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Competing risks with applications to oncology

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Joint work with Jan Beyersmann and others

Basel Biometrics Society Seminar
Competing Risks and Multi-State Models: Overview and Case Studies

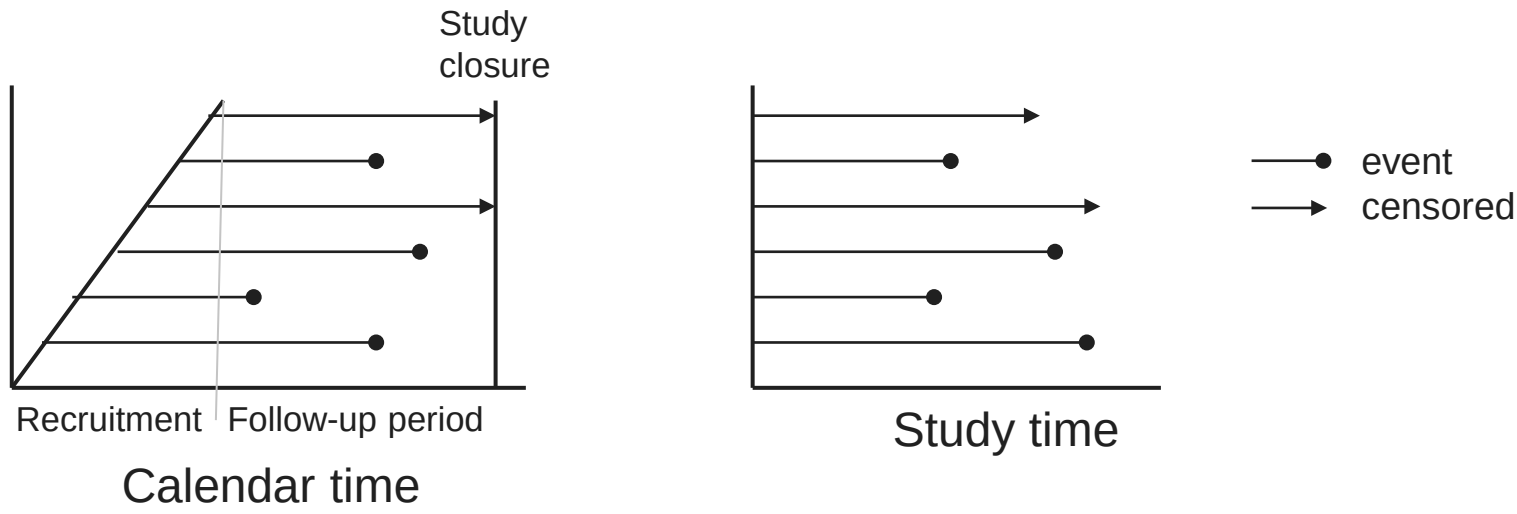
March 20, 2018

Overview

- **Introduction**
  - What is specific of competing risks?
- **Example of clinical trial in hematopoietic cell transplantation**
  - Various competing risks present
- **Statistical methods for competing risks data**
  - Illustrated and discussed by means of example
- **Analysis of adverse events**
  - Methods for time-to-event and competing risks relevant
- **Discussion**

Introduction: Time-to-event endpoints

- **Majority of clinical trials in oncology based on time-to-event endpoints**
- **Specific characteristics of time-to-event endpoints**
  - Time from patient entry to occurrence of an interesting event
  - Not all patients experience the interesting event during follow-up



- **Statistical methods for censored observations required**

Introduction: Composite endpoints

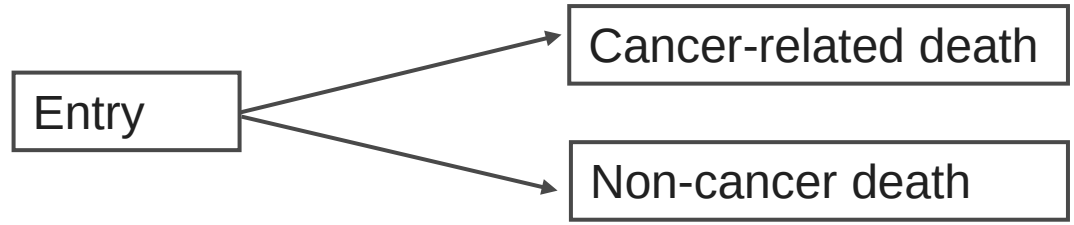
- **Often composite time-to-event endpoints**

Composite time-to-event endpoint	Events
Overall survival	Cancer-related death
	Non-cancer death
Progression-free survival	Progression
	Death without diagnosed progression

- **Composite endpoints are all-encompassing**
  - every patient will experience it (although potentially after study closure)
- **This is the reason why standard survival analysis techniques are adequate**
  - Estimation of probability of being event-free over time:
    - Kaplan-Meier estimator
  - Comparison of groups:
    - Cox regression model
    - w.r.t. hazards and w.r.t. event probabilities equivalent

Introduction: Competing risks

- **Interest not only on composite endpoint, but on specific type of event**
  - Example in oncology: Cancer-related death interesting event
- **Competing risks model**



precludes occurrence of cancer-related death

- **Standard survival analyses assume that in the long run every patient will experience event of interest**
- **Statistical methods for competing risks**
  - Estimation of event probability over time:
    - Aalen-Johansen estimator (= cumulative incidence function, CIF)
  - Comparison of groups:
    - w.r.t. event hazards: event-specific hazards (Cox model)
    - w.r.t. event probabilities: subdistribution hazards (Fine & Gray model)

Competing risks: An old topic

1456 THE NEW ENGLAND JOURNAL OF MEDICINE Nov. 30, 1995

REANALYSIS AND RESULTS AFTER 12 YEARS OF FOLLOW-UP IN A RANDOMIZED CLINICAL TRIAL COMPARING TOTAL MASTECTOMY WITH LUMPECTOMY WITH OR WITHOUT IRRADIATION IN THE TREATMENT OF BREAST CANCER

BERNARD FISHER, M.D., STEWART ANDERSON, PH.D., CAROL K. REDMOND, SC.D., NORMAN WOLMARK, M.D., D. LAWRENCE WICKERHAM, M.D., AND WALTER M. CRONIN, M.P.H.

- **NSABP Trial B-06**
  - RCT on mastectomy vs. breast conserving surgery in > 2000 breast cancer pts
- **Interesting event**
  - Local recurrence in breast conserving surgery group
- **Cumulative local recurrence rate in different analyses**
  - After 8 years follow-up (1989): 39%
  - After 9 years follow-up (1991): 43%
  - After 12 years follow-up (1995): 35%
- **How is it possible, that cumulative rates decrease over time?**

Competing risks: An old topic

Reason: Change of statistical methods

- **Statistical methods section of the paper**

4 to 9, ⩾10). In accordance with recently recommended statistical methods[12,13] for estimating the probability of a recurrence of tumor in the ipsilateral breast in the presence of competing risks — that is, recurrences at other sites or death — cumulative incidence curves are used. This differs from our previous reports[8,14] in which life-table estimates and cumulative hazard rates were used to present such information.

Competing risks: An old topic

Breast Cancer Research and Treatment **49**: 87–91, 1998.

