# Analysing competing risks data using flexible parametric survival models: what tools are available in Stata, which ones to use and when?

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# Overview

1. Introduction to survival analysis & competing risks
2. Fundamental relationships
3. Modelling on the cause-specific hazards scale
    - Cause-specific Cox PH model
    - Flexible parametric models (log-cumulative cause-specific hazards)
4. Modelling directly on the cause-specific cumulative incidence
    - Fine & Gray model
    - Flexible parametric models (log-cumulative subdistribution hazards)
5. Which scale is most appropriate?
6. Summary

# Survival analysis: the fundamentals

# Key components of a survival analysis

The study of time to a particular event of interest:

- Engineering e.g. time to failure of a component
- Economics e.g. duration of unemployment
- Medical e.g. time to death (survival time) of a cancer patient

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  - Emmigration
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- Right censoring: survival time > follow-up time
  - Emmigration
  - Administrative (most common)
- Non-informative censoring: Loss to follow-up is not associated with factors related to the study
- Independent and identically distributed (i.i.d) censoring: independence between survival time and censoring time (untestable)

# Some important notation

Let $T$ be a non-negative random variable that denotes observed survival time:

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**(All-cause) Survival function**

$$S(t) = P(T \geq t) = 1 - F(t)$$

**(All-cause) Cumulative incidence function (CIF)**

$$F(t) = P(T < t)$$

# A typical survival analysis: two-state model

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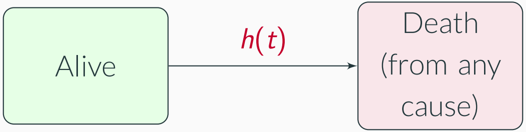


Alive

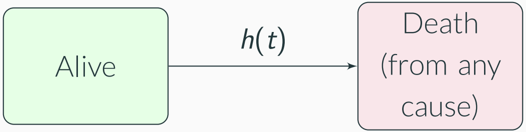
$h(t)$

Death (from any cause)

**(All-cause) Hazard rate, $h(t)$**

Instantaneous mortality (failure) rate from any cause, given that the individual is still alive up to time $t$

# A typical survival analysis: two-state model



**(All-cause) Hazard rate, $h(t)$**

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t \mid T \geq t)}{\Delta t}$$

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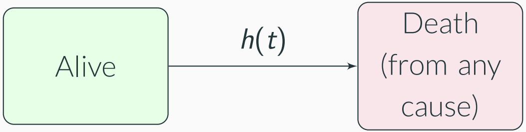


### (All-cause) Hazard rate, $h(t)$

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t \mid T \geq t)}{\Delta t}$$

### (All-cause) Survival function, $S(t)$

$$S(t) = \exp\left( - \int_0^t h(u) \mathrm{d}u \right)$$

# Example dataset

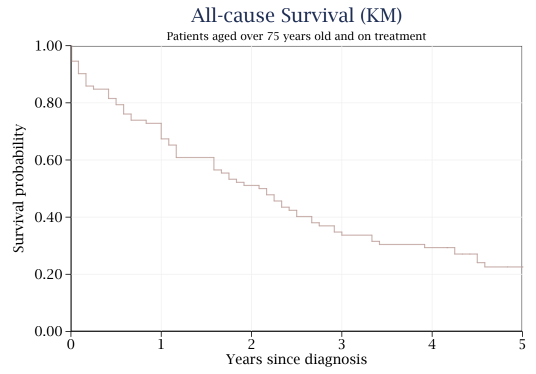
Load public-use prostate cancer dataset:

```
. use "http://www.stata-journal.com/software/sj4-2/st0059/prostatecancer", clear

. tab status

     status |      Freq.     Percent        Cum.
------------+-----------------------------------
     Censor |        150       29.64       29.64
     Cancer |        155       30.63       60.28
        CVD |        141       27.87       88.14
      Other |         60       11.86      100.00
------------+-----------------------------------
      Total |        506      100.00
```

# The Kaplan-Meier estimator



```
. stset time, f(status==1,2,3) id(id) exit(time 60) scale(12)

. sts graph if agegrp == 1 & treatment == 1, ...
```

# What are competing risks?

# Competing risks

Competing risks = when a patient dies from other causes that exclude the disease under study.

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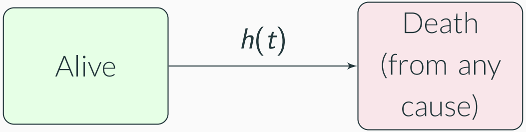
- Not valid under competing risks
- Death from ``competing'' causes may be due to adverse effects of treatment for disease

Due to informative censoring - specialised competing risks methods are required to avoid biased estimation.

# No competing risks



Alive

$h(t)$

Death
(from any
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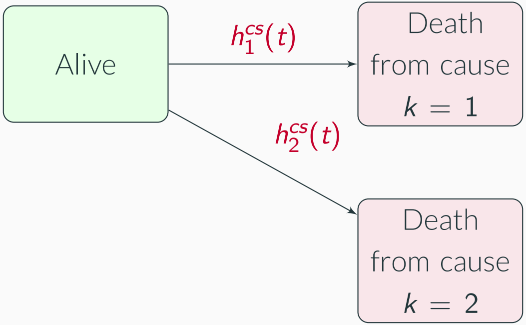
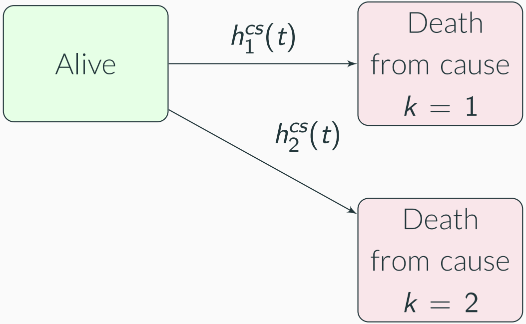
# With competing risks



**Cause-specific hazard (CSH) rate, $h_k^{cs}(t)$**

Instantaneous mortality (failure) rate from cause $k$, given that the individual is still alive up to time $t$

# With competing risks



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$$h_k^{cs}(t) = \lim_{\Delta t \to 0} \frac{P(t < T \leq t + \Delta t, D = k | T > t)}{\Delta t}$$

# The cause-specific CIF (transition probability)

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# The cause-specific CIF (transition probability)

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# The cause-specific CIF (transition probability)

Estimating the cause-specific CIF is of interest:

- Awkward interpretation on survival scale - what does it mean?
- The cause-specific survival function does not account for those who die from other competing causes before time $t$
- Those who die from competing causes are removed from risk-set
- Better interpretation on mortality scale

**Cause-specific CIF,** $F_k(t)$

Probability a patient will die from cause $D = k$ by time $t$ whilst also being at risk of dying from other competing causes of death

# CSH relationship with cause-specific CIF

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**Cause-specific CIF, $F_k(t)$**

$$F_k(t) = \int_0^t S(u) h_k^{cs}(u) \mathrm{d}u$$

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**Cause-specific CIF, $F_k(t)$**

$$F_k(t) = \int_0^t S(u) h_k^{cs}(u) \mathrm{d}u$$

$$S(t) = \prod_{k=1}^{K} S_k^{cs}(t) = \exp\left( - \sum_{k=1}^{K} \int_0^t h_k^{cs}(u) \mathrm{d}u \right)$$

