A TUTORIAL ON ACCOUNTING FOR COMPETING RISKS IN SURVIVAL ANALYSIS

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OUTLINE

- Background
  - When does the problem occur, when does it matter?
- Methods and illustrations
  - Survival curves and other graphical methods
  - Regression models
  - Number-needed-to-treat (NNT)
- Interpretation
  - Cause-specific hazard versus sub-distribution hazard:
    - which to use and when?
- Discussion
  - Best practices and caveats
  - Limitations and research gaps
  - Further reading and resources

BACKGROUND

- Clinical research studies often record the time to more than one outcome:
  - Examples: death, cardiovascular disease (CVD), end stage renal disease (ESRD)
- A competing event is one that precludes the occurrence of the event of interest:
  - Example: after transplant or death, patient is no longer at risk for primary outcome of interest (ESRD or CVD).

BACKGROUND, CONTINUED

- If a patient experiences a competing event, standard survival analysis methods treat that patient as *censored* for the outcome of interest (e.g., ESRD or CVD).
- Why is this a problem?
  - Kaplan-Meier curves overestimate the incidence of the outcome over time
  - Cox models inflate the relative differences between groups, resulting in biased hazard ratios

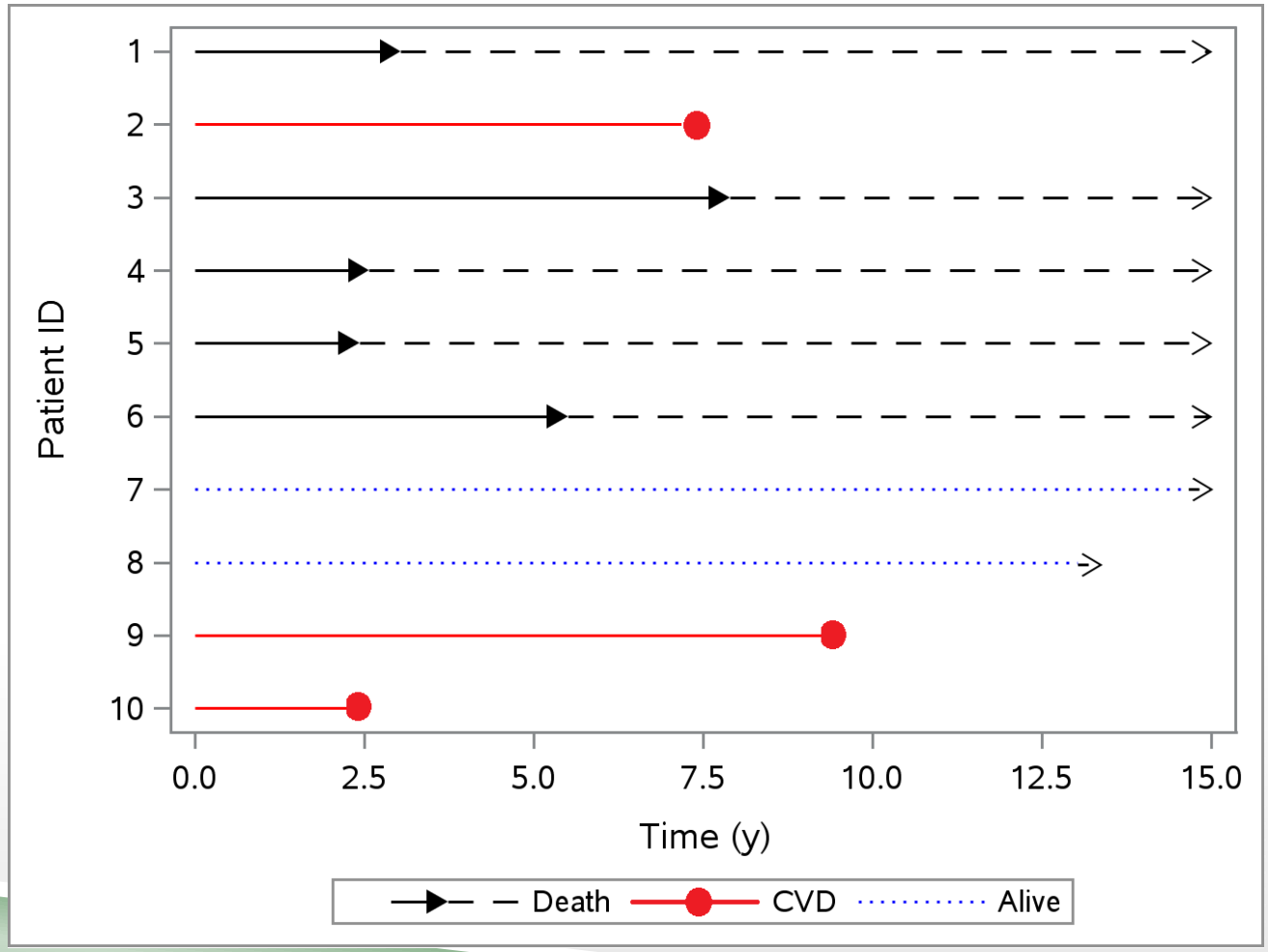
ALTERNATIVES TO STANDARD METHODS:

- **Survival curves:** Cumulative Incidence Function (CIF)
  - Non-parametric CIF
  - Fine-Gray (1999) CIF
  - Inverse probability weighting (IPW) corrected Kaplan-Meier

- **Options for regression models:**
  - Sub-distribution hazard ratio (SHR)
    - Fine-Gray (1999)
    - Klein-Andersen (2005)
  - Cause-specific hazard ratio (CHR)

- **Number-needed-to-treat (NNT):**
  - Gouskova et al (2014)

FINE-GRAY (FG) MODEL



METHODS:
PLOTTING THE CUMULATIVE INCIDENCE

- In each case, we code the event categories as follows:
  - event=0: censored, event=1: outcome of interest, event=2: competing event.

	Non-parametric:	Fine-Gray:
SAS	proc lifetest; time year*event(0) / eventcode=1; run;	proc phreg; model year*event(0)=x / eventcode=1; run;
Stata	stset year, failure(event==1) stcrreg , compete(event==2) stcurve, cif	stset year, failure(event==1) stcrreg x, compete(event==2) stcurve, cif
R	library(cmprsk) plot (cuminc (year, event, cencode=0))	library(cmprsk) result<- crr(year, event, x, failcode=1, cencode=0) plot(predict(result, x))

ILLUSTRATION:

NON PARAMETRIC ESTIMATION GIVES VISUAL COMPARISON OF CUMULATIVE RISK OF CVD AND DEATH:

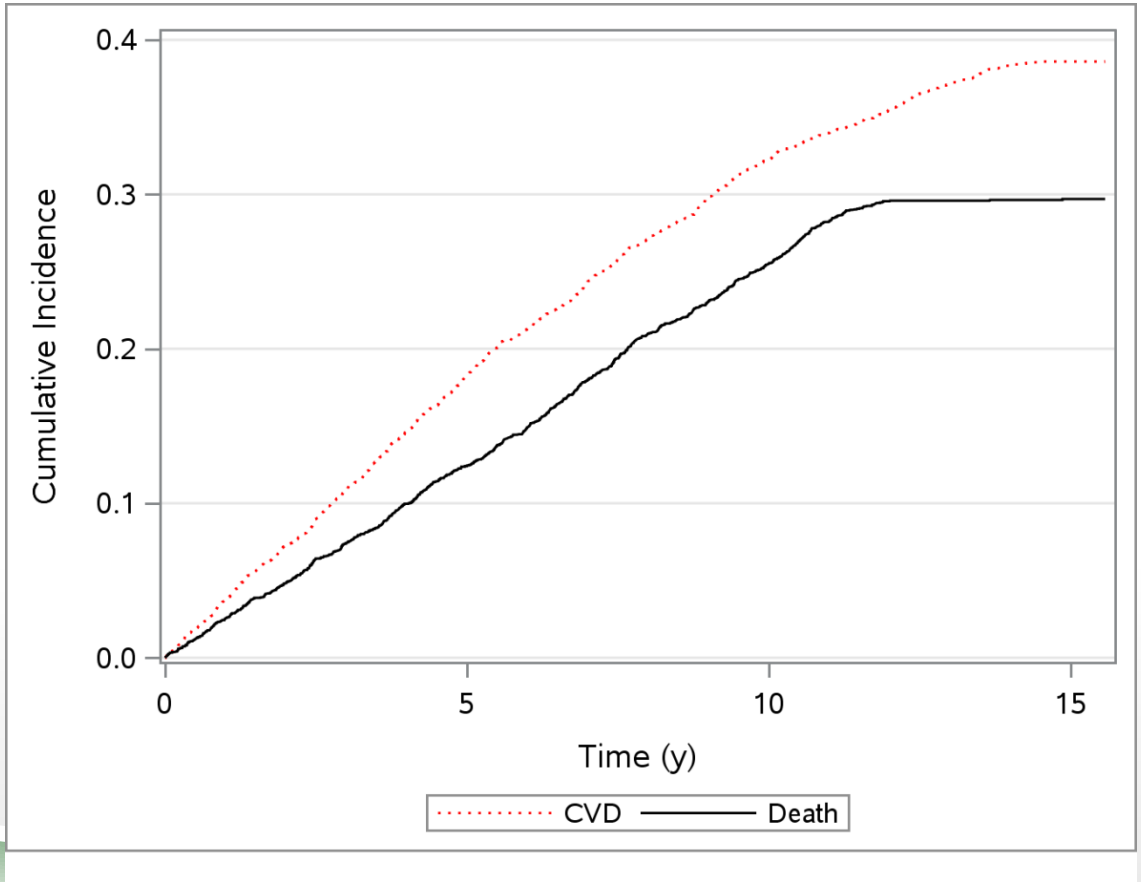


ILLUSTRATION:

COMPARISON OF CUMULATIVE INCIDENCE ESTIMATES BY WALKING SPEED, CVD VS. DEATH:

METHODS:

CALCULATION OF SUB-DISTRIBUTION HAZARD RATIO (SHR):

- Stata:
  - stset year, id(idno) failure (event==1)
  - stcrreg x, compete(event==2)
- SAS:
  - proc phreg;
  - model year*event(0)=x / eventcode=1;
  - run;
- R:
  - library(cmprsk)
  - crr(year, event, x, failcode=1,censcode=0)

METHODS:

CALCULATION OF CAUSE-SPECIFIC HAZARD RATIO (CHR)

- Stata:
  - stset year, id(idno) failure (event==1)
  - stcox x
- SAS:
  - proc phreg;
  - model year*event(0,2)=x / eventcode=1;
  - run;
- R:
  - coxph(formula=Surv (year, event=="1") ~x)

COMPARISON OF MODELS SHOWS INFLATED HAZARD RATIOS FOR COX CHR VERSUS FG SHR

- Example 1: slower walking speed and risk of CVD

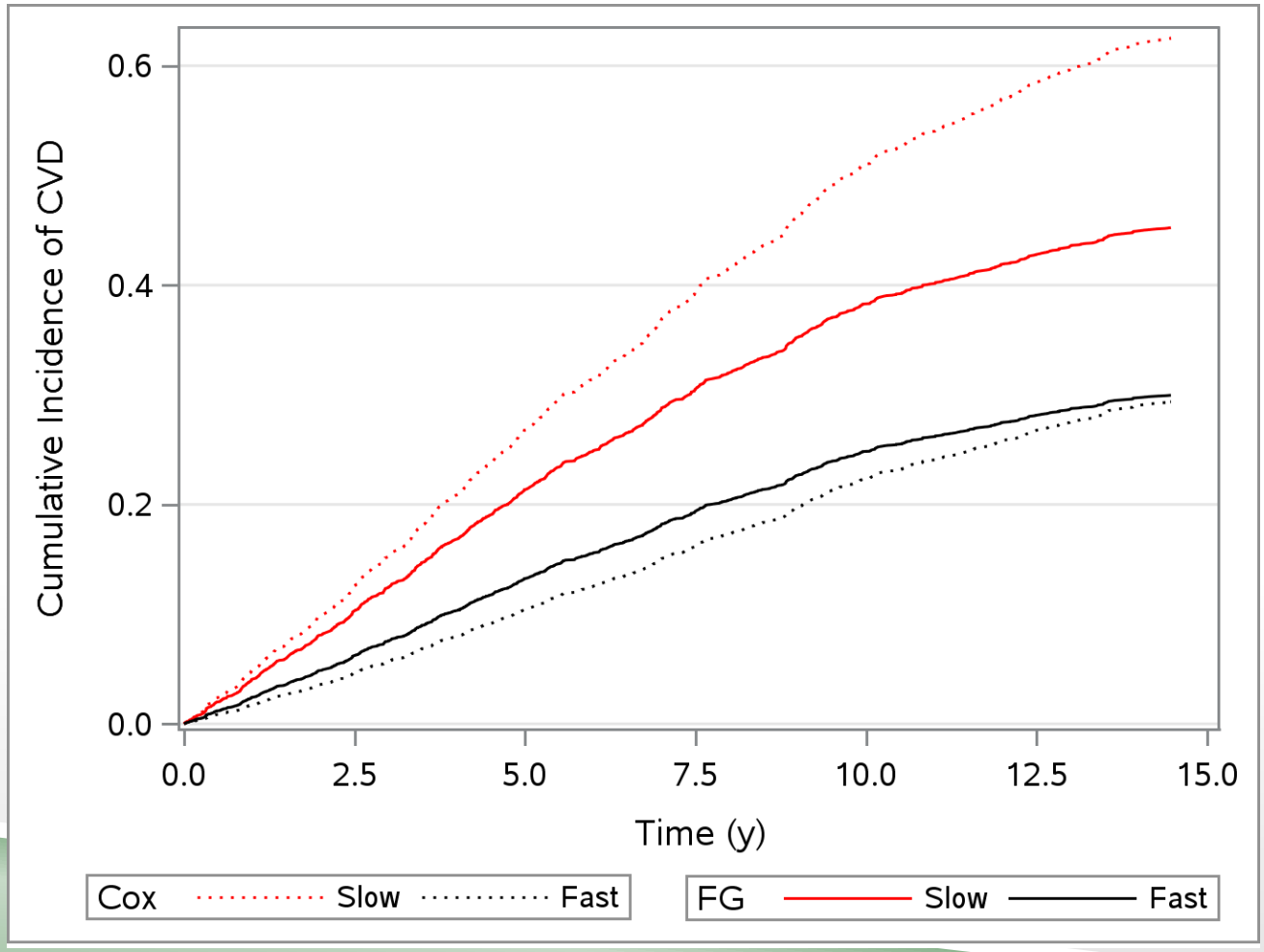
Method	Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
Fine-Gray SHR	1.69	1.29	2.21	0.0001
Cox CSH	2.82	2.12	3.76	<.0001

