Recurrent event endpoints in cardiovascular outcome trials – What is the estimand of interest?

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Acknowledgments

- Jim Gong
- Marty Lefkowitz
Outline

- Background
- Clinical relevance of recurrent events
- Challenges – how to deal with death?
- Estimand framework
- Estimands in the recurrent event data context
- Case study in chronic heart failure
- Conclusions
Traditional approach in CV outcome studies

- Time-to-first event approach commonly used for a composite of disease-related morbidity and mortality (M&M) endpoints
  - Used in many trials that have changed the practice of cardiovascular medicine
  - Attempts to measure the “overall benefit”
  - Avoids competing risk and multiplicity problem (morbidity/mortality)
Limitations of time-to-first event approach

Wu & Cook (2010), Neaton et al (2005)

- Focuses on the first event and ignores repeated events, which can lead to a substantial loss of information
  - Not even all disease related deaths are counted

- A patient with a single early non-fatal morbidity event may be considered worse than a patient with multiple morbidity events and subsequent CV death

- Clinical interpretation of treatment effect requires component analysis
Heart Failure (HF) is a common and global health problem
- It affects approx. 1-2% of adults in developed countries

HF is an abnormality of cardiac structure and/or function
- Leads to pump failure and insufficient delivery of blood around the body
- Symptoms include shortness of breath, excessive tiredness and leg swelling.

HF is a very serious condition
- High mortality rate
- Recurrent heart failure hospitalizations (HFH)
Recurrent event endpoints

- Utilize substantially more HFH and CV deaths than time-to-first event approach
- Contributions of CV mortality to primary composite endpoints are similar in time-to-first event and in recurrent events analyses

Anker, McMurray. Eur Heart J 2012;33:2764-5
Acceptance of recurrent events as primary endpoint

- Commonly used in areas where mortality is relatively low (e.g., Multiple Sclerosis)

- **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). Regulatory and statistical guidance in this respect will be helpful to industry and academia.”

- **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)

- **EMA (1999, 2015 draft) 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
How to capture treatment benefit in a recurrent event setting?

“The most typical source of bias involves fatal events – the worst patient outcome of death of course precludes all future events for that patient, while patients in less serious condition may remain on trial and realize many recurrent events. The bias will generally be in the direction of masking treatment effects.”

(Tom Fleming)

How to capture treatment benefit in this setting where HFH rate is positively associated with risk of CV death?

Choice of estimand
**Estimand framework** clarifies distinction between

- target of estimation (estimand)
- method of estimation (estimator)
An **estimand** reflects what is to be estimated to address the scientific question of interest posed by a trial.

The choice of an estimand involves:
- Population of interest
- Endpoint of interest
- Measure of intervention effect
Estimands in the context of recurrent events

**Scientific Questions:**
1. Does an experimental treatment reduce disease burden compared to control → Testing for between-group difference in the recurrent event occurrence / processes
2. By how much?
   
   Estimate the effect size compared to a control group

**Population of interest:**
- All randomized patients reflecting the target population

**Endpoint of interest:**
- Total HFH including first and subsequent events
- Composite of CV death and total HFH (CV death as ‘final’ recurrent event)
- CV death and HF hospitalization as co-primary outcomes
Measures of intervention effect for ‘total HFH’ or ‘composite endpoint of CV death and total HFH’

**Measure of intervention effect:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Handling of death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Death as censoring</td>
</tr>
<tr>
<td></td>
<td>Death as terminal event</td>
</tr>
<tr>
<td>Mean ratio</td>
<td></td>
</tr>
<tr>
<td>Rate ratio</td>
<td></td>
</tr>
</tbody>
</table>

Intensity ratio / HR

**Death as censoring:** interpretation conditional on being alive or assuming a latent process after death

**Death as terminal event:** acknowledging the fact that there will be no HFH after death
Mean Cumulative Function (MCF) shows the mean number of recurrent events per subject by a certain time.
Rate function

- MCF $\mu(t) = \mathbb{E}\{N(t)\}$ changes as a function of time and its derivative $r(t)$ at a certain time point gives the rate function:
  
  $$r(t) = \frac{\mathbb{E}\{dN(t)\}}{dt}$$

- Rate function can be interpreted as the average risk in a population at time $t$ without conditioning on the event history.

