UNIVERSITÄTSMEDIZIN GÖTTINGEN UMG

COMPARISON OF STATISTICAL METHODS TO ANALYSE SAFETY DATA

4th EFSPI Workshop on Regulatory Statistics

Basel, 23-24 Sep 2019

Tim Friede

Department of Medical Statistics

University Medical Center Göttingen, Germany

On behalf of The "Survival analysis for AdVerse events with VarYing follow-up times" (SAVVY) project

CONFLICTS OF INTEREST / FINANCIAL DISCLOSURE

- **Personal fees for consultancies** (including data monitoring committees) in the past three years from Bayer, BiosenseWebster, Boehringer Ingelheim, Cardialysis, CSL Behring, DaiichiSankyo, Enanta, Feldmann Patent Attorneys, Fresenius Kabi, Galapagos, Genentech, IQVIA, Janssen, Johnson & Johnson, Mediconomics, Novartis, Penumbra, Roche, Vifor
- **All unrelated to this presentation**

SURVIVAL ANALYSIS FOR ADVERSE EVENTS WITH VARYING FOLLOW-UP TIMES (SAVVY)

Academic leads

- Jan Beyersmann (Ulm)
- Claudia Schmoor (Freiburg)
- Tim Friede (Göttingen)



All the hard work is done by

- Regina Stegherr (Ulm)

SAVVY: THE PROJECT GROUP

- **Steering Committee**
  - To ensure project runs smoothly and on target; to develop strategy for future activities
  - Members: Jan Beyersmann, Claudia Schmoor, Tim Friede, Valentine Jehl (Novartis), Friedhelm Leverkus (Pfizer), Kaspar Rufibach (Roche)
- **Participating organizations**
  - Providing data for empirical study; engaging in discussions on design and analysis of empirical study
  - Bayer, Boehringer Ingelheim, BMS, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, University Medical Center Freiburg

SAVVY: OBJECTIVES OF THE EMPIRICAL STUDY

- **Compare common** (but biased or incomplete) **analyses of adverse events (AEs) with methods accounting for censoring and for competing events** in terms of safety comparison between treatment groups.
- For the present investigation, consider **time-to-first AE** (of a certain kind), observation of which may be precluded by death, some other time-to-event outcome or limited recording (censoring) of AEs over a restricted period of time.
- The target quantity is the **probability to acquire such an AE** over the course of time in order to **compare these probabilities between treatment groups**.
- The aim is to **investigate** in a large number of RCTs **whether the different analyses of AEs lead to different decisions** when comparing safety between groups

STUDY CHARACTERISTICS

- 10 participating organizations contributing 17 randomized controlled trials including 186 adverse events (AEs)

	Frequency (%)
AEs per study: median (Q1, Q3)	7.5 (3, 19)
Type of control: Placebo	8 (47)
Disease area: Oncology	12 (71)

ADVERSE EVENT CHARACTERISTICS

- Out of a total of n=186 adverse events

	Frequency (%)
Serious adverse event	12 (7)
Proportion of censored obs.: median (Q1, Q3)	0.18 (0.12, 0.55)
Frequency category	
Very rare	6 (3)
Rare	0 (0)
Uncommon	6 (3)
Common	86 (46)
Very common	88 (47)
Higher AE probability in experimental group	138 (74)

