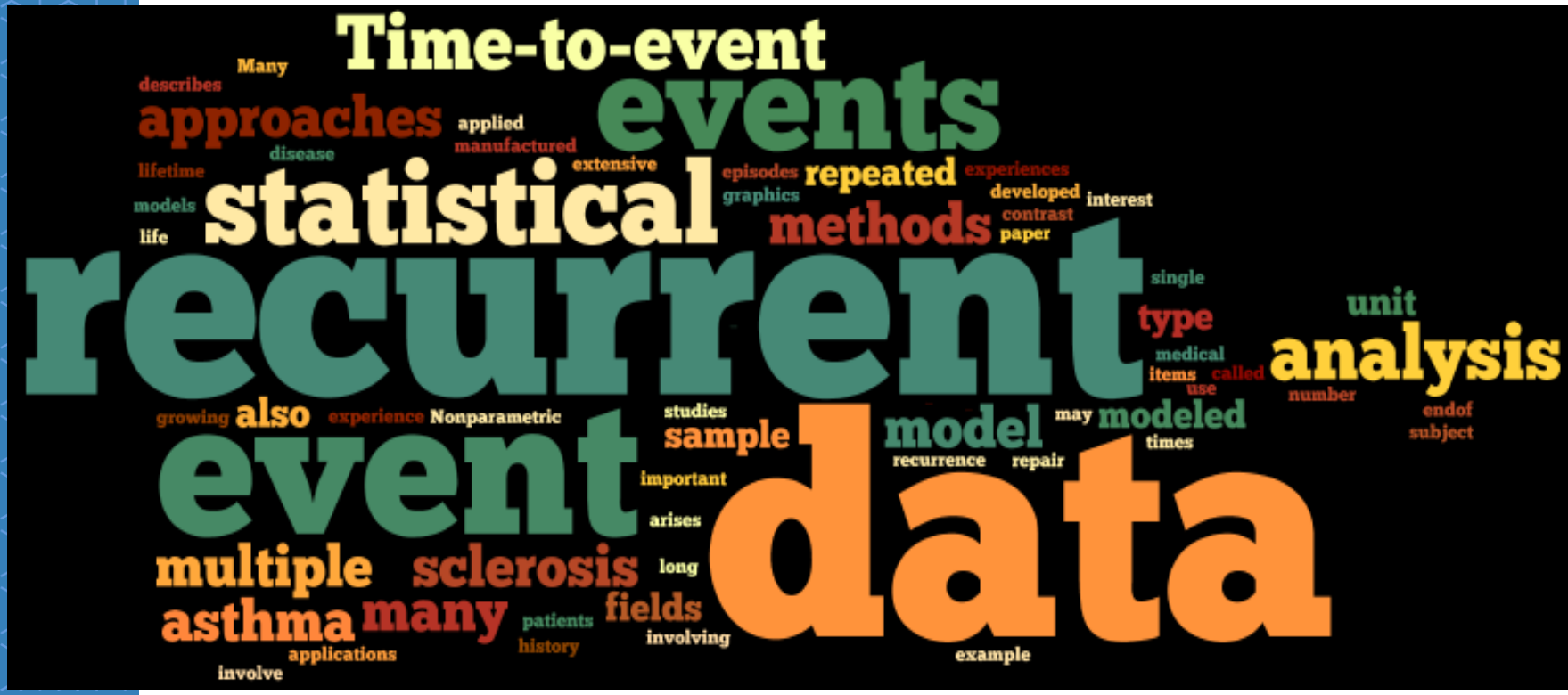


Efficiency comparisons of recurrent event and time-to-first event analysis

Jiawei Wei (Novartis) and Franco Mendolia (Bayer)

3rd EFSPI Workshop on Regulatory Statistics
24-25th September 2018 Basel (CH)

NOVARTIS Bayer

Recurrent event data

Settings of interest: comparing test treatment and control in chronic disease

- Without terminal event (e.g. relapsing-remitting multiple sclerosis)
  - Recurrent event endpoints are well established
  - Recurrent event analysis is more efficient than time-to-first event analysis if treatment affects the first and subsequent events
- With terminal event (e.g. chronic heart failure)
  - Current practice focus more on a time-to-first event endpoint
  - Clinical meaningfulness of recurrent events is acknowledged

Recurrent event data

Settings of interest: comparing test treatment and control in chronic disease

- Without terminal event (e.g. relapsing-remitting multiple sclerosis)
  - Recurrent event endpoints are well established
  - Recurrent event analysis is more efficient than time-to-first event analysis if treatment affects the first and subsequent events
- With terminal event (e.g. chronic heart failure)
  - Current practice focus more on a time-to-first event endpoint
  - Clinical meaningfulness of recurrent events is acknowledged

Are recurrent event analyses more efficient than time-to-first event analyses in the setting "with terminal event"?

Case study: ValHeFT

A RANDOMIZED TRIAL OF THE ANGIOTENSIN-RECEPTOR BLOCKER VALSARTAN IN CHRONIC HEART FAILURE

JAY N. COHN, M.D., AND GIANNI TOGNONI, M.D., FOR THE VALSARTAN HEART FAILURE TRIAL INVESTIGATORS*

N Engl J Med, Vol. 345, No. 23, December 6, 2001, pp 1667-1675

Study design:

- Placebo-contolled study
- Placebo arm: 2499 patients
- Valsartan arm: 2511 patients, i.e. total N=5010
- Mean duration of follow-up: 23 months (range: 0 – 38 months)

Case study: ValHeFT

A RANDOMIZED TRIAL OF THE ANGIOTENSIN-RECEPTOR BLOCKER VALSARTAN IN CHRONIC HEART FAILURE

JAY N. COHN, M.D., AND GIANNI TOGNONI, M.D., FOR THE VALSARTAN HEART FAILURE TRIAL INVESTIGATORS*

N Engl J Med, Vol. 345, No. 23, December 6, 2001, pp 1667-1675

Study design:

- Placebo-contolled study
- Placebo arm: 2499 patients
- Valsartan arm: 2511 patients, i.e. total N=5010
- Mean duration of follow-up: 23 months (range: 0 – 38 months)

Co-primary endpoints:

- All-cause mortality
- Time-to-first event of a combined endpoint of all-cause mortality and morbidity

‘Time-to-first composite event’ approach ignores a lot of information

Number of hosp. for heart failure (HHF)	No. of patients PBO N_{PBO}=2499 N (%)	No. of patients Val N_{Val} =2511 N (%)	Total No. of patients N_{TOT} =5010 N (%)
0	1878 (75.15)	1974 (78.61)	3852 (76.89)
1	344 (13.77)	317 (12.62)	661 (13.19)
2	146 (5.84)	130 (5.18)	276 (5.51)
3	56 (2.24)	51 (2.03)	107 (2.14)
4	36 (1.44)	19 (0.76)	55 (1.10)
5	21 (0.84)	13 (0.52)	34 (0.68)
6	5 (0.20)	3 (0.12)	8 (0.16)
7	6 (0.24)	1(0.04)	7 (0.14)
8	3 (0.12)	2 (0.08)	5 (0.10)
≥ 9	4 (0.16)	1 (0.04)	5 (0.10)
Total number of HHF	1189	922	2111
Total number of CV death (CVD)	419 (16.77)	427 (17.01)	846 (16.89)
Total number of composite ‘first’ events (HHF/CVD)	841	769	**1610**
Number of HHF and CVD	1608	1349	**2957**

