
MAPS | eCademy
Webinar Series
Part 2 of the Webinar Series: Clinical Statistics for Non-Statisticians

Disclaimer

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Agenda

- **Statistical analysis in clinical trials**
  - Null/alternative hypotheses
  - Statistical assumptions (type I error, significance level, type II error, statistical power,)
  - Hypothesis testing
  - Statistical tests
- **Statistics used in RCTs**
  - Type of outcome measures (dichotomous, continuous, time-to-event)
  - Statistics used for analysis of dichotomous data (relative risk, odds ratio, risk difference, NNT)
  - Analysis of time-to-event variables (plotting and interpretation of Kaplan-Meier curves)

Observational vs. Randomized Clinical Trials

- **Observational Studies**
  - Distribution of baseline factors that may impact outcome of the study (e.g., age, meds, comorbidities)
    - Factors to impact outcome, collected:
      - Statistical adjustment, matching
    - Factors to impact outcome, can't be collected
    - Factors that don't impact outcome, not collected
- **Randomized Trials**
  - All factors (known and unknown) that may impact outcome equally distributed among study groups

Clinical trial?

- The clinical trial is the gold standard for evaluation of the applicability of clinical research.
- Prospective study evaluating the effect and value of intervention(s) under pre-specified conditions.
- A controlled clinical trial is a prospective study comparing the effect of an intervention(s) against a control.

Two Issues impacting Finding the Truth and Effective Ways to Address Them

- Bias:
  - Randomization:
    - Remove the potential bias in treatment assignment - conscious or subconscious
    - Produce comparable groups - known or unknown prognostic variables
    - Validity of statistical tests of significance is guaranteed
  - Blinding
    - Single-blinded study: Either pts or physicians are blinded to the tx allocation
    - Double-blinded study: Both pts and physicians are blinded to the tx allocation
  - Intent to treat principle
    - All randomized patients are included in final data analysis
  - Per Protocol Analysis
    - Only patients who complete the trial according to protocol are analyzed

Two Issues impacting Finding the Truth and Effective Ways to Address Them

- Variation:
  - Control or reduce variation
    - No treatment control
      - e.g.: standard practice is observation after surgery
      - Observation versus 'adjuvant' therapy
    - Different types of controls
      - Placebo
      - Active control
        - » standard therapy
        - » new therapy
      - 'sham' treatment control
        - » acupuncture
    - Reciprocal control
      - Tx A: smoking cessation counseling, no dietary intervention
      - Tx B: dietary intervention, no smoking cessation counseling
      - Two endpoints: Smoking cessation and weight loss
  - Increase sample size

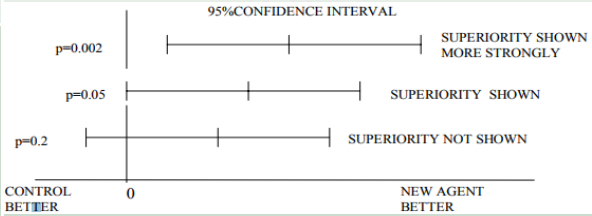
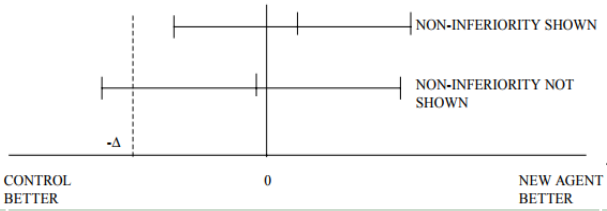
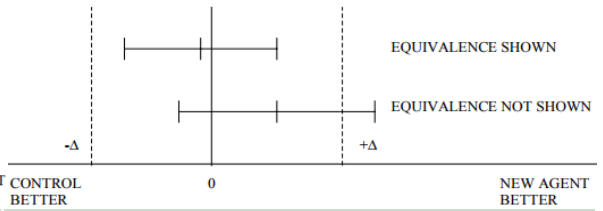
Statistical analysis
Hypothesis testing

