When NOT to use cumulative incidence for competing events data

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joint work with Hein Putter and Saskia le Cessie

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CME Series

NDT
Nephrology Dialysis Transplantation

The analysis of competing events like cause-specific mortality—beware of the Kaplan–Meier method

Marion Verduijn[1], Diana C. Grootendorst[1], Friedo W. Dekker[1], Kitty J. Jager[3] and Saskia le Cessie[1,2]

Clin Orthop Relat Res. 2015 Nov; 473(11): 3431–3442. PMCID: PMC4586188
Published online 2015 Mar 25.
doi: 10.1007/s11999-015-4235-8

Kaplan-Meier Survival Analysis Overestimates the Risk of Revision Arthroplasty: A Meta-analysis

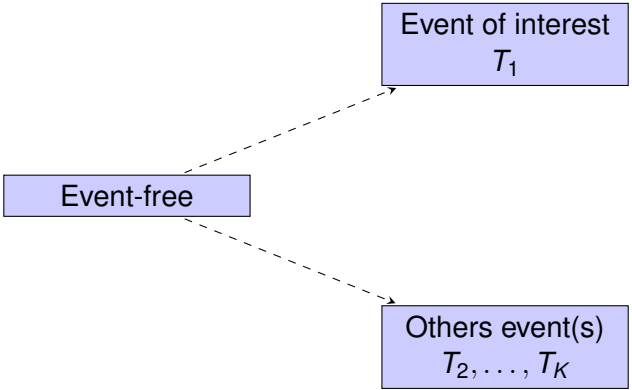
Sarah Lacny, MSc, Todd Wilson, BSc, Fiona Clement, PhD, Derek J. Roberts, MD, Peter D. Faris, PhD, William A. Ghali, MD, MPH, and Deborah A. Marshall, PhD

KAPLAN MEIER OVERESTIMATES THE REVISION SURGERY PROBABILITY IN COMPETING RISKS: AN EXAMPLE USING LONG-TERM FOLLOW-UP DATA FROM HIP REVISION SURGERY

Keurentjes Johan, Fiocco Marta, Schreurs Bw, Pijls Bart, Nouta Klaas-Auke, Nelissen Rob

- Many papers have claimed that 'Kaplan Meier' is biased in presence of competing risks
- Cumulative incidence is considered to be the analysis of choice
- My claim today: this is not always the case

Competing risk setting



Notation

- The earliest of the potential failure types is actually observed and the others are latent
- $\widetilde{T}_k$ the time to failure of cause k
- $T = min(\widetilde{T}_k)$ is what we observe, plus
- D index variable that specifies which event happened first
- $D = 0$ if patient is censored by end of study or loss to follow-up

Estimand 1

- The cumulative incidence function:

$$CI(t) = P(\widetilde{T}_1 \leq t, D = 1) = P(T \leq t, D = 1)$$

  is the cumulative probability of *observing* the event of interest over time
- also goes by the names of:

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- also goes by the names of: absolute risk, actual risk, crude probability, crude cumulative incidence function, absolute cause-specific risk, subdistribution function

Estimand 2

- The marginal distribution function:

$$F_1^{marg}(t) = P(\widetilde{T}_1 \leq t)$$

  is the cumulative probability of the event of interest *occurring* over time in a world where competing events do not exist
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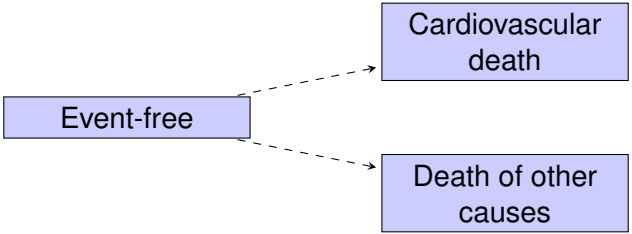
Estimand 2

- The marginal distribution function:

$$F_1^{marg}(t) = P(\widetilde{T}_1 \leq t)$$

  is the cumulative probability of the event of interest *occurring* over time in a world where competing events do not exist
- also goes by the names of: pure risk, net probability (but not often talked about)

Classical competing risk setting



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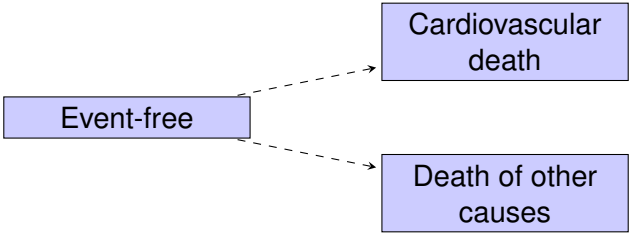

- cumulative incidence: How many and which patients do we expect to die of cardiovascular disease?

