Toward Better Practice of Covariate Adjustment in Analyzing Randomized Clinical Trials

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HPTN
HIV Prevention Trials Network
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Outline

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- Covariate adjustment at the design and analysis stages
- Adjustment using linear working models
- Time-to-event outcomes
- Summary

Important: All the results in this talk hold without assuming the models are correct!

Why adjusting for covariates?

EMA (2015) guideline

“Balance of treatment groups with respect to one or more specific prognostic covariates can ***enhance the credibility*** *of the results of the trial”*

FDA (2021) guidance

“Incorporating prognostic baseline factors in the primary statistical analysis of clinical trial data can result in a ***more efficient*** *use of data to demonstrate and quantify the effects of treatment with minimal impact on bias or the Type I error rate”*

➢ At the design stage:
covariate-adaptive randomization

- balance across baseline covariates to gain credibility and efficiency

➢ At the analysis stage:
model-assisted approach

- more efficient use of data under the *same assumption* required by the unadjusted analysis

Design stage: covariate-adaptive randomization

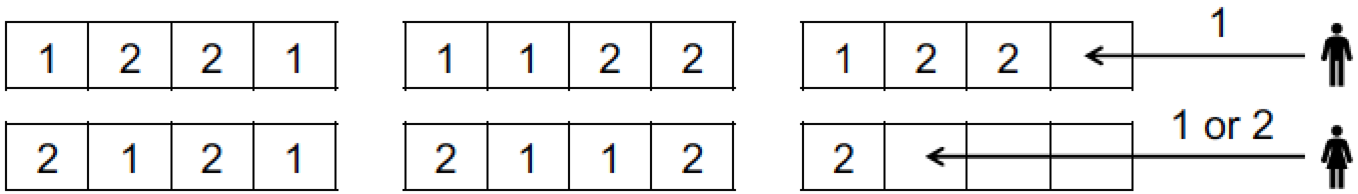
Simple Randomization (SR):

Treatment assignments are completely random

Covariate-Adaptative Randomization (CAR, also known as restricted randomization):

Balance treatment assignments across discrete baseline covariates (stratification variables)

- Example: Pocock-Simon's minimization, stratified urn design, stratified biased coin, stratified permuted-block randomization



Analysis stage: model-assisted approach

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Covariate adjustment in the analysis stage is a statistical method with high potential to improve precision for many trials

- **Pre-planned** adjustment for baseline variables when estimating the treatment effect
- **Target parameter** is the same as when using unadjusted method (e.g., difference in means)
- **Goal** is to avoid making any model assumption beyond what's assumed for the unadjusted method, i.e., **robustness to model misspecification** (FDA 2021)

(e.g., Koch et al. 1998; Yang and Tsiatis, 2001; Rubin and van der Laan, 2008; Tsiatis, 2008; Lin, 2013; Bugni, 2018; Ye and Shao, 2020; Ye et al. 2022)

Example: analysis of covariance (ANCOVA)

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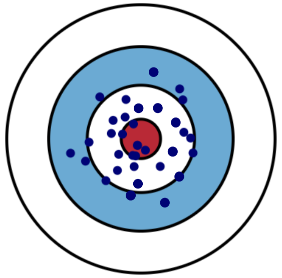
- ❑ Primary endpoint Y: continuous or binary
- ❑ Target parameter: $E(Y|A=1) - E(Y|A=0)$
- ❑ Estimator: $\hat{\theta}$ from fitting a linear model $E(Y|A,X) = \alpha + \theta A + \beta X$

- ➢ When the linear model is **incorrect**:
  - $\hat{\theta}$ still **correctly estimates** $E(Y|A=1) - E(Y|A=0)$
  - However, $\hat{\theta}$ can be **less precise** than simple mean difference $\bar{Y}_1 - \bar{Y}_0$

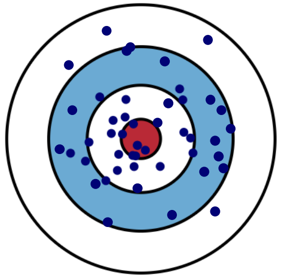
- ➢ Variance estimation should be **robust to model misspecification**

