Identification of patients with stable coronary artery disease who benefit from ACE inhibitors using Cox mixture model for heterogeneous treatment effects

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Introduction

The Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) study [3] found no benefit of using ACE-Inhibitors in patients with stable coronary disease and reduced left-ventricular function. We utilized Cox Mixtures with Heterogeneous Effects (CMHE) [2] to subgroup the PEACE trial population based on response to ACE-inhibitors. We found evidence supporting the hypothesis of existence of heterogeneous treatment effects to ACE-inhibitors.

Methods

8,290 patients randomly assigned to receive Trandolapril at a target dose of 4mg per day (4158 patients) or matching placebo (4132 patients) were included in the analysis. 46 pretrial features were used to train CMHE to prognosticate outcomes. CMHE identified two phenogroups with distinctly different treatment effects. A decision tree classifier was then used to identify confounders affecting the responses.

Results

Among all patients, 5,650 (68.15%) were more likely to benefit from Trandolapril (Hazard Ratio: 0.86 ±0.09), demonstrating decreased long-term mortality. On the contrary, 2,640 patients (31.85%) were apparently harmed with the same treatment (HR: 1.19±0.16) showing increased long-term risk. The classifier revealed patients with a history of smoking and lower SBP and DBP benefit more from Trandolapril.

Conclusion

We applied a novel survival model to the PEACE trial and identified a patient subgroup whose outcomes could improve with treatment, even though population level on-average analysis shows no desirable effects.

References

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[2] Nagpal, Chirag, Willa Potosnak, and Artur Dubrawski. "auton-survival: an Open-Source Package for Regression, Counterfactual Estimation, Evaluation and Phenotyping with Censored Time-to-Event Data." arXiv preprint arXiv:2204.07276 (2022).
[3] PEACE Trial Investigators. "Angiotensin-converting–enzyme inhibition in stable coronary artery disease." New England Journal of Medicine 351, no. 20 (2004): 2058-2068.

Figure 1. Kaplan-Meier curves for patients in the subgroup "Harmed" whose outcomes are less favorable than placebo when treated, and the subgroup "Benefitted" who are more likely to benefit from Trandolapril.

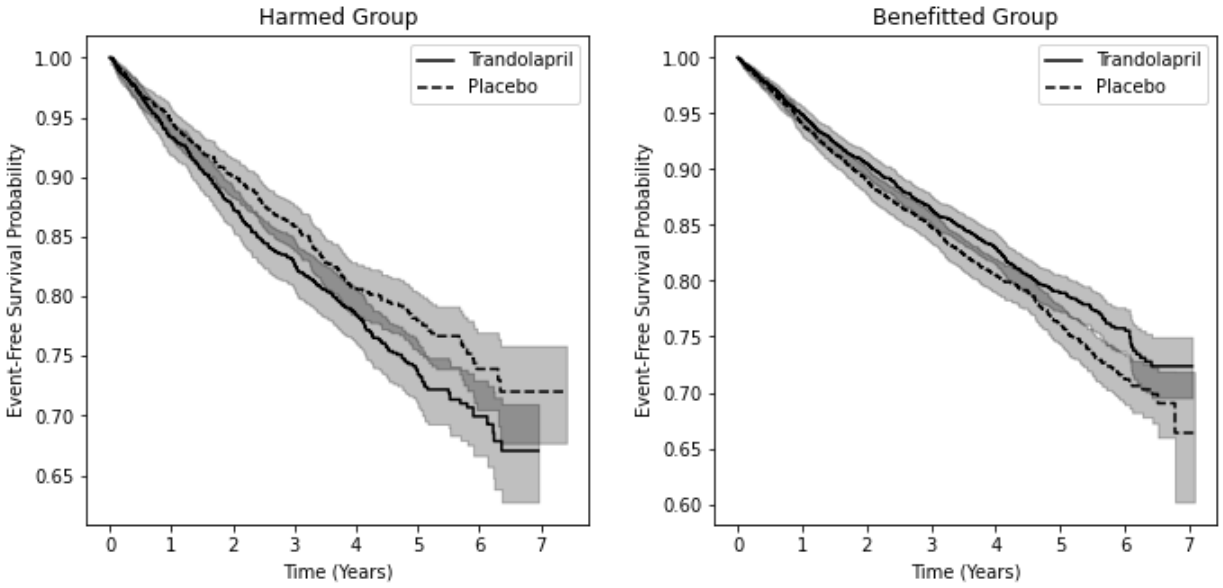

Table 1. Baseline characteristics for subgroups favoring trandolapril or a matching placebo (standard errors in brackets).

Baseline Characteristics/ Model Features	**Entire Cohort (N = 8,290)**	**Group favoring Trandolapril (Benefited group, N = 5,650)**	**Group favoring a matching placebo (Harmed group, N = 2,640)**
Seated Systolic Blood Pressure	127.47±0.18	123.92 ±0.20	135.10±0.32
Seated Diastolic Blood Pressure	74.51±0.11	72.77±0.13	78.77±0.18
Sex (Female)	18.02%	16.02%	22.31%
Never Smoked	24.35%	65.83%	5.05%