Introduction to Competing Risks

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Survival data

Survival data = *single* outcome.

- time from origin (time zero) to event (death)
- right censoring, delayed entry
- basic quantity is the
  intensity
  = rate
  = hazard function
  = $\lambda(t) \approx \text{Prob}(\text{die before } t + dt \mid \text{alive at } t)/dt$

Survival data

The hazard, $\lambda(t)$, provides a **local** (in time) description of the development.

Models for $\lambda(t)$

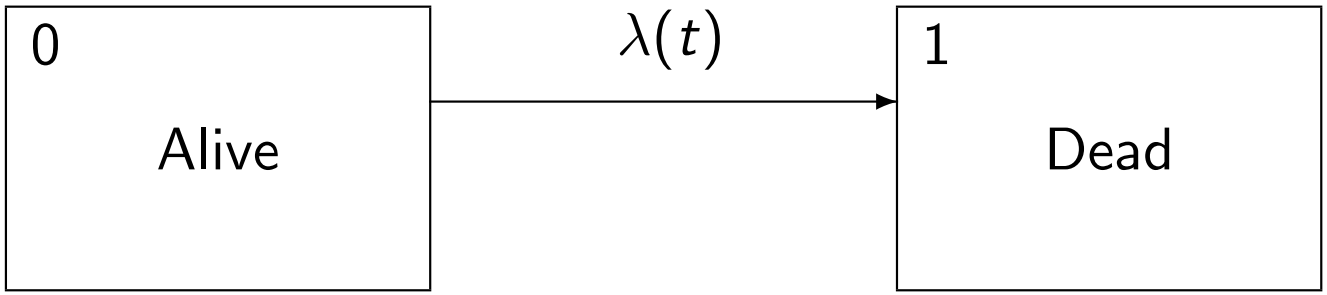
- Cox regression
- Poisson regression

The survival function

$$S(t) = \text{Prob}(\text{alive at time } t)$$

describes the **cumulative** development over time.

Two-state model for survival data



$$\begin{aligned}
\lambda(t) &\approx \text{Prob(state 1 time } t+dt \mid \text{state 0 time } t)/dt \\
S(t) &= \text{Prob(state 0 time } t) \\
F(t) &= 1 - S(t) = \text{Prob(state 1 time } t) \text{ is the cumulative} \\
&\quad \text{probability (''risk'') of death over the interval from 0 to t}
\end{aligned}$$

Relation between rates and risks

We have the relation

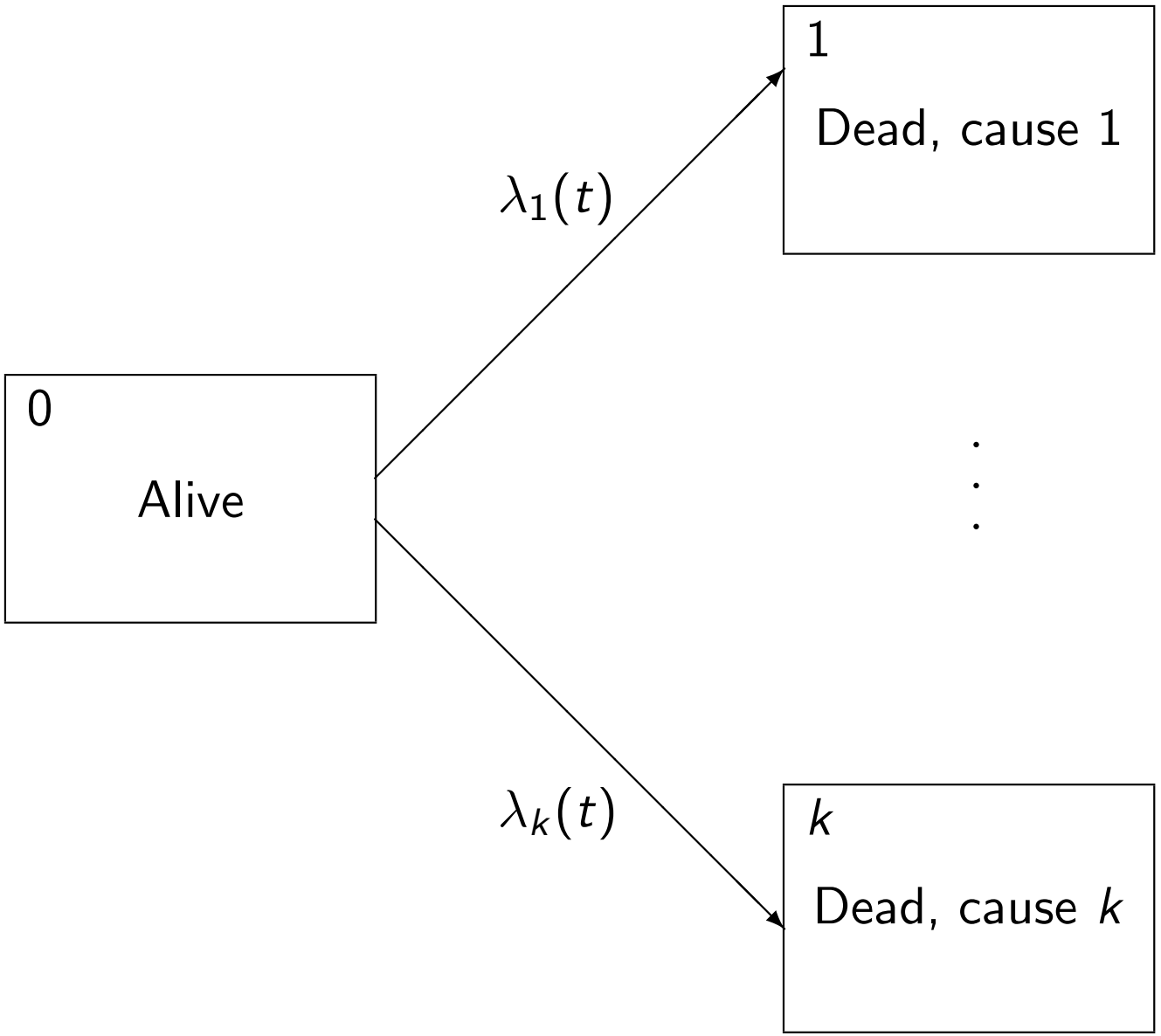
$$F(t) = 1 - \exp(-\int_0^t \lambda(u)\mathrm{d}u).$$

This means that whenever we have a (Cox/Poisson/...) model for the rate, $\lambda(t)$, we also have a model for the risk: $F(t) = 1 - S(t)$.

A **one-to-one** correspondence between hazard and survival (and risk).