# CSH relationship with cause-specific CIF

## Cause-specific CIF, $F_k(t)$

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## Note

$$S_k^{cs}(t) = \exp\left(-\int_0^t h_k^{cs}(u) \mathrm{d}u\right) \neq 1 - F_k(t)$$

# Obtaining Aalen-Johansen (AJ) estimates of the cause-specific CIF

Non-parametric estimates of cause-specific CIFs obtained using `stcompet`:

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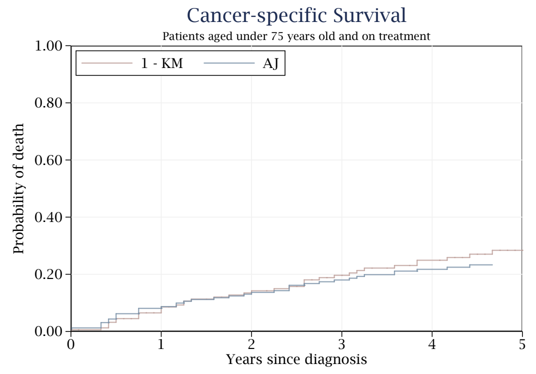
Non-parametric estimates of cause-specific CIFs obtained using `stcompet`:

```
. stset time, f(status==1) id(id) exit(time 60) scale(12)
. stcompet CIF1 = ci if agegrp == 0 & treatment == 1, compet1(2) compet2(3)
. stcompet CIF2 = ci if agegrp == 1 & treatment == 1, compet1(2) compet2(3)
```

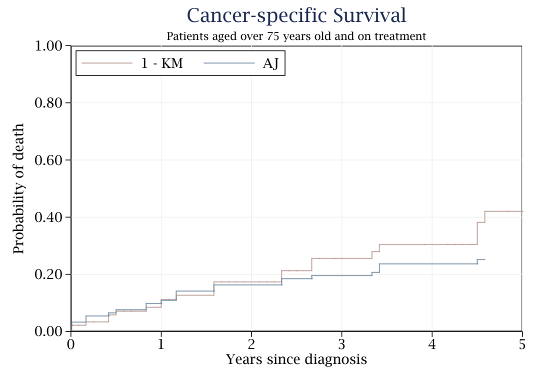
# Comparing AJ with 1 - KM estimates of the cancer-specific CIF



```
. stset time, f(status==1) id(id) exit(time 60) scale(12)

. sts graph if agegrp == 0 & treatment == 1, failure ///
> addplot(line CIF1 _t if status == 1, sort connect(stepstair)) ...
```

# Comparing AJ with 1 - KM estimates of the cancer-specific CIF



```
. stset time, f(status==1) id(id) exit(time 60) scale(12)

. sts graph if agegrp == 1 & treatment == 1, failure ///
> addplot(line CIF2 _t if status == 1, sort connect(stepstair)) ...
```

# Approaches for modelling (all) CSHs in Stata

# Standard approach: cause-specific Cox model

A common approach for modelling CSH function is by assuming proportional hazards (PH) using the Cox model.

**Cause-specific Cox PH model**

$$h_k^{cs}(t \mid \mathbf{x}_k) = h_{0k} \exp\left(\beta_k^{cs} \mathbf{x}_k\right)$$

$\beta_k^{cs}$: row vector of coefficients/log-CSH ratio for cause $k$
$\mathbf{x}_k$: column vector of covariates for cause $k$
$h_{0k}$: the baseline CSH function

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$\mathbf{x}_k$: column vector of covariates for cause $k$
$h_{0k}$: the baseline CSH function

CHR = association on the effect of a covariate on rate of dying from cause $k$

# stcox

```
. stset time, failure(status == 1) id(id) scale(12) exit(time 60)

. stcox treatment, nolog noshow

Cox regression -- Breslow method for ties

No. of subjects =          506                Number of obs    =        506
No. of failures =          145
Time at risk    =  1457.966667
                                              LR chi2(1)       =       6.14
Log likelihood  =   -834.85419                Prob > chi2      =     0.0132

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   treatment |   .6602897   .1116672    -2.45   0.014     .4740025    .9197894
------------------------------------------------------------------------------

. predict h0_cancer, basehc

. gsort _t -_d

. by _t: replace h0_cancer = . if _n > 1

. gen h_cancer_trt0 = h0_cancer

. gen h_cancer_trt1 = h0_cancer*exp(_b[treatment])
```

# stcox

```
. stset time, failure(status == 2) id(id) scale(12) exit(time 60)

. stcox treatment, nolog noshow

Cox regression -- Breslow method for ties

No. of subjects =          506                 Number of obs    =        506
No. of failures =          140
Time at risk    =  1457.966667
                                               LR chi2(1)       =       1.19
Log likelihood  =   -806.46297                 Prob > chi2      =     0.2755

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   treatment |    1.20334   .2048509     1.09   0.277     .8619538    1.679937
------------------------------------------------------------------------------

. predict h0_cvd, basehc

. gsort _t -_d

. by _t: replace h0_cvd = . if _n > 1

. gen h_cvd_trt0 = h0_cvd

. gen h_cvd_trt1 = h0_cvd*exp(_b[treatment])
```

# stcox

```
. stset time, failure(status == 3) id(id) scale(12) exit(time 60)

. stcox treatment, nolog noshow

Cox regression -- Breslow method for ties

No. of subjects =          506                  Number of obs    =          506
No. of failures =           57
Time at risk    =  1457.966667
                                                LR chi2(1)       =         2.67
Log likelihood  =   -324.95951                  Prob > chi2      =       0.1023

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   treatment |   .6460519   .1745103    -1.62   0.106     .3804893    1.096964
------------------------------------------------------------------------------

. predict h0_other, basehc

. gsort _t -_d

. by _t: replace h0_other = . if _n > 1

. gen h_other_trt0 = h0_other

. gen h_other_trt1 = h0_other*exp(_b[treatment])
```

# stcox

```
. drop if missing(h0_cancer) & missing(h0_other) & missing(h0_cvd)

. foreach i in cancer other cvd {
  2.           replace h0_`i´ = 0 if missing(h0_`i´)
  3.           replace h_`i´_trt0 = 0 if missing(h_`i´_trt0)
  4.           replace h_`i´_trt1 = 0 if missing(h_`i´_trt1)
  5. }

. sort _t

. gen S_1 = exp(sum(log(1- h_cancer_trt0 - h_other_trt0 - h_other_trt0)))

. gen S_2 = exp(sum(log(1- h_cancer_trt1 - h_other_trt1 - h_other_trt1)))

. foreach i in cancer other cvd {
  2.           gen cif_trt0_`i´ = sum(S_1[_n-1]*h_`i´_trt0)
  3.           gen cif_trt1_`i´ = sum(S_2[_n-1]*h_`i´_trt1)
  4. }

. foreach i in trt0 trt1 {
  2.           gen totcif2_`i´ = cif_`i´_cancer + cif_`i´_cvd
  3.           gen totcif3_`i´ = totcif2_`i´ + cif_`i´_other
  4. }
```

# stcox

```
. tw (rarea totcif3_trt1 totcif2_trt1  _t, sort connect(stepstair) ...) ///
> (rarea cif_trt1_cancer totcif2_trt1  _t, ...) ///
> (rarea zeros cif_trt1_cancer _t, ...), ...
```