- ➢ Variance estimation should **account for CAR** (FDA, 2021)

Mean Difference



ANCOVA



Proposal: analysis of heterogeneous covariance (ANHECOVA)

- ❑ Primary endpoint Y: continuous or binary
- ❑ Target parameter: $E(Y|A=1) - E(Y|A=0)$
- ❑ Estimator: $\hat{\theta}$ from fitting a linear model $E(Y|A,X) = \alpha + \theta A + \beta X + \gamma A(X - \bar{X})$, with X including indicators of all strata used in CAR

➢ When the linear model is **incorrect**:
- $\hat{\theta}$ still **correctly estimates** $E(Y|A=1) - E(Y|A=0)$
- $\hat{\theta}$ is **never less precise and often more precise** than $\bar{Y}_1 - \bar{Y}_0$

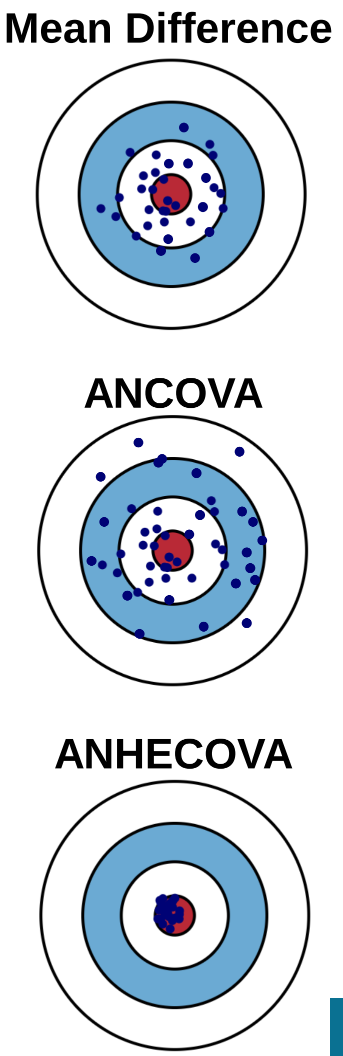
Guaranteed Precision Gain

➢ Variance estimation is (not only) **robust to model misspecification**

Robust Variance Estimation

➢ Variance estimation is (but also) **robust to CAR**

Universal Applicability



Ye, Shao, Yi, Zhao (2022). Toward Better Practice of Covariate Adjustment in Analyzing Randomized Clinical trials. JASA

Time-to-event outcomes (Log-rank Test)

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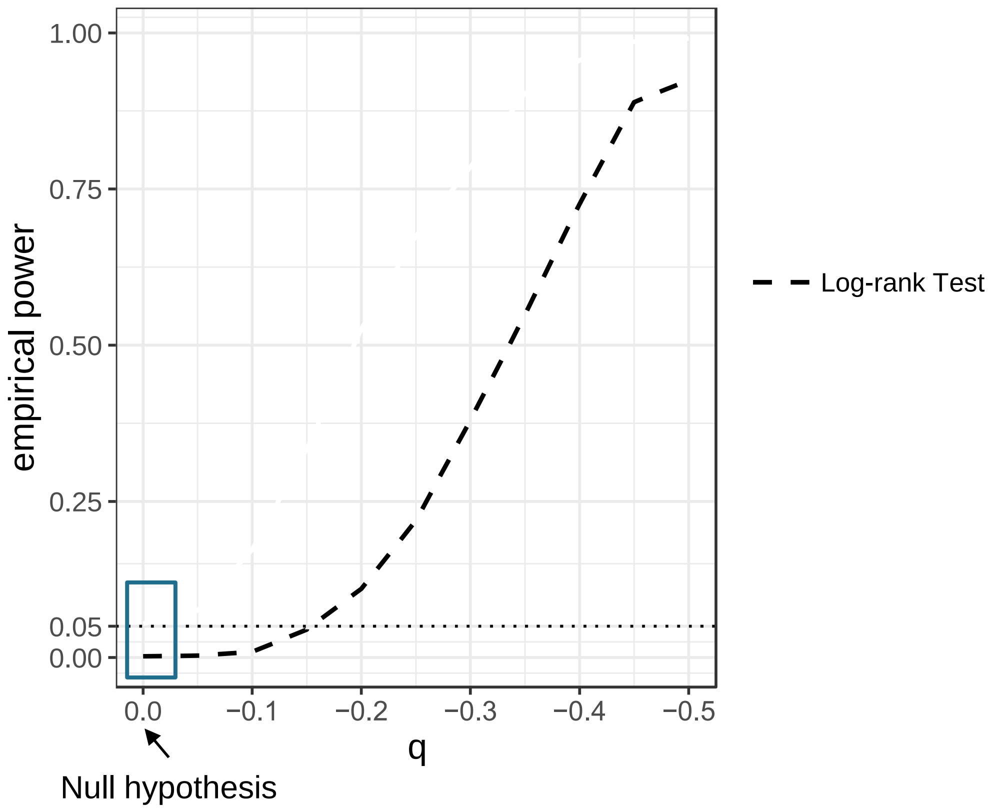
- ❑ Primary endpoint: time-to-event
- ❑ Null Hypothesis $\mathrm{H}_0: \lambda_0(t) = \lambda_1(t)$
- ❑ Test statistics: **Log-rank test**

