Analysis of multistate data with realistic rate models and multiple time scales: A dogmatic approach

Bendix Carstensen Steno Diabetes Center
Gentofte, Denmark
http://BendixCarstensen.com

IARC, Lyon, France,
11 April 2018

The dogma [1]

- do not condition on the future

The dogma [1]

- do not condition on the future
- do not count people after they are dead

The dogma [1]

- do not condition on the future
- do not count people after they are dead
- stick to this world

The dogma [1]

- do not condition on the future — indisputable
- do not count people after they are dead
- stick to this world

The dogma [1]

- do not condition on the future — indisputable
- do not count people after they are dead — disputable
- stick to this world

The dogma [1]

- do not condition on the future — indisputable
- do not count people after they are dead — disputable
- stick to this world — expandable

do not condition on the future

- commonly seen in connection with “immortal time bias”

do not condition on the future

- commonly seen in connection with "immortal time bias"
- allocation of follow-up (risk time) to a covariate value only assumed in the future

do not condition on the future

- commonly seen in connection with “immortal time bias”
- allocation of follow-up (risk time) to a covariate value only assumed in the future
- all follow-up among persons **ever** on insulin allocated to the insulin group
  — including the time **prior** to insulin use (when not on insulin)

do not condition on the future

- commonly seen in connection with "immortal time bias"
- allocation of follow-up (risk time) to a covariate value only assumed in the future
- all follow-up among persons **ever** on insulin allocated to the insulin group
  — including the time **prior** to insulin use (when not on insulin)
- events always with the correct covariate values

do not condition on the future

- commonly seen in connection with "immortal time bias"
- allocation of follow-up (risk time) to a covariate value only assumed in the future
- all follow-up among persons **ever** on insulin allocated to the insulin group
  — including the time **prior** to insulin use (when not on insulin)
- events always with the correct covariate values
- $\Rightarrow$ too **much** PY in insulin group; rates too **small**

do not condition on the future

- commonly seen in connection with "immortal time bias"
- allocation of follow-up (risk time) to a covariate value only assumed in the future
- all follow-up among persons **ever** on insulin allocated to the insulin group
  — including the time **prior** to insulin use (when not on insulin)
- events always with the correct covariate values
- $\Rightarrow$ too **much** PY in insulin group; rates too **small**
- $\Rightarrow$ too **little** PY in non-insulin group; rates too **large**

do not condition on the future

- commonly seen in connection with "immortal time bias"
- allocation of follow-up (risk time) to a covariate value only assumed in the future
- all follow-up among persons **ever** on insulin allocated to the insulin group
  — including the time **prior** to insulin use (when not on insulin)
- events always with the correct covariate values
- $\Rightarrow$ too **much** PY in insulin group; rates too **small**
- $\Rightarrow$ too **little** PY in non-insulin group; rates too **large**
- $\Rightarrow$ insulin vs. non-insulin rates **under**estimated

do not count people after they are dead

- Reference to Fine & Gray's paper on models for the subdistribution hazard [2]

do not count people after they are dead

- Reference to Fine & Gray's paper on models for the subdistribution hazard [2]
- Recall: hazard and cumulative risk for all cause death:

$$F(t) = 1 - \exp\Big(-\Lambda(t)\Big) \quad \Leftrightarrow \quad \lambda(t) = \Lambda'(t) = \Big(\log\big(1 - F(t)\big)\Big)'$$

do not count people after they are dead

- Reference to Fine & Gray's paper on models for the subdistribution hazard [2]
- Recall: hazard and cumulative risk for all cause death:

$$F(t) = 1 - \exp\big(-\Lambda(t)\big) \quad \Leftrightarrow \quad \lambda(t) = \Lambda'(t) = \Big(\log\big(1 - F(t)\big)\Big)'$$

- Subdistribution hazard — with more causes of death (compting risks), for cumulative risk of cause c, $F_c(t)$:

$$\tilde{\lambda}_c(t) = \Big(\log\big(1 - F_c(t)\big)\Big)'$$

do not count people after they are dead

- Reference to Fine & Gray's paper on models for the subdistribution hazard [2]
- Recall: hazard and cumulative risk for all cause death:

$$F(t) = 1 - \exp\big(-\Lambda(t)\big) \quad \Leftrightarrow \quad \lambda(t) = \Lambda'(t) = \Big(\log\big(1 - F(t)\big)\Big)'$$

- Subdistribution hazard — with more causes of death (compting risks), for cumulative risk of cause c, $F_c(t)$:

$$\tilde{\lambda}_c(t) = \Big(\log\big(1 - F_c(t)\big)\Big)'$$

- Note: F_c depends on all cause-specific hazards

do not count people after they are dead

- The estimation of the subdistribution hazard boils down to:

$$\tilde{h}(t) = \mathrm{P}\left\{X(t + \,\mathrm{d}t) = j | X(t) \neq j\right\} / \,\mathrm{d}t$$

  that is, the instantaneous rate of failure per time unit from cause j among those who are either alive or have died from causes other than j at time t

do not count people after they are dead

- The estimation of the subdistribution hazard boils down to:

$$\tilde{h}(t) = \mathrm{P}\left\{X(t + \mathrm{d}t) = j | X(t) \neq j\right\} / \mathrm{d}t$$

  that is, the instantaneous rate of failure per time unit from cause j among those who are either alive or have died from causes other than j at time t
- . . . sounds crazy, but. . .

do not count people after they are dead

- The estimation of the subdistribution hazard boils down to:

$$\tilde{h}(t) = \mathrm{P}\left\{X(t+\,\mathrm{d}t) = j | X(t) \neq j\right\} / \,\mathrm{d}t$$

  that is, the instantaneous rate of failure per time unit from cause j among those who are either alive or have died from causes other than j at time t
- . . . sounds crazy, but. . .
- when modeling the **cumulative risk** you must refer back to the size of the **original** population, which include those dead from other causes.

do not count people after they are dead

- The estimation of the subdistribution hazard boils down to:

$$\tilde{h}(t) = \mathrm{P}\left\{X(t + \mathrm{d}t) = j | X(t) \neq j\right\} / \, \mathrm{d}t$$

  that is, the instantaneous rate of failure per time unit from cause j among those who are either alive or have died from causes other than j at time t
- . . . sounds crazy, but. . .
- when modeling the **cumulative risk** you must refer back to the size of the **original** population, which include those dead from other causes.
- The debate is rather if the subdistribution hazard is a useful scale for modeling and reporting from competing risk settings

stick to this world

- the “net” survival or “cause specific survival”:

$$S_c(t) = \exp\left(\int_0^t \lambda_c(s)\ \mathrm{d}s\right)$$

stick to this world

- the “net” survival or “cause specific survival”:

$$S_c(t) = \exp\left(\int_0^t \lambda_c(s)\ \mathrm{d}s\right)$$

- not a proper probability

stick to this world

- the "net" survival or "cause specific survival":

$$S_c(t) = \exp\left(\int_0^t \lambda_c(s)\ \mathrm{d}s\right)$$

- not a proper probability
- the probability of survival if

stick to this world

- the “net” survival or “cause specific survival”:

$$S_c(t) = \exp\left(\int_0^t \lambda_c(s)\ \mathrm{d}s\right)$$

- not a proper probability
- the probability of survival if
  - all other causes of death than c were absent

stick to this world

- the "net" survival or "cause specific survival":

$$S_c(t) = \exp\left(\int_0^t \lambda_c(s)\ \mathrm{d}s\right)$$

- not a proper probability
- the probability of survival if
  - all other causes of death than c were absent
  - c-specific mortality rate were still the same

stick to this world

- the "net" survival or "cause specific survival":

$$S_c(t) = \exp\left(\int_0^t \lambda_c(s)\ \mathrm{d}s\right)$$

- not a proper probability
- the probability of survival if
  - all other causes of death than c were absent
  - c-specific mortality rate were still the same
- so it is just a transformation of the cause-specific rate with no real world interpretation

stick to this world

- the "net" survival or "cause specific survival":

$$S_c(t) = \exp\left(\int_0^t \lambda_c(s)\ \mathrm{d}s\right)$$

- not a proper probability
- the probability of survival if
  - all other causes of death than c were absent
  - c-specific mortality rate were still the same
- so it is just a transformation of the cause-specific rate with no real world interpretation
- ... do not label quantities "survival" or "probability" when they are not

stick to this world

- the “net” survival or “cause specific survival”:

$$S_c(t) = \exp\left(\int_0^t \lambda_c(s)\ \mathrm{d}s\right)$$

- not a proper probability
- the probability of survival if
  - all other causes of death than c were absent
  - c-specific mortality rate were still the same
- so it is just a transformation of the cause-specific rate with no real world interpretation
- ...do not label quantities “survival” or “probability” when they are not

stick to this world

- the "net" survival or "cause specific survival":

$$S_c(t) = \exp\left(\int_0^t \lambda_c(s)\ \mathrm{d}s\right)$$

- not a proper probability
- the probability of survival if
  - all other causes of death than c were absent
  - c-specific mortality rate were still the same
- so it is just a transformation of the cause-specific rate with no real world interpretation
- ...do not label quantities "survival" or "probability" when they are not (of this world)

(further) dogma for “sticking to this world”

- rates are continuous in time (and “smooth”)

(further) dogma for “sticking to this world”

- rates are continuous in time (and “smooth”)
- rates may depend on more than one time scale

(further) dogma for “sticking to this world”

- rates are continuous in time (and “smooth”)
- rates may depend on more than one time scale
- which, is an empirical question

A look at the Cox model

$$\lambda(t, x) = \lambda_0(t) \times \exp(x'\beta)$$

A model for the rate as a function of t and x.

A look at the Cox model

$$\lambda(t, x) = \lambda_0(t) \times \exp(x'\beta)$$

A model for the rate as a function of t and x.

Covariates:

- x

A look at the Cox model

$$\lambda(t, x) = \lambda_0(t) \times \exp(x'\beta)$$

A model for the rate as a function of t and x.

Covariates:

- x
- t

A look at the Cox model

$$\lambda(t, x) = \lambda_0(t) \times \exp(x'\beta)$$

A model for the rate as a function of t and x.

Covariates:

- x
- t
- ... often the effect of t is ignored (forgotten?)

A look at the Cox model

$$\lambda(t, x) = \lambda_0(t) \times \exp(x'\beta)$$

A model for the rate as a function of t and x.

Covariates:

- x
- t
- ... often the effect of t is ignored (forgotten?)
- *i.e.* left unreported

The Cox-likelihood as profile likelihood

- One parameter per death time to describe the effect of time (i.e. the chosen timescale).

$$\log\big(\lambda(t, x_i)\big) = \log\big(\lambda_0(t)\big) + \underbrace{\beta_1 x_{1i} + \cdots + \beta_p x_{pi}}_{\eta_i} = \alpha_t + \eta_i$$

The Cox-likelihood as profile likelihood

- One parameter per death time to describe the effect of time (i.e. the chosen timescale).

$$\log\big(\lambda(t, x_i)\big) = \log\big(\lambda_0(t)\big) + \underbrace{\beta_1 x_{1i} + \cdots + \beta_p x_{pi}}_{\eta_i} = \alpha_t + \eta_i$$

- Profile likelihood:

The Cox-likelihood as profile likelihood

- One parameter per death time to describe the effect of time (i.e. the chosen timescale).

$$\log\big(\lambda(t, x_i)\big) = \log\big(\lambda_0(t)\big) + \underbrace{\beta_1 x_{1i} + \cdots + \beta_p x_{pi}}_{\eta_i} = \alpha_t + \eta_i$$

- Profile likelihood:
  - Derive estimates of α_t as function of data and βs
    — assuming constant rate between death/censoring times

The Cox-likelihood as profile likelihood

- One parameter per death time to describe the effect of time (i.e. the chosen timescale).

$$\log\big(\lambda(t, x_i)\big) = \log\big(\lambda_0(t)\big) + \underbrace{\beta_1 x_{1i} + \cdots + \beta_p x_{pi}}_{\eta_i} = \alpha_t + \eta_i$$

- Profile likelihood:
  - Derive estimates of α_t as function of data and βs
    — assuming constant rate between death/censoring times
  - Insert in likelihood, now only a function of data and βs

The Cox-likelihood as profile likelihood

- One parameter per death time to describe the effect of time (i.e. the chosen timescale).

$$\log\big(\lambda(t, x_i)\big) = \log\big(\lambda_0(t)\big) + \underbrace{\beta_1 x_{1i} + \cdots + \beta_p x_{pi}}_{\eta_i} = \alpha_t + \eta_i$$

- Profile likelihood:
  - Derive estimates of α_t as function of data and βs
    — assuming constant rate between death/censoring times
  - Insert in likelihood, now only a function of data and βs
  - This turns out to be Cox's partial likelihood

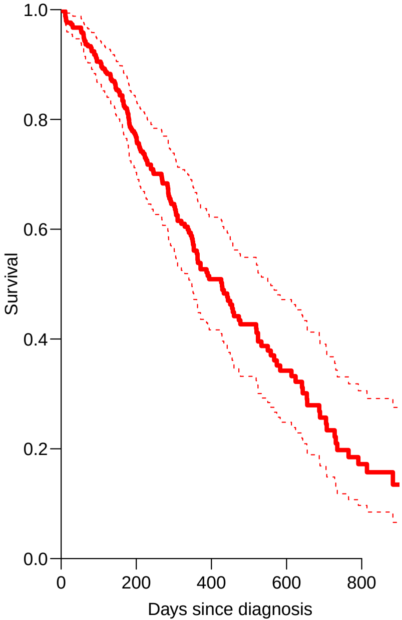
The Cox-likelihood as profile likelihood

- One parameter per death time to describe the effect of time (i.e. the chosen timescale).

$$\log\big(\lambda(t, x_i)\big) = \log\big(\lambda_0(t)\big) + \underbrace{\beta_1 x_{1i} + \cdots + \beta_p x_{pi}}_{\eta_i} = \alpha_t + \eta_i$$

- Profile likelihood:
  - Derive estimates of α_t as function of data and βs
    — assuming constant rate between death/censoring times
  - Insert in likelihood, now only a function of data and βs
  - This turns out to be Cox's partial likelihood
- Cumulative intensity $(\Lambda_0(t))$ obtained via the Breslow-estimator

Mayo Clinic lung cancer data: 60 year old woman



Splitting the dataset a priori

- The Poisson approach needs a dataset of empirical rates (d, y) with suitably small values of y.

