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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Censoring:

- 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

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Censoring:

- Right censoring: survival time > follow-up time
  - Emmigration
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- 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:

(All-cause) Survival function

$$S(t) = P(T \geq t)$$

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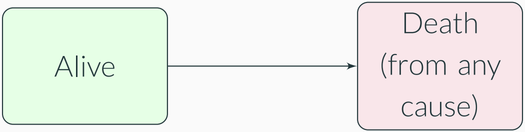
(All-cause) Survival function

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

(All-cause) Cumulative incidence function (CIF)

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

A typical survival analysis: two-state model



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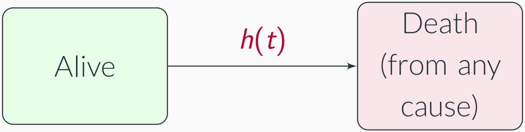
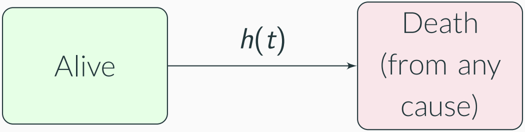


(All-cause) Hazard rate, $h(t)$

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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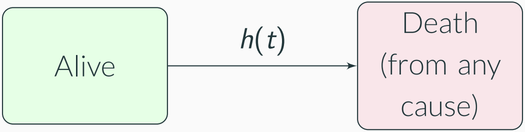


(All-cause) Hazard rate, $h(t)$

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

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

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

Example dataset

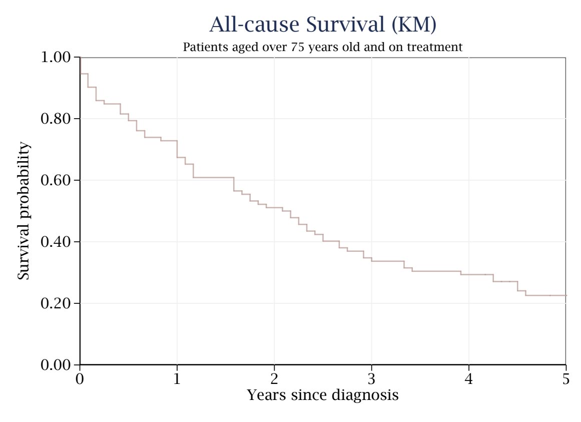
Load public-use prostate cancer dataset:

```
. 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

Competing risks

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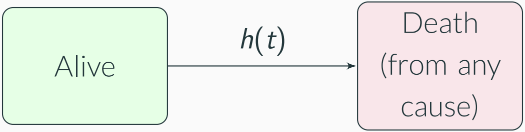
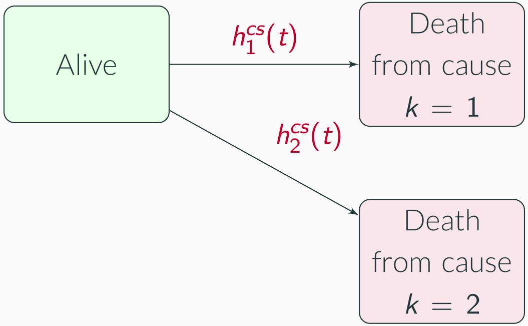
- Not valid under competing risks
- Death from ``competing'' causes may be due to adverse effects of treatment for disease

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

No competing risks



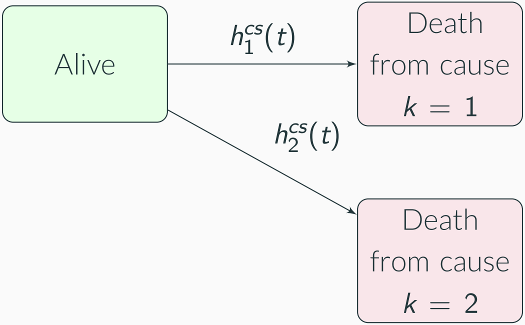
With competing risks



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



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

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

The cause-specific CIF (transition probability)

Estimating the cause-specific CIF is of interest:

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- Those who die from competing causes are removed from risk-set

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

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

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

CSH relationship with cause-specific CIF

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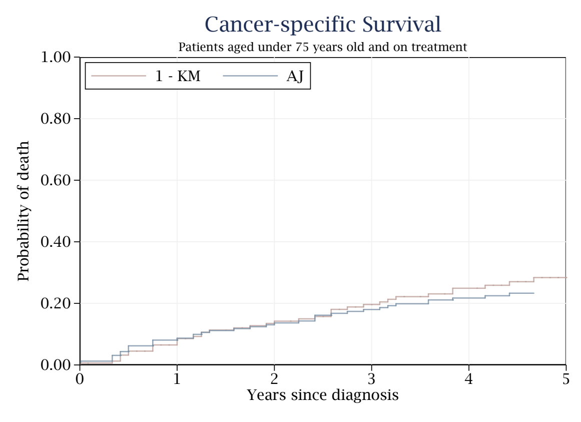
Non-parametric estimates of cause-specific CIFs obtained using `stcompet`:

```
. 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)
```

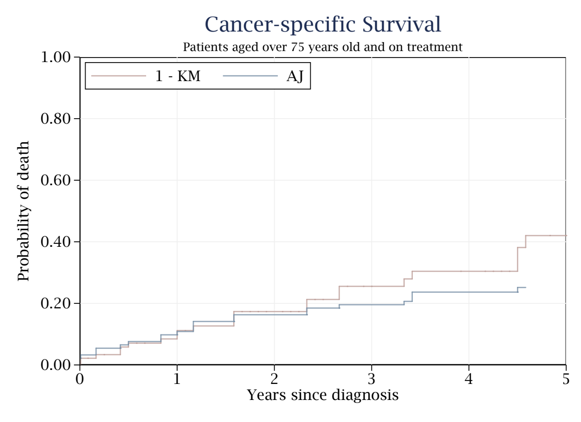
Comparing AJ with 1 - KM estimates of the cancer-specific CIF



```
. 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

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

β_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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β_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

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])
```

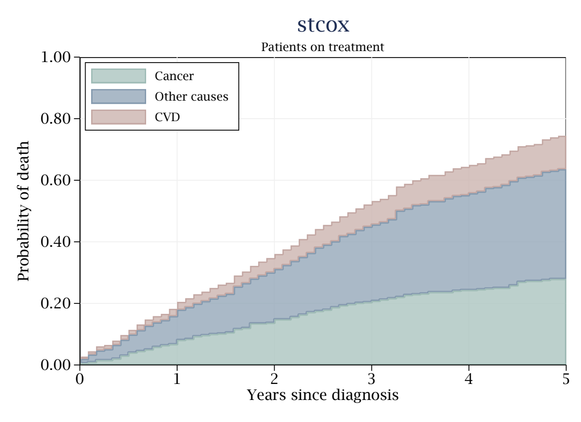
stcox

```
. 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, ...), ...
```

Remarks on Cox PH models for competing risks data

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  - Cause-specific CIF in presence of competing risks

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  - 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

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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   │
     └────────────────────────────────────────────────────┘
```

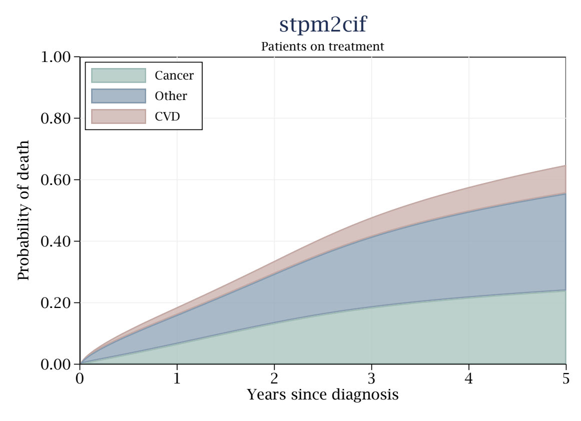
stpm2cif: Fitting the model

```
. 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

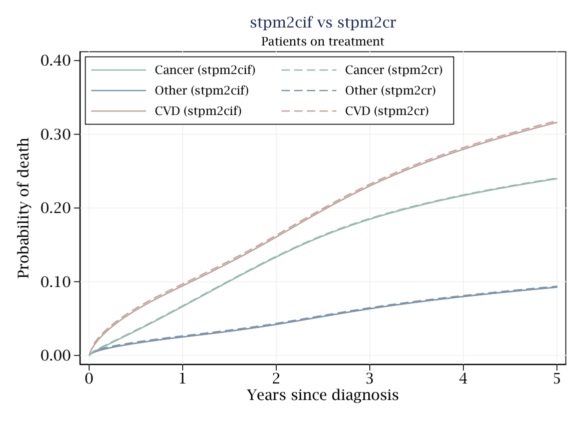


