Optimal Screening Intervals for Biomarkers using Joint Models for Longitudinal and Survival Data

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Workshop on Flexible Models for Longitudinal and Survival Data with Applications in Biostatistics

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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 $\longrightarrow$ 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)

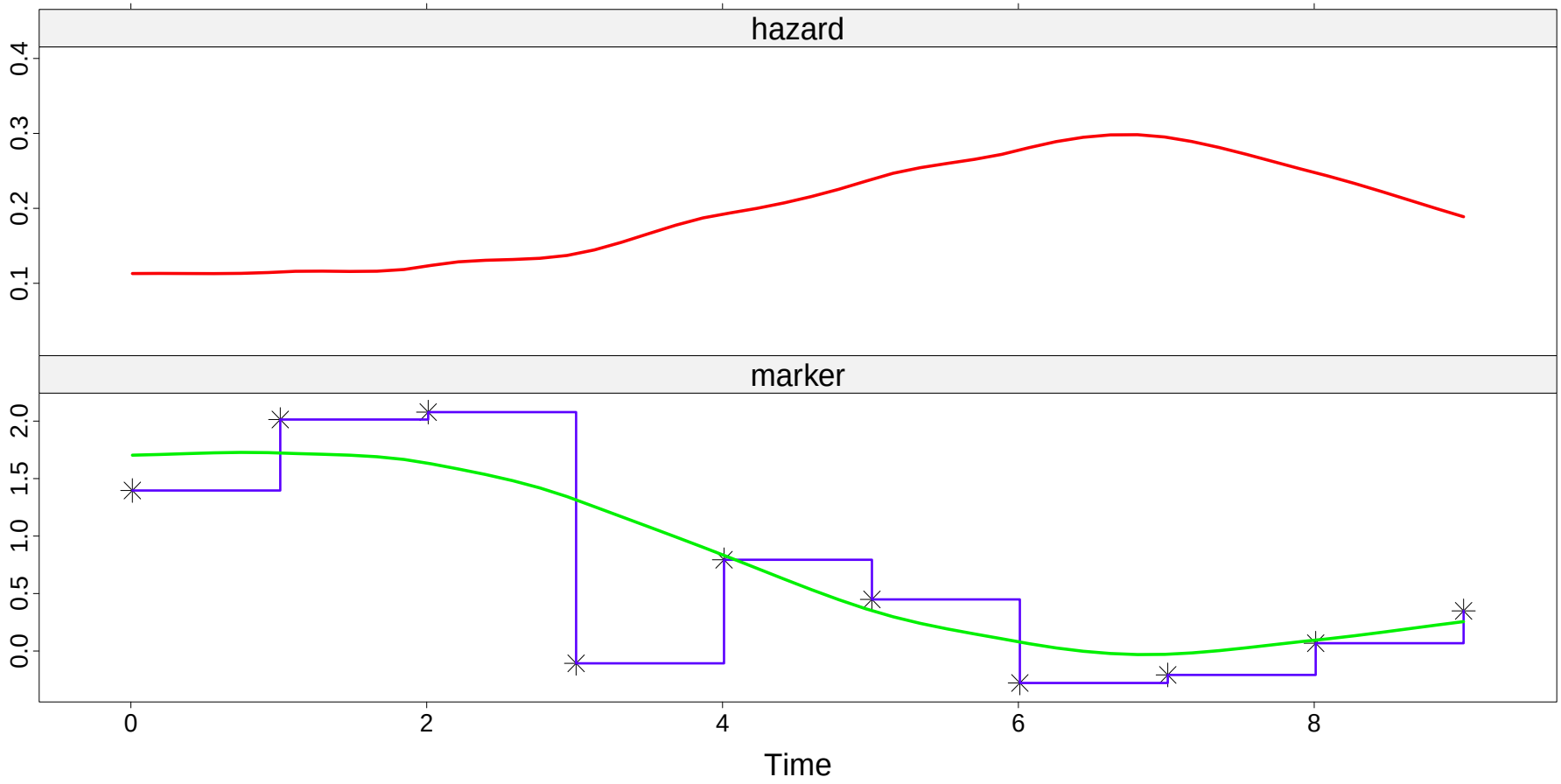
- **Goals of this talk**:
  - ▷ introduce joint models
  - ▷ dynamic predictions
  - ▷ optimal timing of next visit

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)

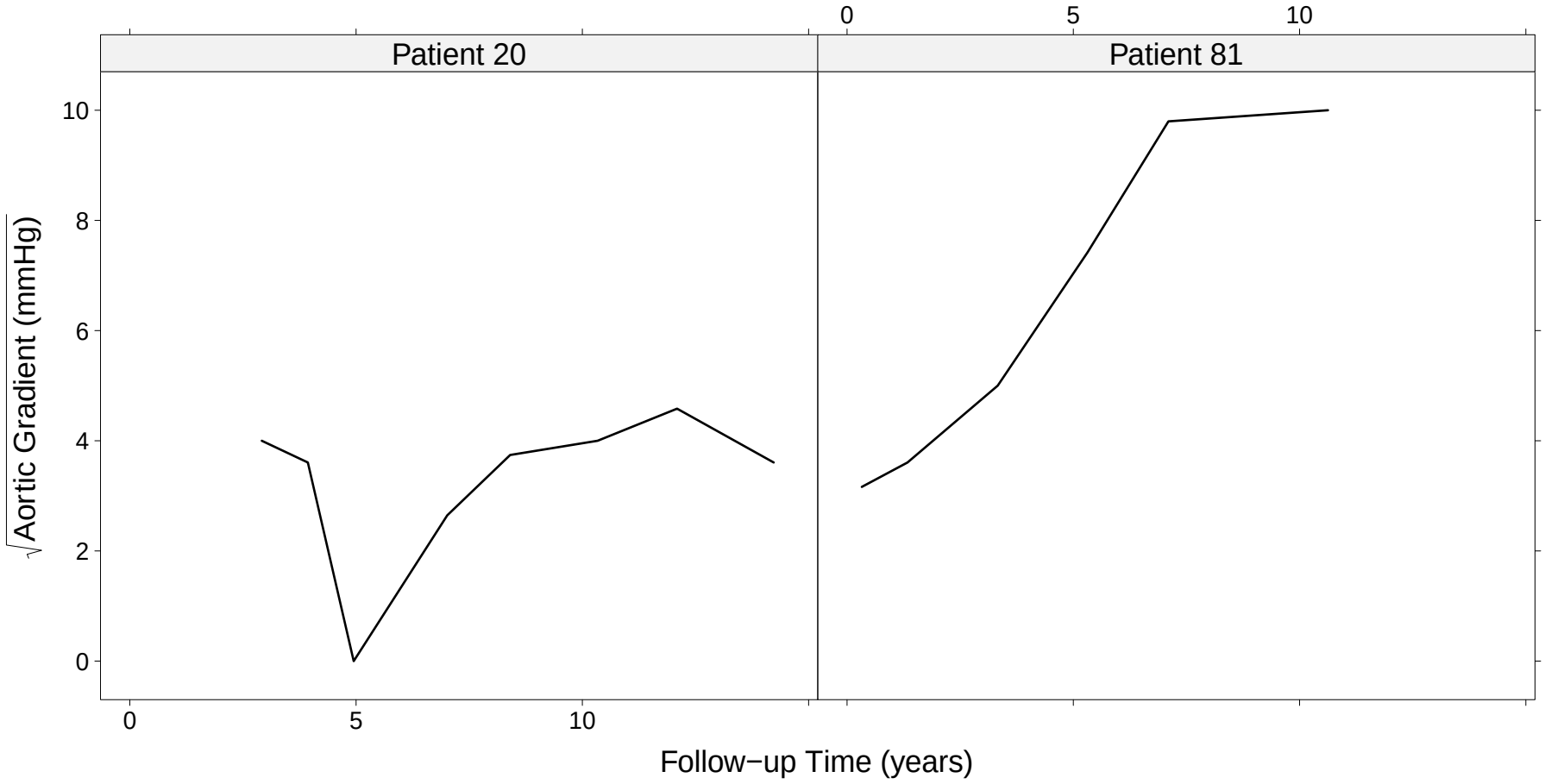
- Here we follow the Bayesian approach because it facilitates computations for our later developments...

3.1 Prediction Survival – Definitions

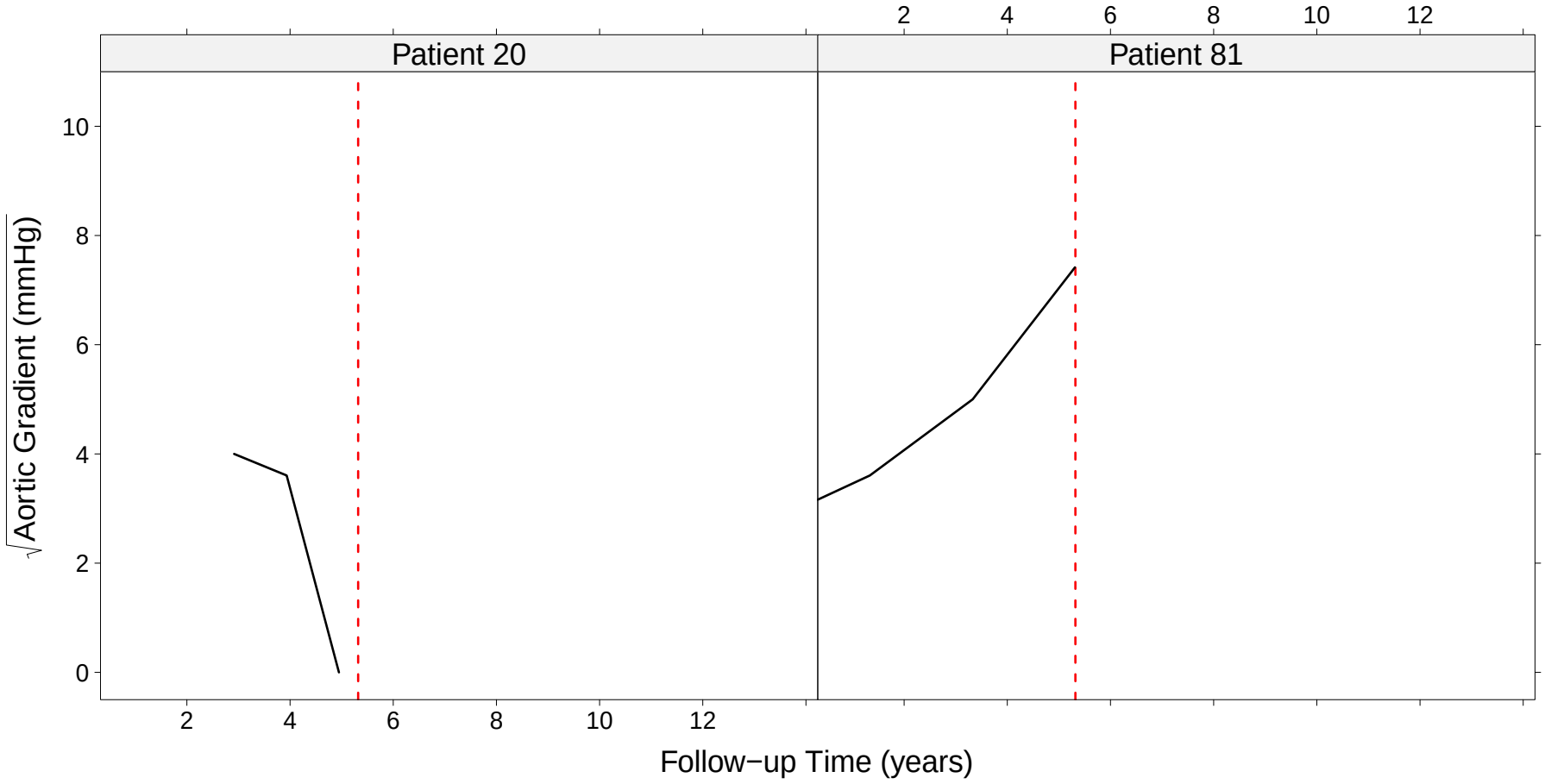
- We are interested in predicting survival probabilities for a new patient j that has provided a set of aortic gradient measurements up to a specific time point t

