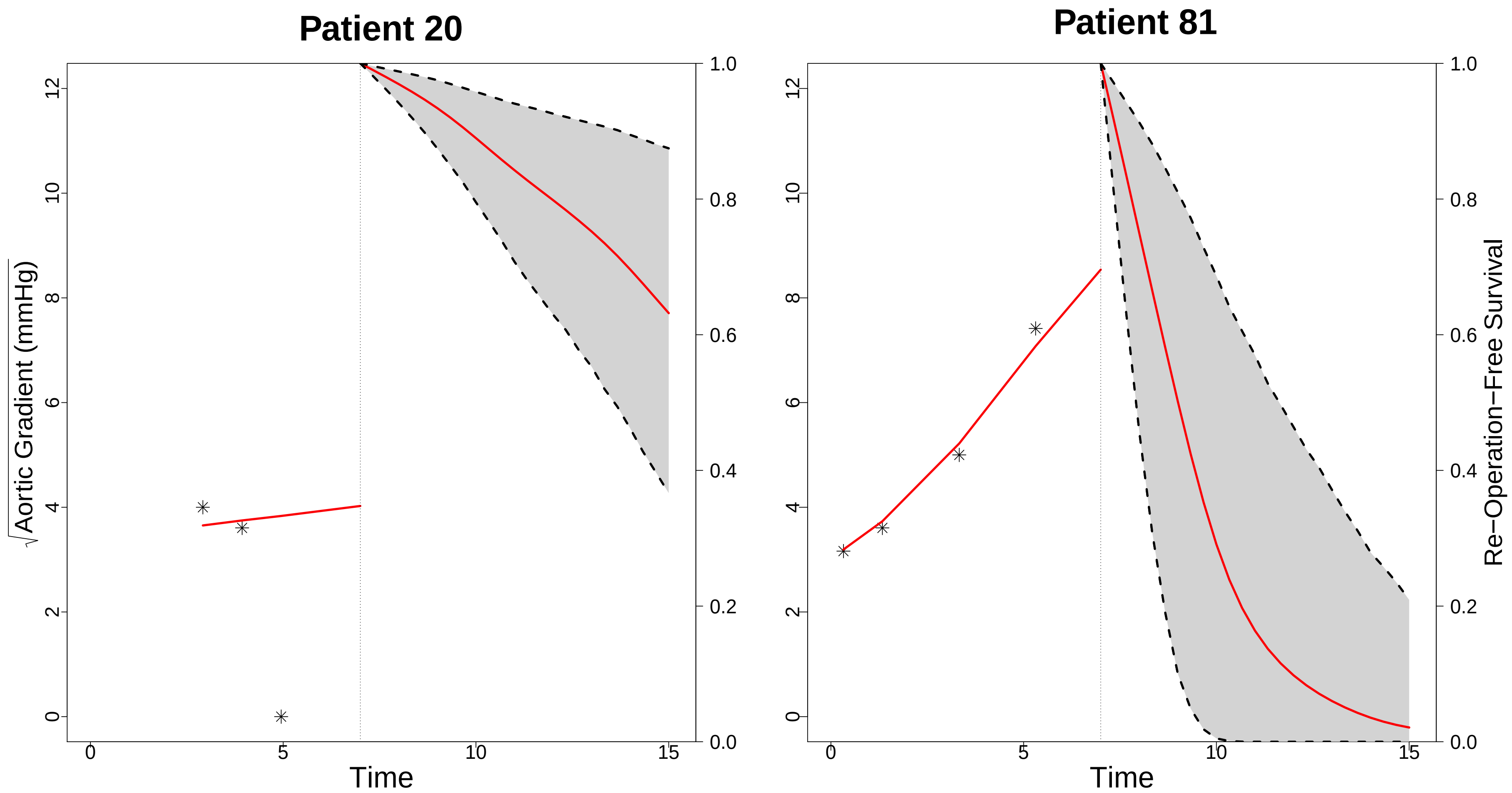

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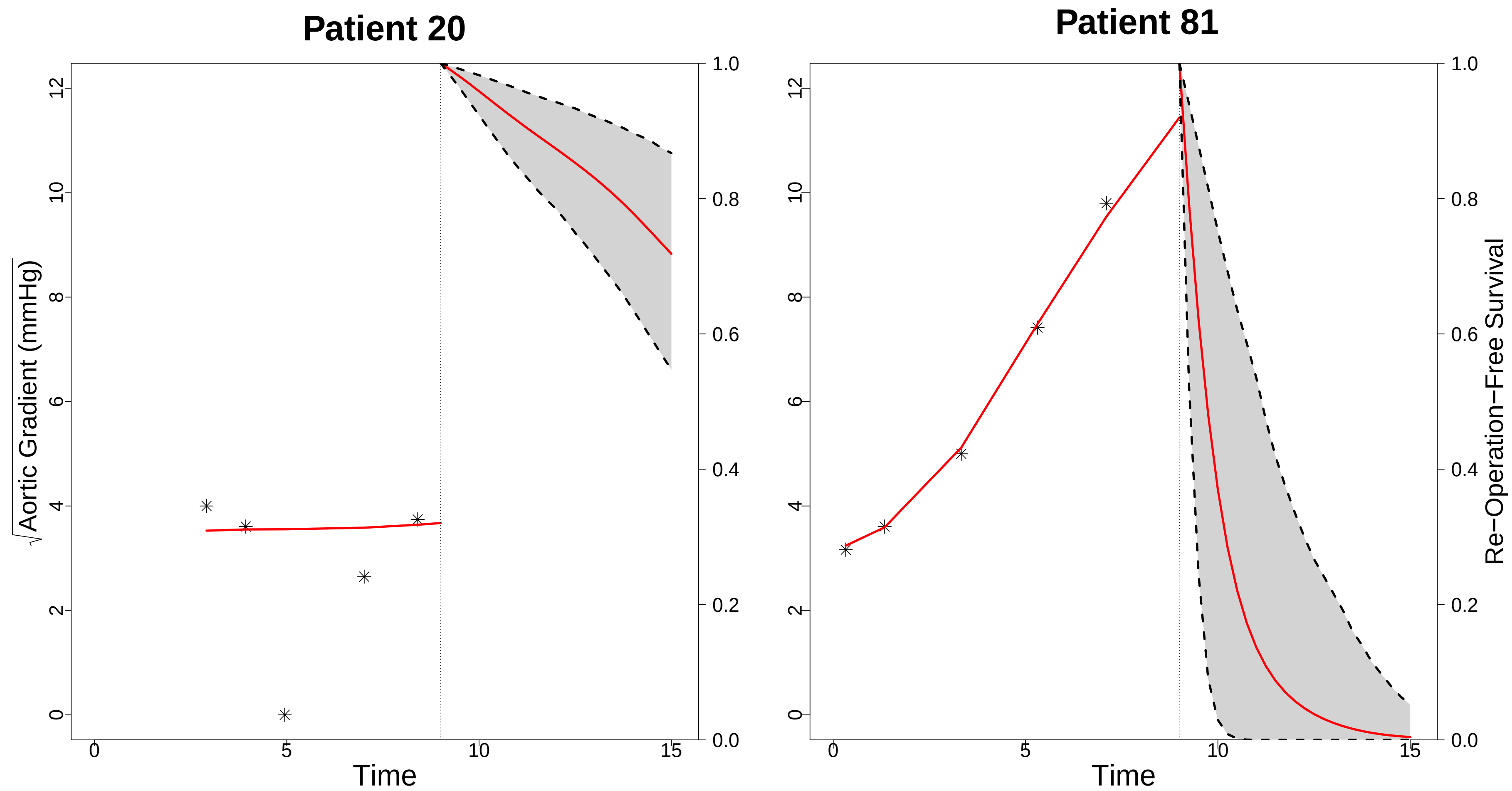

