Statistical Issues in the Analysis of Adverse Events in Time-To-Event Data

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Talk based on

- A. Allignol, J. Beyersmann, C. Schmoor, Statistical Issues in the Analysis of Adverse Events in Time-To-Event Data, *Pharm Stat* 2016 (online)

Introduction

- The analysis of safety in terms of adverse events (AE) is relevant in almost all clinical trials
- In general, AEs can occur at any point in time during the patients' time under observation
- Often, inadequate methods are used for the analysis. They do not take the time-to-event structure of these data into account
  E.g., one might see more AEs, because treatment successfully prolongs survival

Aim of this talk

Explain and illustrate basic concepts of the correct analysis of AEs in patients with different/incomplete observation times

Introduction

- The proportion of adverse events is usually estimated by

$$\frac{\#\text{AE}}{n},$$

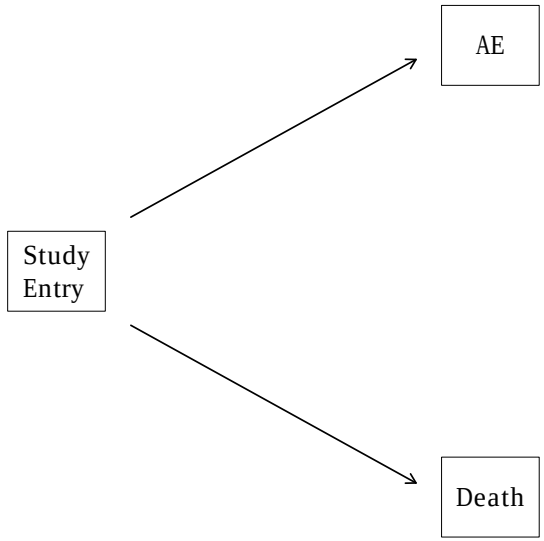
  #AE the number of patients with the interesting AE and n the sample size
- This is usually the quantity that is reported, irrespective of how complete the data are
- If the data are complete, $\#\text{AE}/n$ is the right estimate for $\mathrm{P}(\mathrm{AE})$

(Time to) First AE or Death, Whatever Comes First

No Censoring

Simplified situation:

- (Time to) first AE or death without prior AE, whatever comes first
- We consider AEs of a certain kind, such that #AE $\leqslant n$
- Complete data, i.e., no censoring



- $\frac{\#AE}{n}$ is the right estimate of $P(AE)$ if the data are complete
- Introduce time t (still complete data)

$$\hat{P}(\text{AE in } [0, t]) = \frac{\#\text{AE in } [0, t]}{n}$$

(Time to) First AE or Death, Whatever Comes First

No Censoring

Simplified situation:

- Patients may die without experiencing an AE
- Death is a competing event (competing risk) for AE — after death the AE cannot occur anymore
- Probability to experience the composite event (AE or death without prior AE, whatever comes first)

$$\begin{aligned}&\hat{P}(\text{AE} \in [0, t]) + \hat{P}(\text{Death w/o prior AE in } [0, t])\\ &= \frac{\#\text{ AE or death (whatever comes first) in } [0, t]}{n}\\ &= 1 - \hat{P}(T > t)\end{aligned}$$

T time to first AE or death whatever comes first

(Time to) First AE or Death, Whatever Comes First

With Censoring

Situation with incomplete data (censoring)

- Numerators unknown: # AE or death (whatever comes first) in $[0, t]$
- $\hat{P}(T > t)$ is estimated by the Kaplan-Meier estimator

$$\hat{P}_{KM}(T > t) = \prod_{u<t} \left(1 - \frac{\#\ \textbf{observed}\ \text{composite events at } u}{\#\ \textbf{under observation}\ \text{and no event before } u}\right)$$

The Kaplan-Meier estimator is meant to approximate

$$1 - \frac{\#\ \text{AE or death (whatever comes first) in } [0, t]}{n}$$

- Without censoring, both are equal
- N.B.: 1 - Kaplan-Meier approximates an empirical distribution function. Which approaches 1. I.e., $P(T < \infty) = 1$

(Time to) First AE or Death, Whatever Comes First

With Censoring

Question: How do we estimate $\hat{P}(\text{AE} \in [0, t])$?