- Example: We consider Patients 20 and 81 from the Aortic Valve dataset

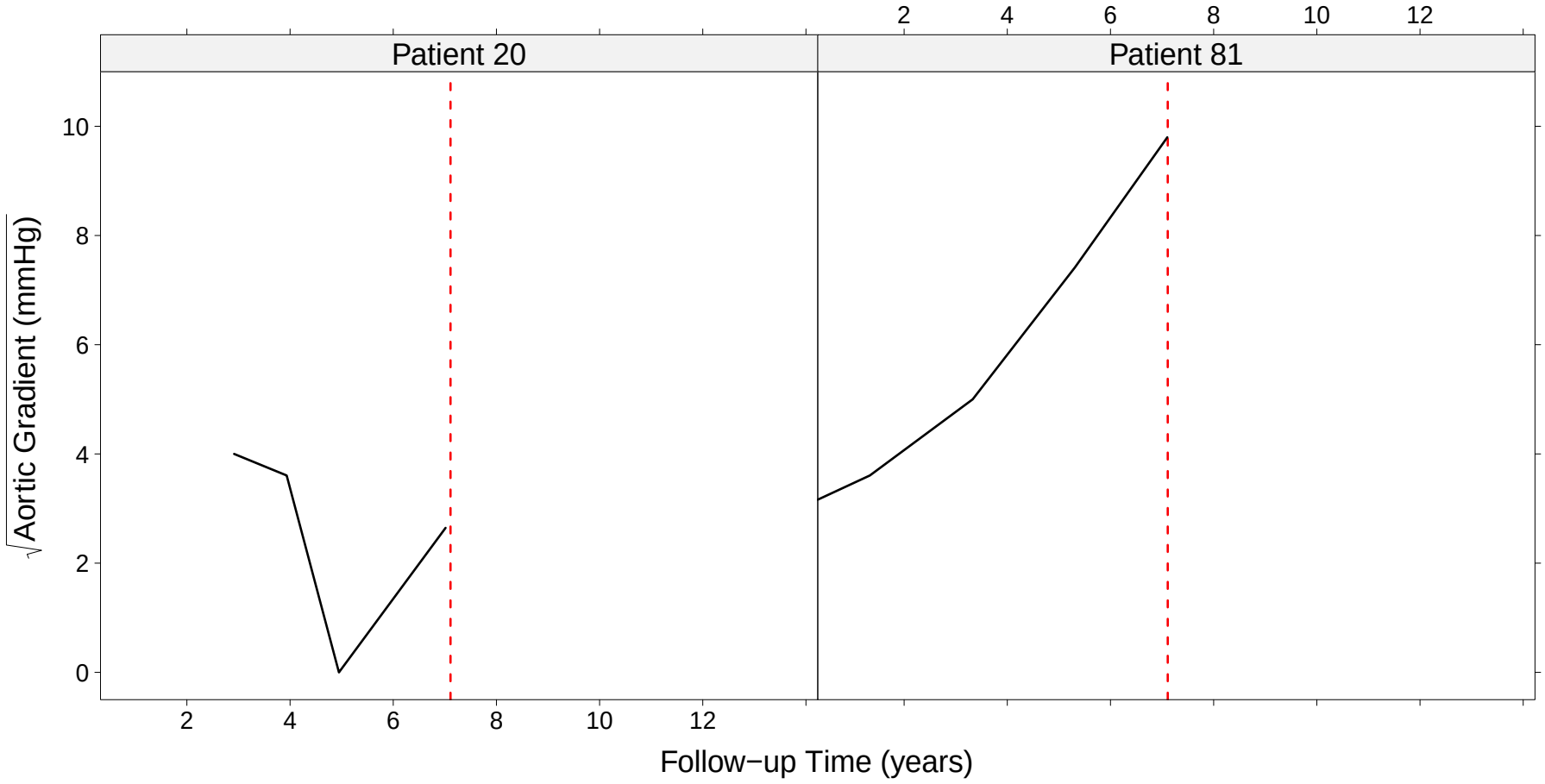
3.1 Prediction Survival – Definitions (cont'd)



