Point Estimation

- Definition: A “point estimate” is a one-number summary of data.
- If you had just one number to summarize the inference from your study…..
- Examples:
  - Dose finding trials: MTD (maximum tolerable dose)
  - Safety and Efficacy Trials: response rate, median survival
  - Comparative Trials: Odds ratio, hazard ratio

Types of Variables

- **The point estimate you choose depends on the "nature" of the outcome of interest**
- Continuous Variables
  - Examples: change in tumor volume or tumor diameter
  - Commonly used point estimates: mean, median
- Binary Variables
  - Examples: response, progression, > 50% reduction in tumor size
  - Commonly used point estimate: proportion, relative risk, <u>**odds ratio**</u>
- Time-to-Event (Survival) Variables
  - Examples: time to progression, time to death, time to relapse
  - Commonly used point estimates: median survival, *k*-year survival, <u>**hazard ratio**</u>
- Other types of variables: nominal categorical, ordinal categorical

Today

- Point Estimates commonly seen (and misunderstood) in clinical oncology
  - odds ratio
  - risk difference
  - hazard ratio/risk ratio

Point Estimates: Odds Ratios

- "Age, Sex, and Racial Differences in the Use of Standard Adjuvant Therapy for Colorectal Cancer", Potosky, Harlan, Kaplan, Johnson, Lynch. JCO, vol. 20 (5), March 2002, p. 1192.
- <u>Example</u>: Is gender associated with use of standard adjuvant therapy (SAT) for patients with newly diagnosed stage III colon or stage II/III rectal cancer?
  - 53% of men received SAT*
  - 62% of women received SAT*
- How do we quantify the difference?

* adjusted for other variables

Odds and Odds Ratios

- Odds = p/(1-p)
- The odds of a man receiving SAT is 0.53/(1 - 0.53) = 1.13.
- The odds of a woman receiving SAT is 0.62/(1 - 0.62) = 1.63.

- Odds Ratio = 1.63/1.13 = 1.44
- Interpretation: "A woman is 1.44 times more likely to receive SAT than a man."

Odds Ratio

- Odds Ratio for comparing two proportions

$$OR = \frac{p_1/(1-p_1)}{p_2/(1-p_2)}$$
$$= \frac{p_1(1-p_2)}{p_2(1-p_1)}$$

OR > 1: increased risk of group 1 compared to 2

OR = 1: no difference in risk of group 1 compared to 2

OR < 1: lower risk ("protective") in risk of group 1 compared to 2

- In our example,
  - p_1 = proportion of women receiving SAT
  - p_2 = proportion of men receiving SAT

Odds Ratio from a 2x2 table

	SAT	No SAT	
Women	a = 298	b = 252	550
Men	c = 202	d = 248	450
	500	500	1000

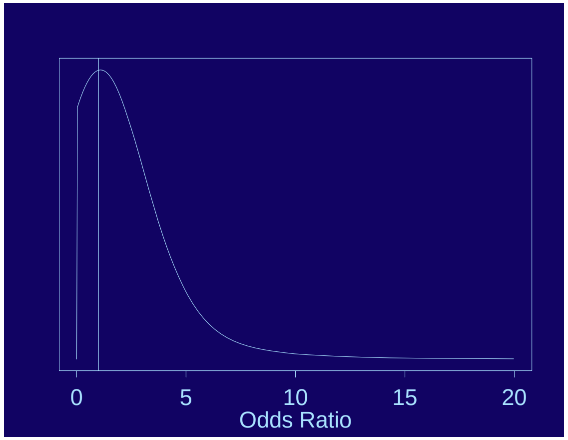
$$OR = \frac{p_1(1-p_2)}{p_2(1-p_1)} = \frac{ad}{bc}$$