```
. gen zeros = 0

. 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

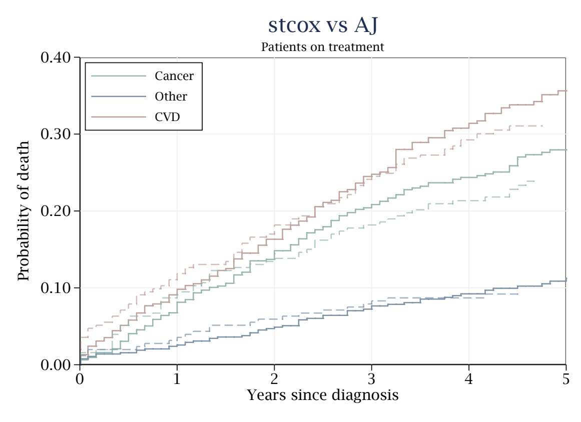
```
. stset time, failure(status == 1,2,3) exit(time 60) scale(12)

. 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

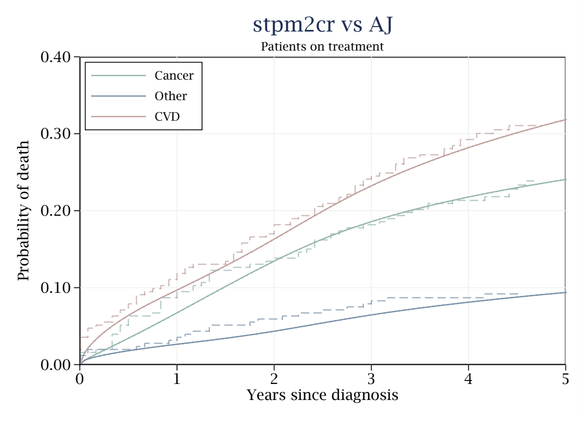