3.1 Prediction Survival – Definitions (cont'd)



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

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

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

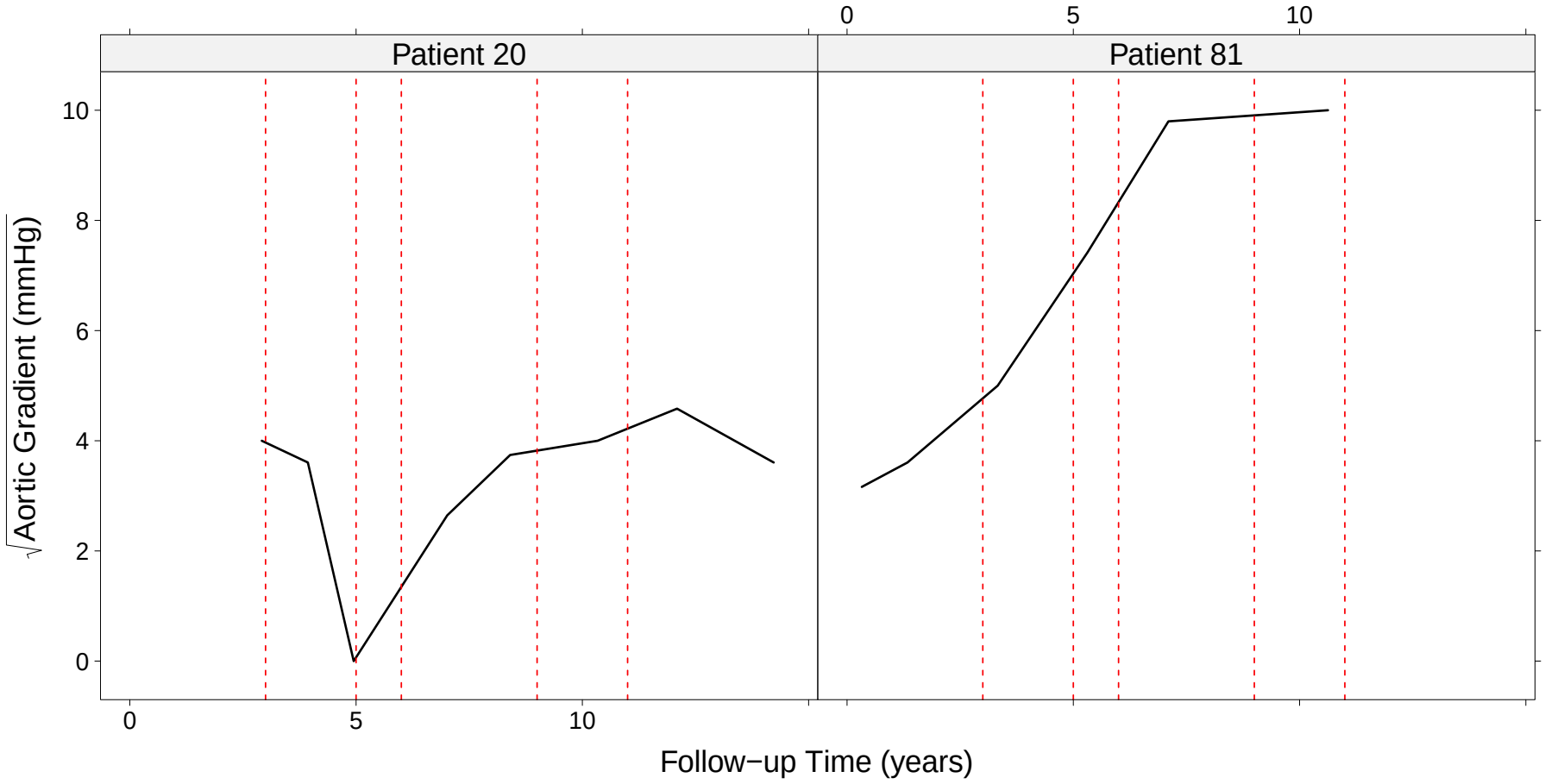
3.3 Prediction Survival – Illustration

- Example: We fit a joint model to the Aortic Valve data

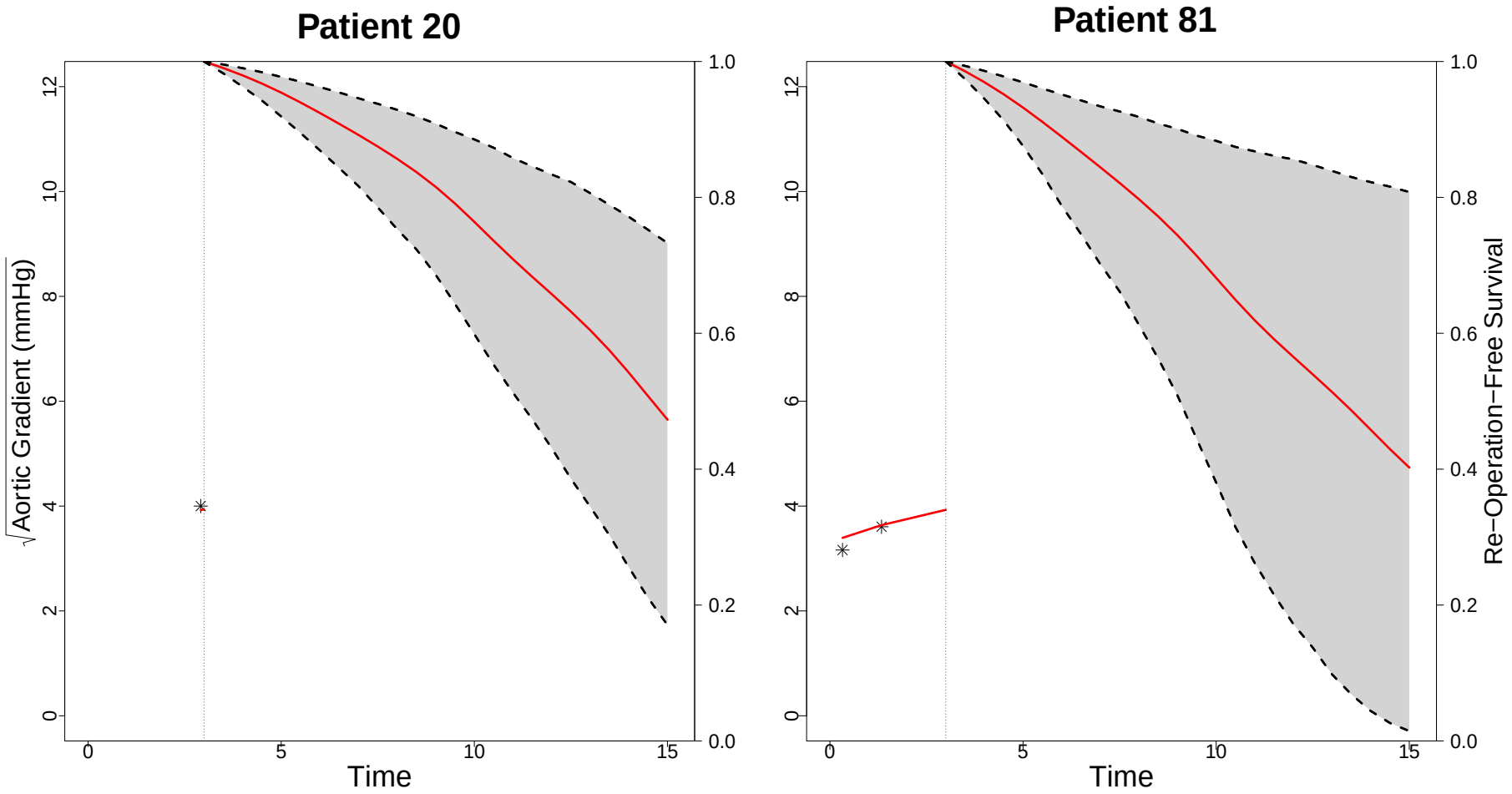
- Longitudinal submodel
  - ▷ fixed effects: natural cubic splines of time (d.f.$= 3$), operation type, and their interaction
  - ▷ random effects: Intercept, & natural cubic splines of time (d.f.$= 3$)

- 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)



3.3 Prediction Survival – Illustration (cont'd)



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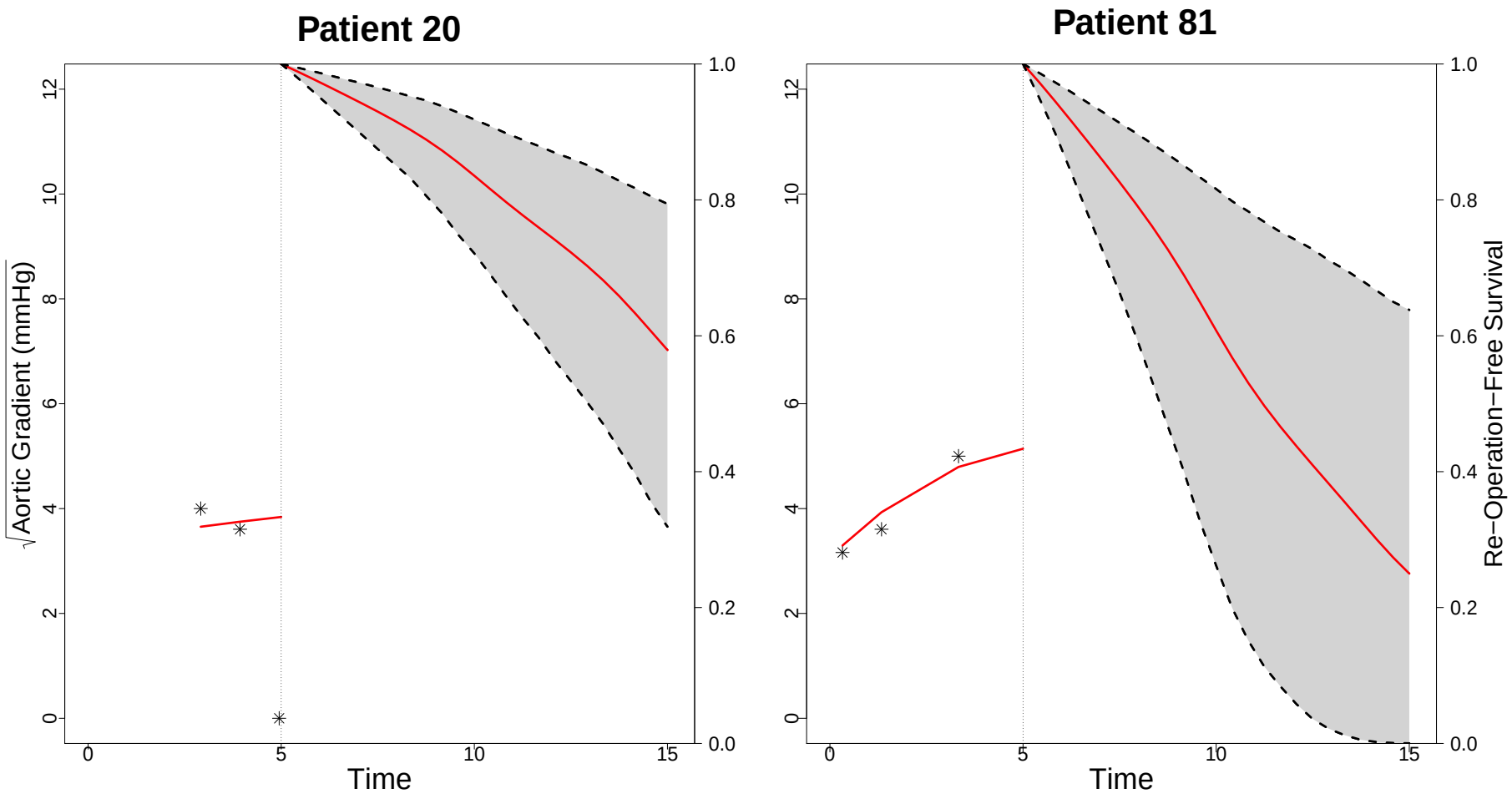