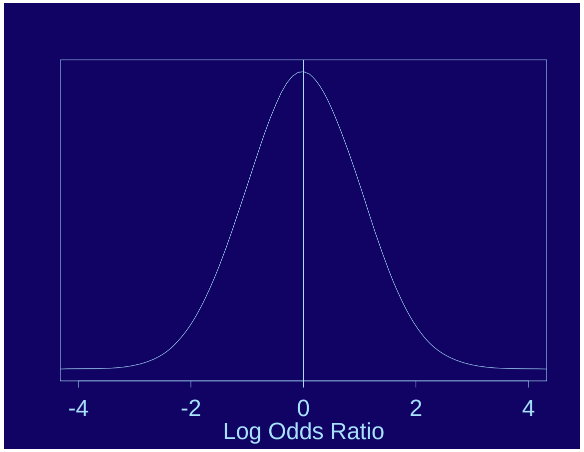
More on the Odds Ratio

- Ranges from 0 to infinity
- Tends to be skewed (i.e. not symmetric)
  - “protective” odds ratios range from 0 to 1
  - “increased risk” odds ratios range from 1 to
- Example:
  - “Women are at 1.44 times the risk/chance of men”
  - “Men are at 0.69 times the risk/chance of women”

More on the Odds Ratio

- Sometimes, we see the *log* odds ratio instead of the odds ratio.





- The log OR comparing women to men is log(1.44) = 0.36
- The log OR comparing men to women is log(0.69) = -0.36

log OR > 0: increased risk

log OR = 0: no difference in risk

log OR < 0: decreased risk

Related Measures of Risk

- Relative Risk: RR = p_1/p_2
  - RR = 0.62/0.53 = 1.17.
  - Different way of describing a similar idea of risk.
  - Generally, interpretation "in words" is the similar:

    "Women are at 1.17 times as likely as men to receive SAT"
  - **RR is appropriate in <u>trials</u> often.**
  - But, RR is not appropriate in many settings (e.g. case-control studies)
  - Need to be clear about RR versus OR:
    - p_1 = 0.50, p_2 = 0.25.
    - RR = 0.5/0.25 = 2
    - OR = (0.5/0.5)/(0.25/0.75) = 3
    - Same results, but OR and RR give quite different magnitude

Related Measures of Risk

- Risk Difference: p_1 - p_2
  - Instead of comparing risk via a ratio, we compare risks via a difference.
  - In many CT's, the goal is to increase response rate by a fixed percentage.
  - Example: the current success/response rate to a particular treatment is 0.20. The goal for new therapy is a response rate of 0.40.
  - If this goal is reached, then the "risk difference" will be 0.20.

Why do we so often see OR and not others?

(1) Logistic regression:

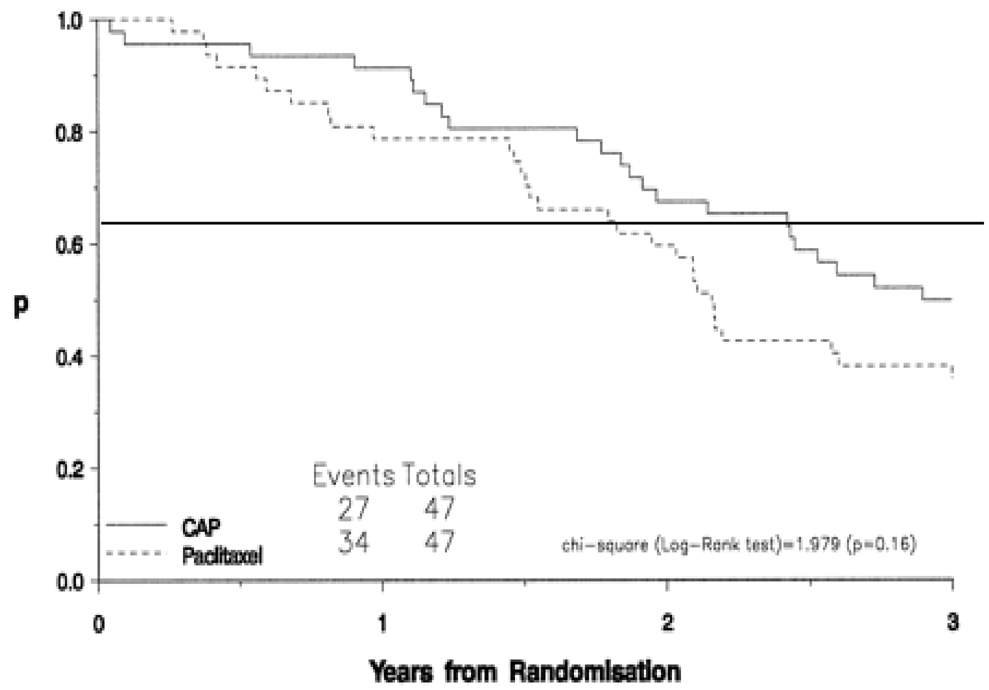
- Allows us to look at association between two variables, adjusted for other variables.
- "Output" is a log odds ratio.
- Example: In the gender ~ SAT example, the odds ratios were evaluated using logistic regression. In reality, the gender ~ SAT odds ratio is adjusted for age, race, year of dx, region, marital status,…..