- Example 2: elevated biomarker and risk of ESRD

Method	Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
Fine-Gray SHR	1.15	1.09	1.22	<.0001
Cox CSH	1.18	1.11	1.25	<.0001

ILLUSTRATION:

COMPARISON OF CUMULATIVE CVD INCIDENCE ESTIMATES BY WALKING SPEED, COX VERSUS FINE-GRAY MODEL:



METHODS:
NUMBER-NEEDED-TO TREAT (NNT)

- NNT is the reciprocal of the absolute risk difference:
  - Example: AR=5% => NNT=20, means that treating 20 patients would prevent one case of disease

- In the presence of competing risks, Gouskova et al (2014) define the NNT at time t using the CIF from the Fine-Gray model :

$$NNT(t) = \frac{1}{CIF^{Ctl}(t) - CIF^{Trt}(t)}$$

METHODS:

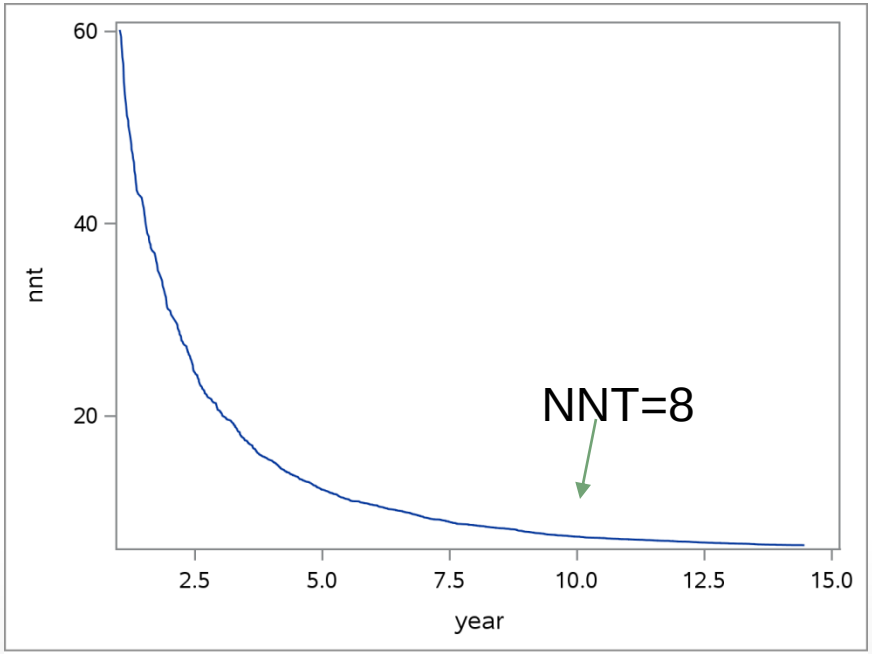
ESTIMATE NNT USING CIF FROM FINE-GRAY MODEL:

- Example 1: Suppose a drug is available that can increase walking speed. How many patients must we treat to prevent CVD, in the presence of competing risk of death?
  - CIF for slow walkers at year 10 = 0.38
  - CIF for fast walkers at year 10 = 0.25
  - AR = 0.38 – 0.25 = 0.13 => NNT at 10 years = 8
- Example 2: Suppose a drug is available that can reduce biomarker levels. How many patients must we treat to prevent ESRD, in the presence of competing risk of death?
  - CIF for elevated biomarker at year 5 = 0.117
  - CIF for normal biomarker at year 5 = 0.102
  - AR = 0.015 => NNT at 5 years = 67