In particular, if the rate increases/decreases with a covariate, X, then also the risk increases/decreases with X.

Competing risks



Competing risks

Cause-specific intensities

$$\begin{aligned}
\lambda_1(t) &\approx \text{Prob}(\text{state 1 time } t+dt \mid \text{state 0 time } t)/dt \\
\lambda_2(t) &\approx \text{Prob}(\text{state 2 time } t+dt \mid \text{state 0 time } t)/dt \\
&\vdots \\
\lambda_k(t) &\approx \text{Prob}(\text{state } k \text{ time } t+dt \mid \text{state 0 time } t)/dt
\end{aligned}$$

State occupation probabilities include the overall survival function:

$$S(t) = P(\text{alive time } t).$$

and the *cumulative incidences* ("sub-distribution function")
$j = 1, \ldots, k$:

$$F_j(t) = P(\text{dead from cause } j \text{ before time } t)$$

Recap: Population and sample

We are used to considering our data as a *sample* from some (target) *population*, and the parameters refer to this population.

That is no different in survival analysis, however, it is important to realize that the target population is a *complete* population, i.e., *without censoring*.

Our ambition in survival analysis is therefore to draw inference on parameters like the survival function $S(t)$ or the hazard function $\lambda(t)$ from a potentially completely observed population based on incomplete (censored) data.

This is quite ambitious and requires certain assumptions.

Target population; censoring

For this ambition to be feasible:

1. the complete population should be well-defined
2. censoring should not leave us with a biased sample

Requirement 1 basically tells that the event under study should be able to happen for every one in the population.

A complete population without censoring is not well-defined if, e.g. the event of interest is AE and death is censoring; the event under study should be able to happen for every one in the uncensored population.

We must acknowledge that individuals may die without an AE and inference for AE risks and rates should be made "in the presence of the competing risk of dying".

Recap: Kaplan-Meier and Nelson-Aalen

Censored (independently) sample of times $0 < t_1 < t_2 < \ldots$ with $d(t_1), d(t_2), \ldots$ being the observed numbers of failures.

The Kaplan-Meier (KM) estimator for the survival function

$$\widehat{S}(t) = \prod_{t_j \leq t} \left(1 - \frac{d(t_j)}{R(t_j)}\right).$$

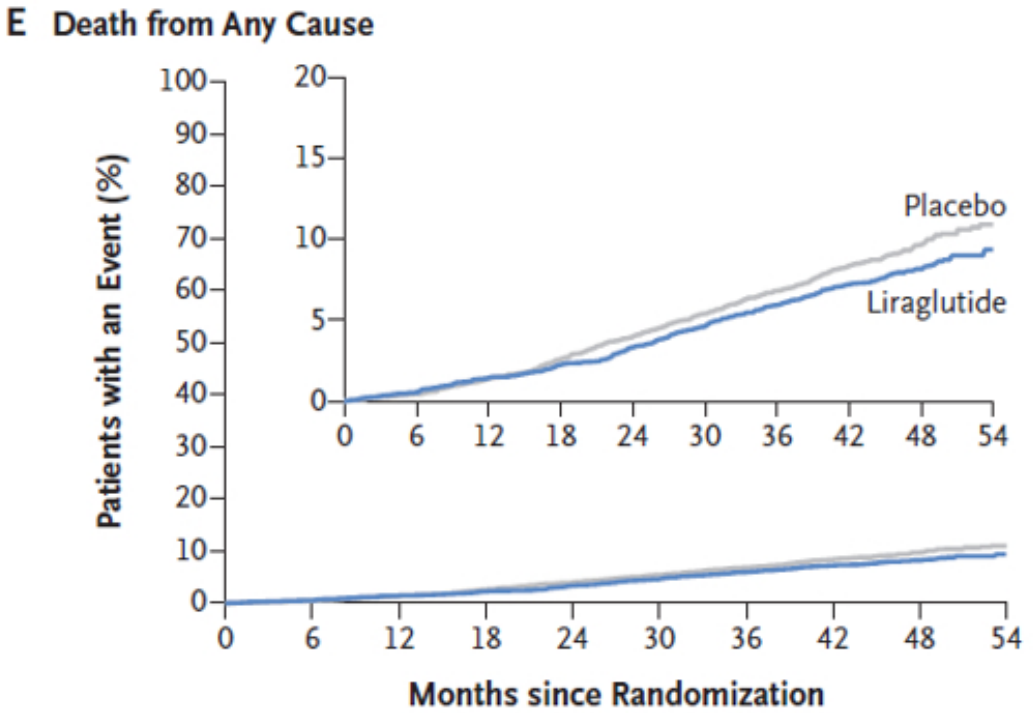
The estimator for the risk $F(t)$, is "1–KM".

The Nelson-Aalen estimator for the cumulative hazard

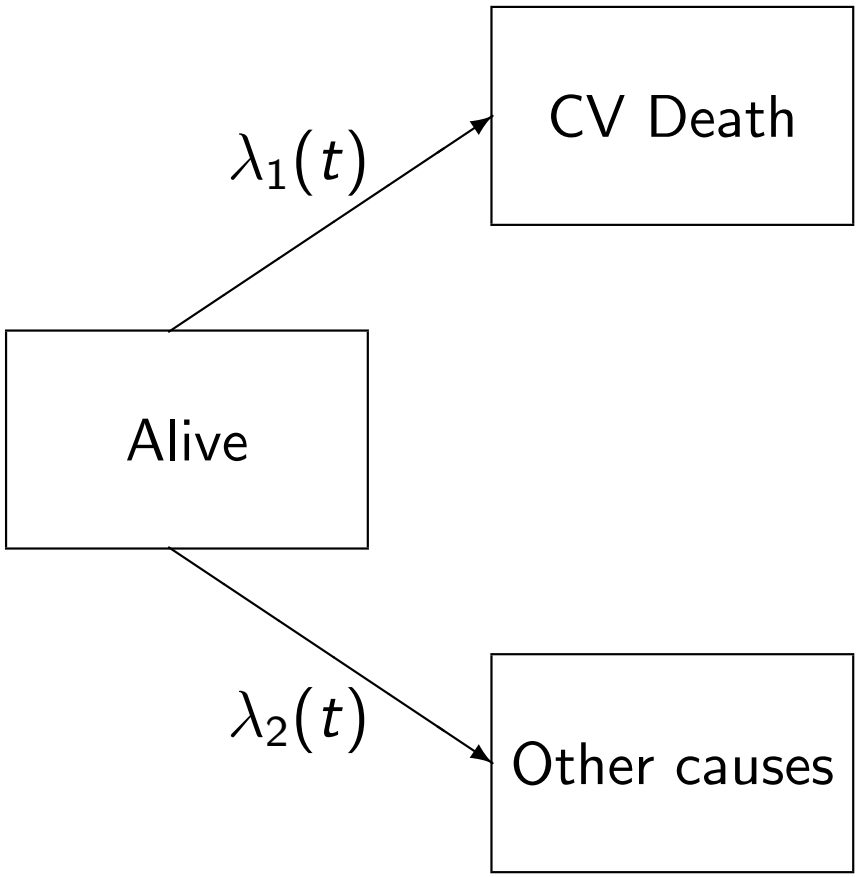
$$\widehat{\Lambda}(t) = \sum_{t_j \leq t} \frac{d(t_j)}{R(t_j)}.$$