(2) Can be more globally applied. Design of study does not restrict usage.

Point Estimates: Hazard Ratios

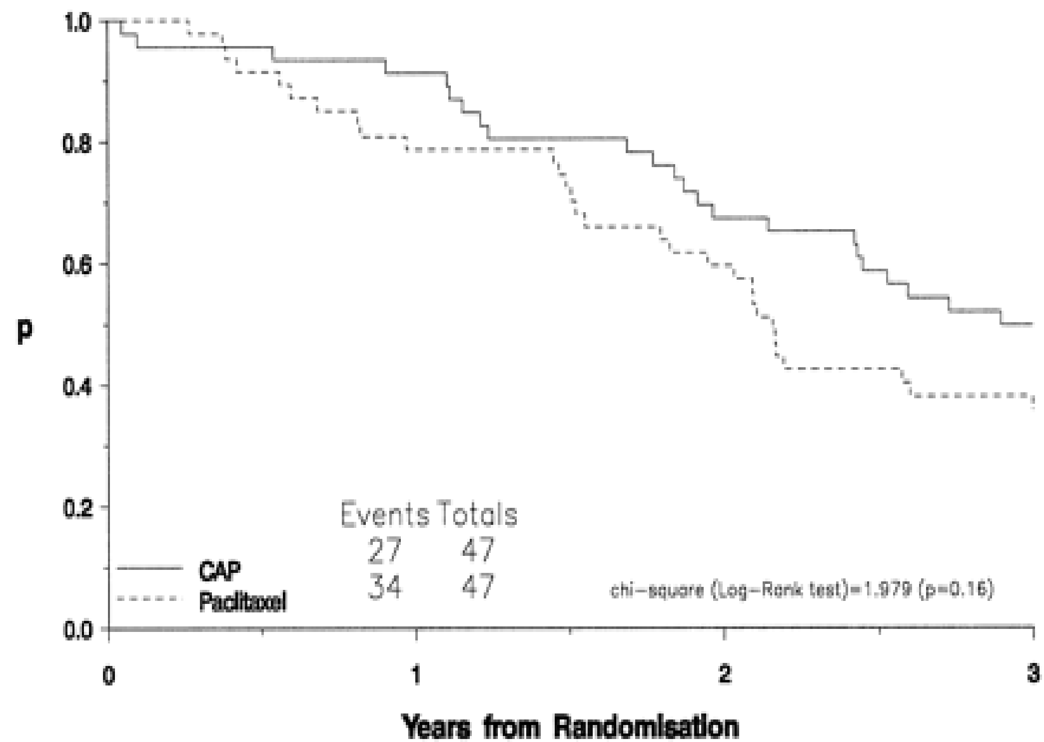
"Randomized Controlled Trial of Single-Agent Paclitaxel Versus Cyclophosphamide, Doxorubicin, and Cisplatin in Patients with Recurrent Ovarian Cancer Who Responded to First-line Platinum-Based Regimens", Cantu, Parma, Rossi, Floriani, Bonazzi, Dell'Anna, Torri, Colombo. JCO, vol. 20 (5), March 2002, p. 1232.

- "What is the effect of CAP on overall survival as compared to paclitaxel?"
  - Median survival in CAP group was 34.7 months.
  - Median survival in paclitaxel group was 25.8 months.
- But, median survival doesn't tell the whole story…..



Hazard Ratio

- Compares risk of event in two populations or samples
- Ratio of risk in group 1 to risk in group 2
- First things first…..
  - Kaplan-Meier Curves (product-limit estimate)
  - Makes a “picture” of survival



Hazard Ratios

- Assumption: "Proportional hazards"
- The risk does not depend on time.
- That is, "risk is constant over time"
- But that is still vague.....

- Example: Assume hazard ratio is 0.7.
  - Patients in temsirolimus group are at 0.7 times the risk of death as those in the interferon-alpha arm, at any given point in time.