Hypothesis Testing Stages

- Selection of the primary endpoint
  - Related to the disease
  - Clinically relevant – reflecting real clinical advantage/disadvantage
  - Frequency allowing to preform statistical analysis
- Definition of research hypotheses
    - Null hypothesis (H0)
    - Alternative hypothesis (H1)
- Setting significance level (α) and power of the statistical analysis (1-β)
- Sample size calculation
- Statistical analysis of clinical data

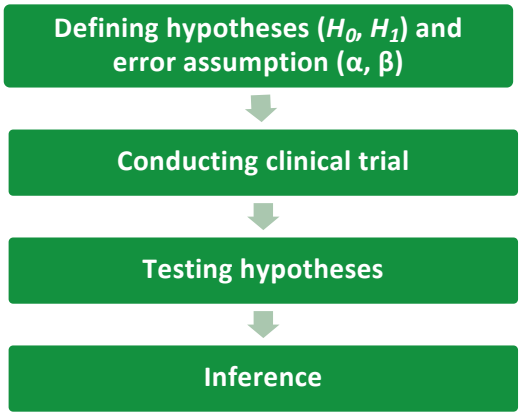
Hypothesis Testing

- Hypothesis – hypothetical (assumed) sampling distribution
- Null hypothesis (H_0)
  - Verified assumption, which we most often want to reject
  - „Worst case scenario”
- Alternative hypothesis (H1)
  - Assumption opposite to H0

Type of trial	Superiority	Non-inferiority	Equivalence
H_0	$\mu_0 - \mu_1 = 0$	$\mu_0 - \mu_1 \leq -\Delta$	$\lvert\mu_0 - \mu_1\rvert \geq \lvert\pm\Delta\rvert$
H_1	$\mu_0 - \mu_1 \neq 0$	$\mu_0 - \mu_1 > 0$	$\lvert\mu_0 - \mu_1\rvert < \lvert\pm\Delta\rvert$
			
Aim	to detect a difference between treatments	to demonstrate new treatment is no less effective than an existing one	to confirm the absence of a meaningful difference between treatments

Hypothesis Testing

- Statistical analysis involves testing the probability that observation, such as clinical trial outcome, belongs to null hypothesis
- When the probability of the observed outcome to belong to null hypothesis is reasonably low, then null hypothesis can be replaced with alternative hypothesis
- There is an indispensable risk of making errors in the inference during the statistical analysis



- **Alpha (α)** - incorrect rejection of the null hypothesis and inference about the signifficant effect when the drug is trully ineffective (false positive inference).
  Alpha < 0.05 is considered low enought to judge that the observation do not belong to null hypothesis
- **Beta (β)** - incorrect acceptance of the null hypothesis and inference about lack of the effect when the drug is trully effective (false negative inference).
- **Power (1-β)** - corresponds to probability of demonstrating effectiveness when the drug is trully effective
- **Significance level (1-α)** - corresponds to probability of demonstrating ineffectiveness when the drug is trully ineffective

Inference	True effect	
	No effect	Effective treatment
H_0 (accept null: non-significant)	1-α (sig. level)	**Type II error (β)**
H_1 (reject null: significant)	**Type I error (α)**	1-β (statistical power)

Dichotomous data
Risk *vs.* Odds

- Risk
  - Probability of an event to occur

$$R_S = \frac{A}{A + C}$$

$$R_C = \frac{B}{B + D}$$

- Odds
  - Ratio of probability of and event to probability of no-event

$$O_S = \frac{A}{A + C}\frac{A + C}{C} = \frac{A}{C}$$

$$O_C = \frac{B}{B + D}\frac{B + D}{D} = \frac{B}{D}$$

	Study group	Control
Event	A	B
No event	C	D
Total	A + C	B + D

Dichotomous data
Relative risk *vs.* Odds ratio

- Relative risk (RR)
  - Ratio of risks in study group to control

$$RR = \frac{R_S}{R_C}$$

- Odds ratio (OR)
  - Ratio of odds in study group to control

$$OR = \frac{O_S}{O_C}$$

- Interpretation
  - How much risk/odds remains in treated patients?