LEADER – Death from any cause

1–KM was used to estimate risk functions $F(t) = 1 - S(t)$ for the treatment groups

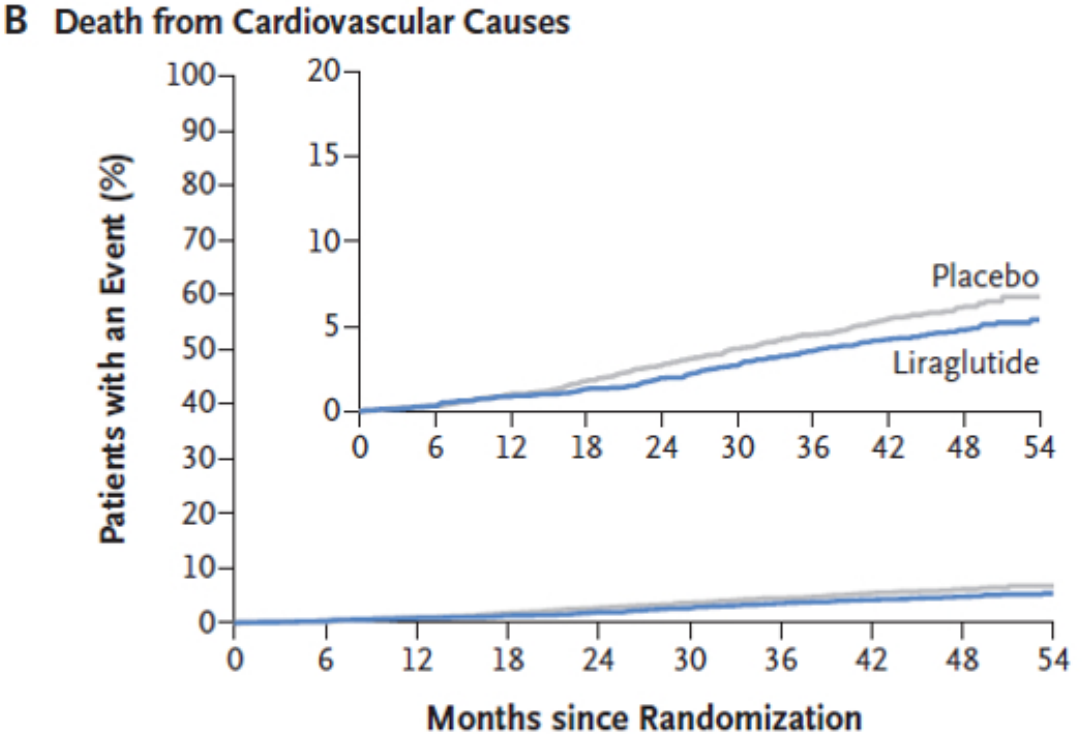


LEADER – CV death and other causes



LEADER – Death from cardiovascular causes

1–KM used to estimate risk functions by censoring for other causes of death



Censor the competing cause

Wish to estimate parameters about CV deaths (for the risk or rate) by censoring for other causes of death. Recall that, for this to be feasible:

1. The complete population (i.e., without censoring) should be well-defined
2. Censoring should not leave us with a biased sample

Requirement 2 is still an issue to be debated, however, requirement 1 will be violated when we censor for other causes:

This is because we attempt to make inference for a potentially completely observed population where other causes of death do not exists. Such a population is hypothetical.

In the competing risks model (2 causes of death)

Cause-specific hazards $j = 1, 2$ ("transition intensities"):

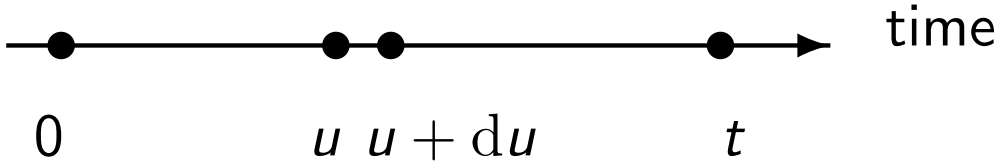
$$\lambda_j(t) \approx P(\text{state } j \text{ time } t + dt \mid \text{state 0 time } t)/dt.$$

State occupation probabilities include the overall survival function:

$$S(t) = P(\text{alive time } t) = \exp[-(\Lambda_1(t) + \Lambda_2(t))].$$

and the *cumulative incidences* ("sub-distribution function") $j = 1, 2$:

$$F_j(t) = P(\text{dead from cause } j \text{ before time } t) = \int_0^t S(u)\lambda_j(u)du$$



NB: $S(t) + F_1(t) + F_2(t) = 1$ for all t.

Rates and risks

Note that the risk for cause 1 depends on the rates for both causes 1 and 2.

For the two-state model for (overall) survival, hazard function λ and failure function F contain *equivalent* information and one may be obtained from the other.

This one-to-one correspondence is lost for competing risks

Both of the cause-specific hazards, λ_1, λ_2, are needed when computing each of the cumulative incidences, F_1, F_2.

Using the Kaplan-Meier estimator on a single cause

We have the relation:

$$F_1(t) = P(\text{dead from cause 1 before time } t) = \int_0^t S(u)\lambda_1(u)du.$$

When $\lambda_2(t) = 0$, i.e. when the competing event is not present, then

$$F_1^0(t) = 1 - \exp(-\int_0^t \lambda_1(u)du) = 1 - S_1(t), \text{ say.}$$

That is, "1–KM for cause 1", $1 - \widehat{S}_1(t)$, estimates

$$P(\text{dead from cause 1 before time } t) \quad \textbf{IF} \quad \lambda_2(t) = 0$$

That is, if the competing risk does not exist.

The Nelson-Aalen estimator with competing risks

The cumulative *cause-specific hazard* can be estimated using the Nelson-Aalen estimator using only failures from the relevant cause, e.g., cause 1:

$$\Lambda_1(t) = \int_0^t \lambda_1(u)du$$

may be estimated by

$$\widehat{\Lambda}_1(t) = \sum_{t_j \leq t} \frac{d(t_j)I(\text{cause} = 1)}{R(t_j)}.$$

This is an increasing step function with steps at each observed time of failure from cause 1.