- When comparing two treatments one can look at mean ratios or rate ratios (or intensity ratios).

Constant rate of events

Monotone increasing rate of events
Measures of intervention effect for ‘total HFH’ or ‘composite endpoint of CV death and total HFH’

**Measure of intervention effect:**

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<tr>
<td>Mean ratio</td>
<td></td>
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<tr>
<td>Rate ratio</td>
<td></td>
</tr>
</tbody>
</table>

→ Various endpoints and measures of intervention effect, i.e., different combinations of parameter and handling of death, have been utilized in the cardiovascular literature
Conditional rate ratio

Primary endpoint: total HFH or composite of CV death and total HFH

Measure of intervention effect
Common rate ratio of composite endpoints in investigational group vs control group conditional on being alive (and at risk)

Estimation:
Proportional rate model based on general counting process could be useful (Lin, Wei, Ying and Yang, 2000)
Assumptions: proportional rates; marginal interpretation requires independent censoring

Solid lines: Nelson-Aalen estimators for mean functions \( \mu_i(t) \)

\[
r(t \mid D \geq t, Z) = e^{\beta Z} r_0(t)
\]

\[
D = \text{Death}
\]

\[
e^\beta = \text{treatment effect (Z=0 control, Z=1 test treatment)}
\]
Marginal mean ratio

**Primary endpoint: total HFH or composite of CV death and total HFH**

### Measure of intervention effect

**Marginal ratio of expected number of primary endpoint events** in investigational group vs control group, acknowledging that there will be no HFH after death

**Estimation:**

- Gosh & Lin (2000) or e.g. LWYY with censoring at end of study (Mao & Lin, 2015)
- Assumption: Counting process continues after death and stays flat (no jumps) until end of the study

### Solid lines: Nelson-Aalen estimators for mean functions \( \mu_i(t) \)

### Dotted lines: Gosh & Lin estimators \( \mu^*_i(t) \)

\[ \text{Mean Ratio} \approx \frac{\mu^*_1(t)}{\mu^*_0(t)} \]

\[ \text{Time (days)} \]

- Favors treatments where more patients die early on and therefore may be less suitable for regulatory purposes
- May be appropriate for cost analysis
Marginal rate (or mean) ratio with latent process after death

**Primary endpoint:** total HFH or composite of CV death and total HFH

### Measure of intervention effect

Marginal rate ratio or ratio of expected number of primary endpoint events in investigational group vs control group assuming latent process continuing after death

**Estimation:**
Negative binomial model (NB; McCullagh and Nelder 1989) may be suitable
Assumptions: death as conditionally independent censoring (MAR), homogenous Poisson process for each subject, proportional intensity conditional on subject-specific frailty

\[
\frac{\mu_1(t)}{\mu_0(t)} \approx \frac{\mu_1^L(t)}{\mu_0^L(t)}
\]

**Solid lines:** Nelson-Aalen estimators for mean functions \(\mu_i(t)\)

**Dotted lines:** Estimators assuming counting process continues after death \(\rightarrow\) adjust upwards in case of positive correlation

\[
r(t|Z, U_i) = r_0 U_i \exp(\beta^T Z)
\]

\(e^\beta\): estimand for treatment effect \((Z=0\ control, Z=1\ test\ treatment)\)

\(U_i=\)subject-specific random effect
Conditional rate ratio and hazard ratio

Co-primary endpoints: HFH and CV death

Measure of intervention effect

Rate ratio of recurrent HFH and hazard ratio of CV death conditional on subject-specific characteristics

Estimation:

- Joint frailty models which account for the correlation between the recurrent event process and the terminal event process
- Marginal interpretation of parameters is not straightforward, e.g. CV death HR from shared frailty model may be different from conventional Cox-regression-based HR
- May be sensitive to the choice of frailty terms

\[ N_i(t) \mid U_i \] is a Poisson process with rate function

\[ r(t \mid U_i) = r_0 \exp(\beta_{1,trt_i} U_i) \]

\[ D_i \mid V_i \] is the terminal process with hazard rate

\[ h(t \mid V_i) = h_0 \exp(\alpha_{1,trt_i} V_i) \]

\[ U_i \] and \[ V_i \] are correlated random effects with mean 1 – usually gamma or log-normally distributed

\[ r_0 \] and \[ h_0 \] are constant baseline rate/hazard functions

\[ \{N_i(t), t > 0\} \sqcup D_i \mid U_i, V_i \]
Study:

