PBC3 data – description

PBC3 was a multi-centre randomized clinical trial conducted in six European hospitals. Between 1 Jan. 1983 and 1 Jan. 1987, 349 patients with the liver disease primary biliary cirrhosis (PBC) were randomized to either treatment with Cyclosporin A (CyA, 176 patients) or placebo (173 patients). The purpose of the trial was to study the effect of treatment on the survival time. However, during the course of the trial an increased use of liver transplantation for patients with this disease made the investigators redefine the main response variable to be time to "failure of medical treatment" defined as either death or liver transplantation. Patients were then followed from randomization until treatment failure, drop-out or 1 Jan, 1989; 61 patients died (CyA: 30, placebo: 31), another 29 were transplanted (CyA: 14, placebo: 15) and 4 patients were lost to follow-up before 1 Jan. 1989. At entry a number of clinical, biochemical and histological variables, including serum bilirubin, serum albumin, sex, age were recorded.

PBC3 data – list of variables

`ptno`	patient identification
`tment`	treatment (0: placebo, 1: CyA)
`sex`	(1: males, 0: females)
`age`	years
`alb`	albumin (g/L)
`bili`	bilirubin (micromoles/L)
`years`	observation time in years
`status`	status at exit (0: censored, 1: liver transpl, 2 : dead)
`biligroup`	Bilirubin categorised by quintiles

Analysis of PBC3

Intro

1. Draw Kaplan-Meier and Nelson-Aalen for each treatment (`tment`)
2. Calculate the occurrence/exposure rate for each treatment (`tment`)
3. Perform a logrank test for treatment and a stratified version by stratifying for the categorised bilirubin (`biligroup`)

Cox

1. Estimate HR for treatment (`tment`)
2. Estimate HR for treatment (`tment`) adjusted for the categorised bilirubin (`biligroup`) as
   - covariate
   - stratification

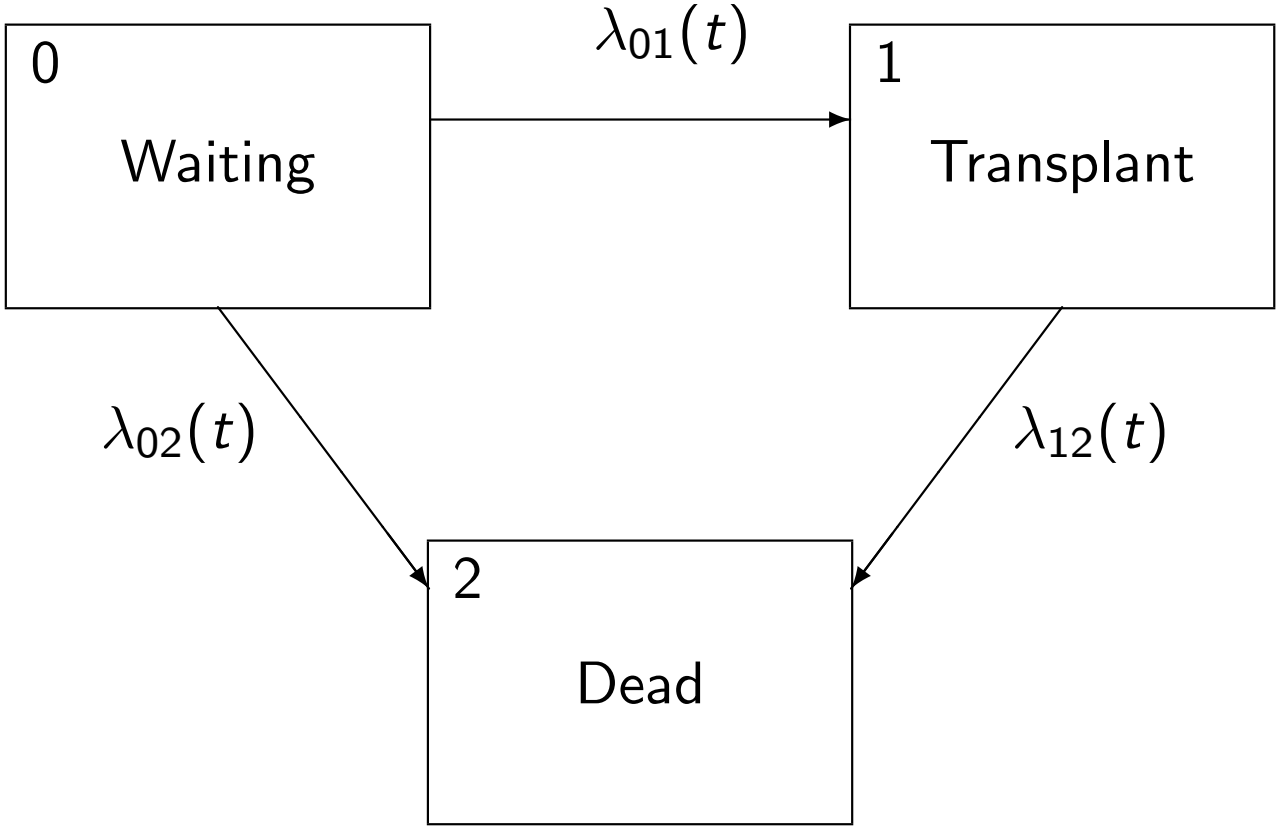
   Any difference? What are the assumptions in the two models?
3. Identify the stratified logrank test in the output from `PROC PHREG` from the previous stratified Cox model
4. Test for same effect of treatment for different levels of `biligroup`
5. Test if the treatment effect in the first year is the same after one year
6. Draw predicted probabilities for each treatment arm from the model adjusted for the categorised bilirubin