$$RR = \frac{0.1}{0.3} = 0.33 = 33\%$$

  - How much risk/odds have been removed due to treatment?
    - Calculate relative risk reduction (RRR)

$$RRR = 1 - RR = 1 - 0.33 = 0.67 = 67\%$$

	Study group	Control
Event	10	30
No event	90	80
Total	100	100

RR = 1 – RRR

RRR = 1- RR

Dichotomous data NNT

- **Risk difference (RD)**
  - Difference between study and control groups expressed in percentage points

$$RD = R_S - R_C$$

- **Number needed to treat**
  - Number of patients that must be treated to avoid one event

$$NNT = -\frac{1}{RD}$$

$$NNT = -\frac{1}{0.1 - 0.3} = \frac{1}{0.2} = 5$$

	Study group	Control
Event	10	30
No event	90	80
Total	100	100

Survival Analysis

Survival Analysis

- Statistical methods for analyzing longitudinal data on the occurrence of events.
- Events may include death, injury, onset of illness, recovery from illness (binary variables) or transition above or below the clinical threshold of a meaningful continuous variable (e.g. CD4 counts).
- Accommodates data from randomized clinical trial or cohort study design.

Survival Analysis – Terms

- Time-to-event:

The time from entry into a study until a subject has a particular outcome

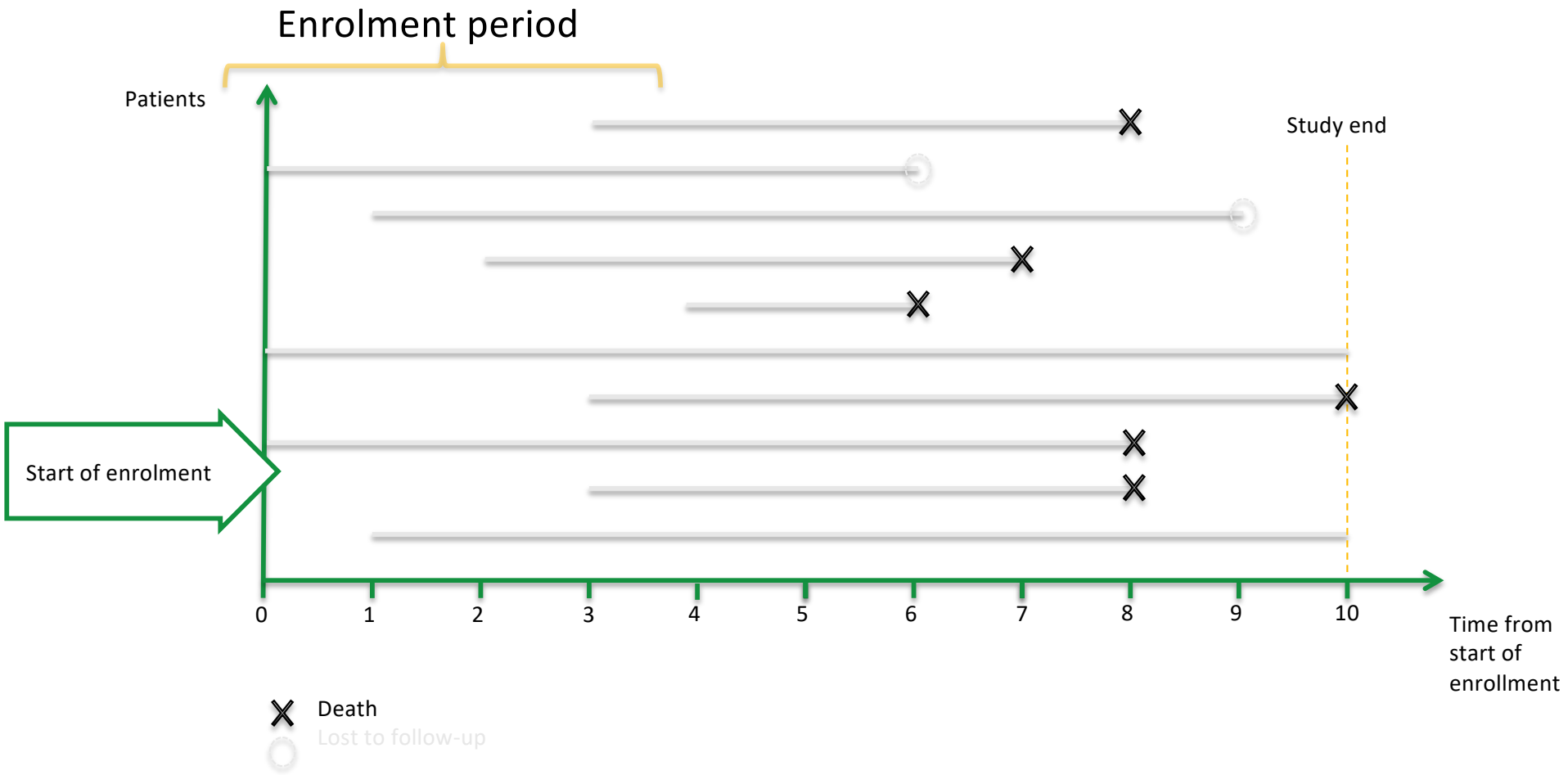
- Censoring:
  - Lost to follow up or drop out of the study
  - If the study ends before they die
  - Have an outcome of interest.

