Risk-based assessment of treatment effect heterogeneity

From subgroups to individuals

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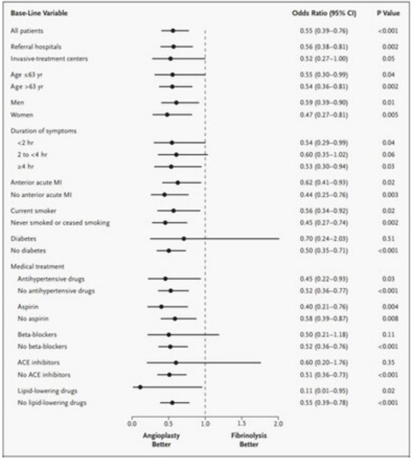
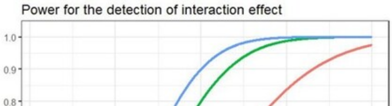
Subgroup analyses

- Generalizing overall treatment effects is often problematic
- Subgroup analyses rarely adequately powered





Subgroup analyses

Subgroup analyses can be divided into 4 categories (***Varadhan et al, 2013***):

- Confirmatory heterogeneity of treatment effect analysis
- Exploratory heterogeneity of treatment effect analysis
- Descriptive heterogeneity of treatment effect analysis
- ***Predictive heterogeneity of treatment effect analysis***

Predictive HTE methods

Risk modeling

- A multivariate regression model f that predicts the risk of an outcome y based on the predictors $x_1 \dots x_p$ is identified or developed.
- The expected outcome of a patient receiving treatment T (where $T = 1$, when patient is treated and 0 otherwise) based on the linear predictor

$$lp(x_1, \dots x_p) = a + \beta_1 x_1 + \dots \beta_p x_p$$

from a previously derived risk model can be described as

$$E\{y|x_1, \dots, x_p\} = f(lp + \gamma_0 T + \gamma T \times lp)$$

Predictive HTE methods

Risk modeling (continued)

- When the assumption of constant relative treatment effect across the entire risk distribution is made (risk magnification), the previous equation takes the form:

$$E\{y|x_1, \ldots, x_p\} = f(lp + \gamma_0 T)$$

Predictive HTE methods

Treatment effect modeling

The expected outcome of a patient with measured predictors $x_1, \dots, x_p$ receiving treatment T can be derived from a model containing predictor main effects and potential treatment interaction terms:

$$E\{y|x_1, \dots, x_p\} = f(\alpha + \beta_1 x_1 + \cdots + \beta_p x_p + \gamma_1 T x_1 + \cdots + \gamma_p T x_p)$$

Predictive HTE methods

Optimal treatment regimes

A treatment regime $T(x_1, \ldots, x_p)$ is a binary treatment assignment rule based on measured predictors. The optimal treatment regime maximizes the overall expected outcome across the entire target population:

$$T_{optimal} = argmax_T E\{E\{y|x_1, \ldots, x_p, T(x_1, \ldots, x_p)\}\}$$

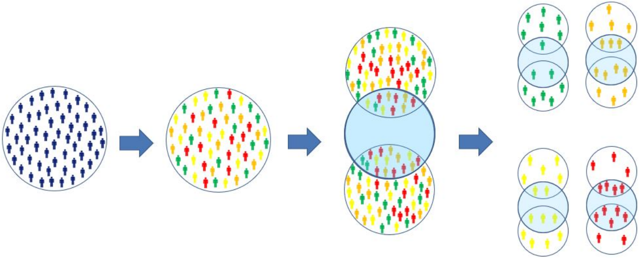
Risk-based HTE

Reasoning

- When risk is described through a combination of factors the control event rate will typically vary considerably across the trial population.
- The absolute risk difference will generally vary across risk strata even if the relative risk is the same
- When a trial population has substantial variation in outcome risk, important differences often exist in harm–benefit tradeoffs

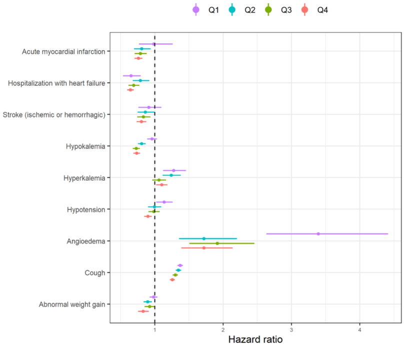
Risk-based HTE in observational data

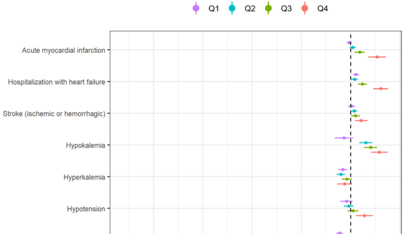
Framework



Applications

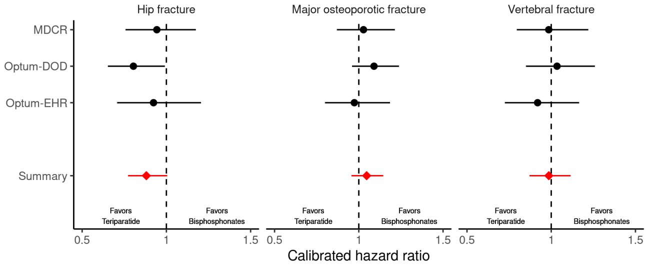
Hypertension





Applications

Osteoporosis



Applications

Osteoporosis