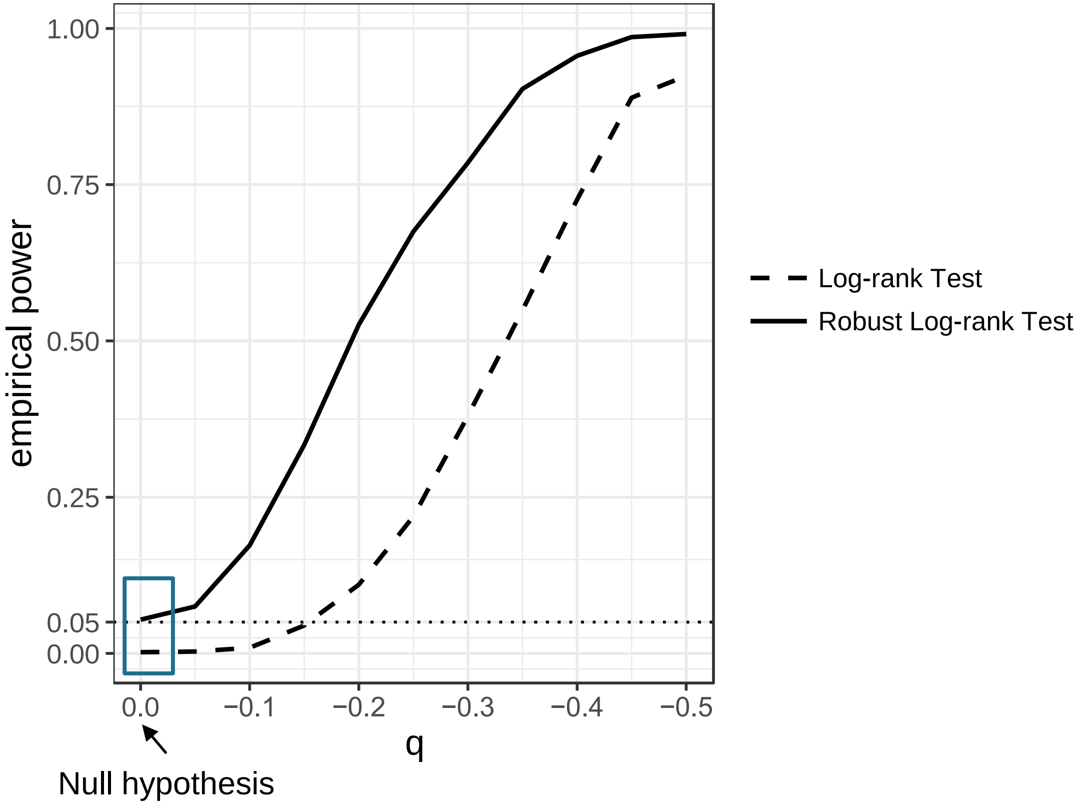
- ➢ Does NOT adjust for any covariate
- ➢ **Conservative** under CAR