Recurrent event estimands (HHF)

Chronic heart failure study

A. Population: defined through inclusion/exclusion criteria to reflect the targeted patient population

B. Variable: number of **HHF** while the patient is alive

C. Intercurrent event:

1. Treatment discontinuation: regardless of treatment discontinuation
2. Any cause death: while being alive

D. Summary measure:

- Exposure-weighted rate: the average number of HHFs patients suffer over the length of the study or until death relative to how long patients can expect to live over the course of the study
- Equal-weighted rate: the average number of HHF a patient can expect per study year s/he is alive [regardless of whether the patient will live for long or short]

Recurrent event estimands (HHF+CVD)

Chronic heart failure study

A. Population: defined through inclusion/exclusion criteria to reflect the targeted patient population

B. Variable: number of **HHF+CVD** (CVD as an additional event), up to and including the time of death

C. Intercurrent event:

1. Treatment discontinuation: regardless of treatment discontinuation
2. Any cause death: while being alive

D. Summary measure:

- Exposure-weighted rate: the average number of HHF+CVDs patients suffer over the length of the study or until death relative to how long patients can expect to live over the course of the study
- Equal-weighted rate: the average number of HHF+CVD a patient can expect per study year s/he is alive [regardless of whether the patient will live for long or short]

Simulation: estimand vs. estimate

RR_{HHF}=0.7, n=100.000 patients

	Exposure-weighted rate based estimand			Equal-weighted rate based estimand			Method	Estimate		
HR_{CV}	0.8	1.0	1.25	0.8	1.0	1.25		0.8	1.0	1.25
HHF	0.783	0.722	0.688	0.752	0.727	0.720	Cox	0.841	0.799	0.782
							NB	0.752	0.700	0.684
							LWYY	**0.784**	**0.722**	**0.687**
HHF+CVD	0.809	0.806	0.822	0.93	1.759	3.737	Cox	0.875	0.898	0.935
							NB	0.766	0.814	0.885
							LWYY	**0.809**	**0.806**	**0.821**

- $RR_{HHF:}$ assumed treatment effect on HHF
- $HR_{CV:}$ assumed treatment effect on CVD
- Both from joint frailty model in data generation, not directly reflecting the values of the estimand

Simulation: estimand vs. estimate

RR_{HHF}=0.7, n=100.000 patients

	Exposure-weighted rate based estimand			Equal-weighted rate based estimand			Method	Estimate		
HR_{CV}	0.8	1.0	1.25	0.8	1.0	1.25		0.8	1.0	1.25
HHF	0.783	0.722	0.688	0.752	0.727	0.720	Cox	0.841	0.799	0.782
							NB	0.752	0.700	0.684
							LWYY	**0.784**	**0.722**	**0.687**
HHF+CVD	0.809	0.806	0.822	0.93	1.759	3.737	Cox	0.875	0.898	0.935
							NB	0.766	0.814	0.885
							LWYY	**0.809**	**0.806**	**0.821**

– LWYY seems target the exposure-weighted rate based estimand

Simulation: estimand vs. estimate

RR_{HHF}=0.7, n=100.000 patients

	Exposure-weighted rate based estimand			Equal-weighted rate based estimand			Method	Estimate		
HR_{CV}	0.8	1.0	1.25	0.8	1.0	1.25		0.8	1.0	1.25
HHF	0.783	0.722	0.688	0.752	0.727	0.720	Cox	0.841	0.799	0.782
							NB	0.752	0.700	0.684
							LWYY	**0.784**	**0.722**	**0.687**
HHF+CVD	0.809	0.806	0.822	0.93	1.759	3.737	Cox	0.875	0.898	0.935
							NB	0.766	0.814	0.885
							LWYY	**0.809**	**0.806**	**0.821**

- LWYY seems target the exposure-weighted rate based estimand
- None of the established approaches targets the equal-weighted rate based estimand.

Simulation: estimand vs. estimate

RR_{HHF}=0.7, n=100.000 patients

	Exposure-weighted rate based estimand			Equal-weighted rate based estimand			Method	Estimate		
HR_{CV}	0.8	1.0	1.25	0.8	1.0	1.25		0.8	1.0	1.25
HHF	0.783	0.722	0.688	0.752	0.727	0.720	Cox	0.841	0.799	0.782
							NB	0.752	0.700	0.684
							LWYY	**0.784**	**0.722**	**0.687**
HHF+CVD	0.809	0.806	0.822	0.93	1.759	3.737	Cox	0.875	0.898	0.935
							NB	0.766	0.814	0.885
							LWYY	**0.809**	**0.806**	**0.821**

- LWYY seems target the exposure-weighted rate based estimand
- None of the established approaches targets the equal-weighted rate based estimand.
- Large values for the equal-weighted rate based estimand of HHF+CVD are caused by patients that die relatively early

Revisit ValHeFT study: recurrent event and time-to-event estimators

	Plug-in estimator (exposure weighted)	Plug-in estimator (equal weighted)	Model based estimator	Estimate	95% CIL	95% CIU	P-value
HHF	**0.77**	0.82	Cox	0.84	0.75	0.95	0.0034
			NB	**0.77**	0.66	0.89	0.0007
			LWYY	**0.77**	0.68	0.88	0.0001
HHF+CVD	**0.83**	0.62	Cox	0.89	0.81	0.98	0.0204
			NB	**0.84**	0.73	0.97	0.0176
			LWYY	**0.83**	0.74	0.93	0.0012

- Exposure-weighted rate ratio plug-in estimator: $\frac{\sum_{k\in A}[N_k]/\sum_{k\in A}[T_k]}{\sum_{k\in B}[N_k]/\sum_{k\in B}[T_k]}$
- Equal-weighted rate ratio plug-in estimator: $\frac{\sum_{k\in A}[N_k/T_k]}{\sum_{k\in B}[N_k/T_k]}$

Simulation setting

Emulate situations observed in previous trials

Simulation setting

Emulate situations observed in previous trials

- CVD process and HHF process are not independent
  - Increase in HHF associated with increased risk of CVD
  - Joint frailty model to incorporate dependency (Rogers et al, 2016)

Simulation setting

Emulate situations observed in previous trials

- CVD process and HHF process are not independent
  - Increase in HHF associated with increased risk of CVD
  - Joint frailty model to incorporate dependency (Rogers et al, 2016)