- Placebo-controlled study
- Placebo arm: 2499 patients and
- Valsartan arm: 2511 patients, i.e. total N=5010
- Mean duration of follow-up: 23 months (range: 0 – 38 months)
Primary Outcomes:
- All-cause mortality
- Time to first event of a combined endpoint of all-cause mortality and morbidity (cardiac arrest with resuscitation, hospitalization for heart failure, or receipt of intravenous inotropic or vasodilator therapy for at least four hours).

Results:
- All-cause mortality was similar in the two groups.
- Combined endpoint:
  - HR (Valsartan/Placebo): 0.87, 97.5% CI [0.77,0.97]; p-value: 0.009.
Post-hoc analysis

‘Time-to-first event’ analysis for composite of CV death / HFH

Composite Endpoint
CV death/ HF hospitalization

log-rank p-value: 0.0204

Hazard-Ratio:
0.89, 95% CI [0.81,0.98]
Potential benefits of recurrent event data

*Time-to-first event approach (1610 events) ignores subsequent events*

<table>
<thead>
<tr>
<th>Number of HFH events</th>
<th>No. of patients PBO, NPBO=2499 N (%)</th>
<th>No. of patients Val, NVal =2511 N (%)</th>
<th>Total number of events NTOT =5010 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1878 (75.15)</td>
<td>1974 (78.61)</td>
<td>3852 (76.89)</td>
</tr>
<tr>
<td>1</td>
<td>344 (13.77)</td>
<td>317 (12.62)</td>
<td>661 (13.19)</td>
</tr>
<tr>
<td>2</td>
<td>146 (5.84)</td>
<td>130 (5.18)</td>
<td>276 (5.51)</td>
</tr>
<tr>
<td>3</td>
<td>56 (2.24)</td>
<td>51 (2.03)</td>
<td>107 (2.14)</td>
</tr>
<tr>
<td>4</td>
<td>36 (1.44)</td>
<td>19 (0.76)</td>
<td>55 (1.10)</td>
</tr>
<tr>
<td>5</td>
<td>21 (0.84)</td>
<td>13 (0.52)</td>
<td>34 (0.68)</td>
</tr>
<tr>
<td>≥6</td>
<td>18 (0.72)</td>
<td>7 (0.28)</td>
<td>25 (0.50)</td>
</tr>
</tbody>
</table>

Total number of HFH HFH 1189 922 2111

Total number of CV deaths 419 (16.77) 427 (17.01) 846 (16.89)

Total number of composite ‘first’ events (HFH/CV death) 841 769 1610

Total number of composite ‘rec.’ events (HFH/CV death) 1608 1349 2957
### Case Study: ValHeFT
Comparison of various approaches*

<table>
<thead>
<tr>
<th>Method</th>
<th>Endpoint</th>
<th>HR/RR</th>
<th>95% CIL</th>
<th>95% CIU</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTFE</td>
<td>CVD/HFH</td>
<td>0.89</td>
<td>0.81</td>
<td>0.98</td>
<td>0.0204</td>
</tr>
<tr>
<td></td>
<td>HFH</td>
<td>0.84</td>
<td>0.75</td>
<td>0.95</td>
<td>0.0034</td>
</tr>
<tr>
<td>LWYY</td>
<td>CVD/HFH</td>
<td>0.83</td>
<td>0.74</td>
<td>0.93</td>
<td>0.0012</td>
</tr>
<tr>
<td></td>
<td>HFH</td>
<td>0.77</td>
<td>0.68</td>
<td>0.88</td>
<td>0.0001</td>
</tr>
<tr>
<td>NB</td>
<td>CVD/HFH</td>
<td>0.84</td>
<td>0.73</td>
<td>0.97</td>
<td>0.0176</td>
</tr>
<tr>
<td></td>
<td>HFH</td>
<td>0.77</td>
<td>0.66</td>
<td>0.89</td>
<td>0.0007</td>
</tr>
<tr>
<td>Joint Frailty</td>
<td>HFH</td>
<td>0.77</td>
<td>0.67</td>
<td>0.89</td>
<td>0.0005</td>
</tr>
<tr>
<td>Gosh&amp;Lin</td>
<td>HFH</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* based on investigator-reported HFH
CV death HR=1.01 (95% CI 0.89 – 1.16; p=0.8569)
Conclusions