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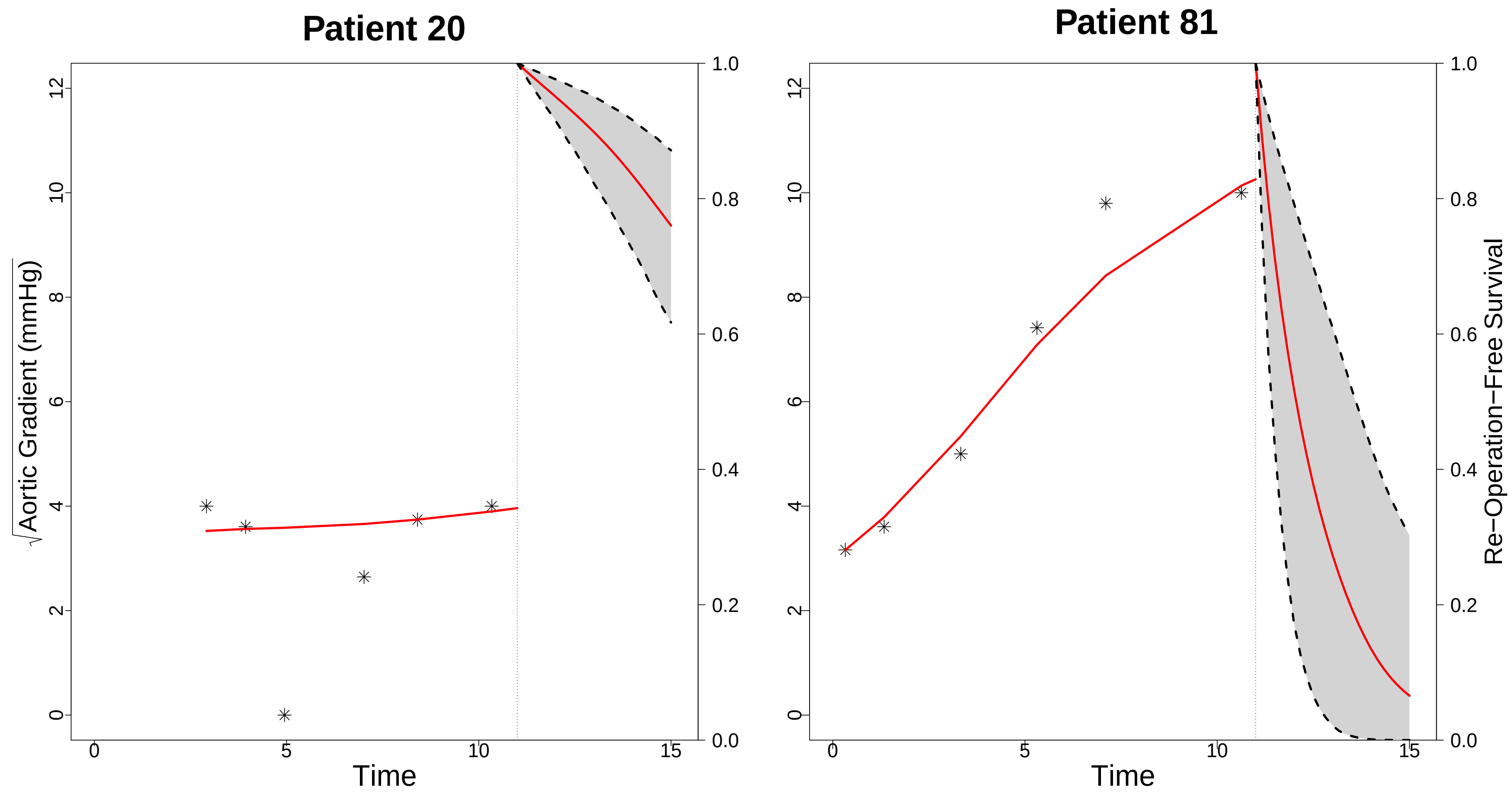


4.1 Next Visit Time – Set up

- **Question 2:**
  - ▷ When the patient should come for the next visit?