- Annualized placebo rate of CVD 4% (events / patient-year)
  - CHARM-Preserved 3.9%; TOPCAT BNP Stratum 3.9%

- Annualized placebo rate of first composite event 9%
  - CHARM-Preserved 9.1%; TOPCAT BNP Stratum 8.5%

BNP: B-type natriuretic peptide

Simulation setting

Emulate situations observed in previous trials

- CVD process and HHF process are not independent
  - Increase in HHF associated with increased risk of CVD
  - Joint frailty model to incorporate dependency (Rogers et al, 2016)

- Annualized placebo rate of CVD 4% (events / patient-year)
  - CHARM-Preserved 3.9%; TOPCAT BNP Stratum 3.9%

- Annualized placebo rate of first composite event 9%
  - CHARM-Preserved 9.1%; TOPCAT BNP Stratum 8.5%

- Overall observed ratio of recurrent to first composite events = 1.8 (Anker and McMurray, 2012)

BNP: B-type natriuretic peptide

Simulation setting

Further settings

- Non-CVD as censoring event ➔ non-CVD was about 30% of all-cause death
- Study duration 5 years / Patient recruitment 3 years
  - Flexible follow-up time

Simulation setting

Further settings

- Non-CVD as censoring event ➔ non-CVD was about 30% of all-cause death
- Study duration 5 years / Patient recruitment 3 years
  - Flexible follow-up time
- Sample size: $N = 4350$, i.e. 2175 patients per treatment arm
  - 90 % power for LWYY (HHF+CVD) when $HR_{CV} = 0.8$ and $RR_{HHF} = 0.7$
  - Note: 0.8 and 0.7 are the simulation parameters for the joint frailty model; not directly reflecting the values of the estimand

Simulation setting

Further settings

- Non-CVD as censoring event ➔ non-CVD was about 30% of all-cause death
- Study duration 5 years / Patient recruitment 3 years
  - Flexible follow-up time
- Sample size: $N = 4350$, i.e. 2175 patients per treatment arm
  - 90 % power for LWYY (HHF+CVD) when $HR_{CV} = 0.8$ and $RR_{HHF} = 0.7$
  - Note: 0.8 and 0.7 are the simulation parameters for the joint frailty model; not directly reflecting the values of the estimand
- Variations, among others
  - Weibull inter-event times
  - Autoregressive event rates

Type I error (1-sided)

RR_{HHF}=1.0, n=4350 patients

	HR_{CV}	Method	Estimate	Type I error
HHF	0.8	Cox	1.027	0.010
		NB	1.035	0.010
		LWYY	1.058	0.005
	1.0	Cox	1.002	0.023
		NB	1.002	0.025
		LWYY	1.002	0.023
	1.25	Cox	0.973	0.058
		NB	0.964	0.057
		LWYY	0.942	0.100
HHF+CVD	1.0	Cox	1.002	0.022
		NB	1.001	0.024
		LWYY	1.001	0.024

Local null hypothesis: $RR_{HHF} \geq 1, HR_{CV} \neq 1$

Global null hypothesis: $RR_{HHF} \geq 1$ & $HR_{CV} \geq 1$

Type I error (1-sided)

RR_{HHF}=1.0, n=4350 patients

	HR_{CV}	Method	Estimate	Type I error
HHF	0.8	Cox	1.027	0.010
		NB	1.035	0.010
		LWYY	1.058	0.005
	1.0	Cox	1.002	0.023
		NB	1.002	0.025
		LWYY	1.002	0.023
	1.25	Cox	0.973	0.058
		NB	0.964	0.057
		LWYY	0.942	0.100
HHF+CVD	1.0	Cox	1.002	0.022
		NB	1.001	0.024
		LWYY	1.001	0.024

Local null hypothesis: $RR_{HHF} \geq 1, HR_{CV} \neq 1$

Global null hypothesis: $RR_{HHF} \geq 1$ & $HR_{CV} \geq 1$

– All methods provide control of Type I error under global null hypothesis with point estimates close 1

Type I error (1-sided)

RR_{HHF}=1.0, n=4350 patients

	HR_{CV}	Method	Estimate	Type I error
HHF	0.8	Cox	1.027	0.010
		NB	1.035	0.010
		LWYY	1.058	0.005
	1.0	Cox	1.002	0.023
		NB	1.002	0.025
		LWYY	1.002	0.023
	1.25	Cox	0.973	0.058
		NB	0.964	0.057
		LWYY	0.942	0.100
HHF+CVD	1.0	Cox	1.002	0.022
		NB	1.001	0.024
		LWYY	1.001	0.024

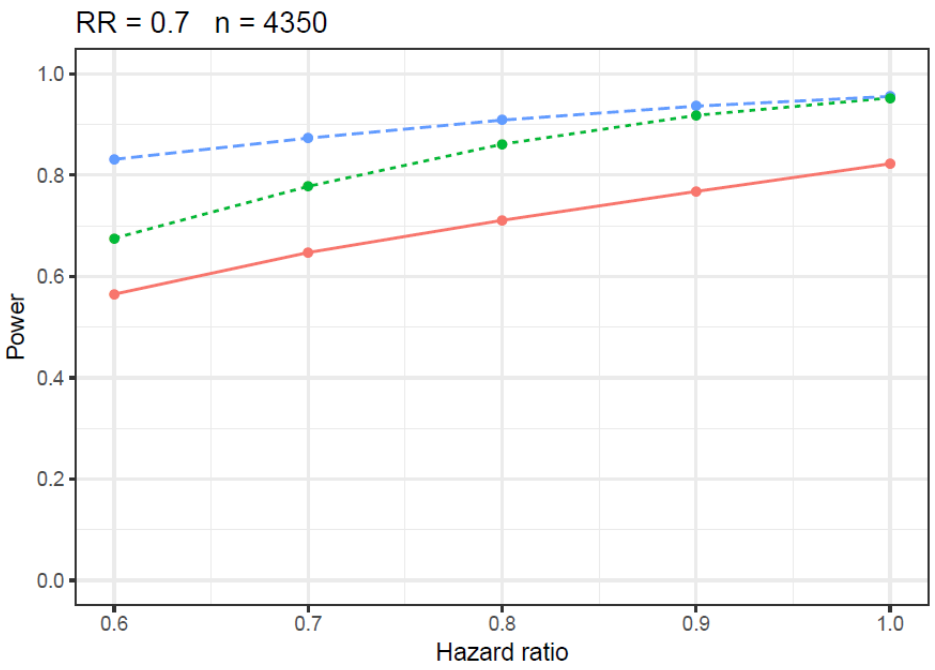
Local null hypothesis: $RR_{HHF} \geq 1, HR_{CV} \neq 1$

