Lecture 6

Monday, October 16, 2023 10:02

BIOS522_Slides6

EMORY ROLLINS SCHOOL OF PUBLIC HEALTH | Department of Biostatistics and Bioinformatics

BIOS 522: Survival Analysis Methods

Lecture 6:

Interpreting the Cox model

Coefficients of the Cox model

- β_j is the **log hazard ratio** for the jth covariate
- $\exp(\beta_j)$ is the **hazard ratio** for the jth covariate

- For a **binary covariate**, this is the hazard ratio comparing the group with $X_{ij} = 1$ vs. the group with $X_{ij} = 0$
  - (*holding all other covariates constant*)
- For a **continuous covariate**, this is the hazard ratio for a one-unit increase in X_{ij}, e.g. $X_{ij} = 10$ vs. $X_{ij} = 9$
  - (*holding all other covariates constant*)

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Statistical inference

- Under the **null hypothesis** of no effect of the covariate on survival:
  - H_0: $\beta_j = 0$
  - H_0: $\exp(\beta_j) = 1$

- Fit the model to our data and obtain estimate $\hat{\beta}_j$ and $\widehat{SE}(\hat{\beta}_j)$
  - Report **hazard ratio**: $\exp(\hat{\beta}_j)$
  - Report **95% CI**: $\left(\exp\left(\hat{\beta}_j - 1.96\,\widehat{SE}(\hat{\beta}_j)\right), \exp\left(\hat{\beta}_j + 1.96\,\widehat{SE}(\hat{\beta}_j)\right)\right)$

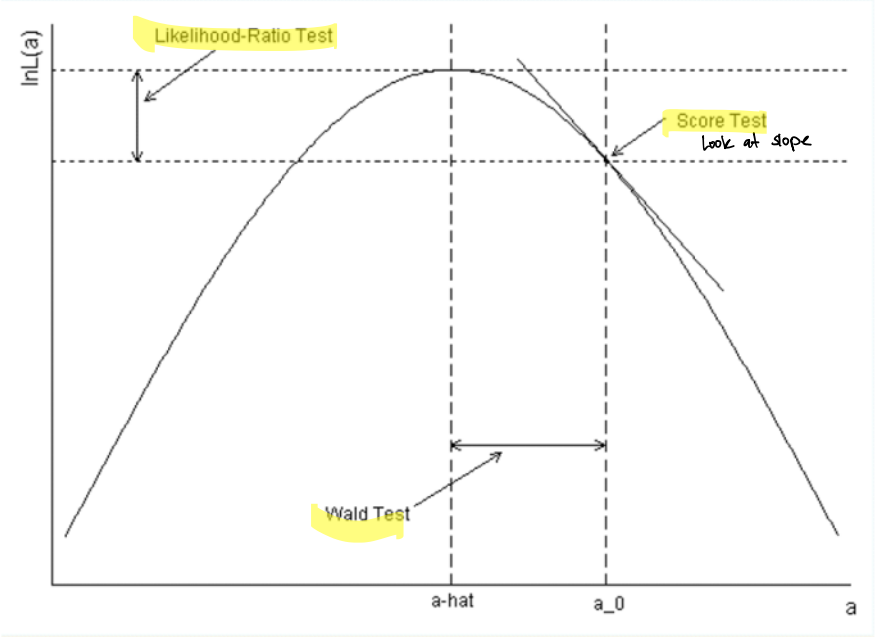
Hypothesis testing

- Global tests
  - Wald test
  - Likelihood ratio test
  - Score test

H_0: $\beta = \beta_0$ for some $\beta_0 = (\beta_{01}, \ldots, \beta_{0p})$
- *Often testing that all are 0*

- Local tests
  - Wald test
  - Likelihood ratio test
  - Score test

Test a subset. H_0: $\beta_J = \beta_{J0}$
- *One variable at a time*
- *A set of variables (e.g. nominal variable)*
- *Interaction terms*



https://stats.oarc.ucla.edu/other/mult-pkg/faq/general/faqhow-are-the-likelihood-ratio-wald-and-lagrange-multiplier-score-tests-different-andor-similar/

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There is a special case where these two are related

The score test and the log-rank test

- Consider the special case where there is a single binary covariate $Z = 0$ or 1.
- It can be shown that the score test reduces to the log-rank test in the two-sample case.
- Because of this relationship, it is common to see a log-rank test p-value reported in a table or figure alongside a hazard ratio from a Cox model.