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  - Cause-specific CIF in presence of competing risks

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- However, leads to difficulties in obtaining predictions to facilitate interpretation of model parameters:
    - Conditional and absolute measures
    - Cause-specific CIF in presence of competing risks
- To obtain such measures baseline hazard can be estimated non-parametrically as described by Breslow (1972)
- For a smooth function, further smoothing techniques must be applied
- Computationally intensive methods such as bootstrapping is required for SEs/CIs

# Flexible parametric survival models (FPMs) [Royston and Parmar, 2002]

- Models and more accurately captures complex shapes of the (log-cumulative) baseline hazard function
- A generalisation of the Weibull distribution is used with restricted cubic splines (RCS) that allows for more flexibility

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**Cause-specific log-cumulative PH FPM**

$$\ln\left(H_k^{cs}(t \mid \mathbf{x}_k)\right) = s_k(\ln t; \boldsymbol{\gamma}_k, \mathbf{m}_{0k}) + \beta_k^{cs}\mathbf{x}_k$$

$s_k(\ln t; \boldsymbol{\gamma}_k, \mathbf{m}_{0k})$: baseline restricted cubic spline function on log-time

# Flexible parametric survival models (FPMs) [Royston and Parmar, 2002]

- Models and more accurately captures complex shapes of the (log-cumulative) baseline hazard function
- A generalisation of the Weibull distribution is used with restricted cubic splines (RCS) that allows for more flexibility
- Can also easily include time-dependent effects (TDE)

**Cause-specific log-cumulative non-PH FPM**

$$\ln\left(H_k^{cs}(t \mid \mathbf{x}_k)\right) = s_k(\ln t; \boldsymbol{\gamma}_k, \mathbf{m}_{0k}) + \beta_k^{cs}\mathbf{x}_k + \sum_{l=1}^{E} s_k(\ln t; \boldsymbol{\alpha}_{lk}, \mathbf{m}_{lk})\mathbf{x}_{lk}$$

$s_k(\ln t; \boldsymbol{\alpha}_{lk}, \mathbf{m}_{lk})\mathbf{x}_{lk}$: interaction between spline variables and covariates for TDEs

# stpm2 [Lambert and Royston, 2009]

```
. stset time, failure(status == 1) id(id) scale(12) exit(time 60)

. stpm2 treatment, scale(hazard) df(4) eform nolog

Log likelihood =   -440.316                    Number of obs     =        506

------------------------------------------------------------------------------
             |     exp(b)   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
xb           |
   treatment |   .6594084    .111509    -2.46   0.014     .4733827    .9185368
       _rcs1 |   3.389716   .4258797     9.72   0.000     2.649838    4.336179
       _rcs2 |   .8879662   .0724157    -1.46   0.145     .7567963    1.041871
       _rcs3 |    1.06315   .0411503     1.58   0.114     .9854806    1.146942
       _rcs4 |   1.016818   .0199075     0.85   0.394     .9785387    1.056594
       _cons |    .229559   .0272468   -12.40   0.000     .1819129    .2896844
------------------------------------------------------------------------------
Note: Estimates are transformed only in the first equation.

. stcox treatment, nolog noshow

Cox regression -- Breslow method for ties

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   treatment |   .6602897   .1116672    -2.45   0.014     .4740025    .9197894
------------------------------------------------------------------------------
```

# stpm2 [Lambert and Royston, 2009]

```
. stset time, failure(status == 2) id(id) scale(12) exit(time 60)

. stpm2 treatment, scale(hazard) df(4) eform nolog

Log likelihood = -448.73758                    Number of obs     =        506

------------------------------------------------------------------------------
             |     exp(b)   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
xb           |
   treatment |   1.202808   .2047249     1.08   0.278     .8616223    1.679097
       _rcs1 |    2.82908   .2642265    11.13   0.000     2.355841    3.397384
       _rcs2 |   .8685486   .0544436    -2.25   0.025     .7681357    .9820878
       _rcs3 |   .9529595   .0319403    -1.44   0.151     .8923696    1.017663
       _rcs4 |   1.027927   .0213538     1.33   0.185      .986915    1.070644
       _cons |     .17767   .0237024   -12.95   0.000     .1367912    .2307651
------------------------------------------------------------------------------
Note: Estimates are transformed only in the first equation.

. stcox treatment, nolog noshow

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   treatment |    1.20334   .2048509     1.09   0.277     .8619538    1.679937
------------------------------------------------------------------------------
```

# stpm2 [Lambert and Royston, 2009]

```
. stset time, failure(status == 3) id(id) scale(12) exit(time 60)

. stpm2 treatment, scale(hazard) df(4) eform nolog

Log likelihood = -231.45608                     Number of obs     =        506

------------------------------------------------------------------------------
             |     exp(b)   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
xb           |
   treatment |   .6432149   .1737196    -1.63   0.102     .3788467    1.092066
       _rcs1 |   2.638735   .3351586     7.64   0.000     2.057219    3.384628
       _rcs2 |   .7913665   .0590788    -3.13   0.002      .683647    .9160589
       _rcs3 |   .9369818   .0467358    -1.30   0.192     .8497164    1.033209
       _rcs4 |   1.029843    .031817     0.95   0.341     .9693337     1.09413
       _cons |    .097687   .0179093   -12.69   0.000     .0681998    .1399235
------------------------------------------------------------------------------
Note: Estimates are transformed only in the first equation.

. stcox treatment, nolog noshow

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   treatment |   .6460519   .1745103    -1.62   0.106     .3804893    1.096964
------------------------------------------------------------------------------
```

# stpm2 [Lambert and Royston, 2009]

```
. stset time, failure(status == 3) id(id) scale(12) exit(time 60)

. stpm2 treatment, scale(hazard) df(4) tvc(treatment) dftvc(2) eform nolog

Log likelihood = -230.90611                        Number of obs     =        506

------------------------------------------------------------------------------------
                  |      exp(b)   Std. Err.        z    P>|z|     [95% Conf. Interval]
------------------+-----------------------------------------------------------------
xb                |
        treatment |     .711078   .2158501     -1.12   0.261      .3922222    1.289147
            _rcs1 |    2.805675   .4977957      5.81   0.000      1.981588    3.972477
            _rcs2 |    .7487466   .0683538     -3.17   0.002      .6260772     .895451
            _rcs3 |    .9426525   .0484762     -1.15   0.251      .8522722    1.042617
            _rcs4 |    1.032005   .0318598      1.02   0.308      .9714123    1.096377
  _rcs_treatment1 |    .9101003   .2468771     -0.35   0.728      .5347974    1.548778
  _rcs_treatment2 |    1.161785   .1848084      0.94   0.346      .8505949    1.586824
            _cons |    .0931347   .0183948    -12.02   0.000      .0632401    .1371608
------------------------------------------------------------------------------------
Note: Estimates are transformed only in the first equation.
```

# Estimating cause-specific CIFs after fitting FPMs

**Cause-specific CIF,** $F_k(t)$

$$F_k(t) = \int_0^t \exp\left(-\sum_{k=1}^{K}\int_0^t h_k^{cs}(u)\mathrm{d}u\right) h_k^{cs}(u)\mathrm{d}u$$

