Joint Modelling of hospitalizations and survival in Heart Failure patients: a discrete nonparametric frailty approach

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Outline

Introduction - Heart Failure & ACE Inhibitors

Definition

Heart failure is a condition characterized by a deterioration in the function of the heart that makes it unable to contract or release adequately to pump enough blood to meet the body's needs[a].

[a] Ministero della Salute della Repubblica Italiana, 2022

- mortality
- (increasing) prevalence over the population
- impact over the sanitary system
- pharmacological treatment: Angiontensin-Converting Enzyme Inhibitors

Introduction - Research Questions

Methodological Discussion

Investigate Survival analysis tools able both to model two correlated processes, the former regarding recurrent events (i.e. hospitalizations) and the latter terminal ones (i.e. deaths), and to assess the effect that exogenous variables (e.g. ACE inhibitors therapy) have on them.

Dataset - ACE Inhibitors Dataset

ID	Sex	Adherent	AgeEvent	Comorbidity	GapEvent	Event	Death
10003004	F	0	75	5	229	1	
10003004	F	1	75	6	131	1	
10003004	F	0	76	6	168	1	
10003004	F	0	77	7	353	1	
10003004	F	1	79	7	1,153	0	1

Table 1: Data table of patient 10003004.

- **GapEvent**: days elapsed from the previous patient's hospitalization to the next one. The last gap time of each patient expresses the time elapsed from the last known hospitalization to the terminal event, which may be death or censoring.
- **Event**: hospitalization (1) or terminal event (0)
- **Death**: death (1) or censoring (0)

Dataset - ACE Inhibitors Dataset

ID	Sex	Adherent	AgeEvent	Comorbidity	GapEvent	Event	Death
10003004	F	0	75	5	229	1	
10003004	F	1	75	6	131	1	
10003004	F	0	76	6	168	1	
10003004	F	0	77	7	353	1	
10003004	F	1	79	7	1,153	0	1

Table 1: Data table of patient 10003004.

- **Sex**: patient's gender
- **Adherent**: specifies whether a patient is considered adherent (1) or not (0) to the ACE inhibitors treatment at current event time
- **AgeEvent**: patient's age at current event time
- **Comorbidity**: number of patient's known comorbidities at current event time

Methods - Proportional Hazard Frailty models

Proportional Hazard Frailty models

Express the hazard like the Cox model, but exploit the introduction of a random unobserved covariate, the *frailty*, to describe the heterogeneity at subject level unexplained by the observed set of covariates. For every subject $i, i = 1, ..., N$

$$h(t|\boldsymbol{X}_i(t), u_i) = h_0(t) \exp\left\{\boldsymbol{\beta}^T \boldsymbol{X}_i(t) + u_i\right\}$$

- applied to account for within-subject correlated times in the recurrent events process
- jointly model the two processes linking the frailties

Methods - Joint Frailty model by Ng et al.

Joint Frailty model by Ng et al.

$$\begin{cases} h_i^R(t|\boldsymbol{x}_i^R(t)) = h_0^R(t)\exp\{\boldsymbol{\beta}^{\boldsymbol{T}}\boldsymbol{x}_i^R(t) + u_i\} \\ h_i^D(t|\boldsymbol{x}_i^D(t)) = h_0^D(t)\exp\{\boldsymbol{\gamma}^{\boldsymbol{T}}\boldsymbol{x}_i^D(t) + v_i\} \end{cases}$$

$$p\left(\begin{bmatrix} u \\ v \end{bmatrix}\right) = N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \theta_u^2 & \rho\theta_u\theta_v \\ \rho\theta_u\theta_v & \theta_v^2 \end{bmatrix}\right)$$

- custom implementation of the estimation routine proposed in Ng, S.K. et al., 2020
- ease of interpretation

