Data Analysis
Time to Event Endpoints

James Ware, PhD
Harvard School of Public Health

Survival Analysis

In some studies, the outcome variable is the time to an event

- Time to the composite endpoint in CORONARY
- Time to progression or death in a cancer trial
- Time to deterioration of functional status in patients with multiple sclerosis

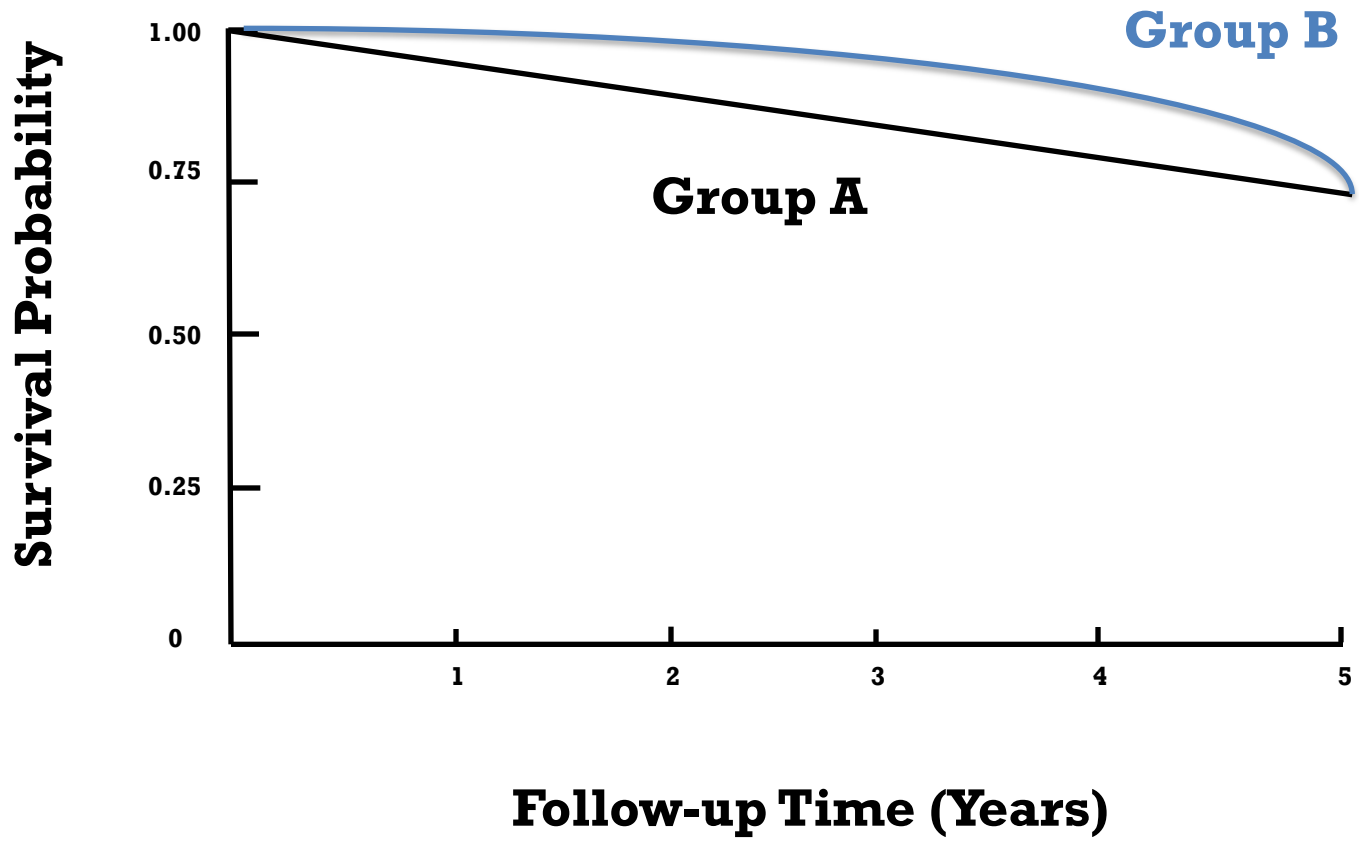
Methods for analyzing time to event data are known as survival analysis

Role of Survival Analysis

Survival analysis is most important when subjects enter at different times and have different durations of follow-up

Survival analysis compares the entire survival experience, not just the percentages who remain alive at the end of the study

