HR and standardised risk curves

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Proportionality assumption in Cox regression

- Assumption

Hazards should be proportional over time – i.e. HR should be constant

- Common suggestion when this assumption was not met

(especially up to a few years ago)

Split the follow-up time and estimate the time-varying HRs using Cox regression

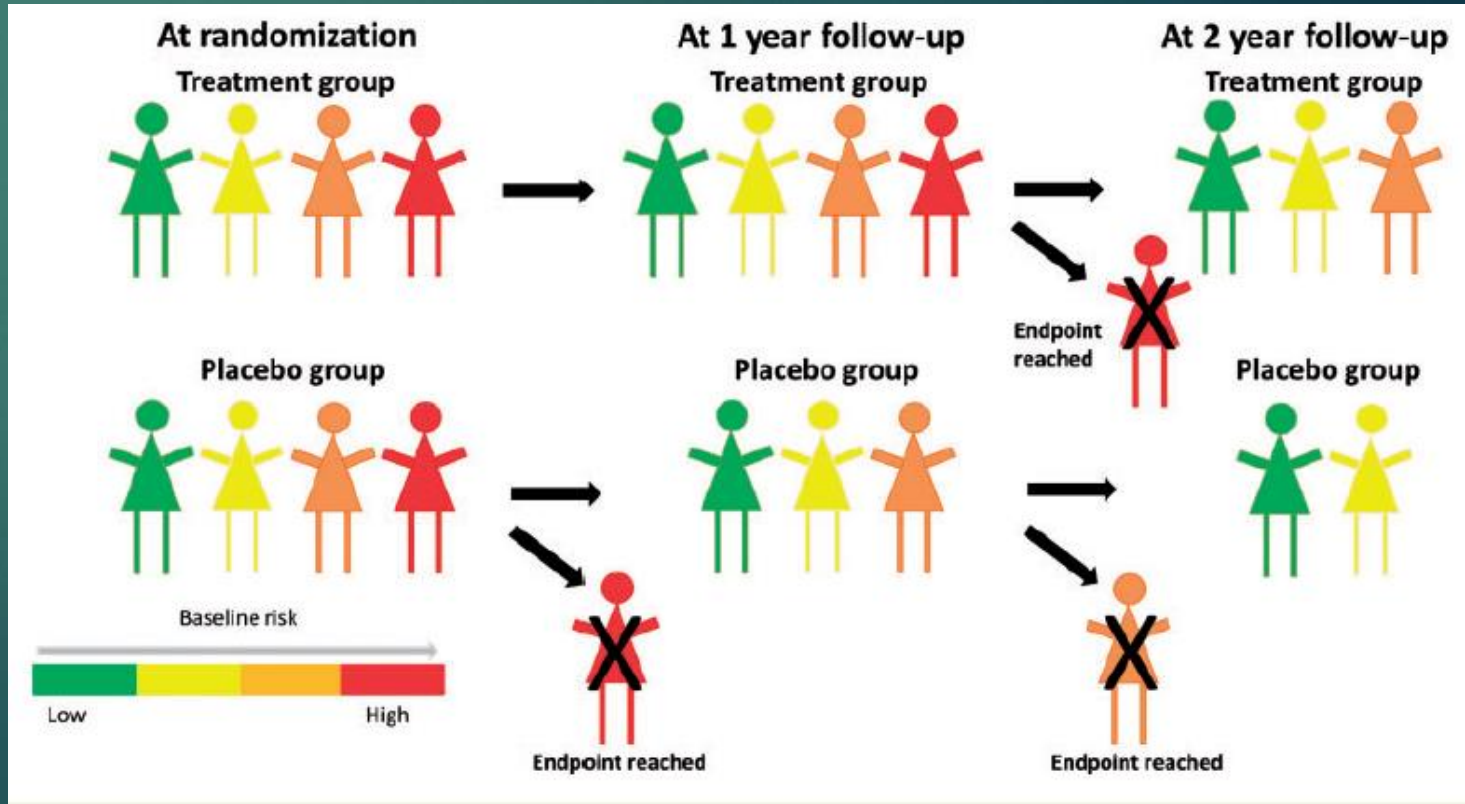
- Is it correct?

Built-in selection bias in Hazard Ratios

- Let's assume we have an RCT and we want to compare treatment vs placebo (Stensrud et al, 2019)

There is a built-in selection bias (Hernan 2010, Stensrud 2019, Stensrud and Hernan 2020)

e.g. HR after year 1: individuals are no longer randomised (cannot be interpreted causally)



What should we do?