Global null hypothesis: $RR_{HHF} \geq 1$ & $HR_{CV} \geq 1$

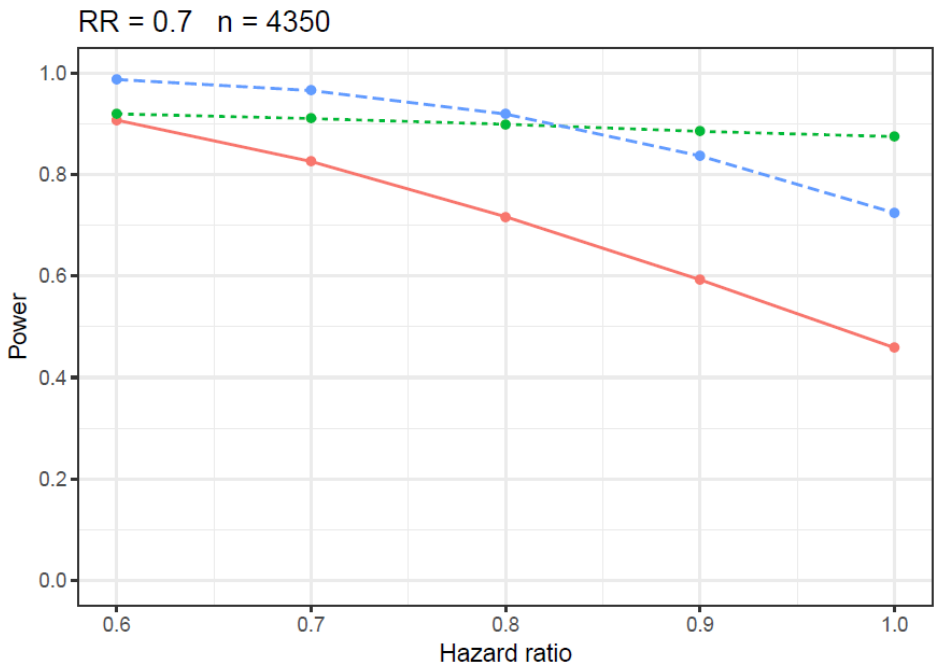
- Type I error inflation in favor of treatment with detrimental effect on CV death
- Severely ill patients in treatment group die earlier and contribute fewer HHF → makes treatment appear more effective in reducing HHF

Power

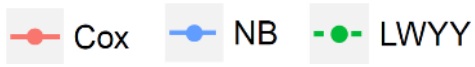
RR_{HHF}=0.7, n=4350 patients



HHF



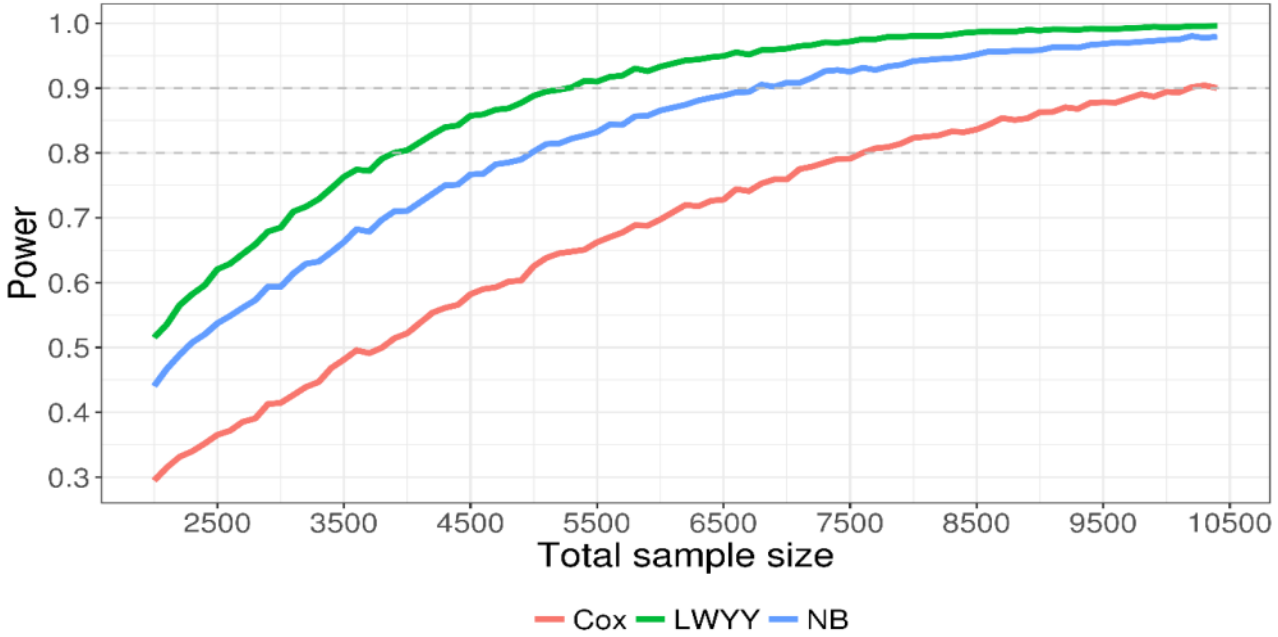
HHF+CVD



Back to ValHeFT example

HHF+CVD

Figure: Power for recurrent event analyses and time-to-first composite event analysis based on ValHeFT



For each given sample size, 10000 bootstrap samples were drawn from ValHeFT data.

Summary

- Recurrent event methods (incl. WLW and PWP) are more efficient than time-to-first methods as they provide higher power in all investigated scenarios
- All methods control Type I error rate under global null hypothesis

WLW: Wei-Lin-Weissfeld model; PWP: Prentice-Williams-Peterson model

Summary

- Recurrent event methods (incl. WLW and PWP) are more efficient than time-to-first methods as they provide higher power in all investigated scenarios
- All methods control Type I error rate under global null hypothesis

- LWYY targets exposure-weighted rate based estimands across all investigated scenarios

WLW: Wei-Lin-Weissfeld model; PWP: Prentice-Williams-Peterson model

Summary

- Recurrent event methods (incl. WLW and PWP) are more efficient than time-to-first methods as they provide higher power in all investigated scenarios
- All methods control Type I error rate under global null hypothesis

- LWYY targets exposure-weighted rate based estimands across all investigated scenarios

- Equal-weighted rate based estimand
  - Highly sensitive to time-changing rates
  - No well-established recurrent event approaches target this estimand

WLW: Wei-Lin-Weissfeld model; PWP: Prentice-Williams-Peterson model

Summary

- Recurrent event methods (incl. WLW and PWP) are more efficient than time-to-first methods as they provide higher power in all investigated scenarios
- All methods control Type I error rate under global null hypothesis

- LWYY targets exposure-weighted rate based estimands across all investigated scenarios

- Equal-weighted rate based estimand
  - Highly sensitive to time-changing rates
  - No well-established recurrent event approaches target this estimand

- Exposure weighted:
  - HHF only: Only appropriate if no or small effect on CVD can be assumed
  - HHF+CVD: Appropriate when effect on CVD is to be assumed

WLW: Wei-Lin-Weissfeld model; PWP: Prentice-Williams-Peterson model

Acknowledgements

Joint work with:

- Arno Fritsch (Bayer)
- Patrick Schlömer (Bayer)

Thank you!

