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DEPARTMENT OF STATISTICS

The Analysis of Recurrent Events: A Summary of Methodology

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13th September 2016

Outline

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Outline

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Composite endpoints
What are composite endpoints?

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Standard approach in many cardiovascular trials

- Include two or more types of related clinical events
- Increase event rate and avoid multiplicity
- Analysis focussed on time to first event

- Examples in cardiovascular trials:
  - CV death, MI and stroke in hypertension trials
  - CV death and HF hospitalisation in heart failure trials

EMPHASIS-HF

Zanad F *et al*, NEJM 2011;364:11-21

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- Eplerenone vs. placebo in 2737 patients with mild HF
- NYHA class II
- Ejection fraction $\leq$35%
- Tested hypothesis that eplerenone would reduce the risk of death and the risk of hospitalisation

- Primary outcome: composite of death from cardiovascular disease or hospitalisation for heart failure
- Analysed as time to first event using Cox proportional-hazards model

Cox proportional-hazards model
Background

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- Most commonly used regression model in survival analysis
- Hazard function: describes conditional probability of an event occurring at time t, given that the event has not yet occurred
  - Instantaneous risk/intensity
  - $h(t) = \lim_{dt \to 0} \left\{ \frac{P(t \leq T < t+dt | T \geq t}{dt} \right\}$
- Models based on the hazard function can assess whether covariates have an effect on the hazard

Cox proportional-hazards model
Analysis strategy

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In heart failure, analysis of composite endpoints proceeds in a standard manner:

Cox proportional-hazards model
Analysis strategy

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In heart failure, analysis of composite endpoints proceeds in a standard manner:

- Exploratory analysis using Kaplan-Meier
  - $t_{(1)} < t_{(2)} < t_{(3)} < \ldots$: ordered event times
  - m_j: number at risk just before time $t_{(j)}$
  - d_j: number with event at time $t_{(j)}$
  - $\hat{S}(t) = \prod_{j=1}^{k} \left(\frac{m_j - d_j}{m_j} \right)$, $t_{(k)} \leq t < t_{(k+1)}$

Cox proportional-hazards model
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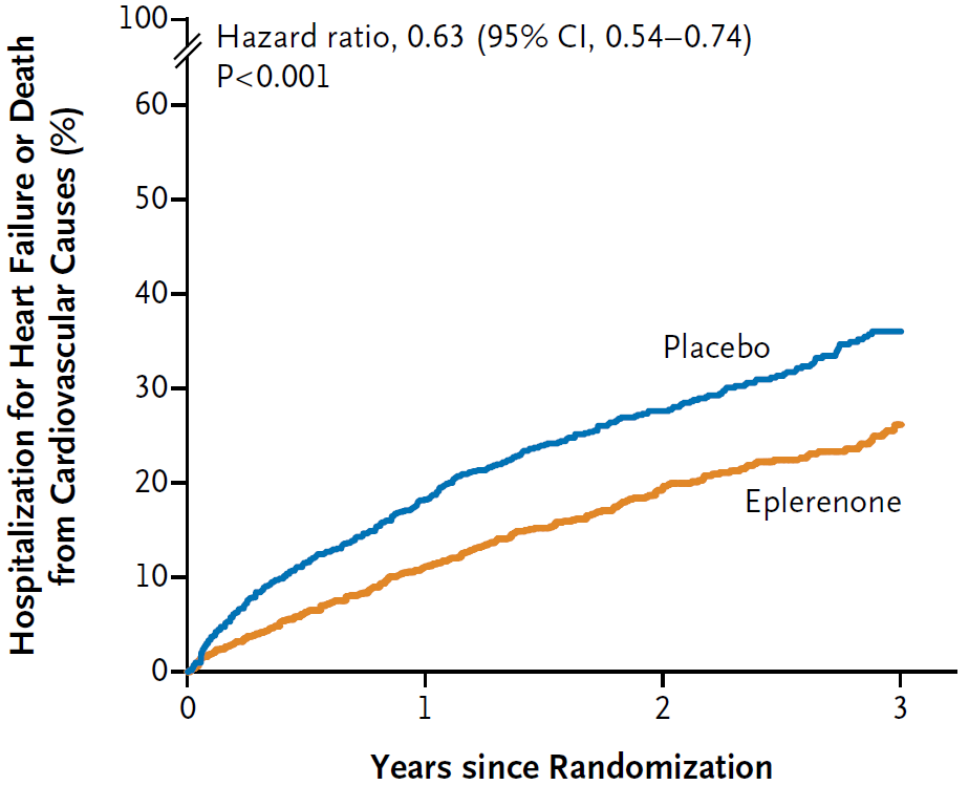
  - $\hat{S}(t) = \prod_{j=1}^{k} \left(\frac{m_j - d_j}{m_j} \right)$, $t_{(k)} \leq t < t_{(k+1)}$
- Estimation using Cox proportional-hazards model
  - $h_i(t) = \exp\{\beta z_i\} h_0(t)$

EMPHASIS-HF

Zanad F *et al*, NEJM 2011;364:11-21



No. at Risk				
Placebo	1373	848	512	199
Eplerenone	1364	925	562	232

CHARM-Preserved

Yusuf S *et al*,The Lancet 2003;362:777-781

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- CHARM: three parallel, independent trials
- Candesartan vs. placebo in 3021 patients with symptomatic heart failure
- CHARM-Preserved: preserved ejection fraction $\geq$ 40%

- Primary outcomes
  - Overall programme: all-cause mortality
  - Component trials: composite of death from cardiovascular disease or hospitalisation for heart failure
- Analysed as time to first event using Cox proportional-hazards model

CHARM-Preserved

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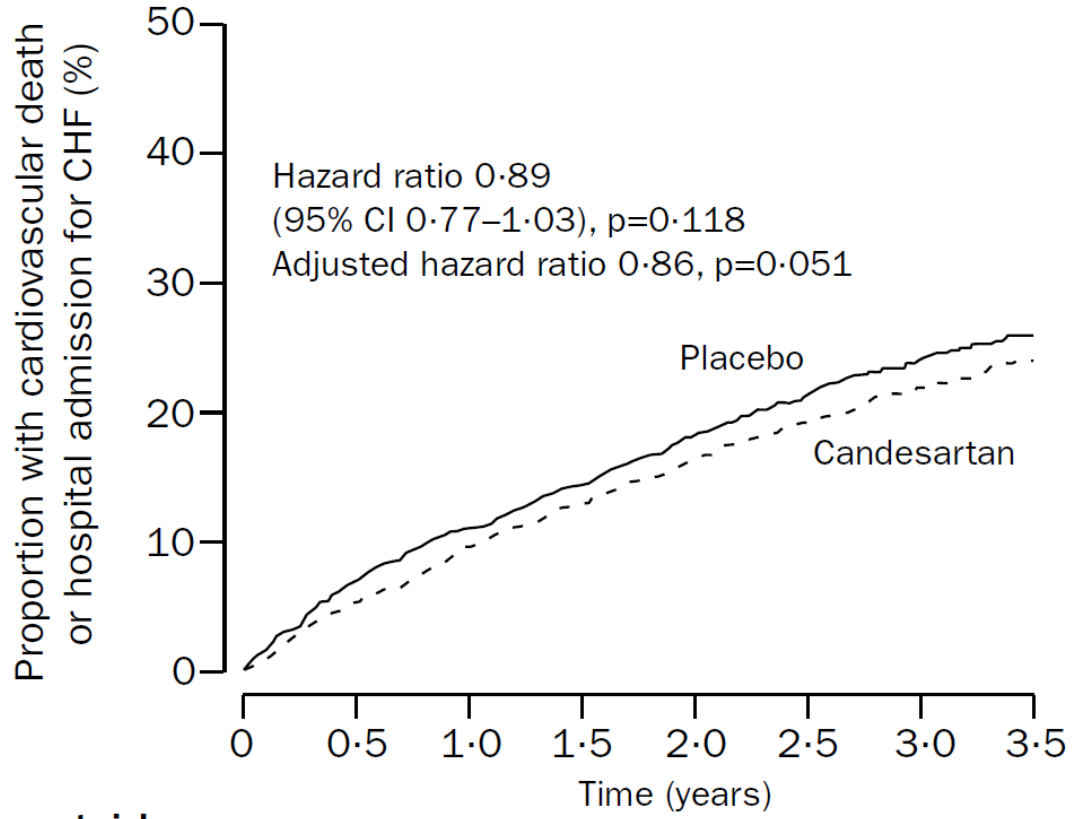

Number at risk

Candesartan	1514	1458	1377	833	182
Placebo	1509	1441	1359	824	195

Problems
What is wrong with composite endpoints?

