Development of a R-package to Explore Heterogeneity of Treatment Effects: A Demonstration in Patients with Hypertension

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Background

Heterogeneity of treatment effect (HTE) is the non-random, explainable variability in the direction and magnitude of treatment effects for individuals within a population. The most common approach to HTE assessment is through subgroup analyses where interactions with various covariates are tested. However, detection of such interactions needs much bigger sample sizes than the detection of main effects and RCTs are rarely powered to detect them. Subgrouping patients on a summary score like their predicted risk of the outcome, can act as a remedy and help identify groups of patients more likely to benefit from specific treatment choices.

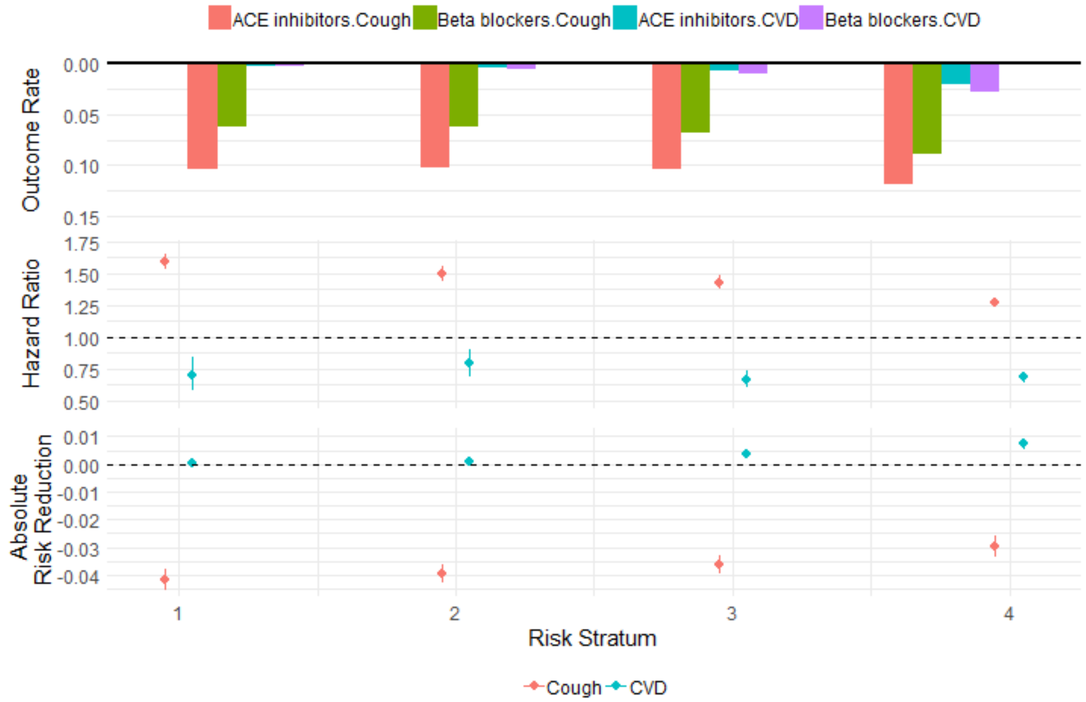
The OMOP-CDM enables a generalized approach, where multiple outcomes can be considered for a broad range of exposures. In this regard, the Large-scale Evidence Generation in Network of Databases (LEGEND) project generated evidence on the effects of almost all medical interventions for the case of hypertension. We aim to develop an OHDSI analytics package that provides insight into treatment effect heterogeneity. We provide a demonstration for hypertension, comparing ACE inhibitors to Beta blockers with respect to cardiovascular disease (CVD) events and cough events in Truven MarketScan Commercial Claims and Encounters (CCAE) database.

Methods

Cohort	Definition
Treatment (ACE inhibitors)	Hypertensive patients receiving drugs within the ACE inhibitor drug major class.
Comparator (Beta blockers)	Hypertensive patients receiving drugs within the Beta blocker drug major class.
Outcome1 (CVD)	Total cardiovascular disease events (ischemic stroke, hemorrhagic stroke, heart failure, acute myocardial infraction or sudden death).
Outcome2 (Cough)	Cough events.

- Personalized predictions of CVD risk were estimated using LASSO logistic regression on the combined treatment and comparator cohorts.
- Propensity scores were estimated using LASSO logistic regression within quartiles of predicted CVD risk.
- Covariates were balanced using inverse probability of treatment weights.
- Relative risks of CVD events were estimated using weighted Cox proportional hazards regression within quartiles of predicted CVD risk.
- Absolute risk reduction in CVD risk was estimated using the difference of the weighted Kaplan-Meier estimators within quartiles of predicted CVD risk
- Relative and absolute risk differences of cough events within quartiles of predicted CVD risk were made in the same way as above.

Results



CVD hazard ratios are quite constant across quartiles of predicted CVD risk, leading to increasing absolute treatment benefits in favor of ACE inhibitors. There appears to be increased cough risk for patients receiving ACE inhibitors. However, absolute cough risk does not increase with CVD risk, encouraging the use of ACE inhibitors for high CVD risk patients.

Conclusions

We are developing an R-package that performs treatment comparisons within strata of predicted outcome risks. We intend to use this package to incorporate treatment effect heterogeneity assessment to the results of the LEGEND project, with regard to hypertension treatment. The under development RiskStratifiedEsimation package can be found at: https://github.com/OHDSI/RiskStratifiedEstimation.

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