References

- **Andersen, P. K. & Gill, R. D. (1982):** Cox's regression model for counting processes: a large sample study. Ann. Stat., 10: 1100–1120.
- **Anker and McMurray (2012).** Time to move on from time-to-rst: should all events be included in the analysis of clinical trials? Eur. Heart J. 33 (22), 2764-2765.
- **Cannon CP (1997):** Clinical perspectives on the use of composite endpoints. Controlled clinical trials 18:517-529.
- **Chi GYH (2005):** Some issues with composite endpoints in clinical trials. Fundamental & Clinical Pharmacology 19:609-619.
- **Cook R.J. (1995):** The design and analysis of randomized trials with recurrent events. Statistics in Medicine, Vol. 14, 2081-2098.
- **Cook RJ, Lawless JF (1997):** Marginal analysis of recurrent events and a terminating event. Statistics in Medicine, Vol 16, 911-924.
- **Cook RJ, Lawless JF, Lakhal-Chaieb L, Lee K-A (2009):** Robust estimation of mean functions and treatment effects for recurrent events under event-dependent censoring and termination: application to skeletal complications in cancer metastatic to bone. JASA, 104:485, 60-75.
- **Cowling BJ, Hutton JL, Shaw JEH (2006):** Joint modeling of event counts and survival times. Appl. Statist. 55, Part 1: pp 31-39.
- **Freemantle N et al. (2003):** Composite outcomes in randomized trials: greater precision but with greater uncertainty? JAMA Vol 289. No.19 2545-2575.
- **Freemantle N, Calvert M. (2007):** Weighing the pros and cons for composite outcomes in clinical trials. Journal of Clinical Epidemiology 60:658-659
- **Ghosh D & Lin DY (2000):** Nonparametric analysis of recurrent events and death. Biometrics, 56, 554–562.
- **Ghosh D & Lin D Y (2002):** Marginal regression models for recurrent and terminal events. Statistica Sinica, 12, 663–688.

References (continued)

- **Li QH, Lagakos SW (1997):** Use of Wei-Lin-Weissfeld Method for the Analysis of a Recurring and Terminating Event. Statistics in Medicine 16: 925-940.
- **Lin, D. Y., Wei, L. J., Yang, I. & Ying, Z. (2000):** Semiparametric regression for the mean and rate functions of recurrent events. J. R. Stat. Soc., B, 62, 711–730.
- **Liu L, Wolfe RA, Huang X (2004):** Shared frailty models for recurrent events and terminal event. Biometrics 60: 747-756
- **McCullagh P, Nelder JA (1989):** Generalized Linear Models, 2nd edn. London: Chapman and Hall
- **Metcalfe C et al (2003):** The use of hospital admission data as measure of outcome in clinical studies of heart failure. European Heart Journal 24: 105-112
- **Metcalfe C, Thompson SG (2006):** The importance of varying the event generation process in simulation studies of statistical methods for recurrent events. Statistics in Medicine 26: 165-179.
- **Metcalfe C, Thompson SG (2007):** Wei, Lin and Weissfeld‘s marginal analysis of multivariate failure time data: should it be applied to a recurrent events outcome) Statistical Methods in Medical Research 16: 103-122.
- **Montori VM, et al., (2005):** Validity of composite end points in clinical trials. BMJ Vol 330 2005.
- **Pfeer et al. (2015):** Regional variation in patients and outcomes in the treatment of preserved cardiac function heart failure with an aldosterone antagonist (TOPCAT) trial. Circulation 131, 34-42.
- **Rogers et al. (2014):** Analysing recurrent hospitalizations in heart failure: a review of statistical methodology, with application to CHARM-Preserved. Eur. J. Heart Fail. 16 (1): 33-40.
- **Rogers et al. (2016):** Analysis of recurrent events with an associated informative dropout time: Application of the joint frailty model. Stat. Med. 35 (13): 2195-2205.
- **Therneau & Grambsch (2000):** Modeling Survival Data: Extending the Cox Model. Springer.

Backup

Plug-in estimators

Treatment effect estimates (i.e. rate ratios) based on the plug-in estimators for the exposure-weighted and equal-weighted rate based estimands. Results are based on 1000 simulations, sample size N = 4350, RR_{HHF}=0.7

		Exposure-weighted based estimand*				Equal-weighted based estimand			
	HR_{CV}	Mean	SD	Min	Max	Mean	SD	Min	Max
Scenario 1: Non-informative HHF	0.80	0.769	0.067	0.571	0.979	0.729	0.114	0.442	2.484
	1.00	0.721	0.062	0.560	0.928	0.724	0.102	0.347	1.353
	1.25	0.670	0.057	0.522	0.886	0.713	0.102	0.399	1.301
Scenario 2: Informative HHF	0.80	0.769	0.067	0.570	1.043	0.737	0.103	0.220	1.235
	1.00	0.726	0.066	0.532	0.978	0.727	0.107	0.281	1.235
	1.25	0.678	0.059	0.488	0.883	0.720	0.124	0.312	2.589
Scenario 3: Non-informative HHF+CVD	0.80	0.794	0.059	0.623	0.981	1.104	2.666	0.001	66.606
	1.00	0.797	0.058	0.637	1.002	1.999	21.026	0.039	663.342
	1.25	0.799	0.055	0.628	0.984	1.930	10.360	0.014	319.777
Scenario 4: Informative HHF+CVD	0.80	0.794	0.058	0.599	1.004	1.295	4.654	0.003	109.483
	1.00	0.800	0.060	0.622	1.012	1.825	15.447	0.022	475.896
	1.25	0.806	0.057	0.627	0.981	3.969	75.013	0.043	2371.761

