Association between hospitalisation and mortality rates in heart failure trials: Consequences for marginal treatment effect estimates

Antje Jahn, University of Applied Sciences, Darmstadt
Gerrit Toenges, University Medical Center, Mainz
Motivation and Objective

The Cardiovascular Round Table of the European Society of Cardiology\(^1\):

- "The negative binomial, Andersen-Gill, and joint-frailty model are appropriate methodologies for analysis of repeat hospitalizations"
- "Consensus has not been achieved on best practice for presenting recurrent events data, and these decisions may need to be considered on a trial-by-trial basis"

**Why, when and how do marginal (Andersen-Gill) and conditional (Joint Frailty) PH analyses differ?**

HF hospitalizations and CV death

\[
\begin{array}{ccc}
\lambda_H(t) & \rightarrow & \text{H1} \\
\text{0} & \rightarrow & \text{D} \\
\lambda_D(t) & \rightarrow & \text{D}
\end{array}
\]

- HFH is a competing event for death when reducing analyses to first events only

\[ \text{H} = \text{Hosp.} \]

\[ \text{D} = \text{Death} \]

time \( t \)
HF hospitalization as competing event for CV death

<table>
<thead>
<tr>
<th>trial</th>
<th># deaths</th>
<th>not 1st event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val-HeFT</td>
<td>846</td>
<td>385 (45.5%)</td>
</tr>
<tr>
<td>CHARM-Added</td>
<td>649</td>
<td>333 (51.3%)</td>
</tr>
<tr>
<td>CHARM-Alternative</td>
<td>471</td>
<td>234 (49.7%)</td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>332</td>
<td>144 (43.4%)</td>
</tr>
<tr>
<td>SHIFT</td>
<td>940</td>
<td>396 (42.1%)</td>
</tr>
<tr>
<td>I-PRESERVE</td>
<td>613</td>
<td>221 (36.1%)</td>
</tr>
<tr>
<td>CHARM-Preserved</td>
<td>340</td>
<td>150 (44.1%)</td>
</tr>
</tbody>
</table>

Recurrent analysis model

\[ \lambda_H(t) \quad H1 \xrightarrow{\lambda_H(t)} H2 \xrightarrow{\lambda_H(t)} H3 \xrightarrow{\lambda_H(t)} \ldots \quad H = \text{Hosp.} \]
\[ \lambda_D(t) \quad 0 \xrightarrow{\lambda_D(t)} D \xrightarrow{\lambda_D(t)} D \xrightarrow{\lambda_D(t)} D \xrightarrow{\lambda_D(t)} \ldots \quad D = \text{Death} \]

- CV Death: Hazard Ratio
- HF Hospitalization: Rate Ratio
  - Andersen-Gill
  - Negative Binomial
  - Joint Frailty
Marginal PH model: Andersen-Gill

Rates of HFH and CVD are independent (conditionally on covariates)

\[
\lambda_H(t|X) = \lim_{\Delta \downarrow 0} \frac{P(N(t + \Delta)^- - N(t^-) = 1 \mid X, D \geq t)}{\Delta} \\
= \lambda_{H0}(t) \exp(\beta'_H X)
\]

\[
\lambda_D(t|X) = \lim_{\Delta \downarrow 0} \frac{P(t \leq D < t + \Delta \mid X, D \geq t)}{\Delta} \\
= \lambda_{D0}(t) \exp(\beta'_D X)
\]
Conditional PH model: Joint Frailty

Rates of HFH and CVD are depend on a common frailty term

\[
\lambda_H(t|X, Z) = \lim_{\Delta \searrow 0} \frac{P(N(t + \Delta)^- - N(t^-) = 1 | X, D \geq t)}{\Delta} \\
= Z \lambda_{H0}(t) \exp(\beta_H'X)
\]

\[
\lambda_D(t|X, Z) = \lim_{\Delta \searrow 0} \frac{P(t \leq D < t + \Delta | X, D \geq t)}{\Delta} \\
= Z \lambda_{D0}(t) \exp(\beta_D'X)
\]