Splitting the dataset a priori

- The Poisson approach needs a dataset of empirical rates (d, y) with suitably small values of y.
- — each individual contributes many empirical rates

Splitting the dataset a priori

- The Poisson approach needs a dataset of empirical rates (d, y) with suitably small values of y.
- — each individual contributes many empirical rates
- (one per risk-set contribution in Cox-modelling)

Splitting the dataset a priori

- The Poisson approach needs a dataset of empirical rates (d, y) with suitably small values of y.
- — each individual contributes many empirical rates
- (one per risk-set contribution in Cox-modelling)
- From each empirical rate we get:

Splitting the dataset a priori

- The Poisson approach needs a dataset of empirical rates (d, y) with suitably small values of y.
- — each individual contributes many empirical rates
- (one per risk-set contribution in Cox-modelling)
- From each empirical rate we get:
  - Poisson-response d

Splitting the dataset a priori

- The Poisson approach needs a dataset of empirical rates (d, y) with suitably small values of y.
- — each individual contributes many empirical rates
- (one per risk-set contribution in Cox-modelling)
- From each empirical rate we get:
  - Poisson-response d
  - Risk time $y \rightarrow \log(y)$ as offset

Splitting the dataset a priori

- The Poisson approach needs a dataset of empirical rates (d, y) with suitably small values of y.
- — each individual contributes many empirical rates
- (one per risk-set contribution in Cox-modelling)
- From each empirical rate we get:
  - Poisson-response d
  - Risk time $y \rightarrow \log(y)$ as offset
  - time scale covariates: current age, current date, ...

Splitting the dataset a priori

- The Poisson approach needs a dataset of empirical rates (d, y) with suitably small values of y.
- — each individual contributes many empirical rates
- (one per risk-set contribution in Cox-modelling)
- From each empirical rate we get:
  - Poisson-response d
  - Risk time $y \rightarrow \log(y)$ as offset
  - time scale covariates: current age, current date, ...
  - other covariates

Splitting the dataset a priori

- The Poisson approach needs a dataset of empirical rates (d, y) with suitably small values of y.
- — each individual contributes many empirical rates
- (one per risk-set contribution in Cox-modelling)
- From each empirical rate we get:
  - Poisson-response d
  - Risk time $y \rightarrow \log(y)$ as offset
  - time scale covariates: current age, current date, ...
  - other covariates
- Contributions not independent, but likelihood is a product

Splitting the dataset a priori

- The Poisson approach needs a dataset of empirical rates (d, y) with suitably small values of y.
- — each individual contributes many empirical rates
- (one per risk-set contribution in Cox-modelling)
- From each empirical rate we get:
  - Poisson-response d
  - Risk time $y \rightarrow \log(y)$ as offset
  - time scale covariates: current age, current date, ...
  - other covariates
- Contributions not independent, but likelihood is a product
- Same likelihood as for independent Poisson variates

Splitting the dataset a priori

- The Poisson approach needs a dataset of empirical rates (d, y) with suitably small values of y.
- — each individual contributes many empirical rates
- (one per risk-set contribution in Cox-modelling)
- From each empirical rate we get:
  - Poisson-response d
  - Risk time $y \rightarrow \log(y)$ as offset
  - time scale covariates: current age, current date, ...
  - other covariates
- Contributions not independent, but likelihood is a product
- Same likelihood as for independent Poisson variates
- Poisson `glm` with spline/factor effect of time

Example: Mayo Clinic lung cancer

- Survival after lung cancer

Example: Mayo Clinic lung cancer

- Survival after lung cancer
- Covariates:

Example: Mayo Clinic lung cancer

- Survival after lung cancer
- Covariates:
  - Age at diagnosis

Example: Mayo Clinic lung cancer

- Survival after lung cancer
- Covariates:
  - Age at diagnosis
  - Sex

Example: Mayo Clinic lung cancer

- Survival after lung cancer
- Covariates:
    - Age at diagnosis
    - Sex
    - Time since diagnosis

Example: Mayo Clinic lung cancer

- Survival after lung cancer
- Covariates:
  - Age at diagnosis
  - Sex
  - Time since diagnosis
- Cox model

Example: Mayo Clinic lung cancer

- Survival after lung cancer
- Covariates:
  - Age at diagnosis
  - Sex
  - Time since diagnosis
- Cox model
- Split data:

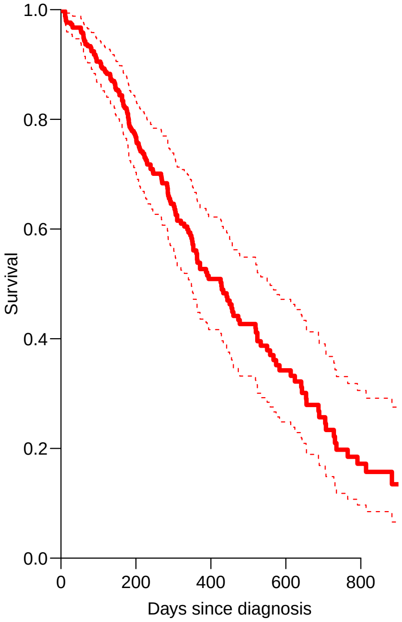
Example: Mayo Clinic lung cancer

- Survival after lung cancer
- Covariates:
  - Age at diagnosis
  - Sex
  - Time since diagnosis
- Cox model
- Split data:
  - Poisson model, time as factor

Example: Mayo Clinic lung cancer

- Survival after lung cancer
- Covariates:
  - Age at diagnosis
  - Sex
  - Time since diagnosis
- Cox model
- Split data:
  - Poisson model, time as factor
  - Poisson model, time as spline

Mayo Clinic
lung cancer
60 year old woman



Example: Mayo Clinic lung cancer I

```
> library( survival )
> library( Epi )
> Lung <- Lexis( exit = list( tfe=time ),
+                exit.status = factor(status,labels=c("Alive","Dead")),
+                data = lung )

NOTE: entry.status has been set to "Alive" for all.
NOTE: entry is assumed to be 0 on the tfe timescale.

> summary( Lung )

Transitions:
     To
From    Alive Dead  Records:  Events: Risk time:  Persons:
  Alive    63  165       228      165      69593       228
```

Example: Mayo Clinic lung cancer II

```
> system.time(
+ mL.cox <- coxph( Surv( tfe, tfe+lex.dur, lex.Xst=="Dead" ) ~
+                    age + factor( sex ),
+                    method="breslow", data=Lung ) )

   user  system elapsed
  0.010   0.001   0.009

> Lung.s <- splitLexis( Lung,
+                          breaks=c(0,sort(unique(Lung$time))),
+                          time.scale="tfe" )
> summary( Lung.s )

Transitions:
     To
From     Alive Dead  Records:  Events: Risk time:  Persons:
  Alive 19857  165     20022      165      69593       228

> subset( Lung.s, lex.id==96 )[,1:11] ; nlevels( factor( Lung.s$tfe ) )
```

Example: Mayo Clinic lung cancer III

```
     lex.id tfe lex.dur lex.Cst lex.Xst inst time status age sex ph.ecog
9235     96   0       5   Alive   Alive   12   30      2  72   1       2
9236     96   5       6   Alive   Alive   12   30      2  72   1       2
9237     96  11       1   Alive   Alive   12   30      2  72   1       2
9238     96  12       1   Alive   Alive   12   30      2  72   1       2
9239     96  13       2   Alive   Alive   12   30      2  72   1       2
9240     96  15      11   Alive   Alive   12   30      2  72   1       2
9241     96  26       4   Alive    Dead   12   30      2  72   1       2

[1] 186

> system.time(
+ mLs.pois.fc <- glm( lex.Xst=="Dead" ~ - 1 + factor( tfe ) +
+                                 age + factor( sex ),
+                                 offset = log(lex.dur),
+                      family=poisson, data=Lung.s, eps=10^-8, maxit=25 )
+             )

   user  system elapsed
 13.550  17.334   8.761
```

Example: Mayo Clinic lung cancer IV

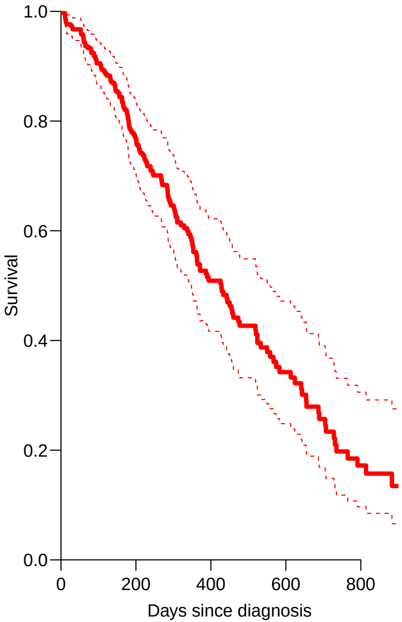
```
> length( coef(mLs.pois.fc) )

[1] 188

> t.kn <- c(0,25,100,500,1000)
> dim( Ns(Lung.s$tfe,knots=t.kn) )

[1] 20022     4

> system.time(
+ mLs.pois.sp <- glm( lex.Xst=="Dead" ~ Ns( tfe, knots=t.kn ) +
+                               age + factor( sex ),
+                     offset = log(lex.dur),
+                     family=poisson, data=Lung.s, eps=10^-8, maxit=25 )
+              )

   user  system elapsed
  0.418   0.510   0.317
```

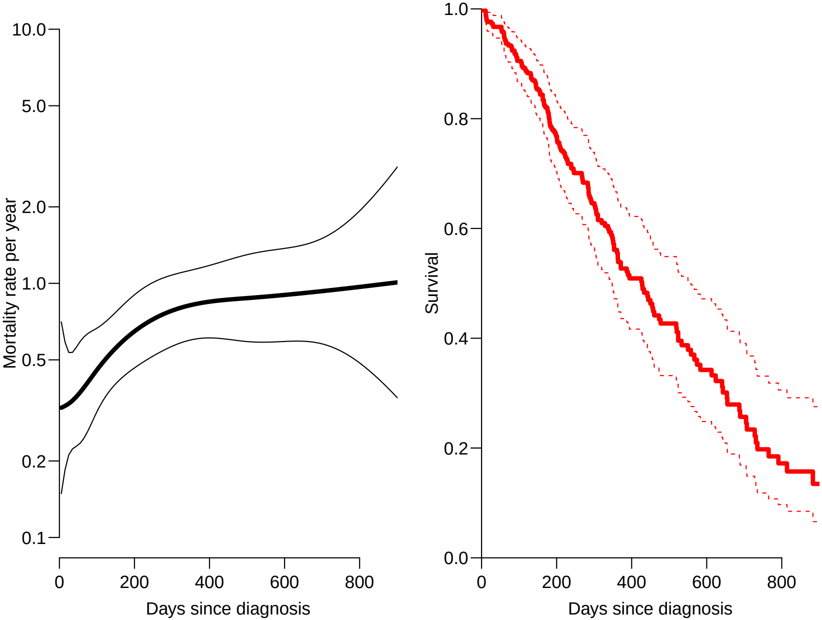
Example: Mayo Clinic lung cancer V

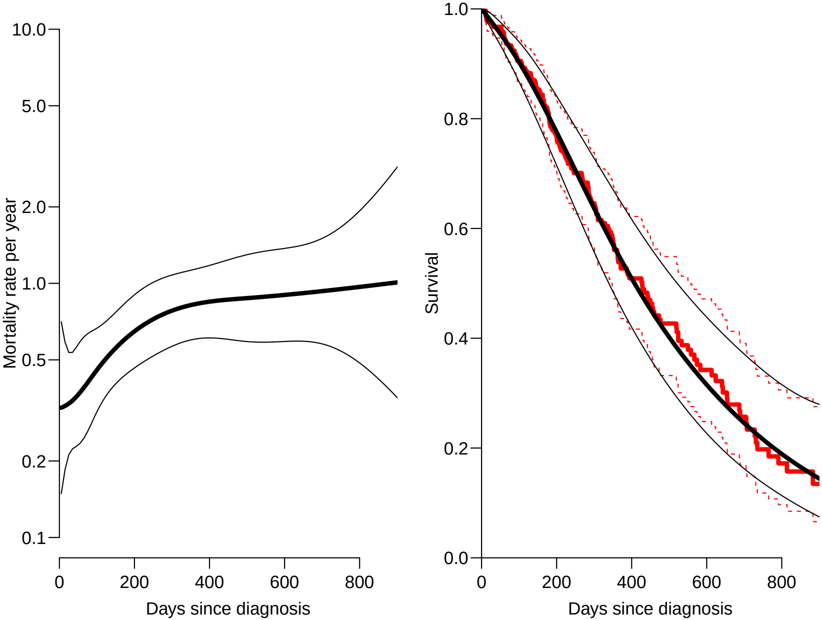
```
> ests <-
+ rbind( ci.exp(mL.cox),
+        ci.exp(mLs.pois.fc,subset=c("age","sex")),
+        ci.exp(mLs.pois.sp,subset=c("age","sex")) )
> cmp <- cbind( ests[c(1,3,5)  ,],
+               ests[c(1,3,5)+1,] )
> rownames( cmp ) <- c("Cox","Poisson-factor","Poisson-spline")
> colnames( cmp )[c(1,4)] <- c("age","sex")
```