Simple proportions

- Simple proportions should not be used because they are biased, e.g.,

$$\frac{\#\ \textbf{observed}\ \text{AEs in}\ [0, t]}{n}$$

estimates $P(\text{AE in } [0, t] | T \leqslant \text{observation time})$, which is not relevant

(Time to) First AE or Death, Whatever Comes First

With Censoring

Question: How do we estimate $\hat{P}(\text{AE} \in [0, t])$?

Kaplan-Meier estimator censoring the competing event

- Often the Kaplan-Meier estimator is used for estimation of $P(\text{AE in } [0, t])$ by treating death without prior AE as censored observation.
- 1 - Kaplan-Meier approximates a distribution function, i.e.,

$$1 - \text{ Kaplan-Meier} \to 1,$$

but $P(\text{AE}) + P(\text{Death w/o prior AE}) \to 1$

- Thus using Kaplan-Meier to approximate $P(\text{AE in } [0, t])$ overestimates

(Time to) First AE or Death, Whatever Comes First

With Censoring

Question: How do we estimate $\hat{P}(AE \in [0, t])$?

Aalen-Johansen estimator of the cumulative incidence function (CIF)

- The Aalen-Johansen estimator of CIF for estimating the probability of event is the correct method when competing events are present

Cumulative Incidence Function

The CIF of AE, $P(T \leqslant t, AE)$ is the expected proportion of patients experiencing an AE over the course of time

- $1 - \hat{P}(T > t)$ is the probability to experience the composite event (AE or death w/o prior AE) in $[0, t]$
- One can show that

$$1 - \hat{P}(T > t) = \sum_{u} \hat{P}(T > u-) \cdot \frac{\#\text{ AE or death at } u}{\#\text{ under observation just before } u}$$

with $\hat{P}(T > u-)$ the Kaplan-Meier estimator evaluated just before time u

Cumulative Incidence Function

The CIF of AE, $P(T \leqslant t, AE)$ is the expected proportion of patients experiencing an AE over the course of time

- Aalen-Johansen estimator of the CIF: Same estimator, but counting only AE as event

$$\hat{P}(T \leqslant t|AE) = \sum_{u} \hat{P}(T > u-) \cdot \frac{\#\text{ AE at } u}{\#\text{ under observation just before } u},$$

- $\hat{P}(T \leqslant t|AE)$ equals $\frac{\#AE \text{ in } [0,t]}{n}$ in the absence of censoring
- Note that

$$1 - \text{Kaplan-Meier of all events} \quad = \quad \text{CIF AE} \quad + \quad \text{CIF death}$$

Illustration

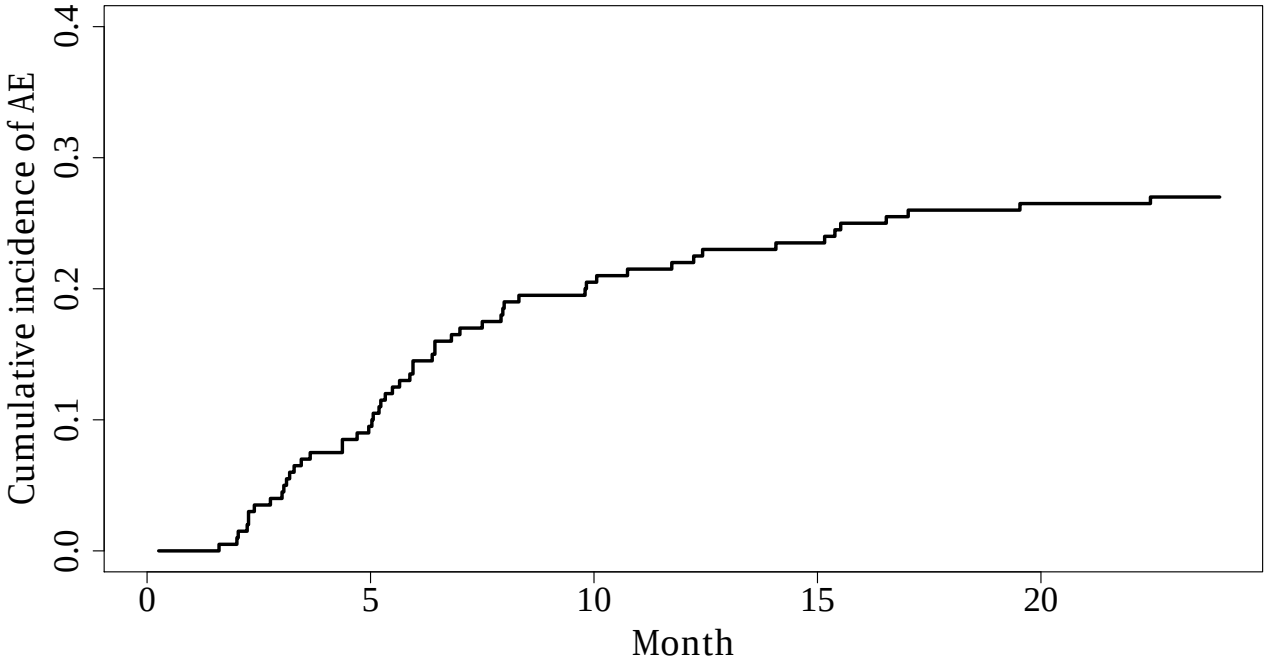
- Data of 200 patients with complete follow-up of 2 years for all patients
- We are interested in a specific type of AE
- Patients can die before the AE occurs
- At the end of the follow-up
  - 54 patients with AE
  - 48 deaths without prior AE