  They are counted as alive or disease-free for the time they were enrolled in the study.

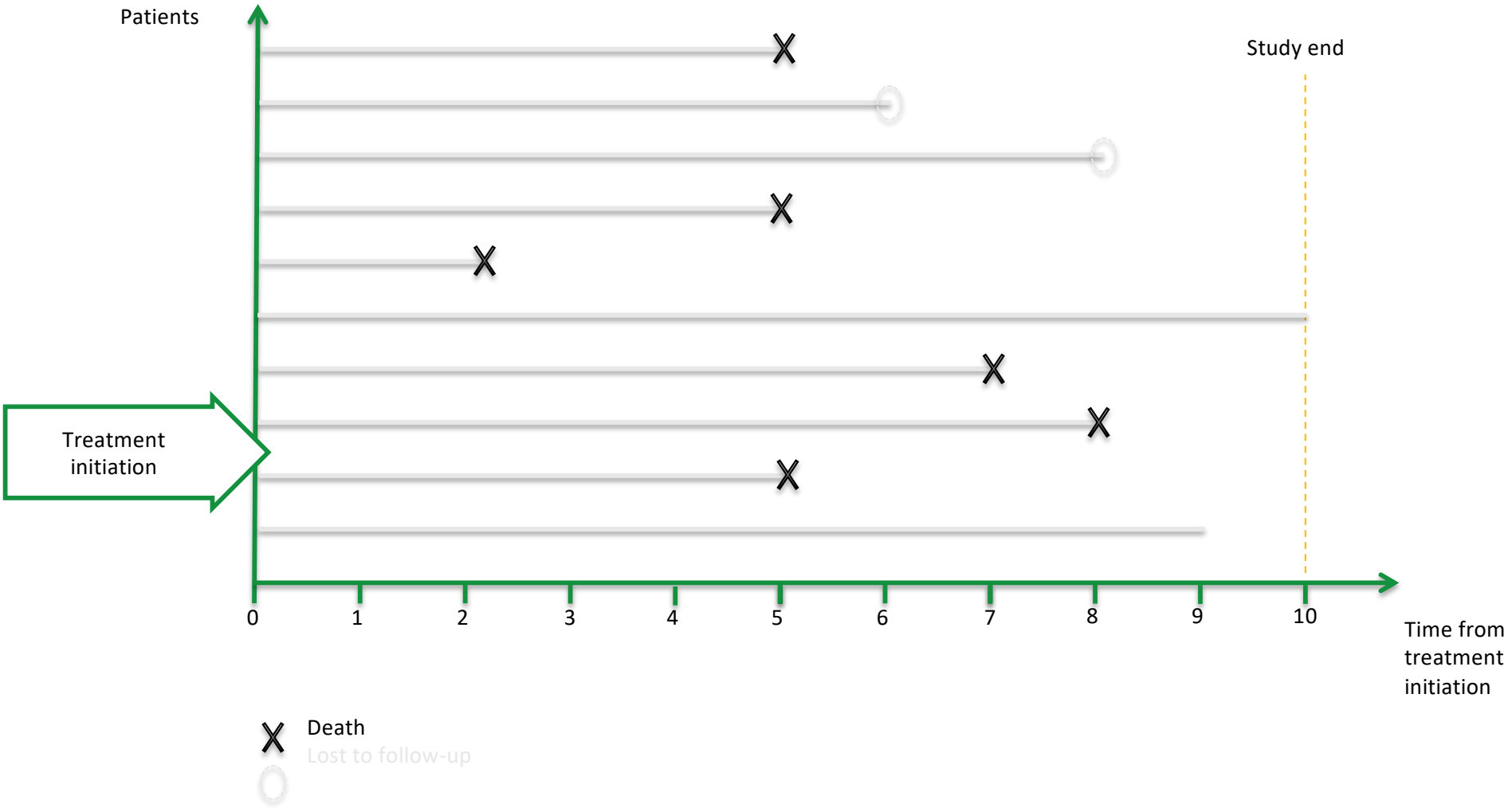
Introduction to Kaplan Meier

- Non-parametric estimate of the survival function.
- Commonly used to describe survivorship of study population/s.
- Commonly used to compare two study populations.
- Intuitive graphical presentation.