ESTIMATING AE PROBABILITIES

- Incidence Proportion (IP): $\frac{\#\text{AE in}[0,\tau]\text{in group A}}{\#\text{of patients in group A}}$
- Probability Transform incidence density (PT IDens): $1 - \exp\left(-ID_{\mathrm{A}}(\tau) \cdot \tau\right)$ with $ID_{\mathrm{A}}(\tau) = \frac{\#\text{AE in } [0,\tau] \text{ in group A}}{\text{patient-time at risk in group A (restricted by}\tau)}$
- 1 - Kaplan-Meier (1-KM): $1 - \hat{S}_{\mathrm{A}}(\tau) = 1 - \prod_{u \in (0,\tau]} \left(1 - \Delta\hat{\Lambda}_{\mathrm{A}}(u)\right)$
- Aalen-Johansen estimator (Gold standard) (AJE): $CIF_{\mathrm{A}}(\tau) = \sum_{u \in (0,\tau]} \prod_{v \in (0,u)} \left(1 - \Delta\hat{\Lambda}_{\mathrm{A}}(v) - \Delta\hat{\overline{\Lambda}}_{\mathrm{A}}(v)\right) \Delta\hat{\Lambda}_{\mathrm{A}}(u)$
- Probability transform of incidence density accounting for competing events (PT IDens CE): $\frac{ID_{\mathrm{A}}(\tau)}{ID_{\mathrm{A}}(\tau)+\overline{ID}_{\mathrm{A}}(\tau)} \left(1 - \exp(-\tau \cdot [ID_{\mathrm{A}}(\tau) + \overline{ID}_{\mathrm{A}}(\tau)])\right)$ with $\overline{ID}_{\mathrm{A}}(\tau) = \frac{\#\text{competing event in } [0,\tau] \text{ in group A}}{\text{patient-time at risk in group A (restricted by}\tau)}$

SOME CHARACTERISTICS OF THE ESTIMATORS

- **Incidence Proportion (IP)**: assumes identical follow-up times in all individuals
- **Probability Transform incidence density (PT IDens)**: 1-Kaplan-Meier like but parametric (constant hazard assumption for AE hazard and censors competing events)
- **1 - Kaplan-Meier (1-KM)**: non-parametric and censors competing events
- **Aalen-Johansen estimator (Gold standard) (AJE)**: non-parametric and accounts for competing events and censoring
- **Probability transform of incidence density accounting for competing events (PT IDens CE)**: Aalen-Johansen like but parametric (constant hazards assumption for AE and CE hazard)

DEFINITIONS OF COMPETING EVENTS

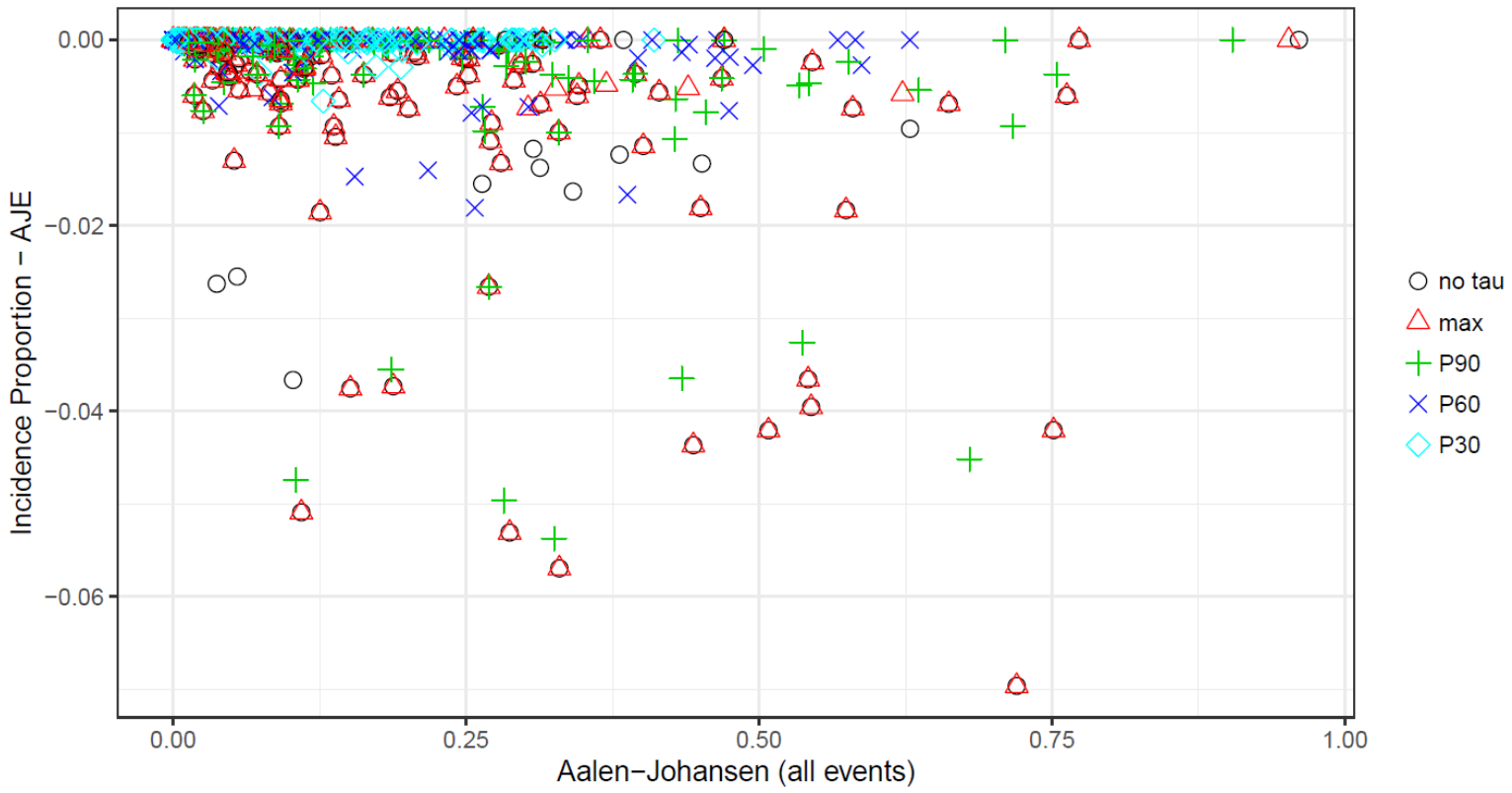
- **Death only**
  - death without prior AE, i.e., events after which an AE could definitely not occur any more
- **All events** (that preclude the observation of the AE of interest)
  - death, loss to follow up, withdrawal of consent, treatment discontinuation, and progression without prior AE
  - i.e., competing events after which an AE in principle still could occur, but not observed because of premature end of follow-up