Methods - Discrete Nonparametric frailty model

Discrete Nonparametric frailty model

$$\begin{cases} h_i^R(t|\boldsymbol{x}_i^R(t)) = h_0^R(t)\exp\{\boldsymbol{\beta}^{\boldsymbol{T}}\boldsymbol{x}_i^R(t) + u_i\} \\ h_i^D(t|\boldsymbol{x}_i^D(t)) = h_0^D(t)\exp\{\boldsymbol{\gamma}^{\boldsymbol{T}}\boldsymbol{x}_i^D(t) + v_i\} \end{cases}$$

$$p\left(\begin{bmatrix} u \\ v \end{bmatrix}\right) = P^* \quad \text{measure on } \mathbb{R}^2$$

- discrete measure with finite support
- a priori unknown number of support points (L)

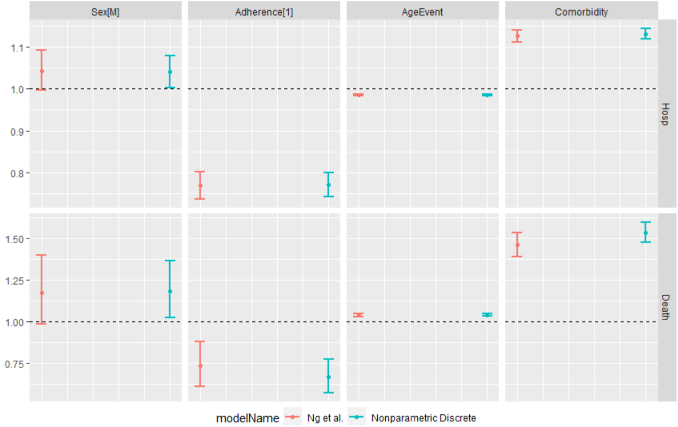
Support	$\boldsymbol{P}$	P_1	P_2	...	P_L
Weight	$\boldsymbol{w}$	w_1	w_2	...	w_L

Methods - Discrete Nonparametric frailty model

- Likelihood Formulation
  - known support cardinality
  - mixture approach
- Expectation-Maximization algorithm
  - closed form Expectation Step
  - multi-step Maximization Step
- Support Reduction procedure
  - grid initialization
  - support reduction
    - *MinDist* threshold
  - convergence

Results - Coefficients' Estimation

- Hazard ratios and 95% confidence intervals comparison



Results - Coefficients' Estimation

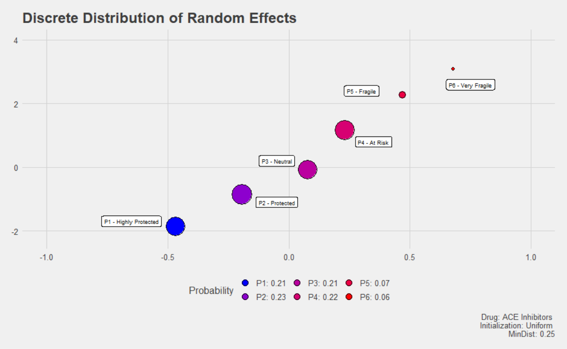
- **Sex**: male subjects are suggested to be slightly more prone to risk of hospitalization (HR=1.035) and death (HR=1.197).
- **Adherent**: being adherent yields a 22.9% decrease in the risk of a new hospitalization (HR=0.771) and a 33.5% decrease in the risk of death.
- **AgeEvent**: 1.5% reduction of the risk of hospitalization per year (HR=0.985), 4.1% increase of the risk of death (HR=1.040).
- **Comorbidity**: increase of 13.1% in the risk of hospitalization and a very high increase of 53.5% in the risk of death per comorbidity registered.

Results - Frailties' Characterization

- Ng et al.:

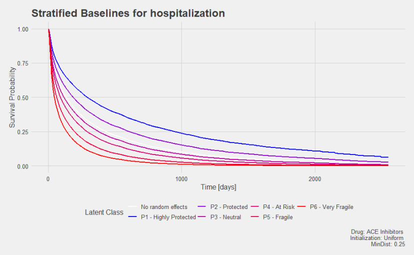
$$\begin{cases} \theta_u^2 = 0.124 \\ \theta_v^2 = 1.378 \\ \rho = 0.879 \end{cases}$$