Simulation: estimand vs. estimate

RR_{HHF}=0.7, n=100.000 patients

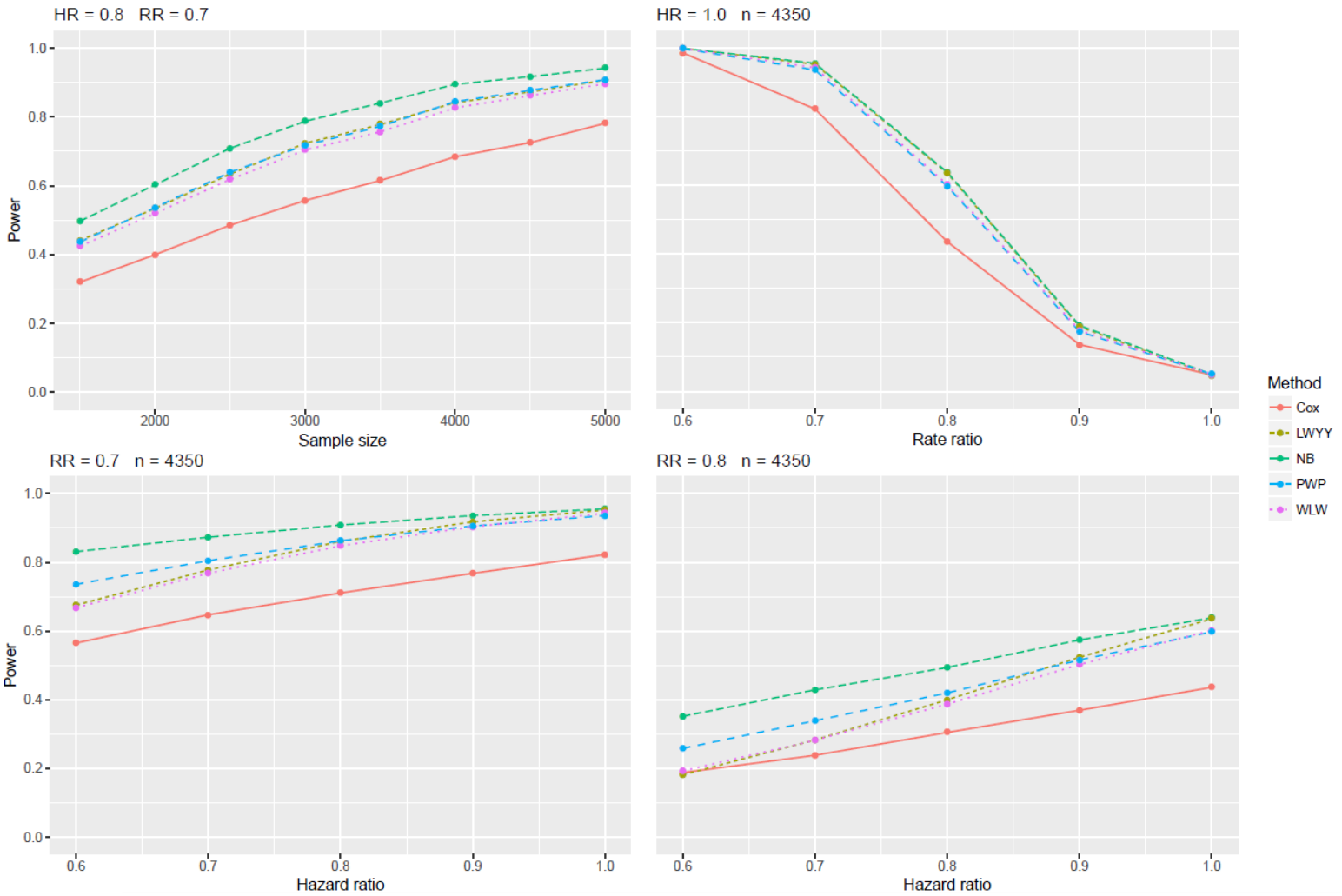
	Exposure-weighted rate based estimand*			Equal-weighted rate based estimand			Method	Estimates		
HR_{CV}	0.8	1.0	1.25	0.8	1.0	1.25		0.8	1.0	1.25
Scenario 1: Non-informative HHF	0.783	0.722	0.688	0.752	0.727	0.72	Cox	0.841	0.799	0.782
							NB	0.752	0.700	0.684
							LWYY	0.784	0.722	0.687
							WLW	0.789	0.731	0.702
							PWP	0.849	0.811	0.791
Scenario 2: Informative HHF	0.770	0.728	0.686	0.745	0.794	0.728	Cox	0.822	0.789	0.769
							NB	0.741	0.704	0.679
							LWYY	0.771	0.727	0.684
							WLW	0.774	0.731	0.692
							PWP	0.843	0.817	0.787
Scenario 3: Non-informative HHF+CVD	0.809	0.806	0.822	0.93	1.759	3.737	Cox	0.875	0.898	0.935
							NB	0.766	0.814	0.885
							LWYY	0.809	0.806	0.821
							WLW	0.817	0.818	0.839
							PWP	0.878	0.907	0.944
Scenario 4: Informative HHF+CVD	0.800	0.800	0.820	0.799	1.498	1.737	Cox	0.859	0.881	0.929
							NB	0.767	0.797	0.889
							LWYY	0.801	0.800	0.819
							WLW	0.807	0.806	0.831
							PWP	0.879	0.900	0.944

Type I error (1-sided)