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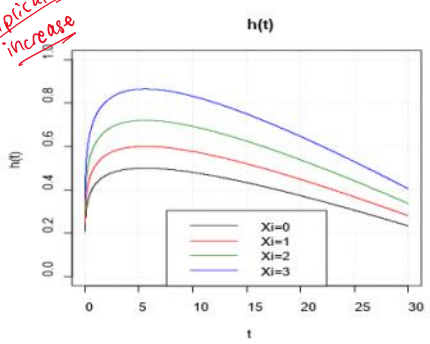
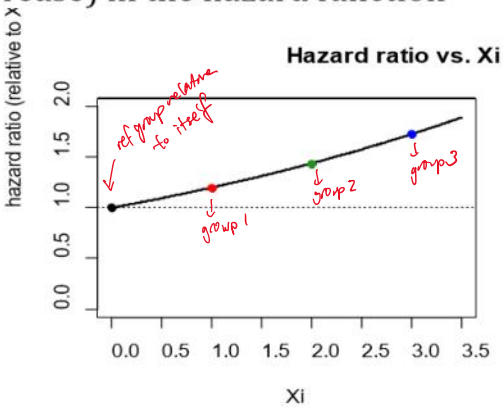
Modeling a continuous covariate

- Each one-unit change in our covariate corresponds to a **multiplicative** increase (or decrease) in the hazard function

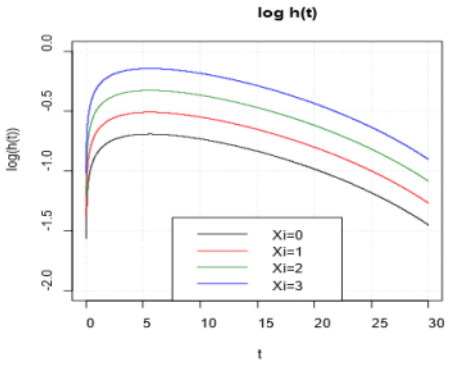


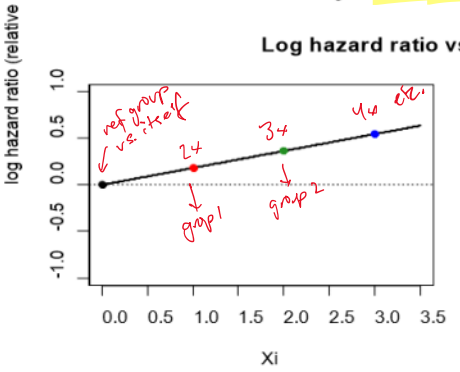


7

Modeling a continuous covariate

- Each one-unit change in our covariate corresponds to an **additive** increase (or decrease) in the log hazard function
- The **log hazard ratio** for a continuous covariate vs. X_i is linear





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Modeling a categorical covariate

- For a categorical covariate with k levels, we select a single level of the covariate as a reference and use $k-1$ indicator variables to model the hazard ratio between each level and the reference.

$$h_i(t) = h_0(t)\exp(\beta_1 I[X_i = 1] + \cdots + \beta_{k-1} I[X_i = k-1])$$

Reference is often the largest group

ARTICLES

Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial

Claudio Ronco, Rinaldo Bellomo, Peter Homel, Alessandra Brendolan, Maurizio Dan, Pasquale Piccinni, Giuseppe La Greca

Goal: Investigators initiated a prospective, randomized study to **evaluate different continuous venovenous hemofiltration methods** for the treatment of acute renal failure in critically ill patients.