  were observed

$$\frac{54}{200} = 0.27$$

Illustration

Example with complete follow-up of 2 years for all patients (no censoring)
Recall: $\frac{\#AE}{n} = 0.27$



Cumulative incidence of AE is 0.27 at the plateau

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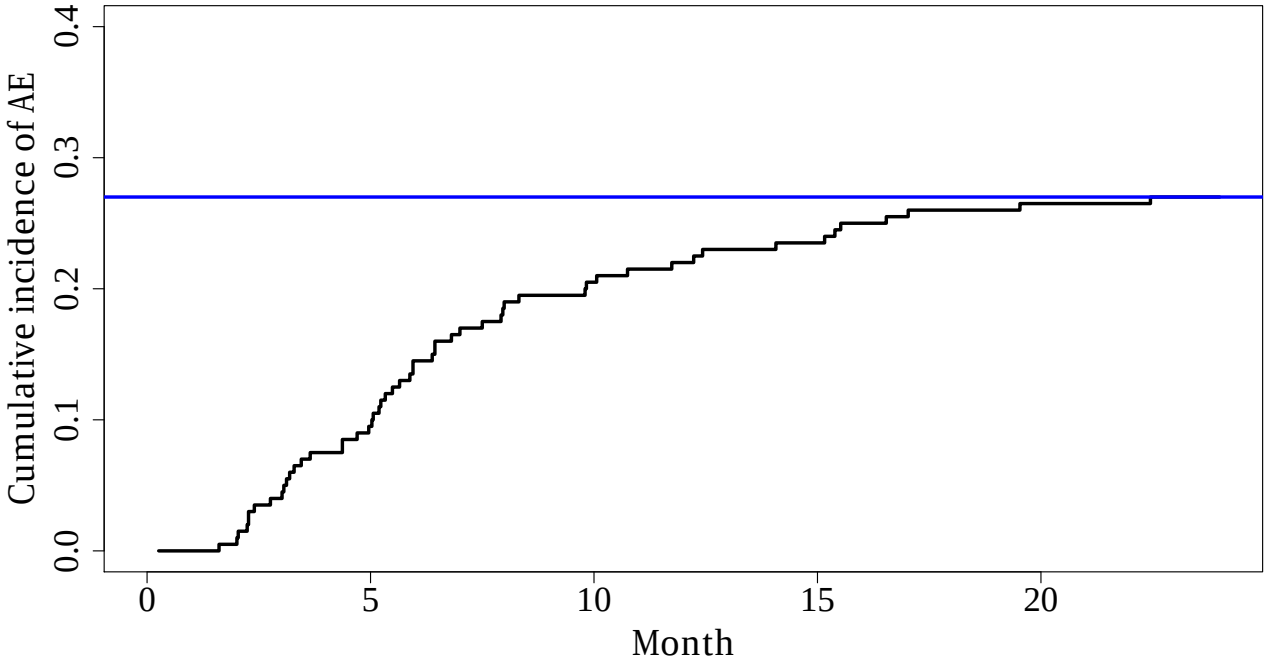
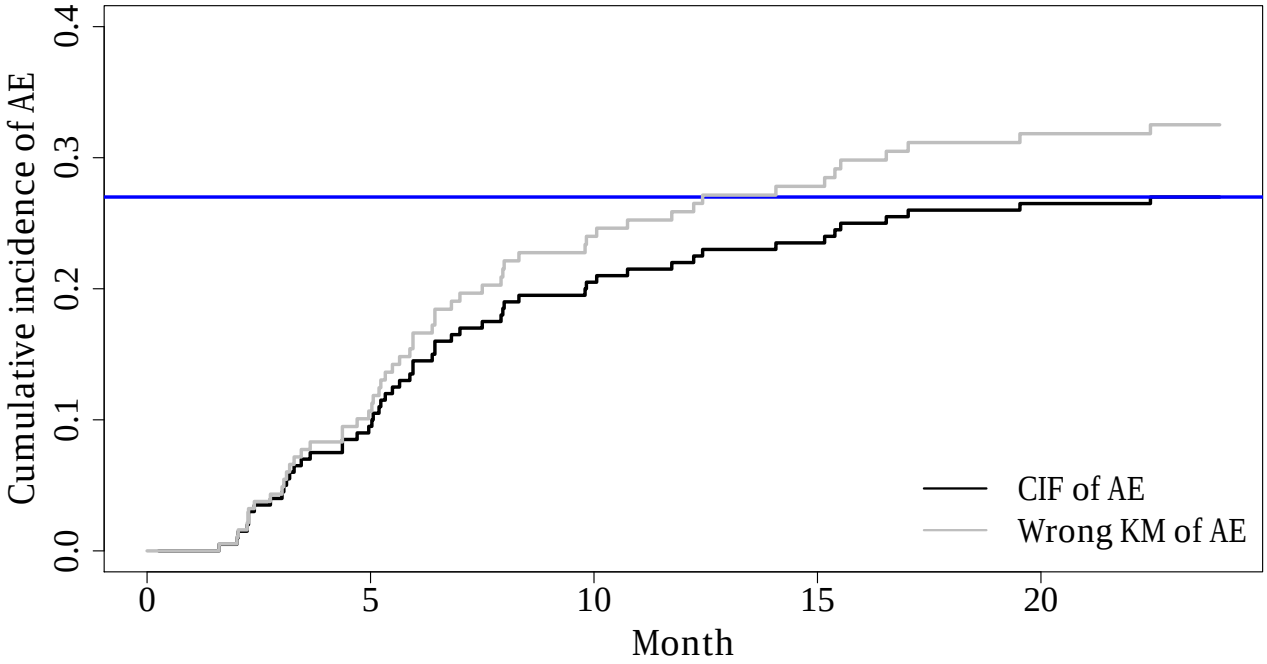