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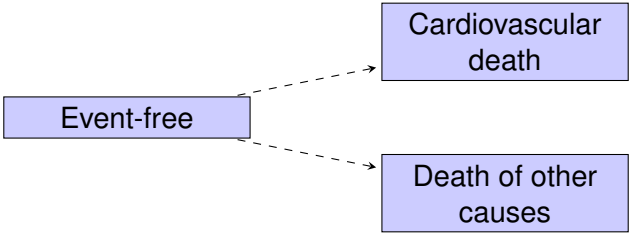

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- marginal distribution: How many and which patients would die of cardiovascular disease if we could prevent all other causes of death?

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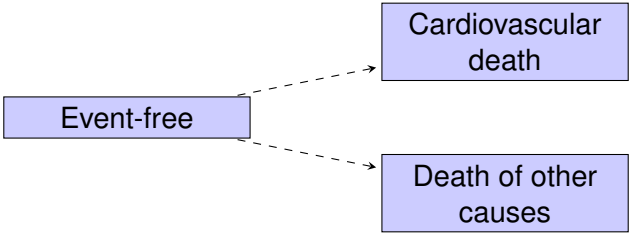
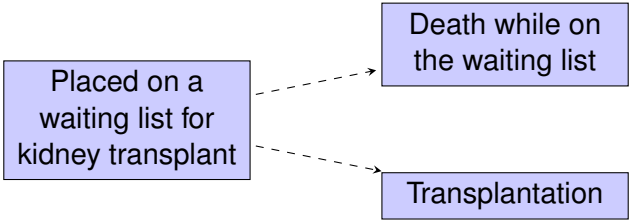


- cumulative incidence: How many and which patients do we expect to die of cardiovascular disease?
- marginal distribution: How many and which patients would die of cardiovascular disease if we could prevent all other causes of death? Not a realistic question

Transplant as a competing risk



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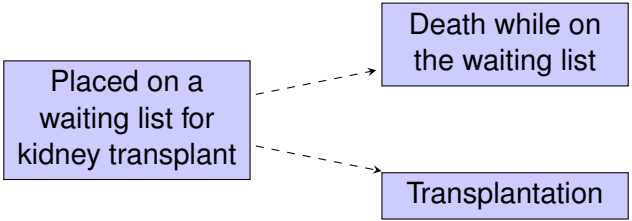

- cumulative incidence: How many and which patients do we expect to die before transplantation?

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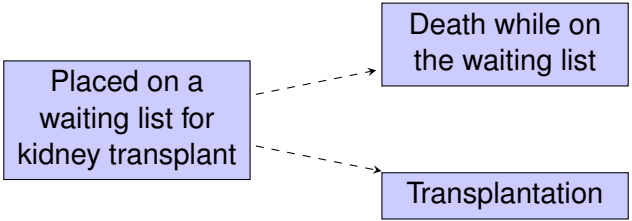

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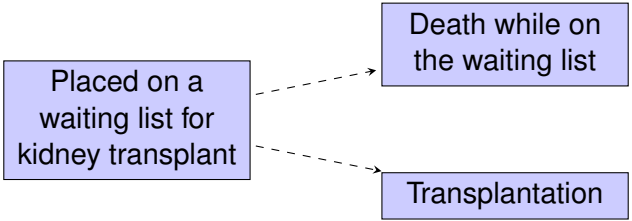

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- marginal distribution: How many and which patients would die if they are not transplanted?