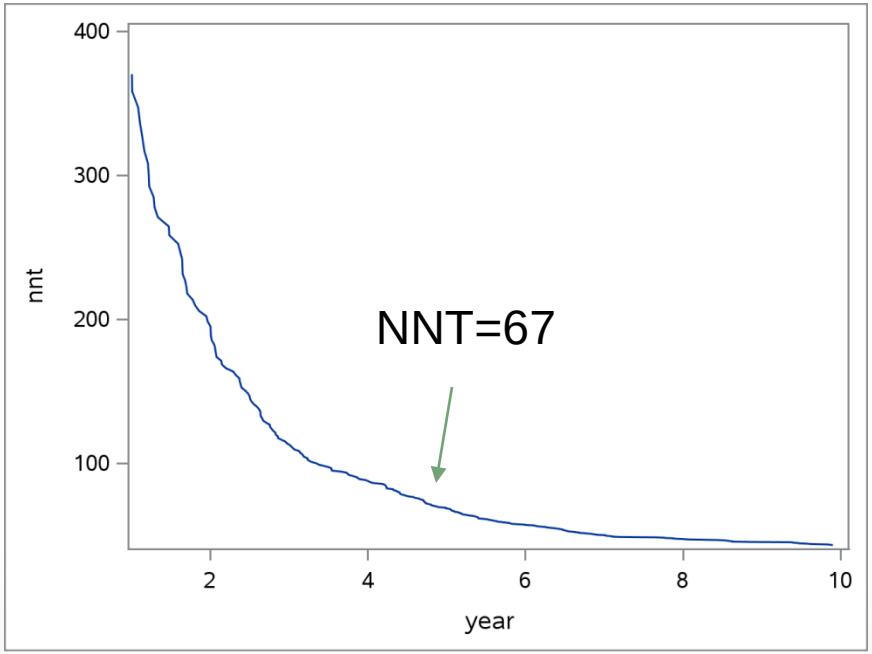
ILLUSTRATION:

ESTIMATION OF NNT OVER TIME:

Example 1: walk speed and CVD



Example 2: biomarker and ESRD



WHEN DO COX AND FG RESULTS DIFFER?

- If competing event is frequent
- If competing event occurs early
- Effect of censoring proportion …
- Effect of event time correlation …

Table 4

Comparison of competing risks regression models examining treatment and two covariates for competing outcomes in prostate cancer (RTOG 8610)

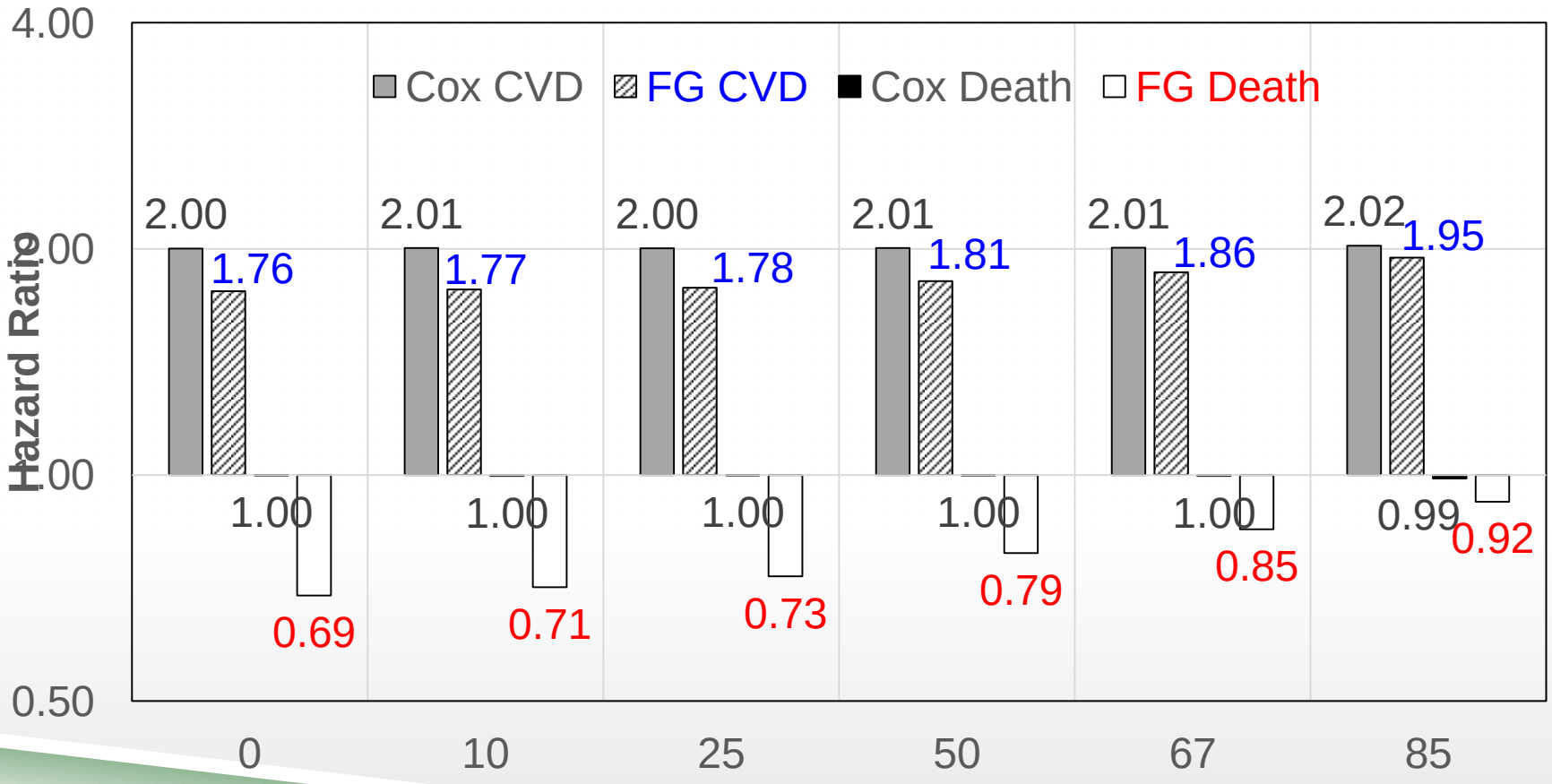
	Model Effect Estimates					
	Cox CSH		Fine-Gray SDH		Klein-Andersen	
Event type (death)	**CHR**	**95% CI**	**SHR**	**95% CI**	**SHR**	**95% CI**
A. Prostate Cancer						
ADT (vs RT only)	0.67	0.49–0.92	0.66	0.48–0.91	0.67	0.49–0.93
Age*	0.89	0.71–1.13	0.75	0.60–0.95	0.79	0.63–1.00
Grade 2 vs 1	1.84	1.04–3.23	1.83	1.05–3.17	1.87	1.06–3.31
Grade 3 vs 1	2.87	1.66–4.98	2.83	1.65–4.87	2.94	1.70–5.08
B. Other causes						
ADT (vs RT only)	1.13	0.85–1.51	1.26	0.95–1.68	1.20	0.89–1.61
Age	2.02	1.60–2.57	1.93	1.54–2.43	1.88	1.49–2.38
Grade 2 vs 1	0.87	0.59–1.28	0.75	0.52–1.08	0.82	0.56–1.20
Grade 3 vs 1	0.91	0.62–1.35	0.60	0.41–0.87	0.61	0.41–0.90
All deaths						
ADT (vs RT only)	0.88	0.71–1.09	-	-	-	-
Age	1.36	1.15–1.61	-	-	-	-
Grade 2 vs 1	1.13	0.83–1.55	-	-	-	-
Grade 3 vs 1	1.44	1.06–1.97	-	-	-	-