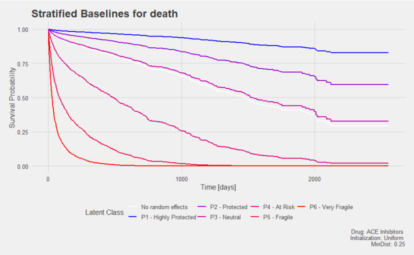
- Nonparametric ($MinDist$=0.25)



Results - Frailties' Characterization

- Induced stratification of baseline survival functions





Conclusions

- ✓ Coherent in coefficients' estimation with Ng et al. model
  - adherent patients are significantly less at risk of a new hospitalization event and likely to survive longer than non adherent ones
- ✓ Coherent in frailties' characterization with Ng et al. model
  - $\oplus$ ease of interpretation of the identified frailties' discrete distribution
  - $\oplus$ insightful latent partition analysis

References

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Additional Material - HF Dataset

HFData

Administrative database of Regione Lombardia and reports information about patients which were hospitalized, due to heart failure, during the period from 2000 to 2012. In particular, it comprises hospitalization discharges, ambulatory care events, ER services and drugs prescriptions [a].

[a] Mazzali et al., 2016

- Drug Prescriptions available from January 1st, 2006 to December 31st, 2012
- Focus on hospitalizations
- Focus on patients who undergo an ACE inhibitors therapy
- Gap times timescale approach

Additional Material - Adherence

Adherence

Adherence (or compliance) generally refers to whether a patient takes a prescribed medication according to schedule. To quantify it, one of the most widely used approaches is to look at the proportion of days covered (PDC) by prescriptions in a certain period [a].

[a] Karve et al., 2009

$$PDC(t) = \frac{\text{number of distinct coverage days up to time } t}{\text{number of days from index date to time } t} \in [0,1].$$

$$\textbf{Adherent}(t) = \begin{cases} 0, & \text{if } PDC(t) \in [0, 0.8) \\ 1, & \text{if } PDC(t) \in [0.8, 0.1] \end{cases}$$

Additional Material - Considered Models

Considered models

- Disjoint Proportional Hazard Frailty models
- Joint Frailty Model by Rondeau, V. et al., 2007
- Joint Frailty Model by Ng, S.K. et al., 2020
- Discrete Nonparametric Frailty Model

Additional Material - Considered Models

Disjoint models

$$h_i^R(t|\boldsymbol{x}_i^R(t)) = h_0^R(t)\exp\{\beta^{\boldsymbol{T}}\boldsymbol{x}_i^R(t) + u_i\}$$
$$h_i^D(t|\boldsymbol{x}_i^D(t)) = h_0^D(t)\exp\{\gamma^{\boldsymbol{T}}\boldsymbol{x}_i^D(t) + v_i\}$$

$$p(u) = N(0, \theta_u^2)$$
$$p(v) = N(0, \theta_v^2).$$

- Estimation performed through R package `coxme`
- Processes' correlation is not modelled

Additional Material - Considered Models

Joint Frailty model by Rondeau et al.

$$\begin{cases} h_i(t|\eta_i, \boldsymbol{x}_i^R(t)) = h_0^R(t)\exp\{\eta_i + \boldsymbol{\beta}^T \boldsymbol{x}_i^R(t)\} \\ h_i(t|\eta_i, \alpha, \boldsymbol{x}_i^D(t)) = h_0^D(t)\exp\{\alpha\eta_i + \boldsymbol{\gamma}^T \boldsymbol{x}_i^D(t)\} \end{cases}$$

$$p(\eta) = N(0, \theta_\eta^2)$$

- Estimation performed through R package `frailtypack`
- Simple frailty formulation
- Complex estimation routine

Additional Material - Estimation Routine

- Model likelihood
  - Let $\boldsymbol{\Omega} = [\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{w}, \boldsymbol{P}, h_0^R(t), h_0^D(t)]$ the quantities to be estimated
  - Assume L to be known
  - Introduce a set of auxiliary random variables z_{il} which express if patient i is assigned to point P_l
  - Each patient's contribution to the likelihood is written as a mixture of L components

$$L(\boldsymbol{\Omega}; data|z_{il}) = \prod_{i=1}^{N} \prod_{l=1}^{L} \left[w_l \times L_i(\boldsymbol{\Omega}; data|[u,v]_i = P_l) \right]^{z_{il}}$$