For example, the survival distributions may differ even though the five-year survival rates are similar


Survival Probability
1.00
0.75
0.50
0.25
0
Group B
Group A
1
2
3
4
5
Follow-up Time (Years)

Estimating the Survival Distribution

Survival data differ from other types of outcome data

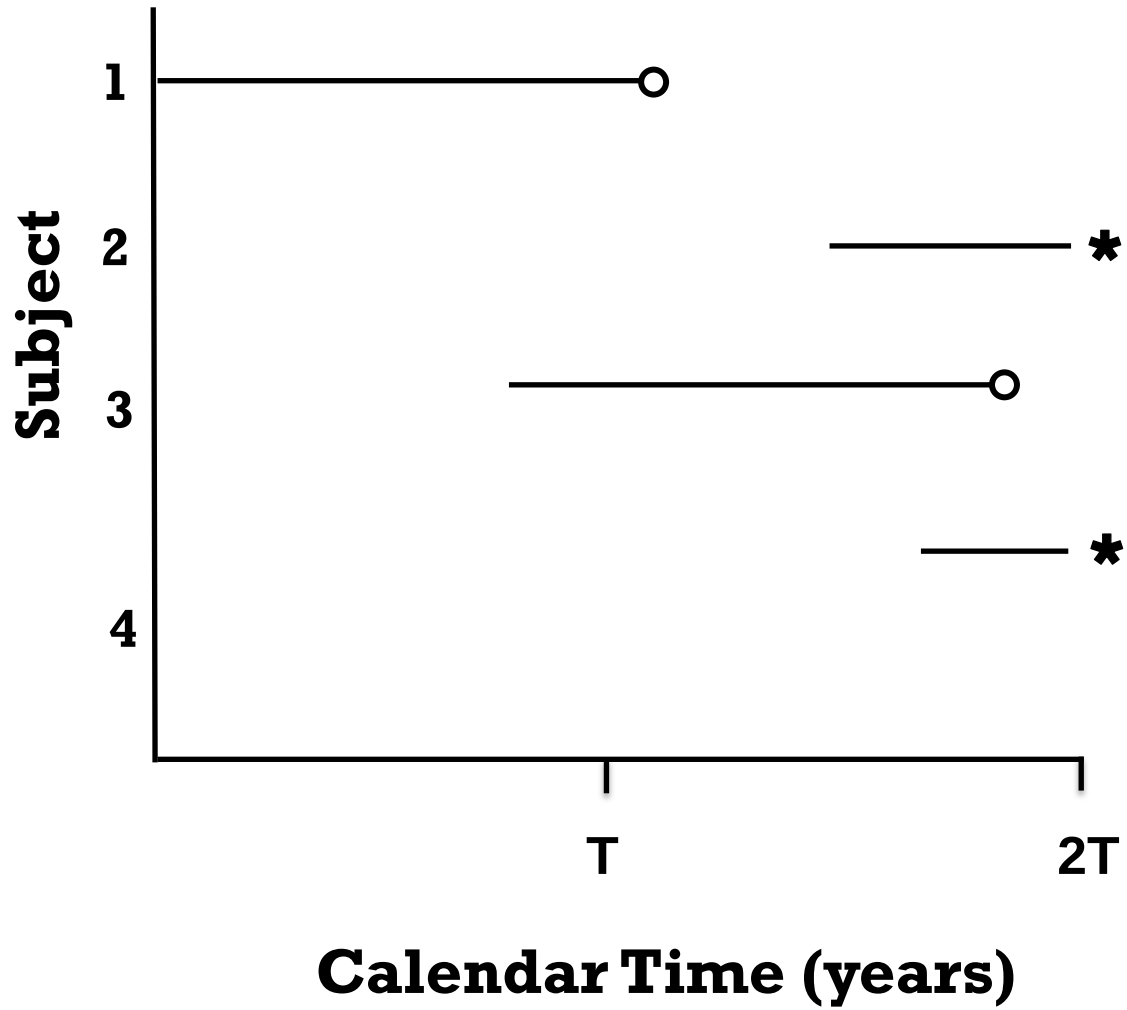
- It is not appropriate to assume normality
- Observations can be censored because
  - Study follow-up ends before a participant has experienced the event
  - Participants withdraw or are lost to follow-up, again prior to observing the event

Survival Analysis

This segment will focus on two issues:

- Estimating the survival distribution
- Comparing the survival distributions in two groups.

