Time-to-Event Analyses

Outcomes Involving Time

- In many studies, success or failure is measured by the length of time to the outcome aka time-to-event
  - Examples: Time-to-pregnancy or time until an infection occurs
  - In cancer studies may be survival, time of remission or time-to-progression, etc.
- However, reporting time-to-event outcomes is potentially biased because subjects may spend different amounts of time in the study
  - Example: The proportion of patients not having reach the outcome by the end of the study would give you misleading information if some patients entered a study late and, thus, were not followed for a sufficient period of time to reach the event of interest because of termination of the study
- Techniques called “time-to-event analysis” were developed in an effort to address this problem
  - Synonyms: Life table analysis and survival analysis which refers to the method regardless of whether survival is the outcome
Features of Time-to-Event Analysis

- Time-to-event analysis tries to deal with “person-time” issues --
  - How long the individuals were observed
  - When they died
  - If they were lost to follow-up
- Time-to-event analysis requires that the outcome variable (aka “dependent variable”) be dichotomous
  - E.g., survival/death, success/failure, improvement/absence of improvement
- Generally the risk of the outcome should not greatly change over the period of observation (e.g., a study comparing medical Rx vs surgery is problematic because there may be a high post-op mortality immediately after surgery but not later)
- Analysis of time-related outcomes is frequently reported via life tables which are simply depictions of the loss of people, as is the case with survival, or of reaching the event of interest
  - A “survival curve” is an example of a life table

Time-to-Event Analysis

- There are two main approaches –
  - Kaplan-Meier method
  - Actuarial method
- Both methods utilize “censoring”
  - Censoring is the practice of not including a patient’s data from a part of the study
  - Typical reasons include late-entry patients, patients lost to f/u or patients who die before the outcome of interest is reached
  - Data for those patients is not included after the point they are censored
Kaplan-Meier Survival Curves

- The Kaplan-Meier method has become the most commonly used approach to survival analysis in medicine.

- The following information is required for each subject –
  - Date of entry
  - Reason for withdrawal (death, loss to follow-up or censorship)
  - Date of withdrawal (due above reasons)

What Kaplan-Meier Curve Looks Like

- Designed to account for (censored) subjects who are not in the study for the entire time period.
- Curve is created as people exit the study.

![Kaplan-Meier Curve Diagram](image)
Creating the Kaplan-Meier Curve

- Creating the curve involves computing the number of people who experience the outcome at a certain time point, divided by the number of people who were still in the study at that time taking into account the censored patients.
- For each time interval the probability of not experiencing the event at the end of the period is calculated.
  - E.g., the probability of surviving for two months is the probability of surviving the first month times the probability of surviving the second month.

Numerators and Denominators in a Time-to-Event Analysis

- When a patient’s data is censored, the number of patients "at risk" (numerator and denominator decrease) is reduced by one when the calculation is performed for that time segment.
- When a patient experiences the outcome, the “survival” for the interval is calculated (numerator decreases) according to the number remaining at risk at the time of event.
- Example: If, at the start of a time interval, 76 patients are alive and, during the interval, one patient is censored (numerator and denominator decrease) - then at the time a patient dies (numerator decreases) 75 patients were at risk (76-1 censored patients). So the chance of surviving the interval is 74/75. (Next slides illustrate)
An event triggers a calculation for this first time segment and the curve drops down (numerator drops, denominator stays the same)

Two patients are censored and removed from the numerator and denominator

With the next event, another patient is removed from the numerator

Here is where you can read the proportion of the subjects who have not yet experienced the event

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**Numerator and Denominators**

- To calculate the “survival” (i.e., the likelihood of not having experienced the event) at the end of a time period on the curve (the calculation is triggered by a subject experiencing the outcome) you multiply the chance of not experiencing the event for each time interval

- Example on next slide ➔
### Kaplan Meier Curve

#### No Censoring in Time Interval 1-2

<table>
<thead>
<tr>
<th>Time Interval</th>
<th># Subjects Start</th>
<th>Censored</th>
<th># Died (or other event)</th>
<th>Subjects in Denom</th>
<th>Subjects Surviving Interval</th>
<th>Cumulative Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>8</td>
<td>7/8=0.87</td>
<td>0.87</td>
</tr>
<tr>
<td>1-2</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>4/5=0.8</td>
<td>0.87*0.8=0.7</td>
</tr>
<tr>
<td>2-3</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>2/3=0.67</td>
<td>0.7*.67 =.47</td>
</tr>
</tbody>
</table>

#### Kaplan Meier Curve

![Kaplan Meier Curve Diagram](image-url)
The Effect of Censoring

- When a patient experiences the outcome that ends a time segment and the numerator drops and the curve takes a step down
- Tick marks (frequently omitted) show where patients were censored
- Censoring a patient reduces the number of patients who are contributing to the curve (numerator & denominator) - therefore, **censoring reduces sample size** (which reduces reliability)
Kaplan-Meier Survival Curves