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Only first occurring endpoint is analysed

Furthermore...

- HF not characterised by a single event
- Chronic diseases characterised by recurrent events
- Repeat, non fatal events ignored

EMPHASIS-HF

Median follow-up: 25 months

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HF Hospitalisations	Eplerenone (N=1364)	Placebo (N=1373)
$\geq$ 1 admissions	186	277
$\geq$ 2 admissions	67	110
All admissions	312	481
'Unused' admissions	126	204

CHARM-Preserved

Median follow-up: 37 months

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HF Hospitalisations	Candesartan (N=1513)	Placebo (N=1508)
$\geq$ 1 admissions	230	278
$\geq$ 2 admissions	95	114
All admissions	392	547
'Unused' admissions	162	269

Outline

Recurrent events
What are recurrent events?

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Recurrent events involve repeat occurrences of the same type of event over time

Recurrent events
What are recurrent events?

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Recurrent events involve repeat occurrences of the same type of event over time

Examples include:

- Heart failure hospitalisations in CV studies
- Exacerbations in COPD trials
- Seizures in epilepsy trails
- Asthma attacks in asthma trials

Patient profiles

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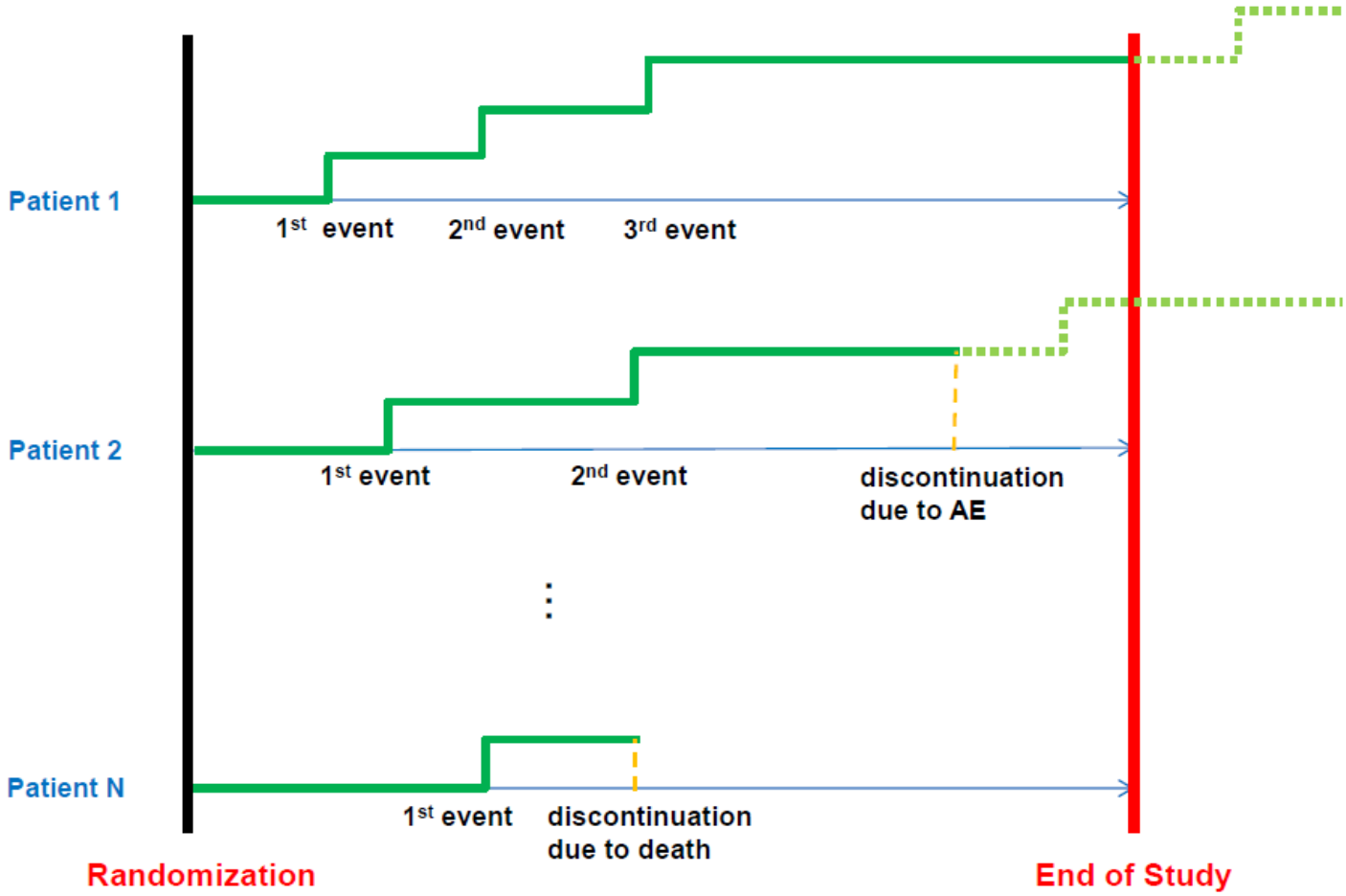

Focus of this tutorial

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- We will consider indications where recurrent events are clinically meaningful
  - Treatment expected to impact first event
  - Treatment also expected to impact subsequent events
- Limit to case where censoring is non-informative
- We shall be focussing more on analysis methods, rather than design aspects

- Events are instantaneous, i.e. they have no duration
- Events do not affect trial conduct, e.g. no treatment switching after an event

EMPHASIS-HF
Patient profiles

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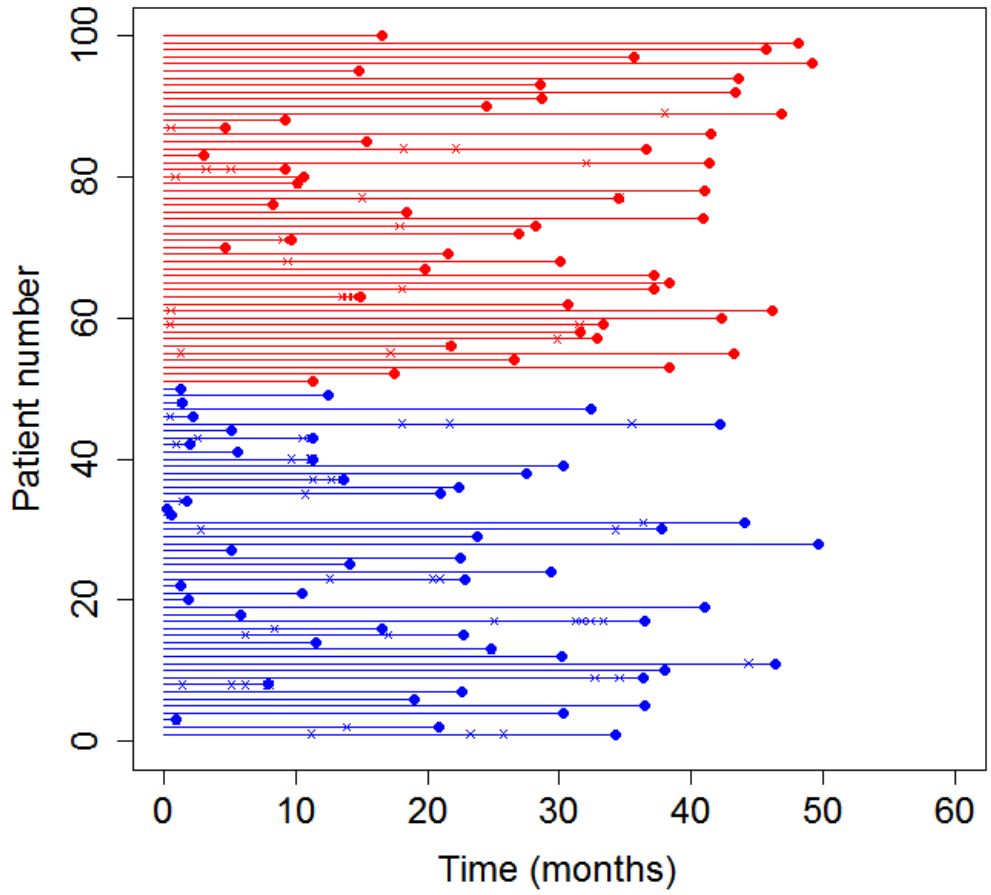