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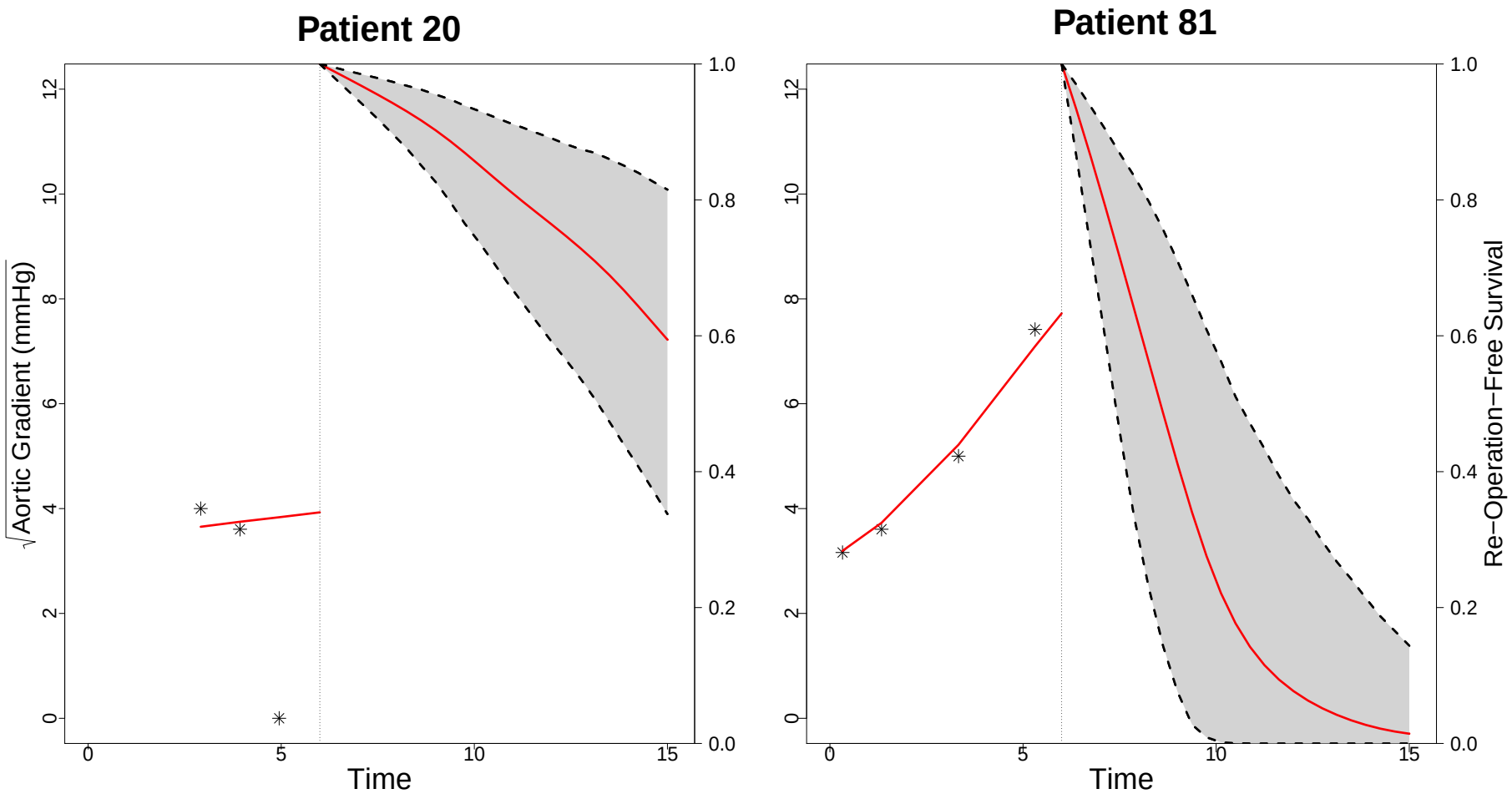
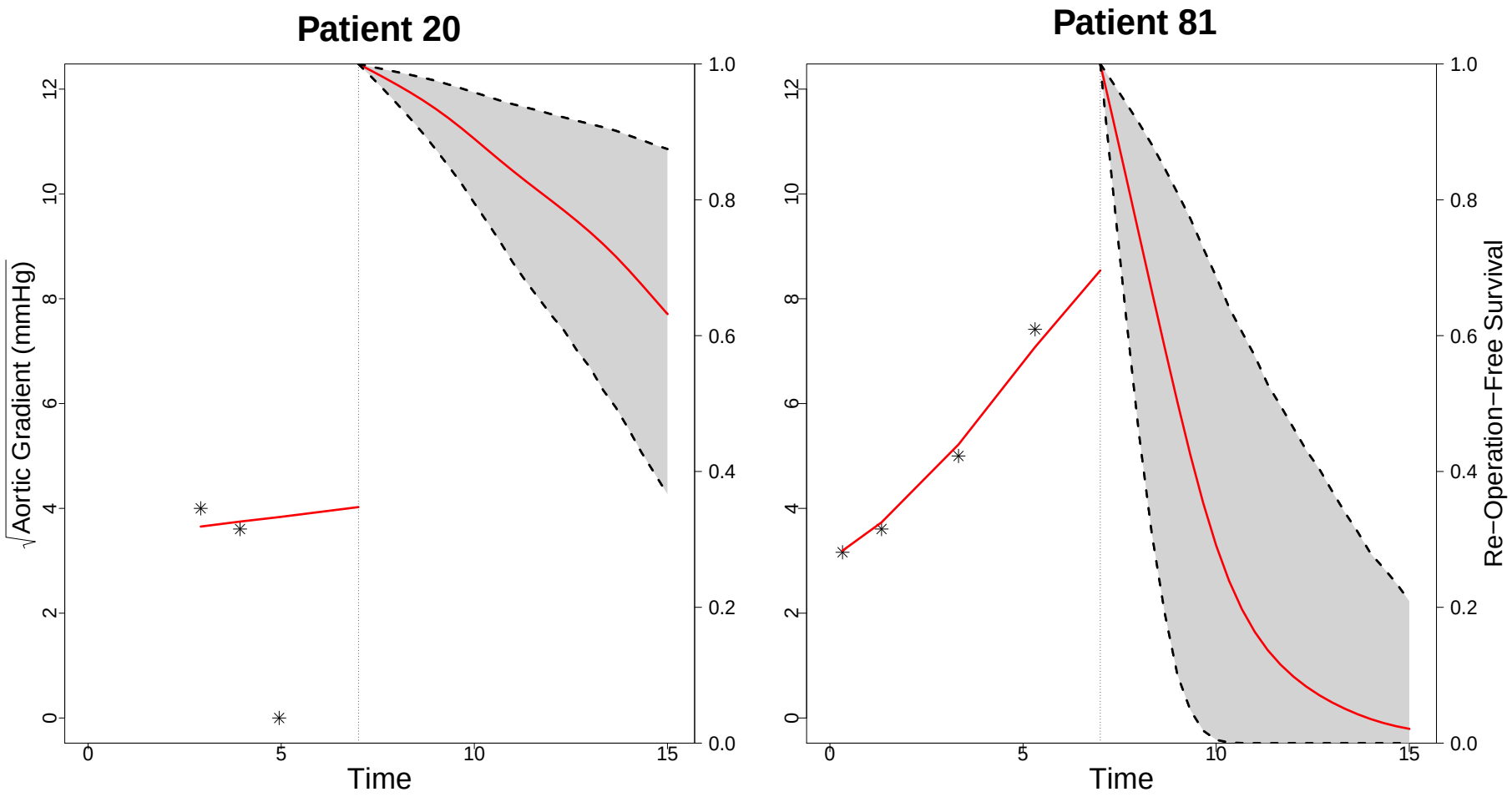


3.3 Prediction Survival – Illustration (cont'd)



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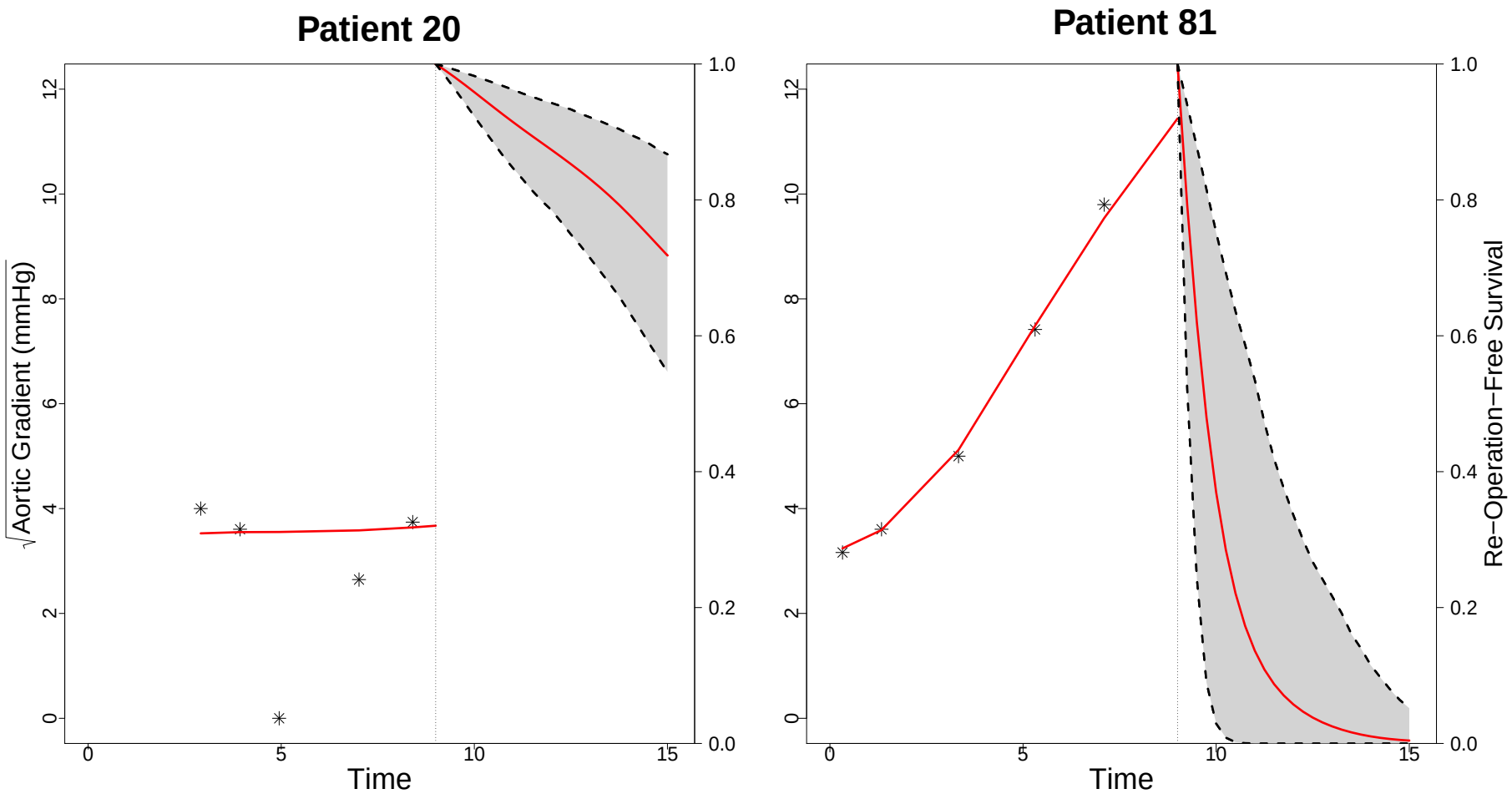

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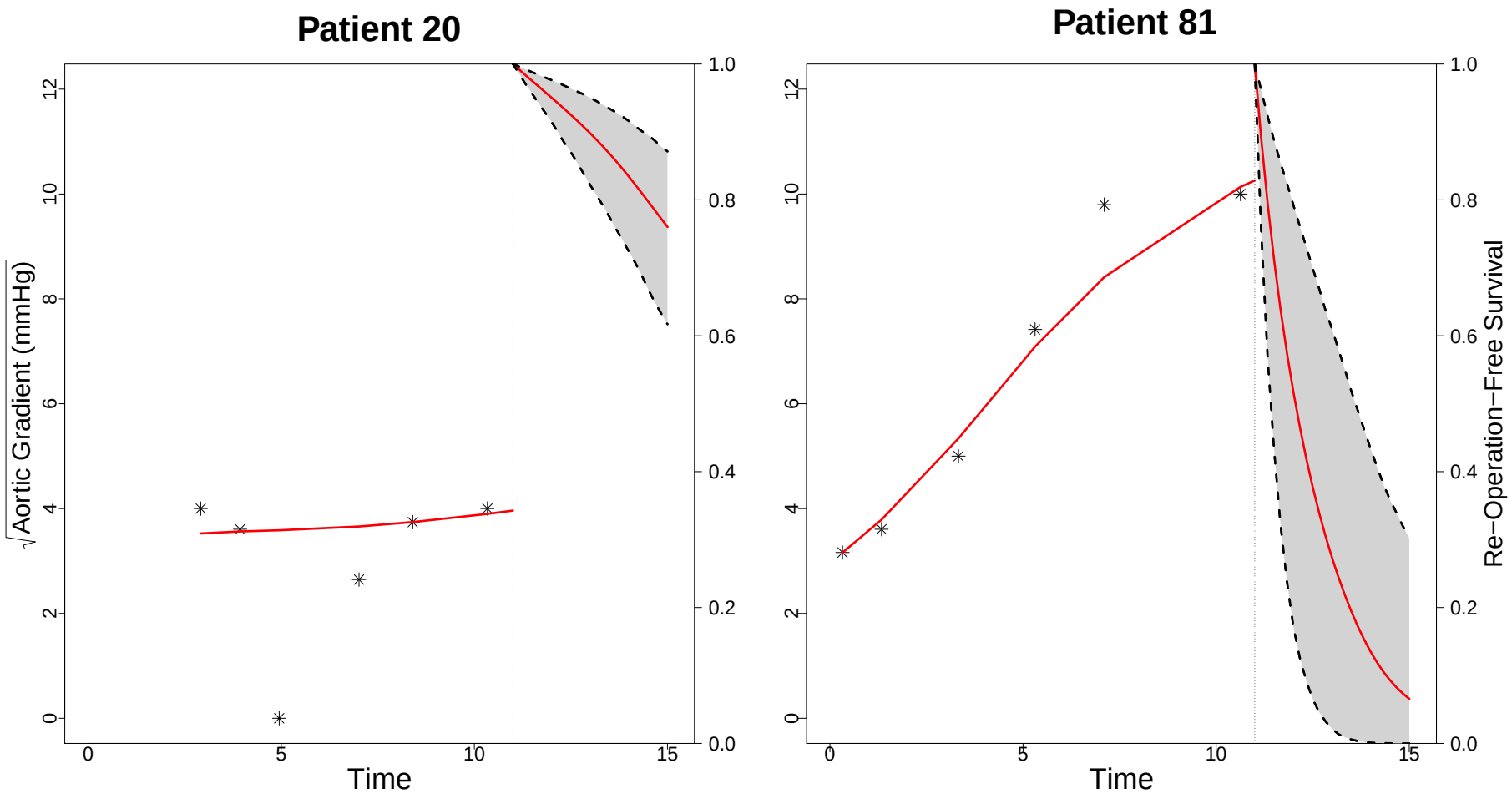