# Estimating cause-specific CIFs after fitting FPMs

**Cause-specific CIF, $F_k(t)$**

$$F_k(t) = \int_0^t \exp\left(-\sum_{k=1}^{K}\int_0^t h_k^{cs}(u)\mathrm{d}u\right) h_k^{cs}(u)\mathrm{d}u$$

Must be obtained by numerical approximation:

- Trapezoid method - `stpm2cif` [Hinchliffe and Lambert, 2013]
- Gauss-Legendre quadrature - `stpm2cr` [Mozumder et al., 2017]

# stpm2cif: Data setup

```
. local knotstvc_opt

. local bknotstvc_opt

. local k = 1

. foreach cause in _cancer _cvd _other {
  2.         stset time, failure(status == `k´) exit(time 60) scale(12)
  3.         cap stpm2 treatment, df(4) scale(h) eform nolog
  4.         estimates store stpm2`cause´
  5.         local bhknots`cause´ `e(bhknots)´
  6.         local boundknots`cause´ `e(boundary_knots)´
  7.         local knotstvc_opt `knotstvc_opt´ `cause´ `bhknots`cause´´
  8.         local bknotstvc_opt `bknotstvc_opt´ `cause´ `boundknots`cause´´
  9.         local k = `k´ + 1
 10. }
```

# stpm2cif: Data setup

```
. expand 3 // augment data k = 3 times

. bysort id: gen _cause=_n

. //create dummy variables for each cause of death
. gen _cvd=_cause==2

. gen _other=_cause==3

. gen _cancer=_cause==1

. //create cause of death event indicator variable
. gen _event=(_cause==status)

. label values _cause status

. foreach cause in _cancer _cvd _other {
  2.         gen treatment`cause´ = treatment*`cause´
  3. }
```

# stpm2cif: Data setup

```
. list id status time treatment _cause _event in 1/9, sep(9)

     +-------------------------------------------------------+
     | id   status   time   treatm~t   _cause   _event |
     |-------------------------------------------------------|
  1. |  1   Censor     72          0        1        0 |
  2. |  1   Censor     72          0        2        0 |
  3. |  1   Censor     72          0        3        0 |
  4. |  2   Cancer      1          0        1        1 |
  5. |  2   Cancer      1          0        2        0 |
  6. |  2   Cancer      1          0        3        0 |
  7. |  3      CVD     40          1        1        0 |
  8. |  3      CVD     40          1        2        1 |
  9. |  3      CVD     40          1        3        0 |
     +-------------------------------------------------------+
```

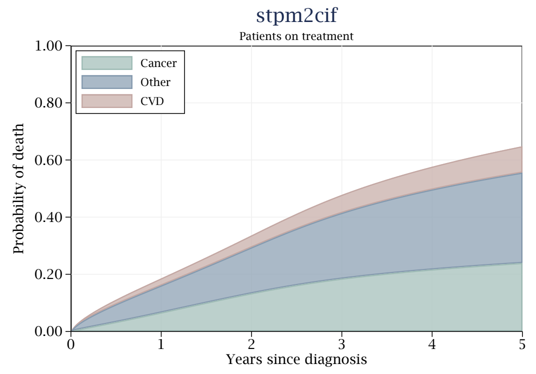
# stpm2cif: Fitting the model

```
. stset time, failure(_event == 1) exit(time 60) scale(12)

. stpm2 treatment_cancer _cancer treatment_cvd _cvd treatment_other _other ///
> , scale(h) knotstvc(`knotstvc_opt´) bknotstvc(`bknotstvc_opt´) ///
> tvc(_cancer _cvd _other) rcsbaseoff nocons eform nolog

Log likelihood = -1120.5192                       Number of obs     =      1,518

-----------------------------------------------------------------------------------
                 |     exp(b)   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------------+-----------------------------------------------------------------
xb               |
treatment_cancer |   .6593781    .111504    -2.46   0.014     .4733607    .9184951
         _cancer |   .2295677   .0272475   -12.40   0.000     .1819204    .2896945
   treatment_cvd |   1.202808   .2047249     1.08   0.278     .8616223    1.679097
            _cvd |     .17767   .0237024   -12.95   0.000     .1367912    .2307651
 treatment_other |   .6432149   .1737196    -1.63   0.102     .3788467    1.092066
          _other |    .097687   .0179093   -12.69   0.000     .0681998    .1399235
  (output omitted)
-----------------------------------------------------------------------------------
Note: Estimates are transformed only in the first equation.
```

# stpm2cif: Post-estimation

```
. stpm2cif cancer cvd other, cause1(treatment_cancer 1 _cancer 1) ///
> cause2(treatment_cvd 1 _cvd 1) cause3(treatment_other 1 _other 1) ci

. gen _totcif2_trt1 = CIF_cancer + CIF_cvd

. gen _totcif3_trt1 = _totcif2_trt1 + CIF_other
```

# stpm2cif: Post-estimation

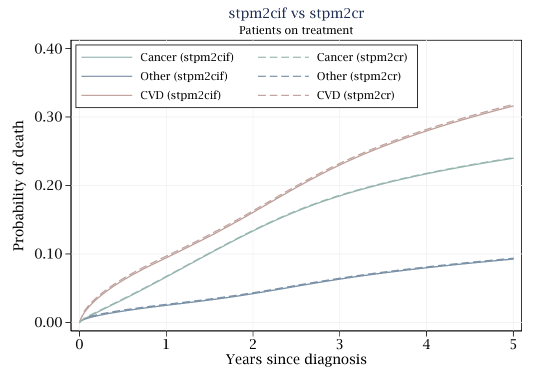


```
. gen zeros = 0

. tw (rarea _totcif3_trt1 _totcif2_trt1  _newt, sort color(erose%80)) ///
> (rarea CIF_cancer _totcif2_trt1  _newt, sort color(emidblue%80)) ///
> (rarea zeros CIF_cancer _newt, sort color(eltgreen%80)), ...
```

# stpm2cr

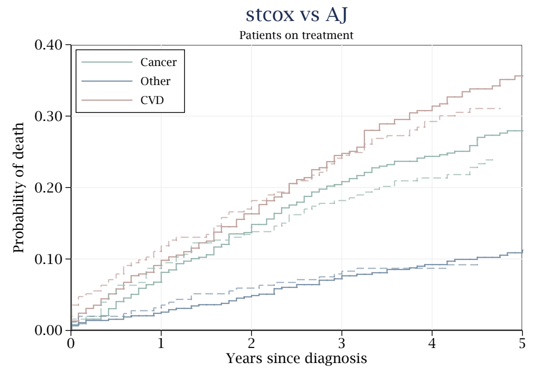
```
. stset time, failure(status == 1,2,3) exit(time 60) scale(12)

. stpm2cr [cancer: treatment, scale(hazard) df(4)] ///
> [cvd: treatment, scale(hazard) df(4)] ///
> [other: treatment, scale(hazard) df(4)], ///
> events(status) cause(1 2 3) cens(0) eform model(csh)
```