* per 10 year increment in age

Adapted from T4, Dignam et al. 2012, Clin Cancer Res

EFFECT OF CENSORING ON HR:

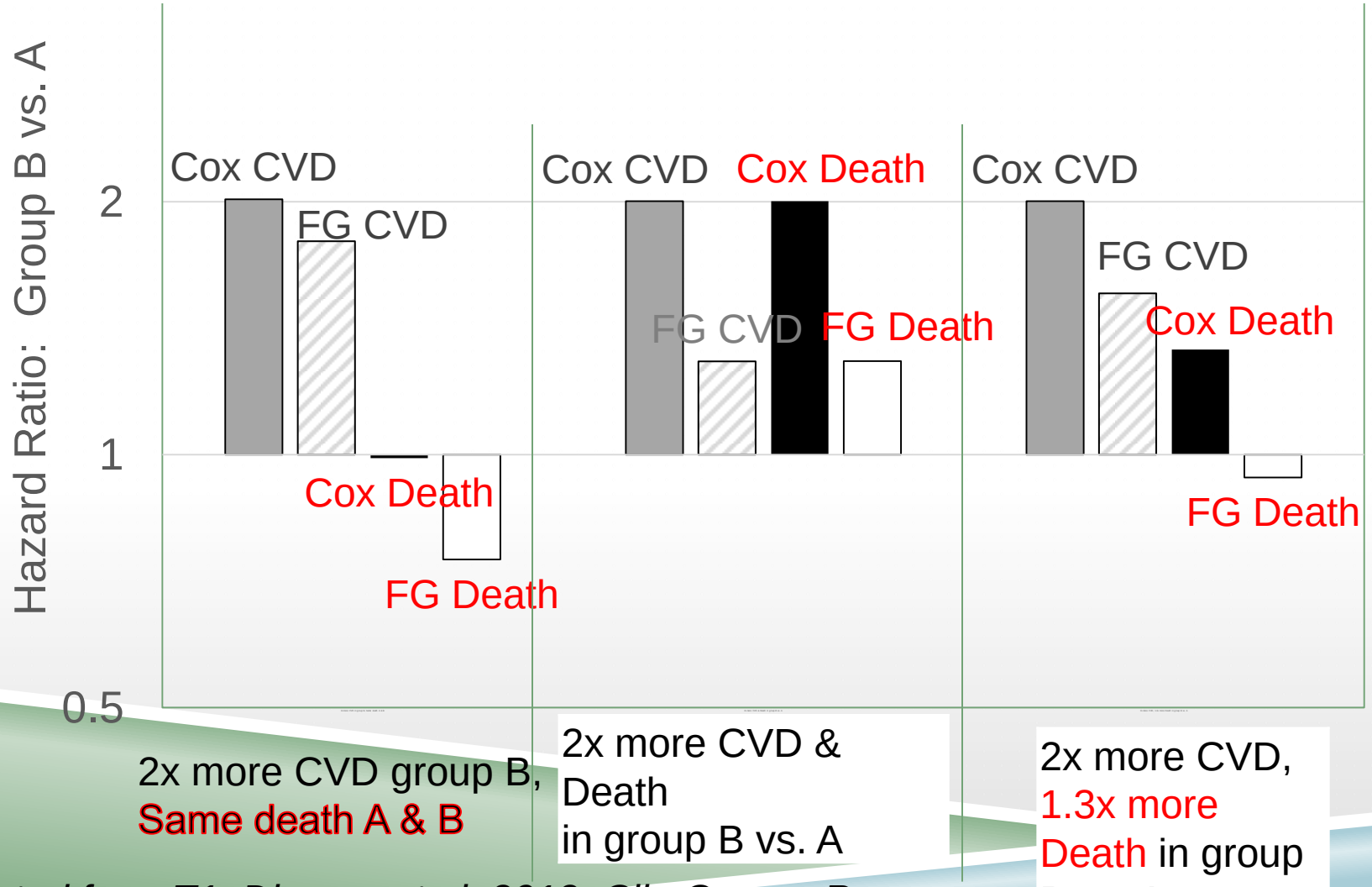
Scenario: 2x CVD rate in Group B vs. Group A, same death rate in both groups