4.1 Next Visit Time – Set up

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

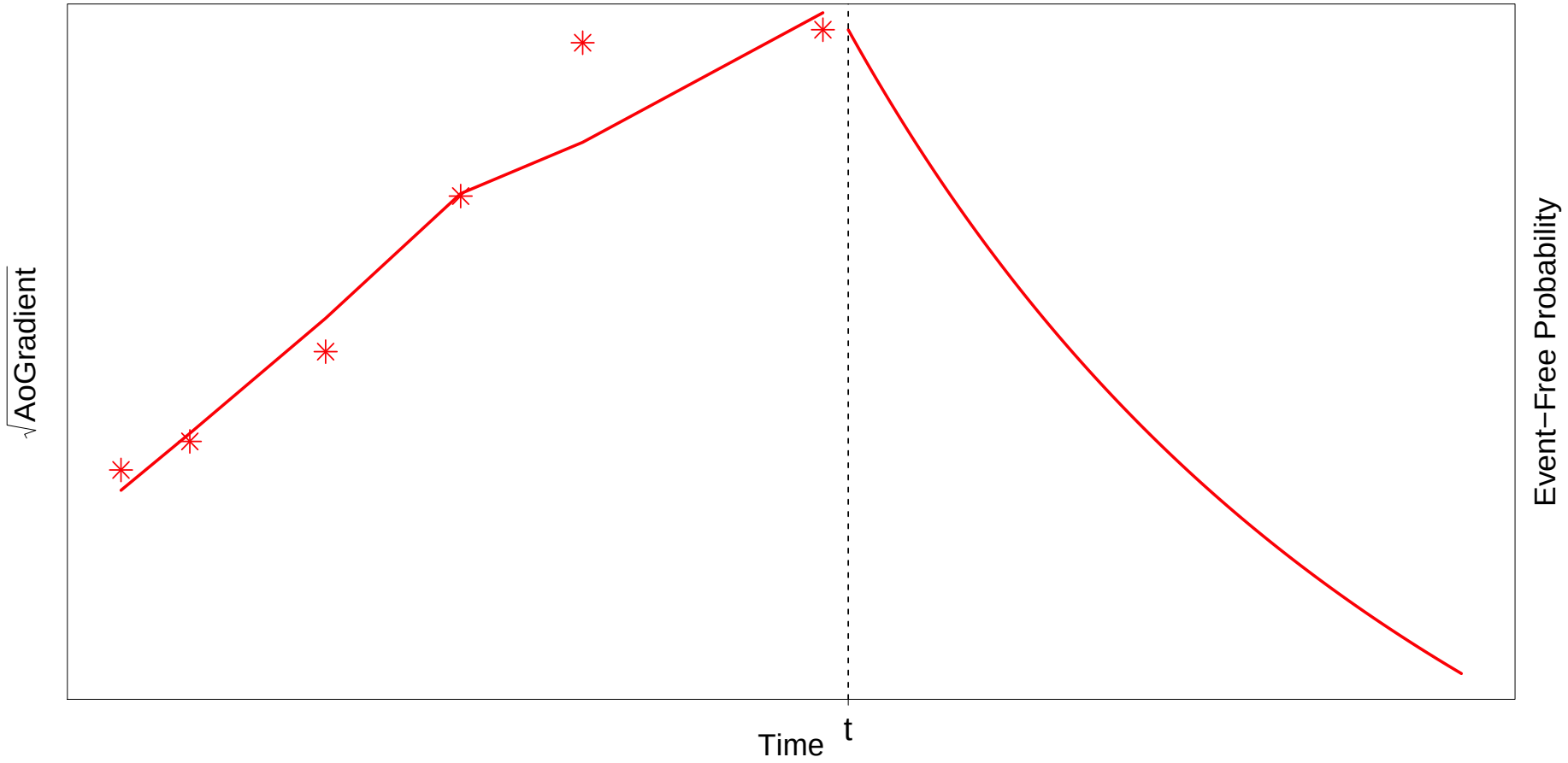
4.1 Next Visit Time – Set up (cont'd)

This is a difficult question!

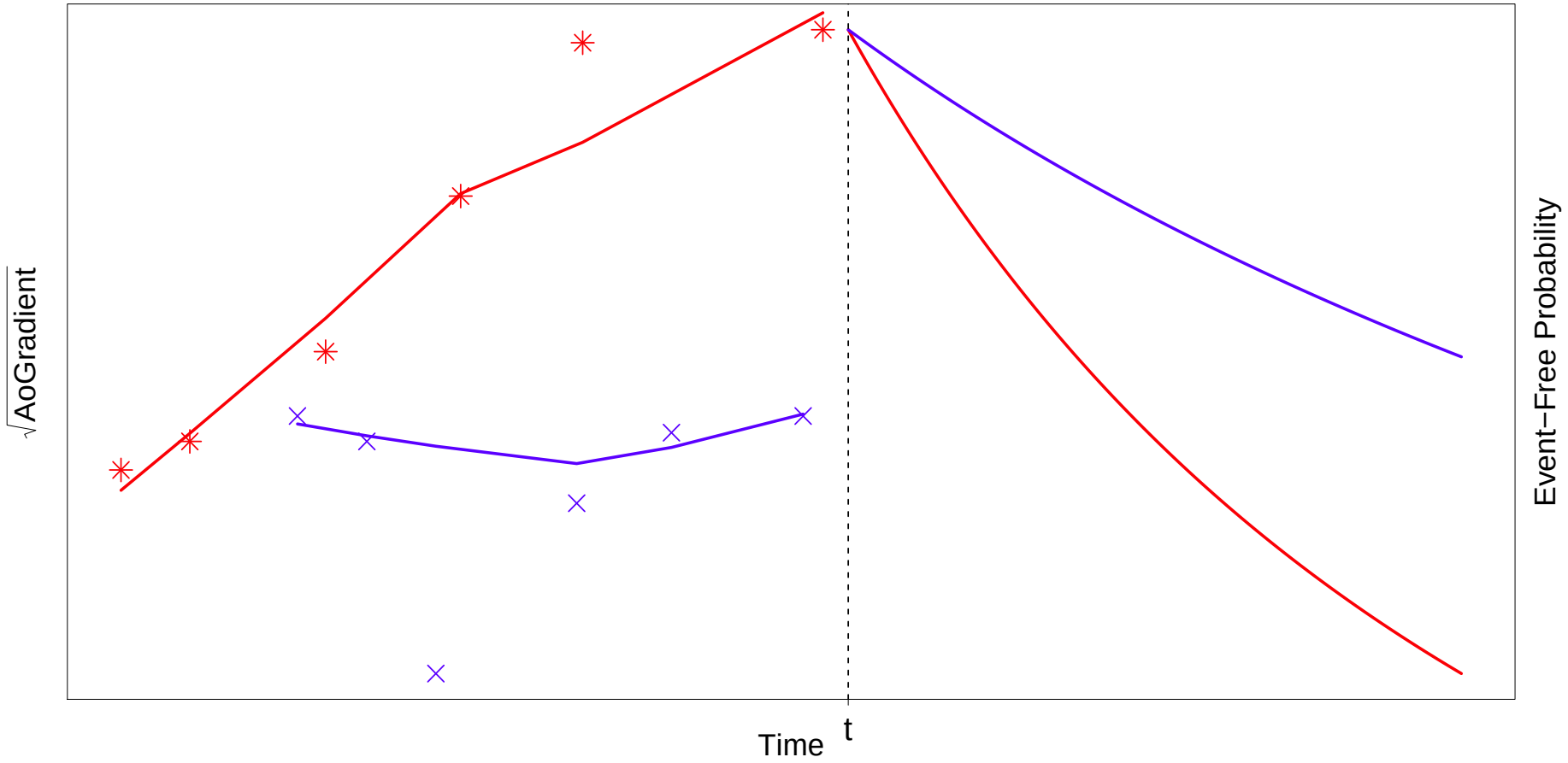
- Many parameters that affect it
  - ▷ which model to use?
  - ▷ what criterion to use?
  - ▷ change in treatment?
  - ▷ ...

