Adjusting a hazard ratio for all-or-nothing compliance: The MASS trial

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10th UK Stata Users Meeting, London, June 2004

Overview

- 1. Motivation – the MASS trial
- 2. Methodology
- 3. Application to the MASS trial
- 4. Implementation in STATA

Setting the scene: the MASS trial

- 67,800 men randomised to control or invitation to aneurysm screening
- Compliance data: attendance at screening
- Observed 80% attendance amongst invited group; no known screening in controls
- Outcome: time to aneurysm-related death
- Aim: estimate effect of screening for attenders

Methodology

- Loeys & Goetghebeur
  - *Biometrics* 2003; **59**:100-105
- Proportional hazards methods
- Control arm individuals classified as potential compliers/ non-compliers
- Proportion non-compliers (α) = as observed in invited group

Notation

- α = proportion of non-compliers
- $S_{nj}(t)$ = survival for non-compliers in arm j (j=0 controls; j=1 invited to screening)
- $S_{cj}(t)$ = survival for compliers in arm j
- $S_j(t) = \alpha\, S_{nj}(t) + (1-\alpha)\, S_{cj}(t)$

Assumptions

- Assume allocation to invitation:
  - Has no effect on outcome for non-compliers

$$S_{n0}(t) = S_{n1}(t)$$

  - Has hazard ratio ψ for compliers

$$S_{c0}(t) = S_{c1}(t)^{1/\psi}$$

- Where ψ = intervention effect for compliers

Survival function

- Using Kaplan-Meier estimates of $S_{n1}(t)$ and $S_{c1}(t)$, estimate survival function in controls:

$$\hat{S}_0^*(t \mid \psi) = \hat{\alpha}\hat{S}_{n1}(t) + (1-\hat{\alpha})\hat{S}_{c1}(t)^{1/\psi}$$

- Calculated over a range of ψ to find value that matches observed control deaths

Estimation of adjusted HR

- Hazard: $\hat{\Lambda}_0^*(t\,|\,\psi) = -\log \hat{S}_0^*(t\,|\,\psi)$
- Difference between expected and observed events in control arm:

$$G_0^*(\psi) = \sum_j \left[\hat{\Lambda}_0^*(T_j\,|\,\psi) - \delta_j\right]$$

- T_j=censoring/ event time δ_j=fail indicator
- Solving for $G_0^*(\psi)=0$ gives an estimate for $\hat{\psi}$

Confidence intervals

- Assume $G_0^*(\psi) \sim N(0, s(\psi)^2)$

- Where $s(\psi)^2 = 2\sum_j \hat{\Lambda}_0^*(T_j \mid \psi)$

- CI then given by solutions for:

$$G_0^*(\psi) = \pm z_{crit} s(\psi)$$

Application to the MASS trial

- ITT hazard ratio: 0.58 (95% CI: 0.42, 0.78)

- Hazard ratio adjusted for all-or-nothing compliance in invited group: 0.47 (95% CI: 0.36, 0.70)

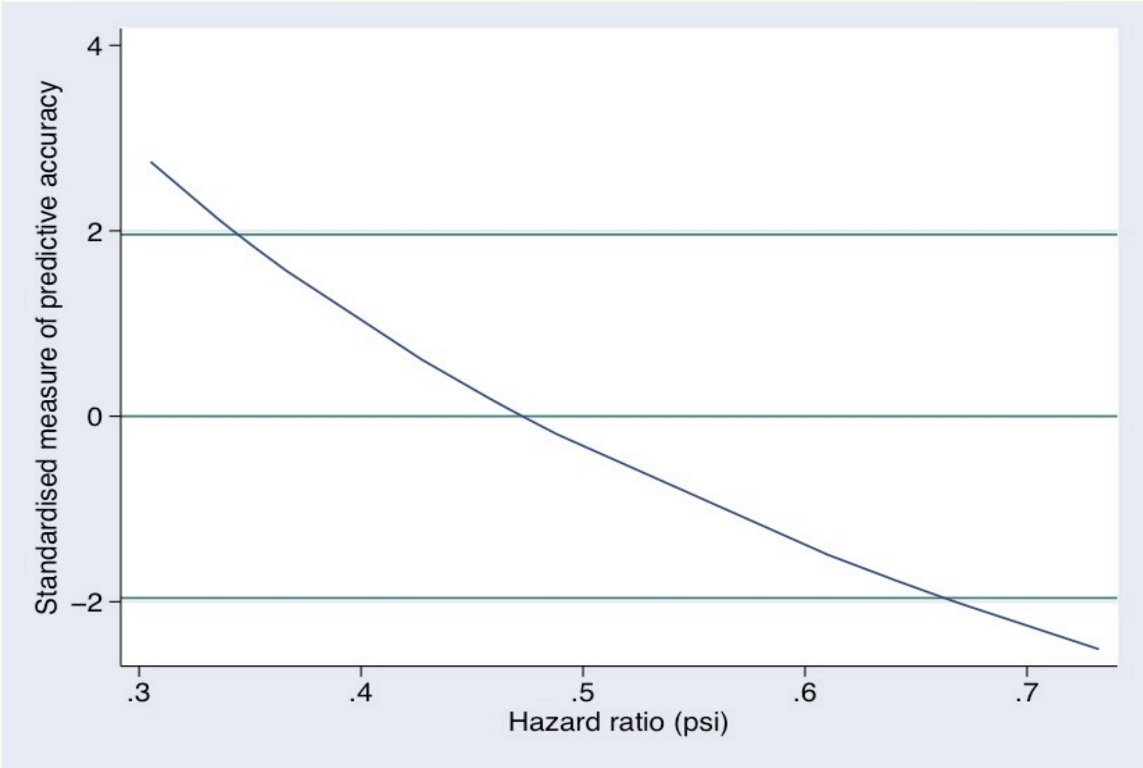
- i.e. treatment considerably more effective amongst those actually attending screening!

Application in STATA

- `stcomply` implements this methodology in Stata
- Provides intervention effect for compliers, together with confidence intervals
- `stcomply` searches over values of ψ, by means of an interval mid-point search, to solve for $G_0(\psi) = 0$. Accuracy of search specified by option `convcrit`

Graph options (1)

$G_0(\psi)$ for a range of values of ψ

- 

Graph options (2)

Observed and expected survival curves for control arm