EMPHASIS-HF

Hospitalisation counts

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	Eplerenone (N=1364)	Placebo (N=1373)
Follow-up years	2916.07	2830.91
Deaths	205	253
CV deaths	178	215
HF Hospitalisations:		
1	119	167
2	41	60
3	13	24
4	6	12
5	2	10
6	1	4
7	2	0
8	1	0
10	1	0
All admissions	312	481

CHARM-Preserved

Patient profiles

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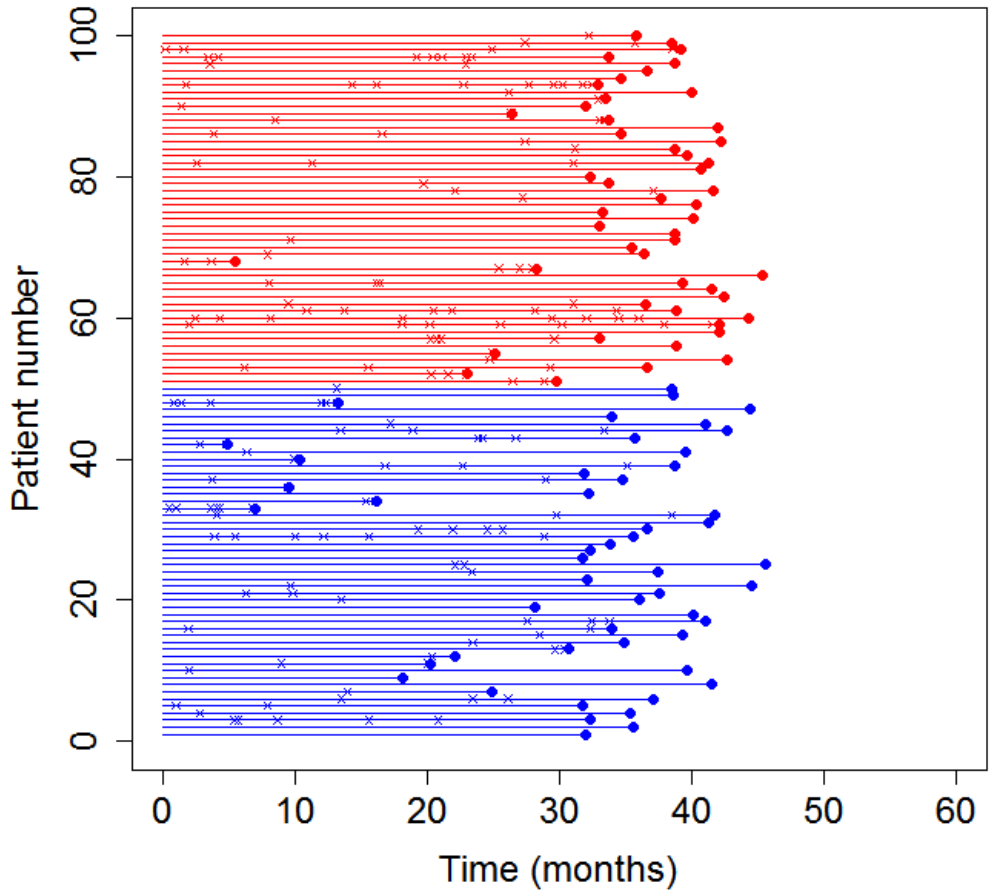

CHARM-Preserved
Hospitalisation counts

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	Candesartan (N=1514)	Placebo (N=1509)
Follow-up years	4424.62	4374.03
Deaths	244	237
CV deaths	170	170
HF Hospitalisations:		
1	135	164
2	56	55
3	23	25
4	9	13
5	4	9
6	1	4
7	2	2
8	0	2
$\geq$9	0	4
All admissions	392	547

Similarities
Heart failure clinical trials

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- Repeated hospitalisations are an indicator for worsening condition
- Relatively long follow-up
- Staggered study entry
- No fixed follow-up time (fixed date)

Outline

Scientific questions
What are we interested in?

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- Does the intervention decrease the event number over the study period compared to control?

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- How many events does the intervention prevent, on average, compared to control?

Scientific questions
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- Does the intervention decrease the event number over the study period compared to control?
- How many events does the intervention prevent, on average, compared to control?
- What is the intervention effect on the number of higher-order events, e.g. 3rd event, compared to control?

Scientific questions
What are we interested in?

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- Does the intervention decrease the event number over the study period compared to control?
- How many events does the intervention prevent, on average, compared to control?
- What is the intervention effect on the number of higher-order events, e.g. 3rd event, compared to control?
- What is the effect of intervention on the number of subsequent events among those who experienced a preceding event?

Measure of intervention effect

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Need to decide which aspect of the recurrent event data process is of interest

1. Cumulative number of events over a specified time period
    - Number of events by end of study events
2. Rate of events
    - Number of events per unit time
3. Time to event
    - Times to successive events
4. Gap times between successive events
    - Times between successive events

Measure of intervention effect

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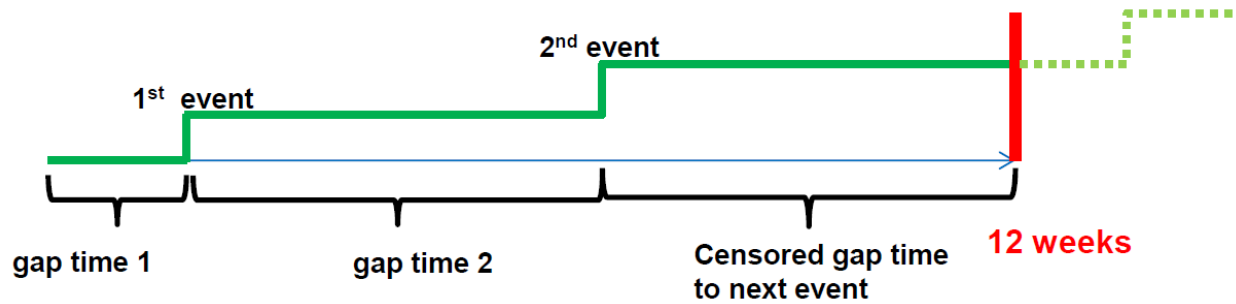
1. Cumulative number of events over a specified time period
   - Number of events by end of study: 2 events



Measure of intervention effect

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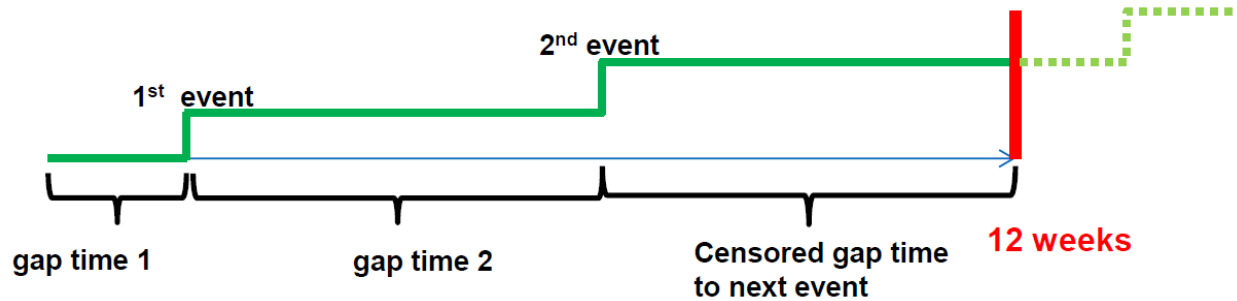
2. Rate of events