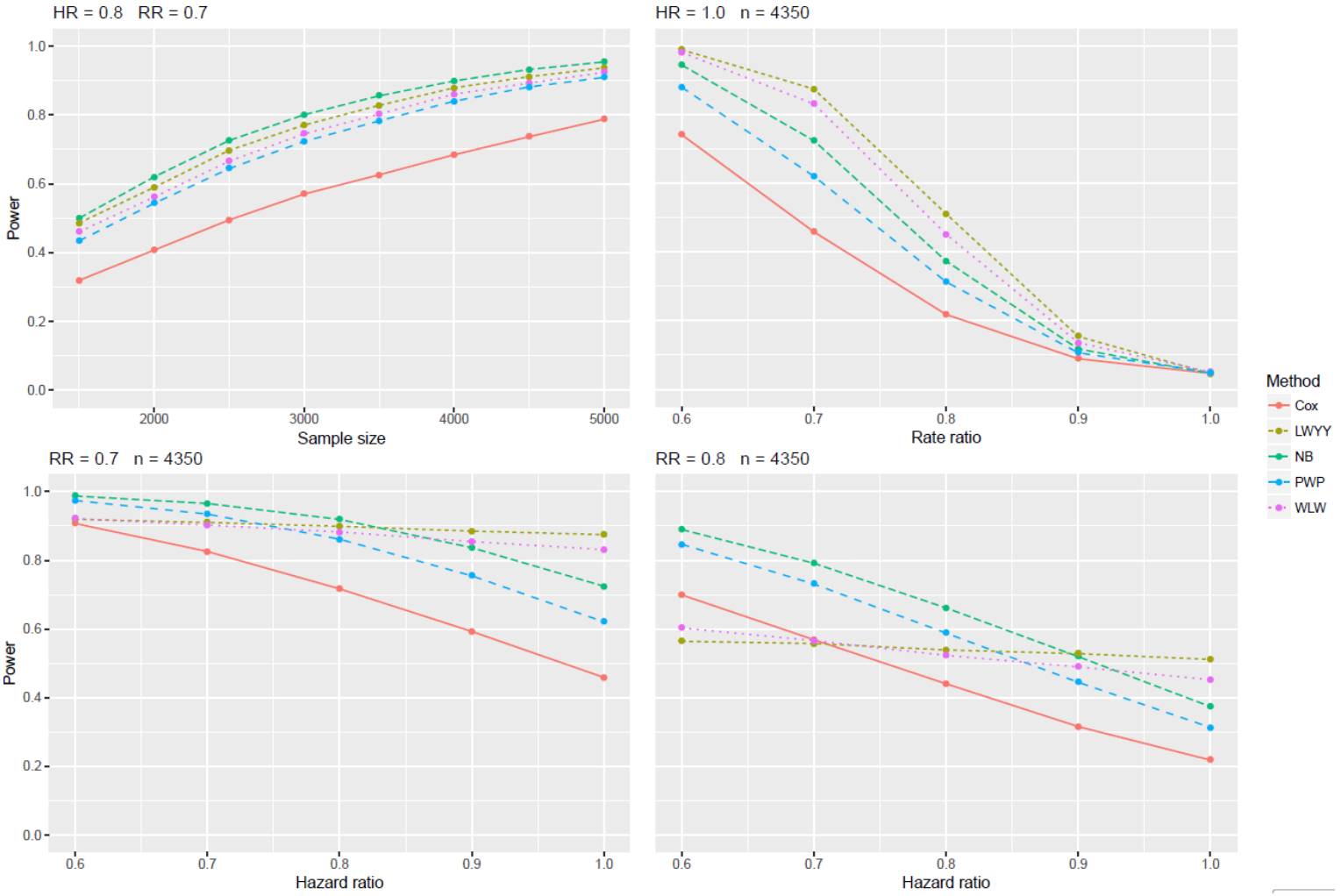
RR_{HHF}=1.0, n=4350 patients

Endpoint	HR_{CV}	Method	Estimate	Type I error
HHF	0.8	Cox	1.027	0.010
		NB	1.035	0.010
		LWYY	1.058	0.005
		WLW	1.048	0.006
		PWP	1.024	0.008
	1.0	Cox	1.002	0.023
		NB	1.002	0.025
		LWYY	1.002	0.023
		WLW	1.002	0.024
		PWP	1.001	0.025
	1.25	Cox	0.973	0.058
		NB	0.964	0.057
		LWYY	0.942	0.100
		WLW	0.951	0.088
		PWP	0.974	0.068
HHF+CVD	1.0	Cox	1.002	0.022
		NB	1.001	0.024
		LWYY	1.001	0.024
		WLW	1.001	0.025
		PWP	1.000	0.024

Power – HHF


HR = 0.8 RR = 0.7
HR = 1.0 n = 4350
RR = 0.7 n = 4350
RR = 0.8 n = 4350
Power
Sample size
Rate ratio
Hazard ratio
Method
Cox
LWYY
NB
PWP
WLW

Power – HHF+CVD



Event generating process (1)

With terminal event

$$\lambda^*_{CV} = \lambda_{CV}\ z_i^{\alpha}\ \exp(x_i\beta_{CV}),$$
$$\lambda^*_{HHF} = \lambda_{HHF}\ z_i\ \exp(x_i\beta_{HHF}),$$

- Frailties z_i gamma distributed with mean 1 and variance θ
- Control rates λ_{CV} and λ_{HHF} and frailty variance θ such that previous CHF trials are emulated
- Basecase:
  - Inter-event time are exponential
  - $\lambda_{CV} = 0.07032,\ \lambda_{HHF} = 0.15444, \theta = 5.7$
  - $\alpha = 0.75$ frailty correlation between two processes (Rogers et al., 2106)
- Treatment discontinuation:
  - Non-informative: rate of annual treatment discontinuation is 5 %
  - Informative: treatment only discontinued directy after HHF event with prob. 0%, 5%, … , 20%

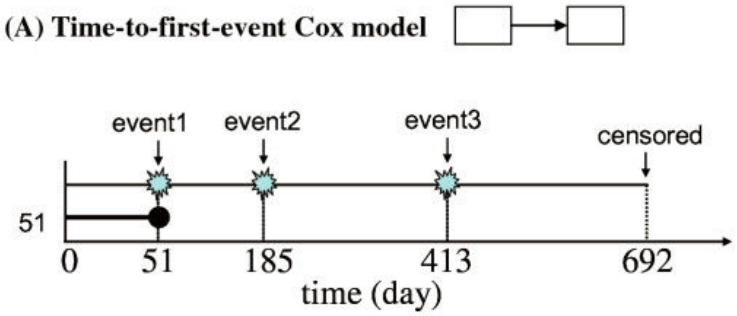
Event generating process (2)

With terminal event

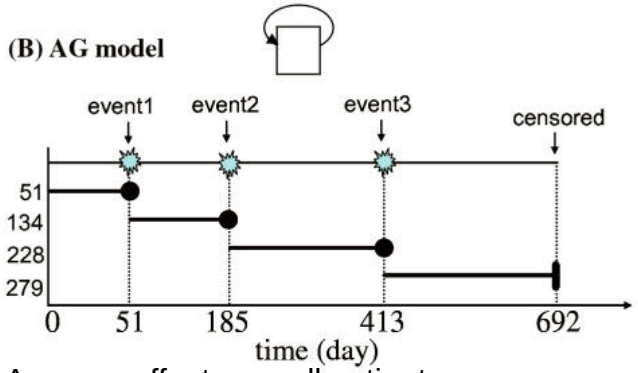
- Variations:
  - Weibull inter-event times (shape=0.75)
    - Increased hazard shortly after HHF
  - Autoregressive event rate: Rate of CVD and HHF multiplied by additional factor (1.1 and 1.2)
    - Deterioration in health after each HHF
  - Frailty correlation: $\alpha = 0.5$ and $\alpha = 1$
    - Lower (0.5) and higher (1) correlation between HHF and CVD
  - Detrimental CVD effect
    - Positive effect on HHF, but negative effect on CVD

Recurrent Events methods

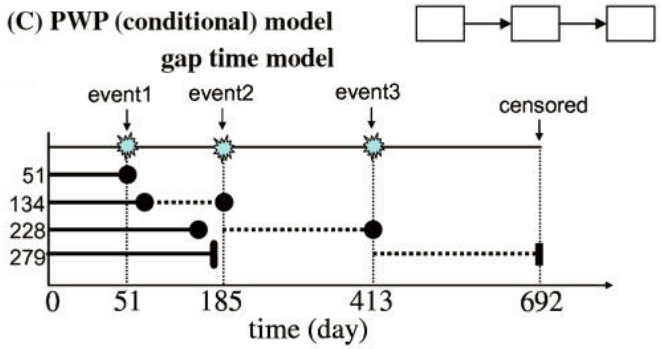
see e.g. Therneau & Grambsch, 2000 for details



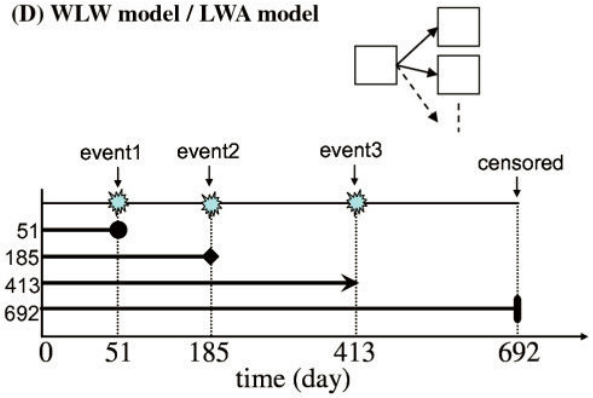
Only first event considered



Average effect over all patients
Hazards / HRs for all events are identical



Hazards / HRs for different events can differ
Randomization is not preserved for Event 2, 3,..