Additional Material - Estimation Routine

Each component $L_i(\boldsymbol{\Omega}; data|[u,v]_i = P_l)$ is the product of the full likelihood of two Cox models with a fixed intercept (specified by the abscissa and ordinata of P_l), modelling recurrent and terminal events respectively

$$L_i^R(\boldsymbol{\Omega}; data|u_i = P_l^{(1)}) = \prod_{j=1}^{k_i} \left[h_0^R(t_{ij}^R) \exp\{\boldsymbol{\beta}^T \boldsymbol{X}_{ij}^R + P_l^{(1)}\} \right]^{\delta_{ij}^R} \times$$
$$\exp\left[- H_0^R(t_{ij}^R) \exp\{\boldsymbol{\beta}^T \boldsymbol{X}_{ij}^R + P_l^{(1)}\} \right]$$

$$L_i^D(\boldsymbol{\Omega}; data|v_i = P_l^{(2)}) = \left[h_0^D(t_i^D) \exp\{\boldsymbol{\gamma}^T \boldsymbol{X}_i^D + P_l^{(2)}\} \right]^{\delta_i^D} \times$$
$$\exp\left[- H_0^D(t_i^D) \exp\{\boldsymbol{\gamma}^T \boldsymbol{X}_i^D + P_l^{(2)}\} \right]$$

Additional Material - Estimation Routine

Loglikelihood

$$l(\boldsymbol{\Omega}; data|\mathcal{Z}) = l_w(\boldsymbol{\Omega}_w; data|\mathcal{Z}) + l_R(\boldsymbol{\Omega}_R; data|\mathcal{Z}) + l_D(\boldsymbol{\Omega}_D; data)|\mathcal{Z})$$

$$l_w(\boldsymbol{\Omega}_w; data|\mathcal{Z}) = \sum_{l=1}^{L}\sum_{i=1}^{N} z_{il}\log(w_l)$$

$$\begin{aligned} l_R(\boldsymbol{\Omega}_R; data|\mathcal{Z}) = \sum_{l=1}^{L}\sum_{i=1}^{N} z_{il}\Bigg[\sum_{j=1}^{k_i}\delta_{ij}^R\left[log(h_0^R(t_{ij}^R)) + \boldsymbol{\beta}^T\boldsymbol{X}_{ij}^R + P_l^{(1)}\right] \\ - H_0^R(t_{ij}^R)\exp\{\boldsymbol{\beta}^T\boldsymbol{X}_{ij}^R + P_l^{(1)}\}\Bigg] \end{aligned}$$

$$\begin{aligned} l_D(\boldsymbol{\Omega}_D; data|\mathcal{Z}) = \sum_{l=1}^{L}\sum_{i=1}^{N} z_{il}\Bigg[\delta_{i}^D\left[log(h_0^D(t_{i}^D)) + \boldsymbol{\gamma}^T\boldsymbol{X}_{i}^D + P_l^{(2)}\right] \\ - H_0^D(t_{i}^D)\exp\{\boldsymbol{\gamma}^T\boldsymbol{X}_{i}^D + P_l^{(2)}\}\Bigg] \end{aligned}$$

Additional Material - Estimation Routine

Algorithm 3.3 Support Reduction Estimation Procedure

Set K
Grid Initialization (Gaussian, Uniform, ...)
Choose distance (Euclidean, Manhattan,...)
Set $MinDist$
Set $epsw = 1$
Set $converged = False$, $MaxIt = 200$,$eps = 1e - 03$,$it = 0$
while !$converged$ and $it < MaxIt$ **do**
    Support Reduction: merge points nearer than MinDist
    Expectation step: compute $\mathbb{Z}_{il}$
    Extract the latent partition, delete unassigned masses
    Update $\hat{\boldsymbol{w}}$
    Update $\hat{\boldsymbol{P}}$
    Update $\hat{\boldsymbol{\beta}}$,$\hat{\boldsymbol{\gamma}}$,$\hat{H}_0^R$,$\hat{H}_0^D$
    if Reduction in the current iteration **then**
        $converged = FALSE$
    else
        compute $epsw$
        if $epsw < eps$ **then**
            $converged = TRUE$
        end if
    end if
end while

