RWD76

Application Of Causal Inference Methods for Analyzing Randomized Controlled Trial Data Combined with Real-Word Data

[1*]Alfredo E. Farjat, [2]Kaisa Laapas, [3]James Potts

[1]Bayer BV, Hoofddorp, Netherlands; [2]Bayer Oy, Espoo, Finland; [3]Bayer Corporation, Whippany, USA

*corresponding author: Alfredo E. Farjat, alfredo.farjat@bayer.com.

Introduction

- Randomized controlled trials (RCTs) augmented with real-world data (RWD) can provide high-quality evidence to evaluate safety and effectiveness for new medical products in regulatory settings
- Several methods have been developed for creating statistically comparable groups and evaluating treatment effect
- However, poor balance between the baseline characteristics of comparing groups can be a critical limitation

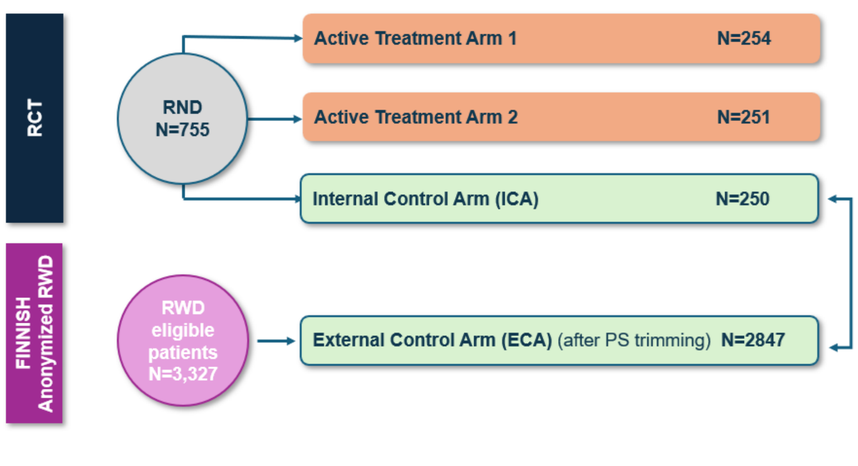
Objectives

- Compare different matching/weighting methods for the evaluation of treatment effect in a RCT augmented with RWD in the presence of poor balance of baseline characteristics

Methods

- **RCT Phase II**: Participants were randomized to one of two experimental arms or an **internal control arm (ICA)** and were evaluated for bleeding events within three months
- **External control arm (ECA)**: The Finnish healthcare records was used to develop an ECA, fulfilling eligibility for the RCT
- Matching and weighting methods based on 28 known confounders were used to create statistically comparable groups between RCT participants and those eligible from RWD
- After **propensity score (PS)** trimming[1], inverse probability of treatment weighting (**IPTW**)[2], G-computation (**G-comp**)[3], Augmented IPTW (**AIPTW**)[2], Targeted Maximum Likelihood Estimation (**TMLE**)[3], and Overlapping Weights (**OW**)[1] methodologies were applied for comparing the ICA to ECA, and then to evaluate the treatment effect of the combined ICA+ECA to the RCT experimental arm
- In addition, treatment effect was evaluated using the propensity score composite likelihood (**PSCL**)[4] approach

Figure 1: RCT design and Finnish anonymized RWD



Results

- The RCT had n=505 participants randomized to the experimental arms and n=250 to the ICA
- A pool of eligible RWD Finnish subjects (n=3327) was established, of which n=2847 were included after trimming (480 excluded)
- **Figure 4** shows no difference in bleeding outcomes between the ICA and the matched ECA across methods
- **Figure 5** shows treatment effect by method for RCT and RCT with augmented control arm (ICA n=250 + ECA n=2847 = 3097 control subjects). Precision is increased with external data augmentation but point estimates moved towards zero difference