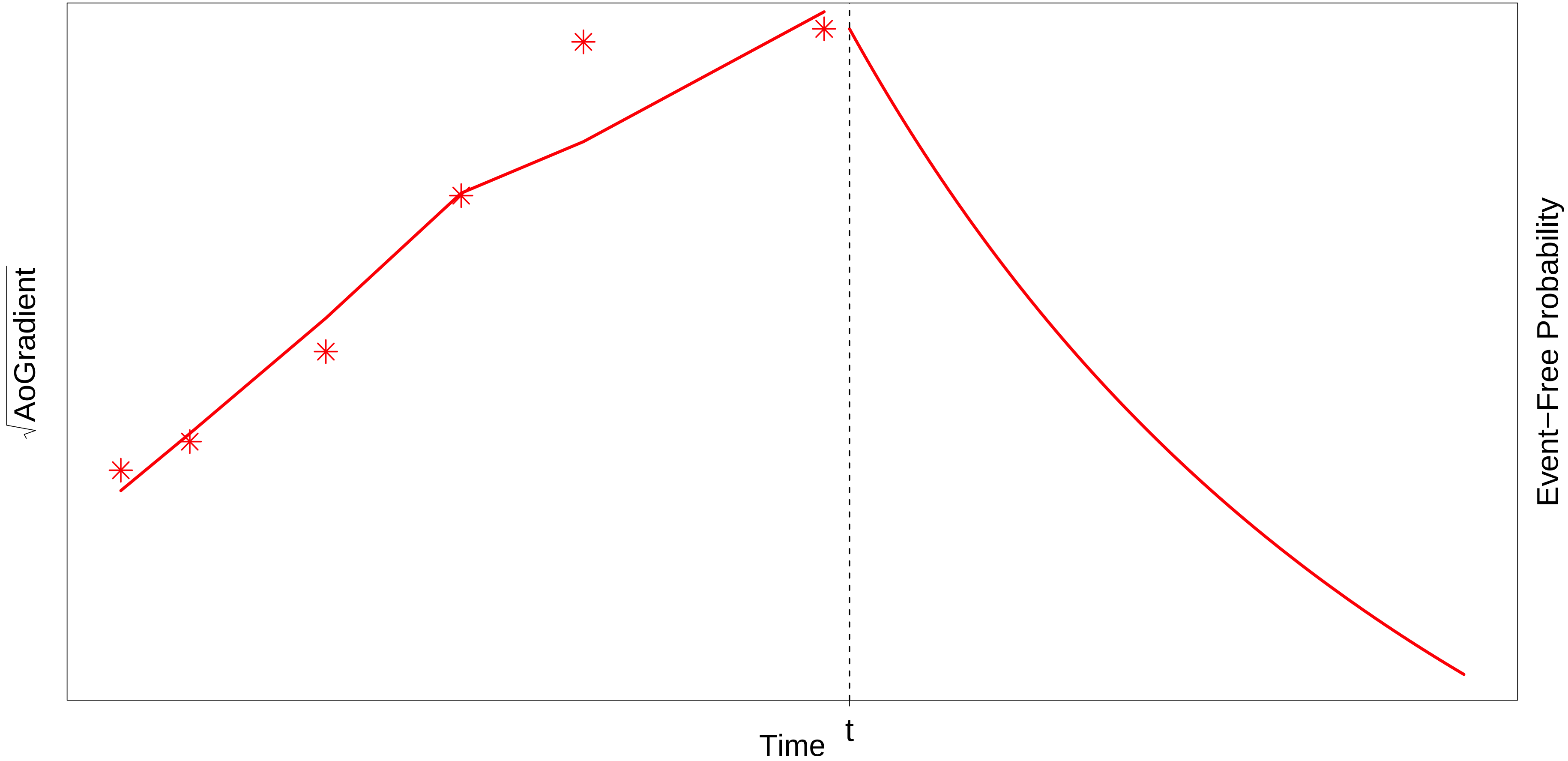
4.1 Next Visit Time – Set up (cont'd)

This is a difficult question!

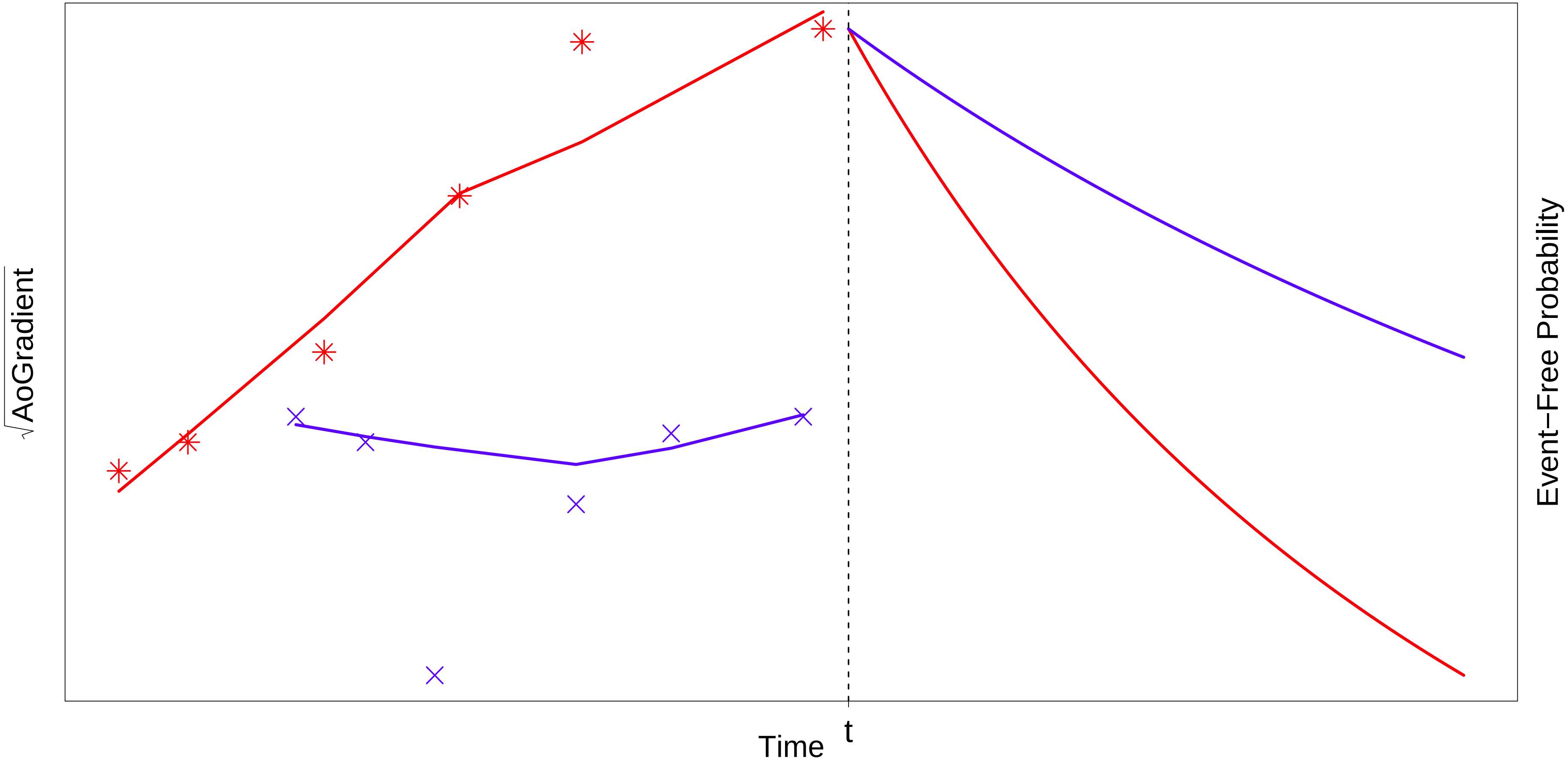
- Many parameters that affect it
  - ▷ which model to use?
  - ▷ what criterion to use?
  - ▷ change in treatment?
  - ▷ ...

