Large-scale evaluation of treatment effect heterogeneity in hypertension

Alexandros Rekkas, MSc¹, David Van Klaveren, PhD¹, Peter R. Rijnbeek, PhD¹

¹Erasmus University Medical Center, Rotterdam, The Netherlands
Abstract

Average treatment effect estimates derived from population-level analyses may sometimes be uninformative for guiding decision-making on individual patients. Traditional subgroup analyses are rarely adequately powered to evaluate subgroup effects while they also fail to capture the multivariate nature of treatment effect heterogeneity. We focus on heterogeneity of effect of first-line treatments for hypertension. Our aim is to supplement the OHDSI LEGEND-Hypertension study with risk-based assessment of treatment effect heterogeneity (HTE). The analyses will be done using the standardized framework implemented in the RiskStratifiedEstimation R-package. We will stratify patients into strata of predicted risk for acute myocardial infarction, hospitalization with heart failure and stroke. Within risk strata we evaluate treatment effects with regard to 55 outcomes of interest. In our primary results, our prediction model demonstrated adequate discrimination (c-index of around 0.77 in the entire study population) which—in combination with the relative constant hazard ratios close to 0.7 in favor of ACE inhibitors compared to beta blockers—resulted in an increasing trend in terms of absolute benefit with increasing risk.

Research category

Population-level estimation, Patient-level prediction

Background

The LEGEND-Hypertension study (1) was a major contribution to hypertension research, as it generated an immense volume of information from real-world data on the effects of all available first-line treatments for hypertension. However, such overall results may not provide the full picture required to guide medical decision-making.

It is widely recognized that average treatment effects found in randomized clinical trials may not always apply to all individual patients, giving rise to heterogeneity of treatment effects (HTE) that can often be quite substantial (2). Conventional subgroup analyses are incongruent with the goals of predictive HTE analyses. As such methods allow patients to differ on one measured variable at a time—while they may adequately detect relative effect modification—they fail to capture the multivariate nature of patient heterogeneity, i.e. a patient has an indefinite number of attributes causing them to belong in an indefinite number of subgroups (3). Prioritizing outcome risk as the subgrouping variable may resolve many of the issues arising from conventional analyses. Outcome risk is a summary score and—unlike individual variables that may or may not modify treatment effect—determines treatment effect (4).

Our goal is to supplement the population-level results of LEGEND-Hypertension with risk-based assessment of HTE using the standardized framework implemented in RiskStratifiedEstimation R-package developed for the OHDSI methods library (https://github.com/mi-erasmusmc/RiskStratifiedEstimation). This R-package combines functionality from the PatientLevelPrediction and the CohortMethod R-packages, is easily scalable and provides a standardized output that can be explored with a built-in shiny dashboard.

Methods

The proposed framework consists of five steps: 1) definition of the problem, i.e. the population, the treatment, the comparator and the outcome(s) of interest; 2) identification of the database(s); 3) development of a prediction model for the outcome(s) of interest; 4) estimation of propensity scores
within strata of predicted risk and estimation of relative and absolute treatment effects within strata of predicted risk—in our case we stratified on the propensity scores but matching and weighting are also viable options; 5) evaluation and presentation of results.

We are going to compare the treatment classes of ACE inhibitors, Alpha-1 blockers, angiotensin receptor blockers, beta blockers, calcium channel blockers, direct vasodilators and diuretics with regard to 55 main and safety outcomes of interest. We will implement our analyses in 3 US claims databases (CCAE, MDCD, MDCR).

**Results**

We present preliminary results on the comparison of ACE inhibitors to beta blockers regarding 9 outcomes of interest. Risk stratification was performed based on hospitalization with heart failure risk. The internally developed prediction model for hospitalization with heart failure had a c-statistic of 0.77, providing adequate discrimination. As hazard ratios remained quite constant around 0.7 in favor of ACE inhibitors, we observed a clearly increasing trend in terms of absolute benefit (line 1 of Figure 1). For safety outcomes, the absolute ACE inhibitor-related harm in terms of coughing remained rather constant—even with a decreasing trend—as heart failure risk increased (line 8 of Figure 1). This would indicate that in lower risk subgroups the harms may outweigh the benefits in the case of treatment with ACE inhibitors. The entire standardized output can be explored in a Shiny application (link).

![Figure 1. Absolute risk differences comparing ACE inhibitors to beta blockers within strata of predicted hospitalization with heart failure risk with regard to 9 outcomes of interest.](image)

**Conclusions**

Risk stratified estimation of treatment effects can provide a simple and meaningful exploration of HTE. Based on the infrastructure provided by the OMOP-CDM and the OHDSI libraries we were able to develop a scalable standardized framework that can be used to supplement population-level treatment effect estimates and provide significant aid to guide medical decision-making. We plan to demonstrate the usefulness of our framework by presenting a re-analysis of the highly impactful LEGEND-Hypertension study.
References