VARYING FOLLOW-UP TIMES

- As the Incidence Proportion is usually only calculated at the end of follow-up all estimators are evaluated at the end of follow-up (no tau) in each group
- To account for different follow-up in groups A and B all estimators are evaluated at $\tau = \min(\tau_A, \tau_B)$ (max), with τ_A and τ_B largest observed event time in group A and B, respectively
- As estimators at the end of follow-up may have larger variability due to small numbers still at risk:
  - Evaluate estimators at earlier time point when more patients are still at risk
  - Evaluate estimators at $\tilde{\tau} = \min(\tilde{\tau}_A, \tilde{\tau}_B)$, with $\tilde{\tau}_A(p)$ and $\tilde{\tau}_B(p)$ defined as event time when $p \cdot 100\%$ of all patients in group A and group B, respectively, are still at risk
  - Here, $p = 0.9$ (P90), $p = 0.6$ (P60) and $p = 0.3$ (P30) are considered

BIAS IN ESTIMATING AE PROBABILITIES

- Incidence Proportion compared to Aalen -Johansen (all events)



BIAS IN ESTIMATING AE PROBABILITIES

- Random effects meta-analyses of log ratios (estimator / AJE) with bootstrapped standard errors
- Ratios resulting from meta-analyses:

	IP	PT IDens	1-KM	PT IDens CE	AJE death-only
no tau	0.976	2.097	1.214	1.130	1.170
max	0.977	1.817	1.187	1.099	1.146
P90	0.985	1.361	1.128	1.026	1.100
P60	1.000	1.138	1.062	1.006	1.050
P30	1.000	1.057	1.031	1.001	1.025

WHAT DRIVES THE SIZE OF THE BIAS?