Population: The study enrolled 425 patients who had acute renal failure in intensive care at St. Bartolo Hospital, Vinceza, Italy. Enrolment started in 1994, and the last patient was recruited in September 1999.

Outcome variable: The primary analysis considered the **time from discontinuation of hemofiltration treatment to death**.

Source: Ronco et al. (2000) The Lancet DOI: 10.1016/S0140-6736(00)02430-2

Predictor variables: Patients were **randomized to one of three doses** of ultrafiltration:

- 20 mL h^{-1} kg^{-1} (**group 1**) lowest level
- 35 mL h^{-1} kg^{-1} (**group 2**)
- 45 mL h^{-1} kg^{-1} (**group 3**)

Other baseline covariates collected included sex, weight, age, causes of acute renal failure (surgical, medical, trauma), presence of sepsis (yes/no), blood urea nitrogen, and APACHE II score (measurement of severity of illness). ↓ in blood

Statistical analysis: The primary analysis consisted of a set of **pairwise comparisons** of survival **between the three randomized groups**. These were performed by **standard log-rank tests**.

Because some chance imbalances were observed in baseline characteristics (age, APACHE II score) across the groups, a **Cox proportional hazards model** was fit to **assess the differences between trial groups, adjusting for other key covariates**.

Sex and presence of sepsis were **binary variables**. Weight, age, and blood urea nitrogen were **continuous variables**. Cause of acute renal failure and trial group were **categorical variables**.

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Results: **Figure 2** summarizes the survival distributions of the three trial groups.

- Median survival was 19.0 days for **group 1** (95% CI 14.7-23.3)
- Median survival was 33.0 days for **group 2** (no CI reported)
- 53% of **group 3** were alive at day 46
  ↳ No median because more than half was still alive
- **Groups 2 and 3** did not have significantly different survival (log-rank p=0.87)
- **Group 1** had significantly poorer survival than **group 2** (log-rank p=0.0007) and **group 3** (log-rank p=0.0013)
- These comparisons are not adjusted for other covariates

3 KM curves

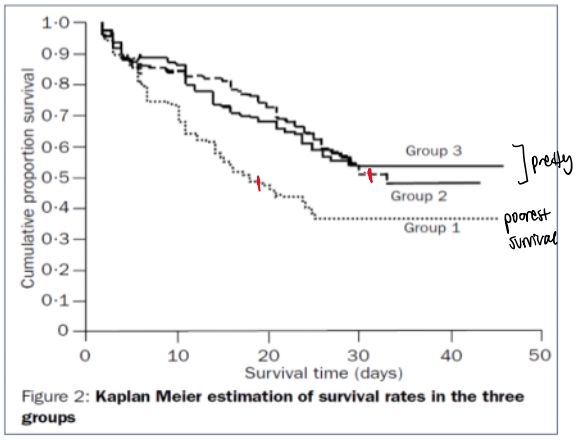

Figure 2: **Kaplan Meier estimation of survival rates in the three groups**

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Results: **Table 2** summarizes the results from the Cox proportional hazards regression models.

- The middle column summarizes results from a series of **univariable models** (*one covariate per model*)
- The right-hand column summarizes results from a single **multivariable model** (*all covariates included in the same model*)

Break it down in the next few slides

Variable	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Sex (female)	0·90 (0·69–1·19)	0·89 (0·66–1·20)
Weight	1·01 (0·99–1·03)	1·00 (0·99–1·02)
Age	1·00 (0·98–1·01)	1·00 (0·98–1·01)
Causes of acute renal failure		
Surgical	1·0	1·0
Medical	0·483 (0·28–0·82)	0·82 (0·46–1·46)
Trauma	1·384 (0·93–2·06)	1·09 (0·72–1·64)
Presence of sepsis	1·71 (1·20–2·44)	0·55 (0·34–0·89)
BUN at start of continuous haemofiltration	1·06 (1·05–1·07)	1·05 (1·04–1·07)
APACHE II score	1·13 (1·09–1·18)	1·11 (1·04–1·19)
Trial groups		
Group 1	1·0	1·0
Group 2	0·55 (0·40–0·77)	0·51 (0·36–0·72)
Group 3	0·57 (0·41–0·78)	0·49 (0·35–0·69)

BUN=blood urea nitrogen.

