

**ESTIMATING THE PROPORTION OF
TREATMENT EFFECT EXPLAINED
BY A SURROGATE MARKER**

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In Collaboration with

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Laboratory markers
(CD4, RNA)

INTRODUCTION

Clinical events
(disease, death)

Surrogate vs. True Endpoints

Prentice Criteria ('89, SIM) $\left\{ \begin{array}{l} X \perp Z \Rightarrow X \perp T \\ X \not\perp Z \Rightarrow X \not\perp T \end{array} \right. \Rightarrow \frac{X \perp T | Z}{Z \not\perp T}$

PTE

X = treatment
 Z = surrogate marker
 T = clinical event

ACTG 019 Study (Choi et al., '93, AIM)

Binary endpoint (Freedman et al., '92, SIM)

Failure time endpoint (Lin et al., '97, SIM)

Interpretation/limitations (DeGruttola et al., '97, JID)

Examples (Fleming & DeMets, 1996, AIM)

- Cardiology
- Cancer
- HIV/AIDS²

- Osteoporosis in postmenopausal women (Riggs et al., '90, NEJM)
Sodium fluoride: bone mineral density \uparrow , fractures \uparrow

METHODS

Models

$$\lambda(t|X) = \lambda_0(t)e^{\beta X}$$

$$\lambda(t|X, Z) = \tilde{\lambda}_0(t)e^{\beta_a X + \gamma' Z(t)}$$

X = treatment indicator

$Z(t)$ = surrogate marker

β = treatment effect

β_a = adjusted treatment effect

γ = effect of surrogate marker

PTE

$$p = 1 - \frac{\beta_a}{\beta} = \frac{\beta - \beta_a}{\beta}$$

$$\left\{ \begin{array}{l} \text{logit} \{ \Pr(T=1|X) \} = \alpha + \beta X \\ \text{logit} \{ \Pr(T=1|X, Z) \} = \tilde{\alpha} + \beta_a X + \gamma' Z \end{array} \right. \quad 3$$

$\beta_a =$ adjusted treatment effect
 $\beta =$ (unadjusted) treatment effect

Do Models Hold?

Only for rare events or weak markers

Is p a True Proportion?

$$p = 1 - \frac{\beta_a}{\beta}$$

$$0 \leq p \leq 1 \Leftrightarrow 0 \leq \beta_a/\beta \leq 1 \Leftrightarrow \beta_a\beta > 0, |\beta_a| \leq |\beta|$$

$$\beta_a > \beta > 0 \Rightarrow p < 0$$

$$\beta > 0, \beta_a < 0 \Rightarrow p > 1$$

$$Z \sim N(\mu_X, 1) \Rightarrow \beta_a = \beta - \gamma(\mu_1 - \mu_0)$$

Estimation of p $p = 1 - \frac{\beta_a}{\beta}$

$$\hat{p} = 1 - \frac{\hat{\beta}_a}{\hat{\beta}}$$

$$\hat{p} \sim N(p, \sigma^2)$$

$$\sigma^2 = \frac{\text{var}(\hat{\beta}_a)}{\beta^2} + \frac{\beta_a^2 \text{var}(\hat{\beta})}{\beta^4} - 2 \frac{\beta_a \text{cov}(\hat{\beta}, \hat{\beta}_a)}{\beta^3}$$

Model misspecification \Rightarrow robust variances (Lin & Wei, '89, JASA)

$\text{cov}(\hat{\beta}, \hat{\beta}_a)$ = covariance between marginal sub-models of bivariate failure times (Wei, Lin & Weissefeld, '89, JASA)

$$(\tilde{T}_i, \delta_i, X_i) \quad (i=1, \dots, n)$$

$$(\tilde{T}_i, \delta_i, X_i, Z_i) \quad (i=1, \dots, n)$$

S-Plus, SAS, STATAS, MULCOX2

(non-zero initial values)

$$\sigma^2 = \frac{\text{var}(\hat{\beta})}{\beta^2} \left\{ \frac{\text{var}(\hat{\beta}_a)}{\text{var}(\hat{\beta})} + (1-p)^2 - 2(1-p) \frac{\text{cov}(\hat{\beta}, \hat{\beta}_a)}{\text{var}(\hat{\beta})} \right\}$$

$$\text{var}(\hat{\beta}) \approx \text{var}(\hat{\beta}_a) \approx \text{cov}(\hat{\beta}, \hat{\beta}_a) \Rightarrow \frac{\sigma}{|p|} \approx \frac{\text{se}(\hat{\beta})}{|\beta|}$$

$$p = 1 \Rightarrow \sigma = \text{se}(\hat{\beta}_a) / |\beta|$$

95% CI

δ method: $\hat{p} \pm 1.96 * se(\hat{p})$

Fieller's method: requires $|\hat{\beta}/se(\hat{\beta})| > 1.96$

$$\Pr (p_L > f | p = 1) \approx \Phi \left\{ (1 - f) \frac{\beta}{se(\hat{\beta}_a)} - 1.96 \right\}$$