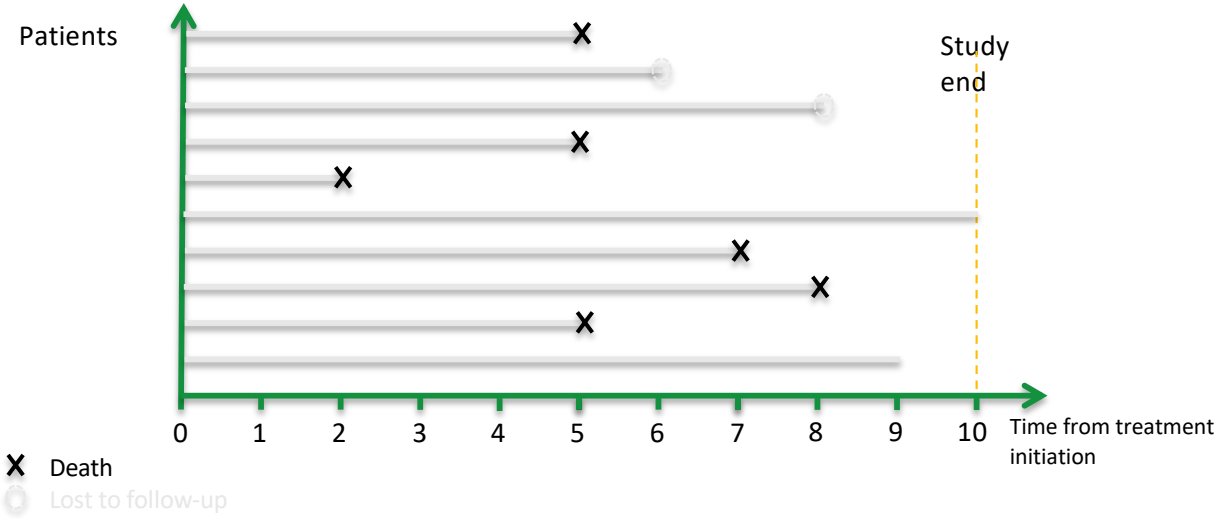
Time-to-event variables



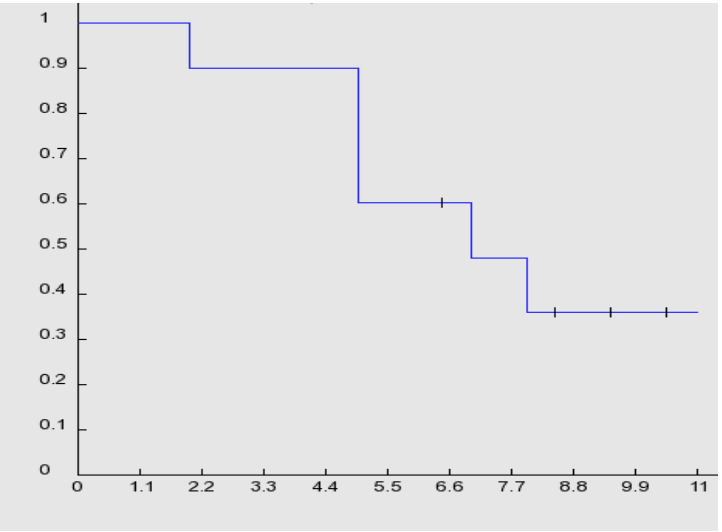
Time-to-event data



Time-to-event variables



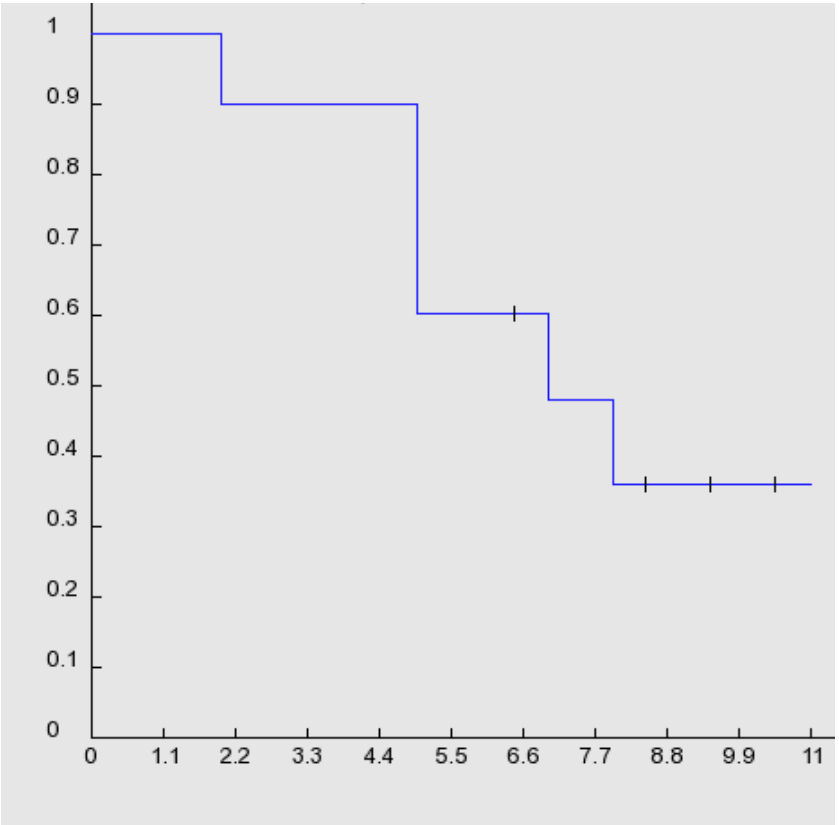
Kaplan-Meier estimator



Period	Patients at risk	No events	Censoring	Survival within time span		Overall survival estimate
0	10					**1**
0-2	10	1		9/10	0.9	**0.9**
2-5	9	3		6/9	0.67	**0.6**
5-6	6		1	6/6	1	**0.6**
6-7	5	1		4/5	0.8	**0.48**
7-8	4	1	1	3/4	0.75	**0.36**
8-9	2		1	2/2	1	**0.36**
9-10	1		1	1/1	1	**0.36**