We will work under the following setting ⇒

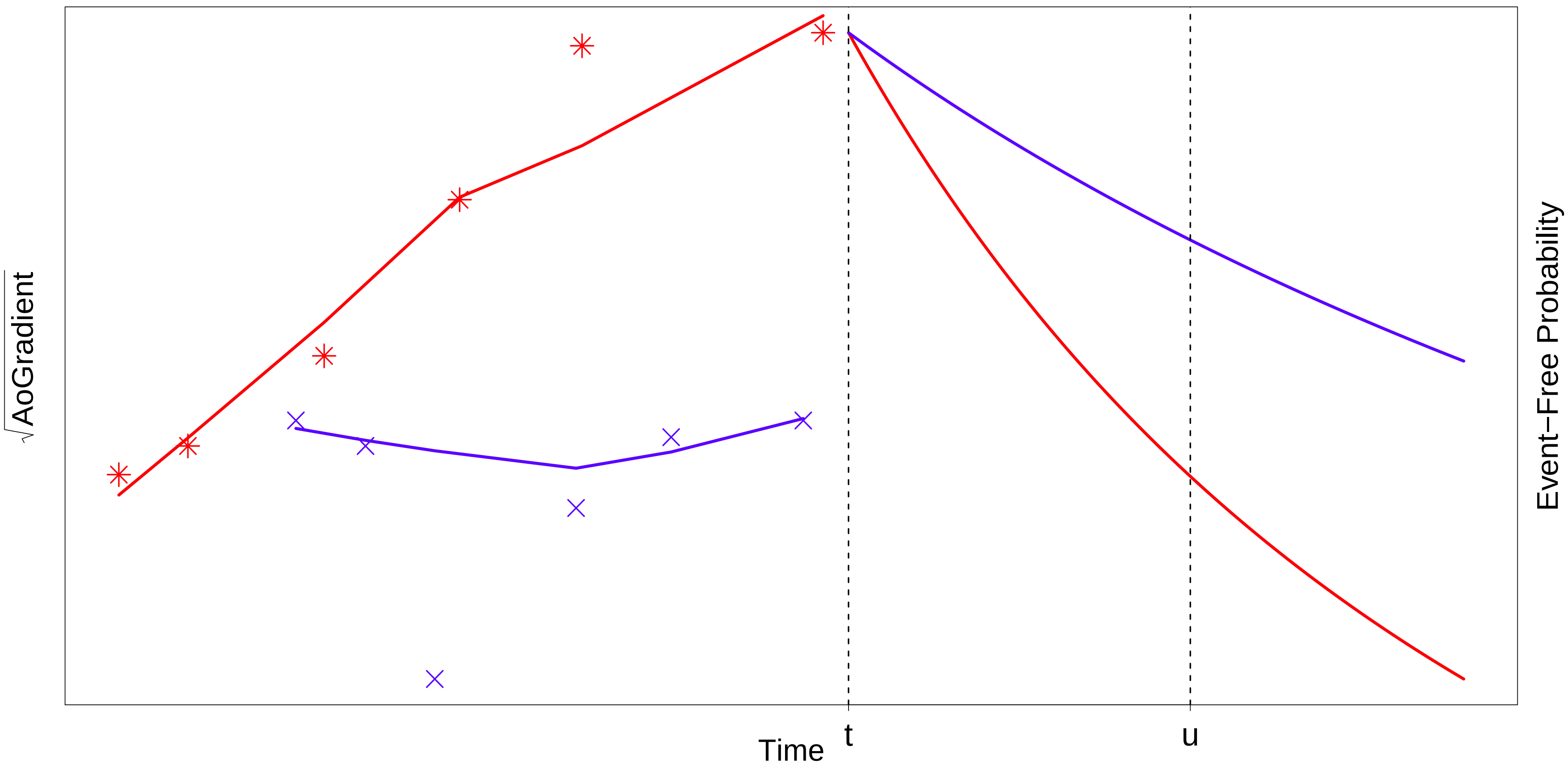
4.1 Next Visit Time – Set up(cont'd)