- Recurrent events approaches have shown a reduction in total HFH in studies with large reduction in mortality (EMPHASIS, PARADIGM-HF) and in studies with no significant impact on mortality (CHARM-Preserved, SHIFT)

- Consensus on appropriate estimands would facilitate the recurrent event approach to play a larger role in future cardiovascular drug development (in particular in CHF)

- Composite M&M endpoint naturally extends the traditional TTFE approach and more fully captures the disease burden + may increase statistical power

- ‘Marginal rate ratio of composite events with latent process after death’ or the ‘rate ratio of composite events conditional on being alive (and at risk)’ could be meaningful measures of intervention effect
Conclusions

- **Estimates** for the composite endpoint have to be interpreted with caution if the number of deaths is non-negligible and treatment affects mortality.

- Like in the case of time-to-first-event analysis, the quantification of treatment effects on individual components is essential for the interpretation of the results.

- **Alternative estimands/endpoints** not discussed here:
  - WLW, PWP, Multi-state models
  - Win-Ratio approach (Pocock et al, 2011), non-parametric rank-based approaches
  - Days alive and out of hospital
References


- **Castaneda J, Gerritse B (2010):** Appraisal of several methods to model time to multiple events per subject: Modelling time to hospitalization and death. Revista Colombiana de Estadistica 33: 43-61.


- **Cook RJ, Lawless JF (1997):** Marginal analysis of recurrent events and a terminating event. Statistics in Medicine, Vol 16, 911-924.


References (continued)


- **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.


Potential benefits of recurrent event analysis

*Inclusion of all HF hospitalizations may lead to increased power*

For each given sample size, 1000 bootstrap samples were drawn from ValHeFT data – a placebo-controlled study, N=5010, mean follow-up 23 months, max 38 months data

*Lin, Wei, Yang, & Ying (2000)*
Overview of estimands and analysis methods used in selected CHF trials

**Composite CV death / total HFH and treat death as censoring**

- Marginal rate ratio:
  - NB: CHARM-Preserved, PARAGON, PARADIGM*
- Conditional rate ratio:
  - LWYY: PARAGON, CHARM-Preserved, PARADIGM*
- Intensity ratio / Hazard ratio:
  - Poisson: CHARM-Preserved
  - WLW: PARAGON, PARADIGM*

**Composite CV death / total HFH and treat death as terminal event**

- Marginal mean ratio:
  - LWYY with censoring at end of study: HF-ACTION

**Consider CV death and HF hospitalization as two separate outcomes**

- Rate ratio of HFH and hazard ratio of CV death conditional on frailty:
  - JM: CHARM-Preserved, CUPID-2, PARAGON, PARADIGM*

**Focus on non-fatal events (HFH) and treat death as censoring event**

- Marginal rate ratio:
  - NB: PARADIGM, EMPHASIS, CHAMPION
- Conditional rate ratio:
  - LWYY: PARADIGM*
- Intensity ratio / HR:
  - Poisson: SHIFT, EMPHASIS, MADIT-CRT, CHAMPION
  - WLW: SHIFT
  - PWP: SHIFT

**Focus on non-fatal events (HFH) and treat death as terminal event**

- Marginal mean ratio:
  - G&L: EMPHASIS, COMPANION, PARAGON

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Green color indicates pre-specification, red color post-hoc analyses. **Bold red indicates primary post-hoc analysis approach, bold green and underlined indicates pre-specified primary endpoint analysis approach**

* Not published yet

**NB**: Negative binomial model

**G&L**: Mean cumulative incidence function model “adjusted for death as terminal event”

**JM**: Joint model for recurrent and terminal events with shared frailty

**WLW**: Multivariate failure time analysis based on proportional hazards

**LWYY**: Proportional rate model based on general counting process

**PWP**: Proportional hazards gap time model
### Overview of some Recurrent Event Approaches, Measures of Intervention Effect and Analysis Methods