Cumulative incidence of AE is 0.27 at the plateau

Illustration: Don't use Kaplan-Meier

Example with complete follow-up of 2 years for all patients (no censoring)
Recall: $\frac{\#AE}{n} = 0.27$

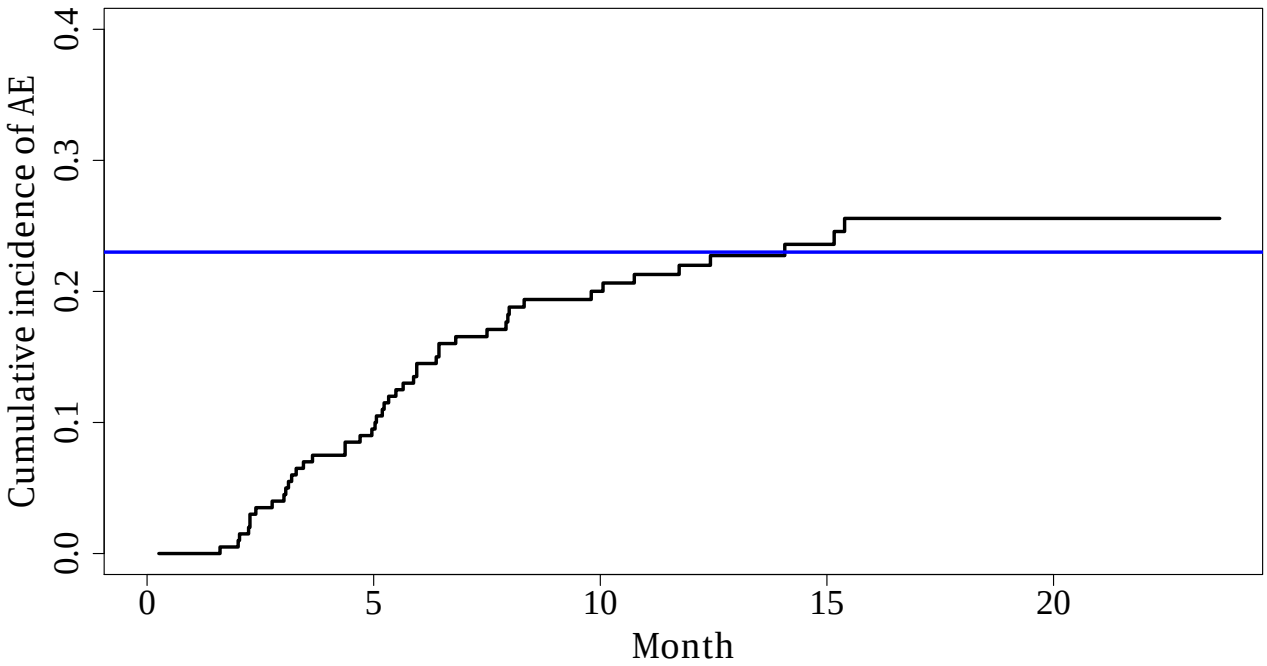


Cumulative incidence of AE is 0.27 at the plateau

Illustration

Example with **artificial censoring**

$\frac{\#AE}{n} = \frac{46}{200} = 0.23$; 42 deaths