- **Hazard function= probably of dying at time t given you survived to time t**

Survival (S(t)) vs. Hazard (h(t))

- Not the same thing.
- Hard to ‘envision’ the difference
- technically, it is the the negative of the slope of the log of the survival curve

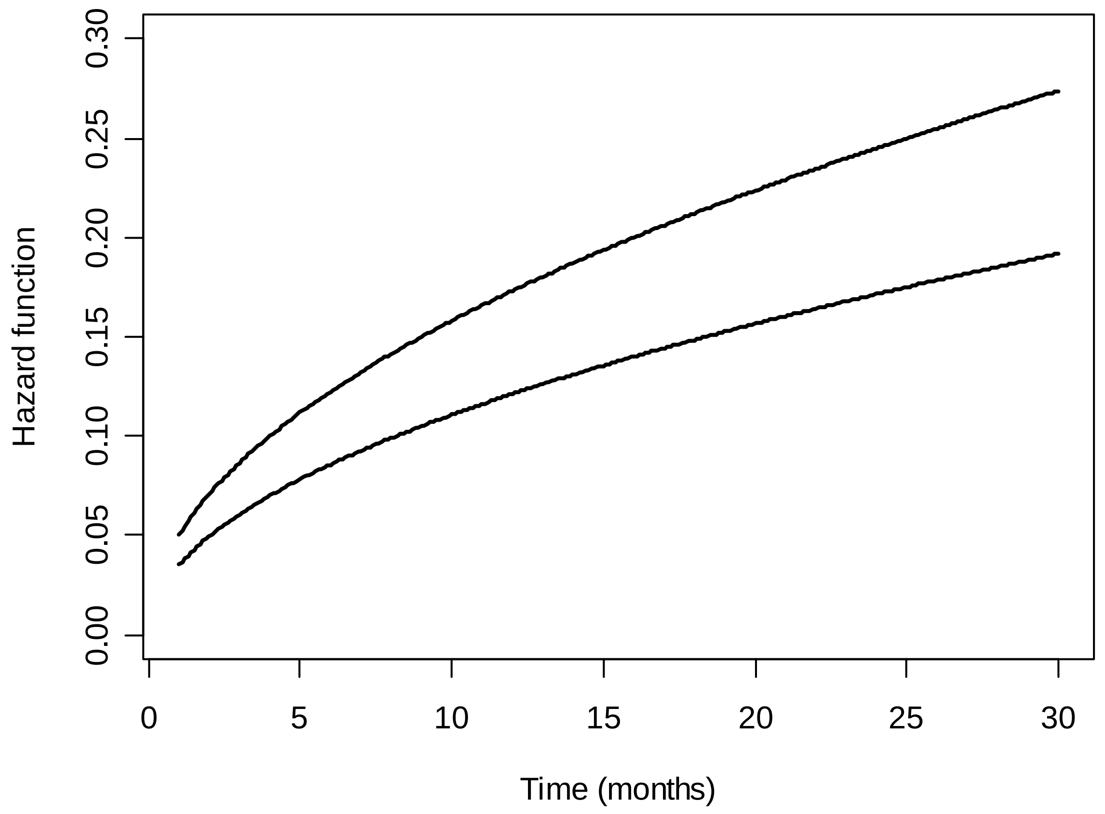
$$h(t) = \frac{d}{dt}(-\log(S(t))$$

- Yikes….don’t worry though
- the statisticians deal with this stuff

- just remember:
  - the hazard ratio is not the ratio of the survival curves
  - it is a ratio of some function of the survival curves

Hazard Ratios

- Hazard Ratio = $\dfrac{\text{hazard function for T}}{\text{hazard function for IA}}$
- Makes the assumption that this ratio is constant over time.