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

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

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

- ▷ 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

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

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

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

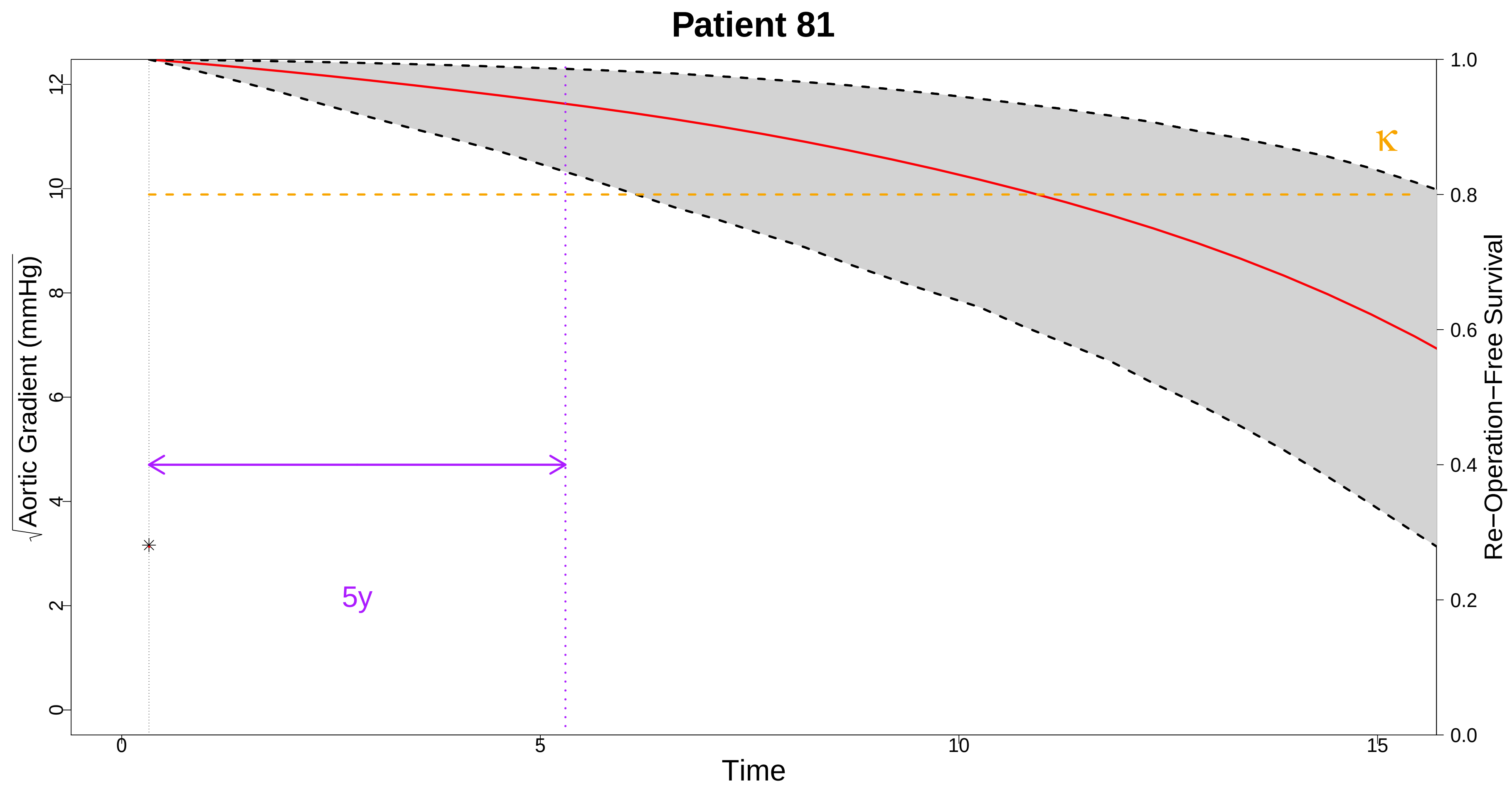
  - ▷ After each visit we calculate the optimal timing for the next one using

$$\underset{u}{\text{argmax}}\, \mathsf{EKL}(u \mid t) \qquad \text{where} \quad u \in (t, t^{up}]$$