<table>
<thead>
<tr>
<th>Composite CV death / total HFH and treat death as censoring</th>
<th>Composite CV death / total HFH and treat death as terminal event</th>
<th>Consider CV death and HF hospitalization as two separate outcomes</th>
<th>Focus on non-fatal events (HFH) and treat death as censoring event</th>
<th>Focus on non-fatal events (HFH) and treat death as terminal event</th>
</tr>
</thead>
</table>
| - Marginal rate ratio or ratio of expected number of composite events assuming latent process continuing after death: **NB**  
- Common rate ratio of composite events conditional on being alive and at risk: **LWYY**  
- Common hazard ratio for time to k-th composite event: **WLW** | - Marginal ratio of expected number of composite events, acknowledging the fact that there will be no event after death: **G&L, or NB, LWYY with censoring at end of study** | - Rate ratio of HFH and hazard ratio of CV death conditional on frailty: **JM**  
- Common intensity ratio of transitions between different states – to HFH and to CV death separately: **MS**  
- Common hazard ratio for HFH and CV death separately: **WLW** | - Marginal rate ratio or ratio of expected number of HFH assuming latent process continuing after death: **NB**  
- Common rate ratio of HFH conditional on being alive and at risk: **LWYY**  
- Common hazard ratio for time to k-th HFH: **WLW** | Marginal ratio of expected number of HFH, acknowledging the fact that there will be no HFH after death: **G&L, or NB, LWYY with censoring at end of study** |

**NB:** Negative binomial model  
**LWYY:** Proportional rate / mean cumulative incidence function model based on general counting process  
**WLW:** Multivariate failure time analysis based on proportional hazards  
**JM:** Joint model for recurrent and terminal events with shared frailty  
**G&L:** Mean cumulative incidence function model “adjusted for death as terminal event” / cause-specific rate function  
**MS:** Multistate model
## Case Study: PARADIGM
Comparison of various analysis approaches

<table>
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<th>95% CIU</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTFE</td>
<td>CVD/HFH</td>
<td>0.80</td>
<td>0.73</td>
<td>0.87</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>HFH</td>
<td>0.79</td>
<td>0.71</td>
<td>0.89</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LWYY</td>
<td>CVD/HFH</td>
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<td>0.71</td>
<td>0.87</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>HFH</td>
<td>0.78</td>
<td>0.68</td>
<td>0.90</td>
<td>0.0005</td>
</tr>
<tr>
<td>NB</td>
<td>CVD/HFH</td>
<td>0.76</td>
<td>0.67</td>
<td>0.85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>HFH</td>
<td>0.77</td>
<td>0.67</td>
<td>0.89</td>
<td>0.0004</td>
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<td>0.75</td>
<td>0.65</td>
<td>0.87</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

CV death HR=0.80 (95% CI 0.71 – 0.89)
### Estimands and analysis methods used in other cardiovascular trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Indication</th>
<th>Endpoint</th>
<th>Estimand</th>
<th>Method</th>
<th>Analysis Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRITON-TIMI38¹</td>
<td>ACS</td>
<td>Total composite of CV death, MI and stroke</td>
<td>Rate Ratio</td>
<td>Poisson regression</td>
<td>Post-hoc</td>
</tr>
<tr>
<td>ACTIV-I²</td>
<td>AFib</td>
<td>Composite of (1) Stroke, MI, or vascular death, (2) same as (1) plus HFH</td>
<td>Rate Ratio</td>
<td>LWYY</td>
<td>Secondary</td>
</tr>
<tr>
<td>PROVE-IT TIMI 2²</td>
<td>Lipid-lowering</td>
<td>Composite of death, MI, UA requiring re-hospitalization, stroke, or revascularization</td>
<td>Rate Ratio</td>
<td>Poisson regression</td>
<td>Post-hoc</td>
</tr>
<tr>
<td>IDEAL⁴</td>
<td>Lipid-lowering</td>
<td>Composite of CHD death, MI, resuscitated cardiac arrest, stroke, revascularization, hospitalization for UA, HFH, and PAD</td>
<td>Hazard Ratio from time to 1st, 2nd, ..5th event</td>
<td>WLW</td>
<td>Post-hoc</td>
</tr>
</tbody>
</table>

¹ Murphy, 2008, ² Yusuf, 2011, ³ Murphy, 2009, ⁴ Tikkanen, 2009
Case Study: ValHeFT

Placebo-controlled study, N=5010, mean duration of follow-up 23 months (range, 0 to 38 months).