# stpm2cr: Post-estimation

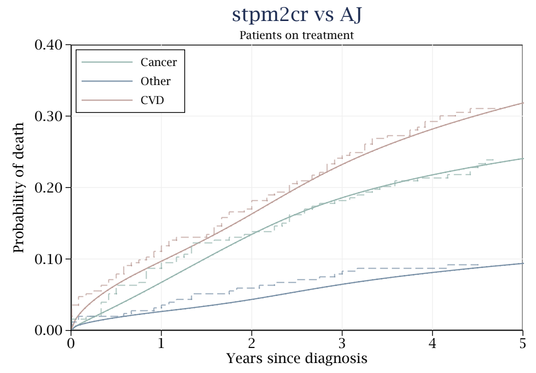


```
. range newt 0 5 100

. predict cifgq_trt1, cif at(treatment 1) timevar(newt) ci
```

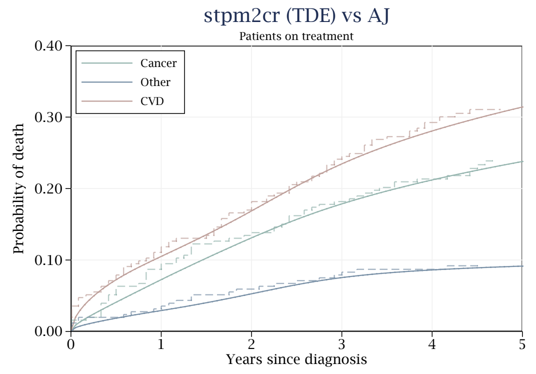
# Comparison with AJ estimates



# Comparison with AJ estimates



# Comparison with AJ estimates



```
. stpm2cr [cancer: treatment, scale(hazard) df(4) tvc(treatment) dftvc(3)] ///
> [cvd: treatment, scale(hazard) df(4) tvc(treatment) dftvc(3)] ///
> [other: treatment, scale(hazard) df(4) tvc(treatment) dftvc(3)], ///
> events(status) cause(1 2 3) cens(0) eform model(csh)
```

# Note on computational time

```
. expand 500 //now 253,000 observations

. replace time = time + runiform()*0.0001

. replace id = _n
variable id was int now long
```

| | Time (secs) |
|---|---|
| **stpm2cr model** | 52.60 |
| **stpm2 (stacked data)** | 76.59 |
| **stpm2cr predict (w/ CIs)** | 2.56 |
| **stpm2cif (w/ CIs)** | 11.10 |

# stpm2cr: Other predictions

- Restricted mean lifetime (RML) [Royston and Parmar, 2013; Andersen, 2013]

- Absolute & relative CIF measures
- Subdistribution hazard [Beyersmann et al., 2009]
- ***Standardisation (to come)***

# stpm2cr: Other predictions

- Restricted mean lifetime (RML) [Royston and Parmar, 2013; Andersen, 2013] - double integration
- Absolute & relative CIF measures
- Subdistribution hazard [Beyersmann et al., 2009]
- ***Standardisation (to come)***- predict for and average over every individual in study population

# Using the multistate package

# multistate [Crowther and Lambert, 2017]

- Written mainly by Michael (& Paul) for more complex multi-state models e.g. illness-death models
- Competing risks is a special case of multi-state models
- Can use `multistate` package to obtain equivalent non-parametric estimates and fit parametric models in presence of competing risks
- Uses a simulation approach for calculating transition probabilities i.e. cause-specific CIFs

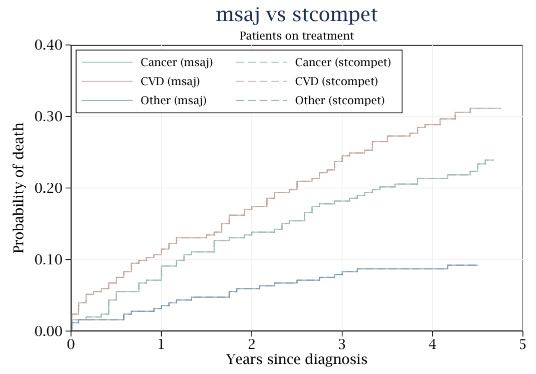
# msset

```
. tab status, gen(cause)

. rename cause2 _cancer

. rename cause3 _cvd

. rename cause4 _other

. msset, id(id) states(_cancer _cvd _other) times(time time time) cr

. li id treatment status time _from _to _trans _start _stop _status _flag in 1/9, sep(9) noobs

  +------------------------------------------------------------------------------------------------+
  | id   treatm~t   status      time   _from   _to   _trans   _start        _stop   _status   _flag |
  |------------------------------------------------------------------------------------------------|
  |  1          0   Censor   72.0024       1     2        1        0    72.002434         0       0 |
  |  1          0   Censor   72.0024       1     3        2        0    72.002434         0       0 |
  |  1          0   Censor   72.0024       1     4        3        0    72.002434         0       0 |
  |  2          0   Cancer   1.00301       1     2        1        0    1.0030106         1       0 |
  |  2          0   Cancer   1.00301       1     3        2        0    1.0030106         0       0 |
  |  2          0   Cancer   1.00301       1     4        3        0    1.0030106         0       0 |
  |  3          1      CVD    40.008       1     2        1        0    40.007992         0       0 |
  |  3          1      CVD    40.008       1     3        2        0    40.007992         1       0 |
  |  3          1      CVD    40.008       1     4        3        0    40.007992         0       0 |
  +------------------------------------------------------------------------------------------------+
```

# msaj

```
. stset _stop, failure(_status == 1) scale(12) exit(time 60)

. msaj if treatment == 1, cr //ci

. sort _t

. li id status _trans _d _t P_AJ_? if P_AJ_1 != . in 1/45, noobs

  ┌──────────────────────────────────────────────────────────────────────────────────────────┐
  │  id   status   _trans   _d          _t     P_AJ_1     P_AJ_2     P_AJ_3     P_AJ_4 │
  ├──────────────────────────────────────────────────────────────────────────────────────────┤
  │ 202   Cancer        1    1   .00841895   .99604743  .00395257          0          0 │
  │ 105      CVD        2    1   .00854265   .99209486  .00395257  .00395257          0 │
  │ 151    Other        3    1   .00855531   .98814229  .00395257  .00395257  .00395257 │
  │ 382      CVD        2    1   .00866204   .98418972  .00395257  .00790514  .00395257 │
  │ 437      CVD        2    1   .00869011   .98023715  .00395257  .01185771  .00395257 │
  ├──────────────────────────────────────────────────────────────────────────────────────────┤
  │ 120   Cancer        1    1   .00869888   .97628458  .00790514  .01185771  .00395257 │
  │ 502   Cancer        1    1   .00881231   .97233202  .01185771  .01185771  .00395257 │
  │ 464      CVD        2    1   .00886007   .96837945  .01185771  .01581028  .00395257 │
  │  93    Other        3    1   .00898155   .96442688  .01185771  .01581028  .00790514 │
  │ 492      CVD        2    1   .00904977   .96047431  .01185771  .01976285  .00790514 │
  └──────────────────────────────────────────────────────────────────────────────────────────┘

. bysort P_AJ_2 (_t): gen first1 = _n==1

. bysort P_AJ_3 (_t): gen first2 = _n==1

. bysort P_AJ_4 (_t): gen first3 = _n==1
```