Table 2: **Results of Cox's proportional hazards regression**

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Results: (*Sex*)

- The unadjusted hazard ratio for females vs. males is 0.90 (95% CI 0.69 to 1.19)
- The hazard ratio is similar after adjusting for other covariates (0.89, 95% CI 0.66 to 1.20)
- Females have slightly lower hazard of death than males
- As the CIs include the null value of 1, there is **no evidence** of a significant difference in survival between the sexes

Variable	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Sex (female)	0·90 (0·69–1·19)	0·89 (0·66–1·20)
Weight	1·01 (0·99–1·03)	1·00 (0·99–1·02)
Age	1·00 (0·98–1·01)	1·00 (0·98–1·01)
Causes of acute renal failure		
Surgical	1·0	1·0
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BUN=blood urea nitrogen.

Table 2: **Results of Cox's proportional hazards regression**

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Results: (*Blood urea nitrogen - BUN*)

- The unadjusted hazard ratio for a one-unit increase in BUN is 1.06 (95% CI 1.05 to 1.07)
- The hazard ratio is similar after adjusting for other covariates (1.05, 95% CI 1.04 to 1.07)
- Each one mmol/L increase in BUN at baseline was associated with 1.05 times higher hazard, adjusting for other covariates
- Patients with higher BUN had higher hazard, lower survival
- As the CIs are above the null value of 1, there is evidence of a **significant association** between BUN and survival

Variable	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Sex (female)	0·90 (0·69–1·19)	0·89 (0·66–1·20)
Weight	1·01 (0·99–1·03)	1·00 (0·99–1·02)
Age	1·00 (0·98–1·01)	1·00 (0·98–1·01)
Causes of acute renal failure		
Surgical	1·0	1·0
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BUN=blood urea nitrogen.

Table 2: **Results of Cox's proportional hazards regression**

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Results: (*Trial group*)

- Group 1 is arbitrarily set as the **reference group**
- The model is fit using dummy variables for Group 2 and Group 3
- The second highlighted row compares **Group 2 vs. Group 1**; the adjusted hazard ratio is 0.51 (95% CI 0.36 to 0.72); patients in Group 2 have lower hazard, better survival
- The third highlighted row compares **Group 3 vs. Group 1**; the adjusted hazard ratio is 0.49 (95% CI 0.35 to 0.69); patients in Group 3 have lower hazard, better survival
- The results do not provide a direct comparison of **Group 3 vs. Group 2**, though we can see they are similar

Variable	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Sex (female)	0·90 (0·69–1·19)	0·89 (0·66–1·20)
Weight	1·01 (0·99–1·03)	1·00 (0·99–1·02)
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BUN=blood urea nitrogen.

Table 2: **Results of Cox's proportional hazards regression**

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Author's summary (*from the abstract*):

- "Survival in group 1 was significantly lower than in groups 2 (p=0.0007) and 3 (p=0.0013). Survival in groups 2 and 3 did not differ significantly (p=0.87).
- Adjustment for possible ~~confounding factors~~ did not change the pattern of differences among the groups.
- Survivors in all groups had lower concentrations of blood urea nitrogen before continuous haemofiltration was started than non-survivors."

she wouldn't call them "confounding factors"

- "Mortality among these critically ill patients was high, but increase in the rate of ultrafiltration improved survival significantly.
- We recommend that ultrafiltration should be prescribed according to patient's bodyweight and should reach at least 35 mL h^{-1} kg^{-1}."