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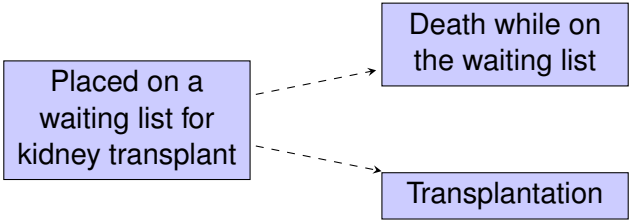
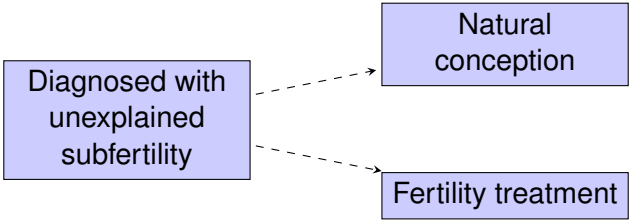


- cumulative incidence: How many and which patients do we expect to die before transplantation? maybe relevant for counseling
- marginal distribution: How many and which patients would die if they are not transplanted? very relevant question for medical decisions / prioritizing patients on the waiting list

Treatment as a competing risk



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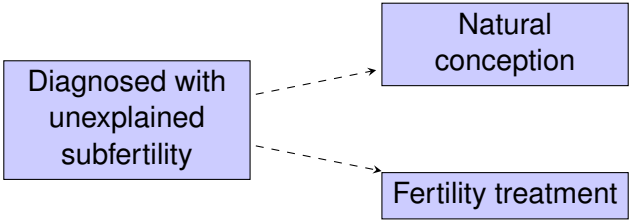

- cumulative incidence: How many and which patients do we expect to conceive naturally before starting fertility treatment?

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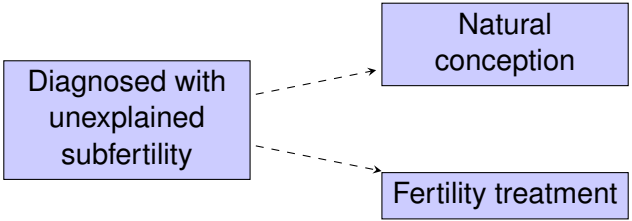

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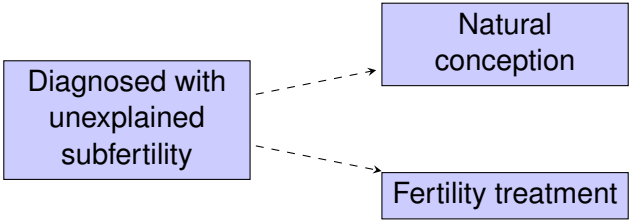

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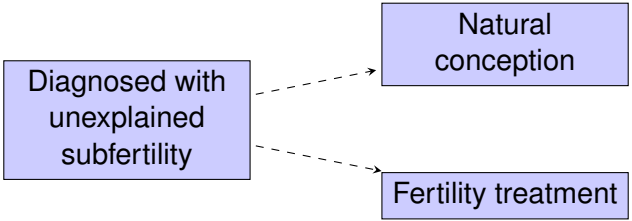

- cumulative incidence: How many and which patients do we expect to conceive naturally before starting fertility treatment? not such a relevant question, depends on treatment strategy
- marginal distribution: How many and which patients would conceive naturally without fertility treatment? very relevant question, these patients may not need treatment

The difference

- death is a fatal, generally inevitable competing cause
- medical interventions such as transplant, fertility treatment are not inevitable
- in case of an intervention (or in general a modifiable) competing event *CI* may not be the quantity of interest

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- without censoring ($D > 0$ for all patients): simply the proportion of events of type 1 divided by total sample size
- with censoring: part of these are assumed to get the event of interest, part of these are assumed to get a competing event

Estimating $CI(t)$

$CI_1(t)$ can be estimated using the cause specific hazard function and the joint (total) distribution:

$$\lambda_k(t) = \lim_{\Delta \to 0} \frac{P(t \leq T < t + \Delta t, D = k | T \geq t)}{\Delta t}$$

$$\Lambda_k(t) = \int_0^t \lambda_k(s) ds$$

$$S(t) = P(T > t) = \exp(-\sum_{k=1}^{K} \Lambda_k(t))$$

$$CI_1(t) = \int_0^t \lambda_1(s) S(s) ds$$

Estimating $CI(t, X)$

either with a cause specific regression model

$$\lambda_k(t, X) = \lambda_{k,0}(t) \exp(\beta_k^T X)$$

$$CI_1(t, X) = \int_0^t \lambda_1(s, X) S(s, X) ds$$

or with a subdistribution regression model (Fine and Gray)

$$\lambda_1^{sub}(t, X) = -\frac{d \log(1 - CI_1(t, X))}{dt} = \lambda_{1,0}^{sub} \exp(\beta_1^T X)$$