Ye and Shao (2020). Robust Tests for Treatment Effect in Survival Analysis under Covariate-Adaptive Randomization. JRSSB

Time-to-event outcomes (Ye-Shao's Robust Log-rank Test)

- Primary endpoint: time-to-event
- Null Hypothesis $\mathrm{H}_0: \lambda_0(t) = \lambda_1(t)$
- Test statistics: Ye-Shao's **Robust log-rank test**

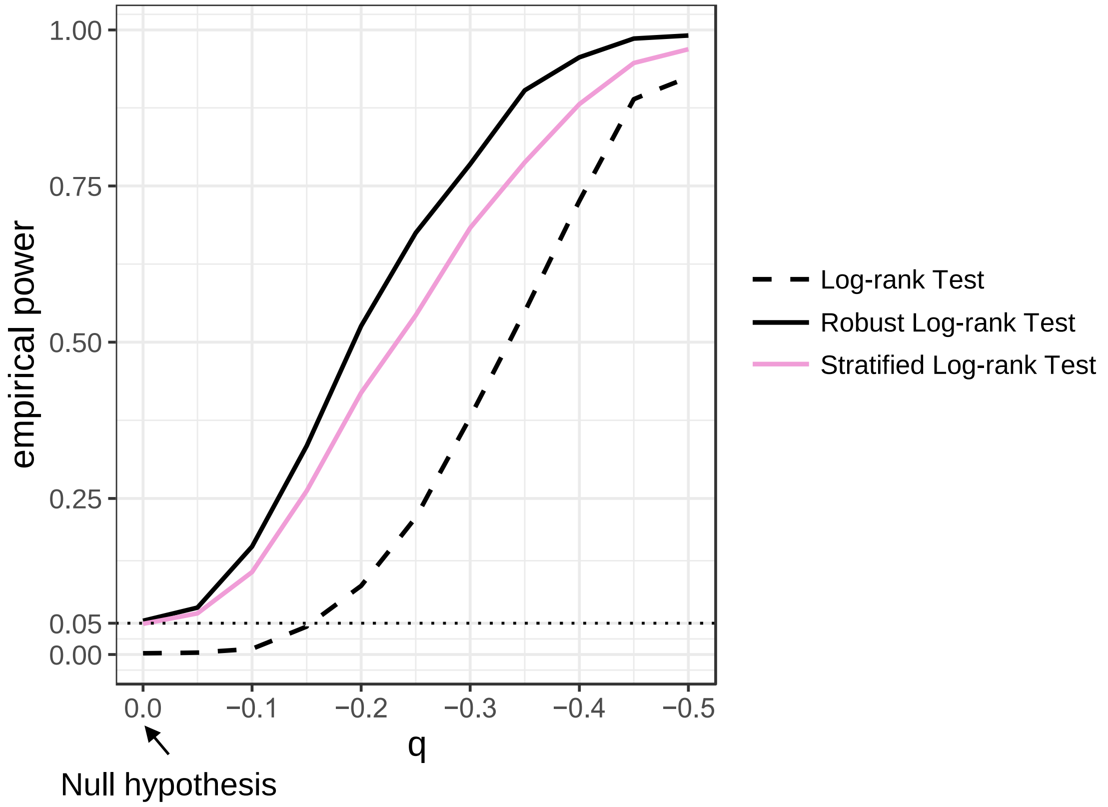


- Does NOT adjust for any covariate
- **Correct** under CAR
  - but NOT universally applicable

Ye and Shao (2020). Robust Tests for Treatment Effect in Survival Analysis under Covariate-Adaptive Randomization. JRSSB

Time-to-event outcomes (Stratified Log-rank test)

- ❑ Primary endpoint: time-to-event
- ❑ Null Hypothesis $\mathrm{H}_0: \lambda_{0z}(t) = \lambda_{1z}(t)$
- ❑ Test statistics: **Stratified Log-rank test**



- ➢ Adjust for discrete covariate
- ➢ **Correct** under CAR
  - **universally applicable**
- ➢ Can be **less powerful** than Ye-Shao's Robust Log-rank Test

Ye and Shao (2020). Robust Tests for Treatment Effect in Survival Analysis under Covariate-Adaptive Randomization. JRSSB