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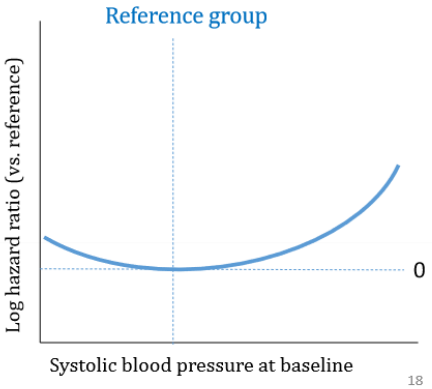
What if it isn't linear?

- There may be settings where the log hazard ratio vs. X_i is non-linear

- *Example*: *Time to stroke*
  - Baseline systolic blood pressure is an important predictor of stroke
  - Patients with high blood pressure have increased hazard of stroke
  - Extremely low blood pressure can also elevate hazard of stroke



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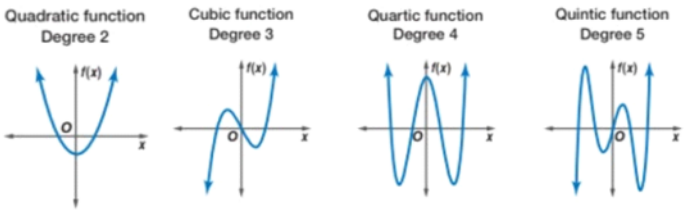
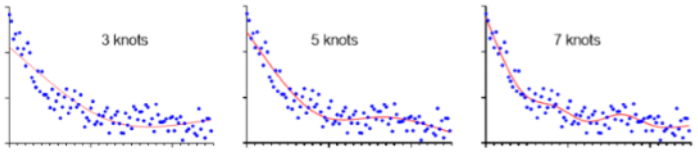
Modeling non-linear relationships

- Polynomials
  - $X_i, X_i^2, X_i^3, \ldots$



The more knots you have, the more "subsections" ↳ more wiggly shapes

- Splines
  - Flexible functions



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Dose-response analyses using restricted cubic spline functions in public health research

Loic Desquilbet[a*†] and François Mariotti[b]

"Not too wiggly"
↑
Restricted cubic spline

- Analyzing data from the NHANES III database, out of 14,757 individuals, 975 (8%) **died from a cardiovascular event**.
- The researchers fit a restricted spline for the relationship between **serum HDL cholesterol** and hazard ratio.
- Four knots are selected at 0.8, 1.0, 1.5, and 2.0 mmol/l, which approximately corresponded to the 5th, 25th, 75th and 95th percentiles of HDL. (These are represented by dots on the figure.)
- The Y-axis is the **adjusted hazard ratio** for cardiovascular-related death for any value of HDL cholesterol compared to individuals with 1 mmol/l of HDL cholesterol (**reference group**).
- The hazard ratio is adjusted for sex, race/ethnicity, education, smoking status, and age.
- Dashed lines are 95 percent confidence intervals.

Don't want to force a linear ratio

Can manually select, or software can select them

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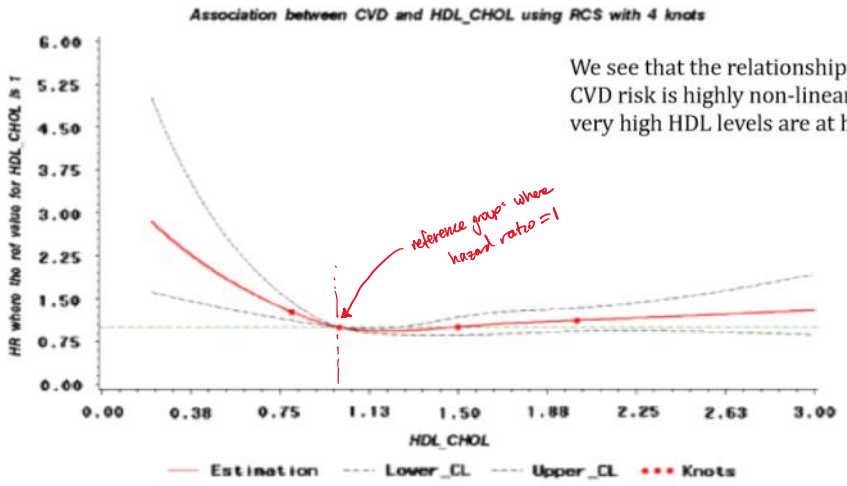
Source: Desquilbet & Mariotti (2009) Statistics in Medicine DOI: 10.1002/sim.3841