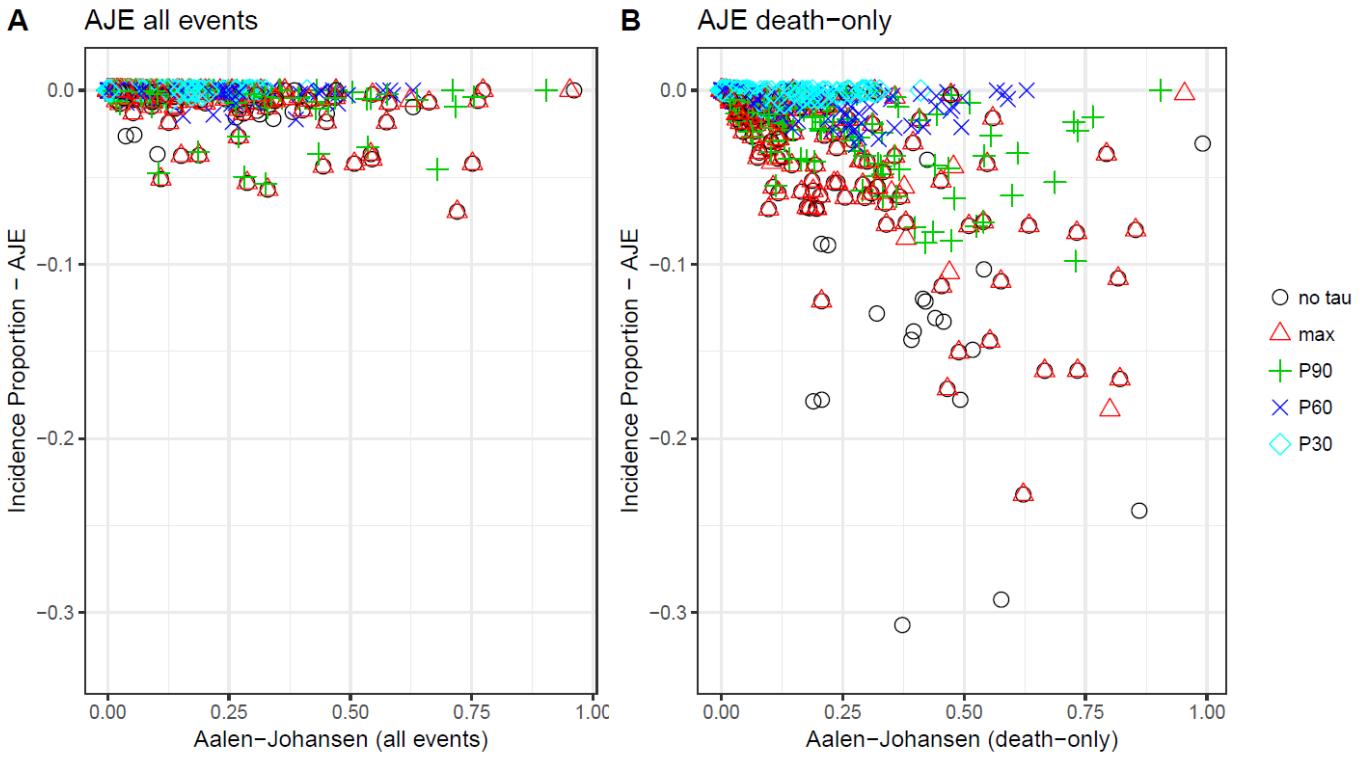
- **Meta-regression**: e.g. Probability Transform Incidence Density (PT IDens) vs. AJE

Factors	$\exp(\hat{\beta}_i)$	95% CI	p value
$\hat{\theta}$	2.407	[2.348;2.468]	$<$0.0001
AJE in A	0.323	[0.284;0.366]	$<$0.0001
max time in A	1.036	[1.021;1.051]	$<$0.0001
censoring (%)	0.313	[0.285;0.344]	$<$0.0001

THE IMPACT OF COMPETING EVENT DEFINITION

- AJE with ‘death only’ and ‘all events’ as competing events
- AE probability on average 17% higher with ‘death only’ compared to ‘all events’ (meta-analysis 1.17 (CI: [1.145,1.195])

Comparison to Incidence Proportion



CONCLUSIONS

AE probability

- Choice of estimator crucial
- Incidence Proportion similar to Aalen-Johansen estimator with ‘all events’ definition of competing events (resulting here in low censoring); differences in studies with substantial (especially late) censoring
- Kaplan-Meier estimator not appropriate as it censors competing events
- Ignoring competing events is more of a problem than falsely assuming constant hazards
- Death-only definition of competing events censors other competing events and therefore results in overestimation of AE probability

CONCLUSIONS

Between-group comparisons (results not shown)

- Choice of estimator also crucial for group comparisons
- In most cases the results of the group comparisons at no tau and at max are equal, but be careful with situations characterized by many late AEs in one group
- Hazard ratios for the AE hazard from Cox analyses: Need to model additionally competing event hazards