20 years ago

Brief communication

A note on estimating local recurrence rates in clinical trials on the treatment of breast cancer

Gabi Schulgen, Claudia Schmoor, Willi Sauerbrei, and Martin Schumacher
Institute of Medical Biometry and Medical Informatics, University of Freiburg, Germany

Estimators of these cumulative incidence rates have already been introduced in the textbook of Kalbfleisch and Prentice [10] and, in a more general context, by Aalen and Johansen [11], and are there-

11. Aalen OO, Johansen S: An empirical transition matrix for non-homogeneous Markov chains based on censored observations. Scand J Statist 5: 141–150, 1978

40 years ago

Competing risks: An even much older topic

- **2018:** **Today**

  20 years

- **1998:** **My first contact with this topic**

  20 years

- **1978:** **Aalen – Johansen** (event probability in presence of competing risks)

  20 years

- **1958:** **Kaplan – Meier** (event probability in presence of censoring)

  6 x 20 years

- **1838:** **William Farr**
  "On prognosis" (British Medical Almanack, 1838):
  Competing risks analysis of mortality and recovery from smallpox
  (see Beyersmann & Schrade, JRSS A, 2017)

Competing risks: A still relevant topic

Literature reviews on presence and analysis of competing risks in high-ranking clinical journals

- **Koller et al (Stat Med, 2012)**
  - 50 articles on relevant diseases in high-ranking journals **(2007-2010)**
  - 35/50 = 70%: Competing risks present
  - 24/35 = **67%: inadequate methods for competing risks**
- **Schumacher et al (J Clin Epi, 2016)**
  - 136 articles with time-to-event endpoints in the NEJM **(2015)**
  - 51/136 = 38%: Competing risks present
  - 25/51 = **49%: inadequate methods for competing risks**

Competing risks: A still relevant topic

www.thelancet.com Vol 390 December 9, 2017

Correspondence

Overestimation of cardiovascular outcome incidence

for high-risk patients. Böhm and colleagues[1] used Kaplan-Meier curves and Cox regression for the outcomes, stratified by different values of systolic blood pressure and diastolic blood pressure. However, because this study[1] regards prediction of cardiovascular outcomes for patients, we caution about overestimation of the cumulative incidence of each outcome in the presence of competing events.[2]

Authors' reply

We thank Yuanzi Ye and Ricardo Fonseca for their interest in our Article.[1] We agree that the cumulative incidence of each outcome is slightly overestimated when the simple technique for calculating Kaplan-Meier curves is used instead of a more sophisticated method accounting for competing risks. However, the effect of overestimation is modest and, because it affects all strata simultaneously, the hazard ratios (HRs) between strata are nearly unchanged.

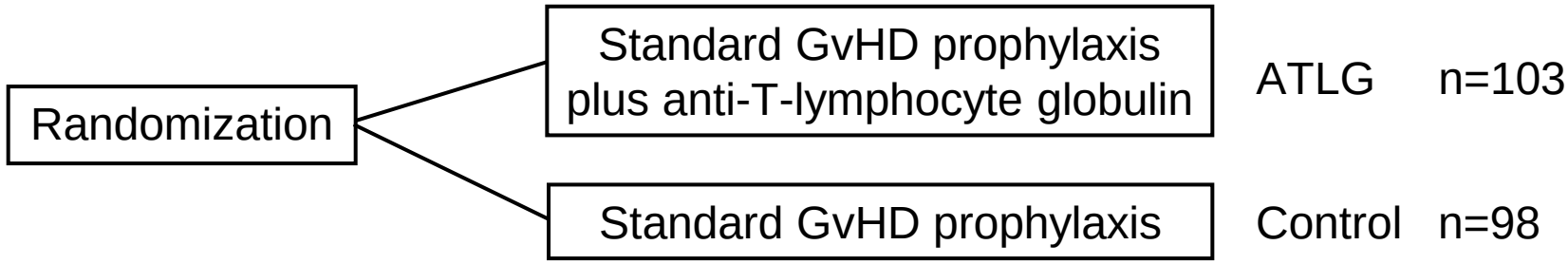
Reasoning not adequate in general

Example: Hematopoietic cell transplantation (HCT)

- **Patients with hematologic malignancies**
  - may receive hematopoietic cell transplantation (HCT), with stem cells from bone marrow or peripheral blood of related or unrelated donors
- **After HCT, various risks in the course of disease**
  - acute graft-versus-host-disease (aGvHD) within the first 100 days
  - chronic graft-versus-host-disease (cGvHD) after day +100
  - undergo immunosuppressive therapy (IST)
  - relapse of disease
  - death after relapse (relapse mortality)
  - death without former relapse (non-relapse mortality)

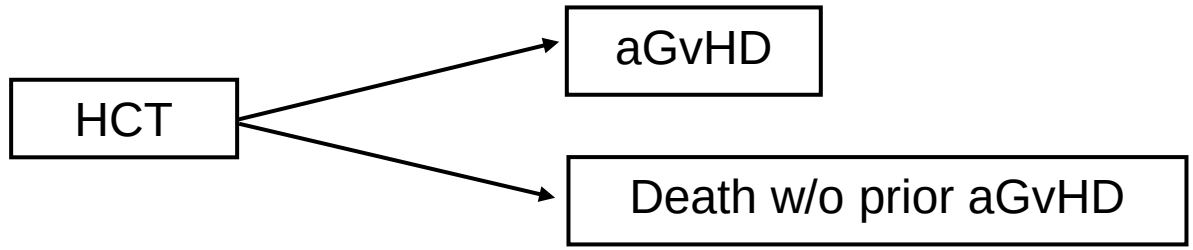
Example: RCT on GvHD prophylaxis

- **201 leukemia patients to be transplanted from matched unrelated donors**



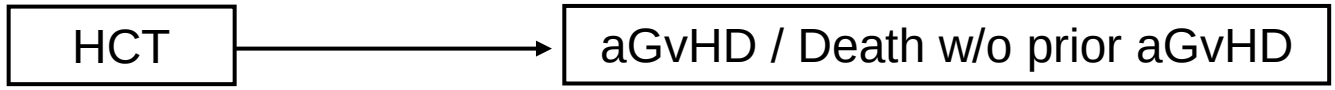
- **Primary objective**
  - Show reduction of severe acute GvHD (grade III-IV) by ATLG
  - **Interesting event:** aGvHD
  - **Competing event:** death without prior aGvHD

- **Competing risks model**



Example: RCT on GvHD prophylaxis

- **Planning the trial**
  - **Ensure** that ATLG does **not** decrease the risk of aGvHD by **increasing the risk of** the competing event **death w/o prior aGvHD**
- **Primary endpoint**
  - **All-encompassing composite event:** aGvHD or death w/o prior aGvHD
- **Primary analysis**
  - Two-state survival model