CV death

Composite Endpoint
CV death / HFH

**log-rank p-value:** 0.8568

**log-rank p-value:** 0.0204

HR (Valsartan/Placebo): 0.89, 95% CI [0.81,0.98]
Recurrent events approach utilizes substantially more events than time to first-event analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Time-to-first-event (CV death or HF hospitalization): CV death as % of primary outcome (n/n = N)</th>
<th>Recurrent events (all CV deaths and all HF hospitalizations): CV death as % of all events (n/n = N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARM-Added</td>
<td>316/705 = 1021 (31.0%)</td>
<td>649/1443 = 2092 (31.0%)</td>
</tr>
<tr>
<td>CHARM-Alternative</td>
<td>237/503 = 740 (32.0%)</td>
<td>471/1053 = 1524 (30.9%)</td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>188/417 = 605 (31.1%)</td>
<td>332/702 = 1034 (32.1%)</td>
</tr>
<tr>
<td>SHIFT</td>
<td>544/1186 = 1730 (31.4%)</td>
<td>940/2113 = 3053 (30.7%)</td>
</tr>
<tr>
<td>I-PRESERVE</td>
<td>392/661 = 1053 (37.2%)</td>
<td>613/1176 = 1789 (34.3%)</td>
</tr>
<tr>
<td>CHARM-Preserved</td>
<td>190/509 = 699 (27.2%)</td>
<td>340/968 = 1308 (26.0%)</td>
</tr>
<tr>
<td>ValHeFT</td>
<td>461/1149 = 1610 (28.6%)</td>
<td>846/2111 = 2957 (28.6%)</td>
</tr>
</tbody>
</table>

ValHeFT n/n, CV death/HF hospitalization; N, CV death or HF hospitalization (time-to-first event) or total number of CV deaths plus total number of HF hospitalizations (recurrent events).

CV, cardiovascular; HF, heart failure.

Anker, McMurray. Eur Heart J 2012;33:2764-5
Case Study ValHeFT

Smoothed estimates of conditional rate function and conditional rate ratio

Common rate ratio conditional on being alive and at risk = 0.83
Case Study ValHeFT
Poisson and negative binomial estimates of mean function

Total Heart Failure Hospitalizations

Total Heart Failure Hospitalizations and CV death

- LCZ Cumulative Nelson-Aalen rate
- ENA Cumulative Nelson-Aalen rate
- LCZ Poisson estimated mean function
- ENA Poisson estimated mean function
- LCZ NB estimated mean function
- ENA NB estimated mean function

Cumulative recurrent event rates (Events per-patient)
Days from randomization
Case Study: ValHeFT

Non-parametric analysis (Ghosh & Lin, 2000) for mean cumulative number of events with death as terminal event

Mean cumulative number of hospitalizations for HF; Death ignored and considered

Mean function adjusted downwards since patients who died cannot be hospitalized anymore.
Case Study: ValHeFT

Non-parametric analysis (Ghosh & Lin, 2000) for mean cumulative number of events with death as terminal event

Difference and pointwise 95% CI

Ratio and pointwise 95% CI

Difference in mean cum. numbers of HF Hosp/100 patients

Ratio between mean cum. numbers of HF Hosp

Days

Days

Valsartan - PBO

Generalized weighted logrank: p<0.0001

Ratio: Valsartan/PBO
### Case Study: ValHeFT
Parametric joint modeling applied to ValHeFT

\( N_i(t) | U_i \) is a counting process with rate function
\( D_i | V_i \) is the terminal process with hazard rate
\( U_i \) and \( V_i \) are random effects with mean 1
\( \{N_i(t), t > 0\} \sqcup D_i | U_i, V_i \)

\[
\begin{align*}
\lambda_0 &\exp(\beta_{1,\text{trt}}) U_i \\
\gamma_0 &\exp(\alpha_{1,\text{trt}}) V_i
\end{align*}
\]

\( \lambda_0 \) and \( \gamma_0 \) are constant baseline rate/hazard functions.

