1. Overview
2. Competing-risks events
3. Cumulative incidence functions
4. The Cox regression approach
5. The Fine and Gray approach (stcrreg)
6. Concluding remarks
• Competing risks are events that prevent an event of interest from occurring, rather than just prevent you from seeing it happen (censoring)

• When you have competing events, you want to focus on the cumulative incidence function rather than the survival function

• You can use Cox regression with competing risks, but you have to either
  1. Modify your interpretations
  2. Go through a lot of work to assess covariate effects

• Competing-risks regression by the method of Fine and Gray (1999) is a useful alternative

• Implemented in the `stcrreg` command, new to Stata 11
A competing-risk event is an event that impedes what a researcher actually “wants” to see.

For example, if a researcher is interested in recurrence of breast cancer, a heart attack would be competing event.

This is not the same as censoring. With censoring, the event of interest still happens at a later time. You just don’t get to see when.

What confuses the matter is that, for some purposes, it is okay to think of competing events as censorings.
. sysuse cancer, clear
(Patient Survival in Drug Trial)
.stset studytime died
(output omitted)
.sts graph

Kaplan–Meier survival estimate
If the event of interest is recurrent breast cancer, a Kaplan-Meier curve answers the question "What is the probability of no breast cancer before 5 months?"

In a competing-risks setting, a Kaplan-Meier curve is inadequate for two reasons:

First, it fails to acknowledge that breast cancer may never occur, i.e. the probability of breast cancer after time zero is not equal to 1.0
Second, with competing risks it is better to reverse the temporal ordering of the question.

It makes better sense to ask “What is the probability of breast cancer within 5 months?” than to ask “What is the probability that nothing happens for the first five months, but when something does happen I want it to be breast cancer and not a heart attack?”

As such, you should use the cumulative incidence function (CIF) instead.

A CIF is just the probability that the event of interest occurs before a given time.
Competing-risks regression

Cumulative incidence functions

Cumulative incidence curve

![Graph showing cumulative incidence function over analysis time]
Example

- Geskus (2000) analyzed data from 324 HIV-positive men from the Amsterdam Cohort Studies on HIV infection and AIDS.
- During the course of infection, the syncytium inducing (SI) phenotype appeared in some instances.
- Appearance of SI typically means bad news.
- Time to SI appearance in the absence of AIDS is the analysis of interest.
- In this context, AIDS with no SI acts as the competing event.
- Covariate of interest is variable ccr5 indicating a mutation in the C-C chemokine receptor 5 gene.
. webuse hiv_si, clear
(HIV and SI as competing risks)
.
describe
   obs:     324 HIV and SI as competing risks
   vars:      4 3 Apr 2009 13:40
  size:   5,184 (99.9% of memory free) (_dta has notes)

+-----------------+-----------------+-----------------+-----------------+
<table>
<thead>
<tr>
<th>variable name</th>
<th>storage type</th>
<th>display format</th>
<th>value label</th>
</tr>
</thead>
<tbody>
<tr>
<td>patnr</td>
<td>int</td>
<td>%8.0g</td>
<td>ID</td>
</tr>
<tr>
<td>time</td>
<td>float</td>
<td>%9.0g</td>
<td>Years from HIV infection</td>
</tr>
<tr>
<td>status</td>
<td>byte</td>
<td>%10.0g</td>
<td>stat 1 = AIDS, 2 = SI, 0 = event-free</td>
</tr>
<tr>
<td>ccr5</td>
<td>byte</td>
<td>%9.0g</td>
<td>ccr5 1 if WM (deletion in C-C chemokine receptor 5 gene)</td>
</tr>
</tbody>
</table>
+-----------------+-----------------+-----------------+-----------------+

Sorted by:
The research question is: “How does the ccr5 mutation affect the incidence of SI in the presence of AIDS as a competing risk?”

Standard Cox regression does not answer that question.

That does not mean it is completely useless, however.

First, you can modify your interpretation if you wish.

Second, you can use more Cox regression to answer our research question, but it is a lot of work. But it is possible.
. stset time, failure(status == 2) // SI is the event of interest
(output omitted)
. stcox ccr5
(output omitted)
Cox regression -- no ties

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>_t</td>
<td>Haz. Ratio</td>
<td>Std. Err.</td>
<td>z</td>
<td>P&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.7755334</td>
<td>.1846031</td>
<td>-1.07</td>
<td>0.286</td>
</tr>
</tbody>
</table>

No. of subjects = 324 Number of obs = 324
No. of failures = 107
Time at risk = 2261.959996
LR chi2(1) = 1.19
Prob > chi2 = 0.2748
The previous results may be interpreted as those for a world where the competing event does not occur.

A full CIF analysis with Cox regression would require the following additional steps:

1. Predict the hazard contributions from the previous Cox regression.
2. Fit a Cox regression with AIDS instead as the event of interest.
3. Predict the hazard contributions from that model fit.
4. Calculate the estimated CIF manually for both ccr5==0 and ccr5==1; see page 209 of [ST] for details.
5. Plot the results.

Moral: Assessing covariate effects on the CIF using Cox regression is a lot of work.
Competing-risks regression

- The Cox regression approach
- Comparative CIF curves

![Graph showing cumulative incidence for different ccr5 values over analysis time](image-url)
An easier way to do CIF covariate analysis is with competing risks regression, according to the model of Fine and Gray (1999).

They posit a model for the hazard of the subdistribution for the failure event of interest, known as the subhazard.

Put simply, they model the CIF directly knowing full well it is not a proper distribution function.

Covariates affect the subhazard proportionally, similar to Cox regression.

You do this in Stata 11 using stcrreg. stcurve after stcrreg will plot comparative CIFs for you.
Competing-risks regression

The Fine and Gray approach (stcrreg)

Using stcrreg

. stset time, failure(status == 2)  // SI is the event of interest
   (output omitted)
. stcrreg ccr5, compete(status == 1)  // AIDS is the competing event
   (output omitted)

Competing-risks regression

No. of obs = 324
No. of subjects = 324
Failure event : status == 2
No. failed = 107
No. competing = 113
No. censored = 104
Competing event: status == 1
Wald chi2(1) = 0.01
Prob > chi2 = 0.9172

Log pseudolikelihood = -579.06241

<table>
<thead>
<tr>
<th></th>
<th>Robust</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>_t</td>
<td>SHR</td>
<td>Std. Err.</td>
<td>z</td>
<td>P&gt;</td>
<td>z</td>
</tr>
<tr>
<td></td>
<td>1.023865</td>
<td>.2324119</td>
<td>0.10</td>
<td>0.917</td>
<td>.6561827</td>
</tr>
</tbody>
</table>

R. Gutierrez (StataCorp)  Competing-risks regression  November 5, 2009  16 / 19
. stcurve, cif at1(ccr5=0) at2(ccr5=1) title(SI) range(0 13) yscale(range(0 0.5))
• Competing risks are events that prevent an event of interest from occurring

• If you have competing risks, you want to look at CIFs instead of survival functions

• CIF analysis with Cox regression is possible, but difficult

• `stcrreg` followed by `stcurve` is the easier way to go

• Keep in mind, however, that easier does not mean correct. There are model assumptions to be made for either of the two approaches