Treatment effect estimates on HFH - Charm-Preserved¹:

Hazard Ratio

Poisson

Andersen-Gill

Joint Frailty

0.5  0.6  0.7  0.8  0.9  1  1.1

Treatment effect estimates on HFH - CORONA$^1$:

Hazard Ratio

1st HFH – Cox
Poisson
Andersen–Gill
Joint Frailty

Methods

Under dependent risk processes (joint frailty model), we derive

A: the marginal hazard rates over time
B: the marginal hazard ratio over time
C: the marginal hazard ratio as estimated by Andersen-Gill method
A: Marginal hazard rates over time

\[ \lambda_H(t|X, D \geq t) \]

\[ = \lim_{\Delta \to 0} \frac{P(N(t + \Delta)^- - N(t^-) = 1|X, D \geq t)}{\Delta} \]

\[ = \int_0^\infty \lambda_{H0}(t) \exp(\beta_H X) \cdot z \cdot f_{Z|X,D\geq t}(z) \, dz \]

\[ = \lambda_{H0}(t) \exp(\beta_H X) \cdot E(Z|X, D \geq t) \]

\[ = \lambda_{H0}(t) \exp(\beta_H X) \cdot \frac{L_Z'(\exp(\beta_D X)\Lambda_{D0}(t))}{L_Z(\exp(\beta_D X)\Lambda_{D0}(t))} \]
A: Marginal hazard rates over time

\[ \beta_H = \log(0.75) \]

\[ \beta_H = 0 \]

Parameters: \( \beta_D = \log(0.75), \lambda_{H0} = 1, \lambda_{D0} = 0.2, \theta = 1 \)
B: Marginal hazard ratio over time

\[ HR(t) = \frac{r_1(t|X = 1, D \geq t)}{r_1(t|X = 0, D \geq t)} \]

\[ = \exp(\beta_H) \cdot \frac{\mathcal{L}'_{Z} (\exp(\beta_D) \Lambda_{D0}(t)) \mathcal{L}_{Z} (\Lambda_{D0}(t))}{\mathcal{L}'_{Z} (\Lambda_{D0}(t)) \mathcal{L}_{Z} (\exp(\beta_D) \Lambda_{D0}(t))} \]

\[ = \exp(\beta_H) \cdot f(t) \]

with

- \( f(t) \) depending on mortality rates and frailty distribution only
B: Marginal hazard ratio over time

\[ HR(t) = \frac{r_1(t|X = 1, D \geq t)}{r_1(t|X = 0, D \geq t)} \]

\[ = \exp(\beta_H) \cdot \frac{L'_Z (\exp(\beta_D)\Lambda_{D0}(t)) L_Z (\Lambda_{D0}(t))}{L'_Z (\Lambda_{D0}(t)) L_Z (\exp(\beta_D)\Lambda_{D0}(t))} \]

\[ = \exp(\beta_H) \cdot f(t) \]

with

- \( f(t) \) depending on mortality rates and frailty distribution only

\[ f(t) \begin{cases} \leq 1 \quad \forall t & \iff \beta_D > 0 \\ = 1 \quad \forall t & \iff \beta_D = 0 \\ \geq 1 \quad \forall t & \iff \beta_D < 0 \end{cases} \]
B: Marginal hazard ratio over time: $\beta_D = \log(0.75)$

Parameters: $\lambda_{H0} = 1$, $\lambda_{D0} = 0.2$, $\theta = 1$
B: Marginal hazard ratio over time ($\beta_D = \log(1.25)$)

$\beta_H = \log(0.75)$

Parameters: $\lambda_{H0} = 1, \lambda_{D0} = 0.2, \theta = 1$
B: Marginal hazard ratio over time ($\beta_D = 0$)

\[ \beta_H = \log(0.75) \]

\[ \beta_H = 0 \]

Parameters: $\lambda_{H0} = 1$, $\lambda_{D0} = 0.2$, $\theta = 1$
C: Marginal Hazard Ratio Estimate:

The marginal HR estimate is $\exp(\hat{\beta}_H)$ with $\hat{\beta}_H$ satisfying

$$0 = \int_0^{t_{max}} w(t, \hat{\beta}_H) \left[ \lambda_H(t|X = 1, D \geq t) - \exp(\hat{\beta}_H)\lambda_H(t|X = 0, D \geq t) \right]$$

with positive weights $w(t, \hat{\beta}_H)$

$$\Rightarrow \hat{HR} = \exp(\hat{\beta}_H) \in [HR(0), HR(t_{max})]$$
C: Marginal Hazard Ratio Estimate:

\[ \beta_D = \log(0.75) \]

\[ \beta_D = \log(1.25) \]

- Marginal
- Conditional
C: Marginal Hazard Ratio Estimate:

\[ \theta = 0 \]

\[ \theta > 0, \beta_D = 0 \]

- Marginal hazard ratio
- Conditional hazard ratio
C: Marginal Hazard Ratio Estimate:

The marginal HR estimate is $\exp(\hat{\beta}_H)$ with $\beta_H$ satisfying

$$0 = \int_0^{t_{\text{max}}} w(t, \hat{\beta}_H) \left[ \lambda_H(t|X = 1, D \geq t) - \exp(\hat{\beta}_H)\lambda_H(t|X = 0, D \geq t) \right]$$

with positive weights $w(t, \hat{\beta}_H)$

Numerical solutions
Effects of patient heterogeneity ($\theta$) and length of FU

![Graph showing the relationship between $\hat{\beta}_H/\beta_H$ and $\beta_D$ (Treatment effect on mortality). The line indicates the value of $\theta = 0$.](image-url)
Effects of patient heterogeneity ($\theta$) and length of FU

\[ \frac{\hat{\beta}_H}{\beta_H} \]

\[ \beta_D \text{ (Treatment-effect on mortality)} \]

\[ \theta = 0 \quad \theta = 1, \text{ FU 2 years} \]
Effects of patient heterogeneity ($\theta$) and length of FU

\[ \hat{\beta}_H / \beta_H \]

$\beta_D$ (Treatment–effect on mortality)

- $\theta = 0$
- $\theta = 1$, FU 2 years
- $\theta = 2$, FU 2 years
Effects of patient heterogeneity ($\theta$) and length of FU
CHARM-Preserved: Expected vs observed - $\theta = 3$

Hazard Ratio

0.5 0.6 0.7 0.8 0.9 1 1.1

- Poisson
- Andersen-Gill
- Joint Frailty
CHARM-Preserved: Expected vs observed - $\theta = 10$

Hazard Ratio

Poisson

Andersen–Gill

Joint Frailty

0.5 0.6 0.7 0.8 0.9 1.0 1.1
CORONA: Expected vs observed - $\theta = 3$

Hazard Ratio

- 1st HFH - Cox
- Poisson
- Andersen-Gill
- Joint Frailty

x-axis: 0.5 to 1.1
Type I error rates - simulation study

Parameters: $\lambda_H=3$, $\lambda_D=0.178$, $\beta_H = 0$, $\theta = 1$, $N=1000$, $FU=2$
Summary and discussion

- Our methods can explain differences between marginal and conditional estimates
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- Consensus is needed on the "true effect", that we want to estimate.
True Effect

EMA Guideline: “terminal events’ will ... need to be addressed ... since naïve approaches to the analysis of hospitalisation rate data will not reflect the true effect of the investigational agent."\(^1\)
True Effect

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- Rogers et al: "We advocate the use of the JFM for future trials that consider recurrent events as the primary outcome."\(^2\)
True Effect

- EMA Guideline: “terminal events’ will ... need to be addressed ... since naïve approaches to the analysis of hospitalisation rate data will not reflect the true effect of the investigational agent."¹

- Rogers et al: "We advocate the use of the JFM for future trials that consider recurrent events as the primary outcome."²

- Why dont we discuss differences between marginal and conditional effects in univariate survival (that is also prone to selection effects)?

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¹ EMA (2016): Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure (Draft)
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