Dose-response analyses using restricted cubic spline functions in public health research

Loic Desquilbet[a*†] and François Mariotti[b]



We see that the relationship between HDL cholesterol and CVD risk is highly non-linear. Individuals with very low and very high HDL levels are at highest risk.

reference group: where hazard ratio = 1

Source: Desquilbet & Mariotti (2009) Statistics in Medicine DOI: 10.1002/sim.3841

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"Sorry for the poor quality, you can blame the authors"

10/16

"Who picked these axes labels?"

Interactions

- When we have several covariates, it is common to assume that their effects on the hazard function are **multiplicative**

It's what's built into the model

$$h_i(t) = h_0(t)\exp\left(\beta_{trt}X_{i,trt} + \beta_{age}X_{i,age}\right)$$
$$= h_0(t)\exp\left(\beta_{trt}X_{i,trt}\right)\exp\left(\beta_{age}X_{i,age}\right)$$

rules of exponentials

- Thus, the effect of a covariate on the hazard is the same regardless of the value of the other covariate

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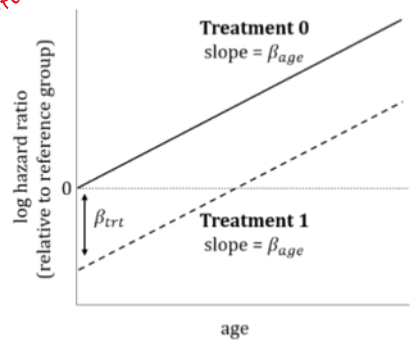
Interactions

- Where this assumption is not reasonable, we can add an **interaction**

$$h_i(t) = h_0(t)\exp\left(\beta_{trt}X_{i,trt} + \beta_{age}X_{i,age} + \beta_{int}X_{i,trt}X_{i,age}\right)$$

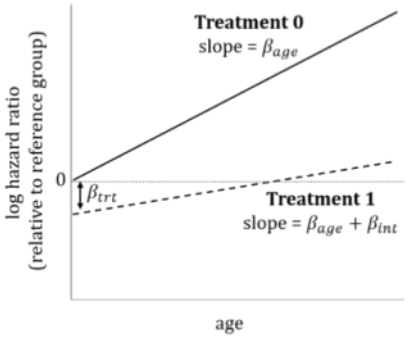
- The interaction term adds flexibility to the model, allowing the effect of a covariate to vary depending on the value of the other covariate
  - *Example*: the treatment is more effective for older populations

Ref group: 0 years old Not treated



Model with no interaction

- Hazard increases with age
- Treatment reduces the hazard for all age groups
- The effect of treatment is the same for all ages



Model with an interaction

- Hazard increases with age
- Treatment reduces the hazard for all age groups
- The reduction in hazard is smallest for young participants
- The reduction in hazard is largest for older participants

Diff amount of reduction for diff groups

Example: Lipid therapy

Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus

The ACCORD Study Group*

- Goal: The investigators sought to compare **combination therapy** (statin + a fibrate) versus statin **monotherapy** to reduce cardiovascular disease in **patients with type 2 diabetes**.

- Population: **5518 patients** with type 2 diabetes who were already receiving a statin were randomized to receive either a **fibrate or placebo**.

Source: ACCORD Study Group (2010) NEJM https://www.nejm.org/doi/full/10.1056/nejmoa1001282

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Example: Lipid therapy

COMPOSITE ENDPOINT

- Outcome variable: The **primary outcome** was first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. Several secondary outcomes were defined. Mean follow-up was 4.7 years after randomization.