Additional Material - Estimation Routine

E step

At each iteration compute

$$\mathbb{E}_{\mathcal{Z}|\hat{\mathbf{\Omega}}}\left[l(\mathbf{\Omega}; data)\right]$$

- It reduces to computing the expected values for the auxiliary random variables

$$\mathbb{Z}_{il} = \mathbb{E}\left[z_{il}|\hat{\mathbf{\Omega}}, data\right]$$

and plug these quantities in the loglikelihood equation

Additional Material - Estimation Routine

Given $\hat{\mathbf{\Omega}}$, the $\mathbb{Z}_{il}$ computation can be done in closed form using Bayes theorem, finally yielding

$$\mathrm{Z}_{il} = \frac{w_l \exp\left\{ \sum_{j=1}^{k_i} \left(\delta_{ij}^R P_l^{(1)} - H_0^R(t_{ij}^R)\exp\{\boldsymbol{\beta}^T \boldsymbol{X}_{ij}^R + P_l^{(1)}\}\right) + \delta_i^D P_l^{(2)} - H_0^D(t_i^D)\exp\{\boldsymbol{\gamma}^T \boldsymbol{X}_i^D + P_l^{(2)}\}\right\}}{\sum_{k=1}^{\hat{k}} w_k \exp\left\{ \sum_{j=1}^{L} \left(\delta_{ij}^R P_k^{(1)} - H_0^R(t_{ij}^R)\exp\{\boldsymbol{\beta}^T \boldsymbol{X}_{ij}^R + P_k^{(1)}\}\right) + \delta_i^D P_k^{(2)} - H_0^D(t_i^D)\exp\{\boldsymbol{\gamma}^T \boldsymbol{X}_i^D + P_k^{(2)}\}\right\}}$$

- As the $\mathbb{Z}_{il}$ represent the probabilities of assigning patient i to point l given the current state of parameters, from them we can extract a latent partition of subjects
- The E step is joint with respect to the two processes, since it involves in the computation all the parameters in $\mathbf{\Omega}$

Additional Material - Estimation Routine

M step

The averaged logl

$$l(\boldsymbol{\Omega}; data|\mathbb{Z}_{il}) = l_w(\boldsymbol{\Omega}_w; data|\mathbb{Z}_{il}) + l_R(\boldsymbol{\Omega}_R; data|\mathbb{Z}_{il}) + l_D(\boldsymbol{\Omega}_D; data)|\mathbb{Z}_{il})$$

is optimized following a multi-step approach

- l_w involves $\boldsymbol{w}$;
- l_R involves $\boldsymbol{\beta}$, $H_0^R(t)$ and the abscissa of the points composing the support of the discrete distribution;
- l_D involves γ, $H_0^D(t)$ and the ordinata of the points composing the support of the discrete distribution.

Additional Material - Estimation Routine

l_w

Using Lagrangian optimization ($\boldsymbol{w}$ is constrained to be unitary)

$$\hat{w}_l^{(up)} = \frac{1}{N} \sum_{i=1}^{N} \mathbb{Z}_{il} \quad \forall l = 1, ..., L$$