Aalen-Johansen estimator

Non-parametric estimation of risks/probabilities.

The overall survival function $S(t)$ can be estimated by the Kaplan-Meier estimator, $\widehat{S}(t)$, *using all failures* (LEADER).

The *cumulative incidences*: $F_1(t)$ and $F_2(t)$ may be estimated by *plugging-in* estimates for $S(t)$, $\Lambda_1(t)$ and $\Lambda_2(t)$. E.g., for cause 1:

$$\widehat{F}_1(t) = \sum_{t_j \leq t} \widehat{S}(t_{j-1}) \frac{d(t_j) I(\text{cause} = 1)}{R(t_j)}.$$

This is often called the *Aalen-Johansen estimator*.

LEADER?

Aalen-Johansen estimator

$$
\begin{aligned}
\widehat{F}_1(t) &= \sum_{t_j \le t} \widehat{S}(t_{j-1}) \frac{d(t_j) I(\text{cause} = 1)}{R(t_j)} \\
&= \sum_{t_j \le t} \widehat{S}(t_{j-1}) (\widehat{\Lambda}_1(t_{j-1}) - \widehat{\Lambda}_1(t_j)) \\
&= \sum \text{KM} \cdot (\text{increments in cause-specific N-Aa})
\end{aligned}
$$

1-Kaplan-Meier vs. Aalen-Johansen

We always have:

$$F_1(t) \leq F_1^0(t) = 1 - S_1(t).$$

The risk is over-estimated by using 1–KM instead of Aalen-Johansen.

The degree of bias depends on the magnitude of the competing risk (cause 2): if there are no competing risks ($\lambda_2(t) = 0$) then they are identical, and the difference between the two increases with $\lambda_2(t)$.

At best, the simple 1–KM estimator can be considered an *approximation* to the cumulative incidence that may be used if the competing risk is *small*. However, the best advice is *never* to use 1-KM in the presence of competing risks.

Kaplan-Meier vs. Nelson-Aalen

Why does Nelson-Aalen work with competing risks when Kaplan-Meier doesn't?

This has to do with the fact that the Nelson-Aalen estimates the (cumulative) *rate*, and rates describe the "local" (in time) behavior of the failure process for a given cause. "Therefore", when assessing the local strength of cause 1, then cause 2 need not be taken into account.

Risks, however, cumulate over (long) time periods and the impact of cause 2 must be accounted for when assessing the strength of cause 1.

More on this later

Inference for cause-specific hazards

As a consequence, all standard hazard-based models for survival data apply when analyzing **cause-specific hazards**

- non-parametric: estimate $\Lambda_j(t) = \int_0^t \lambda_j(u)du, j = 1, 2$ by Nelson-Aalen estimator, compare using, e.g. logrank tests
- Cox regression
- Poisson regression

More on this later today.

SAS/STAT 13.2

Aalen-Johansen estimator using macro %CIF (SAS macro library).
The macro requires SAS/IML.

```
%CIF(DATA=dropout, TIME=week, STATUS=state,
    EVENT=1, CENSORED=0, GROUP=drug);
```

The estimates are saved in a data set.

The %CIF macro has been included in PROC LIFETEST in SAS/STAT 14.2.

PROC LIFETEST – SAS/STAT 14.2

Aalen-Johansen estimator

```
PROC LIFETEST DATA=dropout PLOTS=CIF;
   TIME week*state(0) / FAILCODE=1;
   STRATA drug;
RUN;
```

Make CIF for all three causes:

```
PROC LIFETEST DATA=dropout PLOTS=CIF;
   TIME week*state(0) / FAILCODE;
   STRATA drug;
RUN;
```

PROC PHREG – SAS/STAT 13.2

```
PROC PHREG DATA=dropout PLOTS(OVERLAY=ROW)=CIF;
  MODEL week*state(0)=/ eventcode=1;
  STRATA drug;
RUN;
```

NB

PROC PHREG does not use the Aalen-Johansen estimator but the Fine-Gray model for cumulative incidence regression to estimate CIF.

PROC PHREG – SAS/STAT 13.2

For the Cox model from standard survival analysis we have

$$\log(-\log(S(t \mid X))) = \log(\Lambda_0(t)) + \beta' X.$$

The *sub-distribution* version for competing risks is

$$\log(-\log(1 - F_j(t \mid X))) = \log(\widetilde{\Lambda}_{0j}(t)) + \widetilde{\beta}' X.$$

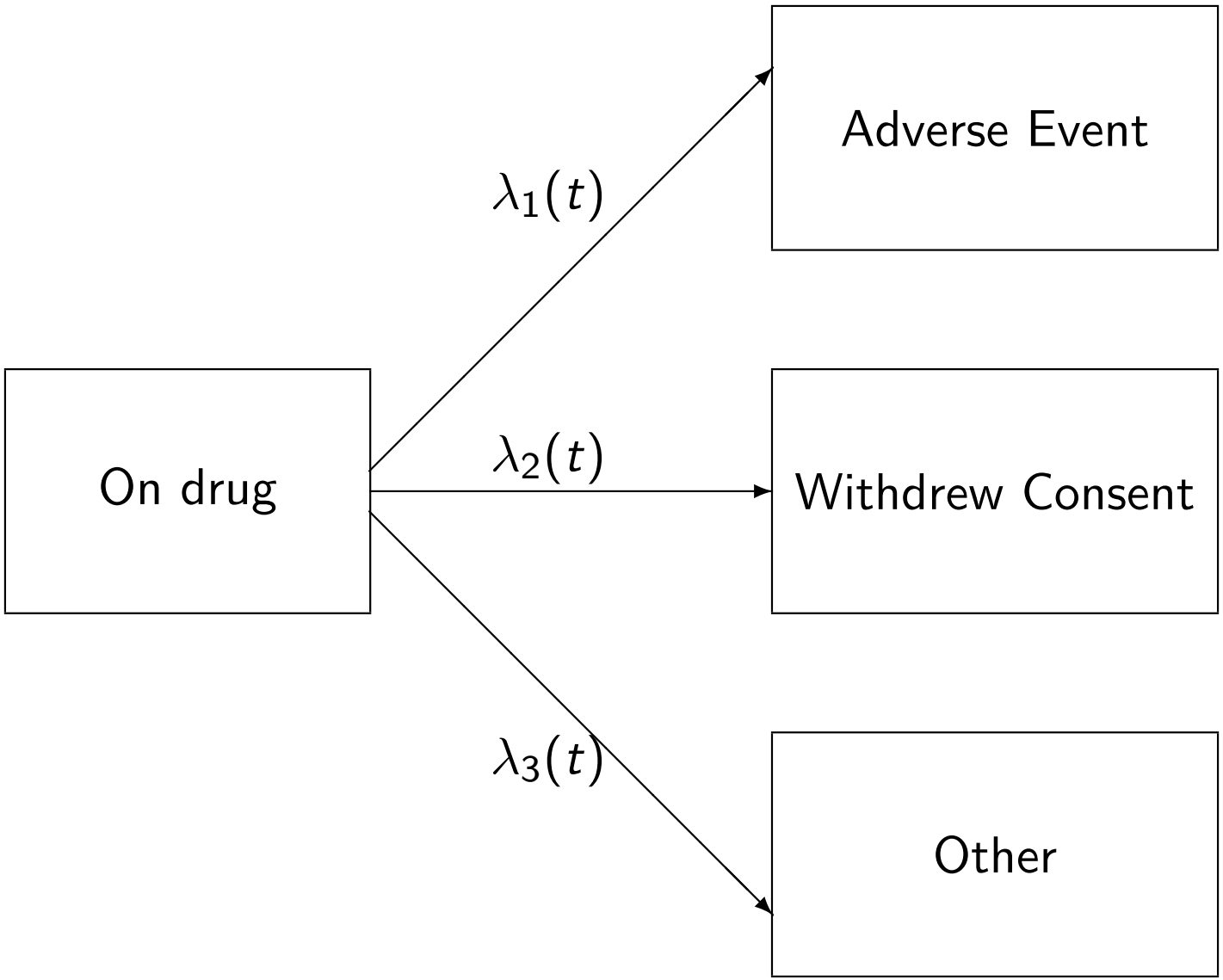
`PROC PHREG` uses an estimator for $\widetilde{\Lambda}_{0j}(t)$ which involves Inverse Probability of Censoring Weights (IPCW) for subjects who have experienced a competing event – more on this later.