	$\beta/se(\hat{\beta}_a)$				
	2	4	6	8	10
$f = 0.5$	0.169	0.516	0.851	0.979	0.999
$f = 0.75$	0.072	0.169	0.323	0.516	0.705

SIMULATION STUDIES

$$\Pr(X = 1) = 1/2$$

$$Z \sim N(\mu_X, 1)$$

$$\lambda(t|X, Z) = e^{\beta_a X + \gamma Z}$$



$$\beta = \beta_a + \gamma(\mu_1 - \mu_0)$$

$$\text{Censoring} \sim U[0, \tau]$$

$$\mu_0 = 0, \mu_1 = 2$$

$$\beta_a = 1$$

$$\gamma = \{0.25, 0.5, 1\}$$

$$\beta \approx (1.5, 2, 3)$$

$$p \approx (1/3, 1/2, 2/3)$$

τ = lower 25th percentile of T (85% censoring)

ACTG 019 STUDY

Placebo-controlled, double-blind, randomized trial on the efficacy of zidovudine for asymptomatic HIV-infected persons

$n = 1075$: 350 on placebo, 725 on zidovudine.

Maximum followup = 90 weeks

44 patients progressed to AIDS: 24 on placebo, 20 on zidovudine

Two-sided p -value for log-rank test = 0.04

Surrogate markers = CD4 measures at week 16

True endpoint = development of AIDS

Progression to AIDS After Week 16

Surrogate	\hat{p}	se(\hat{p})	95% CI
CD4 Count	0.46	0.31	(-0.14, 1.08)
Net CD%	0.74	0.47	(-0.20, 1.65)

Progression to AIDS After Randomization

Surrogate	\hat{p}	se(\hat{p})	95% CI
CD4 Count	0.19	0.16	(-0.13, 0.51)
Net CD%	0.38	0.22	(-0.05, 0.81)

DISCUSSION

p is a useful measure

\hat{p} is highly variable

No strong evidence of large p for CD4 or RNA

p is only part of the story

Statistics is of limited use

CD4⁺ Lymphocytes Are an Incomplete Surrogate Marker for Clinical Progression in Persons with Asymptomatic HIV Infection Taking Zidovudine

Sungsub Choi, PhD; Stephen W. Lagakos, PhD; Robert T. Schooley, MD; and Paul A. Volberding, MD

Table 4. Effect of Zidovudine in Delaying Subsequent Progression to AIDS in Patients Who Had Not Progressed by 16 Weeks, Adjusted for Its Effect on CD4⁺ Lymphocyte Levels

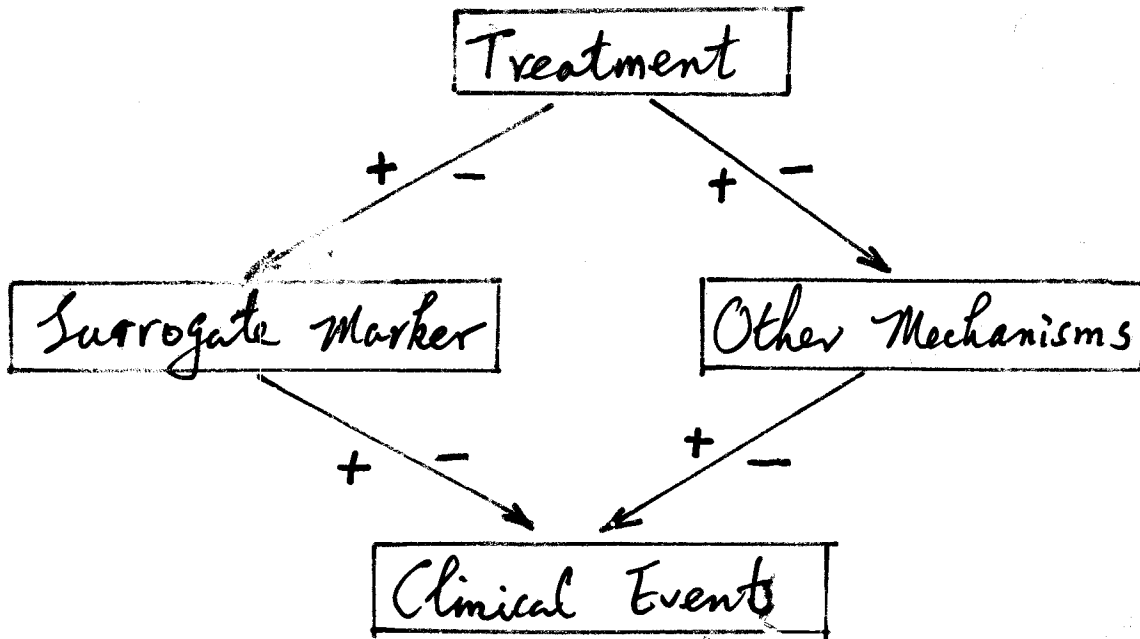
Adjustment for CD4 ⁺ Lymphocyte Levels at Week 16	Placebo-Zidovudine Relative Risk (95% CI)	P Value
None	1.70 (0.89 to 3.22)	0.11
CD4 ⁺ cell count	1.33 (0.70 to 2.51)	46% >0.2
Net CD4 ⁺ percent	1.15 (0.61 to 2.19)	74% >0.2