- Number of events per unit time: assuming constant rate leads to 1/6 events per week



Measure of intervention effect

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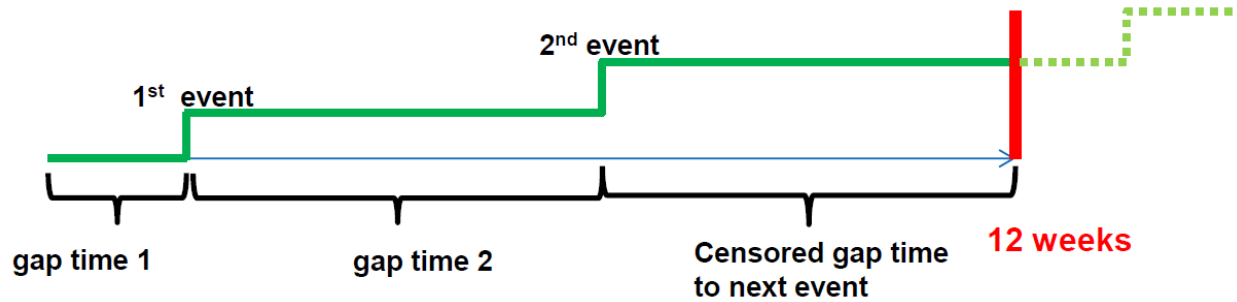
3. Time to event
   - Times to successive events: time to 1st and 2nd event, time to 3rd event censored at 12 weeks



Measure of intervention effect

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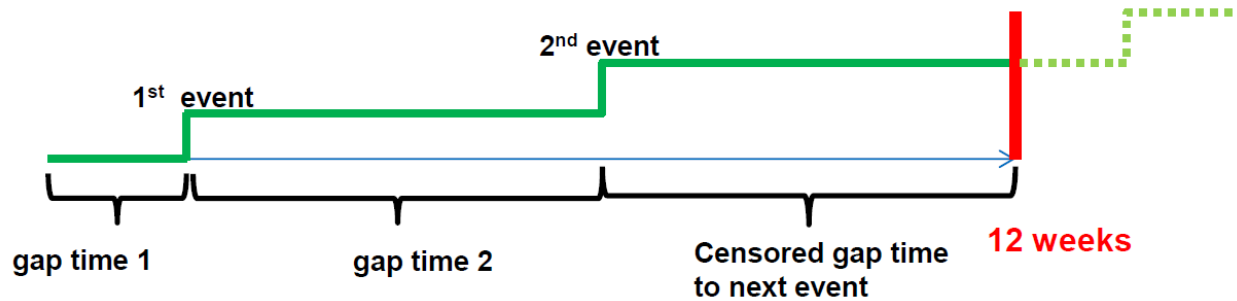
4. Gap times between successive events
   - Times between successive events: gap times 1 & 2 and third gap time censored at 12 weeks



Recurrent event analysis
Comparison with time-to-event

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- Time-to-event endpoints
  - Statistical approaches well established
  - Gold standard in many indications
  - Substantial experience in regulatory assessment

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- Recurrent event endpoints
  - Statistical approaches more complex
  - Less regulatory experience
  - Good experience in some indications do exist (e.g. MS and asthma)

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Comparison with time-to-event

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- Recurrent event endpoints
  - Statistical approaches more complex
  - Less regulatory experience
  - Good experience in some indications do exist (e.g. MS and asthma)
  - More efficient as information beyond the first event is used

Outline

Recurrent Events
Existing Methodology

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- Non-parametric estimator for mean cumulative function
- Time-to-event approaches
- Methods based on event rates

Recurrent Events
Existing Methodology

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- Non-parametric estimator for mean cumulative function
- Time-to-event approaches
  - WLW: cumulative time from randomisation to events
  - PWP: analyses gap times, conditional risk sets
  - Andersen-Gill: extension of Cox proportional-hazards model
- Methods based on event rates

Recurrent Events
Existing Methodology

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- Methods based on event rates
  - Poisson: total events divided by follow-up
  - Negative Binomial: individual Poisson rates which vary according to Gamma

Mean Cumulative Function
Notation and derivation

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- $N(t)$: Counting process, i.e. number of events a subject has experienced by time t
- Arbitrary MCF: $\mu(t) = \mathbb{E}\{N(t)\}$

How do we estimate $\mu(t) = \mathbb{E}\{N(t)\}$?

Mean Cumulative Function
Notation and derivation

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- $dN(t)$: jump of N over a small time interval $[t, t + dt)$

Mean Cumulative Function
Notation and derivation

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- $dN(t)$: jump of N over a small time interval $[t, t + dt)$
- $Y_i(t)$: indicator for subject i being at risk over $[t, t + dt)$

Mean Cumulative Function

Notation and derivation

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- $dN(t)$: jump of N over a small time interval $[t, t + dt)$
- $Y_i(t)$: indicator for subject i being at risk over $[t, t + dt)$
- $Y_\Sigma(t) = \sum_{i=1}^{n} Y_i(t)$: total number at risk over $[t, t + dt)$, where n is number of randomised subjects

Mean Cumulative Function

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- $dN_\Sigma(t) = \sum_{i=1}^{n} Y_i(t) dN_i(t)$: total number of events observed over $[t, t + dt)$

Mean Cumulative Function

Notation and derivation

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- $dN_\Sigma(t) = \sum_{i=1}^{n} Y_i(t)dN_i(t)$: total number of events observed over $[t, t + dt)$
- $t_{(1)}, t_{(2)}, \ldots, t_{(H)}$: H distinct event times across all n patients

Mean Cumulative Function
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Nelson-Aalen estimator for the MCF is given by:

$$\hat{\mu}(t) = \sum_{\{h | t_{(h)} \leq t\}} \frac{dN_\Sigma(t_{(h)})}{Y_\Sigma(t_{(h)})}$$