Stanford data

In the Stanford Heart Transplantation Study, patients identified as been eligible (N=103) for a heart transplant were put on a waiting list (time 0) and followed until transplantation, death or censorship. In total 69 received transplant during follow-up, whereas 34 did not. The variables are:

`age`	age (in years) at entry into the study.
`cens`	0 = Censoring 1 = Dead
`days`	number of days from entry to dead/censoring.
`trans`	1 = if the person had a heart transplantation 0 = otherwise.
`wait`	number of days from entry to transplantation NB: if trans=0 then wait=.
`mismatch`	1 = mismatch between HLA type in donor and patient 0 = no mismatch NB: if trans=0 then mismatch=.

Stanford – multi-state model



Stanford exercise

Assess the effect of transplantation on survival:

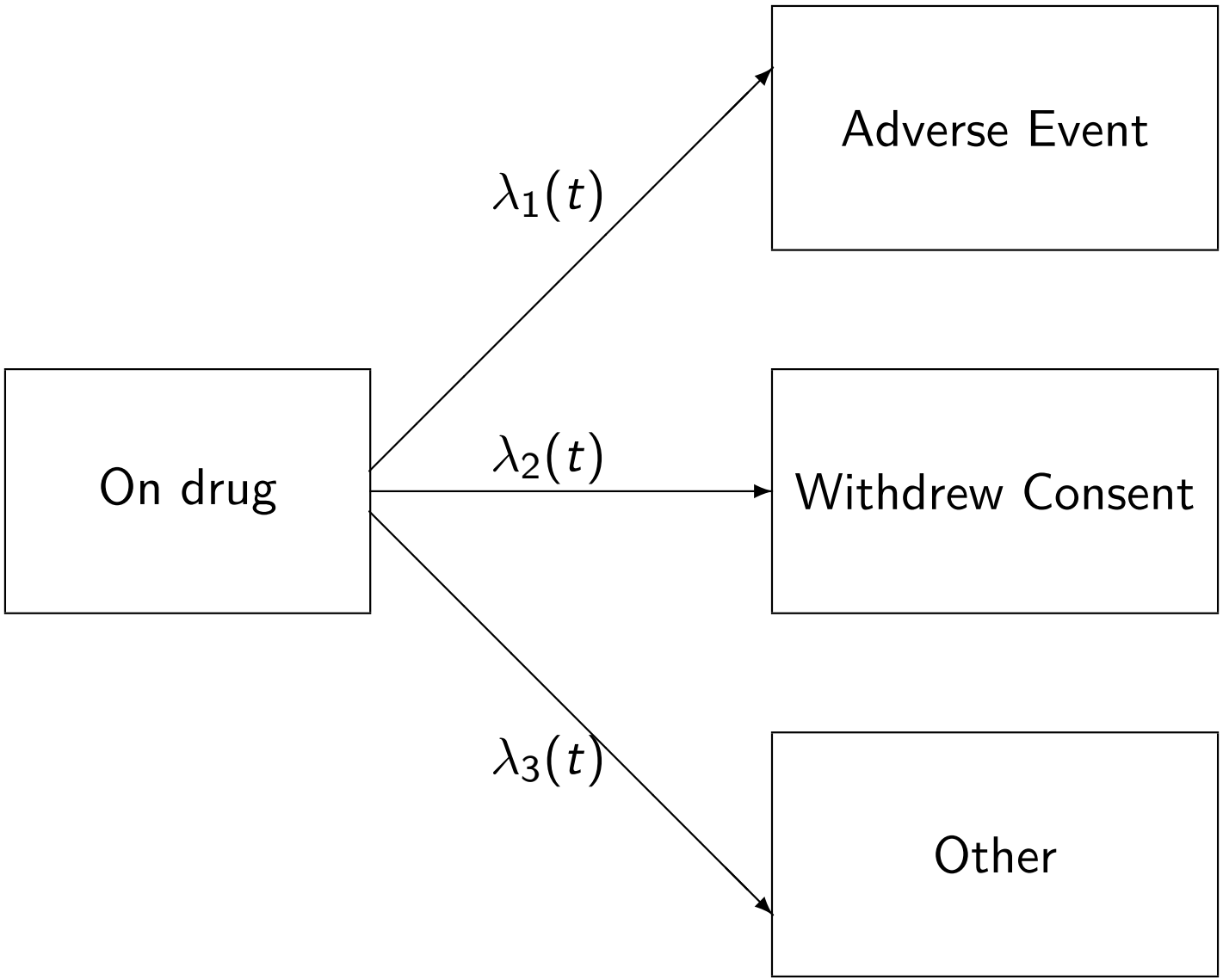
1. Make the erroneous analysis where you evaluate the effect of transplantation using transplantation status as a time-fixed variable
2. Make the correct analysis. Which of the cause-specific rates in the multi-state model are compared here?
3. Does mismatch between HLA type in donor and patient have an influence on effect of transplantation?
4. Evaluate the effect of transplantation when the *time* in the Cox model is current age.
   NB: variable `age` is in years and variable `days` is in (well) days

