Was the Effect of Intensive Blood Pressure Intervention on CVD Risk Heterogeneous in the SPRINT Study?

Yizhe Xu[1,3], Jian Ying[2, 3], Guo Wei[2, 3], Andrew Moran[4], William Weintraub[5], Adam Bress[1, 3], Jincheng Shen[1, 3], Tom Greene[1, 2, 3]

[1]Department of Population Health and Science, University of Utah [2]Department of Medicine, University of Utah [3] Study Design and Biostatistics Center, University of Utah, [4] Columbia University, [5] MedStar

INTRODUCTION

Investigation of treatment effect heterogeneity is challenging in randomized clinical trials because statistical power is limited within subgroups and because evaluating multiple subgroups leads to increased risk of false positive conclusions due to multiple testing. Nonetheless, three different approaches to evaluation of treatment effect heterogeneity have been considered in the literature. In the setting of a survival outcome, these are:

1) Assume a constant treatment effect on the relative risk scale, and develop a model for heterogeneity of treatment effects on the absolute risk difference scale as:
   Risk Difference = Absolute Risk x Relative Risk
   In this model, the estimated risk difference for an effective treatment will be larger in subjects with greater absolute risk and smaller in subjects with lower absolute risk.
2) Perform a targeted evaluation of interactions between the treatment and a small number of designated subgroups (e.g., with or without chronic kidney disease). This method can employ multiple comparison adjustment for the number of subgroup factors investigated.
3) Use modern machine learning methods developed from a modern causal inference framework to estimate the "conditional average treatment effect" as a function of a large number of possible baseline variables that could be effect modifiers.

This research investigates methods for combining all three of these approaches to model heterogeneity of the effect of the intensive systolic blood pressure (SBP) intervention on the risk of the primary cardiovascular event outcome in the SPRINT trial.

METHODS

We investigated three different approaches to modeling treatment effect heterogeneity associated with 61 baseline factors identified as possible effect modifiers in SPRINT:

1) Pairwise evaluation of the interactions of the intensive SBP intervention with 61 baseline covariates.
   - Interactions evaluated on relative risk and absolute risk difference scales
   - Quantitative variables divided into quartiles
2) Elastic net Cox regression
   - Hazard Function Model: $h(t, A, X) = h_0(t) * \exp\{A\alpha + X\beta + AX\gamma\}$
     (baseline hazard; Interactions that describe how treatment effect differs between patients with different baseline characteristics; time; covariates; treatment; Treatment main effect; Effects of covariates on overall risk)
   - Elastic net used a class of models that includes lasso regression and ridge regression to "regularize" or shrink estimates effects towards 0 to avoid undue overfitting
   - Regularization of the part of the model that account for treatment effect heterogeneity (AXγ) on relative risk scale
   - Uses a standard regression-type model for effects of covariates (best when treatment effect heterogeneity follows a relatively simple "additive" pattern)
3) Bayesian Adaptive Regression Trees (BART)
   - BART is an machine learning technique that provides a highly flexible Bayesian predictive modeling, so it can be used to detect nonlinear relationships and complex interactions.
   - BART uses tree-based models, but averages over many trees to improve prediction.
   - BART first builds a model that predicts the outcome based on the treatment and patient factors. Then, by assigning the treatment to "usual goal" and then to "low goal" in succession for all patients, the model predicts the outcomes each patient would have under both the treatment (denoted Y(1)) and the control (denoted Y(0)).
   - BART gives two types of patient specific treatment effects for a yes/no outcome: the difference Y(1) - Y(0) can be used to estimate the absolute risk difference (ARD) and the ratio Y(1)/Y(0) can be used to estimate the relative risk (RR).

ACKNOWLEDGEMENTS

- R01 HL139837 01 and University of Utah
- NCATS, NIH 5UL1TR001067-05

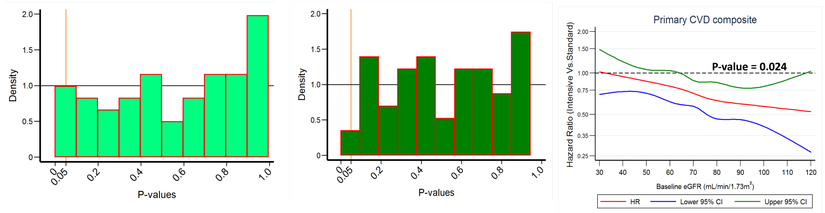
REFERENCES

1. Hui Zou, Trevor Hastie. Regularization and variable selection via elastic net (2005).
2. Donald P. Green. Modeling Heterogeneous Treatment Effects in Survey Experiments with BART (2012).
3. Rodney A. Sparapani. Nonparameteric survival analysis using BART (2016).

RESULTS

Part 1. Pairwise Interactions of the Intensive SBP Intervention with 61 Baseline Factors.

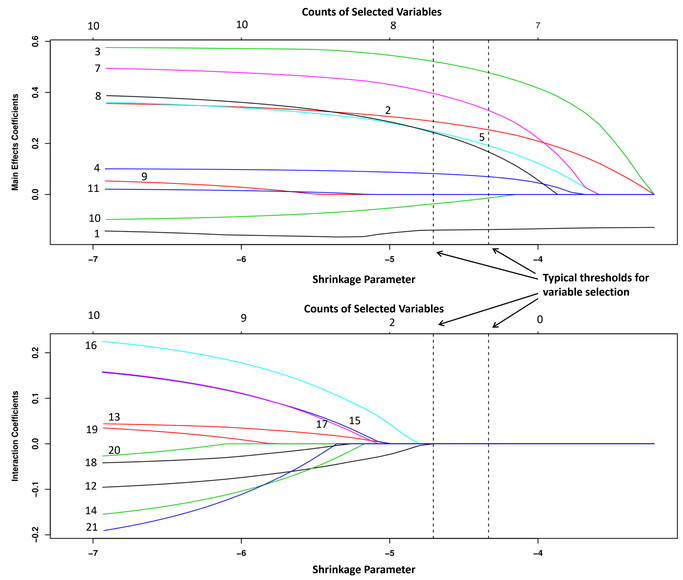
Figure 1. Univariate Interaction of Treatment with Baseline eGFR