Exercise: 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



Example: Drug discontinuations as competing risks

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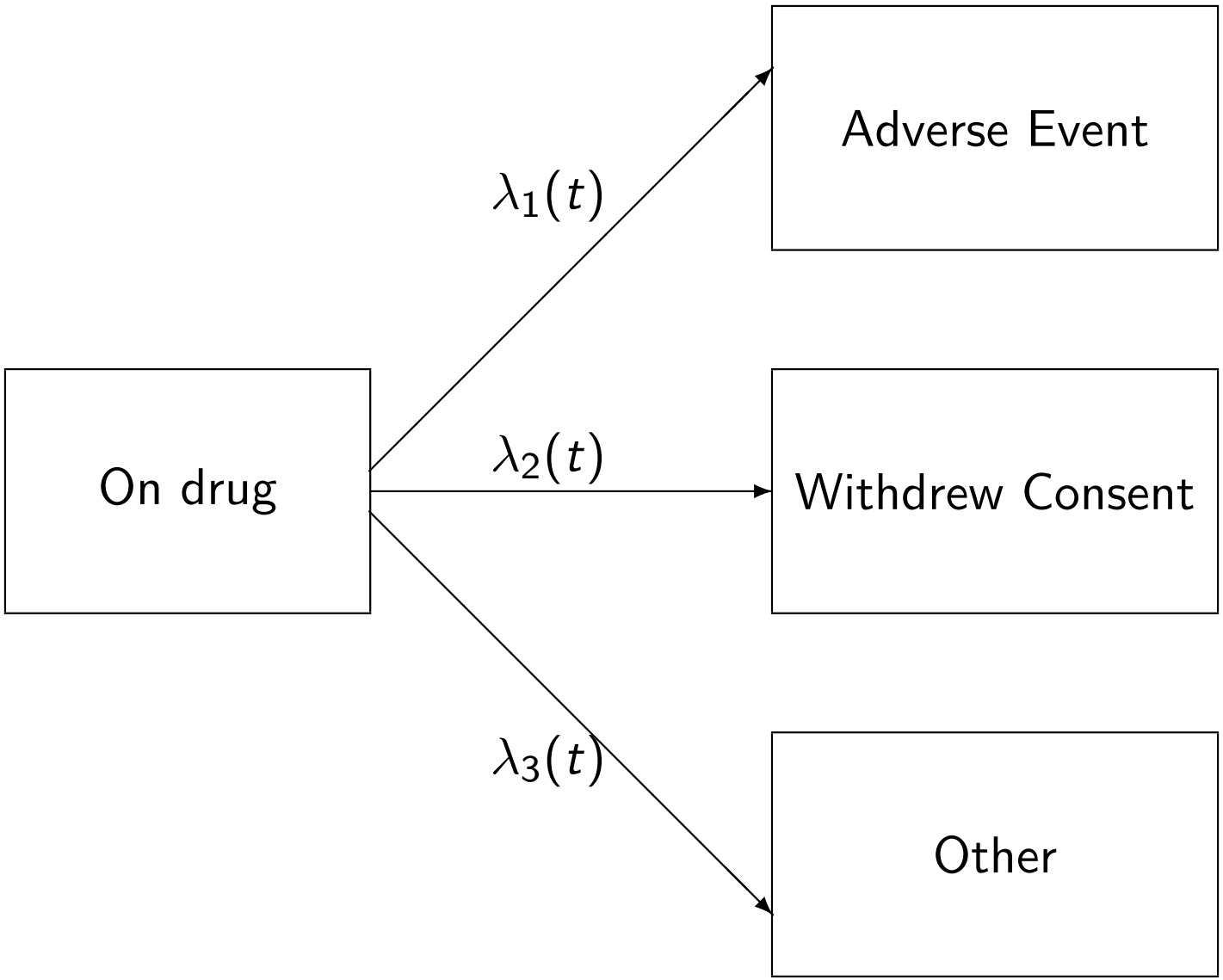
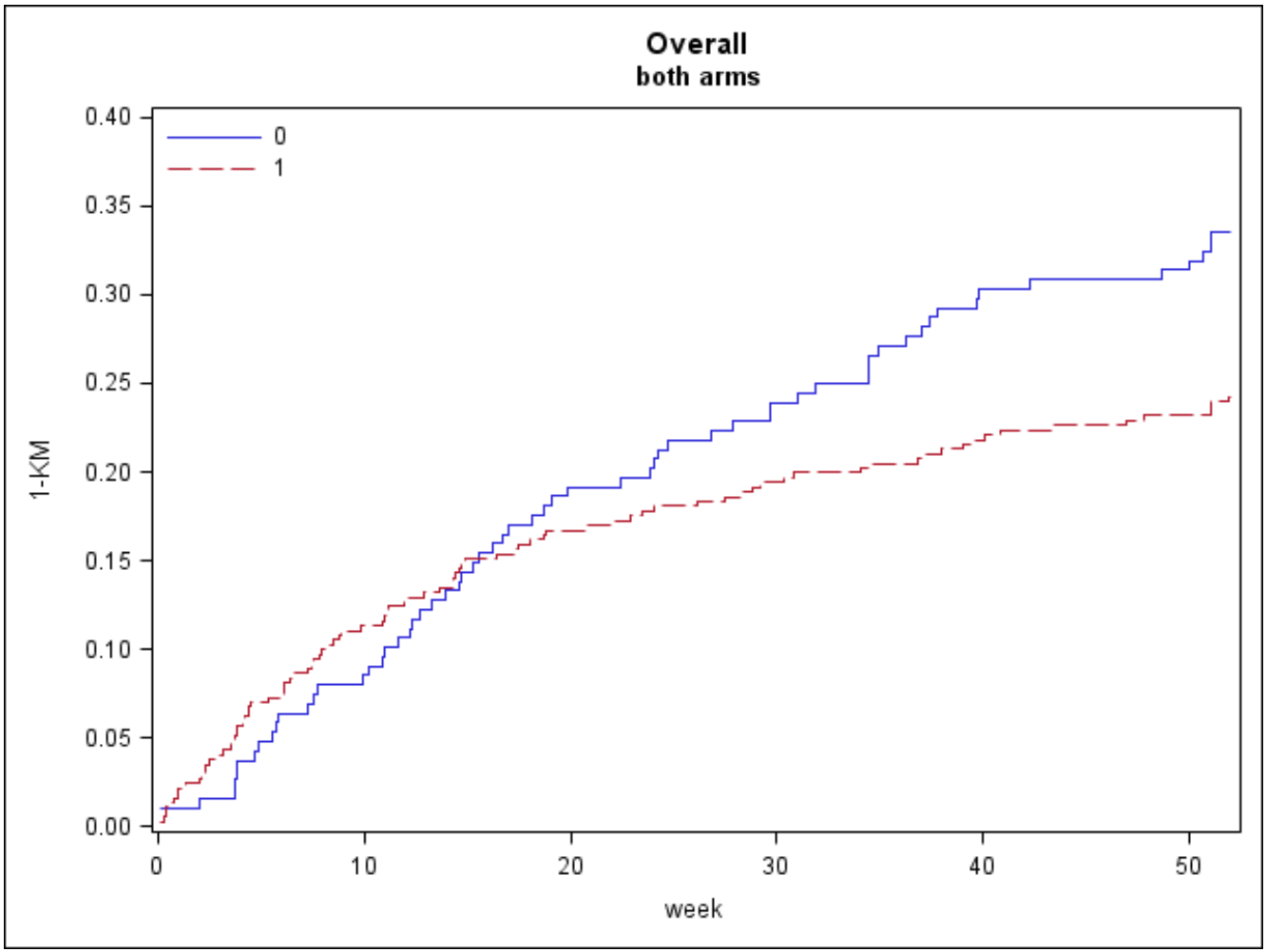
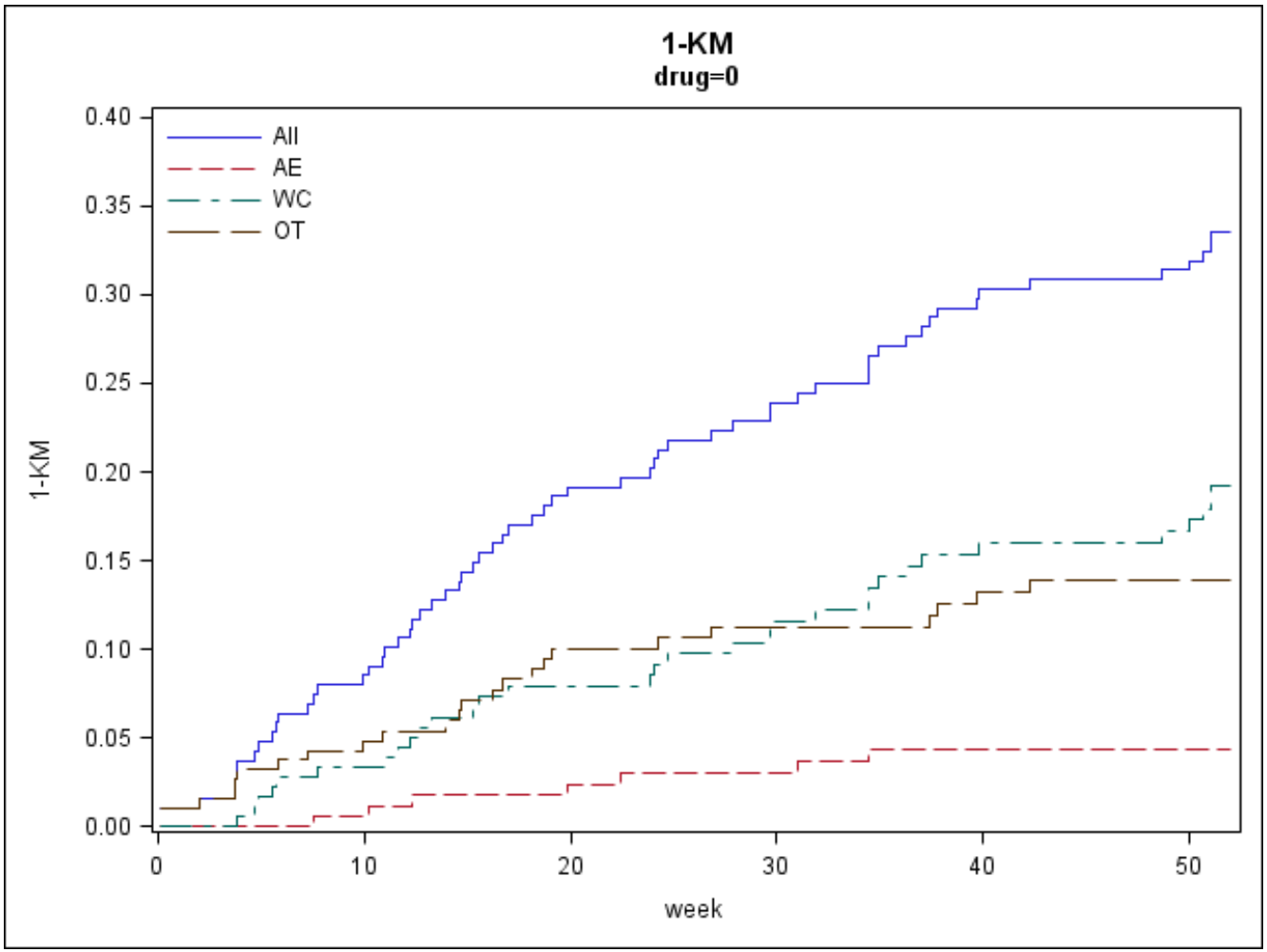
Example: Drug discontinuations as competing risks