Cumulative incidence of AE is 0.26 at the plateau

Using simple proportions to estimate $P(\text{AE in } [0, t])$ leads to underestimation

Illustration

Example with **artificial censoring**

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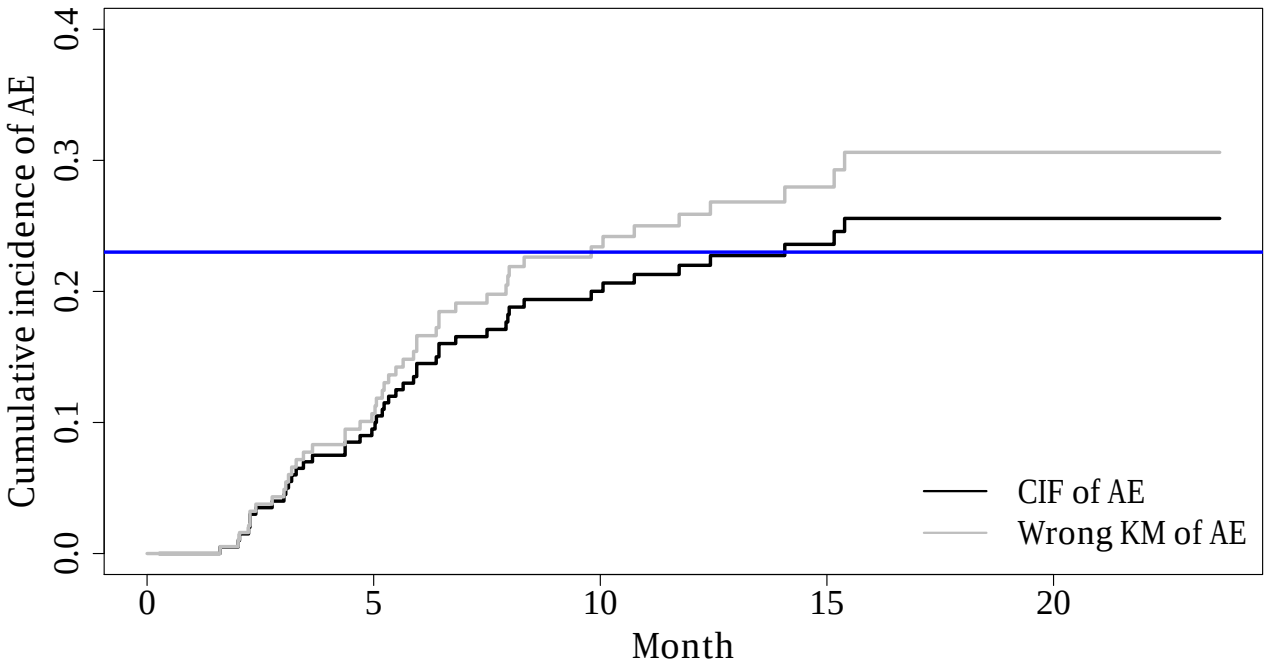


Cumulative incidence of AE is 0.26 at the plateau

Using the Kaplan-Meier estimator to estimate $P(\text{AE in } [0, t])$ leads to overestimation