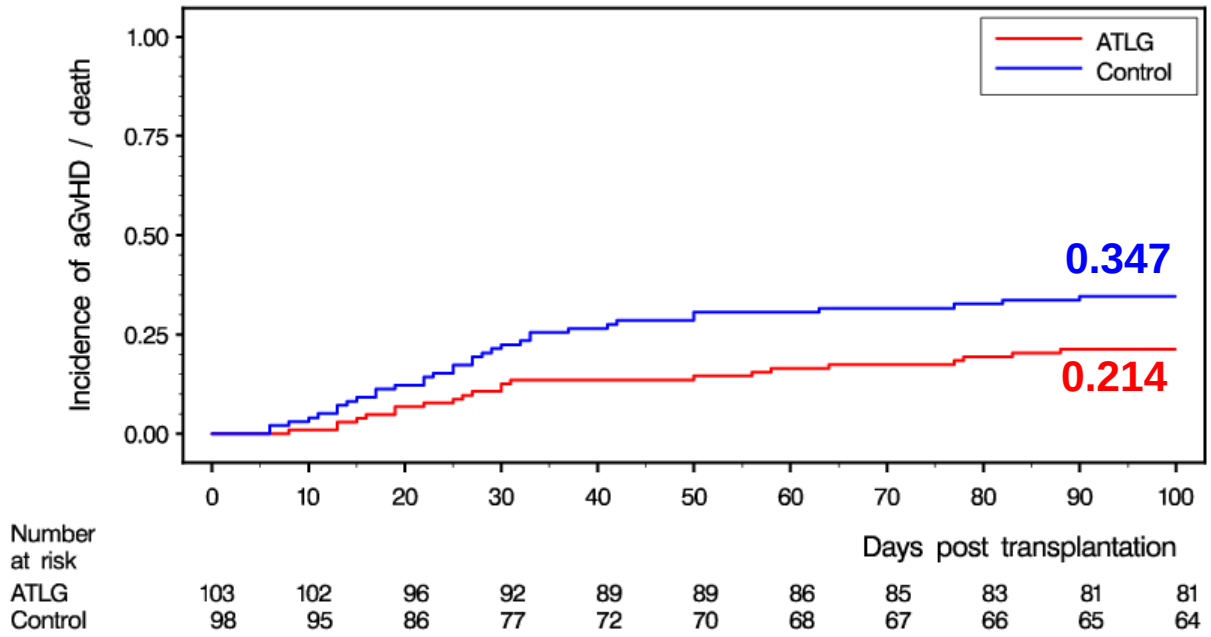


  - Standard survival analysis techniques
    - Kaplan-Meier estimator
    - Cox regression model

RCT: Results of aGvHD / death w/o prior aGvHD

	ATLG n=103	Control n=98
aGvHD or death w/o prior aGvHD	22 (0.214)	34 (0.347)
aGvHD	12 (0.116)	25 (0.255)
Death w/o prior aGvHD	10 (0.097)	9 (0.092)

1 – Kaplan-Meier



Cox model

All events	
Hazard Ratio	**95%-CI**
0.66	**[0.38,1.13]**

no censoring

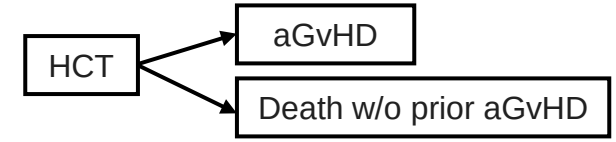
Single events: Event-specific hazards

- **So far:** **Analysis based on all-events hazard**

$$\frac{\#\text{ observed (aGvHD or death) events at time } s}{\#\text{ patients w/o an (aGvHD or death) event and not yet censored just before time } s}$$

Instantaneous risk to experience composite event in patients at risk

- **Now:** **Analysis based on event-specific hazards**



$$\frac{\#\text{ observed (aGvHD) events at time } s}{\#\text{ patients w/o an (aGvHD or death) event and not yet censored just before time } s}$$

$$\frac{\#\text{ observed (death w/o prior aGvHD) events at time } s}{\#\text{ patients w/o an (aGvHD or death) event and not yet censored just before time } s}$$

Instantaneous risk to experience single events in patients at risk

- **Event-specific hazards add up to all-events hazard**

Single events: Event-specific hazards

- **Cox regression to compare the event-specific hazards**
- **As many event-specific hazards and analyses as event types**
- **Technically**
  - In each analysis competing events treated as censored
  - Number of events analyzed identical to composite analysis
  - Analyzed separately by type of event

Single events: Probabilities

- **All-events probability** (1 - Kaplan-Meier)

$$\sum_{s \le t} \hat{S}(s-) \cdot \frac{\#\text{ observed (aGvHD or death) events at time s}}{\#\text{ patients w/o an (aGvHD or death) event and not yet censored just before time s}}$$

all-events hazard

$\hat{S}(s-)$: KM estimator of being free of all events just before time s

- **Single-event probabilities** (Aalen-Johansen = cum. incidence function, CIF)

$$\sum_{s \le t} \hat{S}(s-) \cdot \frac{\#\text{ observed (aGvHD) events at time s}}{\#\text{ patients w/o an (aGvHD or death) event and not yet censored just before time s}}$$

$$\sum_{s \le t} \hat{S}(s-) \cdot \frac{\#\text{ observed (death w/o prior aGvHD) events at time s}}{\#\text{ patients w/o an (aGvHD or death) event and not yet censored just before time s}}$$

event – specific hazards

- P(aGvHD) + P (death w/o prior aGvHD) = P (composite event)

  = 1 – P (no event)

Single events: Aalen-Johansen = CIF vs. 1 - Kaplan-Meier

- **Balance equation**

  P (no event) + P (aGvHD) + P(death w/o prior aGvHD) = 1

- **Can be used to check if event probabilities were estimated correctly**
- **Using the 1 - Kaplan-Meier formula censoring competing events leads to overestimation**
- **1 – Kaplan-Meier tends to one with infinite follow-up**
- **In case of no censoring**
  - CIF identical to the simple event proportion
  - This is not true for 1 – Kaplan-Meier

Single events: Probability vs. Hazard

- **Aalen-Johansen estimators of cumulative event probabilities**

$$\sum_{s \le t} \hat{S}(s-) \cdot \frac{\#\text{ observed (aGvHD) events at time s}}{\#\text{ patients w/o an (aGvHD or death) event and not yet censored just before time s}}$$

$$\sum_{s \le t} \hat{S}(s-) \cdot \frac{\#\text{ observed (death w/o prior aGvHD) events at time s}}{\#\text{ patients w/o an (aGvHD or death) event and not yet censored just before time s}}$$

both depend on all event-specific hazards via

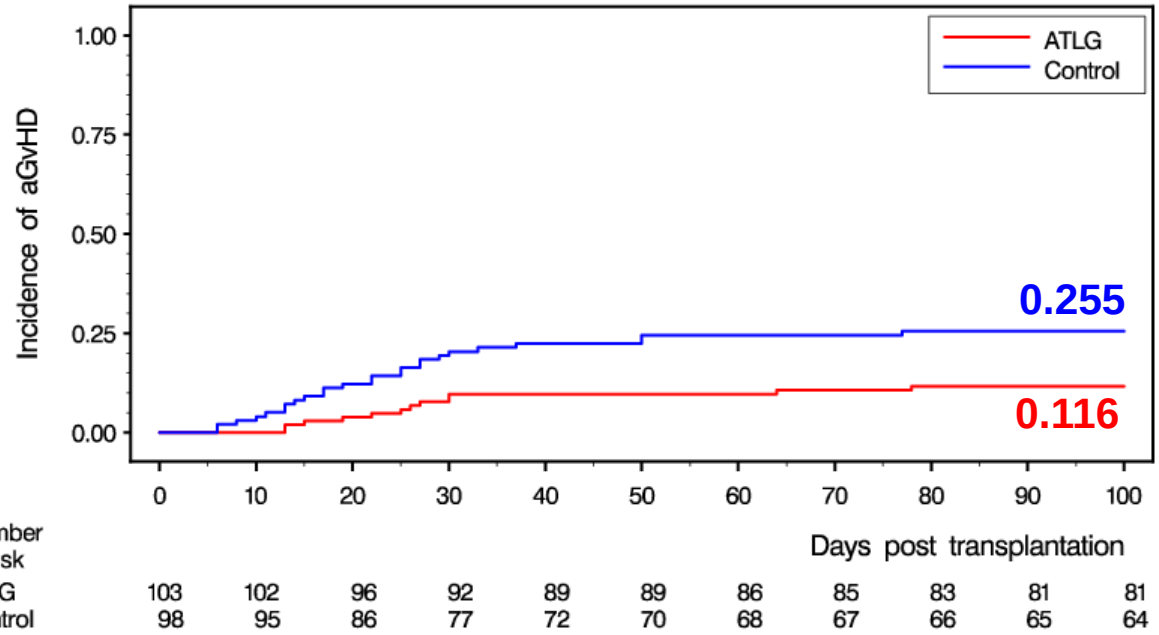
$\hat{S}(s-)$**: KM estimator of being free of all events just before time s**