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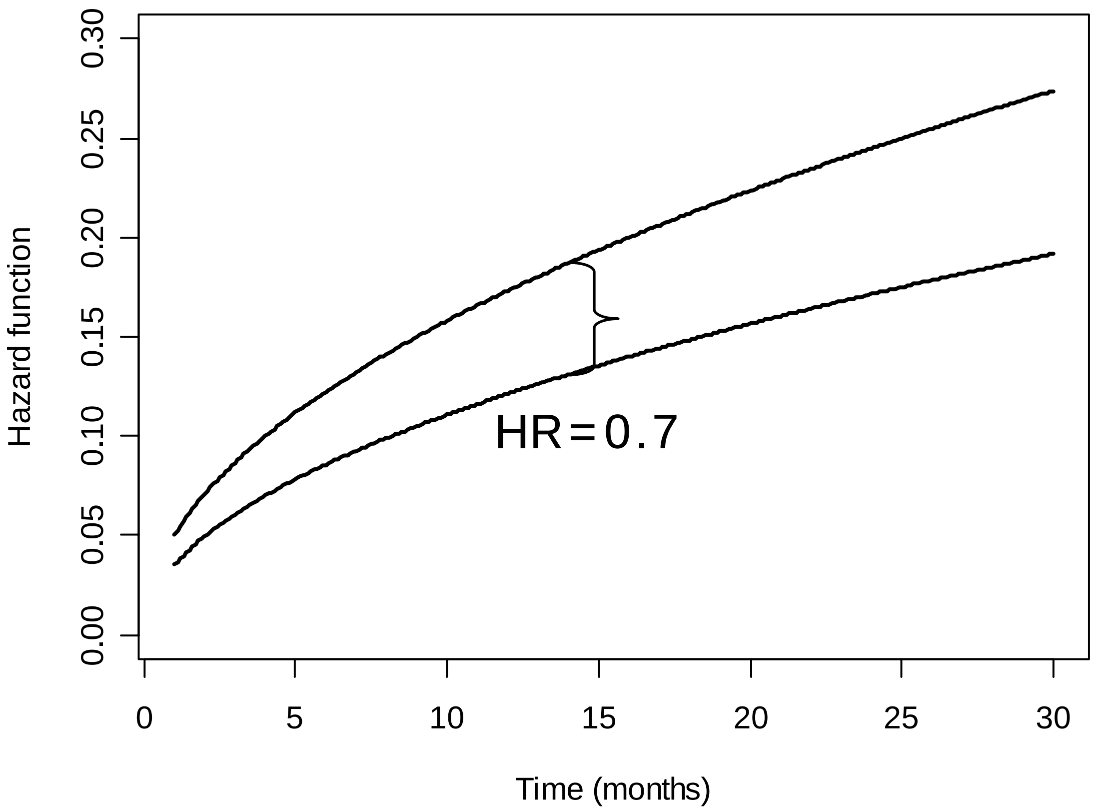