# msaj


msaj vs stcompet
Patients on treatment
Probability of death
0.00
0.10
0.20
0.30
0.40
Years since diagnosis
0
1
2
3
4
5
Cancer (msaj)
CVD (msaj)
Other (msaj)
Cancer (stcompet)
CVD (stcompet)
Other (stcompet)

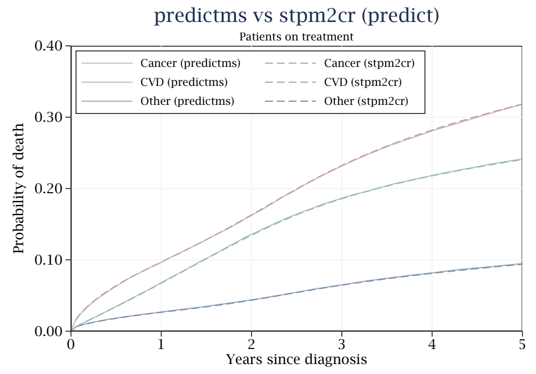
# predictms

```
. stpm2 treatment if _trans==1, df(4) scale(h) eform nolog
. estimates store m1
. stpm2 treatment if _trans==2, df(4) scale(h) eform nolog
. estimates store m2
. stpm2 treatment if _trans==3, df(4) scale(h) eform nolog
. estimates store m3
. range tempt 0 5 100
. predictms , cr timevar(tempt) models(m1 m2 m3) at1(treatment 1)
```

# predictms - without msset

```
. forvalues k = 1/3 {
  2.         stset time, failure(status == `k´) id(id) scale(12) exit(time 60)
  3.         stpm2 treatment, df(4) scale(h) eform nolog
  4.         estimates store m`k´
  5. }

. range tempt 0 5 100

. predictms , cr timevar(tempt) models(m1 m2 m3) at1(treatment 1)
```

# predictms


predictms vs stpm2cr (predict)
Patients on treatment
Cancer (predictms)
CVD (predictms)
Other (predictms)
Cancer (stpm2cr)
CVD (stpm2cr)
Other (stpm2cr)
Probability of death
0.00
0.10
0.20
0.30
0.40
Years since diagnosis
0
1
2
3
4
5

# Summary of FPM tools for estimating cause-specific CIFs using CSHs

- Post-estimation command, `stpm2cif`
    - Requires augmenting data before `stpm2`
    - Fitting a single model means interpretation is difficult and more room for errors
    - Uses a basic numerical integration method - slow for larger datasets

# Summary of FPM tools for estimating cause-specific CIFs using CSHs

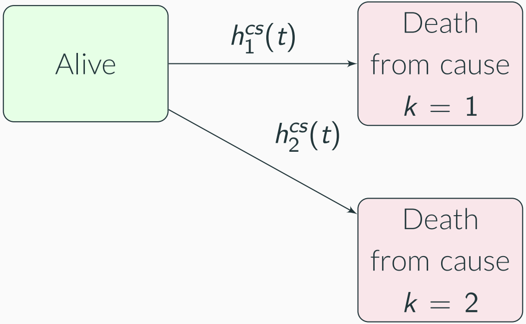
- Post-estimation command, `stpm2cif`
    - Requires augmenting data before `stpm2`
    - Fitting a single model means interpretation is difficult and more room for errors
    - Uses a basic numerical integration method - slow for larger datasets
- Using `stpm2cr` as a wrapper followed by `predict`
    - Fits separate `stpm2` models for each cause of death without data augmentation
    - Uses quicker numerical integration method
    - Can obtain other useful predictions e.g. restricted mean lifetime/comparative predictions

# Summary of FPM tools for estimating cause-specific CIFs using CSHs

- Via the `predictms` command provided as a part of the `multistate` package
    - Uses a simulation approach. Can alternatively use AJ estimator to save on computational time
    - Can also be used without requiring `msset`
    - Extremely versatile - has some very useful features and post-estimation options

# What about modelling covariate effects on the risk of dying from a particular cause?

# Cause-specific hazards



Alive

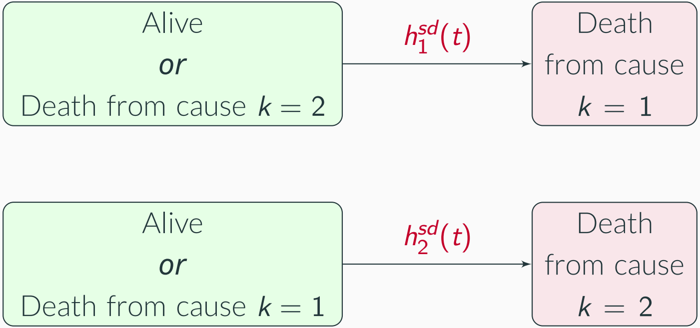
$h_1^{cs}(t)$

Death from cause $k = 1$

$h_2^{cs}(t)$

Death from cause $k = 2$

# Subdistribution hazards



Alive

*or*

Death from cause $k = 2$

$h_1^{sd}(t)$

Death from cause $k = 1$

Alive

*or*

Death from cause $k = 1$

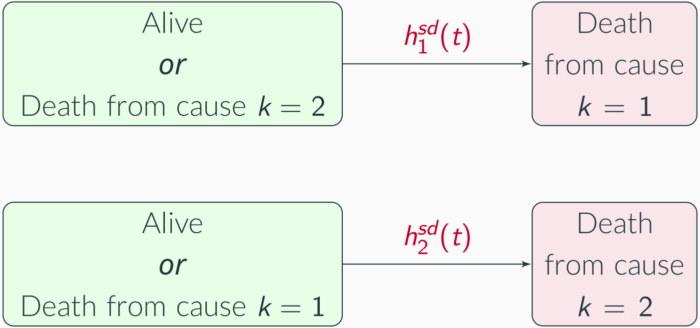
$h_2^{sd}(t)$

Death from cause $k = 2$

**Subdistribution hazard (SDH) rate,** $h_k^{sd}(t)$

The instantaneous rate of failure at time $t$ from cause $D = k$ amongst those who have not died, or have died from any of the other causes, where $D \neq k$

# Subdistribution hazards



**Subdsitribution hazard (SDH) rate, $h_k^{sd}(t)$**

$$h_k^{sd}(t) = \lim_{\Delta t \to 0} \frac{P(t < T \leq t + \Delta t, D = k | T > t \cup (T \leq t \cap D \neq k))}{\Delta t}$$

# SDH relationship with cause-specific CIF

**Cause-specific CIF,** $F_k(t)$

$$F_k(t) = 1 - \exp\left[-\int_0^t h_k^{sd}(u)\mathrm{d}u\right]$$

# SDH relationship with cause-specific CIF

**Cause-specific CIF, $F_k(t)$**

$$F_k(t) = 1 - \exp\left[-\int_0^t h_k^{sd}(u)\mathrm{d}u\right]$$

**Note**

$$1 - F_k(t) = P(D \neq k) + S_k^{sd}(t)$$

# Standard approach: Fine & Gray model

Derived in a similar way to cause-specific Cox PH model as described by Fine and Gray [1999].