- **Consequences**
  - **One-to-one correspondence** between hazard and event probability (being present in standard survival analysis) **no longer exists** with competing risks
  - Comparison of groups w.r.t **hazards** and w.r.t **probabilities** regard **different aspects** and can give different results

RCT: Results of event aGvHD

	ATLG n=103	Control n=98
aGvHD or death without prior aGvHD	22 (0.214)	34 (0.347)
aGvHD	12 (0.116)	25 (0.255)
Death without prior aGvHD	10 (0.097)	9 (0.092)

Aalen-Johansen = CIF



Cox model

Event-specific	
Hazard Ratio	**95%-CI**
0.48	**[0.24,0.96]**

RCT: Results of event death w/o prior aGvHD

	ATLG n=103	Control n=98
aGvHD or death without prior aGvHD	22 (0.214)	34 (0.347)
aGvHD	12 (0.116)	25 (0.255)
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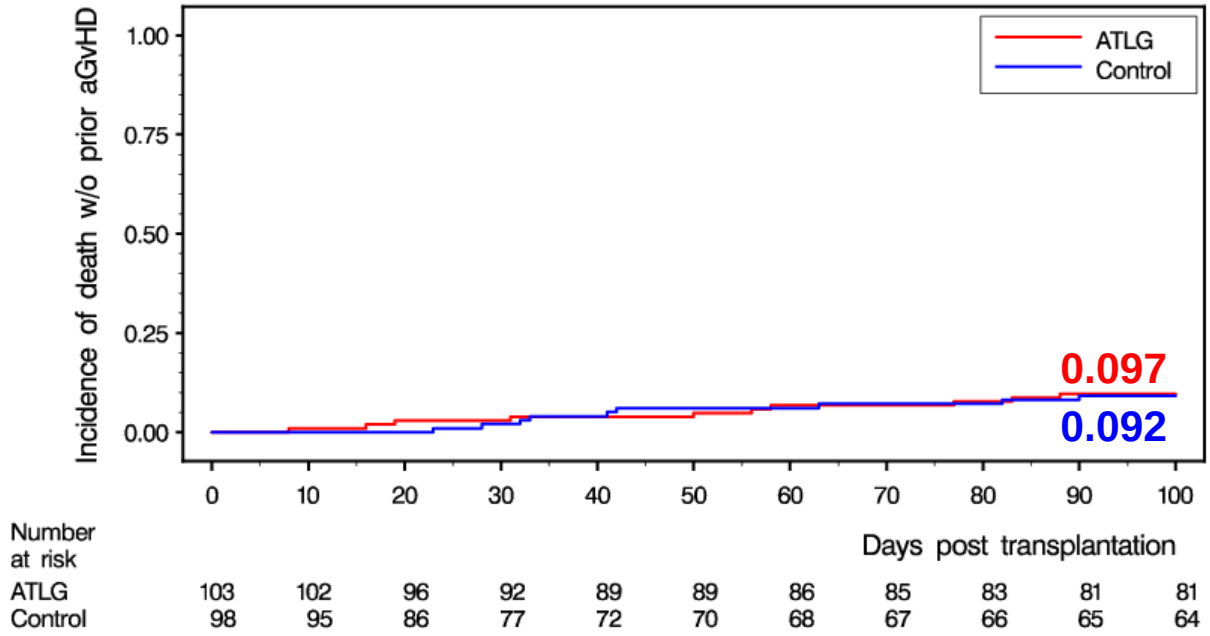
Aalen-Johansen = CIF



Cox model

Event-specific	
Hazard Ratio	**95%-CI**
1.17	**[0.47,2.92]**

RCT: Results of event aGvHD

	ATLG n=103	Control n=98
aGvHD or death without prior aGvHD	22 (0.214)	34 (0.347)
aGvHD	12 (0.116)	25 (0.255)
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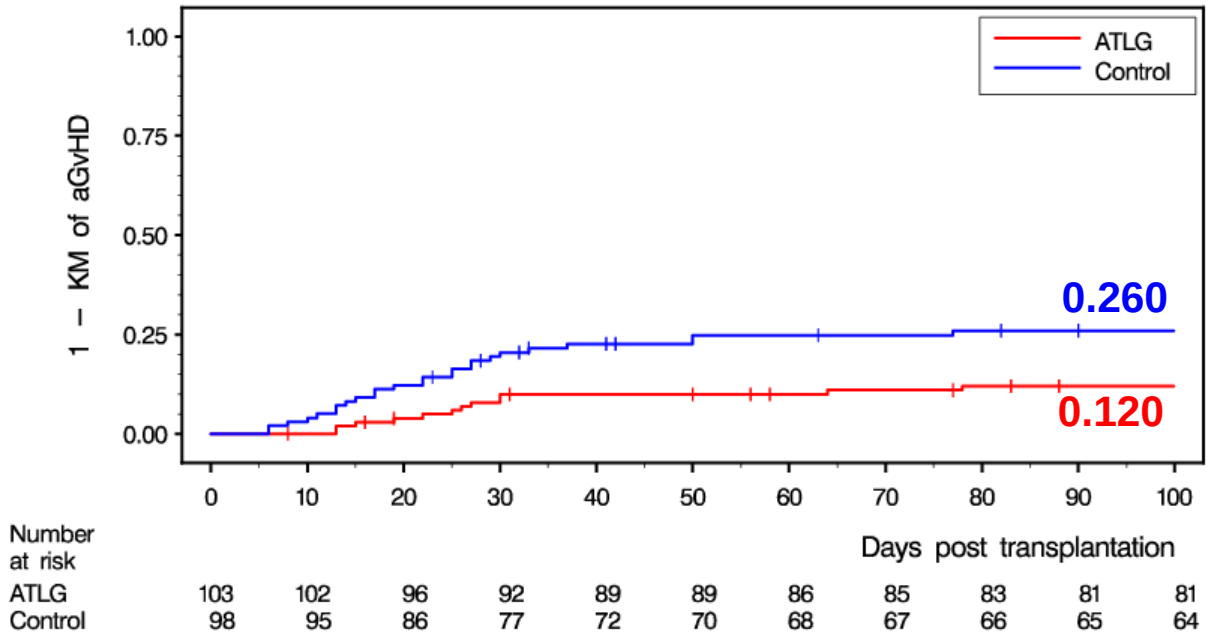
Wrong 1 – Kaplan-Meier



Only slight overestimation due to low # competing events

Another example with larger difference later!