and

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

4.3 Next Visit Time – Example (cont'd)



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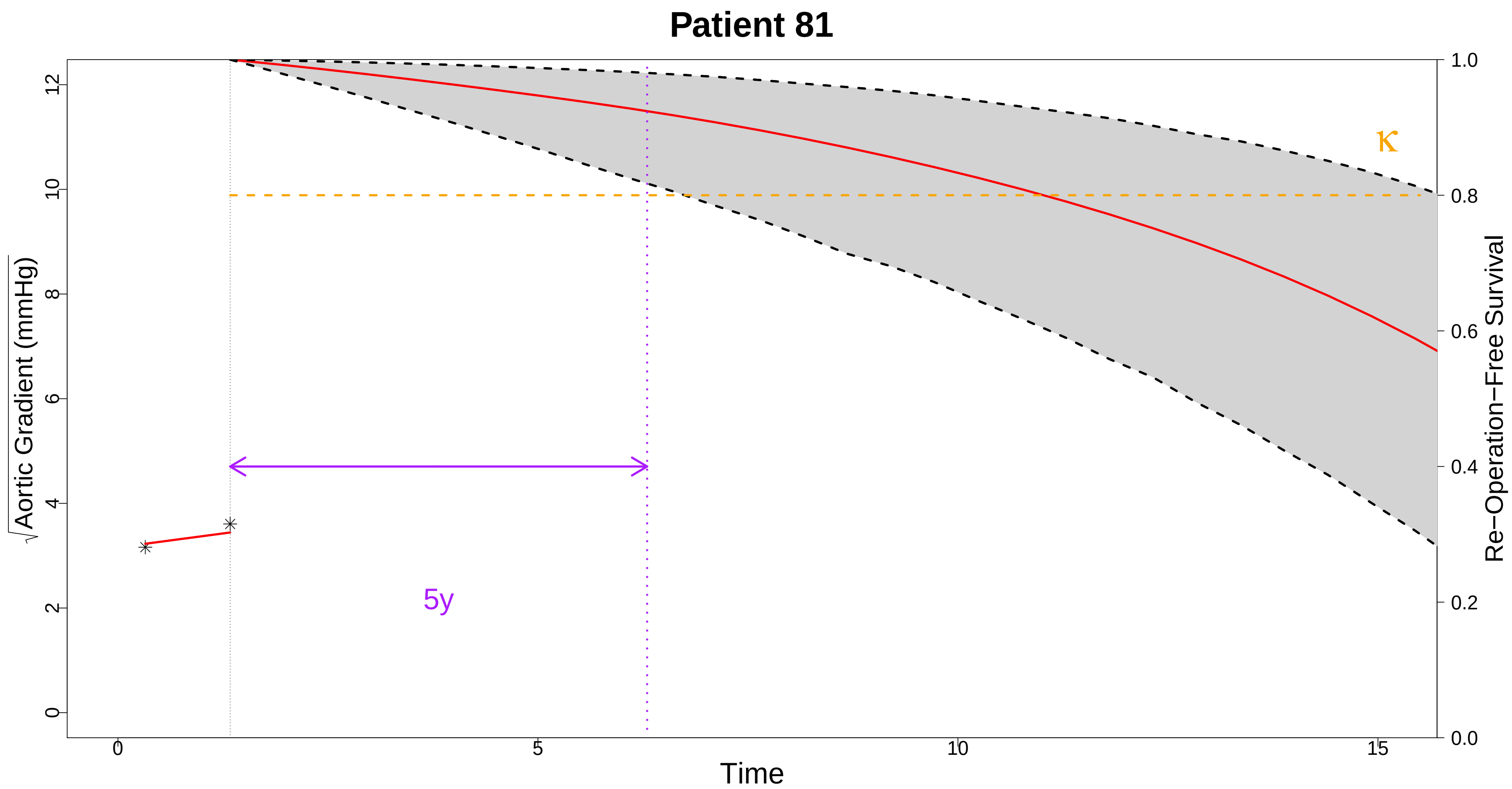

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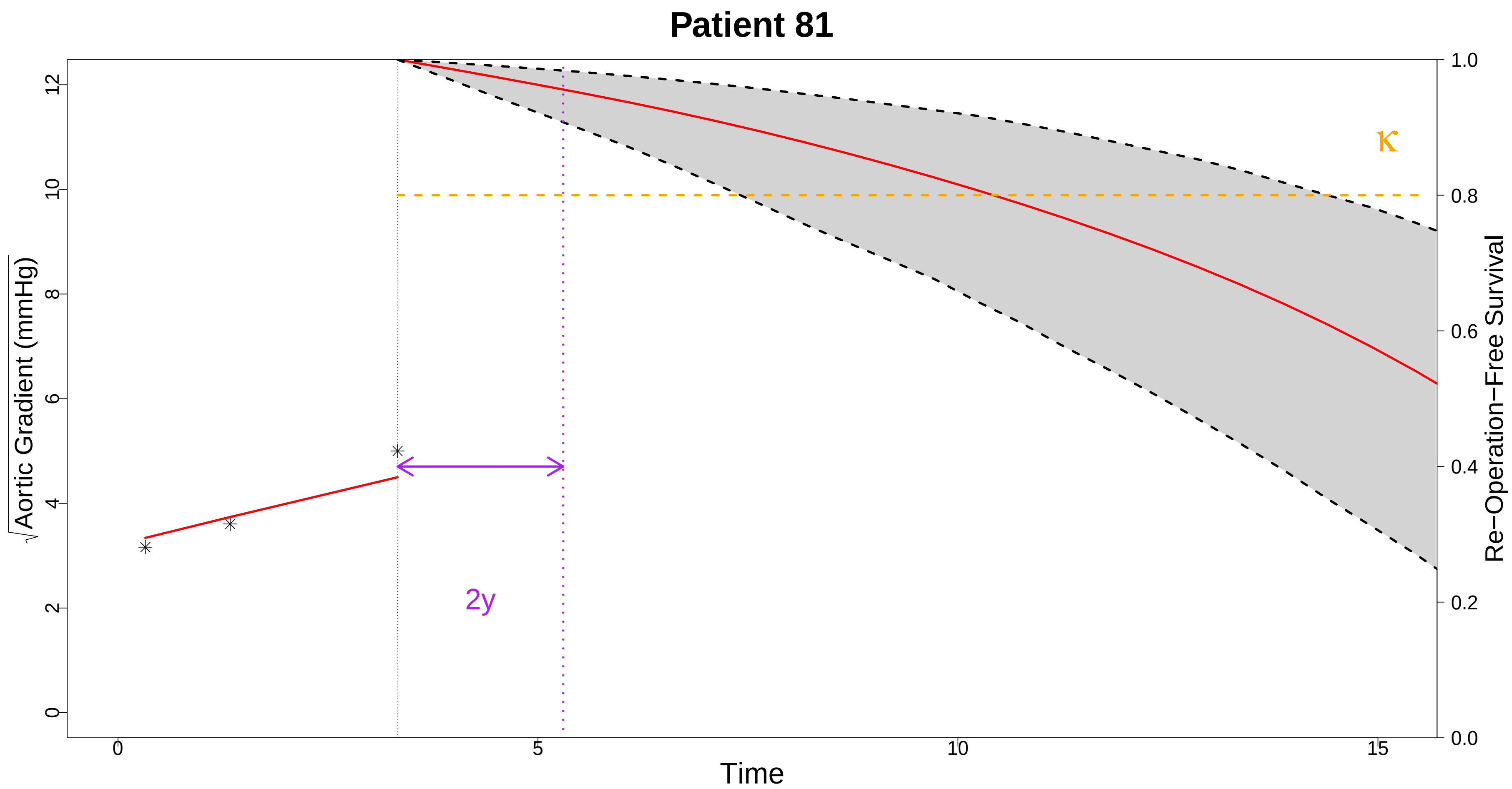