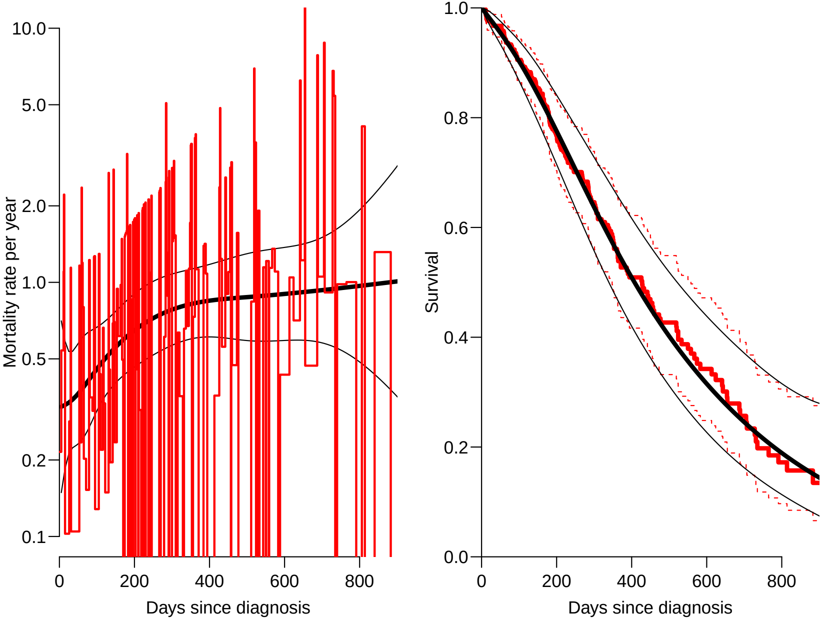
```
> round( cmp, 7 )
```

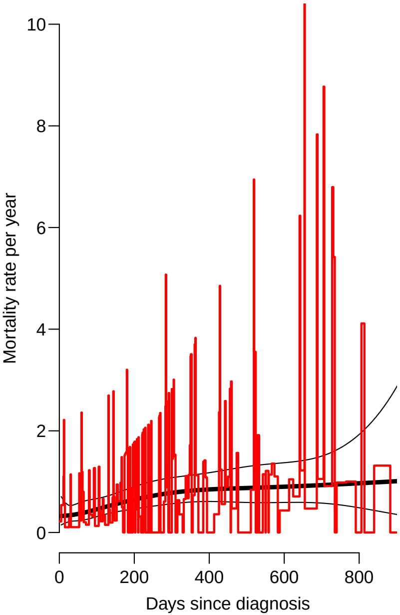
```
                    age      2.5%    97.5%       sex      2.5%     97.5%
Cox            1.017158 0.9989388 1.035710 0.5989574 0.4313720 0.8316487
Poisson-factor 1.017158 0.9989388 1.035710 0.5989574 0.4313720 0.8316487
Poisson-spline 1.016189 0.9980329 1.034676 0.5998287 0.4319932 0.8328707
```


1.0
0.8
0.6
0.4
0.2
0.0
Survival
0
200
400
600
800
Days since diagnosis

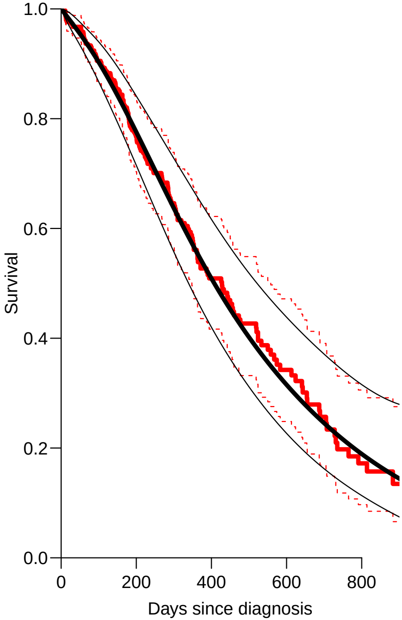

10.0
5.0
2.0
1.0
0.5
0.2
0.1
Mortality rate per year
0
200
400
600
800
Days since diagnosis
1.0
0.8
0.6
0.4
0.2
0.0
Survival
0
200
400
600
800
Days since diagnosis


Mortality rate per year
10.0
5.0
2.0
1.0
0.5
0.2
0.1
0
200
400
600
800
Days since diagnosis
Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
200
400
600
800
Days since diagnosis


Mortality rate per year
10.0
5.0
2.0
1.0
0.5
0.2
0.1
0
200
400
600
800
Days since diagnosis
Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
200
400
600
800
Days since diagnosis



Mortality rate per year
10
8
6
4
2
0
0
200
400
600
800
Days since diagnosis



Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
200
400
600
800
Days since diagnosis

Deriving the survival function

```
> mLs.pois.sp <- glm( lex.Xst=="Dead" ~ Ns( tfe, knots=t.kn ) +
+                                age + factor( sex ),
+                     offset = log(lex.dur),
+                     family=poisson, data=Lung.s, eps=10^-8, maxit=25 )
```

```
> CM <- cbind( 1, Ns( seq(10,1000,10)-5, knots=t.kn ), 60, 1 )
> lambda <- ci.exp( mLs.pois.sp, ctr.mat=CM )
> Lambda <- ci.cum( mLs.pois.sp, ctr.mat=CM, intl=10 )[,-4]
> survP  <- exp(-rbind(0,Lambda))
```

Code and output for the entire example available in
`http://bendixcarstensen.com/AdvCoh/WNtCMa/`

What the Cox-model really is

Taking the life-table approach *ad absurdum* by:

- dividing time very finely and

What the Cox-model really is

Taking the life-table approach *ad absurdum* by:

- dividing time very finely and
- modeling one covariate, the time-scale, with one parameter per distinct value.

What the Cox-model really is

Taking the life-table approach *ad absurdum* by:

- dividing time very finely and
- modeling one covariate, the time-scale, with one parameter per distinct value.
- the **model** for the time scale is really with exchangeable time-intervals.

What the Cox-model really is

Taking the life-table approach *ad absurdum* by:

- dividing time very finely and
- modeling one covariate, the time-scale, with one parameter per distinct value.
- the **model** for the time scale is really with exchangeable time-intervals.
- $\Rightarrow$ difficult to access the baseline hazard (which looks terrible)

What the Cox-model really is

Taking the life-table approach *ad absurdum* by:

- dividing time very finely and
- modeling one covariate, the time-scale, with one parameter per distinct value.
- the **model** for the time scale is really with exchangeable time-intervals.
- $\Rightarrow$ difficult to access the baseline hazard (which looks terrible)
- $\Rightarrow$ uninitiated tempted to show survival curves where irrelevant

Models of this world

- Replace the α_ts by a parametric function $f(t)$ with a limited number of parameters, for example:

Models of this world

- Replace the α_ts by a parametric function $f(t)$ with a limited number of parameters, for example:
  - Piecewise constant

Models of this world

- Replace the α_ts by a parametric function $f(t)$ with a limited number of parameters, for example:
  - Piecewise constant
  - Splines (linear, quadratic or cubic)

Models of this world

- Replace the α_ts by a parametric function $f(t)$ with a limited number of parameters, for example:
  - Piecewise constant
  - Splines (linear, quadratic or cubic)
  - Fractional polynomials

Models of this world

- Replace the α_ts by a parametric function $f(t)$ with a limited number of parameters, for example:
  - Piecewise constant
  - Splines (linear, quadratic or cubic)
  - Fractional polynomials
- the two latter brings model into "this world":

Models of this world

- Replace the α_ts by a parametric function $f(t)$ with a limited number of parameters, for example:
  - Piecewise constant
  - Splines (linear, quadratic or cubic)
  - Fractional polynomials
- the two latter brings model into “this world”:
  - smoothly varying rates

Models of this world

- Replace the α_ts by a parametric function $f(t)$ with a limited number of parameters, for example:
    - Piecewise constant
    - Splines (linear, quadratic or cubic)
    - Fractional polynomials
- the two latter brings model into "this world":
    - smoothly varying rates
    - parametric closed form representation of baseline hazard

Models of this world

- Replace the α_ts by a parametric function $f(t)$ with a limited number of parameters, for example:
  - Piecewise constant
  - Splines (linear, quadratic or cubic)
  - Fractional polynomials
- the two latter brings model into "this world":
  - smoothly varying rates
  - parametric closed form representation of baseline hazard
  - finite no. of parameters

Models of this world

- Replace the α_ts by a parametric function $f(t)$ with a limited number of parameters, for example:
  - Piecewise constant
  - Splines (linear, quadratic or cubic)
  - Fractional polynomials
- the two latter brings model into "this world":
  - smoothly varying rates
  - parametric closed form representation of baseline hazard
  - finite no. of parameters
- Makes it really easy to use rates directly in calculations of

Models of this world

- Replace the α_ts by a parametric function $f(t)$ with a limited number of parameters, for example:
  - Piecewise constant
  - Splines (linear, quadratic or cubic)
  - Fractional polynomials
- the two latter brings model into “this world”:
  - smoothly varying rates
  - parametric closed form representation of baseline hazard
  - finite no. of parameters
- Makes it really easy to use rates directly in calculations of
  - expected residual life time

Models of this world

- Replace the α_ts by a parametric function $f(t)$ with a limited number of parameters, for example:
  - Piecewise constant
  - Splines (linear, quadratic or cubic)
  - Fractional polynomials
- the two latter brings model into "this world":
  - smoothly varying rates
  - parametric closed form representation of baseline hazard
  - finite no. of parameters
- Makes it really easy to use rates directly in calculations of
  - expected residual life time
  - state occupancy probabilities in multistate models

Models of this world

- Replace the α_ts by a parametric function $f(t)$ with a limited number of parameters, for example:
  - Piecewise constant
  - Splines (linear, quadratic or cubic)
  - Fractional polynomials
- the two latter brings model into "this world":
  - smoothly varying rates
  - parametric closed form representation of baseline hazard
  - finite no. of parameters
- Makes it really easy to use rates directly in calculations of
  - expected residual life time
  - state occupancy probabilities in multistate models
  - ...

additional dogma

Not sacred, merely consequenecs of the 3rd commandment:

additional dogma

Not sacred, merely consequenecs of the 3rd commandment:

- Show risk time **in** states and transitions **between** states graphically

additional dogma

Not sacred, merely consequenecs of the 3rd commandment:

- Show risk time **in** states and transitions **between** states graphically
- Model transition rates by smooth parametric functions

additional dogma

Not sacred, merely consequenecs of the 3rd commandment:

- Show risk time **in** states and transitions **between** states graphically
- Model transition rates by smooth parametric functions
- There is no such thing as primary or secondary time scale — time scales and other quantitative covariates should be modeled the same way

additional dogma

Not sacred, merely consequenecs of the 3rd commandment:

- Show risk time **in** states and transitions **between** states graphically
- Model transition rates by smooth parametric functions
- There is no such thing as primary or secondary time scale — time scales and other quantitative covariates should be modeled the same way
- Determine the relevant timescale(s)

additional dogma

Not sacred, merely consequenecs of the 3rd commandment:

- Show risk time **in** states and transitions **between** states graphically
- Model transition rates by smooth parametric functions
- There is no such thing as primary or secondary time scale — time scales and other quantitative covariates should be modeled the same way
- Determine the relevant timescale(s)
- **Then** derive the relevant measures to report.

additional dogma

Not sacred, merely consequenecs of the 3rd commandment:

- Show risk time **in** states and transitions **between** states graphically
- Model transition rates by smooth parametric functions
- There is no such thing as primary or secondary time scale — time scales and other quantitative covariates should be modeled the same way
- Determine the relevant timescale(s)
- **Then** derive the relevant measures to report.
- Time-scale interactions is the proper name for "non-proportional hazards"

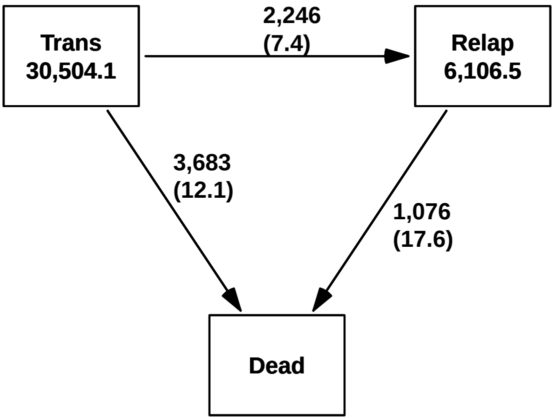
additional dogma

Not sacred, merely consequenecs of the 3rd commandment:

- Show risk time **in** states and transitions **between** states graphically
- Model transition rates by smooth parametric functions
- There is no such thing as primary or secondary time scale — time scales and other quantitative covariates should be modeled the same way
- Determine the relevant timescale(s)
- **Then** derive the relevant measures to report.
- Time-scale interactions is the proper name for "non-proportional hazards"
- Multiple time scales should be reported jointly

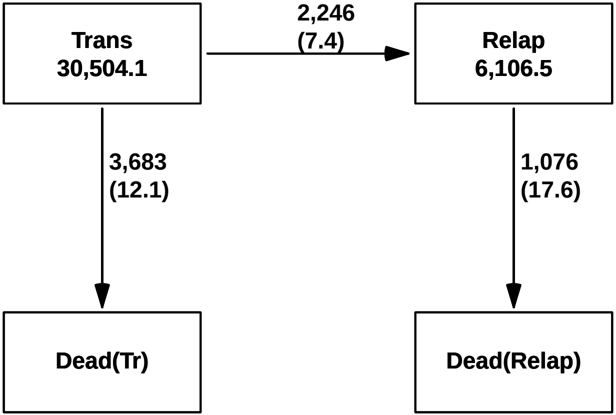
EBMT transplant data

Iacobelli & Carstensen: Multistate Models with Multiple Timescales, Stat Med 2013, [3]