We begin with a simple example: Consider a study with T years of enrollment and T years of follow-up after enrollment ends

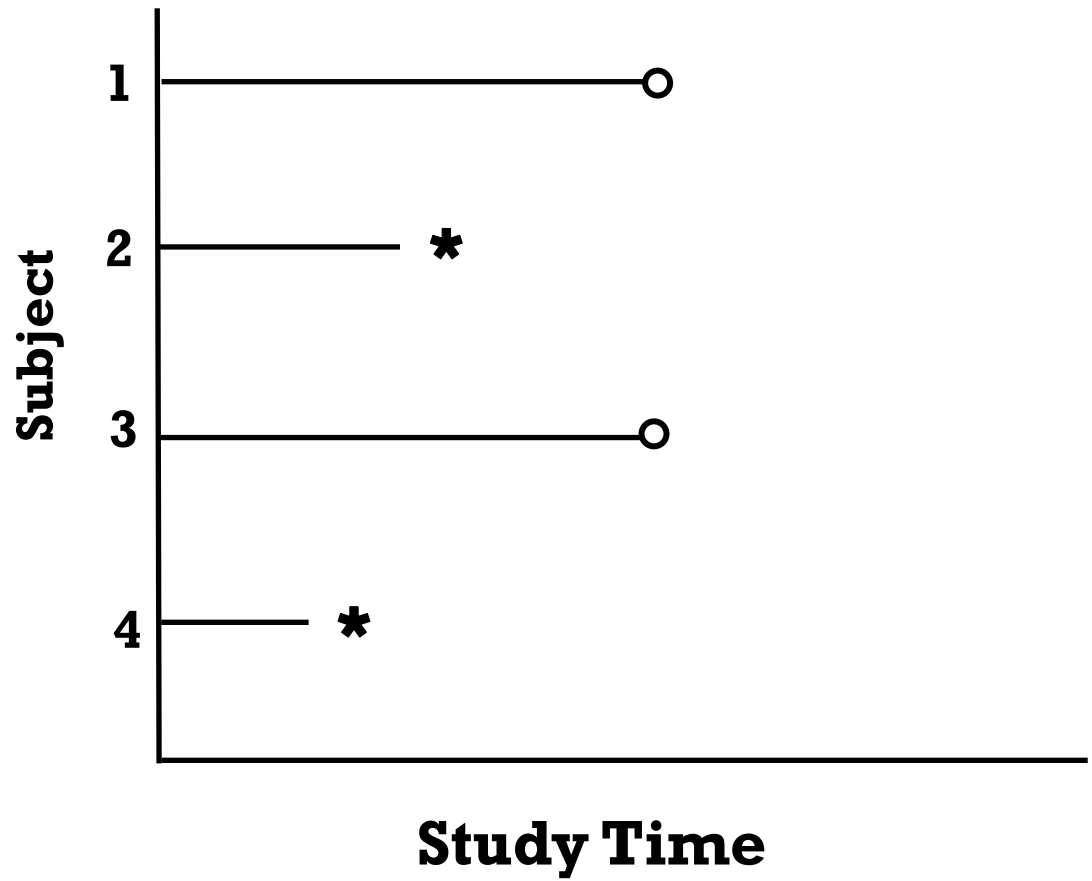

Subject
1
2
3
4
*
*
T
2T
Calendar Time (years)

Features of the Data

Two participants have events, two are censored at time 2T

This is called administrative censoring. It occurs because of the study design

For data analysis, we represent each patient's experience relative to their time on study, i.e., the elapsed time since enrollment


Subject
1
2
3
4
Study Time

Most Survival Data Have Incomplete Follow-up

When the study has an enrollment period and ends at a fixed date, possible follow-up will depend on the enrollment date

Subjects may be censored because the study ends, may withdraw, or may be lost to follow-up

The survival experience for each patient is represented by the duration of follow-up and the survival status at the end of follow-up

Estimating the Survival Distribution

Let T be the time to the event (death) for a randomly selected member of the population

$F(t) = Pr(T<t)$ is the dist of time to death

$S(t) = 1 - F(t)$ is the survival distribution

It would be easy to estimate S(t) if there were no censoring. We need a method for estimating S(t) when observations are censored

The Kaplan-Meier Estimate

The Kaplan-Meier estimate of S(t) builds upon classical methods for the analysis of life tables

It updates S(t) when events occur based on the proportion of study participants followed to that time point who have an event.