EMPHASIS-HF
Mean cumulative function

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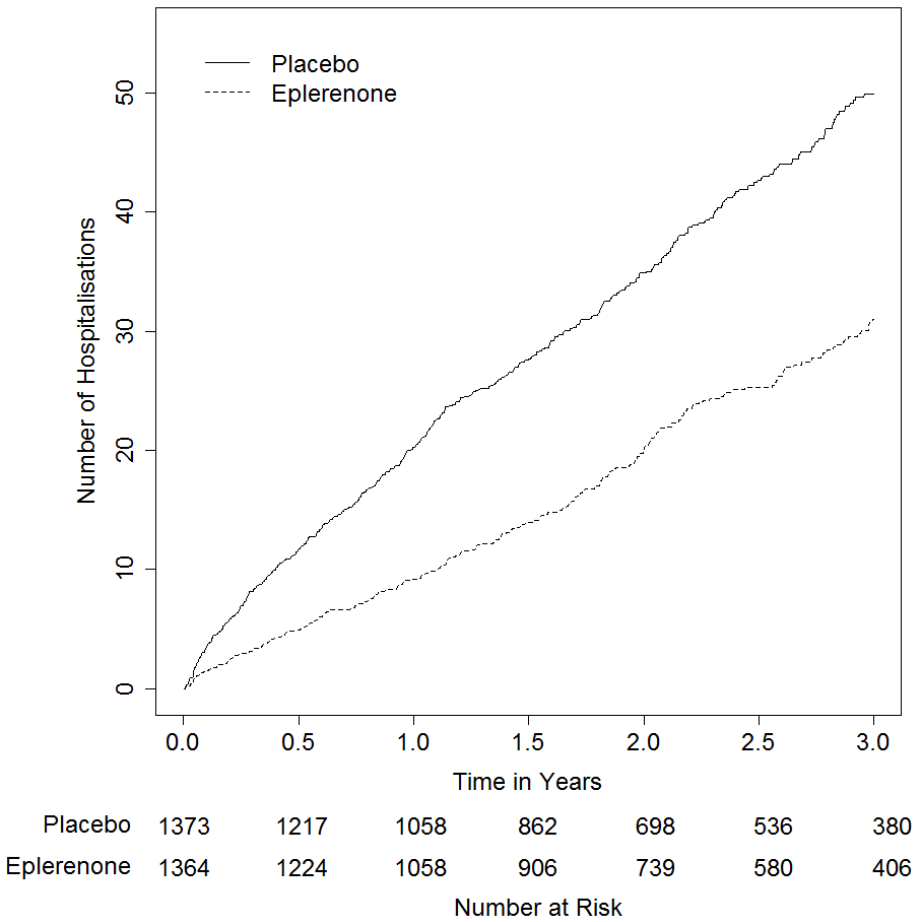
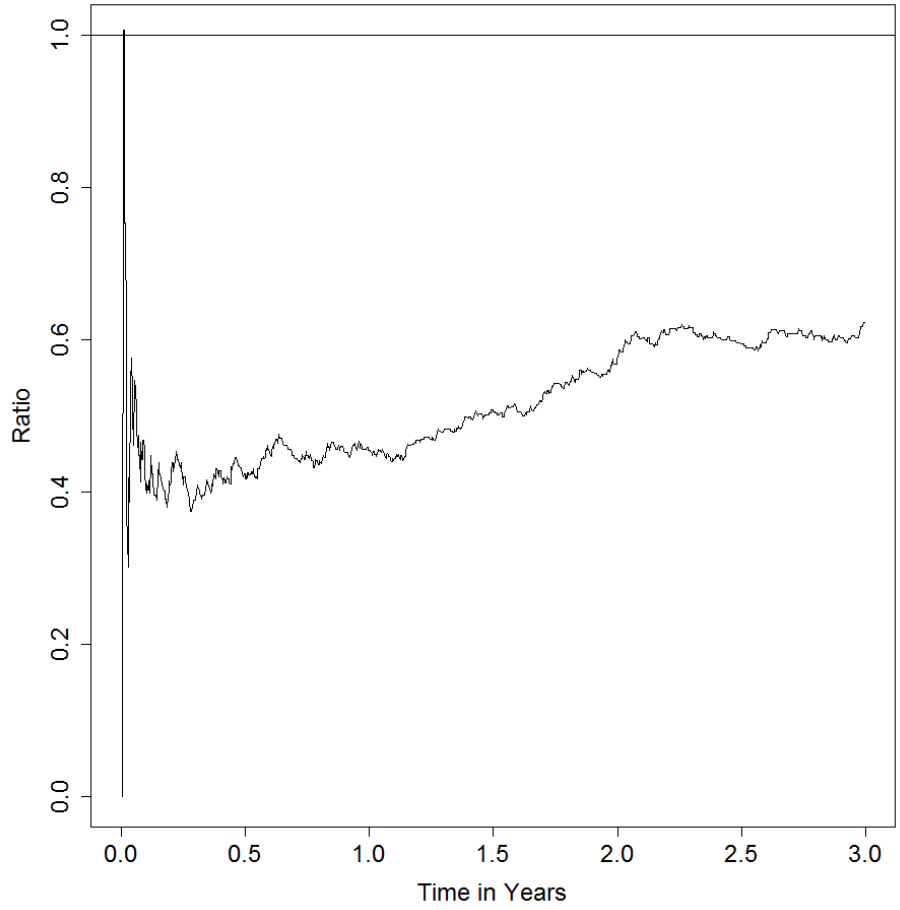


EMPHASIS-HF

Mean cumulative function



EMPHASIS-HF
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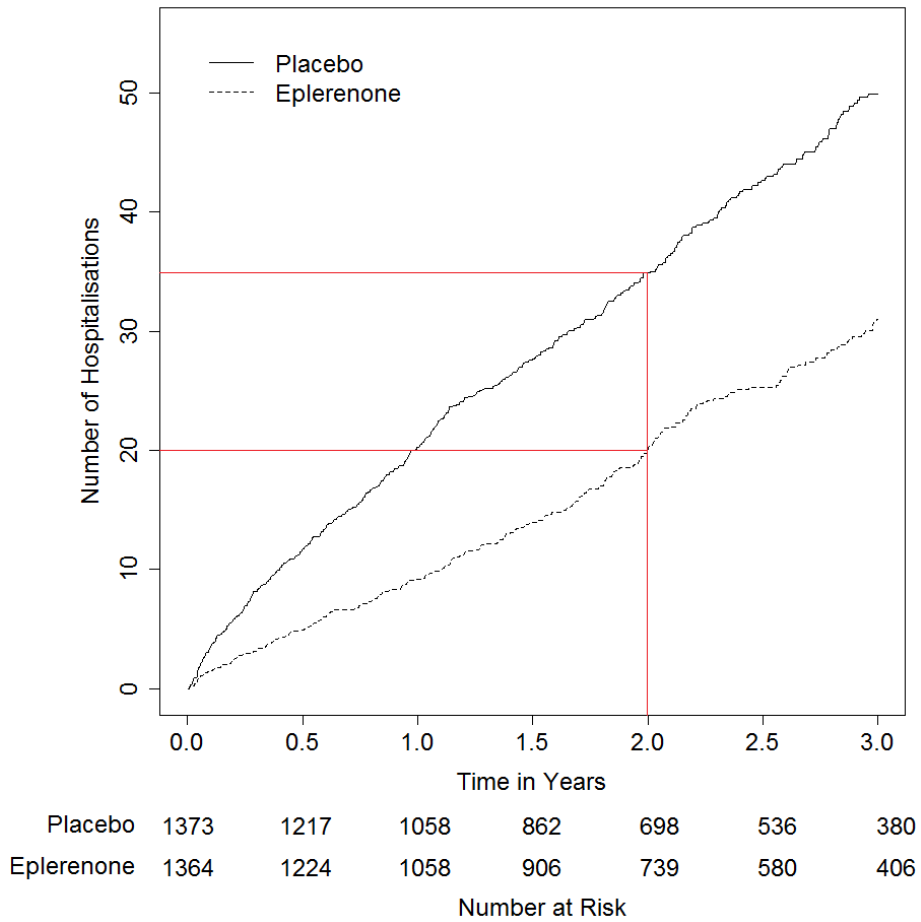
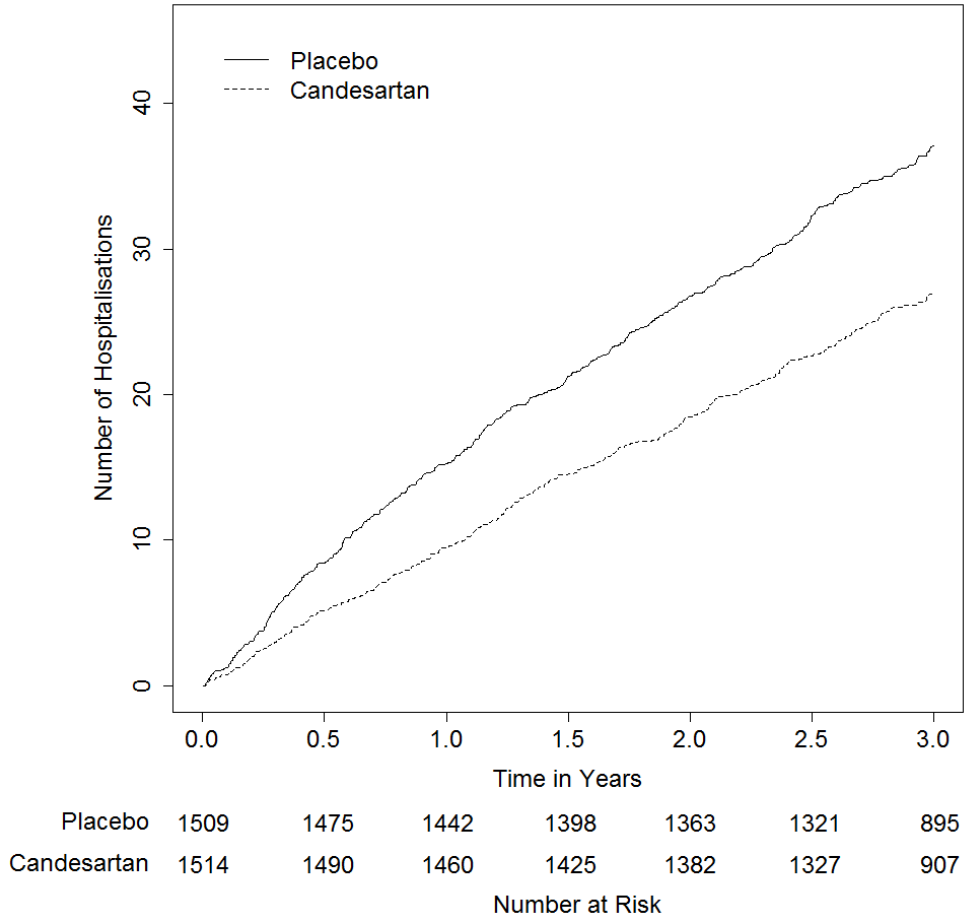