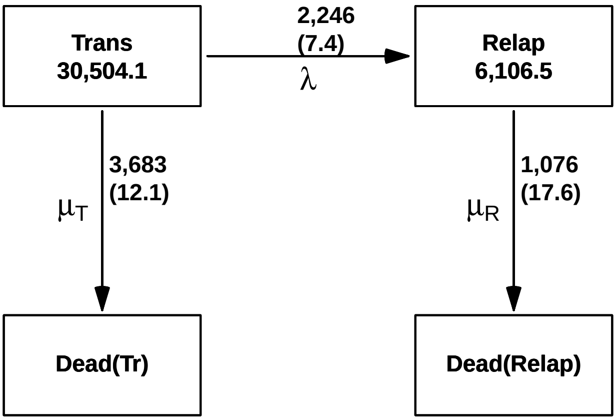
EBMT transplant data

Iacobelli & Carstensen: Multistate Models with Multiple Timescales, Stat Med 2013, [3]



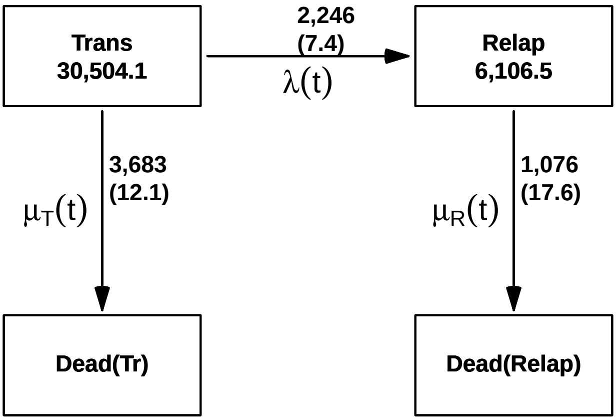
EBMT transplant data

Iacobelli & Carstensen: Multistate Models with Multiple Timescales, Stat Med 2013, [3]



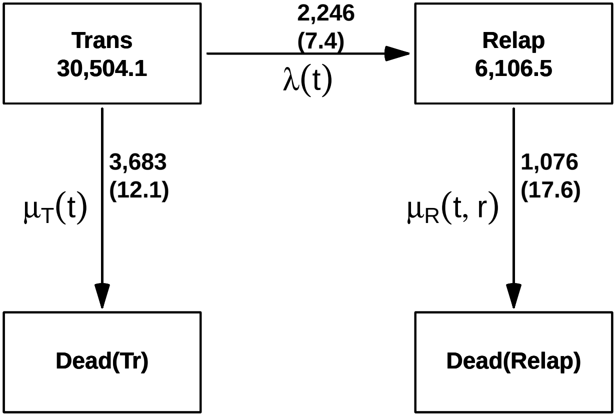
EBMT transplant data

Iacobelli & Carstensen: Multistate Models with Multiple Timescales, Stat Med 2013, [3]



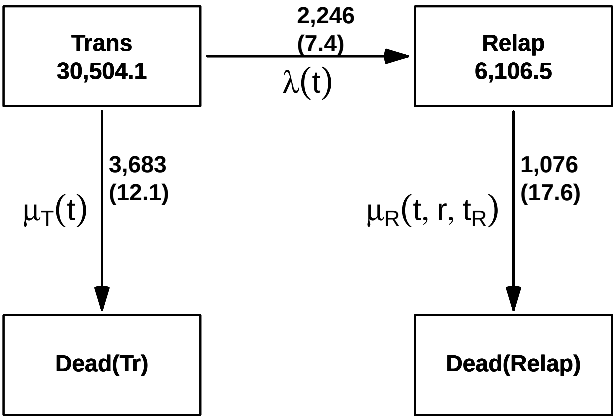
EBMT transplant data

Iacobelli & Carstensen: Multistate Models with Multiple Timescales, Stat Med 2013, [3]



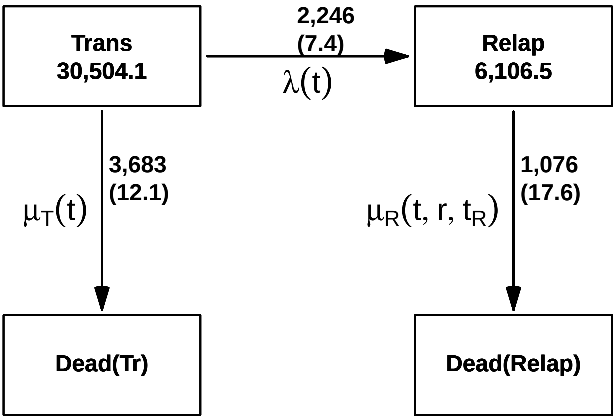
EBMT transplant data

Iacobelli & Carstensen: Multistate Models with Multiple Timescales, Stat Med 2013, [3]

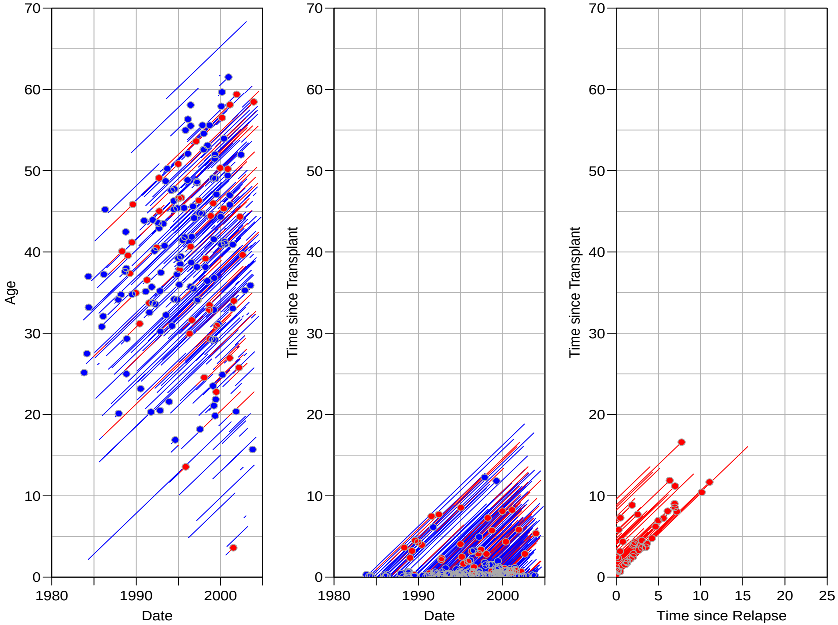


EBMT transplant data

Iacobelli & Carstensen: Multistate Models with Multiple Timescales, Stat Med 2013, [3]



other covariates: Age and date at Tx, sex, donor type, CML type



Age
Date
Time since Transplant
Date
Time since Transplant
Time since Relapse

Markov property: Empirical question

Model for mortality rates:

- t time since transplant

Markov property: Empirical question

Model for mortality rates:

- t time since transplant
- r time since relapse (if relapsed)

Markov property: Empirical question

Model for mortality rates:

- t time since transplant
- r time since relapse (if relapsed)
- t_r time from transplant to relapse

Markov property: Empirical question

Model for mortality rates:

- t time since transplant
- r time since relapse (if relapsed)
- t_r time from transplant to relapse
- Fit the model for all transitions:

Markov property: Empirical question

Model for mortality rates:

- t time since transplant
- r time since relapse (if relapsed)
- t_r time from transplant to relapse
- Fit the model for all transitions:
  - split follow-up time

Markov property: Empirical question

Model for mortality rates:

- t time since transplant
- r time since relapse (if relapsed)
- t_r time from transplant to relapse
- Fit the model for all transitions:
  - split follow-up time
  - fit Poisson model with covariates

Markov property: Empirical question

Model for mortality rates:

- t time since transplant
- r time since relapse (if relapsed)
- t_r time from transplant to relapse
- Fit the model for all transitions:
  - split follow-up time
  - fit Poisson model with covariates
  - and spline terms for each time scale.

Markov property: Empirical question

Model for mortality rates:

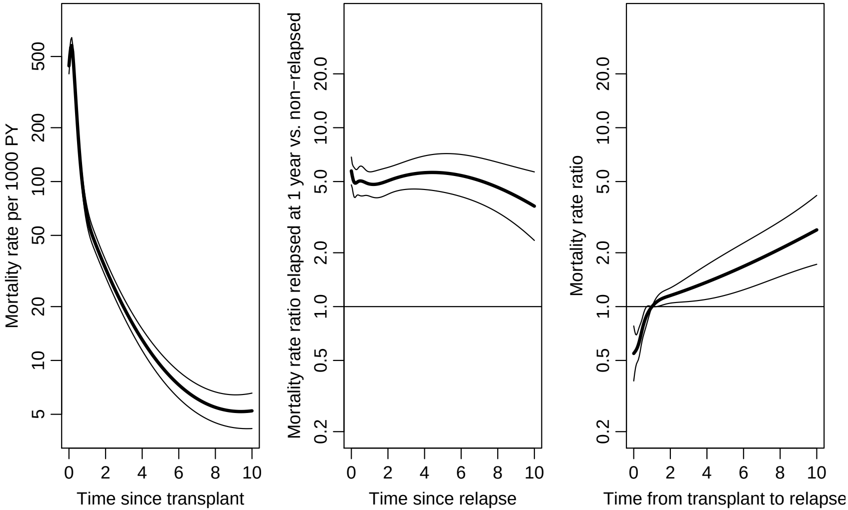
- t time since transplant
- r time since relapse (if relapsed)
- t_r time from transplant to relapse
- Fit the model for all transitions:
  - split follow-up time
  - fit Poisson model with covariates
  - and spline terms for each time scale.
- `Lexis` machinery [4, 5] from the **Epi** package for **R**

Markov property: Empirical question

Model for mortality rates:

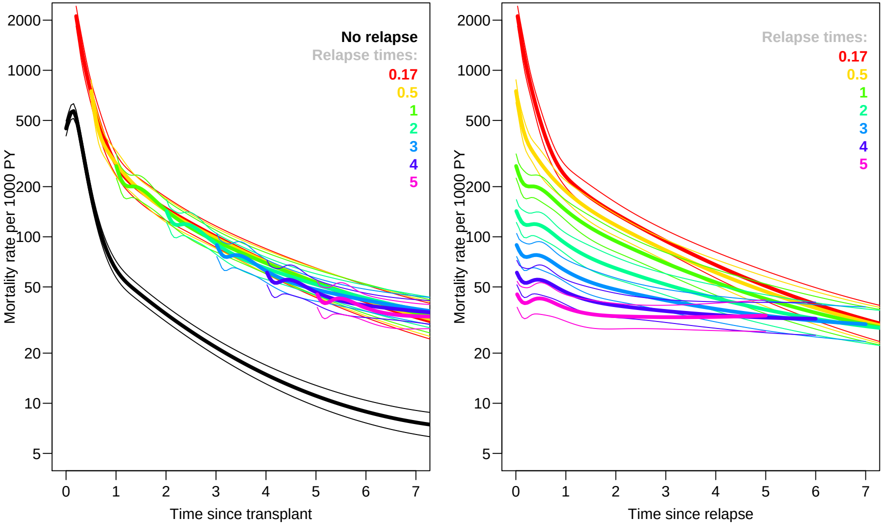
- t time since transplant
- r time since relapse (if relapsed)
- t_r time from transplant to relapse
- Fit the model for all transitions:
  - split follow-up time
  - fit Poisson model with covariates
  - and spline terms for each time scale.
- `Lexis` machinery [4, 5] from the **Epi** package for **R**
- ... for representation and manipulation of follow-up data.

