Competing risks in survival analysis: what does it mean and does it matter?

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Survival analysis - definitions

- Survival analysis concerns the analysis of time-to-event data
  - Time from birth to disease onset (years)
  - Time from treatment initiation to death (days)
- Cumulative incidence *I(t)*: proportion of subjects with an event time less than or equal to *t*
  - I(365): proportion of patients that die within one year of treatment initiation
- Cumulative incidence curve: the plot of *I(t)* against *t*

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Estimation of *I(t)* when all occurences of the event of interest are observed

- **Event times in days (n=10):** 123, 345, 1143, 12, 158, 1045, 2098, 67, 432, 600
- *I(t)* can readily be estimated by dividing the number of subjects with an event time smaller than or equal to *t* by the total sample size
  - I(183) = 3/10 = 0.3
  - I(365) = 5/10 = 0.5

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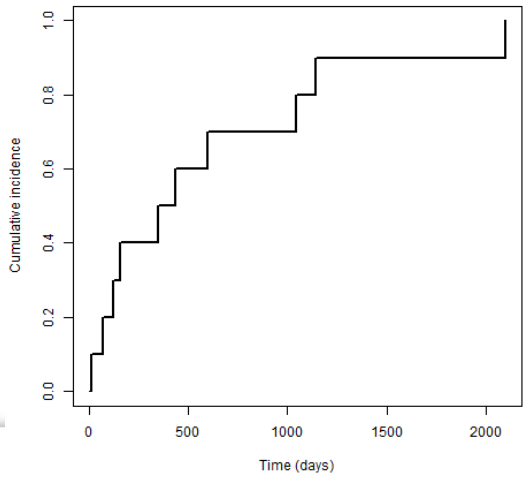
Cumulative incidence curve



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What makes the analysis of time-to-event data special: right-censoring

- A subject's event time is right censored when the recording of his event time is terminated before he has experienced the event of interest
  - Loss to follow-up: subjects withdraw from the study before they experience the event of interest
  - Administrative censoring: the study is closed before each subject has experienced the event of interest

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Estimation of *I(t)* when event times are right-censored

- **Right-censored observations (n=10):** 123, 345, 560*, 12, 101*, 505*, 2098, 67, 303*, 600

- How to estimate *I(t)* in the presence of right-censoring?
  - 1 – minus Kaplan-Meier estimator

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1 – Kaplan-Meier estimator: example

time (t_j)	n.risk (n_j)	n.event (d_j)	$S(t_j-)$	$h(t_j) = d_j/n_j$	$p(t_j) = h(t_j)*S(t_j-)$
12	10	1	1	1/10	1* 1/10 = 0.1
67	9	1	1 – 0.1 = 0.9	1/9	0.9 * 1/9 = 0.1
101	8	0	0.9 – 0.1 = 0.8	0/8	0.8 * 0/8 = 0
123	7	1	0.8 – 0 = 0.8	1/7	0.8 * 1/7 = 0.114
…	…	…	…	…	…

n.risk at time t_j: number of subjects that are still in follow-up and 'alive' just before t_j

$$I(t) = \sum_{j:t_j \le t} p(t_j)$$

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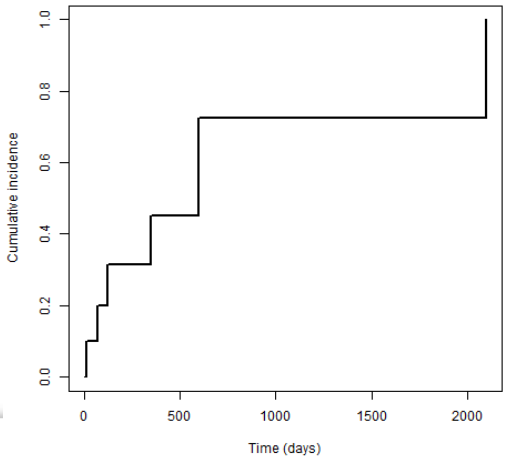
Cumulative incidence curve



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One minus Kaplan-Meier estimator: assumptions

- Uninformative censoring: subjects under observation have the same risk of experiencing the event of interest than subjects whose event time got censored
  - Subjects that are still in the risk set at a certain time *t* can be considered to be representative for all subjects that are still 'alive' at time *t*

Competing risks

- A competing risk is an event other than the event of interest whose occurence precludes (prevents) the event of interest from occuring
- Example 1:
  - Event of interest: cardiovascular-related death
  - Competing event: non-cardiovascular-related death
- Example 2:
  - Event of interest: hospitalization because of heart failure
  - Competing event: all-cause death

Cumulative incidence curves in the presence of competing risks: approach 1 (one minus Kaplan-Meier estimator)

1. Treat the event times of subjects that experience a competing event as right-censored
2. Use the one minus Kaplan-Meier estimator to estimate the cumulative incidence curve for the event of interest

What does this estimate mean?