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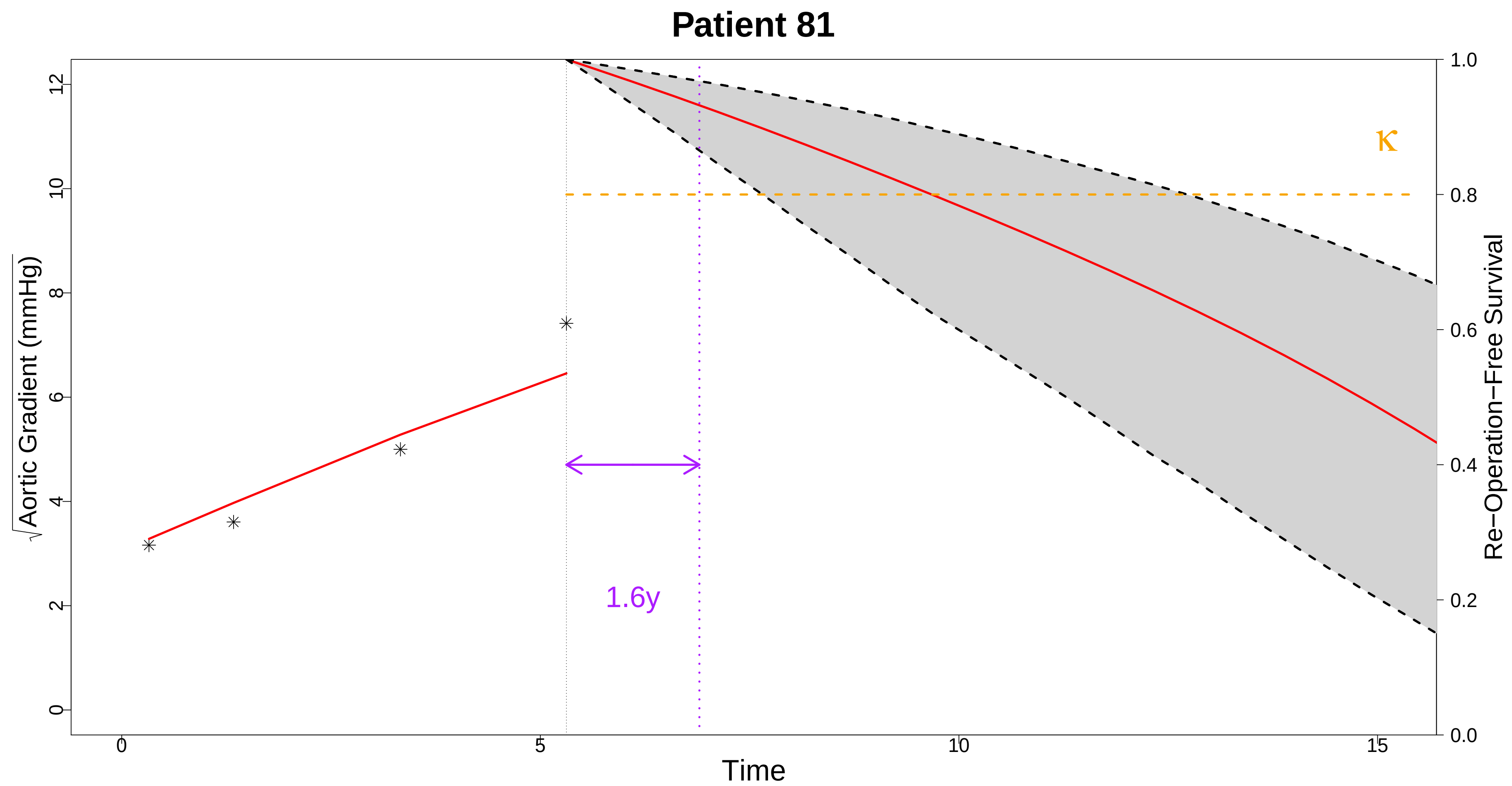
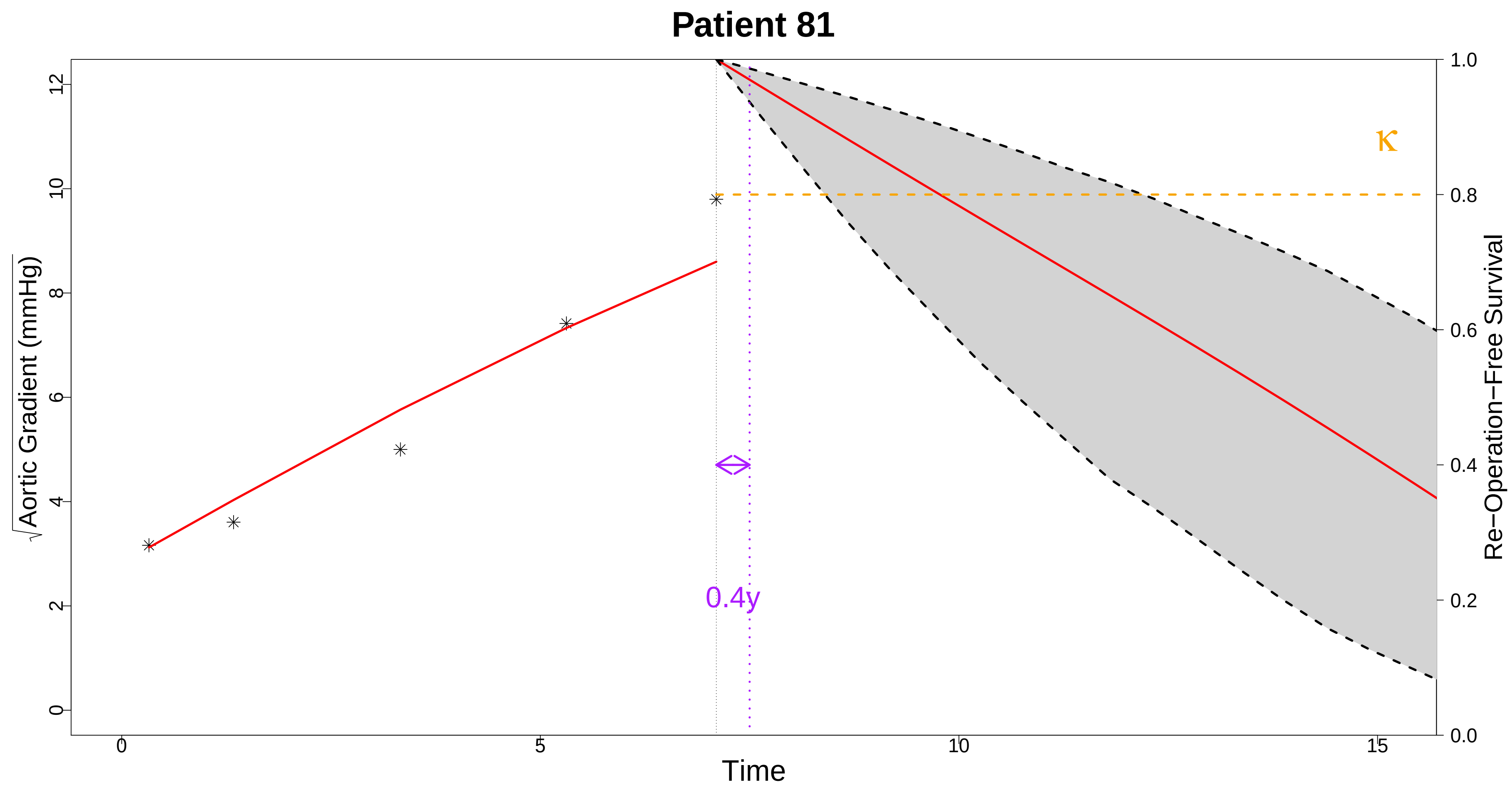