Estimating F^{marg}

- The marginal distribution function:

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  the cumulative probability of the event of interest *occurring* over time, in a world where competing events do not exist
- not identifiable from data alone, one needs to make assumptions
- KM assumes non-informative censoring: patients with competing event have (from that moment on) similar risk of event of interest as those without competing event
- more subtle assumption: removing one type of event does not alter the probability of other events

Estimating F^{marg}

$F_1^{marg}(t)$ can, under the non-informative censoring assumption, be estimated using the cause specific hazard function:

$$\lambda_1(t) = \lim_{\Delta \to 0} \frac{P(t \leq T < t + \Delta t, D = 1 | T \geq t)}{\Delta t}$$

$$\Lambda_1(t) = \int_0^t \lambda_1(s) ds$$

$$S_1(t) = 1 - P(T > t) = \exp(-\Lambda_1(t))$$

$$F_1(t) = \int_0^t \lambda_1(s) \boldsymbol{S_1(s)} ds$$

Estimating $F_1^{marg}(t, X)$

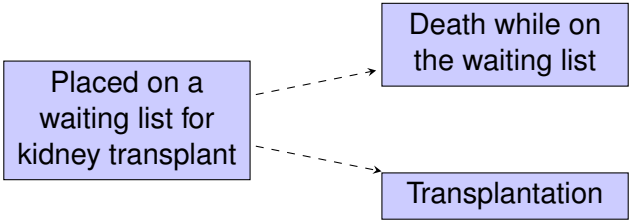
using a cause specific regression model

$$\lambda_1(t, X) = \lambda_{1,0}(t) \exp(\beta_1^T X)$$

$$F_1^{marg}(t, X) = \int_0^t \lambda_1(s, X) S_1(s, X) ds$$

- assumes non-informative censoring by competing event(s), conditional on the covariates in the model

How realistic is non-informative censoring by competing events?



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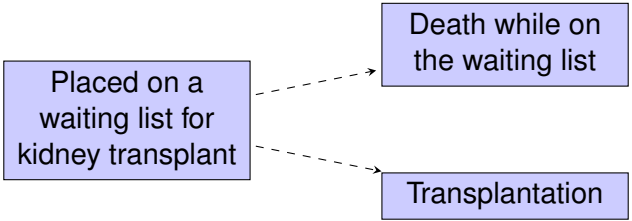

- Sicker patients get transplanted because they would otherwise die soon?

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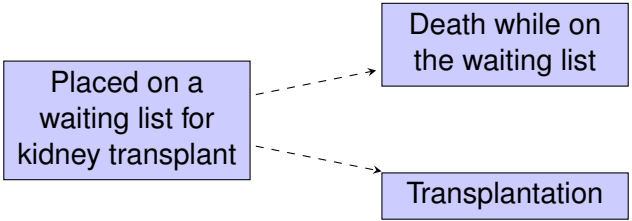
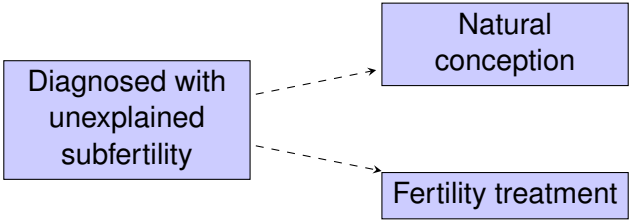


- Sicker patients get transplanted because they would otherwise die soon?
- Healthier patients get transplanted to ensure a long second life for the donor kidney?

Treatment as a competing risk



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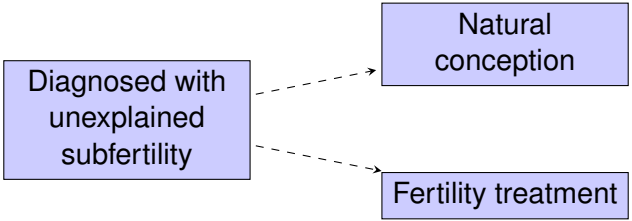

- Patients who are older, are trying for a longer time, don't have children yet may start treatment earlier.