Everything is Based on Hazards

- The Kaplan-Meier estimator is based on estimates of the hazard $\alpha(t)\,dt$

$$\frac{\#\text{ Composite event at } t}{\#\text{ under observation at } t-},$$

- which decomposes into

$$\frac{\#\text{ AE at } t}{\#\text{ under observation at } t-} + \frac{\#\text{ Death at } t}{\#\text{ under observation at } t-}$$

- Motivates the Nelson-Aalen estimator of the cumulative hazard $\int_0^t \alpha(u)\,du$, e.g., of AE

$$\sum_{u} \frac{\#\text{ AE at } u}{\#\text{ under observation at } u-}$$

Censoring by a Competing Event

- Censoring by a competing event is a subtle issue
- I.e., the Nelson-Aalen estimator of the cumulative hazard of AE is

$$\sum_{u} \frac{\#\text{ AE at } u}{\#\text{ under observation at } u-}.$$

  Only AE events are "counted"
- One way to do that in practice is to censor the competing event, e.g., death
- However, we can't "censor away" when computing probabilities

$$\hat{P}(T \leqslant t|AE) = \sum_{u} \hat{P}(T > u-) \cdot \frac{\#\text{ AE at } u}{\#\text{ under observation just before } u}$$

Comparison of (Treatment) Groups

- Cox model for composite event, $\alpha(t|Z) = \alpha_0(t)\exp(\beta Z)$, when comparing groups $Z = 0$ and $Z = 1$
- Cox model for AE

$$\alpha_{AE}(t|Z) = \alpha_{AE;0}(t)\exp(\beta_{AE} Z)$$

For comparison of (treatment) groups with respect to AE-hazard:
Hazard ratio ($Z = 1$ vs $Z = 0$) $= \exp(\beta_{AE})$

- Counts only AEs $\rightarrow$ censor death events
  - In perfect analogy to the Nelson-Aalen estimator
- However the picture is complete only by looking at all the sides, i.e.,

$$\alpha_{death}(t|Z) = \alpha_{death;0}(t)\exp(\beta_{death} Z)$$

For comparison of (treatment) groups with respect to Death-hazard:
Hazard ratio ($Z = 1$ vs $Z = 0$) $= \exp(\beta_{death})$

The Fine and Gray Model

Aim: One model that directly compares (treatment) groups with respect to AE probability instead of the event-specific hazard

- Instead of the event-specific hazard of, e.g., AE

$$\frac{\#\text{ AE at } u}{\#\text{ patients not censored and w/o AE or death at } u-}$$

- Consider the subdistribution hazard

$$\frac{\#\text{ AE at } u}{\#\text{ patients not censored and w/o AE at } u-}.$$

- Fine and Gray model $\Leftrightarrow$ Cox-type model for the subdistribution hazard
- Subdistribution hazard constructed such that

$$1 - \exp\left(\int \text{subdistribution hazard of AE}\right) = \text{CIF of AE}$$

$\rightarrow$ Results directly interpretable in terms of the CIF of AE

Discussion

- While analysing AEs in time to event data, simple proportions should not be used
- AEs are always subject to competing risks, i.e., the occurrence of a certain AE may be precluded by the main outcome of interest or another fatal AE
- Common survival techniques for hazards that censor the competing event are still valid, but incomplete analyses
- The competing event should also be subject to such an analysis
- Incidence rate (density) of AE equivalent to considering $\alpha_{AE}(t) \equiv \alpha_{AE}$. Same considerations about the analysis of the competing event apply
- Common survival techniques for probability estimation with Kaplan-Meier that censor the competing event are not valid

Discussion

Comparison of (Treatment) Groups

- Comparison of event-specific hazards reflects direct effect of treatment on instantaneous (daily) AE risk
  - The competing event should also be subject to such an analysis
- Comparison of the *subdistribution hazards* results in a comparison of (treatment) groups with respect to CIF
  - "Summary" analysis
  - Guidelines for competing risks analysis: Study of **both** event-specific hazards **and** subdistribution hazard of the event of interest (AE)

Censoring by a competing event is

- **Independent** in the sense that it retains the form of the competing process intensity
- **Informative** as it impacts probabilities

