1 Model-based Risk (and Cumulative Incidence) estimates; Number Needed to Treat.

2 Kaplan-Meier-based and Nelson-Aalen-based Risk (Cumulative Incidence) and Survival estimates

i. The individual timecourses (with respect to the primary endpoint) of the 1800 patients in the COMPARE study are given in the .csv file on the c634 website. Use your preferred statistical package to (a) reproduce Fig2A of the article

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Stata v.8 .... [JH did the N-A curve before realizing the au's used K-M]

insheet using 2gStentsIndivData.csv

* Stata doesn't like events occuring exactly at 0: move all times by a small amount

gen days = day + 0.5

stset days, failure(event==1)

sts graph, by(tx) na
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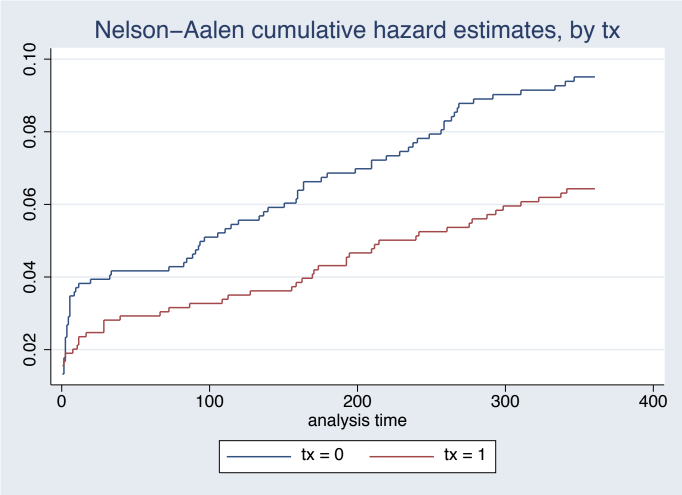


ONE QUESTION: Is this $1 - \exp[-integral\ up\ to\ time\ t]$ i.e. $1 - \widehat{S(t)}$? or is it the *integral up to time t* itself? Publications and textbooks and software are not always clear on what is what. Technically, there is the Nelson-Aalen survival curve $\exp[-integral\ up\ to\ time\ t]$ and there is the Nelson-Aalen cumulative hazard curve. The *integral* up to time *t* is the cumulative hazard curve, and $\exp[-this\ integral]$ is the survival curve, and 1- $\exp[-this\ integral]$ is the N-A cumulative incidence curve.

How different are these two? When the *integral* is small, $1 - \exp[-this\ integral]$ is close to the integral.. try it out on your calculator:

$integral$:	0.005	0.05	0.5	5.0
$1 - \exp[-integral]$:	0.00499	0.04877	0.39347	0.99326

You need to do the last step when the integral is above say 0.05 or 0.10. Below these values, depending on how many significant digits you need, you might be able to take the shortcut approximation.

When Stata says the cumulative hazard function, is that what they actually deliver? Try it out on a small example and see: assume the 5 event times are 2,5,8,10 and 12 and that there are no censored observations. The Stata-supplied values of the NA cumulative hazard functions at these times are 0.20, 0.45, 0.78, 1.28 and 2.28. The answer is clear: these values CANNOT be cumulative incidence or risk, since they go past 1!

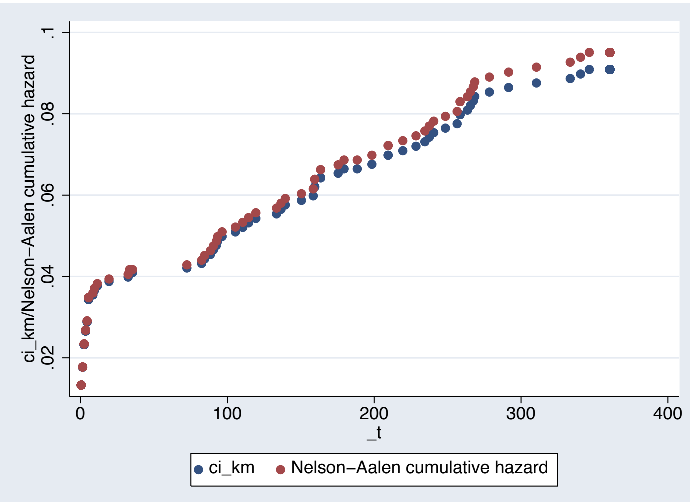
And indeed we can confirm that this is so. The NA integrals are 1/5, 1/5+1/4, 1/5+1/4 + 1/3, 1/5+1/4 + 1/3 + 1/2, and 1/5+1/4 + 1/3 + 1/2 + 1/1, and these are exactly the values graphed by Stata, and called cumulative hazards.

