

# 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:

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

# 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:

$$E\{y|x_1, \dots, x_p\} = f(\alpha + \beta_1 x_1 + \dots + \beta_p x_p + \gamma_0 T + \gamma_1 T x_1 + \dots + \gamma_p T x_p)$$

# Predictive HTE methods

## ***Optimal treatment regimes***

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

$$T_{optimal} = \operatorname{argmax}_T E\{E\{y|x_1, \dots, x_p, T(x_1, \dots, x_p)\}\}$$



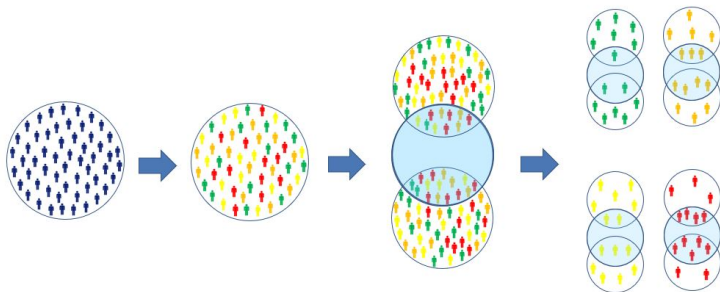
# Risk-based HTE

## *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

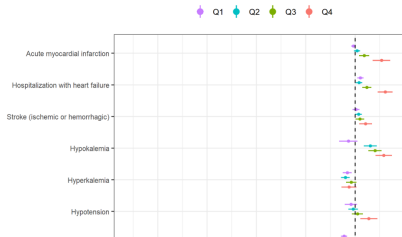
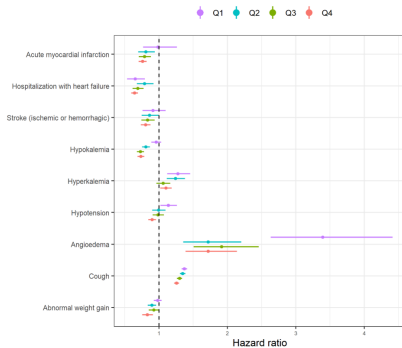
# Risk-based HTE in observational data

## *Framework*



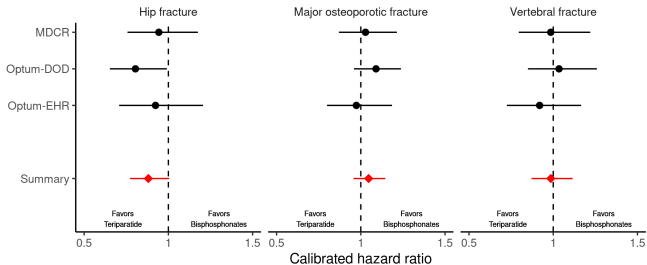
# Applications

## Hypertension



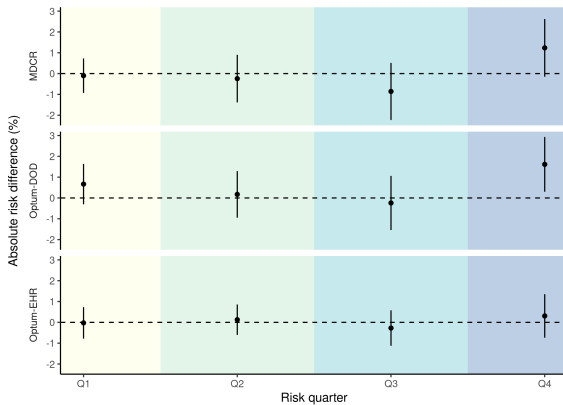
# Applications

## *Osteoporosis*



# Applications

## *Osteoporosis*



# Individualized approaches

- ▶ Stratification approach may not provide adequate prediction of benefit
- ▶ “Jumps” at cut-offs are not realistic
- ▶ Implement a risk-based smoothing approach

## Individualized approaches

Merging treatment arms, we develop prediction models including a constant relative treatment effect:

$$E\{y|x, T\} = P(y|x, T) = f(\alpha + \beta_1 x_1 + \cdots + \beta_p x_p + \gamma_0 T)$$

Individualized predictions are derived setting  $T = 0$ .

$$f_{benefit}(lp|x, \hat{\beta}) = f_{smooth}(lp|x, \hat{\beta}, T = 0) - f_{smooth}(lp|x, \hat{\beta}, T = 1)$$

# Individualized approaches