The estimate is based on the products of the conditional probabilities of surviving each event time

The Kaplan-Meier Estimate

An Example:

Suppose that 100 participants enter a study and are followed until death or for up to two years (Group 1)

At the beginning of year 2, 100 additional patients enter the study and are followed for one year (Group 2)

The data are shown in the following table

Experience of 200 Individuals

Group		Year 1	Year 2
	Entered	100	80
1	Deaths	20	20
	Survivors	80	60
	Entered	100	Group 2
2	Deaths	25	contributes
	Survivors	75	Year 1 data

Estimating the Survival Probability

Year 1: $\hat{S}(1) = 155/200 = 0.775$

Year 2: $\hat{S}(2|1) =$ (Alive at 2 | Alive at 1)

$= 60/80$

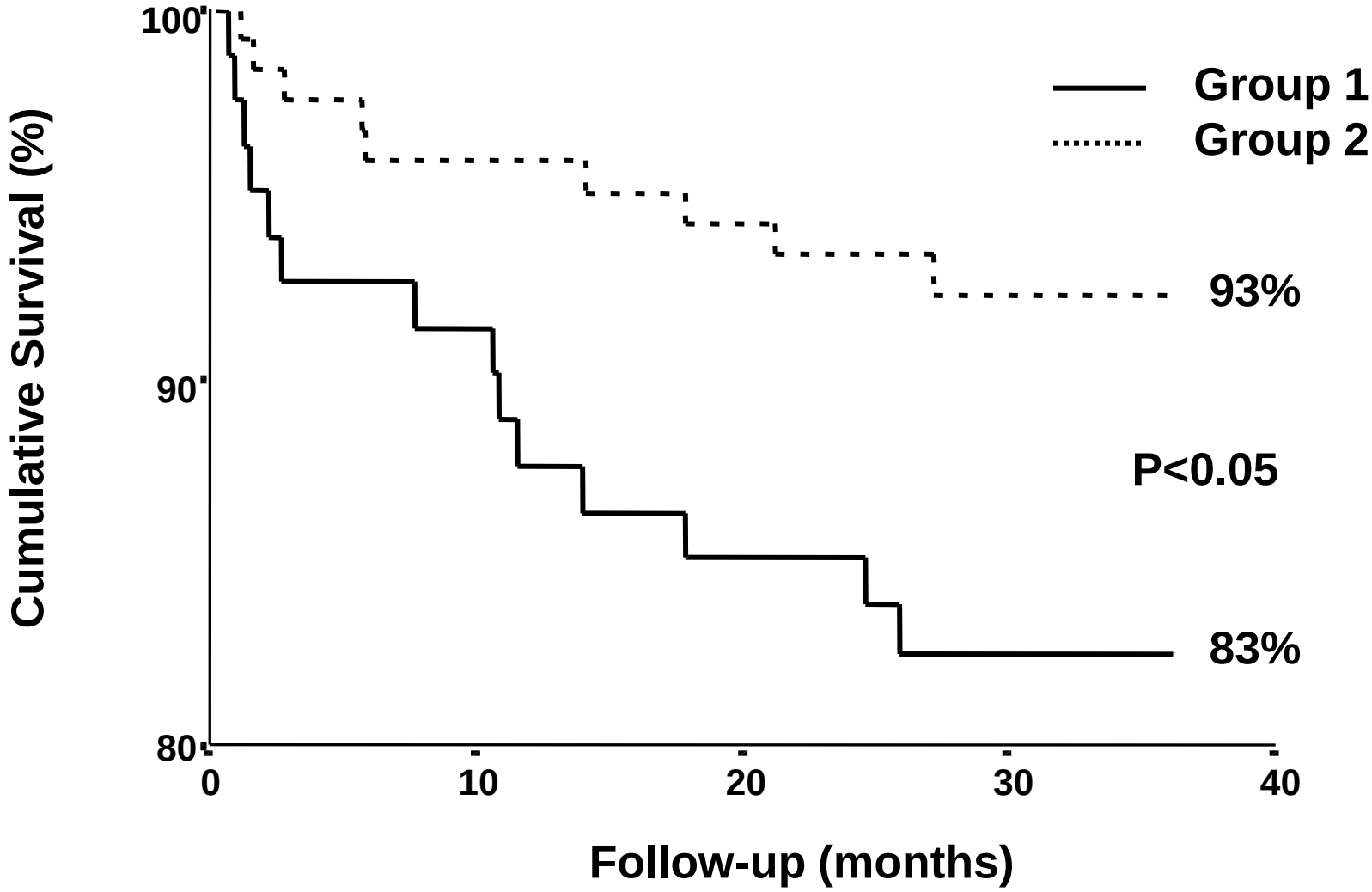
$= 0.75$

Then

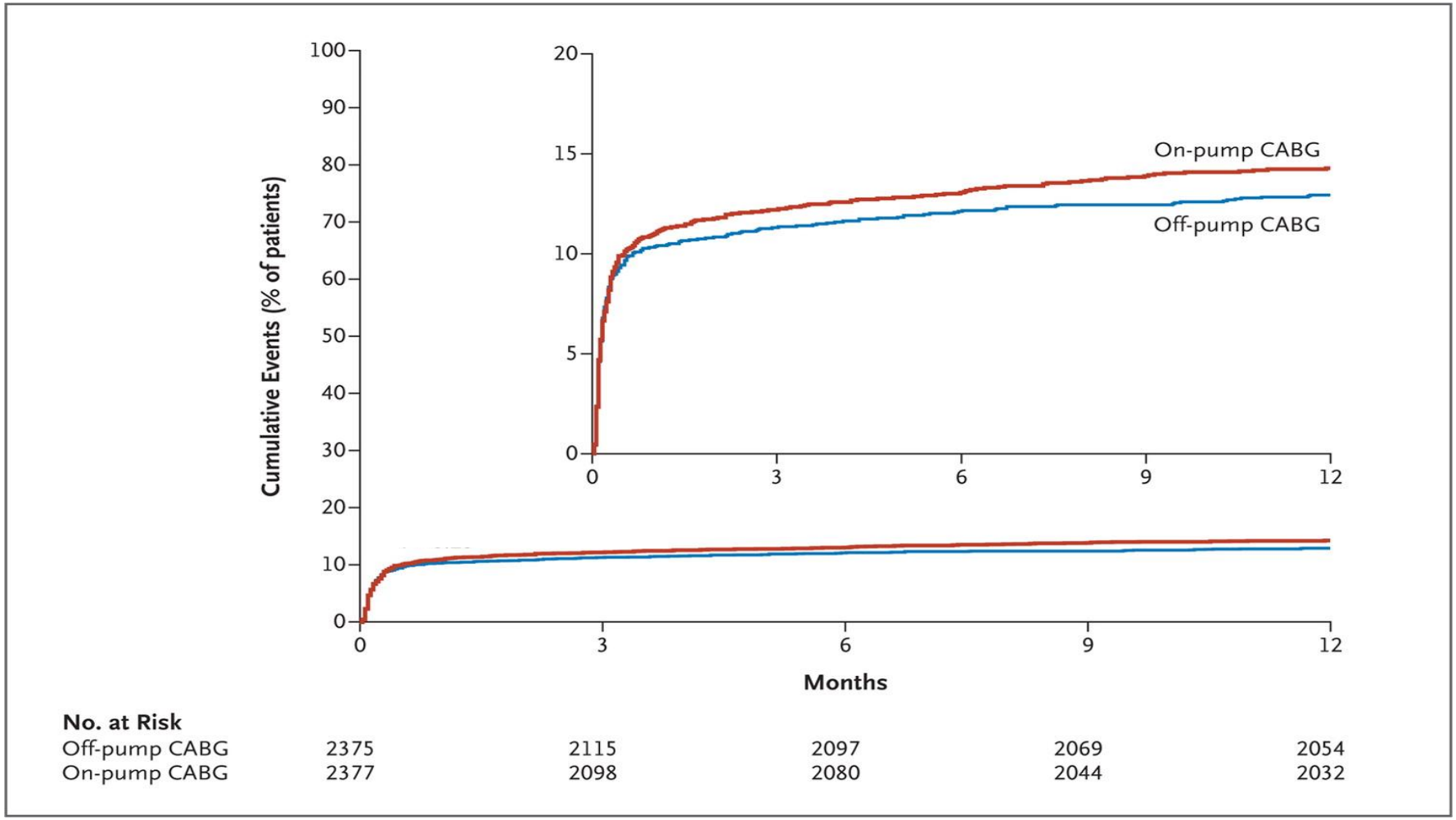
$$\hat{S}(2) = \hat{S}(1) * \hat{S}(2|1)$$

$$= 0.775 * 0.75 = 0.58$$

Kaplan-Meier Survival Curve



The CORONARY Trial: Kaplan–Meier Curves for the Primary Composite Outcome at 1 Year.