<table>
<thead>
<tr>
<th>Log-normal distributed frailties</th>
<th>Parameter</th>
<th>( V_i = U_i )</th>
<th>( V_i = U_i^\psi )</th>
<th>( U_i, V_i ) follow bivariate dist.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in hospitalization rate due to treatment</td>
<td>( \exp(\beta_{1,\text{val}}) )</td>
<td>0.771 p-val=0.0005</td>
<td>0.765 p-val=0.0006</td>
<td>0.774 p-val=0.0003</td>
</tr>
<tr>
<td>Change in CV-death hazard rate due to treatment</td>
<td>( \exp(\alpha_{1,\text{val}}) )</td>
<td>1.013 p-val=0.8908</td>
<td>1.009 p-val=0.9093</td>
<td>1.012 p-val=0.8860</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gamma distributed frailties</th>
<th>Parameter</th>
<th>( V_i = U_i )</th>
<th>( V_i = U_i^\psi )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in hospitalization rate due to treatment</td>
<td>( \exp(\beta_{1,\text{val}}) )</td>
<td>0.770 p-val=0.0003</td>
<td>0.769 p-val=0.0005</td>
</tr>
<tr>
<td>Change in CV-death hazard rate due to treatment</td>
<td>( \exp(\alpha_{1,\text{val}}) )</td>
<td>1.012 p-val=0.8951</td>
<td>1.014 p-val=0.8682</td>
</tr>
</tbody>
</table>
Nelson-Aalen Estimator

- $\Lambda_0(t)$ arbitrary mean function
- $Y_i(t)$ indicates whether subject $i$ is ‘at risk’ at time $t$
- $Y_\Sigma(t) = \sum_{i=1}^{m} Y_i(t)$ are the total number of patients at risk over $[t, t + dt)$
- $dN_\Sigma(t) = \sum_{i=1}^{m} Y_i(t)dN_i(t)$ are the total number of events observed over $[t, t + dt)$
- $t_{(1)}, ..., t_{(H)}$ denote the $H$ distinct event times across all $m$ patients

The Nelson-Aalen Estimator is then given by

$$\Lambda_0(t) = \sum_{\{h \mid t_{(h)} \leq t\}} \frac{dN_\Sigma(t_{(h)})}{Y_\Sigma(t_{(h)})}$$
Common intensity ratio of transitions between different states - Multistate Model

**Estimand**
Common intensity ratio of transitions between different states (can be implemented as stratified Cox regression model with or without inclusion of transition to CV death as an event)

Marginal interpretation of parameters is not straightforward
Modelling Recurrent Event Data – LWYY
(Lin, Wei, Yang and Ying, 2000)
**LWYY: Proportional rate / mean cumulative incidence function model (Lin, Wei, Yang and Ying, 2000)**

- $N_i(t)$ is a general counting process and the rate function is given by
  
  $r(t) = \lambda_0(t) \exp(\beta^T Z_i)$

  where $\lambda_0(t)$ is the unspecified baseline rate function

- Mean number of events by time $t$ is given by
  
  $\mu(t) = \int_0^t r(s) \, ds = \exp(\beta^T Z_i) \int_0^t \lambda_0(s) \, ds = \exp(\beta^T Z_i) \Lambda_0(t)$

- $\Lambda_0(t)$ can be estimated through the Nelson-Aalen estimator

- For estimation of regression coefficients the same partial likelihood score functions as for the **Andersen-Gill** model are used, but Poisson process assumption is relaxed

- A **robust sandwich variance estimate** is used to account for dependence of recurrent events on the same subject (e.g. PROC PHREG in SAS can be used)

- Estimates the common rate ratio of events in the interventional group relative to control group conditional on being at risk. Marginal (unconditional) interpretation requires independent censoring assumption to hold.

- Within treatment rates are time-dependent and can be graphically displayed (Nelson-Aalen estimator). Rate ratio assumed constant over time and common across recurrent events.
Shared frailty model: Joint model for recurrent and terminal events (Cowling et al, 2006; Zeng & Lin, 2009; Liu et al, 2004)

- $N_i(t) | U_i$ is a counting process with rate function
  \[
  r(t| U_i) = \lambda_0(t) \exp(\beta^T Z_i) \ U_i
  \]
  where $\lambda_0(t)$ is an arbitrary baseline rate function.