Additional Material - Estimation Routine

l_R

$$\hat{P}_l^{(1)(up)} = \log\left[\frac{\sum_{i=1}^{N}\mathbb{Z}_{il}\sum_{j=1}^{k_i}\delta_{ij}^R}{\sum_{i=1}^{N}\mathbb{Z}_{il}\sum_{j=1}^{k_i}\hat{H}_0^R(t_{ij}^R)\exp\{\hat{\boldsymbol{\beta}}^T\boldsymbol{X}_{ij}^R\}}\right] \quad \forall l = 1, ..., L$$

$$\hat{H}_0^R(t) = \sum_{ab:t_{ab}^R<t}\frac{m_{ab}}{\sum_{cd\in\mathcal{R}(t_{ab})}\exp\{\hat{\boldsymbol{\beta}}^T\boldsymbol{X}_{cd}^R + \log(\sum_{l=1}^{L}\mathbb{Z}_{il}\exp(\hat{P}_l^{(1)}))\}}$$

$$l_R^{prof}(\boldsymbol{\beta}) = \sum_{i=1}^{N}\sum_{j=1}^{k_i}\delta_{ij}^R\left[\boldsymbol{\beta}^T\boldsymbol{X}_{ij}^R - m_{ij}^R\log\sum_{ab\in\mathcal{R}(t_{ij}^R)}\exp\{\boldsymbol{\beta}^T\boldsymbol{X}_{ij}^R + \log\sum_{l=1}^{L}\mathbb{Z}_{il}\exp(P_l^{(1)}\}\right]$$

Additional Material - Estimation Routine

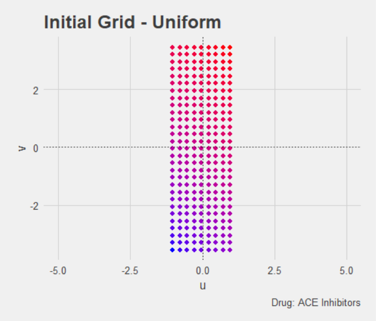
l_D

$$\hat{P}_l^{(2)(up)} = \log\left[\frac{\sum_{i=1}^{N} \mathbb{Z}_{il}\delta_i^D}{\sum_{i=1}^{N} \mathbb{Z}_{il}\hat{H}_0^D(t_i^D)\exp\{\hat{\gamma}^T \boldsymbol{X}_i^D\}}\right] \quad \forall l = 1, ..., L$$

$$\hat{H}_0^{D(up)}(t) = \sum_{a:t_a^D < t} \frac{m_a}{\sum_{c\in\mathcal{R}(t_a)} \exp\{\hat{\gamma}^T \boldsymbol{X}_c^D + \log(\sum_{l=1}^{L} \mathbb{Z}_{il}\exp(\hat{P}_l^{(2)}))\}}$$

$$l_D^{prof}(\boldsymbol{\gamma}) = \sum_{i=1}^{N} \delta_i^D \left[\boldsymbol{\gamma}^T \boldsymbol{X}_i^D - m_i^D \log \sum_{a\in\mathcal{R}(t_i^D)} \exp\{\boldsymbol{\gamma}^T \boldsymbol{X}_i^D + \log \sum_{l=1}^{L} \mathbb{Z}_{il}\exp(P_l^{(2)})\}\right]$$

- Discrete distribution initialization
  - Sampling from a bivariate Gaussian distribution
  - Discrete Uniform distribution over a rectangle in $\mathbb{R}^2$



Additional Material - Estimation Routine

- Support reduction step
  - At the start of each iteration in the EM algorithm, the minimum distance couple of points in the current support whose Euclidean distance is less than the user defined threshold *MinDist* is collapsed in a unique point.
  - The procedure is repeated until any couple of points distance is under the threshold.

$$\boldsymbol{P}^{(new)} = \left[\frac{P_1^{(1)(old)} + P_2^{(1)(old)}}{2}, \frac{P_1^{(2)(old)} + P_2^{(2)(old)}}{2} \right]$$