Hazards / HRs for different events can differ
Randomization is preserved for all events

(E) Negative Binomial

- Individual Poisson rates that follow Gamma distribution
- Total number of events / total follow-up time in each group
- Information on timing of events not used

Mean estimated treatment effects

Without terminal event (RRMS)

	Method	Estimate
Estimand 1 (Treatment-policy)	Cox	0.694
	NB	0.682
	LWYY	0.684
	WLW	0.611
	PWP	0.707
Estimand 2 (Hypothetical)	Cox	0.665
	NB	0.647
	LWYY	0.647
	WLW	0.576
	PWP	0.671

`Estimate' values are calculated based on simulation with "*true*" treatment effect HR = 0.65

Mean estimated treatment effects

Without terminal event (RRMS)

	Estimand value	Method	Estimate
Estimand 1 (Treatment-policy)	0.685	Cox	0.694
		NB	0.682
		LWYY	0.684
		WLW	0.611
		PWP	0.707
Estimand 2 (Hypothetical)	0.65	Cox	0.665
		NB	0.647
		LWYY	0.647
		WLW	0.576
		PWP	0.671

`Estimate' values are calculated based on simulation with "*true*" treatment effect HR = 0.65

Mean estimated treatment effects

Without terminal event (RRMS)

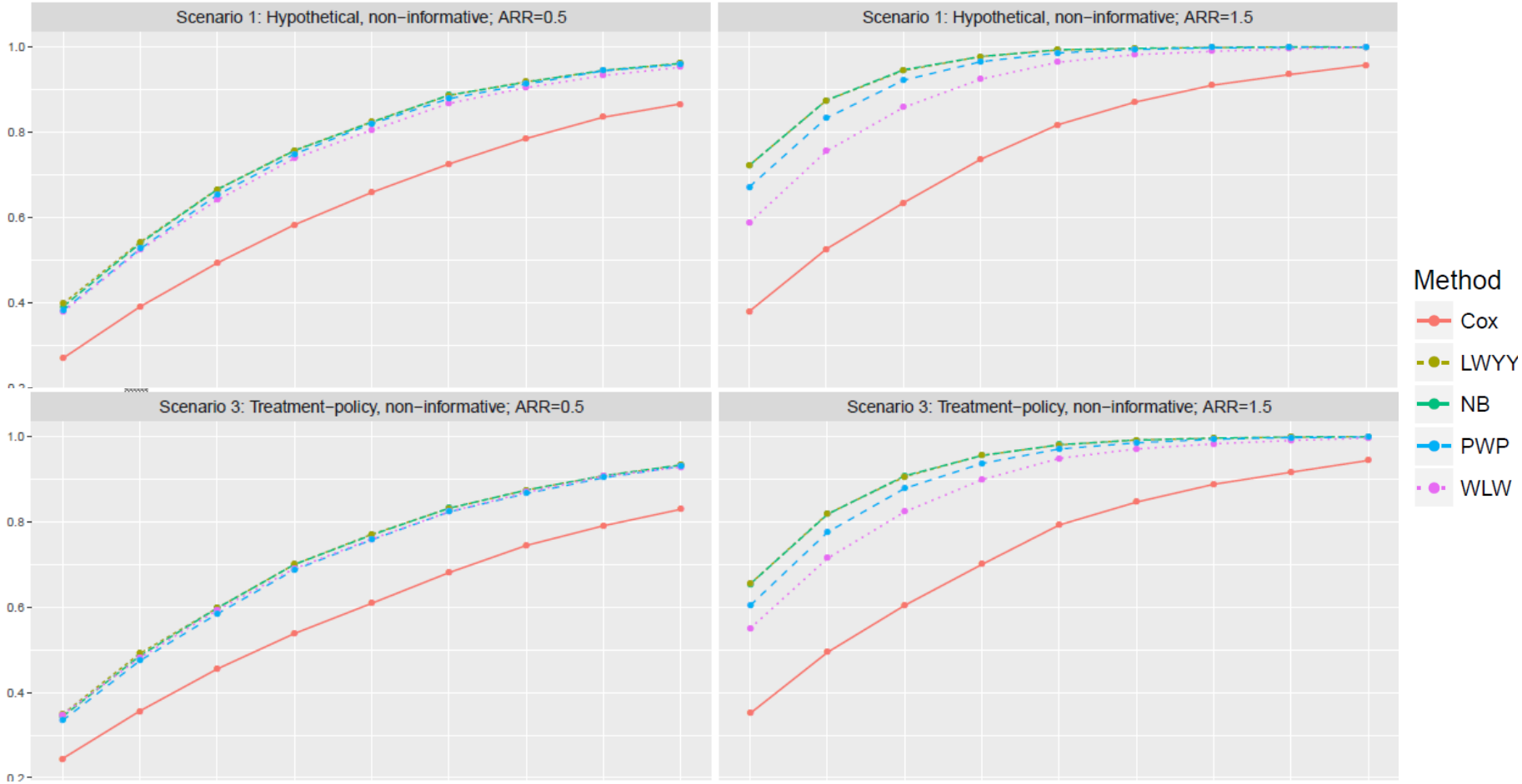
	Estimand value	Method	Estimate	Estimate/Estimand
Estimand 1 (Treatment-policy)	0.685	Cox	0.694	1.013
		NB	0.682	0.996
		LWYY	0.684	0.999
		WLW	0.611	0.892
		PWP	0.707	1.032
Estimand 2 (Hypothetical)	0.65	Cox	0.665	1.023
		NB	0.647	0.995
		LWYY	0.647	0.995
		WLW	0.576	0.886
		PWP	0.671	1.032

- NB and LWYY give consistent mean effects for both estimands
- Cox, WLW and PWP models are not appropriate since their target values are different from the estimand values

*WLW: Wei-Lin-Weissfeld model; PWP: Prentice-Williams-Peterson model

Power comparison

Without terminal event (RRMS)



Acceptance of recurrent event endpoint by regulators

- Commonly used in areas where mortality is relatively low (e.g., Multiple Sclerosis)
- EMA (1999, 2017) guidance for chronic HF acknowledges recurrent HFH as potentially acceptable primary endpoint in some circumstances highlighting the importance of terminal events for analysis and interpretation
- ESC CV Round Table: "... particularly suitable for diseases where reductions in repeat hospitalizations are of interest (e.g. HF with preserved ejection fraction or acute decompensated HF)."
- FDA precedence: In the HF area recurrent HFH has been used as primary endpoint for pivotal/late stage trials of devices (CHAMPION), gene therapies (CUPID-2) and more recently drugs (PARAGON)