Incidence Density

Illustration with artificial censoring

- Incidence density (ID) of AE

$$\frac{\#\text{AE}}{\text{Population time at risk}},$$

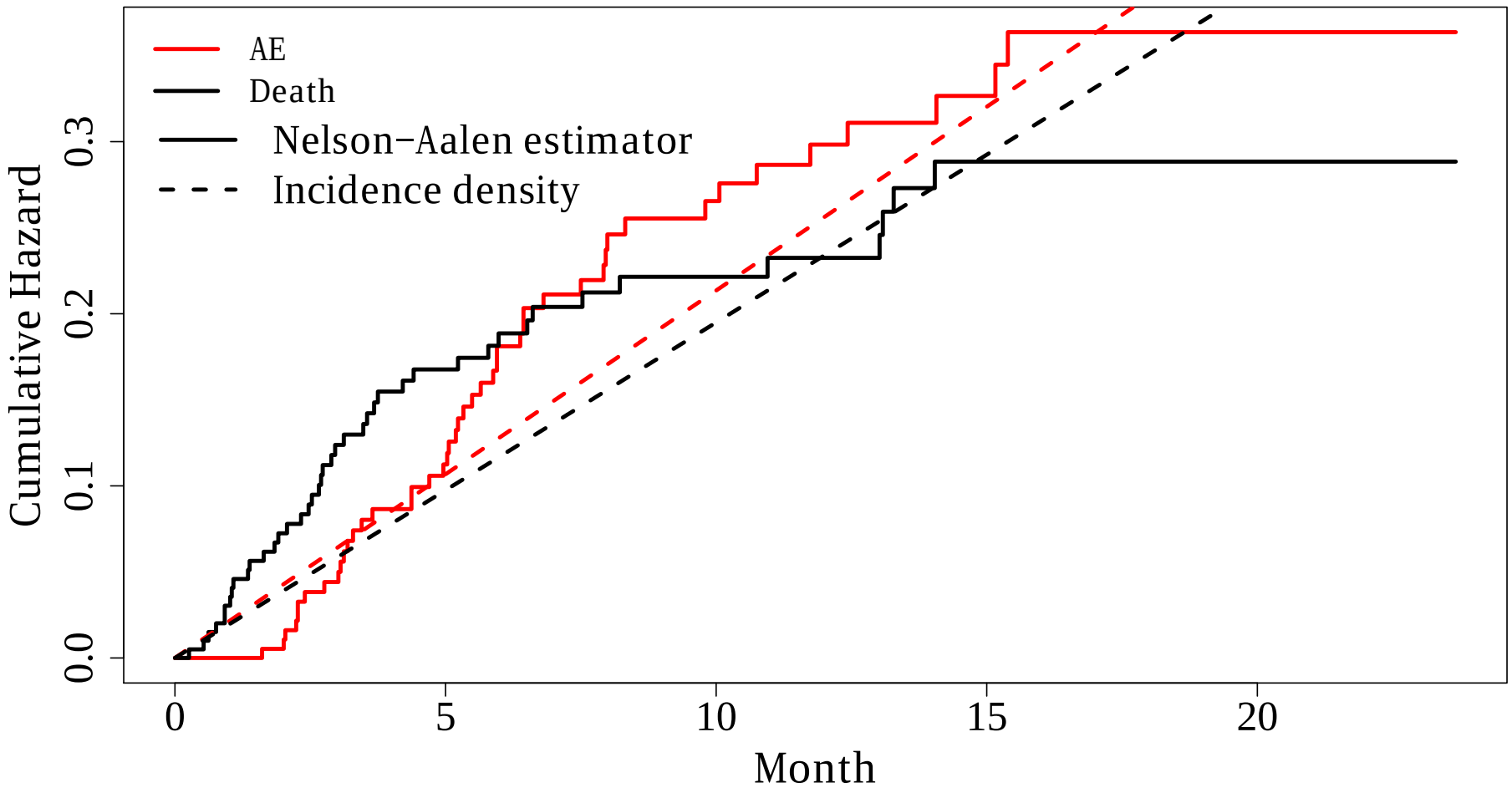
  equivalent to considering $\alpha_{AE}(t) \equiv \alpha_{AE}$
- Not so bad if incidence density of the competing event is also analysed
- E.g., with complete data

$$\frac{\text{ID AE}}{\text{All-cause ID}} = \frac{\#\text{AE}/\text{Population time at risk}}{(\#\text{AE} + \#\text{Deaths})/\text{Population time at risk}} = \frac{\#\text{AE}}{n}$$

  assuming constant hazards

Incidence Density

Illustration with artificial censoring



Incidence Density

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