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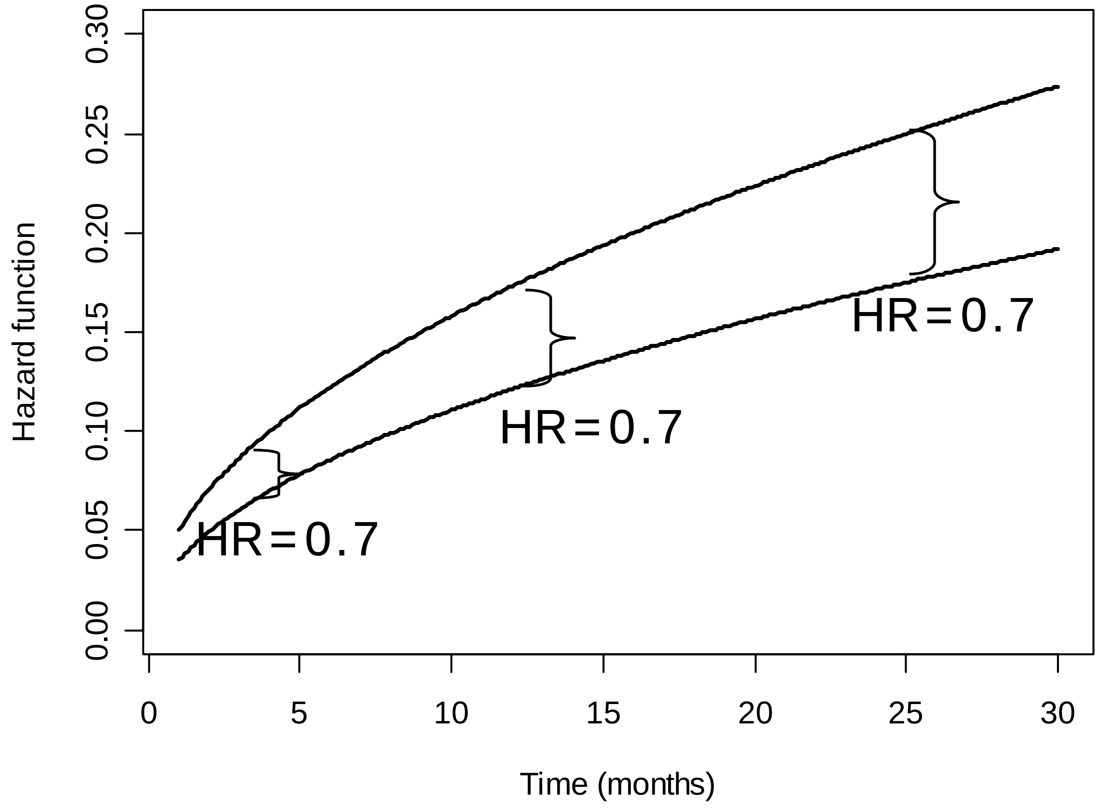
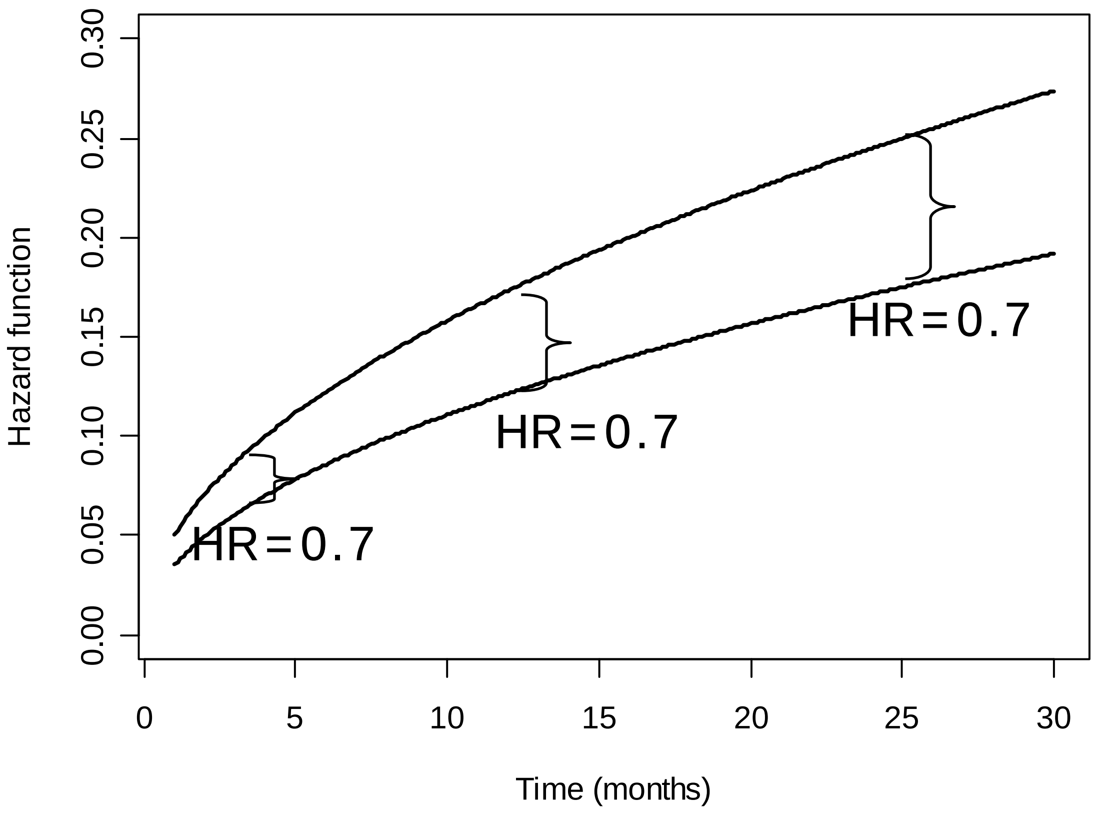
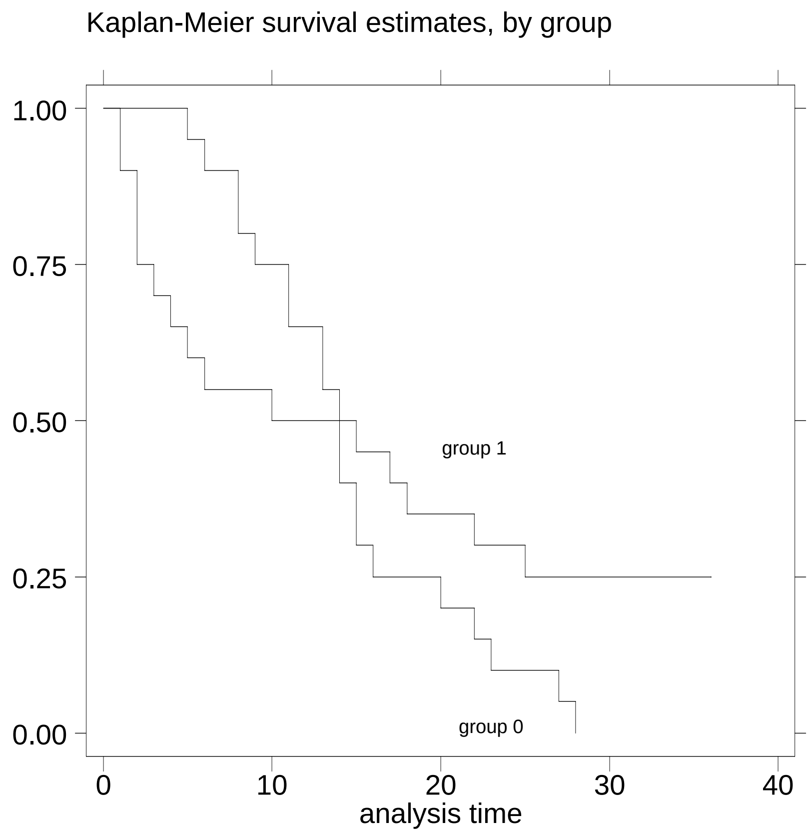