By week 16, significant differences ($P = 0.01$) in markers had developed between the treatment groups; for example, the median CD4⁺ cell count was 341/mm³ in the placebo group and 376/mm³ in the zidovudine groups. Table 4 shows that 46% of zidovudine's subsequent effect was explainable by the higher CD4⁺ cell counts in the zidovudine groups at that time. Including CD4⁺ cell counts beyond week 16 did not make any notable improvement. A stronger relation was observed for net CD4⁺ percent, which explained 74% of zidovudine's effect on subsequent progression to AIDS.

$$\frac{\log 1.70 - \log 1.33}{\log 1.70} = 46\%$$

$$\frac{\log 1.70 - \log 1.15}{\log 1.70} = 74\%$$

(Multiple) Mechanisms of Action



+ favorable effect

- unfavorable effect

Table 2.

Summary Statistics for the Simulation Studies

	$\gamma = 0.25$			$\gamma = 0.5$			$\gamma = 1$		
	$n = 250$	500	1000	$n = 250$	500	1000	$n = 250$	500	1000
mean($\hat{\beta}$)	1.56	1.52	1.50	2.15	2.01	1.97	3.47	2.91	2.78
s.e. ($\hat{\beta}$)	0.47	0.31	0.22	1.10	0.37	0.26	2.47	1.03	0.35
mean($\hat{\beta}_u$)	1.07	1.03	1.01	1.18	1.05	1.02	1.69	1.16	1.04
s.e. ($\hat{\beta}_u$)	0.58	0.38	0.28	1.17	0.43	0.31	2.48	1.05	0.39
corr($\hat{\beta}, \hat{\beta}_u$)	0.80	0.79	0.81	0.96	0.84	0.85	0.99	0.98	0.91
mean(\hat{p})	0.35	0.33	0.33	0.50	0.49	0.49	0.62	0.63	0.64
s.e. (\hat{p})	0.31	0.17	0.13	0.24	0.15	0.11	0.22	0.14	0.10
mean($\hat{\sigma}$)	0.28	0.18	0.13	0.22	0.15	0.11	0.19	0.13	0.09
mean width of 95% C.I.									
δ -method	1.11	0.72	0.50	0.87	0.60	0.42	0.73	0.52	0.37
Fieller's method	1.69	0.84	0.52	1.30	0.66	0.44	0.90	0.57	0.38
coverage of 95% C.I.									
δ -method	0.96	0.96	0.96	0.94	0.95	0.95	0.90	0.94	0.94
Fieller's method	0.94	0.96	0.96	0.94	0.96	0.95	0.91	0.96	0.95

Table 3.

Analysis of the ACTG 019 Study

	Progression After Week 16		Progression After Randomization	
	CD4 Count	Net CD4%	CD4 Count	Net CD4%
$\hat{\beta}$	-0.53	-0.53	-0.62	-0.62
s.e. ($\hat{\beta}$)	0.33	0.33	0.31	0.31
$\hat{\alpha}$ /s.e. ($\hat{\beta}$)	-1.62	-1.62	-1.99	-1.99
$\hat{\beta}_\alpha$	-0.28	-0.14	-0.50	-0.38
s.e. ($\hat{\beta}_\alpha$)	0.32	0.33	0.30	0.31
$\hat{\beta}_\alpha$ /s.e. ($\hat{\beta}_\alpha$)	-0.88	-0.43	-1.66	-1.21
corr($\hat{\beta}, \hat{\beta}_\alpha$)	0.95	0.95	0.95	0.97
\hat{p}	0.46	0.74	0.19	0.38
s.e. (\hat{p})	0.31	0.47	0.16	0.22
\hat{p} /s.e. (\hat{p})	1.51	1.54	1.14	1.74
95% C.I. for p^*				
δ -method	(-0.14, 1.08)	(-0.20, 1.65)	(-0.13, 0.51)	(-0.05, 0.81)
Fieller's method	_____	_____	(-0.27, 7.75)	(0.12, 24.49)