CHARM-Preserved
Mean cumulative function



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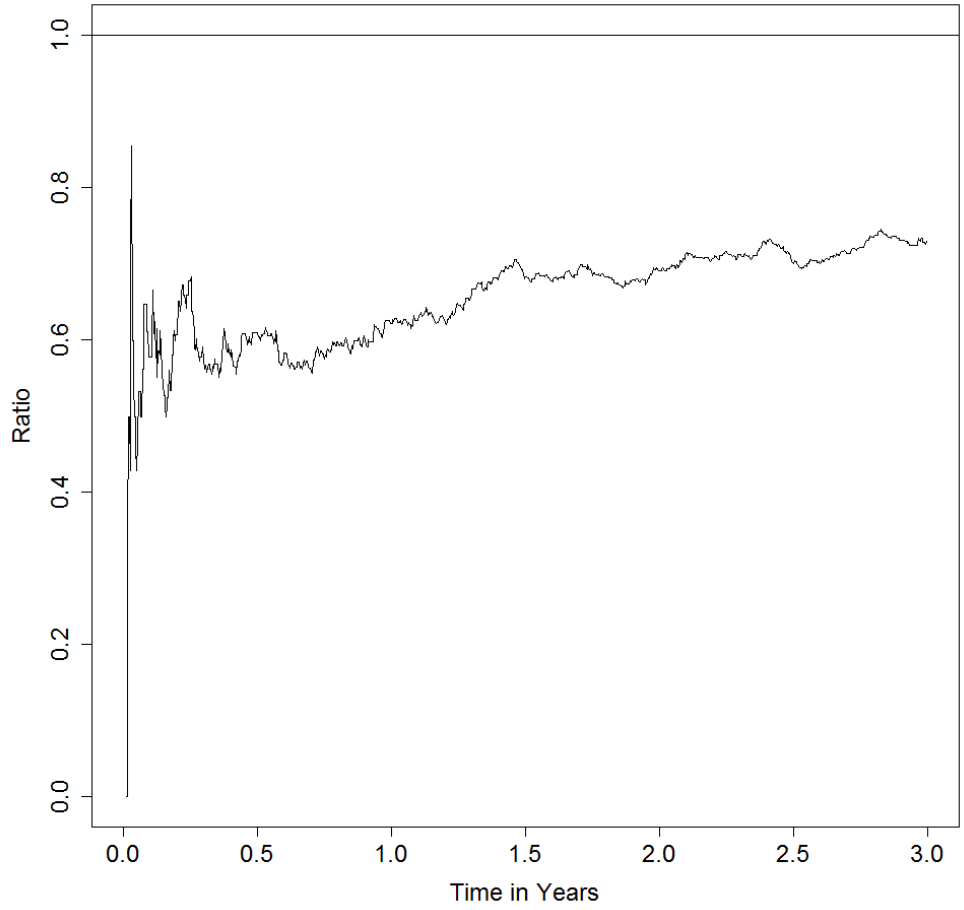

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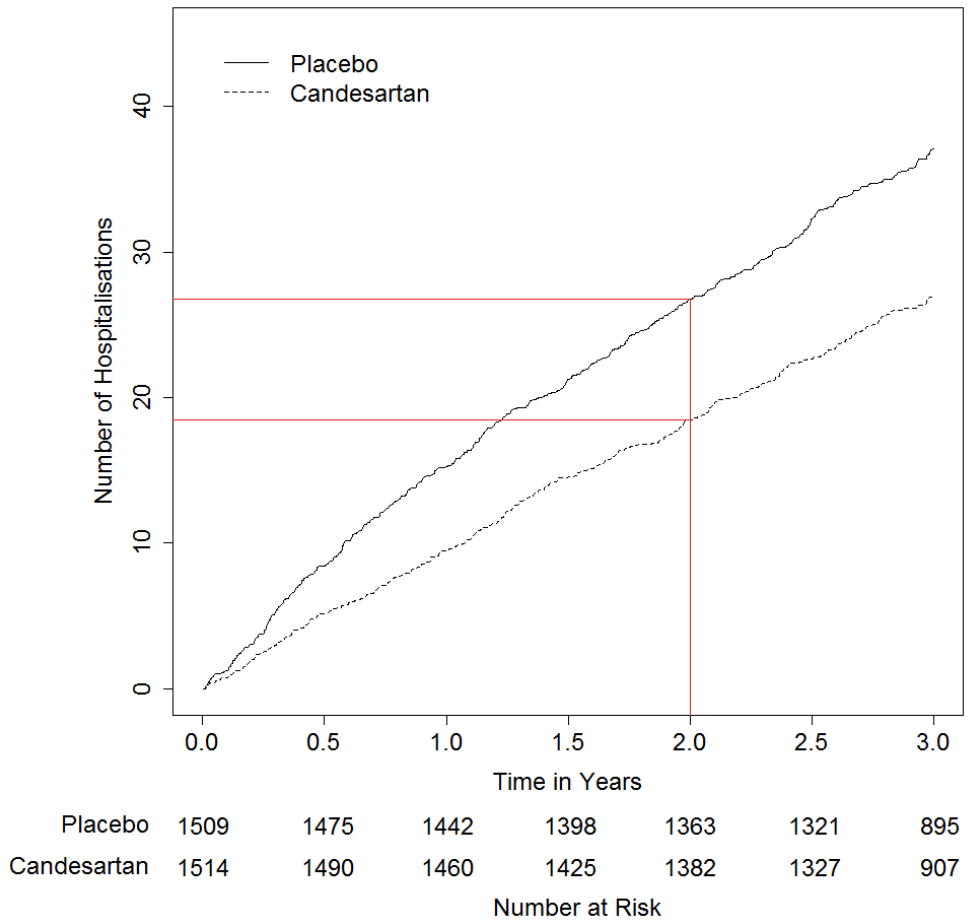