When interactions of the treatment with 61 baseline factors are considered individually, the distribution of the p-values does not deviate significantly from the uniform distribution that would be expected in the absence of treatment effect heterogeneity. However, one group of investigators posited a linear interaction between the treatment and baseline eGFR. If this interaction is viewed as an a-priori hypothesis, the p-value is 0.024.

Part 2. Application of Elastic Net Cox Regression to Model Heterogeneous Treatment Effect (HTE).

Figure 2. Trace Plots for Risk Difference and Hazard Ratio



	Main Effects		Interactions with Treatment
1	Treatment	12	Baseline eGFR
2	Baseline Age	13	Baseline Potassium
3	Clinical CVD	14	Baseline Former Smoker
4	Baseline Urine Albumin/Creatinine Ratio	15	History Skin Cancer
5	Beta-blocker Use	16	Thyroid Disease
6	History of Coronary Revascularization	17	History of Anemia
7	Loop Diuretic use	18	Baseline Number of Antihypertensive Medications
8	Baseline Atrial Fibrillation/Atrial Flutter	19	Baseline BMI
9	Baseline Acute Coronary Syndrome	20	Thiazide Diuretic
10	Baseline eGFR	21	Anxiety Panic Disorder
11	Baseline Number of Antihypertensive Medications		

The two panels show trace plots of the standardized Cox regression coefficients for main effects (top) and treatment interactions (bottom) of the 10 strongest baseline predictors and 10 strongest baseline effect modifiers identified in a preliminary screening procedure. The dominant terms in the model are all main effects, and the coefficients of all treatment interactions attenuate to 0 with only modest penalization. Hence, the fitted elastic net model estimates no HTE on the relative risk scale. However, variation in estimated absolute risk leads to substantial HTE on the ARD scale.

Part 3. Application of BART to Model Heterogeneous Treatment Effect

Figure 3. Plots of Conditional Average Treatment Effect (CATE) Versus Baseline Age and eGFR

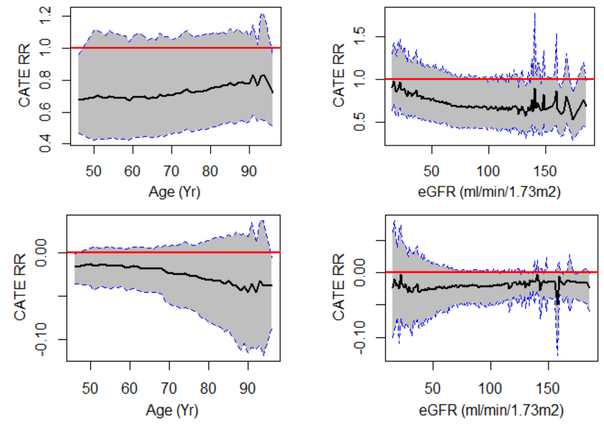


Figure 4. Density Curves for Actual and Permuted CATE Distributions

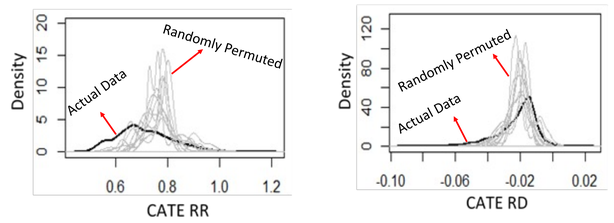


Figure 5. Cross-Validated Calibration Plots for CATE in Deciles

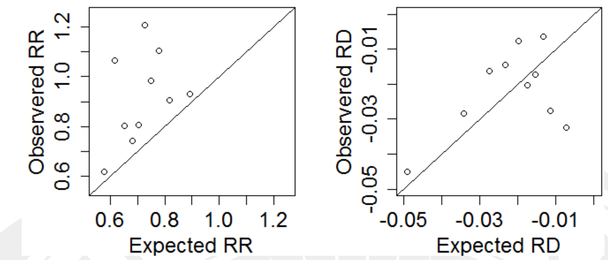


Figure 3 suggests larger treatment benefit on the RR scale at higher baseline eGFR and larger benefit on the RD scale at higher ages, but with very wide 95% credible intervals. Figure 4 suggests that the modeled HTE based on the data may be larger than the modeled HTE for randomly permuted data on both the relative risk and risk difference scales. Figure 5 suggests the predicted risk ratios and risk differences may be positively correlated with observed risk ratios and risk differences.

CONCLUSIONS/DISCUSSIONS

1. If a linear interaction between the treatment and baseline eGFR on the primary CV composite is viewed as an a-priori hypothesis, there is a suggestion of greater benefit of intensive SBP at higher baseline eGFR.
2. However, the observed HTE is compatible with chance variation when all 61 baseline factors are considered individually.
3. If variation in observed HTE is smoothed out on the relative risk scale, application of elastic net provides little evidence of HTE based on relative risk, but indicates substantial HTE on risk difference scale due to patient variation in absolute risk.
4. Flexible analysis using BART suggests possible HTE on both risk difference and relative risk scales.
5. We are using simulation studies to clarify the performance of each method in the setting of SPRINT. These results will guide our final conclusions regarding HTE.