- $D_i| V_i$ is the terminal process with hazard rate
  \[
  h(t| V_i) = h_0(t) \exp(\alpha^T Z_i) \ V_i
  \]
  where $h_0(t)$ is an arbitrary baseline hazard function and $\psi$ an unknown constant.

- $U_i, V_i$ are correlated frailty terms (follow bivariate dist., parametrized through $\gamma$), such that
  \[
  \{N_i(t), t > 0\} \text{ independent of } D_i | U_i, V_i, Z_i
  \]

- Common choices for the distribution of $U_i, V_i$ are the log-normal and gamma distribution.

- Maximization of the joint likelihood requires numerical integration techniques
  \[
  L_{N_i(t),D_i}(\alpha, \beta, \gamma, \psi) = \int p_{N_i(t)|U_i}(\beta) \ p_{D_i|V_i}(\alpha, \psi) \ p_{(U_i,V_i)}(\gamma) \ du_i \ dv_i
  \]

- Estimated rate ratio of recurrent events is conditional on subject-specific frailty $(U_i, V_i)$, i.e. marginal interpretation not straightforward

- R package «frailtypack» can be used to fit the model using arbitrary baseline rate and hazard / SAS PROC NLMIXED can be used to fit the model using parametric models for the baseline rate and hazard
Negative Binomial (Mixed Poisson) Model

- $N_i(t) \mid U_i$ is a Poisson process; $U_i$ is a gamma distributed, with mean 1 and variance $\phi$

- Instantaneous probability of an event occurring is given by the rate function
  \[ r(t \mid U_i) = \frac{\mathbb{E}(dN_i(t) \mid U_i)}{dt} = \frac{\Pr(dN_i(t)=1 \mid U_i)}{dt} = \lambda_0 U_i \exp(\beta^T Z_i) \]
  where $\lambda_0$ is the constant baseline rate

- Mean number of events by time $t$ is therefore given by
  \[ \mu(t \mid U_i) = \int_0^t r(s \mid U_i) \, ds = \lambda_0 U_i \exp(\beta^T Z_i) \, t \]

- Marginally, we obtain
  \[ \mu(t) = \mathbb{E}(N_i(t)) = \lambda_0 \exp(\beta^T Z_i) \, t \quad \text{and} \quad \text{Var}(N_i(t)) = \mu(t) \left( 1 + \phi \mu(t) \right) \]

- Estimates the common rate ratio of events in the interventional group relative to control group. Allows to estimate mean hospitalization rate for each treatment arm separately.

- Easy to understand and implement (PROC NLMIXED, GLIMMIX, GENMOD in SAS).

- Assumes conditionally independent censoring (i.e. censoring is conditionally independent of the counting process, given covariates and measurement history). Corresponds to general concept of ‘missing at random’ (MAR).
Mean cumulative incidence function model “adjusted for death as terminal event” (Ghosh and Lin, 2000, 2002)

- $N_i(t)$ is the actual number of events that subject $i$ has experienced by time $t$ in the presence of death and $D_i$ is the time of death

- **Marginal mean function** $m(t)$ in presence of death is used to quantify frequency of recurrent events, **acknowledging the fact that subjects cannot experience recurrent events after death**

\[
m_i(t) = \int_0^t S_i(u) \ r_i(u) \ du
\]

where $S_i(t) = \Pr(D_i \geq t)$ and $r_i(t) = \frac{\mathbb{E}(dN_i(t)|D_i \geq t)}{dt}$

- An estimator for $m(t)$ can be obtained through integration of the product of Kaplan-Meier and Nelson-Aalen estimators

- Comparing mean frequency functions for two treatments arms can be based on a **generalized log-rank statistic** $L_R$ with appropriate weights

- Assessing the **treatment effect with respect to both the recurrent events and survival times** requires simultaneous testing on both endpoints, which can be accomplished by using a **combined test statistic** (weighted sum of $L_R$ and log-rank statistic for testing equality of survival times).

- Currently not implemented in statistical software (SAS, R).