- The interpretation of the HR when the proportionality assumption is not met is the "average" HR
- A single HR might be uninformative (problematic for causal interpretation). Does not describe the problem adequately
- For both the ITT and the PP analysis, yes, the (average) HR should be calculated but it should not be the only effect measure in a paper
- Researchers should also calculate standardised survival curves/ incidence risk curves

HR for ITT analysis using observational data

- Researchers could use either Cox regression or pooled logistic regression
- Pooled logistic regression can be used if we split the follow-up time in short periods of time for each individual
- Adjustment can be made either directly in the outcome model or through IPW to emulate randomisation at baseline
- Results from Cox regression will be almost identical with pooled logistic regression if we split the follow-up into relatively short periods of time

HR for PP analysis using observational data

- Apart from emulating randomisation at baseline, researchers should account for adherence. The easiest way to do that is through IPW for adherence (Murray 2021, Dickerman 2019, Katsoulis 2021)
- For this analysis we need to

1. Censor individuals who do not adhere to their initial treatment strategy
2. Use pooled logistic regression models to estimate the probability of adherence weights (IPW_A). These weights will create a pseudo-population where everyone either continuously adheres to treatment or no treatment
3. Use pooled logistic regression to model the outcome, weighted by IPW_A

HR for PP analysis using observational data

- We need to calculate unstabilised weights for censoring due to switching treatment

$$IPW\_A_k = \prod_{n=0}^{t} \frac{1}{f(A_k | \overline{A_{k-1}}, \overline{L_k}, \overline{Y_k} = 0)}$$

To estimate the denominator, **we run two models**

The 1st model was fit to person-times who were untreated in the previous time point (that is, $A_{k-1} = 0$):

$$logit(\Pr(A_k = 1 | A_{k-1} = 0, \overline{L_k}, \overline{Y_k} = 0)) = a_0 + a_1^T L_0 + a_2^T L_k$$

Then IPW_A at each time point for the untreated will be

$$IPW\_A_{k,\,untreated} = \frac{1}{1 - (\Pr(A_k = 1 | A_{k-1} = 0, \overline{L_k}, \overline{Y_k} = 0)}$$

Covariate history $\overline{L_k}$ was summarized by baseline L_0 and the most recent measurement of L_k

HR for PP analysis using observational data

- We need to calculate unstabilised weights for censoring due to switching treatment

$$IPW\_A_k = \prod_{n=0}^{t} \frac{1}{f(A_k | \overline{A_{k-1}}, \overline{L_k}, \overline{Y_k} = 0)}$$

The 2nd model was fit to person-times who were treated in the previous time point (that is, $A_{k-1} = 1$):

$$logit(\Pr(A_k = 1 | A_{k-1} = 1, \overline{L_k}, \overline{Y_k} = 0)) = b_0 + b_1^T L_0 + b_2^T L_k$$

Then IPW_A at each time point for the treated will be

$$IPW\_A_{k,\,treated} = \frac{1}{(\Pr(A_k = 1 | A_{k-1} = 1, \overline{L_k}, \overline{Y_k} = 0)}$$

Covariate history $\overline{L_k}$ was summarized by baseline L_0 and the most recent measurement of L_k. IPW_A_k will be multiplied from time 0 to time k

HR for PP analysis using observational data

HR in the PP analysis, i.e. the HR had everybody adhered to the initial strategy

- Run pooled logistic regression among individuals who have not deviated from their initial treatment strategy. Individuals will be censored if they deviate in the PP analysis. This pooled logistic regression will be weighted by IPW_A

$$logit(\Pr(Y_{k+1} = 1 | A_0, L_0, \bar{Y}_k = 0, \overline{C_k} = 0)) = h_{0,t} + h_1 A_0 + h_2^T L_0$$

Standardised risk curves (either for PP or ITT)

1. Fit a discrete-time hazards model (eg, a pooled logistic model with relatively short periods) that estimates, at each time and for each person, the probability of developing the outcome. Use the variable "time of follow-up,", along with time^2 and time^3 or a flexible functional form (splines) and estimate time-varying HRs by adding product terms between exposure and "time of follow-up."

2. Recreate all time points and two exposure groups for each subject (we want to estimate their risk curves both under exposure and under no exposure, regardless of the subject's exposure status)

3. Estimate the probability of being at risk at each time point

4. Estimate the probability of being healthy at each time point (1-probability of being at risk)

Standardised risk curves

6. Multiply the model's predicted values of being healthy through time *t* to estimate the probability of remaining healthy (or probability of survival if the outcome is death) at *t* for subjects with their same combination of covariate values.

6. Predict the probability of being at risk at time *t* for each subject both under exposure and under no exposure, regardless of the subject's exposure status (1-probability of remaining healthy)

7. Separately average the adjusted risk curves under exposure and under no exposure, over all subjects. This last step effectively standardizes the curves to the empirical distribution of the covariates in the study, and results in 2 marginal risk curves: one under exposure, another under no exposure.

* For standardized survival curves, skip step 6 and then average the survival curves in step 7

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Thanks!

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