**SDH Regression Model (Fine & Gray Model)**

$$h_k^{sd}(t \mid \mathbf{x}_k) = h_{0k} \exp\left(\beta_k^{sd} \mathbf{x}_k\right)$$

$\beta_k^{sd}$: row vector of coefficients/log-SDH ratio for cause $k$

$\mathbf{x}_k$: column vector of covariates for cause $k$

$h_{0k}$: the baseline SDH function

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$\beta_k^{sd}$: row vector of coefficients/log-SDH ratio for cause $k$
$\mathbf{x}_k$: column vector of covariates for cause $k$
$h_{0k}$: the baseline SDH function

SHR = association on the effect of a covariate on risk of dying from cause $k$

# Time-dependent censoring weights

- Need to consider those who have already died from other competing causes of death in risk-set
- Calculate missing censoring times for those that died from other causes by applying time-dependent weights to partial likelihood
- Influence of weights decreases over-time as the probability of being censored increases
- Further details given by Lambert et al. [2017] and Geskus [2011]

# stcrreg

```
. *Cancer
. stset time, failure(status == 1) exit(time 60) scale(12)

. stcrreg treatment, compete(status == 2, 3)

         failure _d:  status == 1
   analysis time _t:  time/12
  exit on or before:  time 60

Iteration 0:   log pseudolikelihood = -875.12133
Iteration 1:   log pseudolikelihood =  -875.1123
Iteration 2:   log pseudolikelihood =  -875.1123

Competing-risks regression                       No. of obs       =        506
                                                 No. of subjects  =        506
Failure event   : status == 1                    No. failed       =        145
Competing events: status == 2 3                  No. competing    =        197
                                                 No. censored     =        164

                                                 Wald chi2(1)     =       6.74
Log pseudolikelihood =  -875.1123                Prob > chi2      =     0.0094

------------------------------------------------------------------------------
             |               Robust
          _t |        SHR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   treatment |   .6454653   .1088223    -2.60   0.009      .463836    .8982171
------------------------------------------------------------------------------

. stcurve, cif at(treatment=1) outfile(cancer1, replace) range(0 5)
```

# stcrreg

```
. *CVD
. stset time, failure(status == 2) exit(time 60) scale(12)

. stcrreg treatment, compete(status == 1, 3)

         failure _d:  status == 2
   analysis time _t:  time/12
  exit on or before:  time 60

Iteration 0:   log pseudolikelihood = -848.00112
Iteration 1:   log pseudolikelihood = -847.83627
Iteration 2:   log pseudolikelihood = -847.83627

Competing-risks regression                       No. of obs       =        506
                                                 No. of subjects  =        506
Failure event     : status == 2                  No. failed       =        140
Competing events: status == 1 3                  No. competing    =        202
                                                 No. censored     =        164

                                                 Wald chi2(1)     =       2.79
Log pseudolikelihood = -847.83627                Prob > chi2      =     0.0949

------------------------------------------------------------------------------
             |               Robust
          _t |        SHR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   treatment |   1.326649   .2245377     1.67   0.095     .9521137    1.848517
------------------------------------------------------------------------------

. stcurve, cif at(treatment=1) outfile(cvd1, replace) range(0 5)
```

# stcrreg

```
. *Other causes
. stset time, failure(status == 3) exit(time 60) scale(12)

. stcrreg treatment, compete(status == 1, 2)

         failure _d:  status == 3
   analysis time _t:  time/12
  exit on or before:  time 60

Iteration 0:   log pseudolikelihood = -349.42345
Iteration 1:   log pseudolikelihood = -349.41144
Iteration 2:   log pseudolikelihood = -349.41144

Competing-risks regression                       No. of obs       =        506
                                                 No. of subjects  =        506
Failure event   : status == 3                    No. failed       =         57
Competing events: status == 1 2                  No. competing    =        285
                                                 No. censored     =        164

                                                 Wald chi2(1)     =       2.14
Log pseudolikelihood = -349.41144                Prob > chi2      =     0.1432

------------------------------------------------------------------------------
             |               Robust
          _t |        SHR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   treatment |   .6736976   .1817566    -1.46   0.143     .3970267    1.143169
------------------------------------------------------------------------------

. stcurve, cif at(treatment=1) outfile(other1, replace) range(0 5)
```

# FPMs on (log-cumulative) SDH scale

**Log-cumulative SDH FPM**

$$\ln\left(H_k^{sd}(t \mid \mathbf{x}_k)\right) = s_k(\ln t; \boldsymbol{\gamma}_k, \mathbf{m}_{0k}) + \beta_k^{sd}\mathbf{x}_k$$

# FPMs on (log-cumulative) SDH scale

**Log-cumulative non-proportional SDH FPM**

$$\ln\left(H_k^{sd}(t \mid \mathbf{x}_k)\right) = s_k(\ln t; \gamma_k, \mathbf{m}_{0k}) + \beta_k^{sd}\mathbf{x}_k + \sum_{l=1}^{E} s_k(\ln t; \boldsymbol{\alpha}_{lk}, \mathbf{m}_{lk})\mathbf{x}_{lk}$$

# FPMs on (log-cumulative) SDH scale

**Log-cumulative non-proportional SDH FPM**

$$\ln\left(H_k^{sd}(t \mid \mathbf{x}_k)\right) = s_k(\ln t; \boldsymbol{\gamma}_k, \mathbf{m}_{0k}) + \beta_k^{sd}\mathbf{x}_k + \sum_{l=1}^{E} s_k(\ln t; \boldsymbol{\alpha}_{lk}, \mathbf{m}_{lk})\mathbf{x}_{lk}$$

1. Apply time-dependent censoring weights to the likelihood function for each cause $k$ (`stcrprep`) [Lambert et al., 2017]
2. Model all $k$ causes of death simultaneously directly using the full likelihood function (`stpm2cr`) [Mozumder et al., 2017; Jeong and Fine, 2007]

# stcrprep

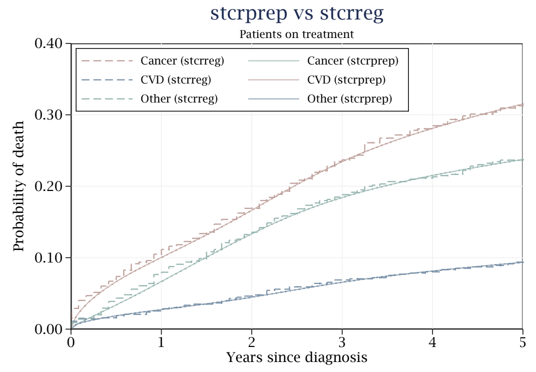
```
. stset time, failure(status == 1,2,3) exit(time 60) scale(12) id(id)
. gen cod2 = cond(_d==0,0,status)
. stcrprep, events(cod2) keep(treatment ) trans(1 2 3) wtstpm2 censcov(treatment) every(1)
. gen event = cod2 == failcode
. stset tstop [iw=weight_c], failure(event) enter(tstart) noshow
```

(*output omitted*)