Figure 2: Overlap of propensity scores' distributions

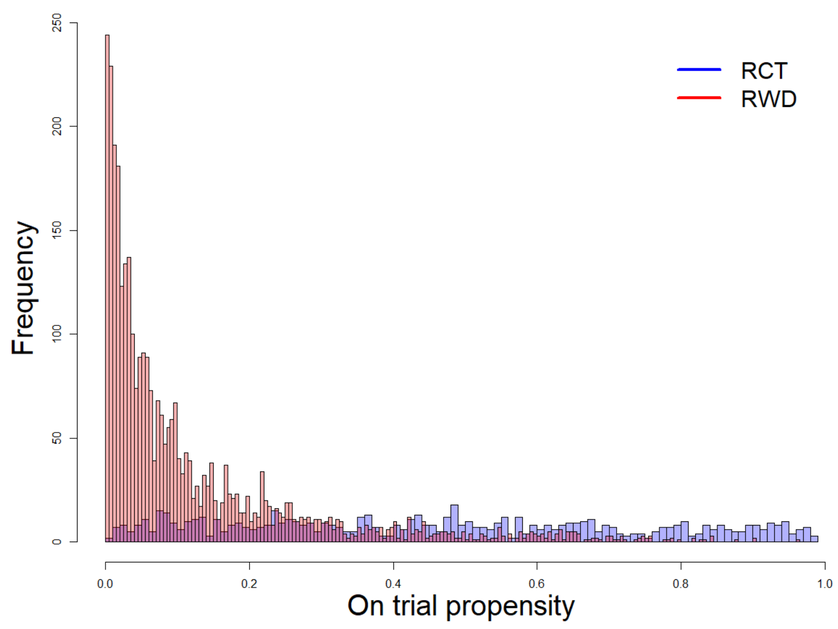


Figure 3: Absolute standardized mean difference between RCT and RWD

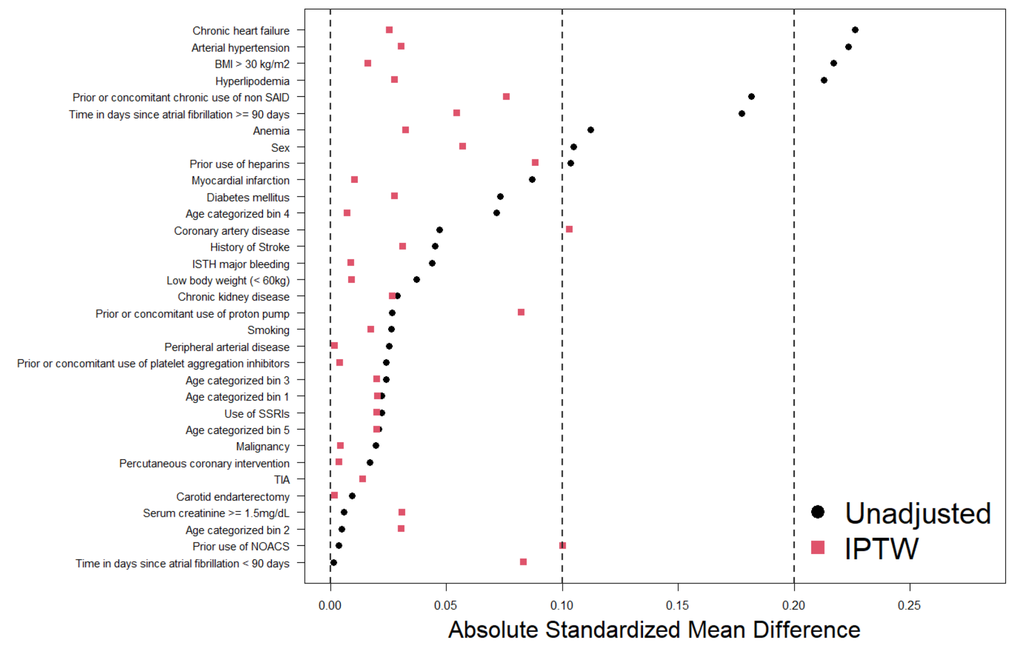


Figure 4: Major bleeding events rate difference between ICA and ECA by method

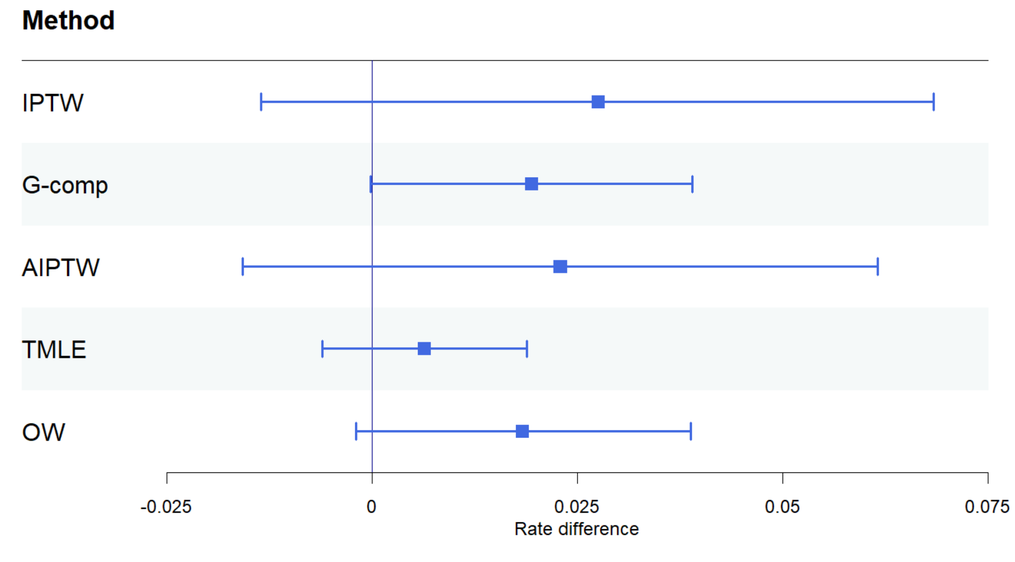
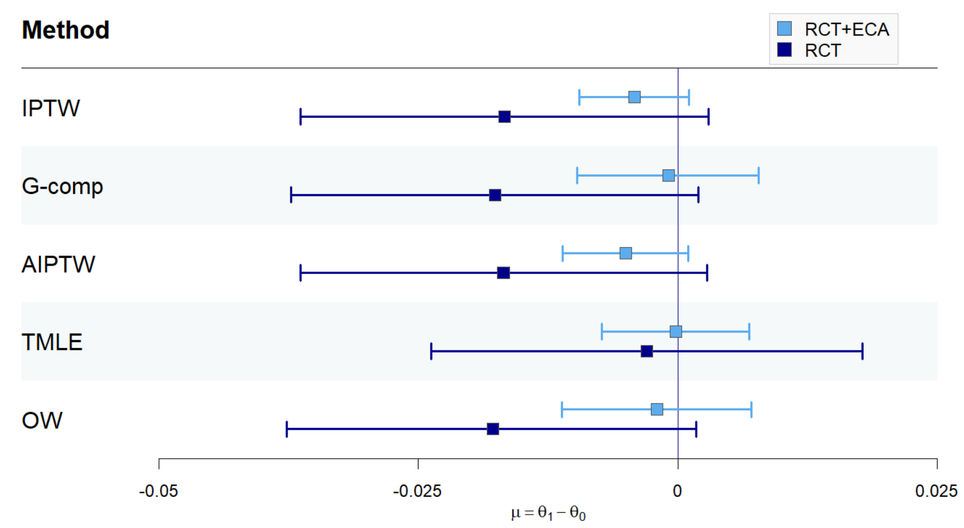


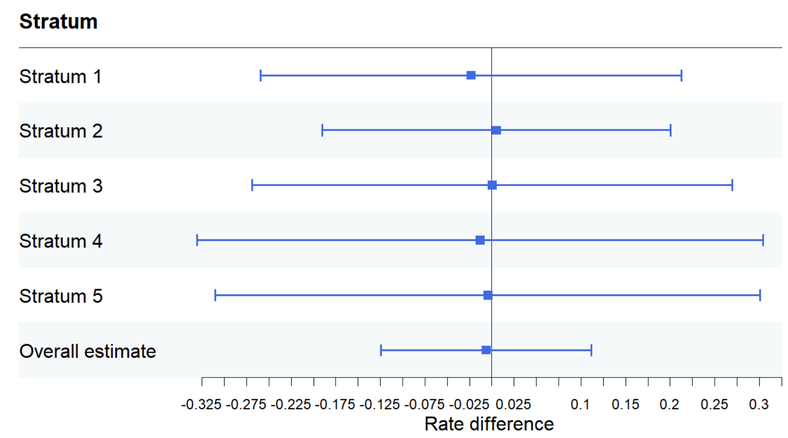
Figure 5: Treatment effect by method for RCT and RCT + ECA



Propensity Score Composite Likelihood

- PS distribution was stratified into 5 strata
- In total, 255 subjects were borrowed from RWD to attain a 1:1 treatment-to-controls ratio
- Subjects were split proportionally to the distance in PS distributions in each stratum
- **Figure 6** indicates no overall difference in bleeding rates

Figure 6: Propensity Score Composite Likelihood



Conclusions

- Several causal inference methods are available for the analysis of RCT data combined with RWD
- Many of these methods were applied and showed similar results arriving to the same conclusion in the presence of poor propensity score distribution overlap

References: 1. Li et al. JASA. 2018, 113(521):390-400; 2. Kurz CF, Medical Decision Making 2021, 42(2):156-167; 3. Schuler MS and Rose S, American Journal of Epidemiology 2017, 185(1):65-73; 4. Chen WC et al. Journal of Biopharmaceutical Statistics 2020, 30(3):508-520.