Competing risks vs. Composite endpoint

- **Competing risk analysis**
  - provides more specific results
  - there are now two results instead of one
- **Summarize the analyses of both event-specific hazards in terms of the resulting effect on the event probability**
- **For this purpose, most popular method**
  - Fine and Gray model for the subdistribution hazard

Single events: Subdistribution hazards (Fine & Gray)

- **Aim:** **One analysis directly reflecting treatment effect on aGvHD probability**

- **Instead of the event-specific hazard**

$$\frac{\#\text{ observed (aGvHD) events at time } s}{\#\text{ patients w/o an (aGvHD or death) event and not yet censored just before time } s}$$

consider the subdistribution hazard

$$\frac{\#\text{ observed (aGvHD) events at time } s}{\#\text{ patients w/o an (aGvHD) event and not yet censored just before time } s}$$

- **Subdistribution hazard re-establishes a one-to-one correspondence between hazard and event probability**

- **The aGvHD probability is a function of**
  - two event-specific hazards
  - one subdistribution hazard

RCT: Results of event aGvHD

	ATLG n=103	Control n=98
aGvHD or death without prior aGvHD	22 (0.214)	34 (0.347)
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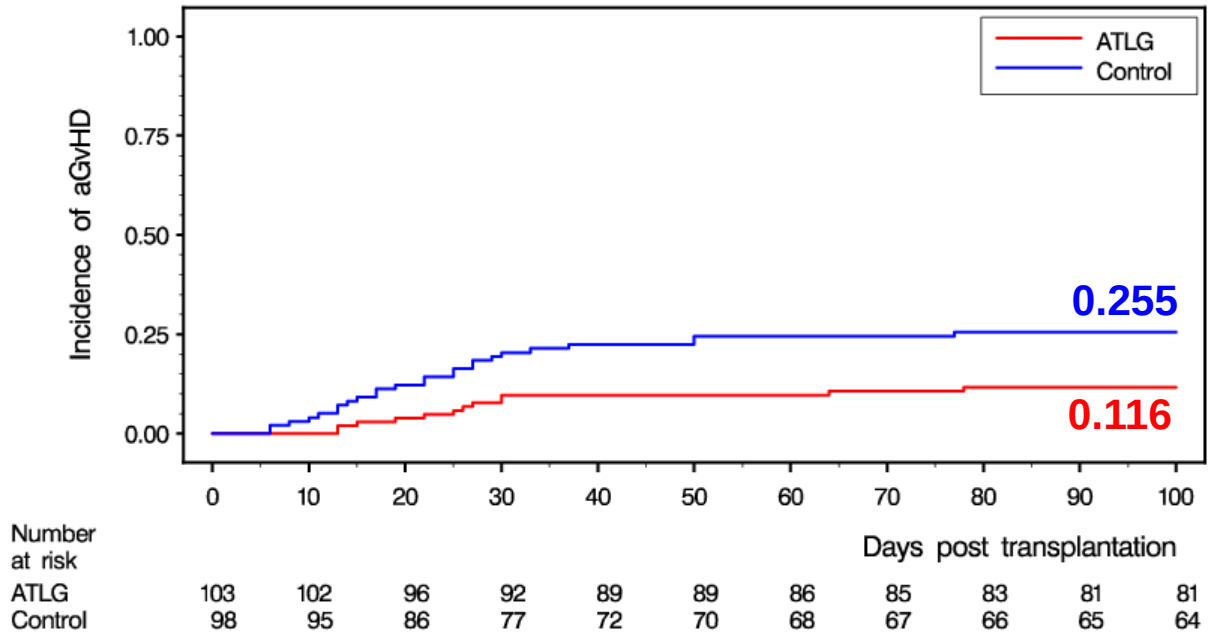
Aalen-Johansen = CIF



Event-specific	
Hazard Ratio	**95%-CI**
0.48	**[0.24,0.96]**

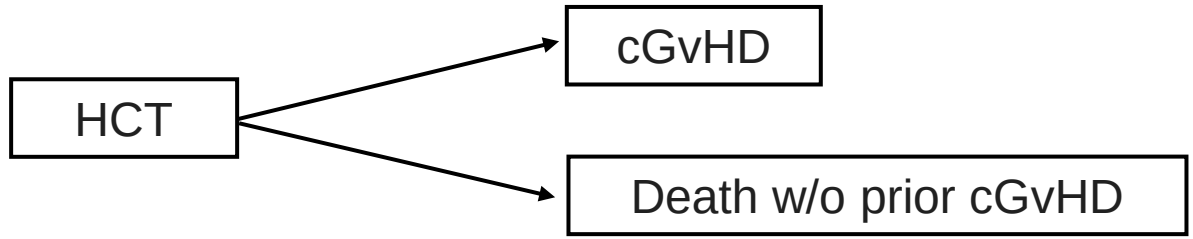
Subdistribution	
Hazard Ratio	**95%-CI**
0.47	**[0.23,0.94]**

RCT: Summary of aGvHD analysis

- **Competing risks analysis**
  - showed beneficial effect of ATLG vs. control on reduction of aGvHD
- **For showing that ATLG decreases the risk of aGvHD without increasing the competing risk, composite event was chosen as primary endpoint**
  - No difference with respect to the competing event
  - But, by adding this component to the primary endpoint, the difference between treatment groups caused by aGvHD was diminished
- **No practical difference between results of event-specific hazard and subdistribution hazard analysis**
  - Was shown to be true in general (Grambauer et al, Stat Med, 2010)
    - if censoring is heavy
    - if no effect on competing risk
  - In other situation maybe different (e.g. chronic GvHD)

RCT: Endpoint chronic GvHD (cGvHD)

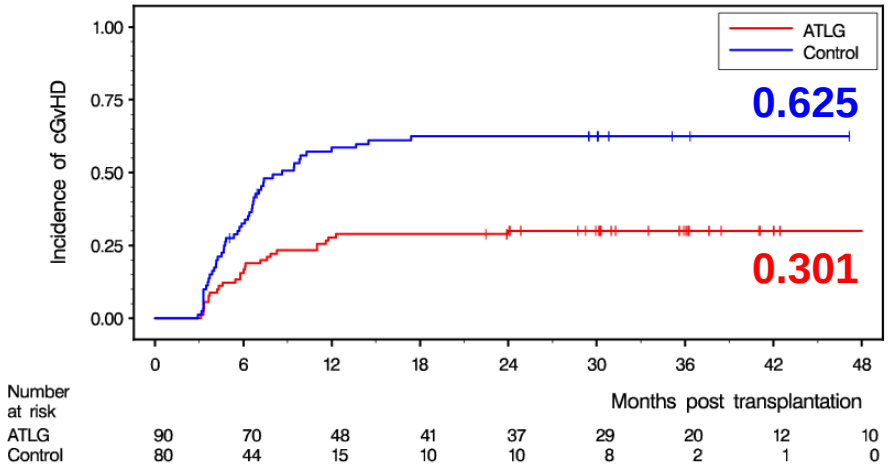
- **So far**
  - acute GvHD (aGvHD) within the first 100 days post HCT
- **Secondary endpoint**
  - chronic GvHD (cGvHD) after day +100 post HCT
- **Competing risks model**