- Censoring because of a competing risk is informative
  - Subjects that are still under observation have some risk of experiencing the event of interest
  - Subjects whose event time got censored because of the occurence of a competing risk will **CERTAINLY NOT** experience the event of interest
- The one minus Kaplan-Meier estimate reflects the cumulative incidence for the event of interest under the assumption that all competing risks have been eliminated

Cumulative incidence curves in the presence of competing risks: approach 2 (Aalen-Johansen estimator)

1. Define the event time as the time of occurrence of **any** event (i.e., either the event of interest or a competing event)
2. Define the risk set n_j at time t_j as the number of subjects that are still in follow-up and 'alive' (i.e., have neither experienced the event of interest nor any of the competing events) just before t_j
3. Estimate the probability of experiencing the event of interest at time t_j conditional on being 'alive' just before t_j by dividing the number of subjects experiencing the event of interest at time t_j by n_j
4. Estimate the unconditional probability of experiencing the event of interest at time t_j by multiplying $h(t_j)$ by the probability of being 'alive' just before time t_j
5. Estimate the cumulative incidence $I(t)$ by summing over all values of $h(t_j)$ between baseline and time t

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ORIGINAL INVESTIGATION

Effect of Moderate or Intensive Disease Management Program on Outcome in Patients With Heart Failure

Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH)

Outcome	Total Patients (N=1023)	Control Group (n=339)	Basic Support Group (n=340)	Intensive Support Group (n=344)
Primary end points				
Death or hospitalization because of HF	**411** (40)	141 (42)	138 (41)	132 (38)
No. of days lost in 18 months	**107 959**	39 960	33 731	34 268
No. of days lost per patient, median (25th and 75th percentiles)	10.0 (0.0-109.0)	12.0 (0.0-173.0)	9.0 (0.0-88.0)	7.5 (0.0-109.0)
Other events				
Hospitalization				
All causes	**567** (55)	181 (53)	192 (57)	194 (56)
Cardiovascular disease	**433** (42)	143 (42)	143 (42)	147 (43)
HF	**260** (25)	84 (25)	84 (25)	92 (27)
No. of hospitalizations				
All causes	**1161**	376	377	408
Cardiovascular disease	**746**	255	236	255
HF	**375**	120	121	134
Death				
All causes	**272** (27)	99 (29)	90 (27)	83 (24)
Cardiovascular disease	**219** (21)	72 (21)	76 (22)	71 (21)
Noncardiovascular disease	**38** (4)	19 (6)	10 (5)	9 (3)
Unknown cause	**15** (2)	8 (2)	4 (1)	3 (1)

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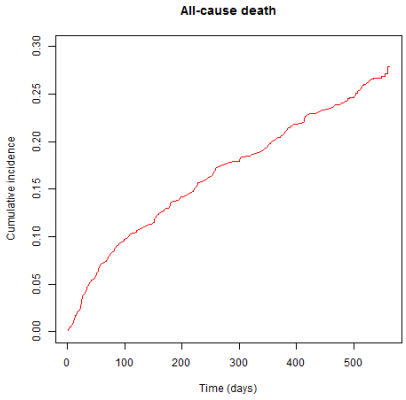
Cumulative incidence curve for all-cause death in the COACH study (n=1023)



- Initiating event (time origin): hospital discharge
- Event of interest: death by any cause
- Event time: calendar time of death – calendar time of hospital discharge (days)