```
. range newt 0 5 100

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

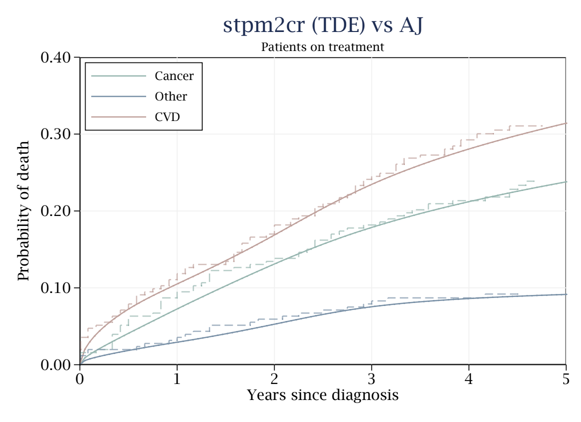
Comparison with AJ estimates



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

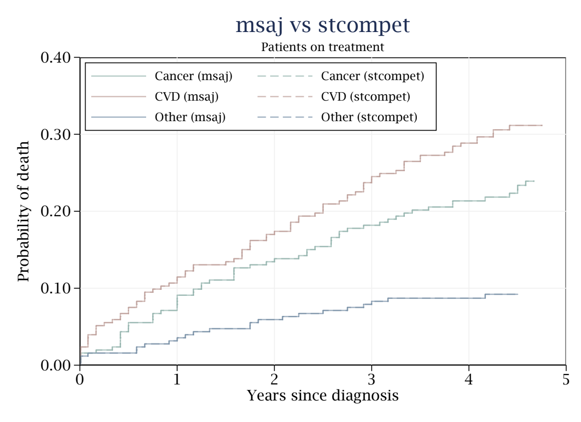
msset

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

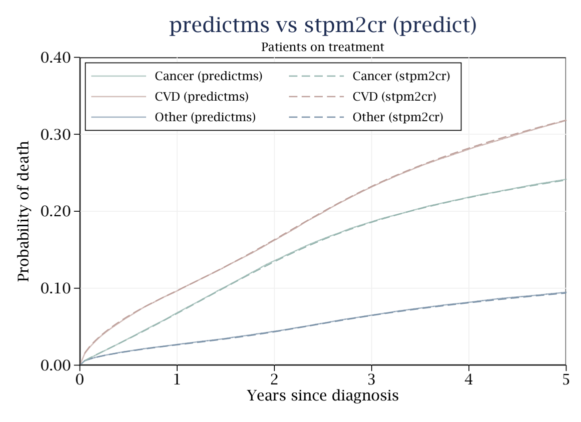
predictms

```
. 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
0.40
0.30
0.20
0.10
0.00
0
1
2
3
4
5
Years since diagnosis

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

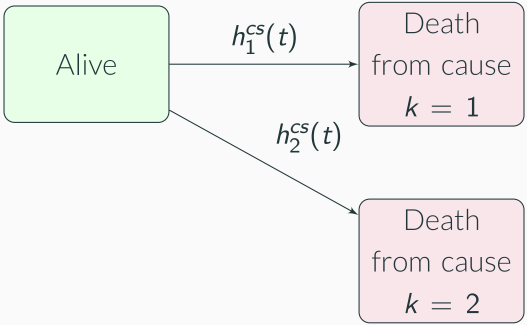
- Post-estimation command, `stpm2cif`
  - Requires augmenting data before `stpm2`
  - Fitting a single model means interpretation is difficult and more room for errors
  - Uses a basic numerical integration method - slow for larger datasets
- Using `stpm2cr` as a wrapper followed by `predict`
  - Fits 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

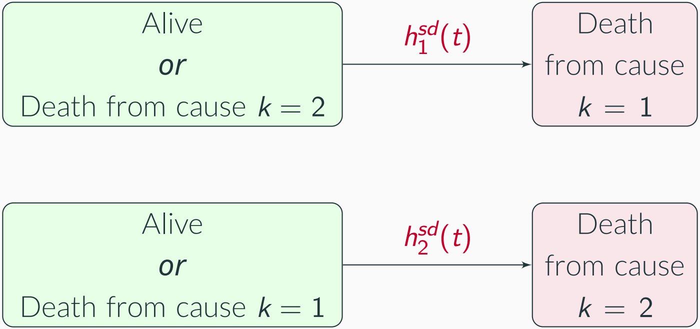
$h_1^{cs}(t)$

Death from cause $k = 1$

$h_2^{cs}(t)$

Death from cause $k = 2$

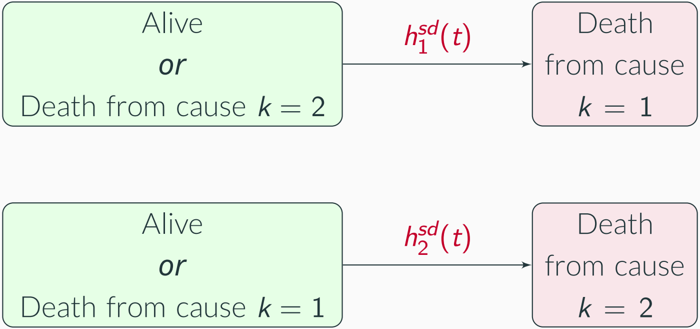
Subdistribution hazards



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



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

$k = 2$

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)

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

β_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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β_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

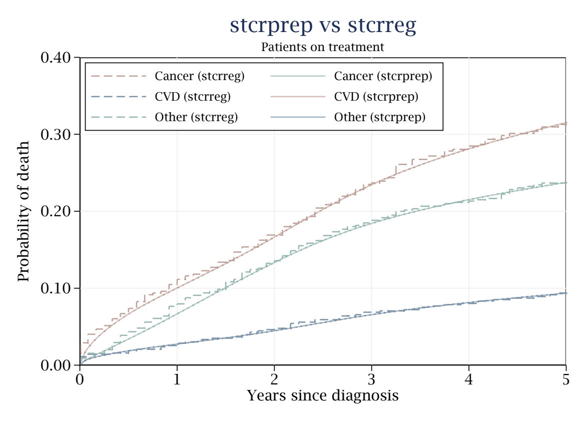
```
. stset time, failure(status == 1,2,3) exit(time 60) scale(12) id(id)

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

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)
------------------------------------------------------------------------------------
```

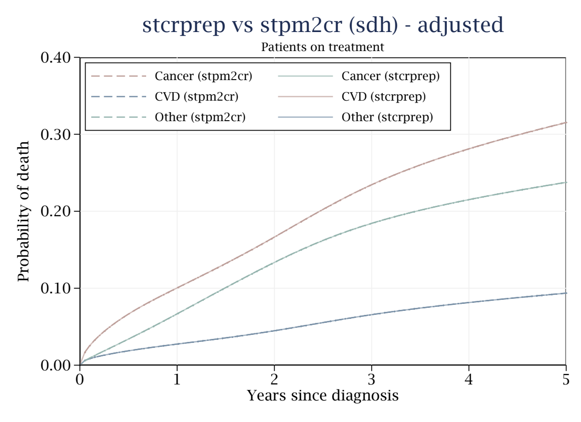
stpm2cr

```
. 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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J. Beyersmann, A. Latouche, A. Buchholz, and M. Schumacher. Simulating competing risks data in survival analysis. ***Stat Med***, 28(6):956--971, 2009.

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J.-H. Jeong and J. P. Fine. Parametric regression on cumulative incidence function. ***Biostatistics***, 8(2):184--196, Apr 2007.

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P. Royston and M. K. B. Parmar. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. ***Stat Med***, 30(19):2409--2421, Aug 2011.

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