Adapted from T3, Dignam et al. 2012, Clin Cancer Res

INDEPENDENT EVENT TIMES:

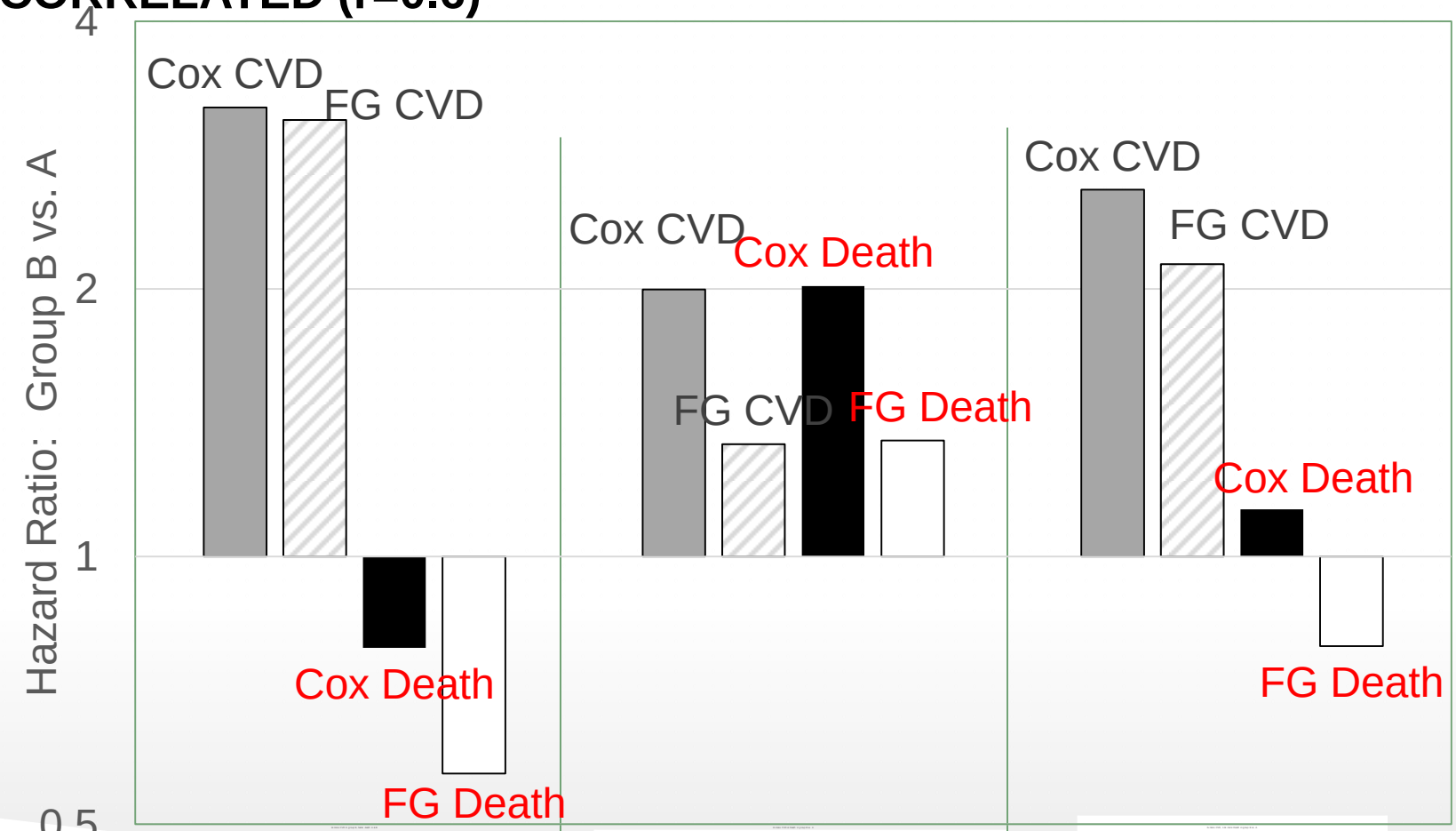
SCENARIO 1: 33% CENSORING, CVD & DEATH EVENT TIMES UNCORRELATED