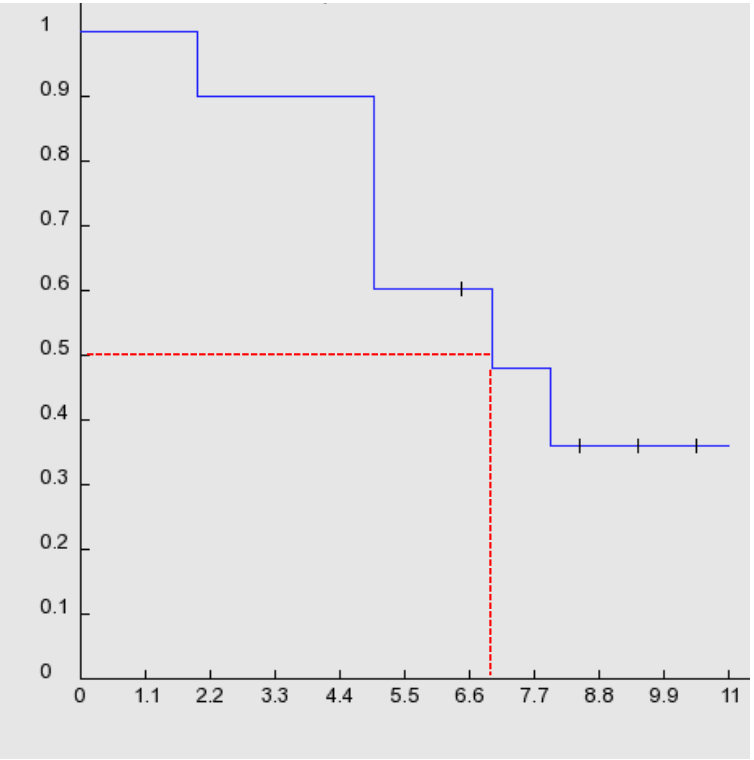
Kaplan-Meier estimator

- Survival function represents probability to survive for a given time from treatment initiation
- The time at which survival is estimated and reported depends on characteristics of disease entity
  - 5-year survival is often reported in oncological studies
  - 1-year survival may be reported if event rate is high (e.g. very aggressive cancer stages)
  - 10-year survival may be reported in case of indolent diseases when study duration allow for appropriate inference in such a long time-frame