To turn these into cumulative incidence or risk values, you need to go from 1/5 to 1-exp[-1/5], 1/5+1/4 to 1- exp[-(1/5+1/4)], 1/5+1/4 + 1/3 to 1-exp[-(1/5+1/4 + 1/3)], 1/5+1/4 + 1/3 + 1/2 to 1-exp[-(1/5+1/4 + 1/3 + 1/2)], and 1/5+1/4 + 1/3 + 1/2 + 1/1 to 1-exp[-(1/5+1/4 + 1/3 + 1/2 + 1/1)] i.e. to the cumulative incidence values 0.18, 0.36, 0.54, 0.72 and 0.90. You can now compare these with the complements of the K-M survival estimates, ie with 0.2-, 0.4-, 0.6-, 0.8- and 1.00.

In fact the article says they used the complements of the K-M curves. Jh doesn't know if one can generate these directly in Stata and so he would first generate and save the KM survival values, then generate their complements, and plot them to get the 'preferred' modern format.

(b) see how similar the Nelson-Aalen and K-M curves are (tx=0 arm)

As we have just seen, the N-A cumulative hazard values are the values of the integral up to the time in question. To formally compare the Nelson-Aalen risk values and K-M risk values, we need to compare the values of 1- exp[- NA.cum.hazard] and the 1 - KM values. *Technically, we should not compare NA.cum.hazard and 1 - KM, since they are not even on the same scale:* the NA.cum.hazard at time t is a mean no. of events if 1 person (not necessarily the same person) were at risk from 0 to t; it is the insertion of this mean or expected no. of events (μ) in a Poisson probability function that allows us to calculate the risk up to time t as 1 - PoissonProb[0 events in timespan 0 to t if mean or expected no. is μ]



The 2 are close in this case: the K-M value is $\prod\{1 - \frac{d}{n}\}$ and this is close to $-\sum \frac{d}{n}$ when the $\sum$ is small; and this in turn is close to $\exp\{-\sum \frac{d}{n}\}$ You should check out whether what the graphs display is the $1 - \sum$ or $1 - \exp\{-\sum\}$. Knowing which is which becomes important if the cumulative incidence approaches 1 (the survival curve approaches 0).

(c) obtain 95% interval estimates for the 1 year risks in the two arms

You can read the 95% interval limits off the Stata graph (click the show pointwise interval estimates) or

```
sts list, by(tx)

           Beg.          Net            Survivor      Std.
  Time    Total   Fail   Lost           Function     Error     [95\% Conf. Int.]

tx=0

360.5      819      0    819              0.9091    0.0096      0.8884    0.9261

tx=1

360.5      841      0    841              0.9376    0.0081      0.9196    0.9516

A symmetric Conf. Interval based on +/- 1.96SE's may extend outside (0,1).

So, symmetric ones preferred, especially in small-sample (small #events) situations.
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(d) obtain the log rank test statistic.

```
. sts test tx, logrank

         failure _d:  event == 1
   analysis time _t:  days


Log-rank test for equality of survivor functions

      |   Events         Events
tx    |  observed       expected
------+-------------------------
0     |        82          68.67
1     |        56          69.33
------+-------------------------
Total |       138         138.00

            chi2(1) =       5.17
            Pr>chi2 =     0.0230

One of the rows of the table is redundant. Test tarcks the OBSERVED #events in ONE group
across risksets, and compares it with  the EXPECTED #events in THAT SAME group
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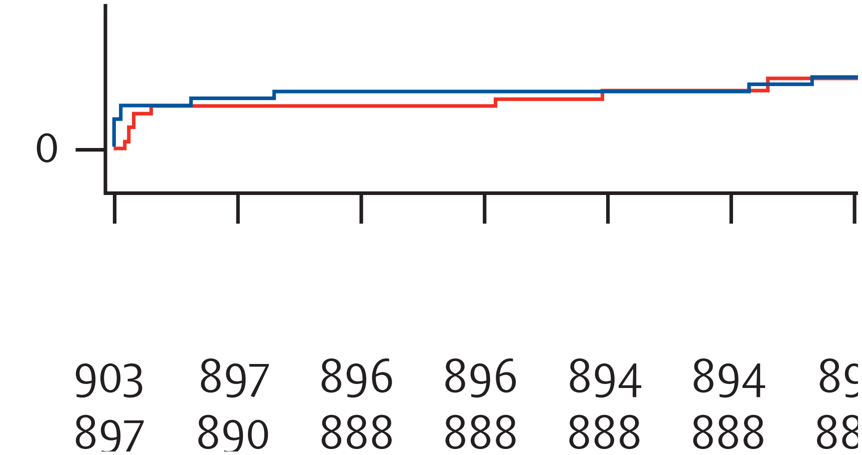
riskset:	1			2			3			4			5		
day:	0			1 (?)			2 (?)			3 (?)			4 (?)		
	Event?			Event?			Event?			Event?			Event?		
tx	Y	N	Tot.	Y	N	Tot.	Y	N	Tot.	Y	N	Tot.	Y	N	Tot.
0 older	0	903	903	0	903	903	1	902	903	2	900	902	2	898	900
1 newer	4	893	897	2	891	893	0	891	891	0	891	891	0	891	891
Tot.	4	1796	1800	2	1794	1796	1	1793	1794	2	1791	1793	2	1789	1791
$E^*_{H_0}$	1.993			0.992			.			.					
V_{H_0}	0.998			0.99			.			.					