We will work under the following setting ⇒

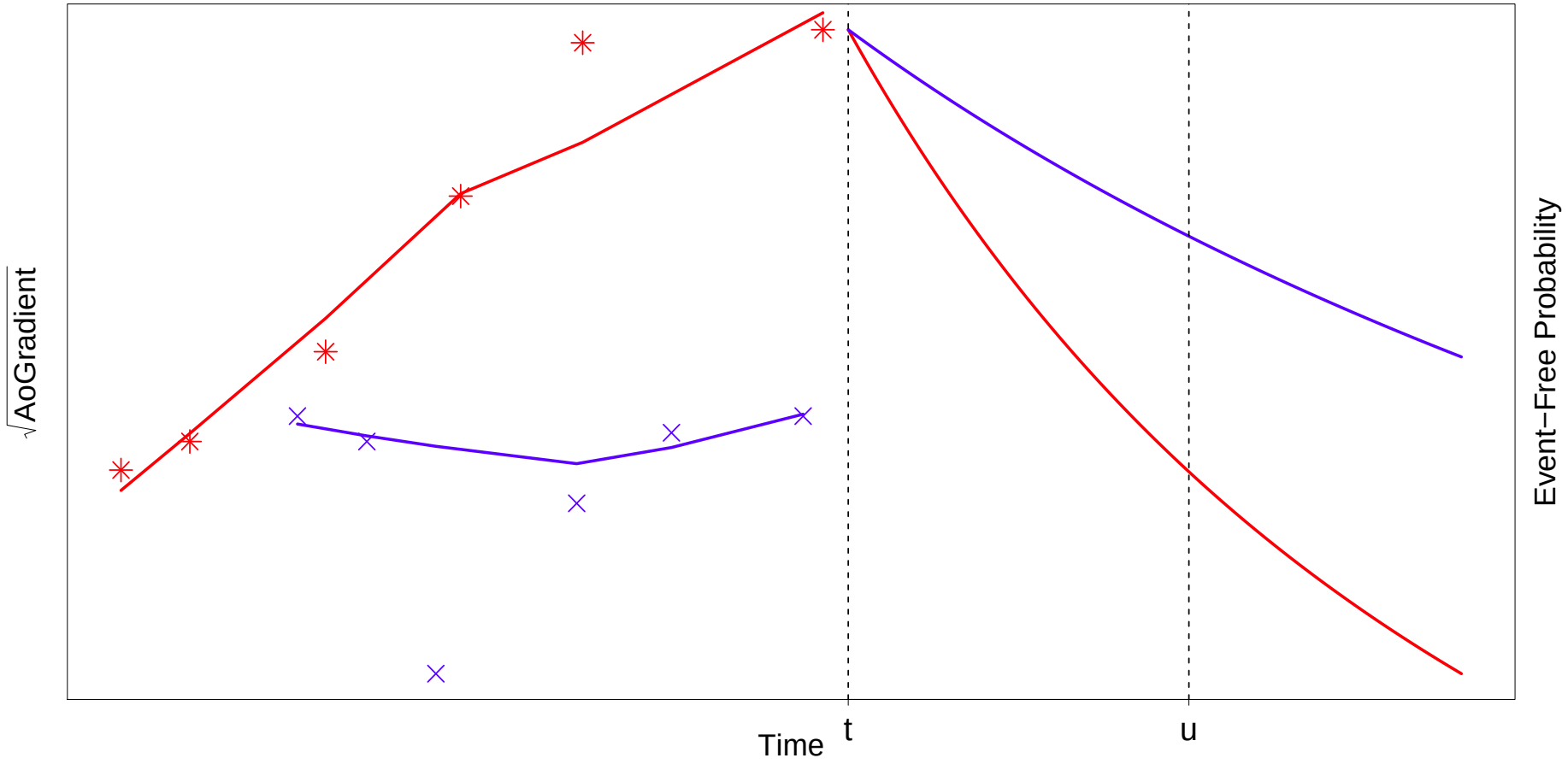
4.1 Next Visit Time – Set up(cont'd)



4.1 Next Visit Time – Set up(cont'd)



4.1 Next Visit Time – Set up(cont'd)



4.2 Next Visit Time – Model

- Defining a joint model entails *many different choices:*
  - ▷ a model for the longitudinal outcome (baseline covs. & functional form of time)
  - ▷ a model for the survival outcome (baseline covs.)
  - ▷ association structure (current value, slope, cum. eff.)

Which model to use for deciding when to plan the next measurement?

4.2 Next Visit Time – Model (cont'd)

- We could use standard approaches:
  - ▷ DIC
  - ▷ (pseudo) Bayes Factors
  - ▷ ...

- These methods provide an overall assessment of a model's predictive ability

- Whereas we are interested in the model that best predicts future events **given survival up to time** t

4.2 Next Visit Time – Model (cont'd)

- We let $\mathcal{M} = \{M_1, \ldots, M_K\}$ denote a set of K joint models
  - ▷ we want the model that best predicts given info up to t

- Tool: **Cross-validatory Posterior Predictive Distribution**

$$p\{T_i^* \mid T_i^* > t, \mathcal{Y}_i(t), \mathcal{D}_{n\backslash i}, M_k\}$$

where

$$\mathcal{D}_{n\backslash i} = \{T_{i'}, \delta_{i'}, \boldsymbol{y}_{i'}; i' = 1, \ldots, i-1, i+1, \ldots, n\}$$

4.2 Next Visit Time – Model (cont'd)

- We let M^* the true model – then we select the model M_k in the set $\mathcal{M}$ that minimizes the cross-entropy (Commenges et al., *Biometrics*, 2012):

$$\mathsf{CE}_k(t) = E\Big\{ -\log\Big[p\big\{T_i^* \mid T_i^* > t, \mathcal{Y}_i(t), \mathcal{D}_{n\backslash i}, M_k\big\}\Big]\Big\}$$

where the expectation is wrt $[T_i^* \mid T_i^* > t, \mathcal{Y}_i(t), \mathcal{D}_{n\backslash i}, M^*]$

- An estimate that accounts for censoring:

$$\mathsf{cvDCL}_k(t) = \frac{1}{n_t}\sum_{i=1}^{n} -I(T_i > t)\log p\big\{T_i, \delta_i \mid T_i > t, \mathcal{Y}_i(t), \mathcal{D}_{n\backslash i}, M_k\big\}$$

4.2 Next Visit Time – Model (cont'd)

- Five joint models for the Aortic Valve dataset
  - ▷ the same longitudinal submodel, and
  - ▷ relative risk submodels

$$h_i(t) = h_0(t)\exp\{\gamma_1 \texttt{Sex}_i + \gamma_2 \texttt{Age}_i + \alpha_1 m_i(t)\},$$

$$h_i(t) = h_0(t)\exp\{\gamma_1 \texttt{Sex}_i + \gamma_2 \texttt{Age}_i + \alpha_2 m_i'(t)\},$$

$$h_i(t) = h_0(t)\exp\{\gamma_1 \texttt{Sex}_i + \gamma_2 \texttt{Age}_i + \alpha_1 m_i(t) + \alpha_2 m_i'(t)\},$$

4.7 Parameterizations & Predictions (cont'd)

$$h_i(t) = h_0(t)\exp\Big\{\gamma_1 \texttt{Sex}_i + \gamma_2 \texttt{Age}_i + \alpha_1 \int_0^t m_i(s)ds\Big\},$$

$$h_i(t) = h_0(t)\exp(\gamma_1 \texttt{Sex}_i + \gamma_2 \texttt{Age}_i + \alpha_1 b_{i0} + \alpha_2 b_{i1} + \alpha_3 b_{i2} + \alpha_4 b_{i3})$$

4.2 Next Visit Time – Model (cont'd)

	Value	Slope	Val.&Slp.	Area	Rand. Eff.
DIC	7237.26	**7186.18**	7195.57	7268.45	**7186.34**
cvD$\widehat{\text{C}}$L$(t = 5)$	−387.67	**−348.96**	−380.82	−441.69	**−356.31**
cvD$\widehat{\text{C}}$L$(t = 7)$	−342.75	**−309.69**	−336.95	−391.78	**−315.26**
cvD$\widehat{\text{C}}$L$(t = 9)$	−289.11	**−260.44**	−284.13	−332.06	**−264.95**
cvD$\widehat{\text{C}}$L$(t = 11)$	−233.56	**−208.11**	−229.27	−270.28	**−212.06**
cvD$\widehat{\text{C}}$L$(t = 13)$	−177.10	**−156.88**	−173.58	−206.40	**−160.03**

4.3 Next Visit Time – Timing

Having chosen the model, **when to plan the next visit?**

4.3 Next Visit Time – Timing (cont'd)

- 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

4.3 Next Visit Time – Timing (cont'd)

- Utility function

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

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

4.3 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

4.3 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

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

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

4.3 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)

4.4 Next Visit Time – Example

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

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

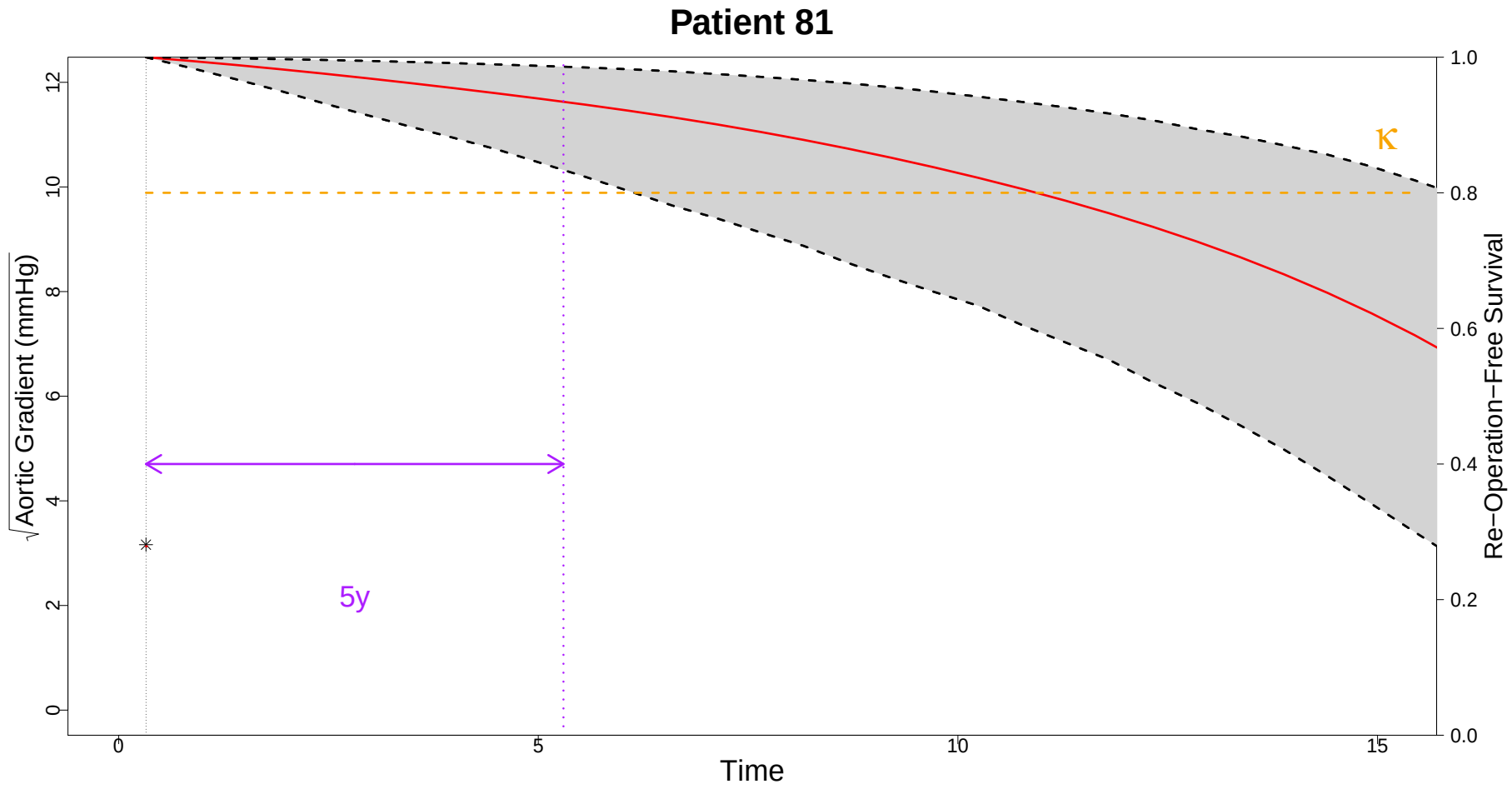
  - ▷ After each visit we calculate the optimal timing for the next one using