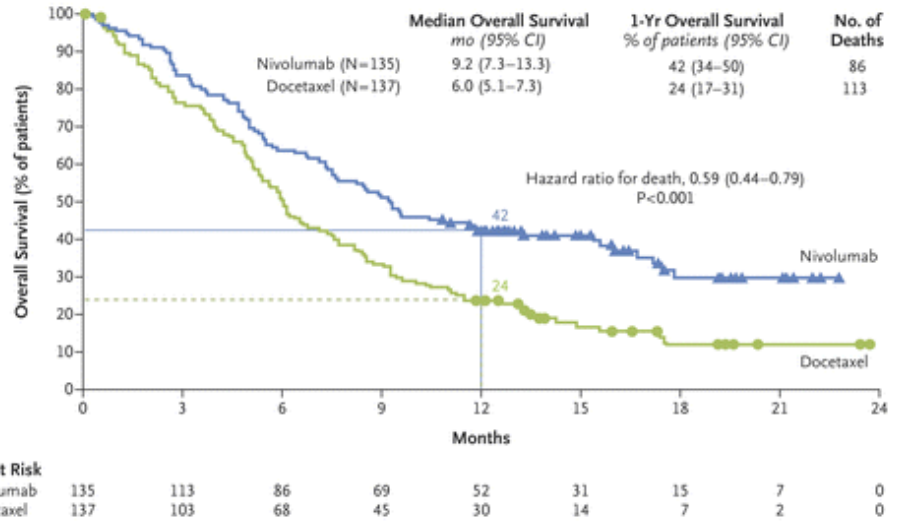
Kaplan-Meier estimator

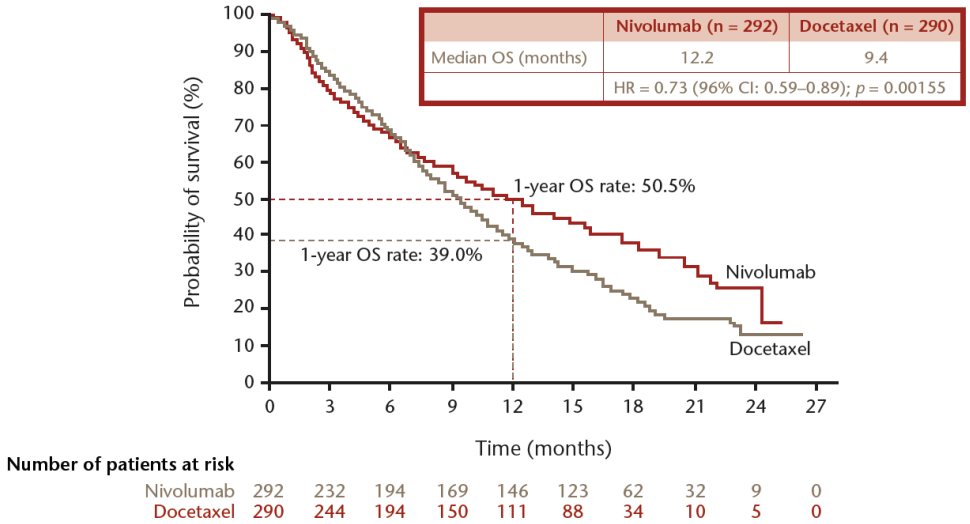
- **Median survival** – time at which estimated survival equals 50%
- Higher median survival indicates a lower rate of mortality.



Comparative survival analysis

- Major statistics
  - Probability to survive given time
  - Median survival
  - Log-rank test
    - p<0.05 indicate statistically significant difference between groups
    - p>0.05 indicate lack of statistically significant difference between groups

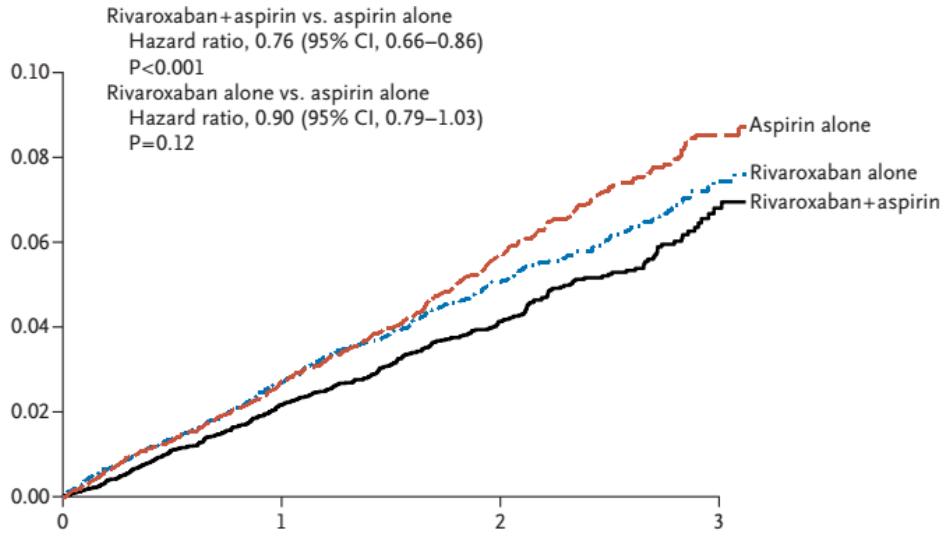




CI = confidence interval; HR = hazard ratio; OS = overall survival

Cumulative survival curves

- K-M estiamtes may also represent cumulative incidence instead of survival
- In this this kind of representation all curves start from probability = 0
- Curves represent probability of failure (death, progression) instead of survival.



Time	Patients at risk	No events	Censoring	Survival within time span		Overall survival estimate	Cumulative failure probability
0	10					**1**	0
2	10	1		9/10	0.9	**0.9**	0.1
5	9	3		6/9	0.67	**0.6**	0.4
6	6		1	6/6	1	**0.6**	0.4
7	5	1		4/5	0.8	**0.48**	0.52
8	4	1	1	3/4	0.75	**0.36**	0.64
9	2		1	2/2	1	**0.36**	0.64
10	1		1	1/1	1	**0.36**	0.64