Adapted from T1, Dignam et al. 2012, Clin Cancer Res

CORRELATED EVENT TIMES

SCENARIO 2: 33% CENSORING, CVD & DEATH EVENT TIMES CORRELATED (r=0.6)



Adapted from T2, Dignam et al. 2012, Clin Cancer Res

Recommendations for Analyzing Competing Risk Survival Data

- Cumulative incidence functions (CIFs) should be used to estimate the incidence of each of the different types of competing risks. Do not use the Kaplan-Meier estimate of the survival function for this purpose.
- Researchers need to decide whether the research objective is on addressing etiologic questions or on estimating incidence or predicting prognosis.
- Use the Fine-Gray subdistribution hazard model when the focus is on estimating incidence or predicting prognosis in the presence of competing risks.
- Use the cause-specific hazard model when the focus is on addressing etiologic questions.
- In some settings, both types of regression models should be estimated for each of the competing risks to permit a full understanding of the effect of covariates on the incidence and the rate of occurrence of each outcome.

Austin et al, 2016

DISCUSSION

- Caveats:
  - Interpretation can be difficult: effect of covariate on CSH may be different (even opposite!) effect on incidence.
  - Still need to check proportional hazard assumption, just as with ordinary Cox models
  - Non-informative censoring assumption:
    - probability of event should be unrelated to mechanism of censoring
    - length of follow-up should not depend on a patient's medical condition
- Best practices:
  - Do the usual regression checks: check for outliers and influential data points, assess linearity, collinearity, etc.
  - Use CIF plots and other visualization to examine covariate effects for each event type

DISCUSSION

- Limitations:
  - When running competing risk models, standard software has fewer options for stratification, shared frailty, tests of model fit, and variable selection methods.
- Research and software gaps:
  - Optimal method for reweighting
  - Left or interval censoring and truncation
  - Censoring assumptions: effect of competing risk on subsequent events (preclude versus change probability)

FURTHER READING AND RESOURCES

- Software:
  - https://cran.r-project.org/web/packages/cmprsk/cmprsk.pdf
  - www.stata.com/manuals13/ststcrreg.pdf
  - https://support.sas.com/rnd/app/stat/papers/2014/competingrisk2014.pdf
  - https://cran.r-project.org/web/packages/mstate/vignettes/Tutorial.pdf

- References:

  - Peter C. Austin, Douglas S. Lee and Jason P. Fine**.** Introduction to the Analysis of Survival Data in the Presence of Competing Risks *Circulation*. 2016;133:601-609, originally published February 8, 2016
  - Dignam JJ, Zhang Q, Kocherginsky MN. The Use and Interpretation of Competing Risks Regression Models. *Clinical Cancer Research*. 2012;18(8):2301-2308.
  - Marlies Noordzij, Karen Leffondré, Karlijn J. van Stralen, Carmine Zoccali, Friedo W. Dekker, Kitty J. Jager; When do we need competing risks methods for survival analysis in nephrology?. *Nephrol Dial Transplant* 2013; 28 (11): 2670-2677.
  - Wolbers M, Koller MT, Stel VS, Schaer B, Jager KJ, Leffondré K, Heinze G. Competing risks analyses: objectives and approaches. *European heart journal.* 2014; 35: 2936-2941.
  - Zhou, Bingqing, et al. “Competing risks regression for stratified data.” *Biometrics* 67.2 (2011): 661-670.
  - Zhou, Bingqing, et al. “Competing risks regression for clustered data.” *Biostatistics* 13.3 (2012): 371-383.