- Statistical analysis: Cox models were fit. Two-sided p-values were obtained from likelihood ratio tests. A pre-specified subgroup analysis tested for an interaction for treatment and sex.

Source: ACCORD Study Group (2010) NEJM https://www.nejm.org/doi/full/10.1056/nejmoa1001282

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Example: Lipid therapy

Note the rows!
They aren't covariates...
they are outcomes!!

Table 2. Prespecified Primary and Secondary Outcomes.

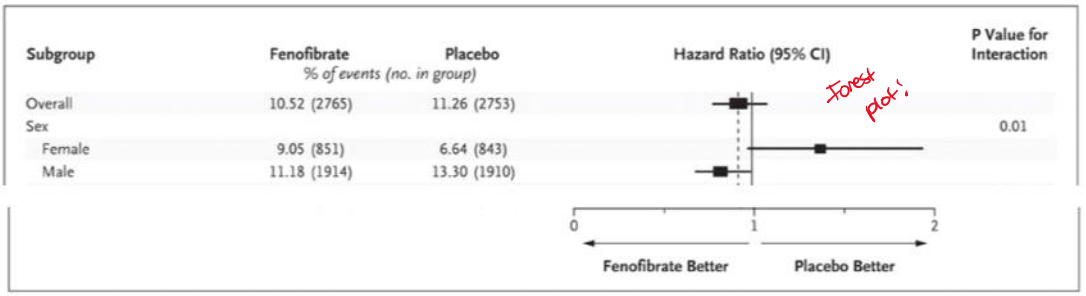
Outcome	Fenofibrate (N=2765)		Placebo (N=2753)		Hazard Ratio (95% CI)	P Value
	no. of events	*rate/yr*	*no. of events*	*rate/yr*		
Primary outcome (major fatal or nonfatal cardiovascular event)	291	2.24	310	2.41	0.92 (0.79–1.08)	0.32*
Secondary outcomes						
Primary outcome plus revascularization or hospitalization for congestive heart failure	641	5.35	667	5.64	0.94 (0.85–1.05)	0.30
Major coronary disease event†	332	2.58	353	2.79	0.92 (0.79–1.07)	0.26
Nonfatal myocardial infarction	173	1.32	186	1.44	0.91 (0.74–1.12)	0.39
Stroke						
Any	51	0.38	48	0.36	1.05 (0.71–1.56)	0.80
Nonfatal	47	0.35	40	0.30	1.17 (0.76–1.78)	0.48
Death						
From any cause	203	1.47	221	1.61	0.91 (0.75–1.10)	0.33*
From cardiovascular cause	99	0.72	114	0.83	0.86 (0.66–1.12)	0.26
Fatal or nonfatal congestive heart failure	120	0.90	143	1.09	0.82 (0.65–1.05)	0.10

Likelihood ratio test?

Sex, see next slide

Source: ACCORD Study Group (2010) NEJM https://www.nejm.org/doi/full/10.1056/nejmoa1001282

Example: Lipid therapy

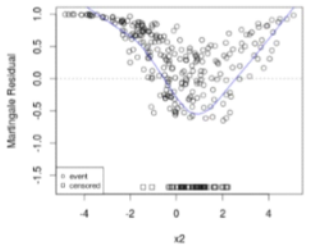


- Results: **Sex** showed evidence of a **significant interaction** according to study group: the primary outcome for men was 11.2% in the fenofibrate group versus 13.3% in the placebo group, whereas the rate for women was 9.1% in the fenofibrate group versus 6.6% in the placebo group (P=0.01 for interaction). This suggests a **benefit for men** and a **possible harm for women**.

Source: ACCORD Study Group (2010) NEJM https://www.nejm.org/doi/full/10.1056/nejmoa1001282

How do we choose the 'right' approach?

- Subject matter knowledge, convention
- Model diagnostics, residual plots
  - **Week 7**
- Model selection procedures
  - AIC, BIC (**Week 7**)



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