Lamy A et al. N Engl J Med 2013;368:1179-1188.

Comparing Two Survival Curves

We would like to build on the methods of life-table analysis to compare two or more time-to-event distributions

We could compare the probabilities of survival at a single time point, but a comparison of the entire survival experience is preferable

Comparing Two Survival Curves

The Mantel-Haenszel test

Each time an event occurs, we form a 2 by 2 table

	No. Deaths	No. Survivors	No. At Risk
Gp1	a_j	b_j	$a_j + b_j$
Gp2	c_j	d_j	$c_j + d_j$
			n_j

Comparing Two Survival Curves

If $S_1 = S_2$, we can assume for each table

$$E(a_j \mid a_j + b_j) = (a_j + c_j)(a_j + b_j)/n_j$$

$$V(a_j) = (a_j + c_j)(b_j + d_j)(a_j + b_j)(c_j + d_j)/(n_j^2(n_j - 1))$$

And

$$MH = \{\sum_{j=1}^{K} a_j - E(a_j)\}^2 / \sum_{j=1}^{K} V(a_j)$$

The Log-rank Test

The MH test is also known as the log-rank test.

When there is no censoring, it is equivalent to a rank test based on the logarithms of the ranks

Proportional Hazards Regression

To develop a regression model for survival data, we need to choose a metric for the influence of covariates

The proportional hazards regression model assumes that covariates modify a shared underlying hazard function

The Hazard Function

If $S(t) = Pr(T>t)$, where T is the time of death, we can define the hazard function at time t as

$$\lambda(t) = Pr(t<T<t+dt)/P(T>t)dt$$

Two survival distributions, $S_1(t)$ and $S_2(t)$, satisfy the proportional hazards assumption if $\lambda_1(t) = K\lambda_2(t)$

The Proportional Hazards Model

More generally, the PH, or Cox, model for survival data assumes that

$$\lambda(t, \mathbf{X}) = \lambda_0(t)\exp(\beta'\mathbf{X})$$

where $\lambda_0(t)$ is an underlying hazard function shared by all members of the population

$$\beta'\mathbf{X} = \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_K X_K$$

$\exp(\beta'\mathbf{X}) > 0$ for all values of $\beta'\mathbf{X}$, which is appropriate since hazard rates are nonnegative

The Proportional Hazards model

β_i = the logarithm of the ratio of the hazards (or relative risk at time t) for two individuals who differ only by one unit in the value of X_i

If X_i is an indicator variable, β_i represents the logarithm of the hazard ratio in the two groups identified by X_i

Estimating β

The estimates of the elements of β depend only on which subject experiences the event at each occasion, not on the times of the events

Estimation requires iterative calculations to maximize the partial likelihood function

The interpretation parallels linear regression, with regression coefficients interpreted in terms of relative risk or hazard

The CORONARY Trial

"We conducted a time-to-event analysis, using Cox regression to report the 1-year outcomes. The time to the first occurrence of any one of the components of the primary outcome was described with the use of Kaplan–Meier survival curves, and the comparisons between the two study groups were performed with the use of a log-rank test."

The treatment effect is expressed as the hazard ratio (with 95% confidence intervals)

The CORONARY Trial

Table 1. Outcomes at 1 Year.*

Outcome	Off-Pump CABG (N = 2375)	On-Pump CABG (N = 2377)	Hazard Ratio (95% CI)	P Value
Primary outcome — no. (%)†	288 (12.1)	316 (13.3)	0.91 (0.77–1.07)	0.24
Components of primary outcome — no. (%)				
Death	122 (5.1)	119 (5.0)	1.03 (0.80–1.32)	
Myocardial infarction	161 (6.8)	178 (7.5)	0.90 (0.73–1.12)	
Stroke	36 (1.5)	40 (1.7)	0.90 (0.57–1.41)	
New renal failure requiring dialysis	30 (1.3)	31 (1.3)	0.97 (0.59–1.60)	

The CORONARY Trial

At 1 year after CABG, there was no significant difference between off-pump and on-pump CABG with respect to the primary composite outcome.

There were also no differences in the rate of repeat coronary revascularization, quality of life, or neurocognitive function.