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

and

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

4.4 Next Visit Time – Example (cont'd)



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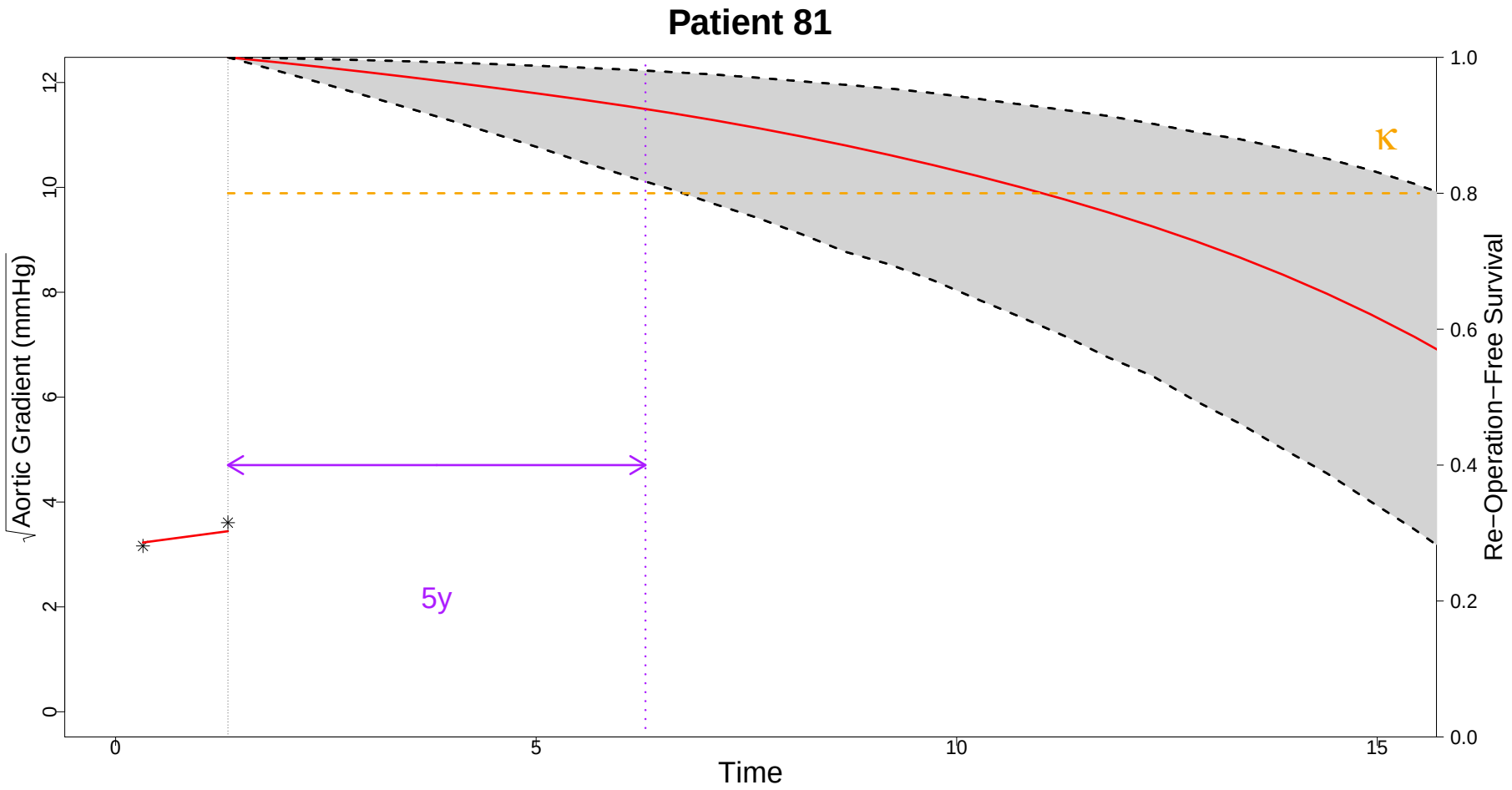

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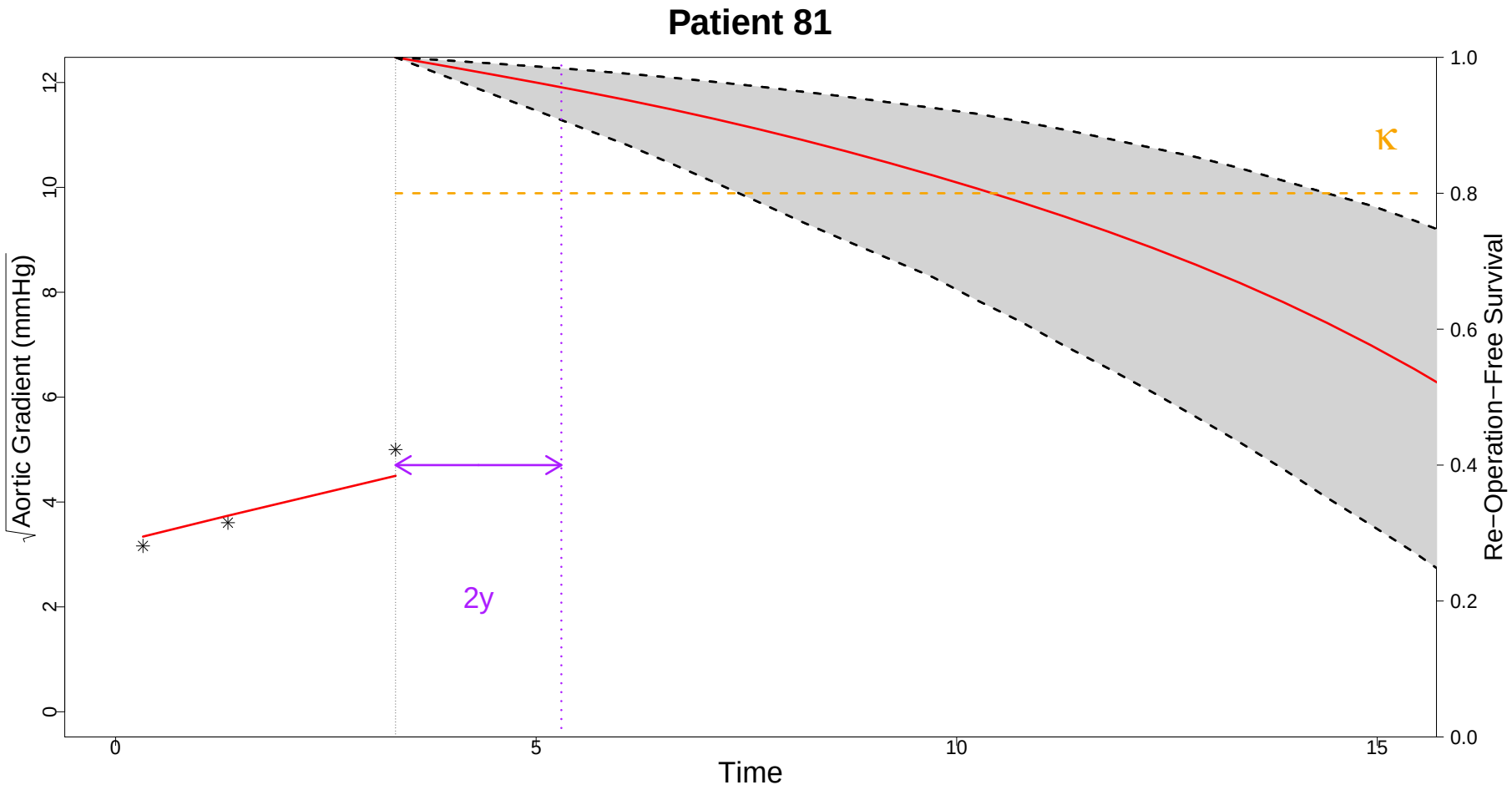