- If any data are available at all for each patient in a study, the investigators frequently state that they analyzed the data according to “the ITT principle”

- Readers should be aware that this is technically not ITT analysis plus there is no imputation of missing values, because the patient's future information is effectively removed at the point at which they have been censored

Actuarial Method

- The actuarial method differs from Kaplan-Meier in that it uses fixed time intervals and assumes that subjects who were censored or lost to follow-up were observed for half of the interval
  - With the Kaplan-Meier method, each death terminates an interval and a new line of the life table is drawn which ultimately creates a curve
  - With the Actuarial method, mortality rate for that interval is calculated by dividing deaths in the interval by total person-years for all subjects at the start of the interval
Considerations When Evaluating Time-to-Event Methods for Bias

- Assumes that subjects lost to follow-up are similar to those who are not lost — they may not be, so amount of loss and loss difference between groups matters.
- Cannot be applied to reoccurring rates so need to ensure double-counting does not occur (e.g., composite endpoint of mortality and MI).
- Should not be used if the rate of the outcome is not otherwise constant between groups (e.g., one would expect more deaths in a surgical group early as compared to deaths in a medically treated group).

Considerations When Evaluating Censoring for Bias

- Administrative censoring (e.g., censuring subjects who enter late and are alive at the end of the study) may not introduce significant bias.
- Non-administrative censoring (e.g., censoring subjects who stop taking Rx, are lost to f/u, etc.) may be more likely to introduce significant bias because “lost” subjects may be different from subjects remaining in study, thereby “derandomizing” the study.
  - Outcomes in completers may be different from what outcomes would have been without data loss.
Delfini’s Bottom Lines on Time-to-Event Analyses Biases

- Even without differential loss between the groups overall, a differential loss could occur in prognostic variables — and readers are rarely going to have access to data about changes in prognostic characteristics post-baseline reporting.

- Assessing outcomes through models (e.g., Kaplan Meier estimates) has been reported to potentially erroneously misrepresent outcomes by a relative 50% or higher (Lachin: PMID 11018568).

- So we continue to offer our conservative approach that loss of around five percent with differential loss is a bias as well as loss of around ten percent or more without differential loss.

Hazard Ratios

- Time-to-event analysis is frequently used to compare outcomes at multiple points.

- The Cox model, a regression method, provides an estimate of the hazard ratio.

- The hazard rate is the slope of the survival curve – a measure of how rapidly subjects are dying.
Hazard Ratios in Time-to-Event Analysis

- The hazard rate is the probability that if the event in question has not already occurred, it will occur in the next time interval

- Example: In a clinical trial where death is the endpoint, the hazard ratio indicates the relative likelihood of death in treated versus control subjects at any point in time. If the hazard ratio is 2.0, then the rate of deaths in one treatment group is twice the rate in the other group.

Case Study: Recalculating APPROVe Trial Survival Curves


Censoring May Distort Results

- APPROVe Trial Kaplan-Meier Curve
- Nissen’s Recalculation Curves
- Psaty’s Recalculation Curves in Alzheimer Studies

TO THE EDITOR:

Steven E. Nissen, M.D.
Cleveland Clinic Foundation
Cleveland, OH 44195

In the original article, the APPROVe investigators reported event rates using an unusual censoring rule in which events were excluded if they occurred more than 14 days after the study drug was stopped. All data in the new report are assessed by a conventional intention-to-treat analysis.
Original Report

P=0.008

Rofecoxib
Placebo

18 months

Nissen’s Recalculation Curve With ITT Calculation

Rofecoxib
Placebo

3 months
Psaty’s ITT Analysis of Total Mortality Including Data From Studies 078 and 091

<table>
<thead>
<tr>
<th>Total Mortality n=1069 Rofecoxib 25 mg (2060 Person-Yrs)</th>
<th>Total Mortality n=1069 Placebo (2269 Person-Yrs)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>57</td>
<td>29</td>
<td>2.13 (1.36 to 3.33)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Sponsor reported to FDA that regarding safety, rofecoxib was “well tolerated.” However —

- Sponsor reported on studies separately with 9 deaths among 346 rofecoxib patients and 2 deaths among 346 placebo patients in one study
- In another article sponsor stated that on Rx or within 14 days of the last dose there were 24 deaths among 725 rofecoxib patients and 15 among 732 placebo patients and an additional 22 deaths in the off-drug period (17 in rofecoxib patients and 5 in placebo patients)
- However, reports did not include analyses or statistical tests of the mortality data
Psaty’s Curve in Alzheimer Studies

Cumulative Death Rate

Rofecoxib

Placebo

4 years

$P < 0.001$