Data: Drug discontinuations as competing risks

Data on time to drug discontinuation for different reasons in a 1-year RCT (N=559) of active drug vs placebo.

`week`	Time in study in weeks (!)
`state`	0 = Complete on drug (n=406)
	1 = Adverse event (n=42)
	2 = Withdrew consent (n=62)
	3 = Other (n=49)
`drug`	0 = Placebo (n=188)
	1 = Active (n=371)

Drug discontinuations – competing risks



Drug discontinuation exercise

Use `PROC PHREG` and `PROC GPLOT/SGPLOT`.

1. How many percent discontinued in total by week 52 in each treatment arm?
2. Draw the overall discontinuation curves for the two treatment groups
3. Draw the 1-KM curves for adverse events (AE) for the two treatment groups by censoring other events. How many percent discontinued due to AE according to this method (in each treatment arm)?
4. Repeat the 1-KM for the 2 other causes of discontinuation and draw in same plot. What is the sum of these 3 curves (for example at week 52) compared to the overall discontinuation?
5. Draw the CIF curves for adverse events for the two treatment groups (use `PROC PHREG`). How many percent discontinued due to AE according this method (in each treatment arm)?
6. Repeat the CIF for the 2 other causes of discontinuation and draw in same plot. What is the sum of these 3 curves (for example at week 52) compared to the overall discontinuation?

Bone marrow transplantation data

A total of 1715 leukemia patients underwent bone marrow transplantation and were followed until relapse, death in remission or censoring. The following variables are available:

`disease`	10=ALL 20=AML 30=CML
`timedxtx`	time from diagnosis to transplant in months
`sex`	0=males 1=females
`karnofsky`	$I(Karn > 90)$
`stage`	1=early 2=intermediate 3=advanced
`time`	time from transplant to event/cens. in months
`donor`	1=HLA-identical sibling 2=HLA-matched 3=HLA-mismatched
`event`	0=censored 1= relapse 2=death

Bone marrow transplantation exercise

1. Plot Nelson-Aalen estimates for the cumulative cause-specific hazards of (1) relapse and (2) death in remission by donor groups.
2. Plot CIF estimates for the cumulative incidences of (1) relapse and (2) death in remission by donor groups. Does donor affect these 'risks' in the same way as it affected the corresponding 'rates'?
3. Fit Cox models for the cause-specific hazards of (1) relapse and (2) death in remission including donor groups as the only covariate.
4. Fit Cox models for the cause-specific hazards of (1) relapse and (2) death in remission including donor, disease, stage, karnofsky as covariates. Does the adjustment change the hazard ratios for donor?
5. Fit Fine-Gray models for the cumulative incidences of (1) relapse and (2) death in remission including donor groups as the only covariate.
6. Fit Fine-Gray models for the cumulative incidences of (1) relapse and (2) death in remission including donor, disease, stage, karnofsky as covariates. Does the adjustment change the estimated effects of donor?