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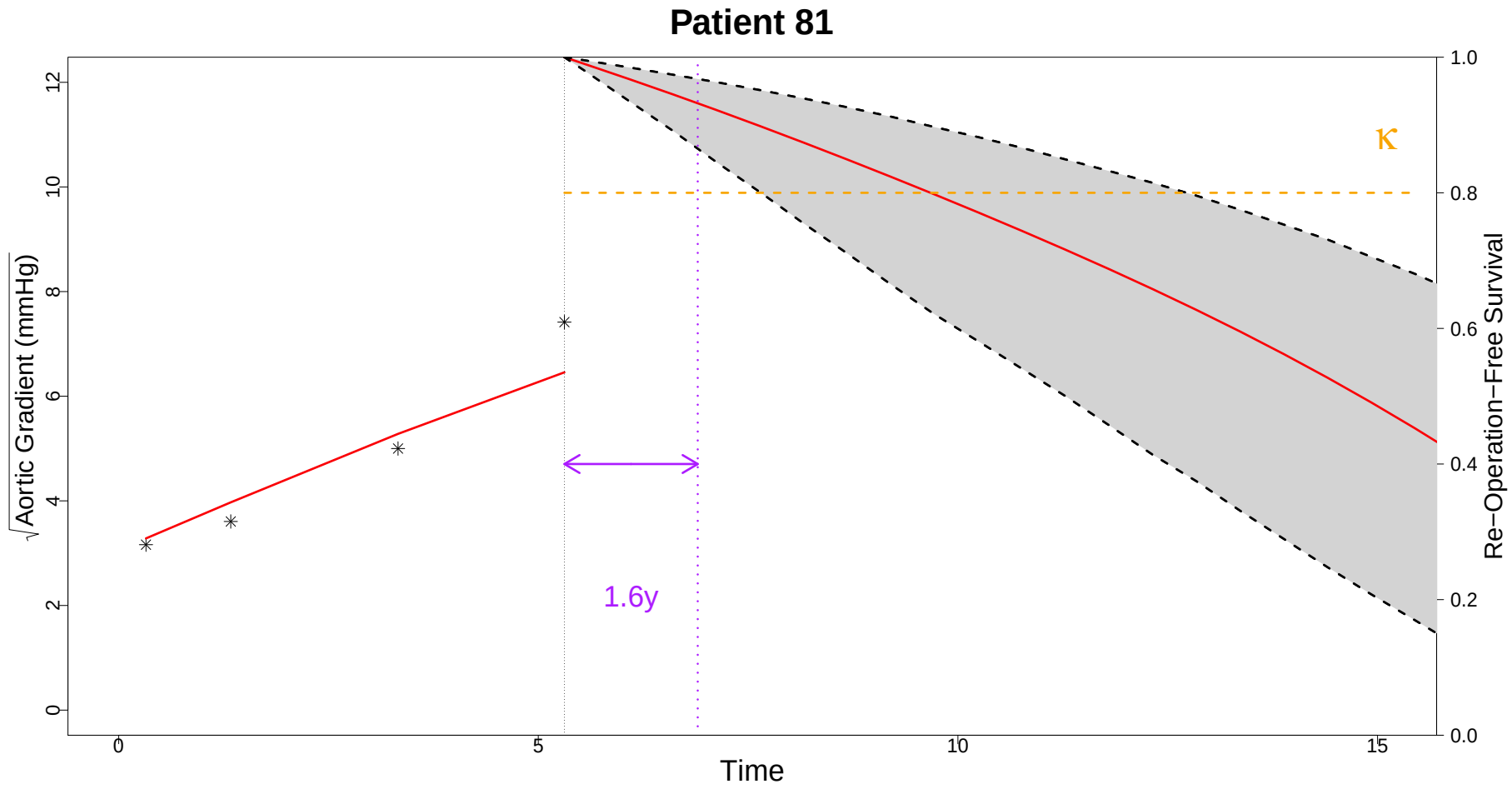

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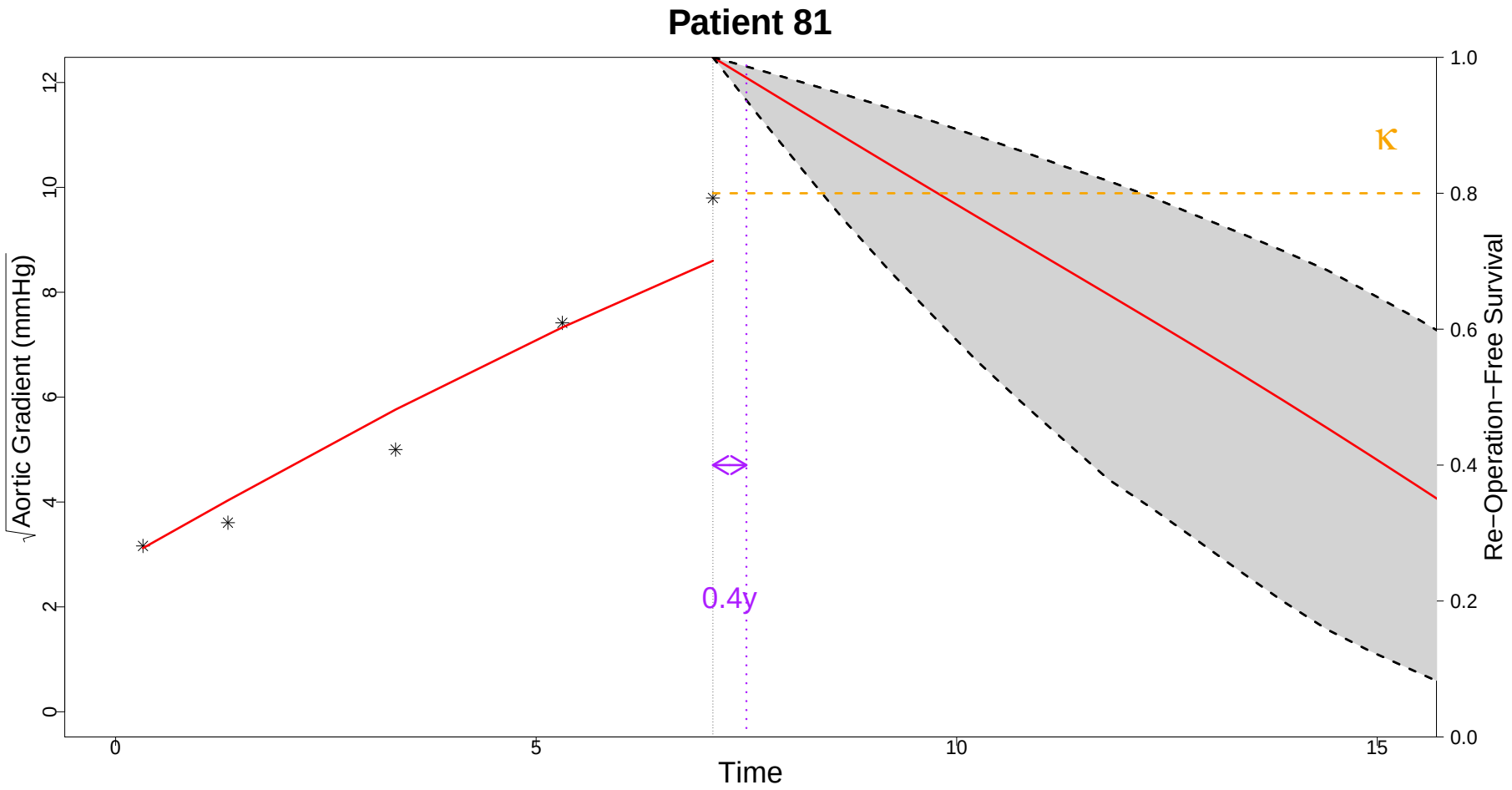

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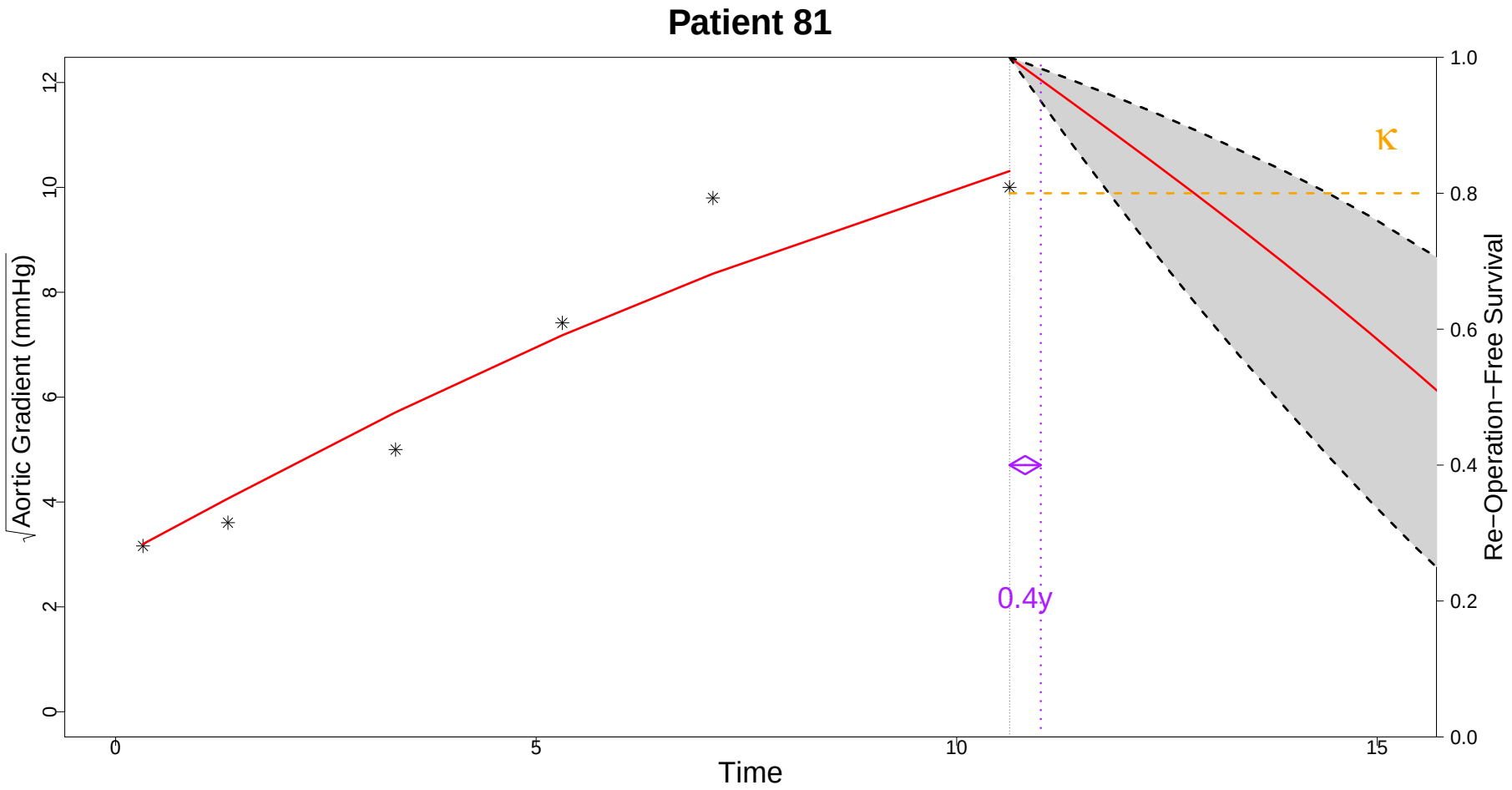

5. Software

- 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!