$$\log(\mu) = h(t) + k(r) + g(t - r) + X\beta$$



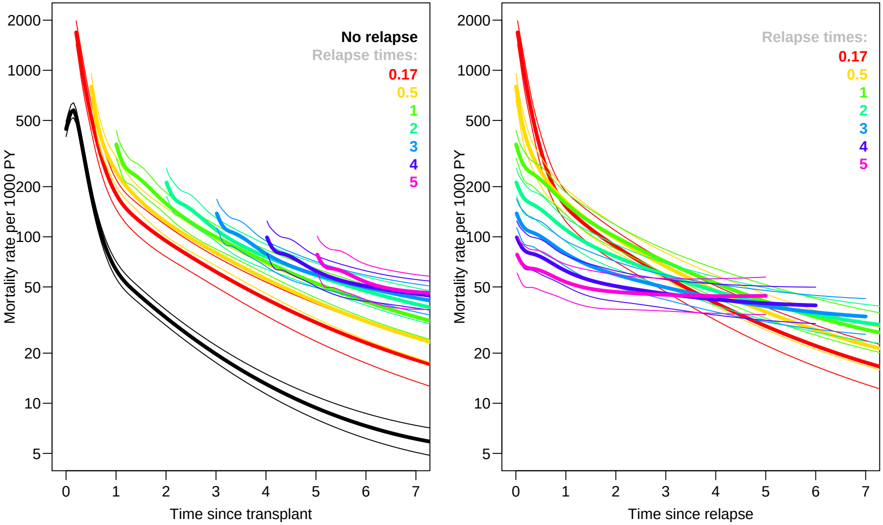
t: time since transplant r: time since relapse

$$\log(\mu) = h(t) + k(r) \qquad + X\beta$$



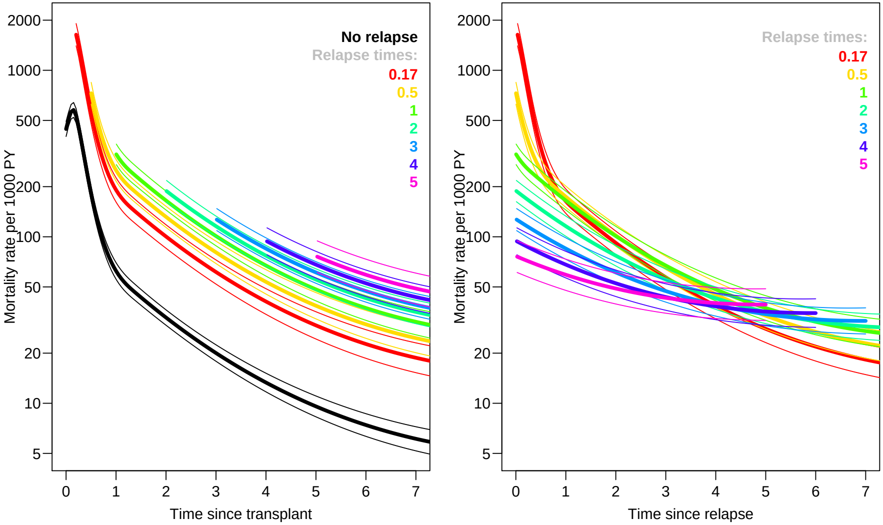
t: time since transplant $\quad$ r: time since relapse

$$\log(\mu) = h(t) + k(r) + g(t - r) + X\beta$$



t: time since transplant $\quad$ r: time since relapse

$$\log(\mu) = h(t) \qquad + g(t-r) + X\beta$$



t: time since transplant $\quad r$: time since relapse

Diabetologia
DOI 10.1007/s00125-016-4065-6

CrossMark

ARTICLE

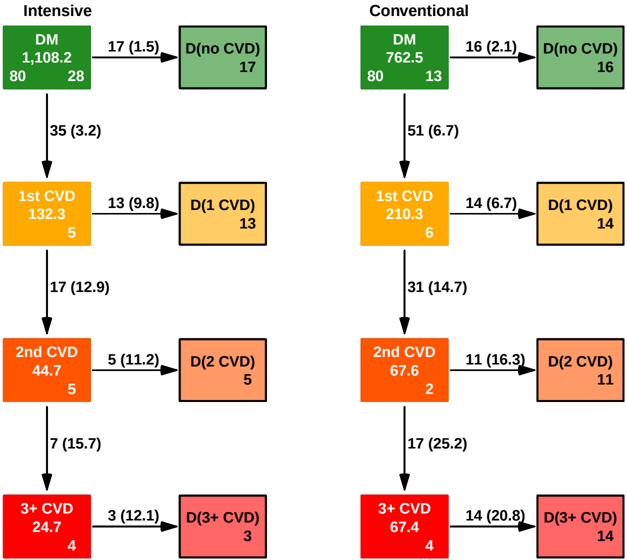
Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial

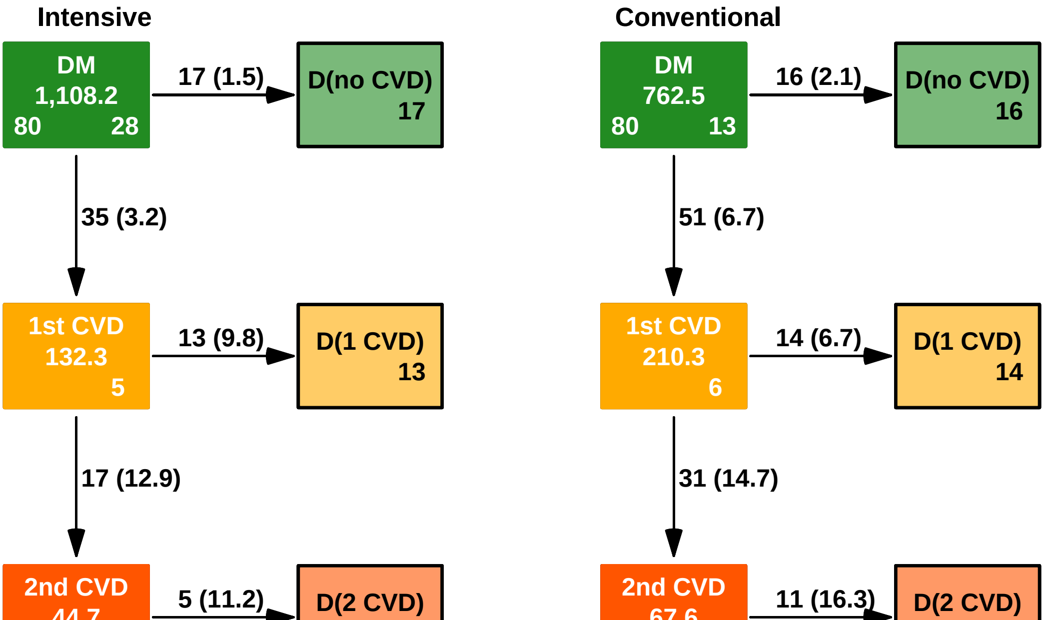
Peter Gæde[1,2] · **Jens Oellgaard**[1,2,3] · **Bendix Carstensen**[3] · **Peter Rossing**[3,4,5] · **Henrik Lund-Andersen**[3,5,6] · **Hans-Henrik Parving**[5,7] · **Oluf Pedersen**[8]

Received: 7 April 2016 / Accepted: 1 July 2016

Abstract

Aims/hypothesis The aim of this work was to study the potential long-term impact of a 7.8 years intensified, multifactorial pharmacological approaches. After 7.8 years the study continued as an observational follow-up with all patients receiving treatment as for the original intensive-therapy group. The pri-


Intensive
DM
1,108.2
80
28
17 (1.5)
D(no CVD)
17
35 (3.2)
1st CVD
132.3
5
13 (9.8)
D(1 CVD)
13
17 (12.9)
2nd CVD
44.7
5
5 (11.2)
D(2 CVD)
5
7 (15.7)
3+ CVD
24.7
4
3 (12.1)
D(3+ CVD)
3
Conventional
DM
762.5
80
13
16 (2.1)
D(no CVD)
16
51 (6.7)
1st CVD
210.3
6
14 (6.7)
D(1 CVD)
14
31 (14.7)
2nd CVD
67.6
2
11 (16.3)
D(2 CVD)
11
17 (25.2)
3+ CVD
67.4
4
14 (20.8)
D(3+ CVD)
14


Intensive
DM
1,108.2
80 28
17 (1.5)
D(no CVD)
17
35 (3.2)
1st CVD
132.3
5
13 (9.8)
D(1 CVD)
13
17 (12.9)
2nd CVD
5 (11.2)
D(2 CVD)
Conventional
DM
762.5
80 13
16 (2.1)
D(no CVD)
16
51 (6.7)
1st CVD
210.3
6
14 (6.7)
D(1 CVD)
14
31 (14.7)
2nd CVD
11 (16.3)
D(2 CVD)

Models used

- One model for the 4 mortality rates

Models used

- One model for the 4 mortality rates
- One model for the 3 CVD rates

Models used

- One model for the 4 mortality rates
- One model for the 3 CVD rates
- ... both models assume:

Models used

- One model for the 4 mortality rates
- One model for the 3 CVD rates
- ... both models assume:
  - proportional hazards between CVD states $(0, 1, 2(, 3)$ CVD events)

Models used

- One model for the 4 mortality rates
- One model for the 3 CVD rates
- ... both models assume:
  - proportional hazards between CVD states $(0, 1, 2(, 3)$ CVD events)
  - proportional hazards between groups (conventional, intervention)

Models used

- One model for the 4 mortality rates
- One model for the 3 CVD rates
- . . . both models assume:
  - proportional hazards between CVD states $(0, 1, 2(, 3)$ CVD events)
  - proportional hazards between groups (conventional, intervention)
  - proportional hazards between levels of sex and age (at entry)

Models used

- One model for the 4 mortality rates
- One model for the 3 CVD rates
- ... both models assume:
  - proportional hazards between CVD states $(0, 1, 2(, 3)$ CVD events)
  - proportional hazards between groups (conventional, intervention)
  - proportional hazards between levels of sex and age (at entry)
- Which just means: multiplicative effects of the covariates: time since baseline, CVD state, group, sex and age

Models used

- One model for the 4 mortality rates
- One model for the 3 CVD rates
- ... both models assume:
  - proportional hazards between CVD states $(0, 1, 2(, 3)$ CVD events)
  - proportional hazards between groups (conventional, intervention)
  - proportional hazards between levels of sex and age (at entry)
- Which just means: multiplicative effects of the covariates: time since baseline, CVD state, group, sex and age
- **Proportional hazards** means:
  no interaction with the time scale

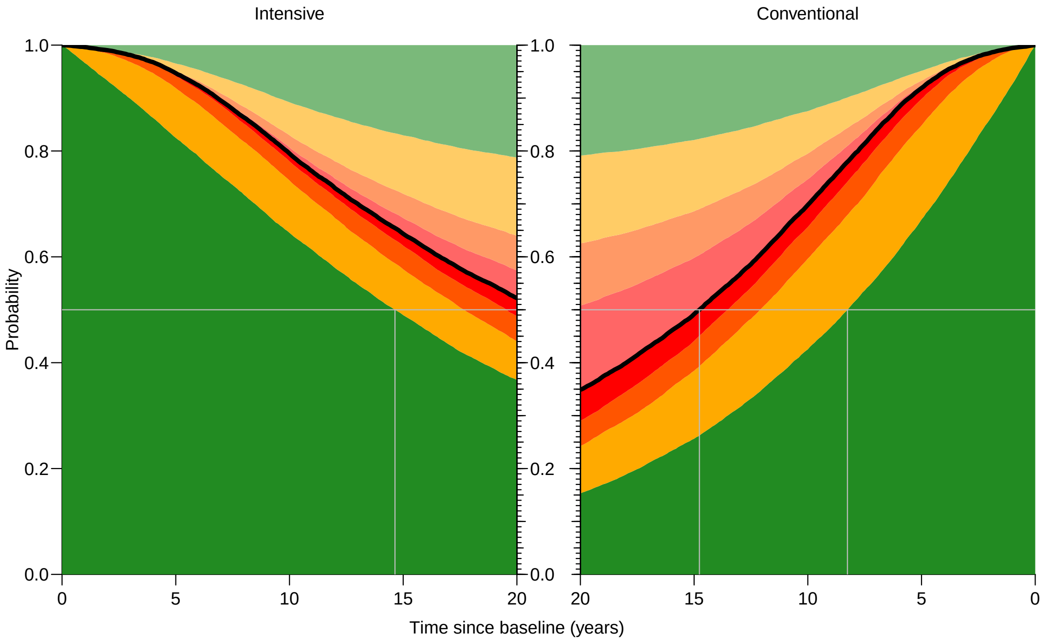
Hazard ratios

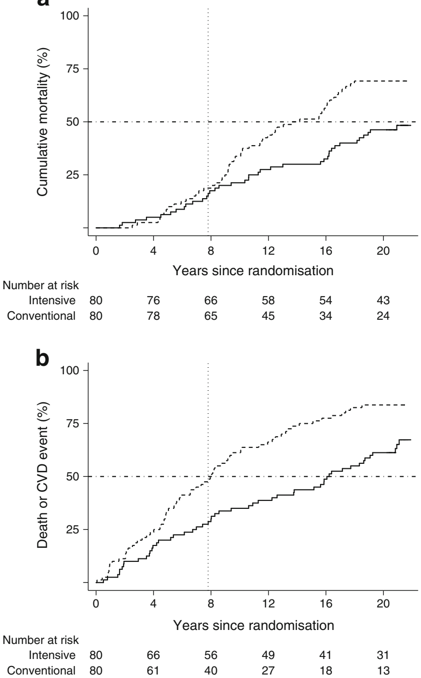
	Mortality	CVD event
HR, Int. vs. Conv.	0.83 (0.54; 1.30)	0.55 (0.39;0.77)
H_0: PH btw. CVD groups	p=0.438	p=0.261
H_0: HR = 1	p=0.425	p=0.001
HR vs. 0 CVD events:		
0 (ref.)	1.00	1.00
1	3.08 (1.82; 5.19)	2.43 (1.67;3.52)
2	4.42 (2.36; 8.29)	3.48 (2.15;5.64)
3+	7.76 (4.11;14.65)	

Hazard ratios

	Mortality	CVD event
HR, Int. vs. Conv.	0.83 (0.54; 1.30)	0.55 (0.39;0.77)
H_0: PH btw. CVD groups	p=0.438	p=0.261
H_0: HR = 1	p=0.425	p=0.001
HR vs. 0 CVD events:		
0 (ref.)	1.00	1.00
1	3.08 (1.82; 5.19)	2.43 (1.67;3.52)
2	4.42 (2.36; 8.29)	3.48 (2.15;5.64)
3+	7.76 (4.11;14.65)	

Then use fitted rates to estimate the probabilities of being in each state at all times. (This is immensely complicated).