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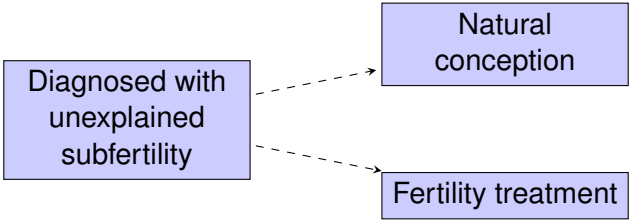

- Patients who are older, are trying for a longer time, don't have children yet may start treatment earlier.
- Patients who are more demanding, doctors who want to make money may start treatment earlier.

Can make additional assumptions

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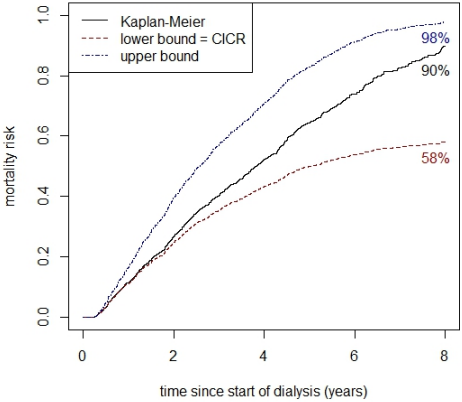
- use external 'after competing event' data: in some situations possible
- multiple imputation: view censored observations as a missing data problem

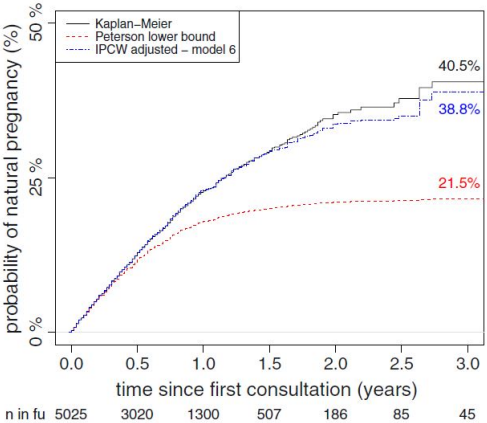
Upper and lower bounds

NECOSAD study: risk of death while on the waiting list for a kidney transplant



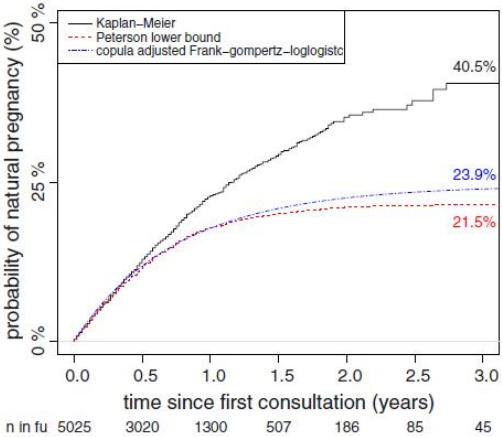
Results from IPCW approach

OFO study: probability of natural conception



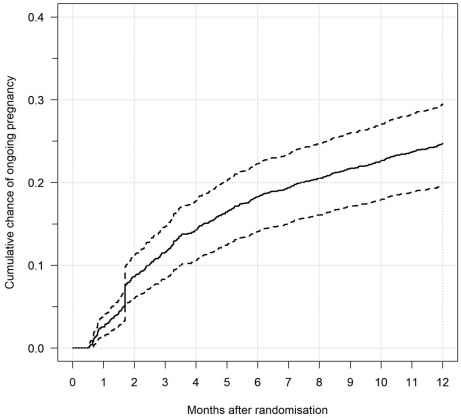
Results from copula approach

OFO study: probability of natural conception



Results from 'after competing event data'

INES trial: probability of natural conception after treatment start



	Will my event happen *before* the competing event(s)?	Will my event happen *in absense of* the competing event(s)?
CI	☹	no
KM	no	☹*
CS regression	☹	☹*
SD regression	☹	no

*under (conditional) non-informative censoring assumption

Take home message:
"KM is not a biased estimator in competing event settings, it is just not an estimator of cumulative incidence."