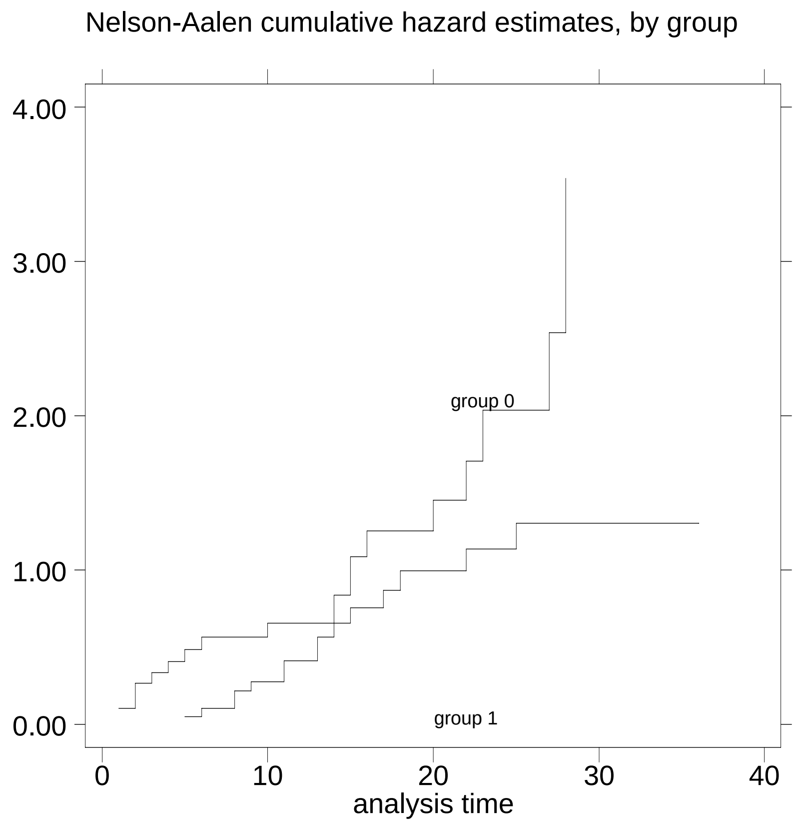
Interpretation Again

- For any fixed point in time, individuals in the T therapy group are at 0.7 times the risk of death as the IA group.



Hazard ratio is not always valid ….





Hazard Ratio = .71