Intensive
Conventional
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
Time since baseline (years)



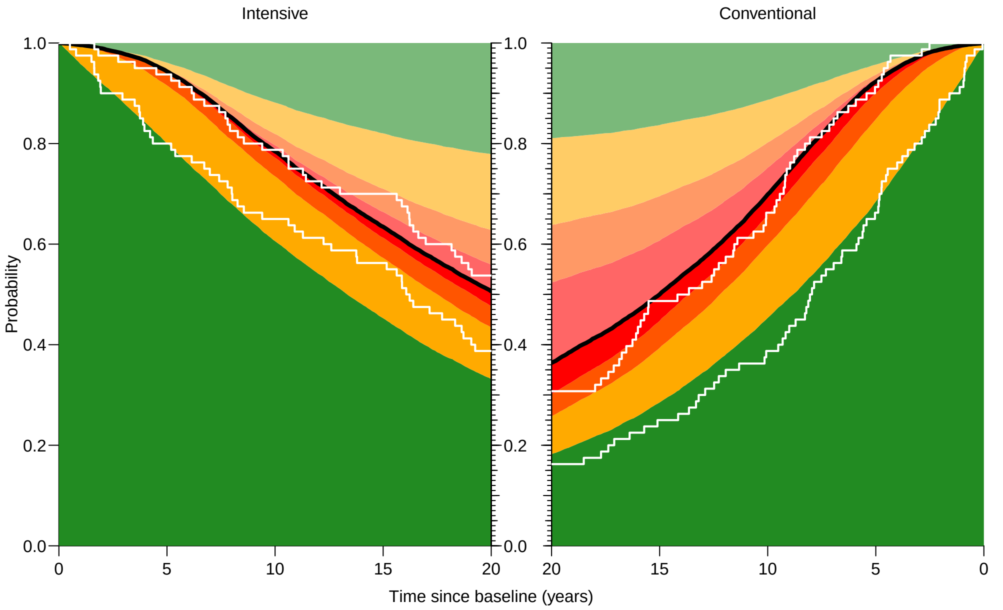
between groups (HR 0.83 [95% CI 0.54, 1.30], $p=0.43$). Thus, the reduced mortality was primarily due to reduced risk of CVD.

The patients in the intensive group experienced a total of 90 cardiovascular events vs 195 events in the conventional group. Nineteen intensive-group patients (24%) vs 34 conventional-group patients (43%) experienced more than one cardiovascular event. No significant between-group difference in the distribution of specific cardiovascular first-event types was observed (Table 2 and Fig. 4).

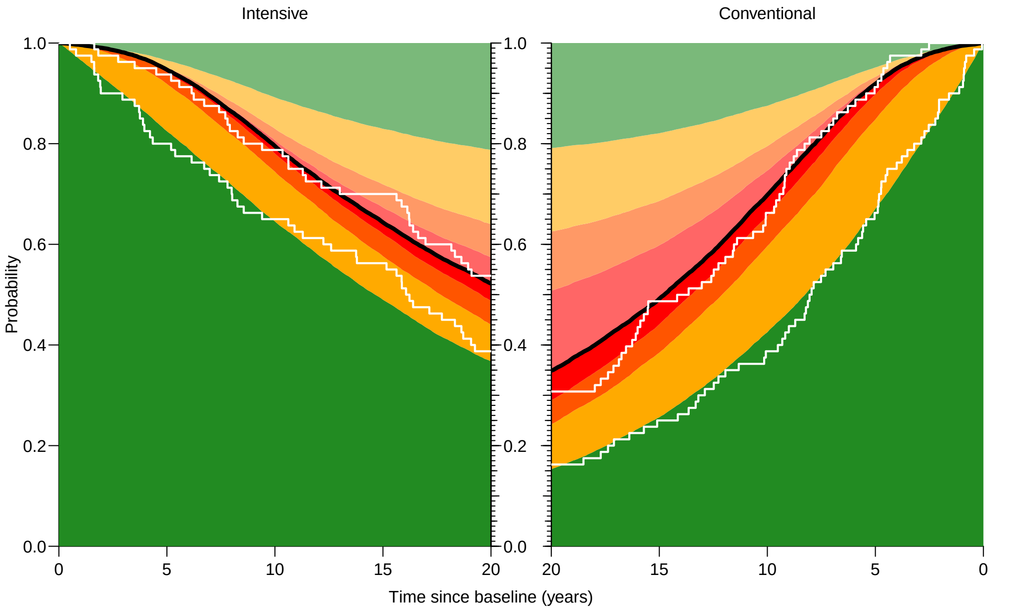
Microvascular complications Hazard rates of progression rates in microvascular complications compared with baseline status are shown Fig. 3. Sensitivity analyses showed a negligible effect of the random dates imputation.

Progression of retinopathy was decreased by 33% in the intensive-therapy group (Fig. 5). Blindness in at least one eye was reduced in the intensive-therapy group with an HR of 0.47 (95% CI 0.23, 0.98, $p=0.044$). Autonomic neuropathy was decreased by 41% in the intensive-therapy group (Fig. 5). We observed no difference between groups in the progression of peripheral neuropathy (Fig. 5). Progression to diabetic nephropathy (macroalbuminuria) was reduced by 48% in the intensive-therapy group (Fig. 5). Ten patients in the conventional-therapy groups vs five patients in the intensive-therapy group progressed to end-stage renal disease ($p=0.061$).

Discussion



Same treatment effects for Death resp. CVD between CVD levels



Different treatment effects for Death resp. CVD between CVD levels

Expected lifetime and YLL (well, gained)

- Expected lifetime (years) in the Steno 2 cohort during the first 20 years after baseline by treatment group and CVD status.

State	where	Int.	Conv.	Int.−Conv.
Alive	under black line	15.6	14.1	1.5
No CVD	green area	12.7	10.0	2.6
Any CVD	orange area	3.0	4.1	−1.1

Expected lifetime and YLL (well, gained)

- Expected lifetime (years) in the Steno 2 cohort during the first 20 years after baseline by treatment group and CVD status.

State	where	Int.	Conv.	Int.−Conv.
Alive	under black line	15.6	14.1	1.5
No CVD	green area	12.7	10.0	2.6
Any CVD	orange area	3.0	4.1	−1.1

- What does “expected” mean?

Expected lifetime and YLL (well, gained)

- Expected lifetime (years) in the Steno 2 cohort during the first 20 years after baseline by treatment group and CVD status.

State	where	Int.	Conv.	Int.−Conv.
Alive	under black line	15.6	14.1	1.5
No CVD	green area	12.7	10.0	2.6
Any CVD	orange area	3.0	4.1	−1.1

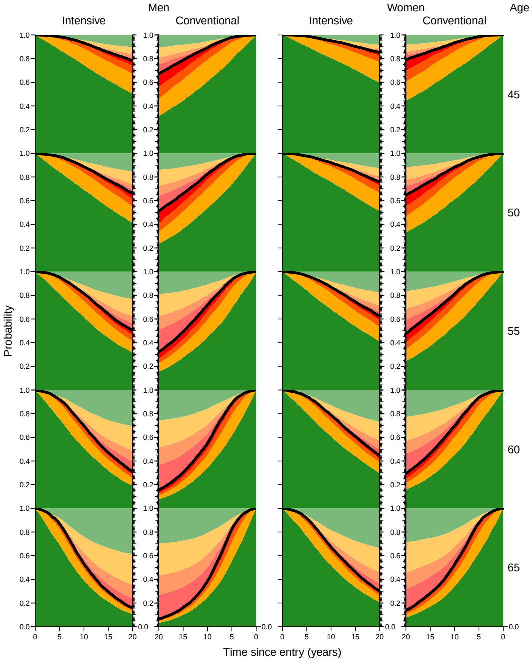
- What does "expected" mean?
- Expectation w.r.t.
  age and sex-distribution in the Steno2 study!

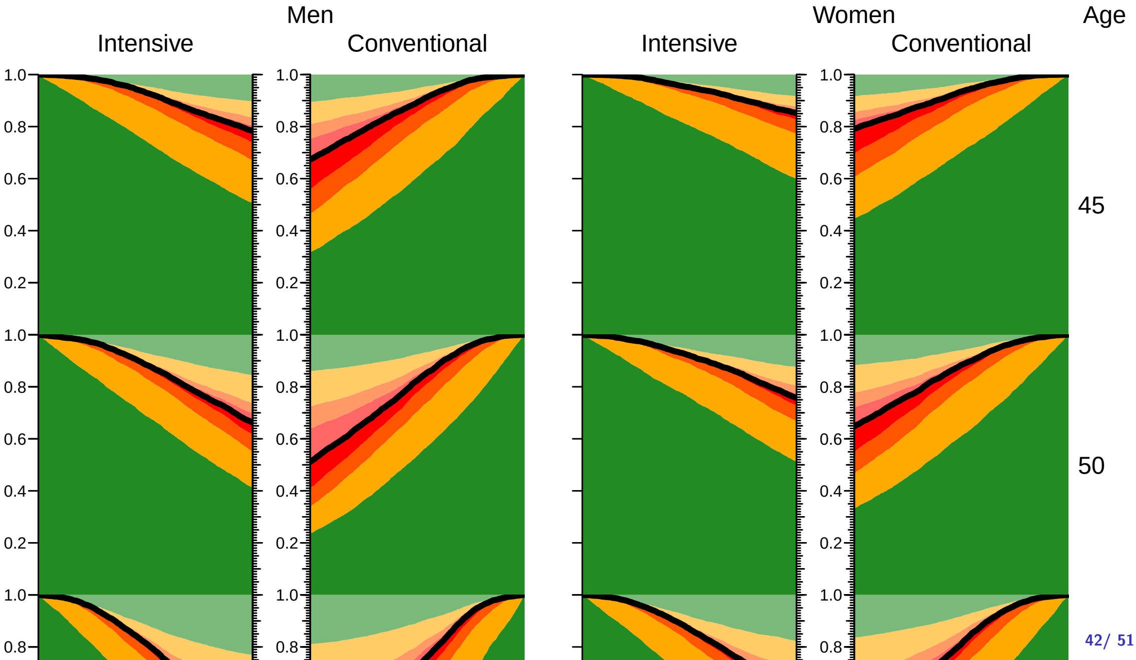
Expected lifetime and YLL (well, gained)

- Expected lifetime (years) in the Steno 2 cohort during the first 20 years after baseline by treatment group and CVD status.

State	where	Int.	Conv.	Int. − Conv.
Alive	under black line	15.6	14.1	1.5
No CVD	green area	12.7	10.0	2.6
Any CVD	orange area	3.0	4.1	−1.1

- What does “expected” mean?
- Expectation w.r.t.
  age and sex-distribution in the Steno2 study!
- Computed as areas under survival curves

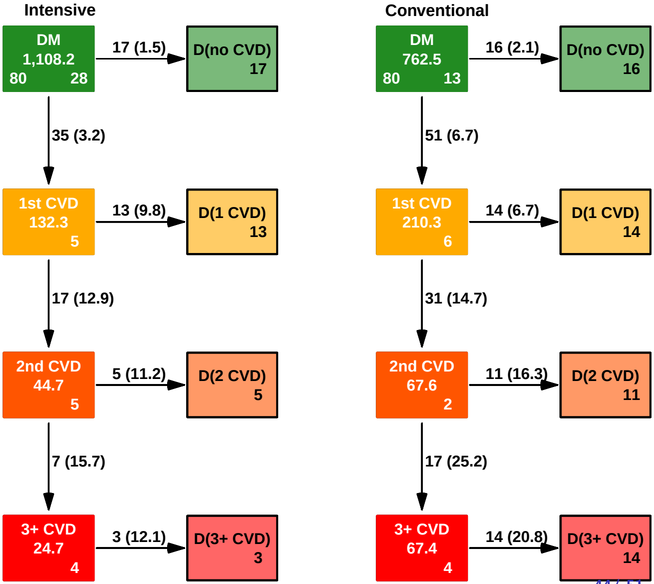

Men
Women
Age
Intensive
Conventional
Intensive
Conventional
45
50
55
60
65
Probability
Time since entry (years)


Men
Women
Age
Intensive
Conventional
Intensive
Conventional
1.0
0.8
0.6
0.4
0.2
45
50

Expected lifetime (years) during the first 20 years after baseline by sex, age, treatment group and CVD status.

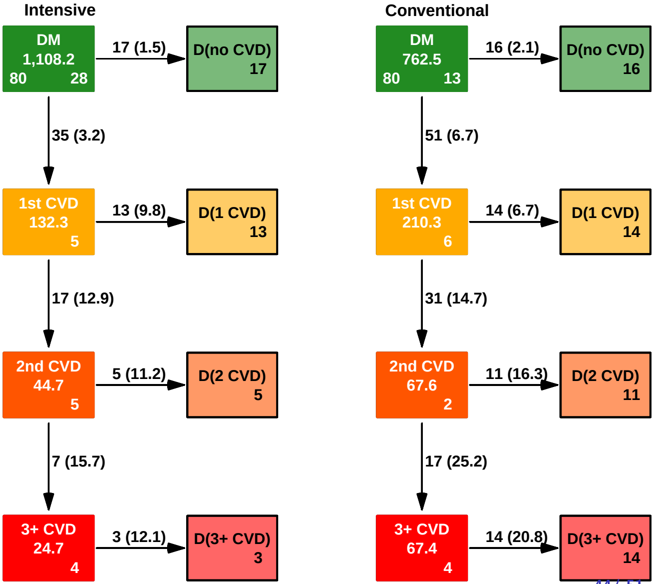
sex		Men			Women		
state	age	Int.	Conv.	Int.−Conv.	Int.	Conv.	Int.−Conv.
Alive	45	18.5	17.5	1.0	19.1	18.4	0.7
	50	17.2	16.1	1.1	18.0	17.2	0.8
	55	15.6	13.8	1.8	17.4	15.9	1.6
	60	13.9	11.6	2.2	15.5	13.7	1.8
	65	11.2	9.5	1.8	13.3	11.4	2.0
No CVD	45	14.9	12.5	2.4	15.8	14.3	1.5
	50	14.0	11.1	2.9	15.1	12.9	2.2
	55	12.2	9.7	2.5	14.3	11.6	2.7
	60	10.9	8.2	2.7	12.4	9.9	2.6
	65	9.0	6.7	2.2	10.7	8.3	2.4

Multistate models in practice:



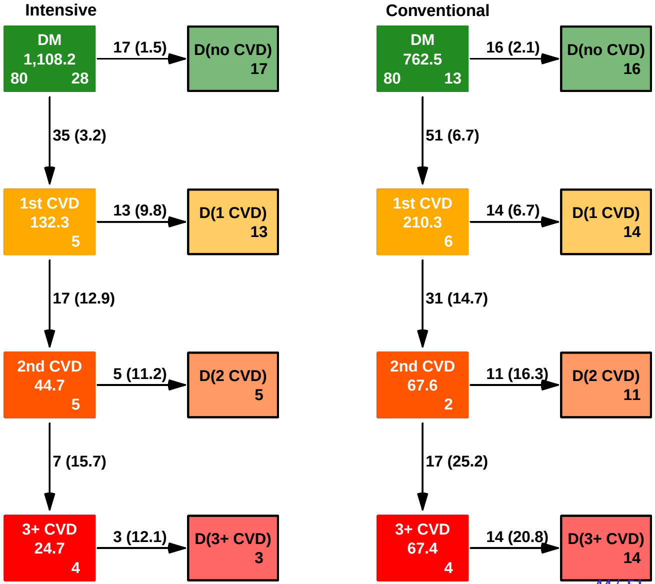
Multistate models in practice:

- Representation:



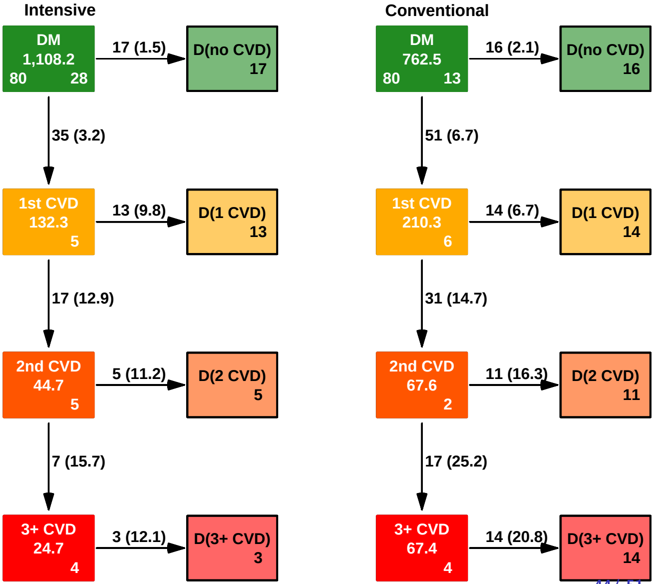
Multistate models in practice:

- Representation:
  - States



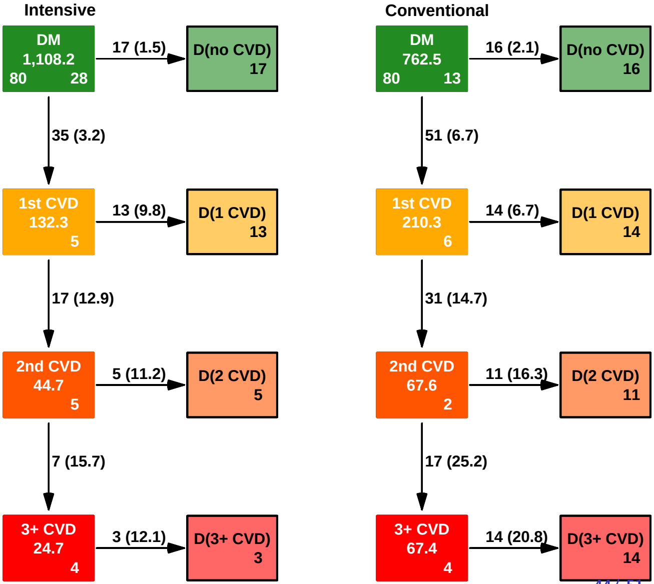
Multistate models in practice:

- Representation:
  - States
  - Transitions



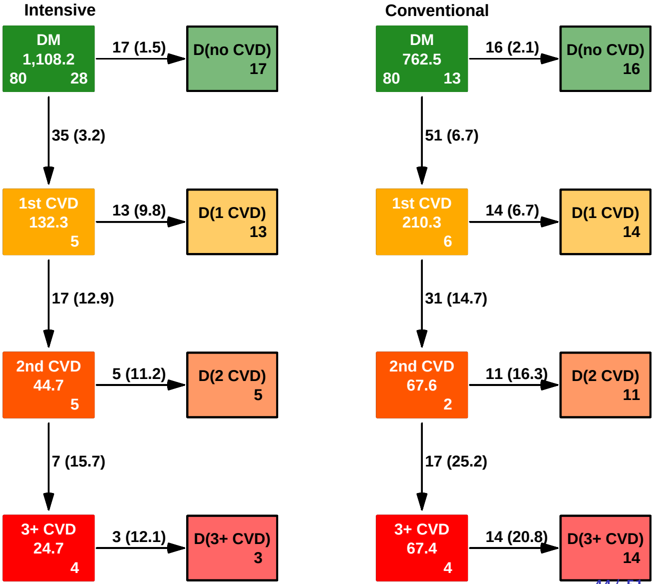
Multistate models in practice:

- Representation:
  - States
  - Transitions
  - Sojourn times



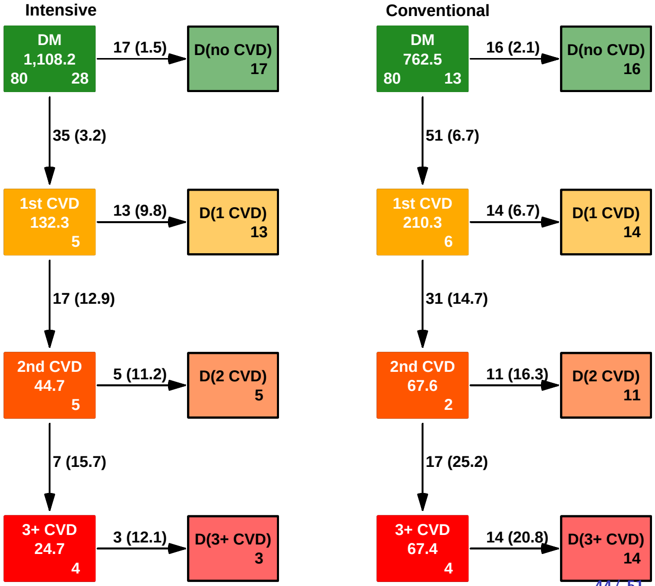
Multistate models in practice:

- Representation:
  - States
  - Transitions
  - Sojourn times
  - Rates



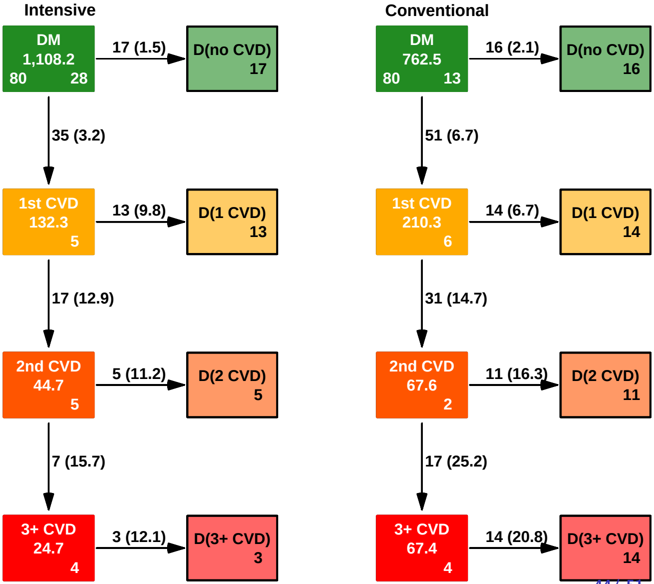
Multistate models in practice:

- Representation:
  - States
  - Transitions
  - Sojourn times
  - Rates
- Analysis of rates:



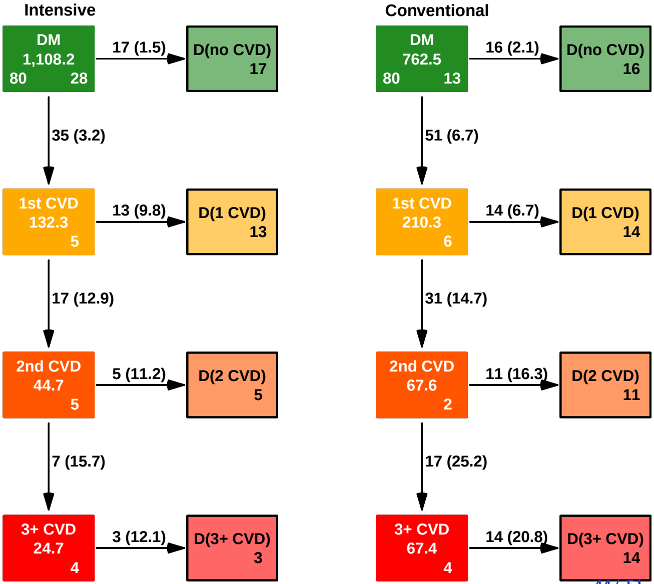
Multistate models in practice:

- Representation:
  - States
  - Transitions
  - Sojourn times
  - Rates
- Analysis of rates:
  - Cox-model



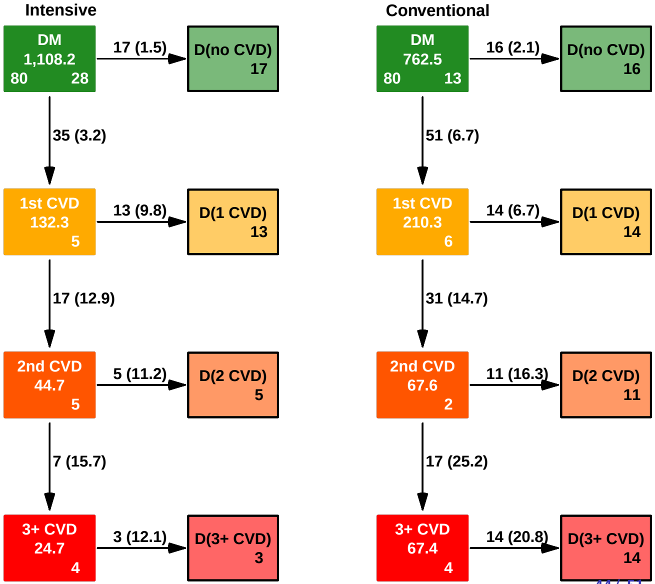
Multistate models in practice:

- Representation:
  - States
  - Transitions
  - Sojourn times
  - Rates
- Analysis of rates:
  - Cox-model
  - Poisson model



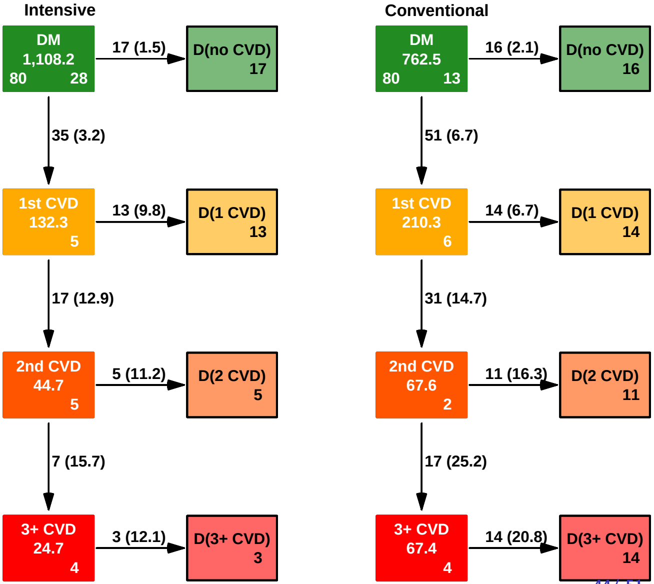
Multistate models in practice:

- Representation:
  - States
  - Transitions
  - Sojourn times
  - Rates
- Analysis of rates:
  - Cox-model
  - Poisson model
- Reporting



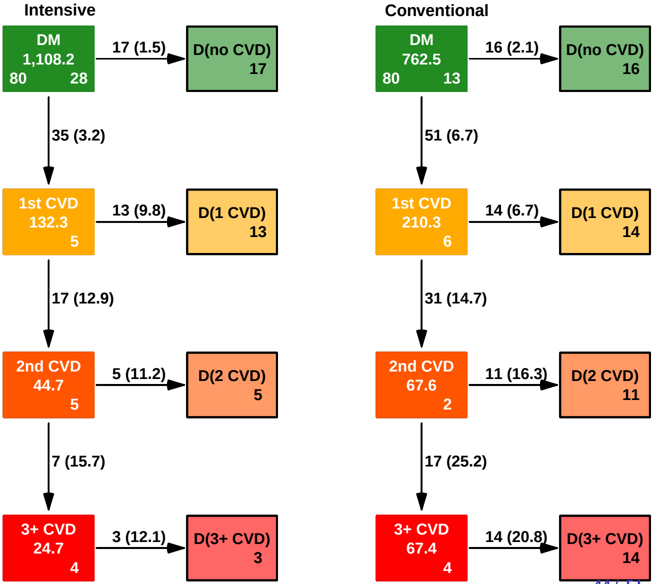
Multistate models in practice:

- Representation:
  - States
  - Transitions
  - Sojourn times
  - Rates
- Analysis of rates:
  - Cox-model
  - Poisson model
- Reporting
  - Rates