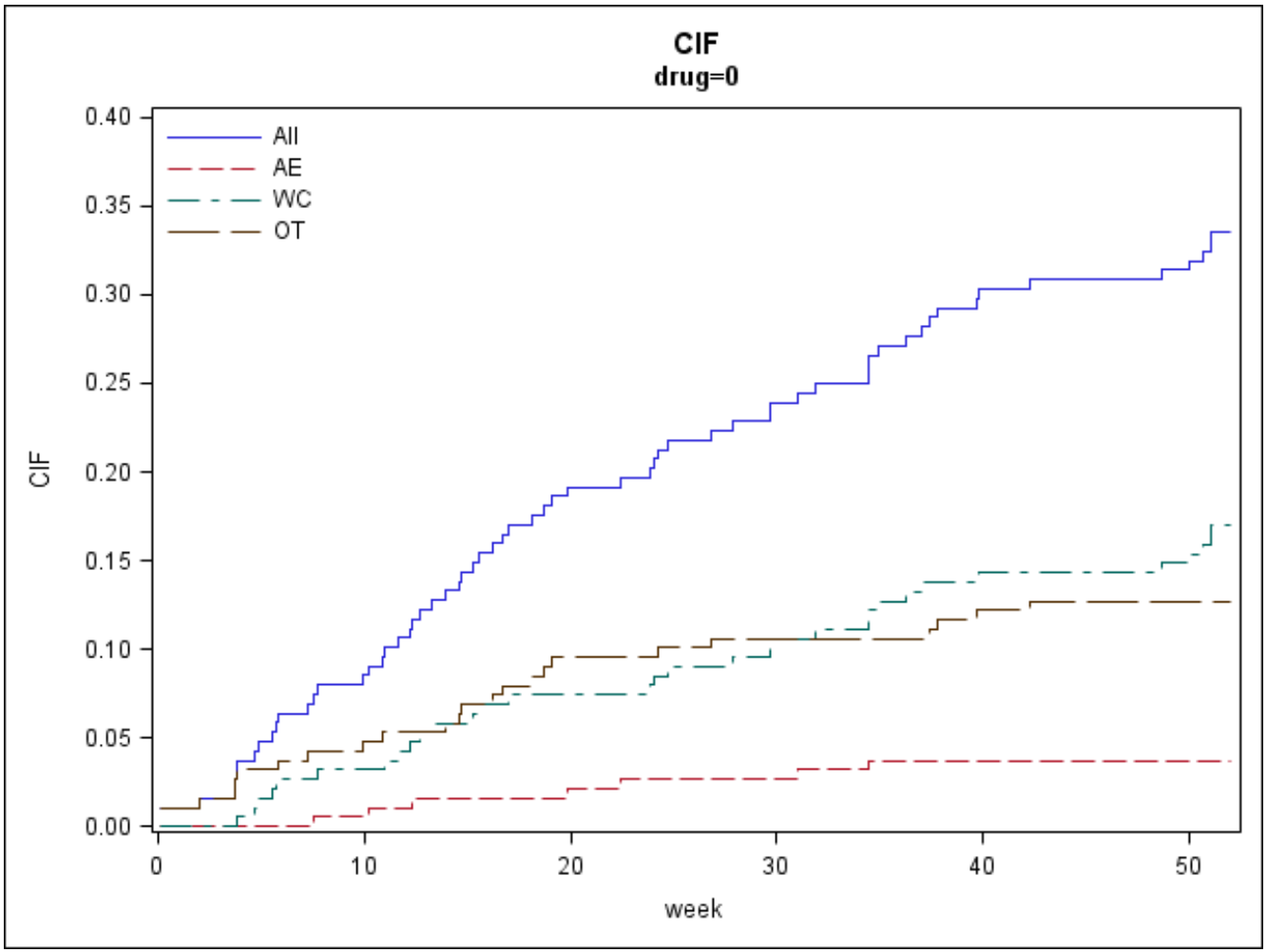
Overall: 1-KM


Overall
both arms
0
1
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
1-KM
0
10
20
30
40
50
week