WLW (Wei-Lin-Weissfeld)
Analysis method

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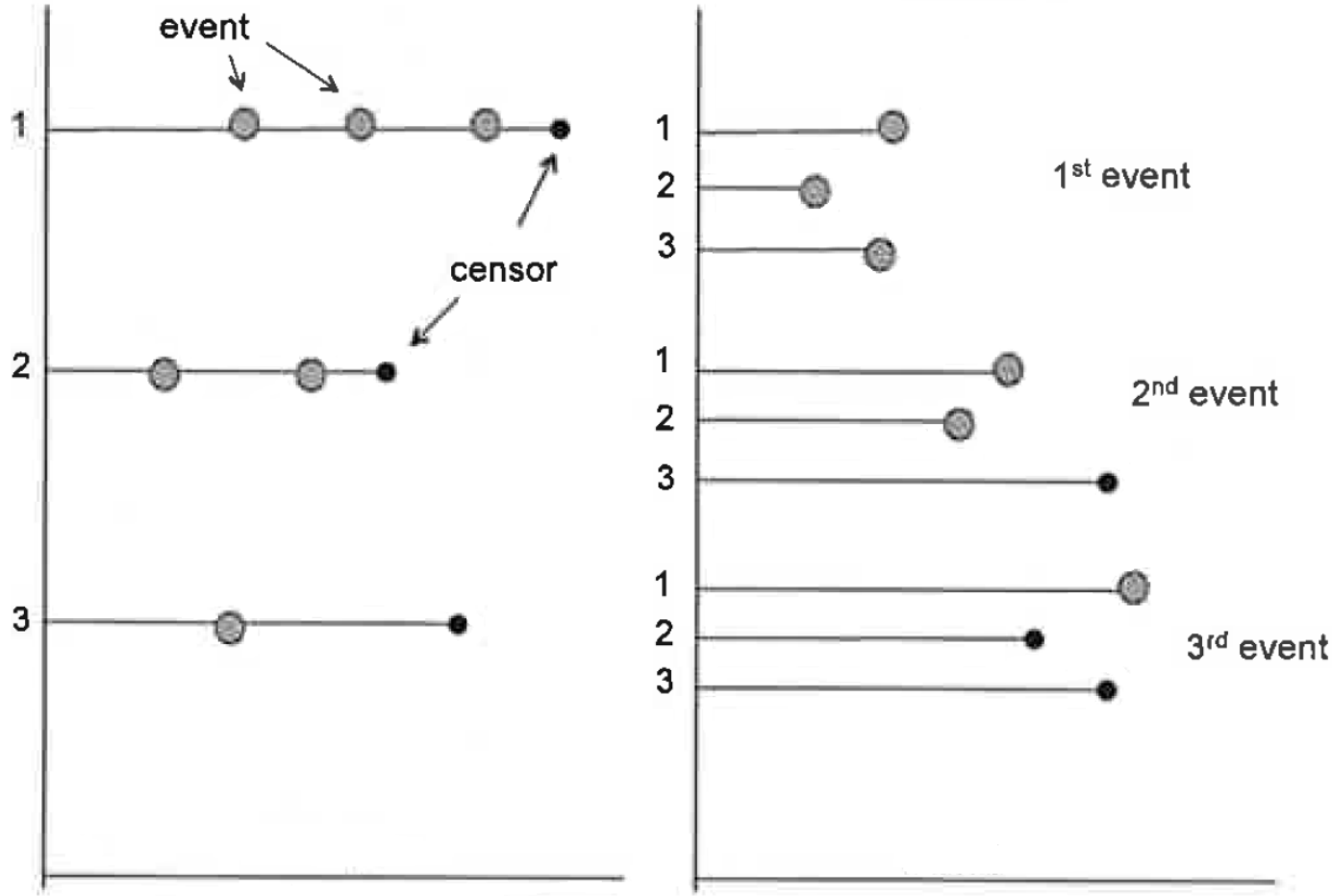
- Interested in first K events
- Analyse each time ordered event using a Cox proportional-hazards model
- Estimate test statistic or hazard ratio for each time ordered event
- Combine K estimates using optimal weights or 1/variance

WLW (Wei-Lin-Weissfeld)
Patient profiles



EMPHASIS-HF
Application

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	HR	95% CI	*p*-value
1st HFH	0.63	(0.53,0.76)	< 0.001
2nd HFH	0.58	(0.43,0.79)	< 0.001
3rd HFH	0.50	(0.31,0.80)	0.004

EMPHASIS-HF
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2nd HFH	0.58	(0.43,0.79)	< 0.001
3rd HFH	0.50	(0.31,0.80)	0.004

- 463 had at least 1 HFH
- 177 had at least 2 HFH
- 76 had at least 3 HFH

EMPHASIS-HF

Hospitalisation counts

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10	1	0
All admissions	312	481

CHARM-Preserved
Application

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	HR	95% CI	*p*-value
1st HFH	0.80	(0.68,0.96)	0.015
2nd HFH	0.82	(0.62,1.07)	0.146
3rd HFH	0.65	(0.43,0.97)	0.036

WLW (Wei-Lin-Weissfeld)
Properties

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- Preserves randomisation
- Analyses cumulative effect of treatment on hospitalisations from randomisation
  - Effect on second includes effect on first
  - Difficult to interpret global treatment effects
- Semi-parametric approach: no assumption on baseline hazard needed
- Can't analyse all hospitalisations due to small numbers for higher order events
- Need to specify K in advance
- Subjects considered to be at risk for event k, even if they haven't experienced event $k-1$

PWP (Prentice-Williams-Peterson)
Analysis method

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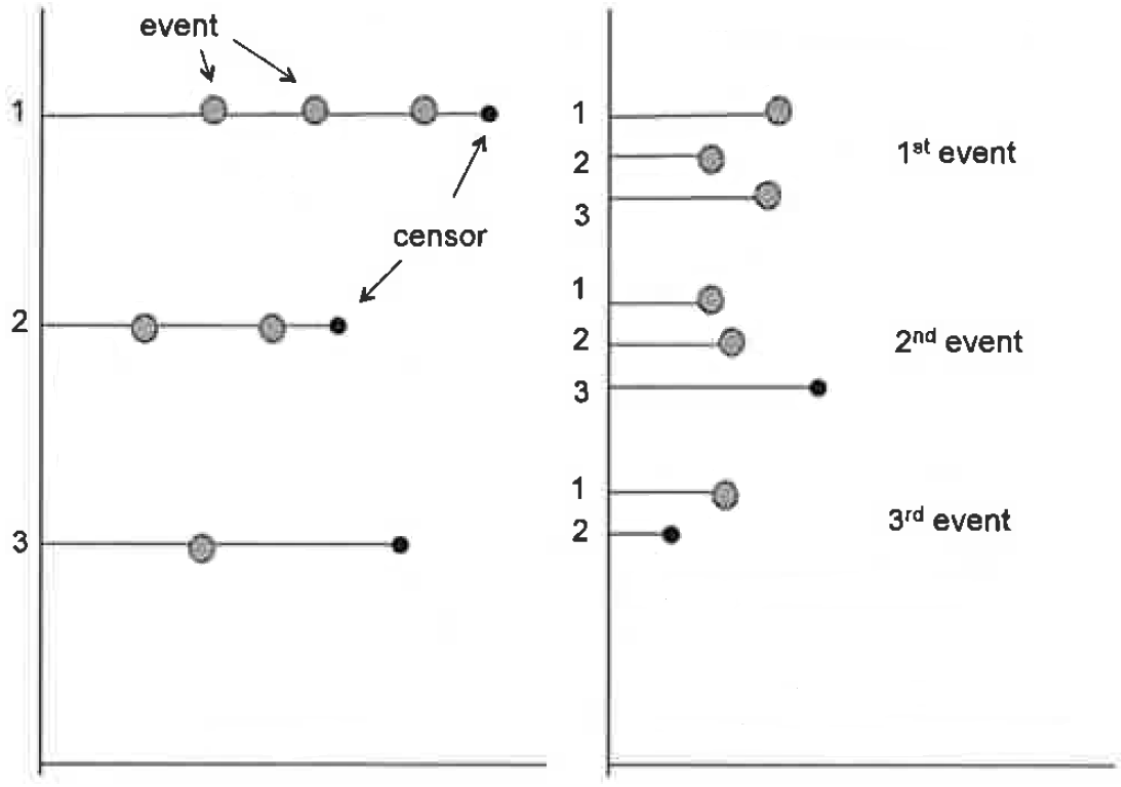
- Analyses gap times between different failures
- Subject not at risk of second event until they've had a first
  - Conditional risk set for event k made up of all subjects who have had event $k-1$
- Analyse each time ordered event using a Cox proportional-hazards model
- Estimate test statistic or hazard ratio for each time ordered event
- Combine K estimates using optimal weights or 1/variance

PWP (Prentice-Williams-Peterson)
Patient profiles



CHARM-Preserved
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	HR	95% CI	*p*-value
1st HFH	0.80	(0.68,0.96)	0.015
2nd HFH	0.99	(0.76,1.30)	0.959
3rd HFH	0.68	(0.46,1.02)	0.066

CHARM-Preserved
Application

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	HR	95% CI	*p*-value
1st HFH	0.80	(0.68,0.96)	0.015
2nd HFH	0.99	(0.76,1.30)	0.959
3rd HFH	0.68	(0.46,1.02)	0.066