*Here, we track the events in the 'older' arm. The chi-sq statistic is the same if you track the newer arm instead.

ii. Fig 2B is based on 18 and 25 deaths respectively. By enlarging the graph determine how many risksets there are and construct the 2×2 tables (used in the log-rank test) for the first 5 risksets and the last 5 risksets. Calculate the expected value and the null variance for one of these tables.

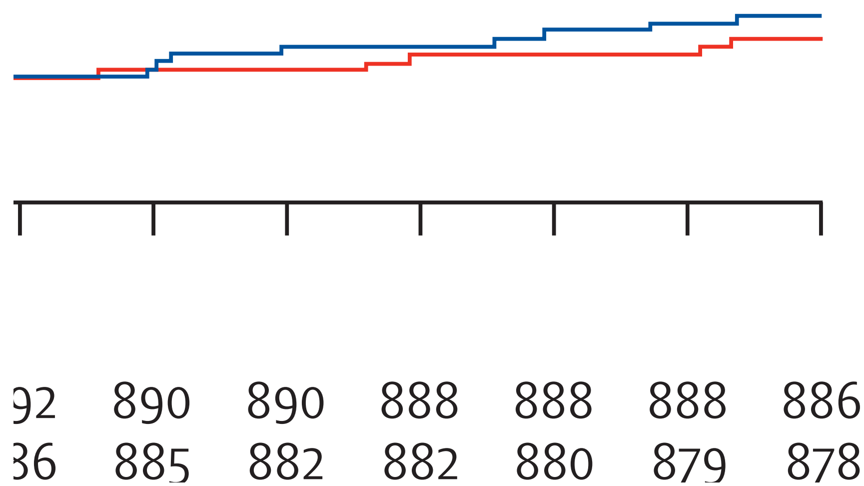
A riskset is defined by a distinct event-time (so $\geq$ 2 deaths on same day define 1 riskset); **each riskset consists of ALL those at risk (in the 2 arms combined) just before the time of the deaths(s) that defines the riskset.** There are jumps (of one colour or other) at 14 distinct times in the first 6 mo. of the graph (7 in blue curve; 7 in the red) and jumps at 13 distinct times in the last 6 mo. of the graph (8 in blue curve and 5 in red), making 27 riskets in all. The authors say there were 15 + 18 = 33 deaths in all, so some risksets involved $\geq$ 2 deaths. Since so few were censored (the au's say 1+2), the drops in the numbers at risk at each 30 day mark must virtually all consist of deaths rather than censorings; and we can also use the differences from one mark to the next to tell how many patients make up each riskset.



In the first 30 days in the blue curve, we have 3 jumps totaling 7 deaths; the numbers of deaths were 4, 2 and 1 in risksets 1, 2 and 7 respectively, whereas in the red curve there were 1, 2, 2 and 1 death(s) in risksets 3, 4, 5 and 6 respectively. So, the 1st 5 risksets are shown above, with = 0, red, older; tx= 1 blue, newer (lower row):

The last riskset is defined by the last jump (death) in the blue (newer) curve (bottom row), when there were in all 1765 in the riskset (879 at risk on the newer stent and 886 at risk on the older stent).

Riskset:	last-but-4	last-but-3	last-but-2	last-but-1	very-last
(approx.) Day:	297	324	332	341	343
No. in Riskset:	1769	1768	1767	1766	1765
No. Deaths:	1	1	1	1	1
Which stent?	newer	newer	older	older	newer
No. on older:	888	888	888	887	886
No. on newer:	881	880	879	879	879



iii. For Fig2B, can you figure out how many observations must have been censored? (JH doesn't think numbers at risk shown in Fig2A are correct.)

The no. at risk in the 'older' arm drops by 17 from 903 to 886; if 15 were deaths, these implies 2 censored. The 'newer' arm drops by 19 from 897 to 878; if 18 were deaths, these implies 1 censored. They tell us in their flow chart that it was the opposite: 1 and 2; JH suspects they have their wires crossed (or maybe JH is himself a bit cross-eyed by this point! Indeed it may well be that some of JH's numbers in his answers are wrong .. if so, let him know.)