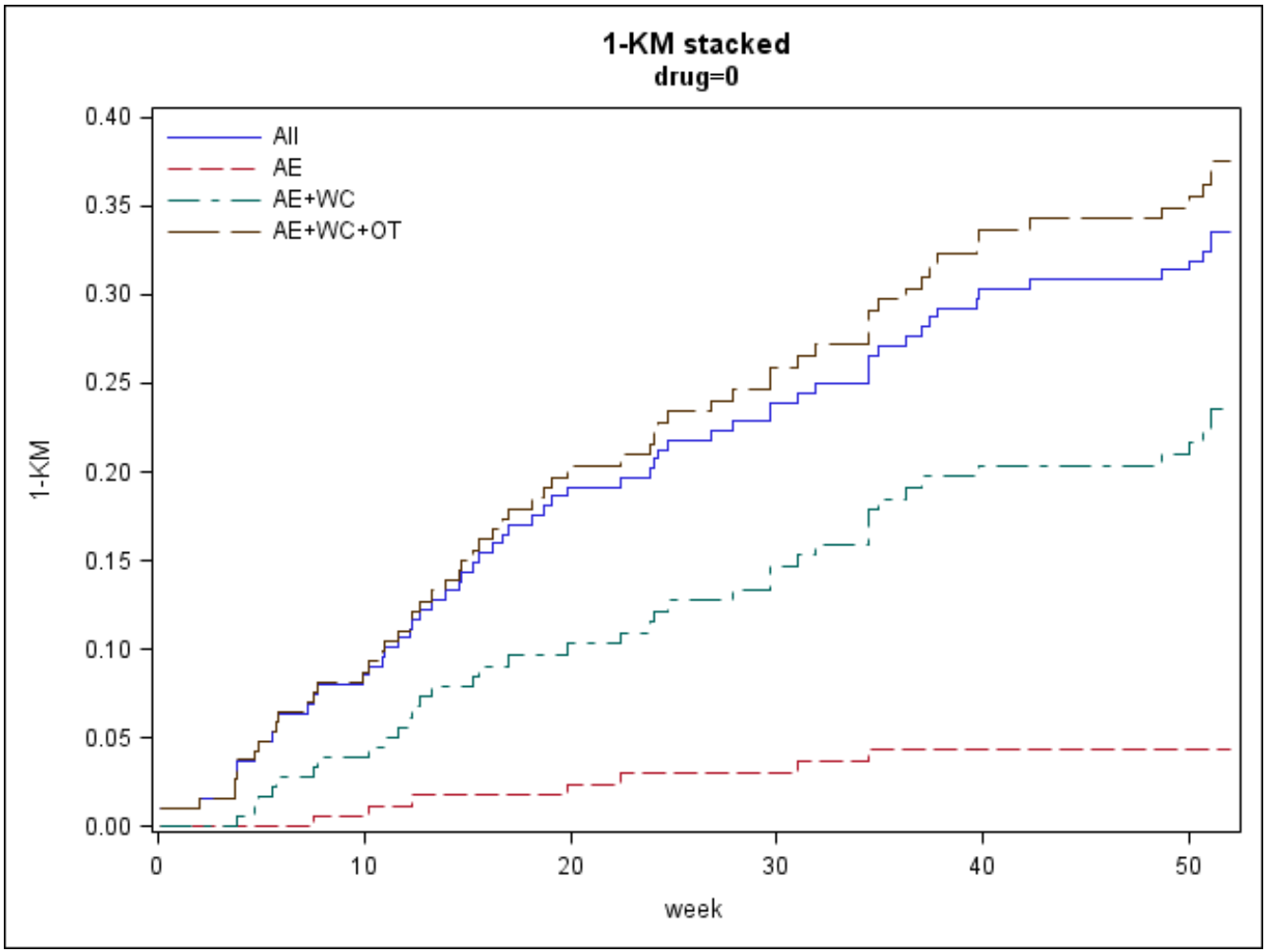
Placebo: 1-KM


1-KM
drug=0
All
AE
WC
OT
1-KM
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
0
10
20
30
40
50
week

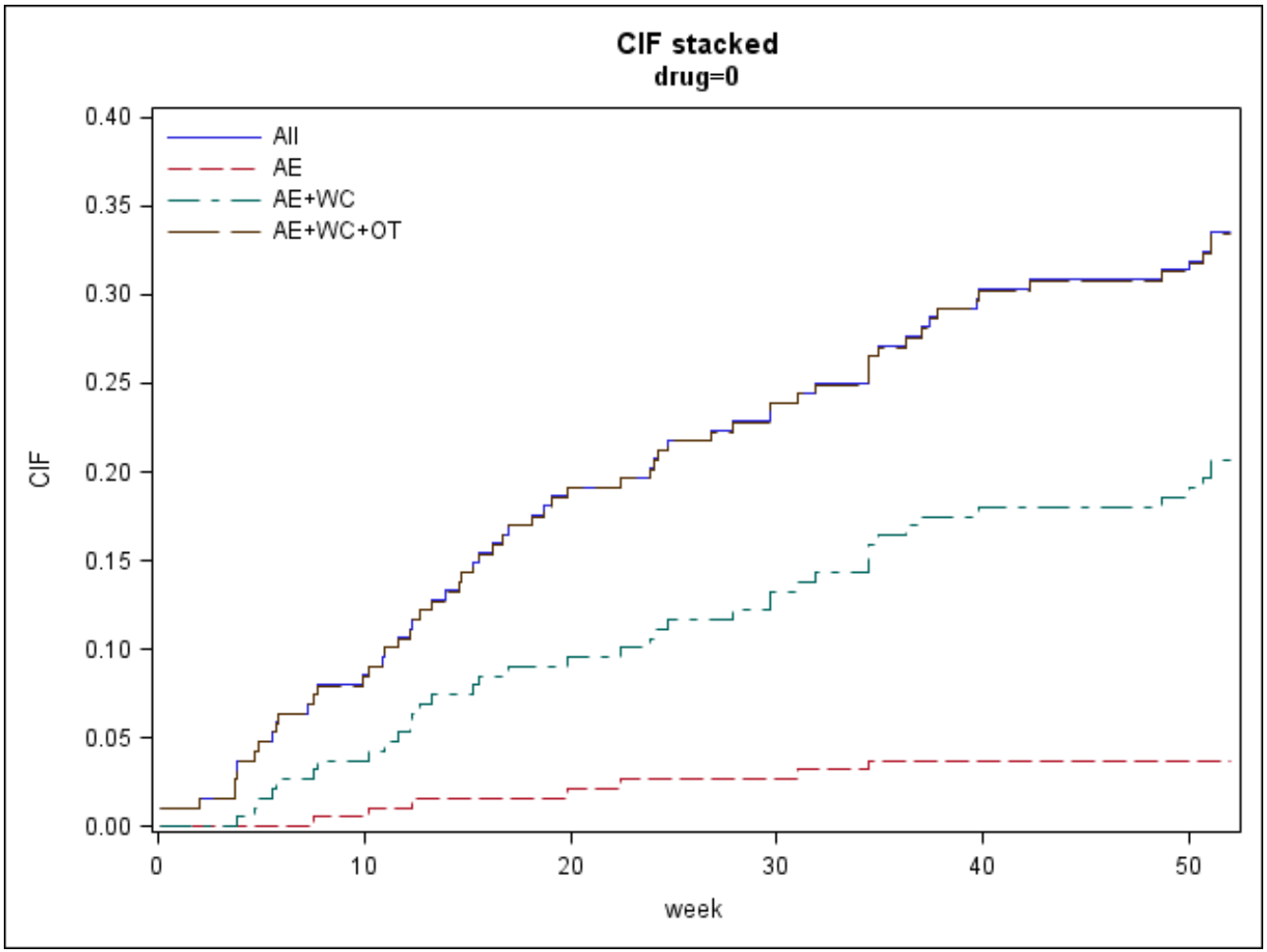
Placebo: CIF


CIF
drug=0
All
AE
WC
OT
CIF
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
0
10
20
30
40
50
week

Placebo: Stacked 1-KM



Placebo: Stacked CIF



Competing risks

- In studies of all-cause mortality, risks (probabilities, cumulative incidences) can be computed from rates (hazards) and vice versa - in other words the two functions contain equivalent information
- In studies of events which will not eventually happen for every one in the population, this is no longer the case and death (and maybe other events) are competing risks which need to be addressed
- In such cases, the risk of a given cause depends on the rates for all competing causes
- Therefore, using '1-Kaplan-Meier for a single cause' as a risk estimator is (upward) biased
- The magnitude of the bias depends on the frequency of the competing events
- A rather simple, unbiased estimator for the risk exists - the "Aalen-Johansen" estimator