4.3 Next Visit Time – Example (cont'd)



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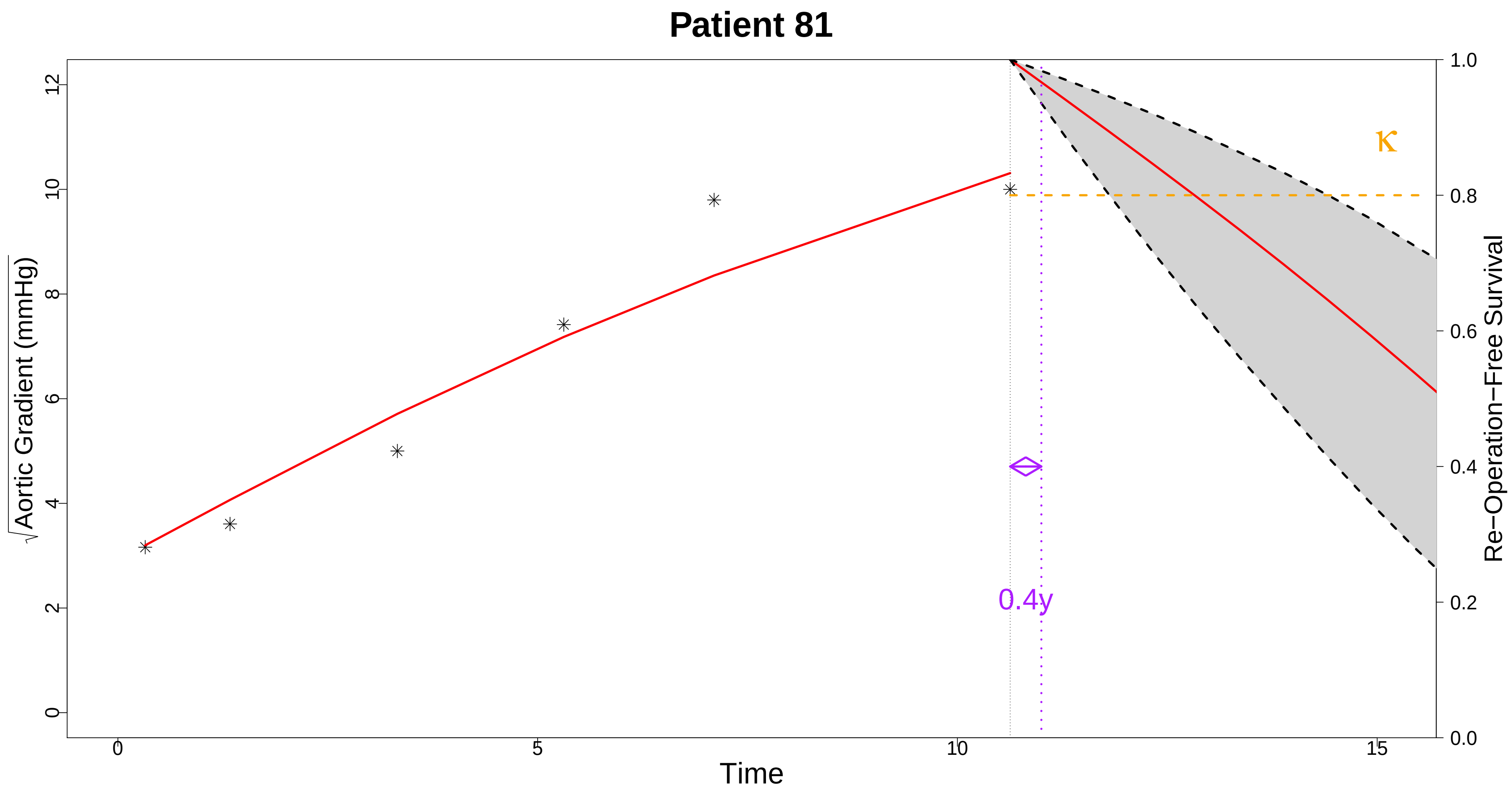

5. Software

- 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!