Time-to-event outcomes (Covariate-adjusted Log-rank test)

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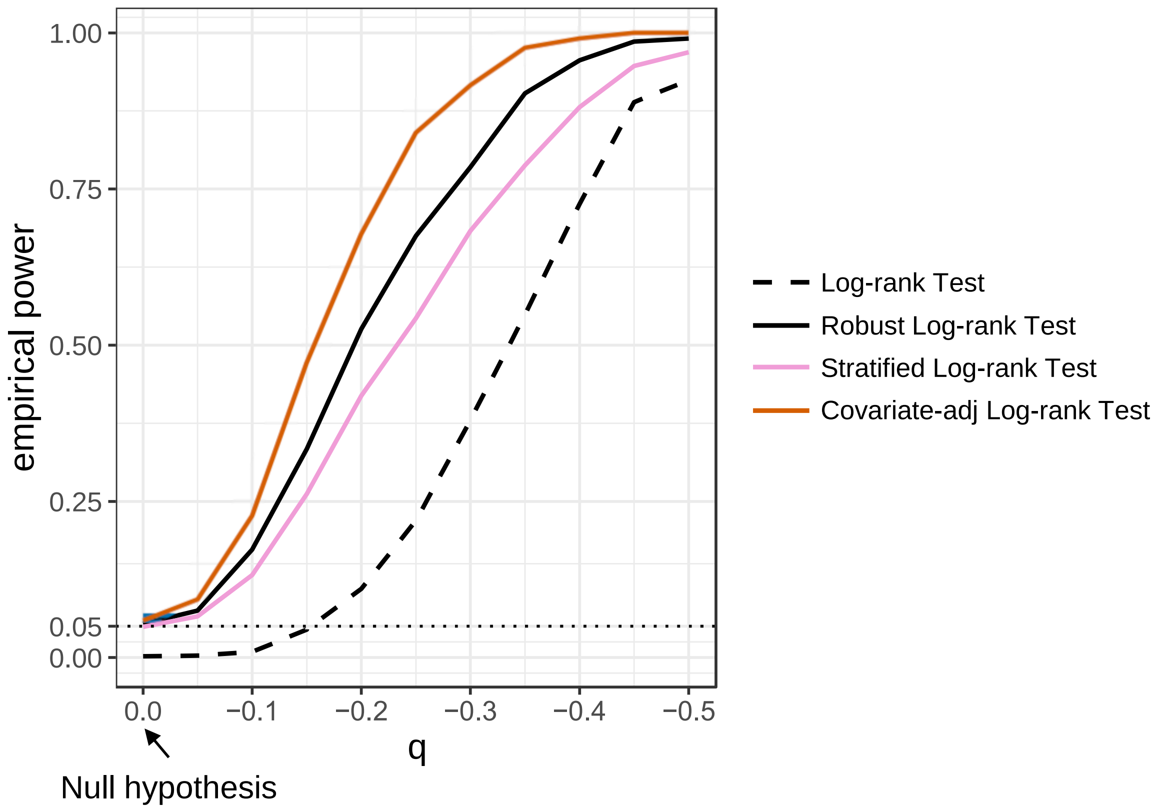
- Primary endpoint: time-to-event
- Null Hypothesis $\mathrm{H}_0: \lambda_0(t) = \lambda_1(t)$
- Test statistics: **Covariate-Adjusted Log-rank test** (apply ANHECOVA to Log-rank test)