$$w^{(new)} = w_1^{(old)} + w_2^{(old)}.$$

Additional Material - Estimation Routine

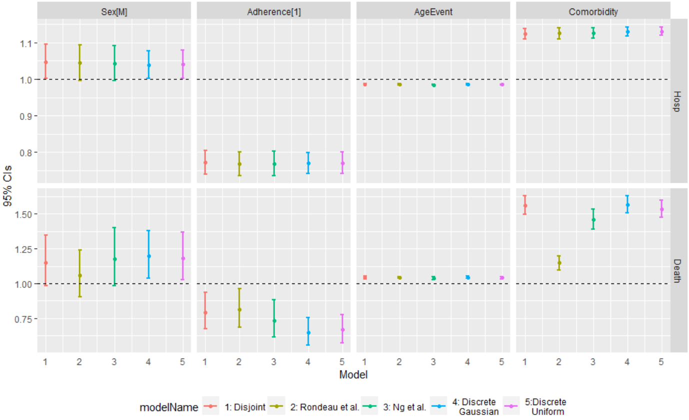
- Unassigned points deletion step
  - After the Expectation Step, the latent partition of patients is extracted.
  - Eventual masses to which no patients are assigned are deleted
- Convergence
  - No support reduction/points deletion in the current iteration
  - the difference between old and updated weights of the discrete distribution, computed in maximum norm, is less than 1e-03.

Additional Material - Results

Variables	Estimate	StdDev	HR	CI95	pvalue
Recurrent Events					
Sex [M]	0.039	0.019	1.039	[1.003,1.079]	0.034
Adherent [1]	-0.259	0.019	0.771	[0.743,0.800]	<2e-16
AgeEvent	-0.015	0.001	0.985	[0.984,0.987]	<2e-16
Comorbidity	0.123	0.005	1.131	[1.119,1.143]	<2e-16
Recurrent Events					
Sex [M]	0.169	0.073	1.184	[1.025,1.366]	0.021
Adherent [1]	-0.407	0.078	0.665	[0.571,0.755]	1.7e-07
AgeEvent	0.039	0.004	1.041	[1.032,1.049]	<2e-16
Comorbidity	0.429	0.020	1.535	[1.476,1.597]	<2e-16

Frailty	P1	P2	P3	P4	P5	P6
u	-0.466	-0.194	0.079	0.231	0.468	0.679
v	-1.872	-0.859	-0.090	1.166	2.277	3.088
w	0.208	0.234	0.206	0.217	0.071	0.063

Additional Material - Results



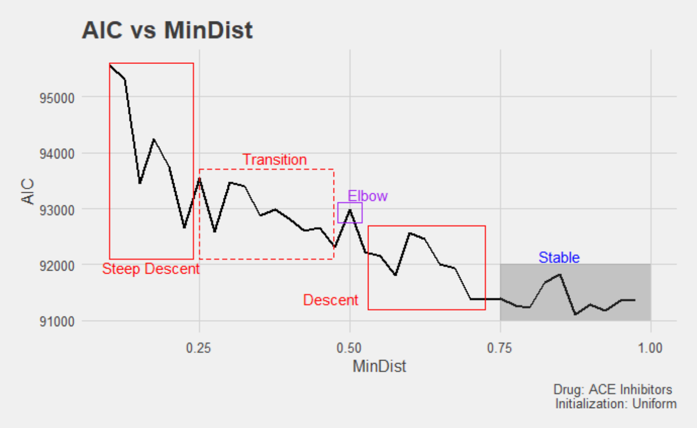
Additional Material - Results

Induced Stratification of Baseline Survival function

$$
\begin{aligned}
h_i^R(t|\boldsymbol{x}_i R(t)) &= \sum_{l=1}^{L} w_l h_0^R(t) \exp\{u_l\} \exp\{\boldsymbol{\beta}^T \boldsymbol{x}_i^R(t)\} \\
&= \sum_{l=1}^{L} w_l h_{0l}^R(t) \exp\{\boldsymbol{\beta}^T \boldsymbol{x}_i^R(t)\}
\end{aligned}
$$

$$
\begin{aligned}
h_i^D(t|\boldsymbol{x}_i^D(t)) &= \sum_{l=1}^{L} w_l h_0^D(t) \exp\{v_l\} \exp\{\boldsymbol{\gamma}^T \boldsymbol{x}_i^D(t)\} \\
&= \sum_{l=1}^{L} w_l h_{0l}^D(t) \exp\{\boldsymbol{\gamma}^T \boldsymbol{x}_i^D(t)\}.
\end{aligned}
$$

Additional Material - *MinDist* Tuning



Additional Material - *MinDist* Tuning