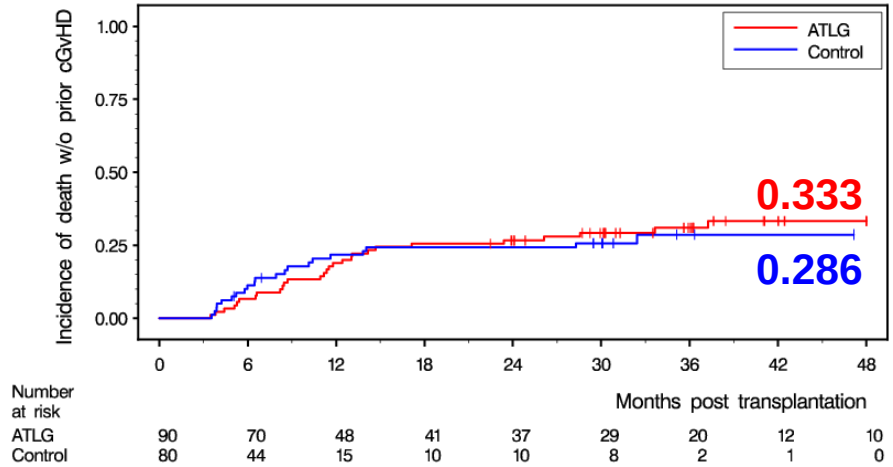
RCT: CIF vs. 1 - Kaplan-Meier for cGvHD

Aalen-Johansen = CIF

cGvHD



Death w/o prior cGvHD

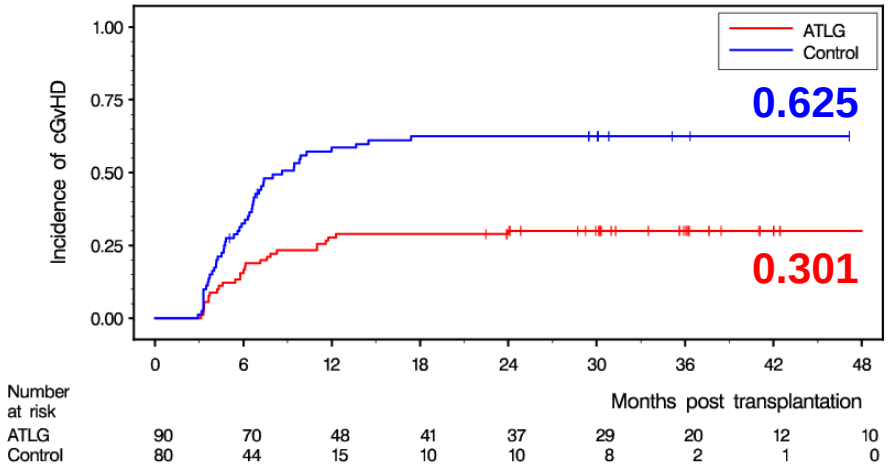


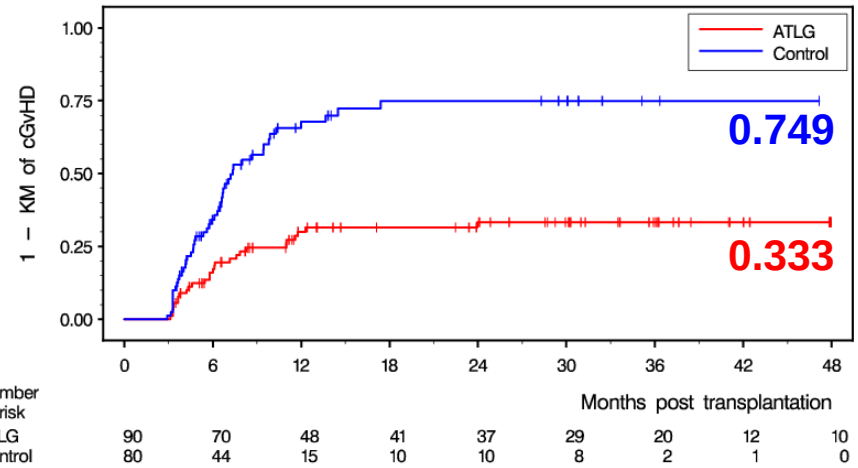
RCT: CIF vs. 1 - Kaplan-Meier for cGvHD

Aalen-Johansen = CIF

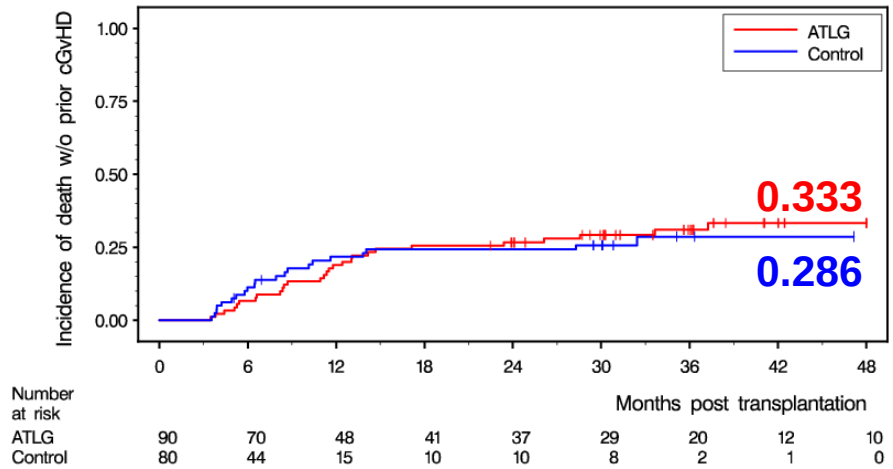
Wrong 1 - KM

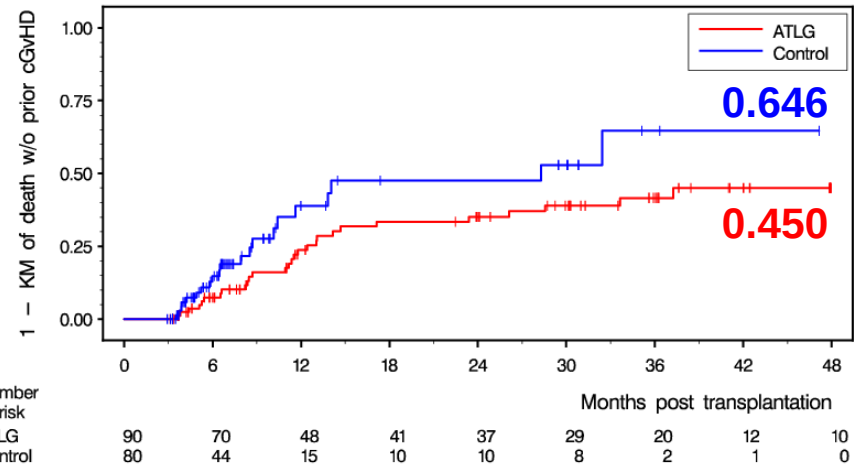
cGvHD





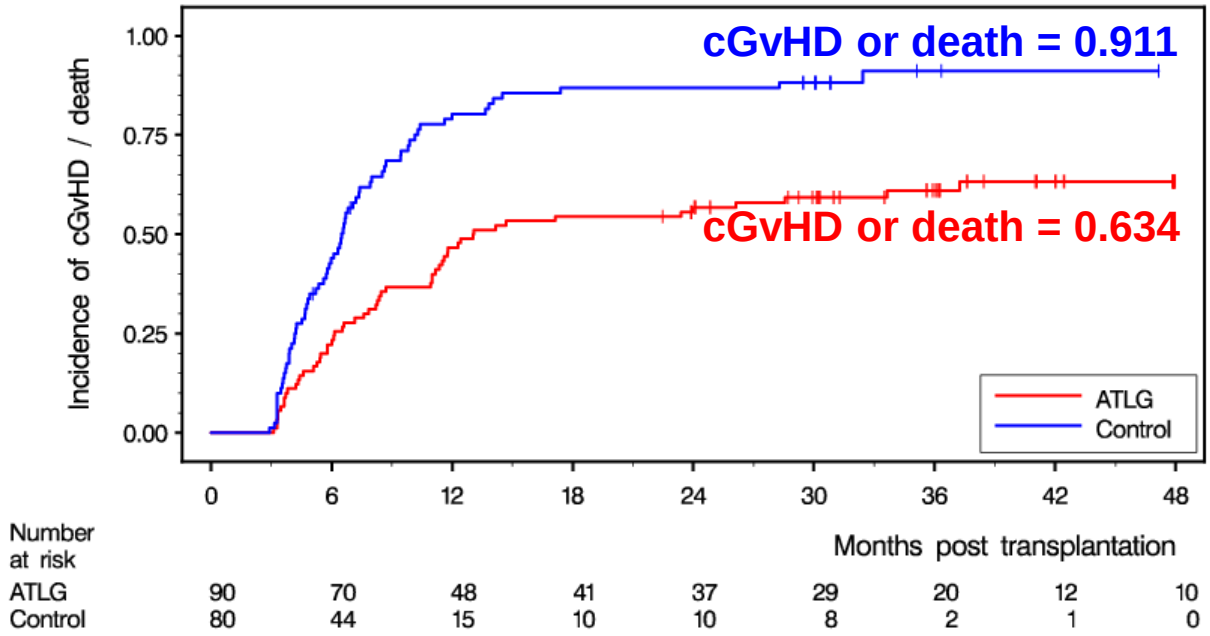
Death w/o prior cGvHD





RCT: Results of cGvHD / death w/o prior cGvHD

- **Probability of composite event (cGvHD or death w/o prior cGvHD)**
  - versus **sum of Aalen-Johansen (CIFs)**
  - versus **sum of 1 – Kaplan-Meier**



= 0.625 + 0.286 **sum of CIFs**

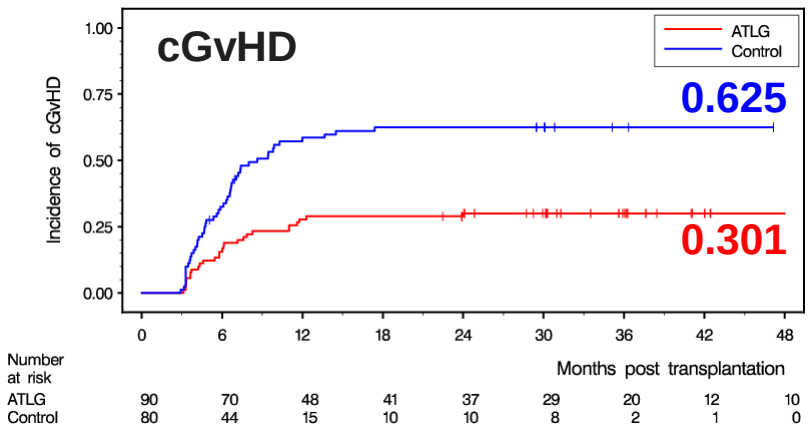
≠ 0.749 + 0.646 **sum of 1 - KM = 1.395**

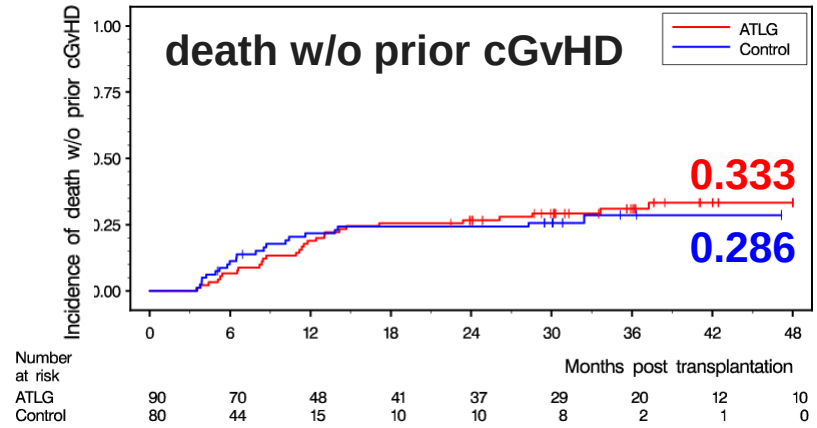
= 0.301 + 0.333 **sum of CIFs**

≠ 0.333 + 0.450 **sum of 1 - KM = 0.783**

RCT: Results of cGvHD

Aalen-Johansen = CIF





HR, 95%-CI	Event-specific	Subdistribution	Event-specific	Subdistribution
	0.33 [0.20,0.54]	0.38 [0.23,0.61]	0.59 [0.33,1.06]	1.17 [0.66,2.07]

- **Different results w.r.t. death w/o prior cGvHD**
- **Reason: # death w/o prior cGvHD related to different risk sets**
  - **Subdistribution:** # patients alive and not censored (**similar in ATLG and control**)
  - **Event-specific:** # patients alive and not censored and without cGvHD (**larger in ATLG**)

    ⟶ **event-specific hazard lower in ATLG vs. control**

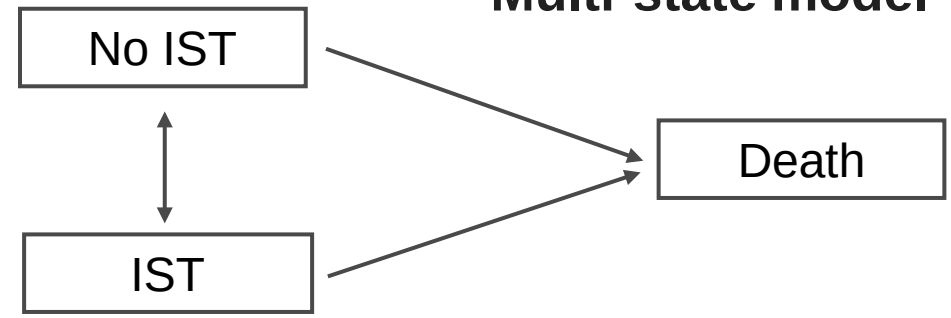