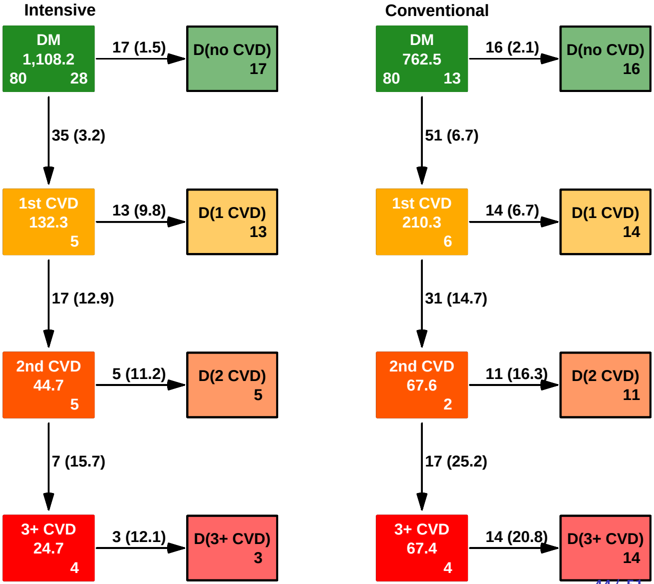
Multistate models in practice:

- Representation:
  - States
  - Transitions
  - Sojourn times
  - Rates
- Analysis of rates:
  - Cox-model
  - Poisson model
- Reporting
  - Rates
  - HRs



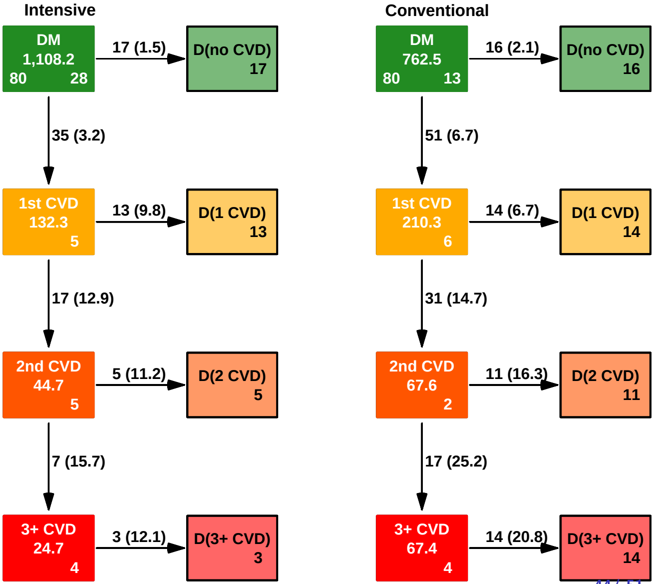
Multistate models in practice:

- Representation:
  - States
  - Transitions
  - Sojourn times
  - Rates
- Analysis of rates:
  - Cox-model
  - Poisson model
- Reporting
  - Rates
  - HRs
  - Probabilities



Multistate models in practice:

- Representation:
  - States
  - Transitions
  - Sojourn times
  - Rates
- Analysis of rates:
  - Cox-model
  - Poisson model
- Reporting
  - Rates
  - HRs
  - Probabilities
  - Expected lifetime



From rates to probabilities

- There is a one-to-one correspondence between:

From rates to probabilities

- There is a one-to-one correspondence between:
  - all rates between states (by time) + initial state distribution

From rates to probabilities

- There is a one-to-one correspondence between:
  - all rates between states (by time) + initial state distribution
  - state distribution by time

From rates to probabilities

- There is a one-to-one correspondence between:
  - all rates between states (by time) + initial state distribution
  - state distribution by time
- Model for rates
  $\Rightarrow$ probability of being in a given state at any given time

From rates to probabilities

- There is a one-to-one correspondence between:
  - all rates between states (by time) + initial state distribution
  - state distribution by time
- Model for rates
  $\Rightarrow$ probability of being in a given state at any given time
- **Analytically** this is a nightmare

From rates to probabilities

- There is a one-to-one correspondence between:
  - all rates between states (by time) + initial state distribution
  - state distribution by time
- Model for rates
  $\Rightarrow$ probability of being in a given state at any given time
- **Analytically** this is a nightmare
- **Simulation** is the answer

From rates to probabilities: `simLexis`

- Assume a person is in "DM" initially

From rates to probabilities: `simLexis`

- Assume a person is in "DM" initially
  - Simulate a time of death (transition to "D(no CVD)")

From rates to probabilities: `simLexis`

- Assume a person is in “DM” initially
  - Simulate a time of death (transition to “D(no CVD)”)
  - Simulate a time of CVD (transition to “1st CVD”)

From rates to probabilities: `simLexis`

- Assume a person is in “DM” initially
  - Simulate a time of death (transition to “D(no CVD)”)
  - Simulate a time of CVD (transition to “1st CVD”)
  - Choose the smaller as the transition

From rates to probabilities: `simLexis`

- Assume a person is in "DM" initially
  - Simulate a time of death (transition to "D(no CVD)")
  - Simulate a time of CVD (transition to "1st CVD")
  - Choose the smaller as the transition
- If transition is to "1st CVD" simulate death / 2nd CVD, etc.

From rates to probabilities: `simLexis`

- Assume a person is in "DM" initially
  - Simulate a time of death (transition to "D(no CVD)")
  - Simulate a time of CVD (transition to "1st CVD")
  - Choose the smaller as the transition
- If transition is to "1st CVD" simulate death / 2nd CVD, etc.
- Repeat for, say, 10,000 persons

  ⇒ simulated cohort study

From rates to probabilities: `simLexis`

- Assume a person is in “DM” initially
  - Simulate a time of death (transition to “D(no CVD)”)
  - Simulate a time of CVD (transition to “1st CVD”)
  - Choose the smaller as the transition
- If transition is to “1st CVD” simulate death / 2nd CVD, etc.
- Repeat for, say, 10,000 persons
  $\Rightarrow$ simulated cohort study
- `simLexis` does this for you, provided you have

From rates to probabilities: `simLexis`

- Assume a person is in "DM" initially
  - Simulate a time of death (transition to "D(no CVD)")
  - Simulate a time of CVD (transition to "1st CVD")
  - Choose the smaller as the transition
- If transition is to "1st CVD" simulate death / 2nd CVD, etc.
- Repeat for, say, 10,000 persons
  $\Rightarrow$ simulated cohort study
- `simLexis` does this for you, provided you have
  - initial state and covariates for all persons

From rates to probabilities: `simLexis`

- Assume a person is in “DM” initially
  - Simulate a time of death (transition to “D(no CVD)”)
  - Simulate a time of CVD (transition to “1st CVD”)
  - Choose the smaller as the transition
- If transition is to “1st CVD” simulate death / 2nd CVD, etc.
- Repeat for, say, 10,000 persons

  $\Rightarrow$ simulated cohort study
- `simLexis` does this for you, provided you have
  - initial state and covariates for all persons
  - models to predict (cumulative) rates

From rates to probabilities: `simLexis`

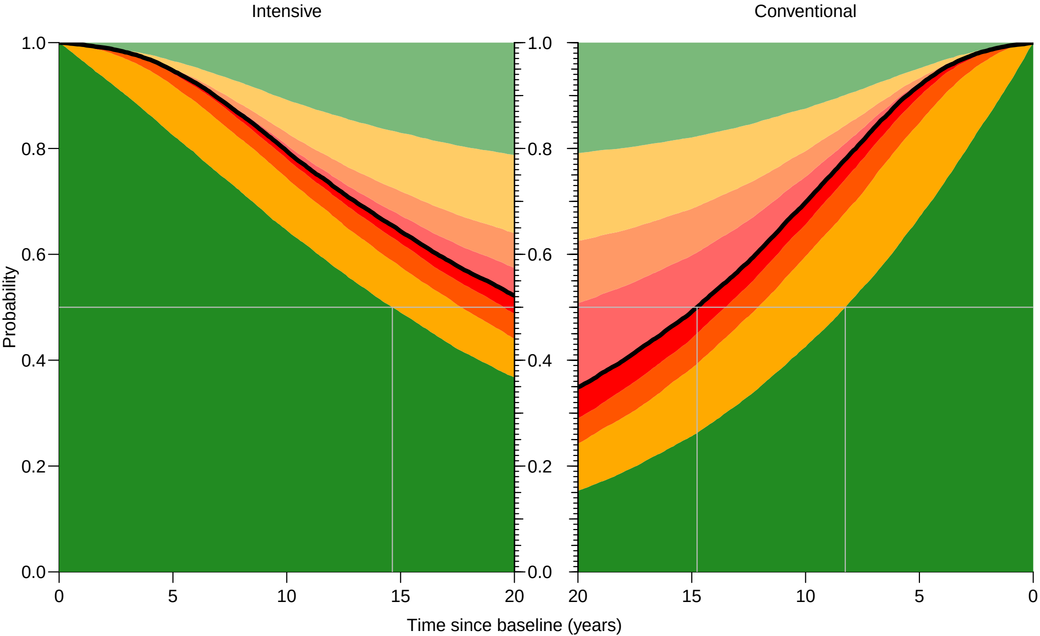
- Assume a person is in "DM" initially
  - Simulate a time of death (transition to "D(no CVD)")
  - Simulate a time of CVD (transition to "1st CVD")
  - Choose the smaller as the transition
- If transition is to "1st CVD" simulate death / 2nd CVD, etc.
- Repeat for, say, 10,000 persons
  $\Rightarrow$ simulated cohort study
- `simLexis` does this for you, provided you have
  - initial state and covariates for all persons
  - models to predict (cumulative) rates
- Count how many is in each state at each time:
  $\Rightarrow$ state occupancy probabilities

From rates to probabilities: `simLexis`

- Assume a person is in “DM” initially
  - Simulate a time of death (transition to “D(no CVD)”)
  - Simulate a time of CVD (transition to “1st CVD”)
  - Choose the smaller as the transition
- If transition is to “1st CVD” simulate death / 2nd CVD, etc.
- Repeat for, say, 10,000 persons

  $\Rightarrow$ simulated cohort study
- `simLexis` does this for you, provided you have
  - initial state and covariates for all persons
  - models to predict (cumulative) rates
- Count how many is in each state at each time:

  $\Rightarrow$ state occupancy probabilities
- `nState` and `pState` does this for you



Intensive
Conventional
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
20
15
10
5
0
Time since baseline (years)

Using the `Lexis` machinery

- Allows estimation of fully parametric rate function

Using the `Lexis` machinery

- Allows estimation of fully parametric rate function
- Simple test for proportional hazards

Using the `Lexis` machinery

- Allows estimation of fully parametric rate function
- Simple test for proportional hazards
- State occupancy probabilities requires simulation: `simLexis` — see vignette in `Epi` package

Using the `Lexis` machinery

- Allows estimation of fully parametric rate function
- Simple test for proportional hazards
- State occupancy probabilities requires simulation: `simLexis` — see vignette in `Epi` package
- Access to other measures such as expected residual lifetime.

Using the `Lexis` machinery

- Allows estimation of fully parametric rate function
- Simple test for proportional hazards
- State occupancy probabilities requires simulation: `simLexis` — see vignette in `Epi` package
- Access to other measures such as expected residual lifetime.
- — similar machinery available in `Stata`:

Using the `Lexis` machinery

- Allows estimation of fully parametric rate function
- Simple test for proportional hazards
- State occupancy probabilities requires simulation:
  `simLexis` — see vignette in `Epi` package
- Access to other measures such as expected residual lifetime.
- — similar machinery available in `Stata`:
  - `multistate`

Using the `Lexis` machinery

- Allows estimation of fully parametric rate function
- Simple test for proportional hazards
- State occupancy probabilities requires simulation: `simLexis` — see vignette in `Epi` package
- Access to other measures such as expected residual lifetime.
- — similar machinery available in `Stata`:
    - `multistate`
    - Crowther & Lambert [6]

Using the `Lexis` machinery

- Allows estimation of fully parametric rate function
- Simple test for proportional hazards
- State occupancy probabilities requires simulation: `simLexis` — see vignette in `Epi` package
- Access to other measures such as expected residual lifetime.
- — similar machinery available in `Stata`:
  - `multistate`
  - Crowther & Lambert [6]
  - Only one timescale, however…

Additional dogma

- Show risk time **in** states and transitions **between** states

Additional dogma

- Show risk time **in** states and transitions **between** states
- Model transition rates by smooth **parametric** functions

Additional dogma

- Show risk time **in** states and transitions **between** states
- Model transition rates by smooth **parametric** functions
- There is no such thing as primary or secondary time scale — **time scales** and other quantitative covariates should be modeled the same way

Additional dogma

- Show risk time **in** states and transitions **between** states
- Model transition rates by smooth **parametric** functions
- There is no such thing as primary or secondary time scale — **time scales** and other quantitative covariates should be modeled the same way
- Time-scale **interactions** is the proper name for "non-proportional hazards"

Additional dogma

- Show risk time **in** states and transitions **between** states
- Model transition rates by smooth **parametric** functions
- There is no such thing as primary or secondary time scale — **time scales** and other quantitative covariates should be modeled the same way
- Time-scale **interactions** is the proper name for "non-proportional hazards"
- **Multiple** time scales should be reported jointly

References I

P. K. Andersen and N. Keiding.
Interpretability and importance of functionals in competing risks and multistate models.
Stat Med, 31:1074–1088, 2012.

J P Fine and R J Gray.
A proportional hazards model for the subdistribution of a competing risk.
Journal of the American Statistical Association, 94(446), 1999.

S. Iacobelli and B. Carstensen.
Multiple time scales in multi-state models.
Stat Med, 32(30):5315–5327, Dec 2013.

Martyn Plummer and Bendix Carstensen.
Lexis: An R class for epidemiological studies with long-term follow-up.
Journal of Statistical Software, 38(5):1–12, 1 2011.

Bendix Carstensen and Martyn Plummer.
Using Lexis objects for multi-state models in R.
Journal of Statistical Software, 38(6):1–18, 1 2011.

References II

M. J. Crowther and P. C. Lambert.
Parametric multistate survival models: Flexible modelling allowing transition-specific distributions with application to estimating clinically useful measures of effect differences.
Stat Med, 36(29):4719–4742, Dec 2017.

`bendixcarstensen.com/AdvCoh/Lexis-ex`