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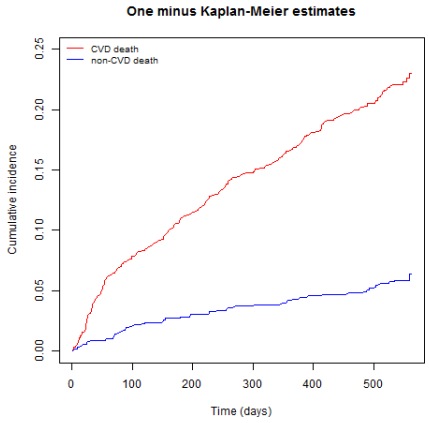
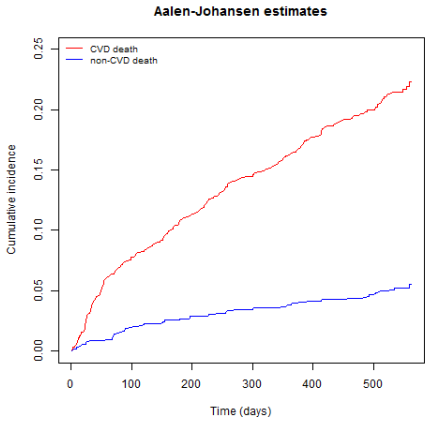
Cumulative incidence curves for CVD death and non-CVD death corresponding to the two different estimates





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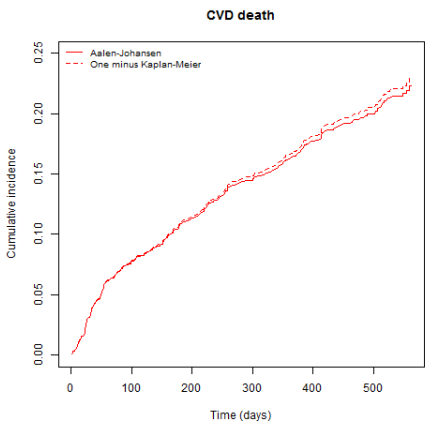
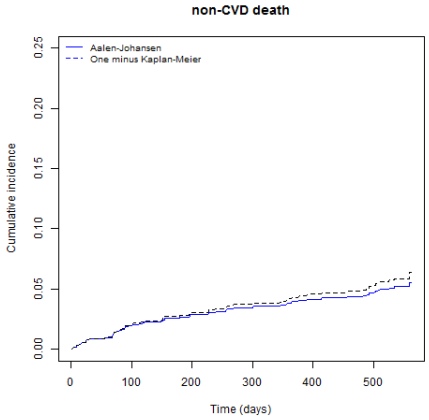
Difference between the two estimates





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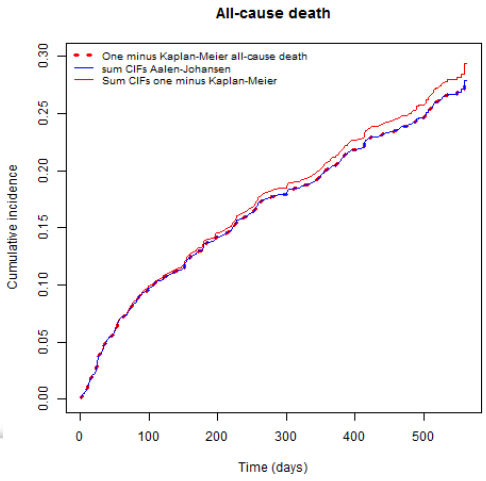
How does this compare to the cumulative incidence curve for all-cause death?



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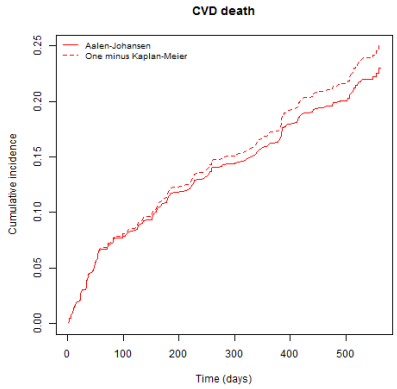
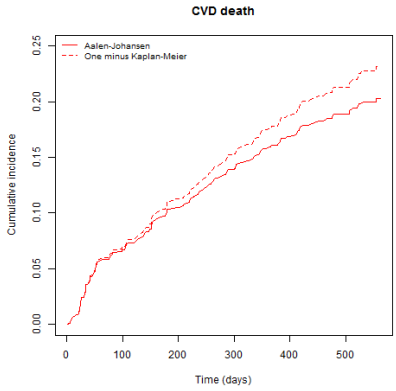
What if the number of non-CVD-related deaths were larger?



15% non-CVD death



25% non-CVD death

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Summary

- Although the one minus Kaplan-Meier estimator is frequently applied to estimate cumulative incidence curves, it gives biased results in the presence of competing risks
- The amount of bias gets larger in populations where subjects are at high risk of experiencing a competing event

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Questions?

Next lecture: 9 May (Hans Burgerhof)
Multiple linear regression

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