Event-specific hazard vs. subdistribution hazard

- **Event-specific hazard (Cox model)**
  - Instantaneous rate of occurrence of specific event in patients who are **free of all events** and not censored (**= still at risk**)
  - Parameters from Cox model have clear **interpretation as hazard ratios**
  - For investigation of **etiological (direct) effects on event rates**
- **Subdistribution hazard (Fine & Gray model)**
  - Instantaneous rate of occurrence of specific event in patients who are **free of specific event** and not censored (**≠ still at risk**)
  - No real hazard interpretation, Fine & Gray model parameters **difficult to interpret**
  - **Useful** due to **direct correspondence to CIF**
  - For investigation of **prognosis in terms of absolute risk**
- **Alternative proposals for comparison of CIFs**
  - e.g. proportional-odds model
  - up to now rarely used in practice

RCT: Endpoint Immunosuppressive therapy (IST)

- **Comparison of treatments with respect to time patients need to undergo IST after transplantation**
  - regarded as indicator of GvHD burden
- **Statistical challenge**
  - Multiple episodes
  - Patients can switch back and forth between states
- **Transition hazards**

Multi-state model



$$\frac{\#\text{ observed switches to IST at time } s}{\#\text{ patients in no IST and not yet censored just before time } s}$$

$$\frac{\#\text{ observed switches to no IST at time } s}{\#\text{ patients under IST and not yet censored just before time } s}$$

RCT: Immunosuppressive therapy (IST)