- 508 had at least 1 HFH
- 209 had at least 2 HFH
- 98 had at least 3 HFH

PWP (Prentice-Williams-Peterson)
Properties

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- Semi-parametric approach: no assumption on baseline hazard needed
- Conditional risk sets better reflect true disease progression
- Doesn't assume common baseline hazard for each gap time
- Can't analyse all hospitalisations due to small numbers for higher order events
- Need to specify K in advance
- Parameters for each of the k events need to be interpreted conditionally: treatment comparisons are not protected through randomisation
- Difficult to interpret global treatment effects

Andersen-Gill
Analysis method

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- Extension of Cox proportional-hazards model (proportional-intensity)
  - $\lambda(t) = \exp\{\beta z_i\}\lambda_0(t)$
  - $\lambda_0(t)$: baseline intensity function
- Each gap time contributes to the likelihood
- Gives a intensity/hazard ratio for recurrent events
- Assumes that events are independent
  - Robust standard errors accommodate heterogeneity

CHARM-Preserved

Patient profiles

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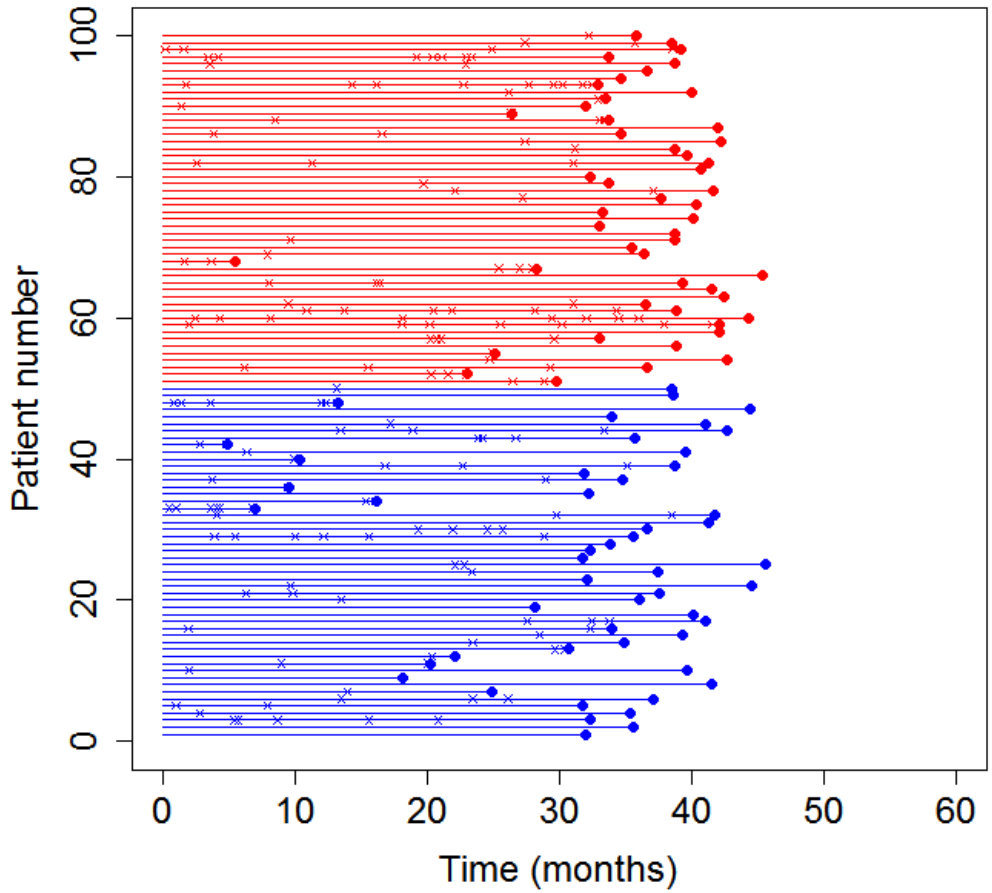

Andersen-Gill
Properties

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- Semi-parametric approach: no assumption on baseline hazard needed
- Can analyse all hospitalisations for all individuals
- Assumes common baseline hazard for each gap time
- Proportionality assumption may be too strong in practice
  - Intensity/hazard ratio assumed to be constant through time and common across recurrent events

Poisson
Analysis method

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- Commonly used for event rates
- Simple: total number of events divided by total follow-up in each group
- Gives a rate ratio for recurrent events
- Assumes that all events are independent
- Perform a Poisson regression on the count data, adjusting for treatment and including an offset for time in the study

Negative Binomial
Analysis method

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- Events within an individual related - naturally accommodated by negative binomial
- Each individual has their own individual Poisson hospitalisation rate
- Poisson rates vary according to Gamma
- Straightforward to implement
- Does not require complex data files
- Perform a negative binomial regression on the count data, adjusting for treatment and including an offset for time in the study

Negative Binomial
Properties

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- Simple and naturally allows for overdispersion
- Correlation of events with the same individual is accounted for through the inclusion of a random effect term
- Poisson process assumption for the conditional counting process may not hold
- Constant baseline assumption may be too strong in practice
  - Could assume other parametric models for conditional counting process
- Rate ratio also assumed to be constant over time and common across recurrent events

EMPHASIS-HF
Application

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	HR	95% CI	*p*-value
Composite	0.69	(0.59,0.81)	< 0.001

	RR	95% CI	*p*-value
Poisson	0.63	(0.55,0.73)	< 0.001
Negative binomial	0.53	(0.42,0.66)	< 0.001

CHARM-Preserved
Application

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	HR	95% CI	*p*-value
Adjudicated composite	0.89	(0.77,1.03)	0.118
Unadjudicated composite	0.86	(0.74,1.00)	0.050

	RR	95% CI	*p*-value
Poisson	0.71	(0.62,0.81)	< 0.001
Negative binomial	0.68	(0.54,0.85)	< 0.001
Andersen-Gill	0.71	(0.57,0.88)	0.002

EMPHASIS-HF
Summary

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	HR	95% CI	*p*-value
Composite	0.69	(0.59,0.81)	< 0.001
WLW 1st HFH	0.63	(0.53,0.76)	< 0.001
WLW 2nd HFH	0.58	(0.43,0.79)	< 0.001
WLW 3rd HFH	0.50	(0.31,0.80)	0.004
Poisson	0.63	(0.55,0.73)	< 0.001
Negative binomial	0.53	(0.42,0.66)	< 0.001

CHARM-Preserved
Summary

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	HR	95% CI	*p*-value
Adjudicated composite	0.89	(0.77,1.03)	0.118
Unadjudicated composite	0.86	(0.74,1.00)	0.050
WLW 1st HFH	0.80	(0.68,0.96)	0.015
WLW 2nd HFH	0.82	(0.62,1.07)	0.146
WLW 3rd HFH	0.65	(0.43,0.97)	0.036
PWP 1st HFH	0.80	(0.68,0.96)	0.015
PWP 2nd HFH	0.99	(0.76,1.30)	0.959
PWP 3rd HFH	0.68	(0.46,1.02)	0.066
Poisson	0.71	(0.62,0.81)	< 0.001
Negative binomial	0.68	(0.54,0.85)	< 0.001
Andersen-Gill	0.71	(0.57,0.88)	0.002

Why?

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- Treatment acts on incidence of first hospitalisations and on recurrences

- EMPHASIS-HF
  - Poisson for firsts: 0.65 (0.54-0.73, P$<$ 0.001)
  - Negative binomial for repeats: 0.52 (0.33-0.82, P=0.004)

- CHARM-Preserved
  - Poisson for firsts: 0.82 (0.69-0.97, P=0.025)
  - Negative binomial for repeats: 0.58 (0.39-0.87, P=0.009)

Outline

Scientific questions
What are we interested in?

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- Does the intervention decrease the event number over the study period compared to control?
- How many events does the intervention prevent, on average, compared to control?
- What is the intervention effect on the number of higher-order events, e.g. 3rd event, compared to control?
- What is the effect of intervention on the number of subsequent events among those who experienced a preceding event?

Statistical Considerations
Summary

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- Modelling framework
  - Fully parametric
  - Semi-parametric
  - Non-parametric

  Event rate
  - Constant
  - Time-varying
  - Unspecified
- Overdispersion
- Censoring
  - Informative censoring assumption
    More hospitalisations$\rightarrow$ increased risk of death
  - Terminal event