# stcrprep

```
. stpm2 treatment_cancer _cancer treatment_cvd _cvd treatment_other _other ///
> , scale(h) knotstvc(`knotstvc_opt´) bknotstvc(`bknotstvc_opt´) ///
> tvc(_cancer _cvd _other) rcsbaseoff nocons eform nolog
note: delayed entry models are being fitted

Log likelihood =  -1228.025                     Number of obs     =      3,688

----------------------------------------------------------------------------------
                 |     exp(b)   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------------+----------------------------------------------------------------
xb               |
treatment_cancer |   .6408643   .1083623    -2.63   0.009     .4600852    .8926761
         _cancer |   .3060732   .0335208   -10.81   0.000     .2469463    .3793569
   treatment_cvd |   1.329932   .2263497     1.68   0.094     .9527038    1.856525
            _cvd |   .2029639   .0262824   -12.32   0.000     .1574686    .2616034
 treatment_other |   .6740861   .1819979    -1.46   0.144     .3970979    1.144282
          _other |   .1034306   .0183681   -12.78   0.000     .0730273    .1464916
  (output omitted)
----------------------------------------------------------------------------------
Note: Estimates are transformed only in the first equation.

. predict cif_stcrprep_cancer, at(treatment_cancer 1 _cancer 1) zeros failure timevar(tempt)

. predict cif_stcrprep_cvd, at(treatment_cvd 1 _cvd 1) zeros failure timevar(tempt)

. predict cif_stcrprep_other, at(treatment_other 1 _other 1) zeros failure timevar(tempt)
```

# stcrprep


stcrprep vs stcrreg
Patients on treatment
Probability of death
0.00
0.10
0.20
0.30
0.40
Years since diagnosis
0
1
2
3
4
5
Cancer (stcrreg)
CVD (stcrreg)
Other (stcrreg)
Cancer (stcrprep)
CVD (stcrprep)
Other (stcrprep)

# stpm2cr

```
. stset time, failure(status == 1,2,3) exit(time 60) scale(12)

. stpm2cr [cancer: treatment, scale(hazard) df(4)] ///
> [cvd: treatment, scale(hazard) df(4)] ///
> [other: treatment, scale(hazard) df(4)], ///
> events(status) cause(1 2 3) cens(0) eform
  (output omitted)

. predict cifgq_trt1, cif at(treatment 1) timevar(tempt)
Calculating predictions for the following causes: 1 2 3
```

# stpm2cr

```
. stset time, failure(status == 1,2,3) exit(time 60) scale(12)

. stpm2cr [cancer: treatment, scale(hazard) df(4)] ///
> [cvd: treatment, scale(hazard) df(4)] ///
> [other: treatment, scale(hazard) df(4)], ///
> events(status) cause(1 2 3) cens(0) eform
  (output omitted)

. predict cifgq_trt1, cif at(treatment 1) timevar(tempt)
Calculating predictions for the following causes: 1 2 3
```

Above is not comparable with time-dependent censoring weights approach as we assume proportionality for the competing causes of death.

# stpm2cr

```
. stpm2cr [cancer: treatment, scale(hazard) df(4)] ///
> [cvd: treatment, scale(hazard) df(4) tvc(treatment) dftvc(3)] ///
> [other: treatment, scale(hazard) df(4) tvc(treatment) dftvc(3)], ///
> events(status) cause(1 2 3) cens(0) eform
  (output omitted)
Log likelihood = -1117.3418                    Number of obs     =        506

------------------------------------------------------------------------------
             |     exp(b)   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
cancer       |
   treatment |    .647454   .1094638    -2.57   0.010      .464834    .9018201
  (output omitted)
       _cons |   .1889881   .0229604   -13.71   0.000     .1489433    .2397993
  (output omitted)
------------------------------------------------------------------------------
```

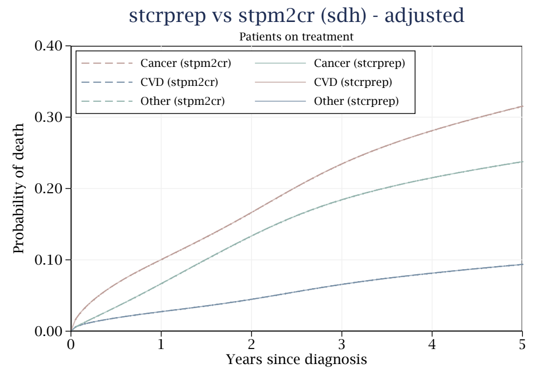
# stpm2cr

```
. stpm2cr [cancer: treatment, scale(hazard) df(4) tvc(treatment) dftvc(3)] ///
> [cvd: treatment, scale(hazard) df(4)] ///
> [other: treatment, scale(hazard) df(4) tvc(treatment) dftvc(3)], ///
> events(status) cause(1 2 3) cens(0) eform
  (output omitted)
------------------------------------------------------------------------------
             |     exp(b)   Std. Err.      z    P>|z|     [95% Conf. Interval]
  (output omitted)
-------------+----------------------------------------------------------------
cvd          |
   treatment |   1.336129   .2273682     1.70   0.089     .9571939    1.865077
  (output omitted)
       _cons |   .1366028   .0187788   -14.48   0.000     .1043385     .178844
  (output omitted)
------------------------------------------------------------------------------
```

# stpm2cr

```
. stpm2cr [cancer: treatment, scale(hazard) df(4) tvc(treatment) dftvc(3)] ///
> [cvd: treatment, scale(hazard) df(4) tvc(treatment) dftvc(3)] ///
> [other: treatment, scale(hazard) df(4)], ///
> events(status) cause(1 2 3) cens(0) eform
  (output omitted)
------------------------------------------------------------------------------
             |     exp(b)   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
             |
  (output omitted)
other        |
   treatment |   .6771057   .1827954    -1.44   0.149     .3988974    1.149349
  (output omitted)
       _cons |   .0720086   .0138407   -13.69   0.000     .0494056    .1049525
------------------------------------------------------------------------------
```

# Comparing stcrprep and stpm2cr



# Comparison of computational time (to all *k* causes)

```
. expand 100 //now 50,060 observations

. replace time = time + runiform()*0.0001

. replace id = _n
variable id was int now long
```

| | Time |
|---|---|
| **stcrreg (total)** | 53 mins |
| **stcrprep (total)** | 1 min |
| **stpm2cr** | 17 secs |

# On which scale should we model?

Cause-specific hazards

- Risk-set is defined in usual way - easy to understand

Subdistribution hazards

- Maintains direct relationship with cause-specific CIF

# On which scale should we model?

Cause-specific hazards

- Risk-set is defined in usual way - easy to understand
- Infer covariate effects on the rate of dying from a cause
  - For research questions on aetiology and causal effects

Subdistribution hazards

- Maintains direct relationship with cause-specific CIF
- Infer covariate effects on the risk of dying from a cause
  - For research questions on prognosis

# On which scale should we model?

Cause-specific hazards

- Risk-set is defined in usual way - easy to understand
- Infer covariate effects on the rate of dying from a cause
  - For research questions on aetiology and causal effects

Subdistribution hazards

- Maintains direct relationship with cause-specific CIF
- Infer covariate effects on the risk of dying from a cause
  - For research questions on prognosis

Many recommend inferences on all CSHs and cause-specific CIFs for a better understanding on the overall impact of cancer [Lambert et al., 2017; Latouche et al., 2013; Beyersmann et al., 2007]

# What next?

- Standardisation post-estimation for FPMs on cause-specific log-cumulative hazard scale
- Standardisation post-estimation after `stpm2cr`
- Restricted mean survival time [Royston and Parmar, 2011] for `stpm2cr` and `stcrprep`
- Expected number of life-years lost decomposed by cause of death [Andersen, 2013]

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