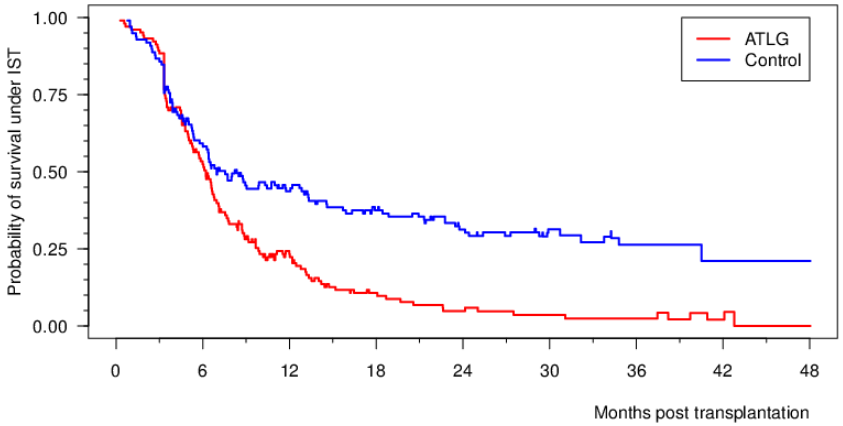
- **Transition hazard ratios can be estimated with Cox model**
  - For each patient: Number of data lines = number of transitions
  - Robust variance estimation or non-parametric bootstrap recommended
- **Transition hazard ratios: ATLG vs. Control**

Transition	Hazard Ratio for		95%-CI
no IST → IST	receiving IST	0.31	[0.18,0.55]
IST → no IST	stopping IST	2.02	[1.41,2.91]

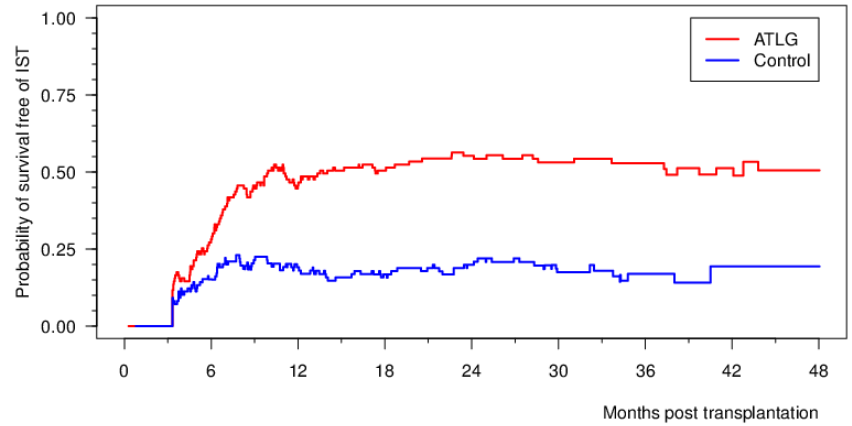
- **Positive effect of ATLG on reduction of time under IST**
- **Probabilities**
  - of **survival under IST** and of **survival free of IST**
  - estimated by Aalen-Johansen estimator with more complex matrix-valued structure involving all transition hazards

RCT: Immunosuppressive therapy (IST)

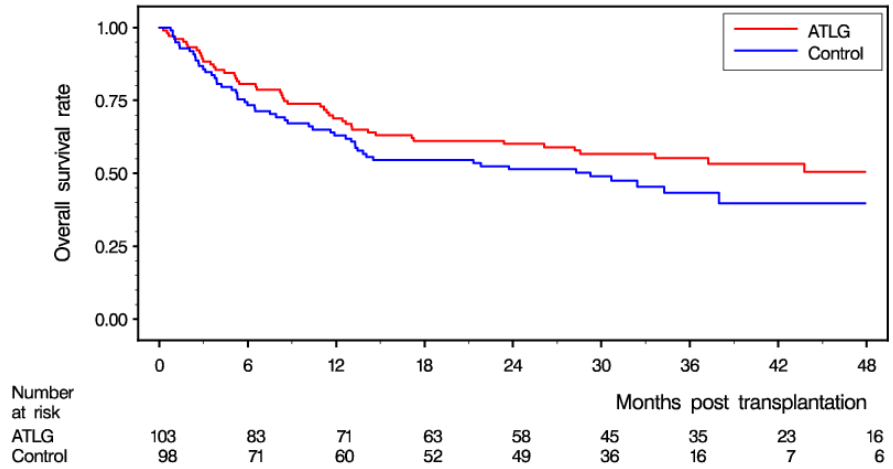
Probability of survival under IST



Probability of survival free of IST



Probability of survival under IST + Probability of survival free of IST = Overall survival probability



RCT: Immunosuppressive therapy (IST)

- **Statistical comparison of treatment groups w.r.t**
  - Probability of survival under IST
  - Probability of survival free of IST

  via confidence bands using a resampling approach
  (Bluhmki et al, Biometrics, 2018)

- **Next talk by Jan on multi-state models**

Analysis of adverse events

- **Safety analyses in terms of adverse events (AE) relevant in almost all clinical trials**
- **Focus on: First AE of a specific type**
- **Most often**
  - P (AE) estimated by the simple **incidence proportion**

    #AE / n

    #AE number of patients who experienced the interesting AE
    n total number of patients
- **If follow-up time for all patients is identical**
  - #AE / n correct estimator

Analysis of adverse events

- **In general**
  - AEs can occur at any point in time during patients' follow-up
  - Follow-up times can be incomplete (censored) and can vary between patients and between treatment groups
- **In case of censoring**
  - Simple incidence proportion **underestimates P(AE)**
- **Sometimes proposed: Incidence rate**
  - **#AE / sum of patient-time at risk**
  - accounts for censoring
  - does not estimate P(AE), not bounded to [0,1]
  - estimates AE hazard under constant hazard assumption

Analysis of adverse events

- **Competing risks can occur**
  - Death w/o prior AE of interesting type
  - Discontinuation of study treatment (stop of follow-up for AEs)
- **In case of competing risks**
  - Parametric estimation: 1 – exp (- t • constant AE hazard)
  - Non-parametric estimation: Kaplan-Meier censoring competing events

  overestimates P(AE)
- **Adequate statistical methods for time-to-event data required taking**
  - patients' time at risk for AEs and
  - competing risks

  into account

Analysis of adverse events

- **Joint project group of IBS-DR and GMDS**
  - established in 09/2016
  - > 20 statisticians from academia, industry, IQWiG and BfArM
  - has identified research requirements for the analysis of AEs in the benefit assessment of therapeutic interventions
  - considers AE analysis in the context of estimands framework
  - manuscript in preparation
- **Initiation of an empirical study**
  - Re-analyse specific types of AE in clinical trials identified by group members from pharmaceutical companies
  - **Aim**
    - Compare different (correct and incorrect) statistical methods in practice
    - Generate insight into possible real world biases

Discussion

- **Competing risks are present in many clinical trials with time-to-event endpoints**
  - Adequate statistical methods exist for a long time, but are still underused
  - To fully understand the results, all competing risks have to analyzed
- **Study planning in the presence of competing risks is challenging because there is more than one event type**
  - In our example composite event was used for planning
  - Other options to be discussed
- **Time-to-event methods in common use in efficacy analyses, but not in safety analyses**
  - general data structure (timing of events, censoring, varying follow-up) same for efficacy and safety
  - situation has to be improved ⟶ we try to work on this

Some own references

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