➢ Adjust for any covariate

➢ **Correct** under CAR
  - **universally applicable**

Universal Applicability

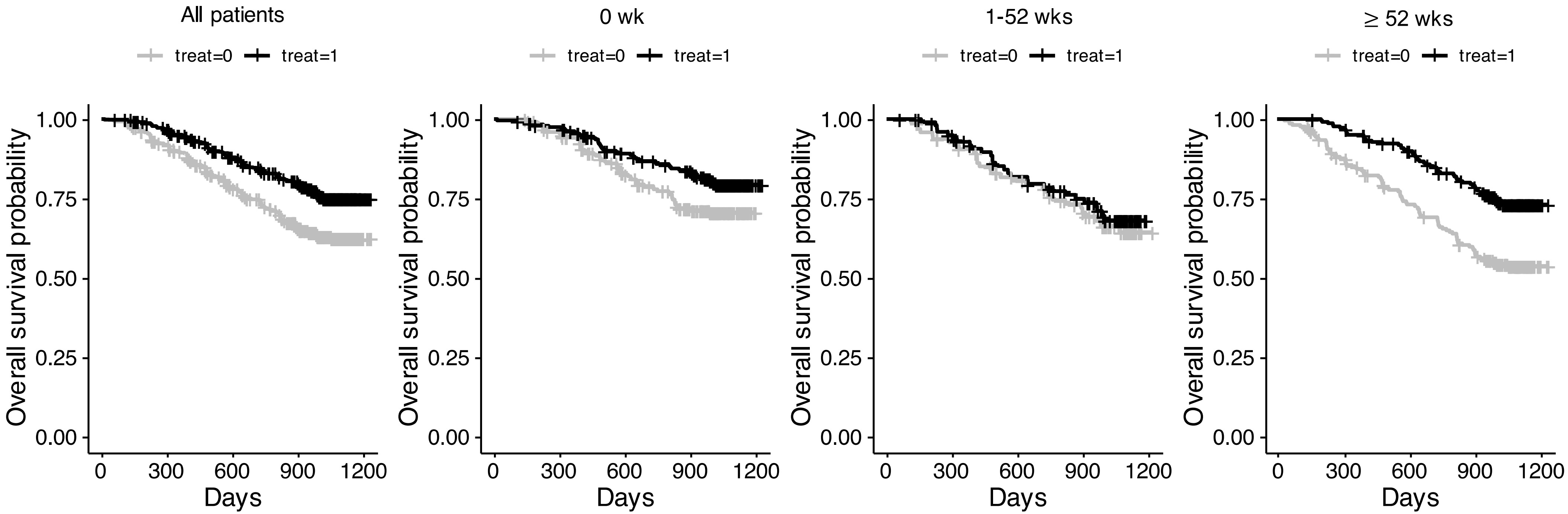
➢ **Never less powerful and often more powerful** than Ye-Shao’s Robust Log-rank Test

Guaranteed Power Gain

Ye, Shao, Yi (2022+). Covariate-Adjusted Log-Rank Test: Guaranteed Efficiency Gain and Universal Applicability. arXiv:2201.11948

Application to ACTG175 (Hammer et al. 1996)

- **Population**: Adults infected with HIV type 1 whose CD4 cell counts were 200-500 per cubic millimeter
- **Primary endpoint**: composite event ($\geq 50\%$ decline in CD4 cell count, an AIDS-defining event, or death)
- **Stratified permuted block randomization**: equal allocation and three strata: 0 week, 1-52 weeks, and ≥ 52 weeks of prior antiretroviral therapy.
- **Treatments**: Zidovudine (control) and Didanosine (treated).
- **Covariates for adjustment**: baseline CD4 cell count and number of days receiving prior antiretroviral therapy.



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	All patients	Sub-group		
		0 wk	1-52 wks	≥ 52 wks
Number of patients	1,093	461	198	434
Log-rank test	$\boxed{4.62}$	2.31	0.53	4.46
Two-sided p-value (adjusted for sub-group analysis)	$\boxed{<0.001}$	0.064	1	<0.001
Covariate-adjusted log-rank test	$\boxed{4.95}$	2.40	0.49	4.90
Two-sided p-value (adjusted for sub-group analysis)	$\boxed{<0.001}$	0.049	1	<0.001

Summary – ANHECOVA and three considerations

- **ANHECOVA: a general covariate adjustment strategy**
  - Adjust for indicators of all strata used in CAR and all treatment-by-covariate interactions

1. **Guaranteed Precision Gain**
   - ANHECOVA does no harm

2. **Robust Variance Estimation**
   - We recommend using variance estimators that are robust to model misspecification

3. **Universal Applicability**
   - Variance estimator for ANHECOVA can be universally used under SR and all CAR

R package [RobinCar] is available on GitHub.

Acknowledgments

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