

Combining Treatment Propensity Scores and Clone-Censor-Weighting to Evaluate Treatment Duration in Active Comparator Studies

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BACKGROUND

Observational research involving individuals with a minimum exposure duration or “threshold” can introduce selection and immortal time biases. **Clone-censor-weighting** (CCW) designs can estimate the effect that would be observed had individuals been assigned to achieve an exposure threshold and can be **combined with treatment propensity scores** (tPS) to emulate randomization to a product of interest in active comparator studies

OBJECTIVES

To demonstrate combined use of the CCW approach plus tPS weighting to compare renal cell carcinoma (RCC) risk had canagliflozin (CANA) initiators been randomized to CANA versus sitagliptin (SITA) and adhered to the treatment strategy of ≥ 180 days of exposure in the 1st year of follow-up

METHODS

Study population: We identified patients with type 2 diabetes (T2D) initiating CANA or SITA between 1 March 2013 and 31 March 2025 among 4 commercial and 2 public Sentinel Data Partners (DPs) in the United States (U.S.)

- Initiation defined as first use of either drug class in prior 365 days.
- Required (in 365 days prior to first eligible initiation [index date]):
 - Continuous enrollment in medical and drug coverage
 - ≥ 1 claim with T2D diagnosis and ≥ 1 oral antidiabetic drug dispensing
 - No evidence of type 1 diabetes, chronic kidney disease stage (CKD) III-V, dialysis, use of glucagon-like peptide-1 receptor agonists (GLP-1RAs), prior RCC or nephrectomy (ever)

Outcome of interest: RCC, based on ≥ 2 RCC diagnosis codes, plus:

- Diagnostic work-up (or symptoms, for metastatic disease)
- Stage-appropriate treatment (or mortality, for metastatic disease)

Cloning: For each initiator, we created two copies (or “clones”) of the initiator (**Figure 1**). Clones were assigned to mutually-exclusive treatment strategies:

- **<180 days covered by a dispensing within 360 days of initiation**
- **≥ 180 days covered by a dispensing within 360 days of initiation**

Artificial censoring: We artificially censored clones that deviated from their assigned treatment strategy (**Figure 1**)

- A clone assigned to the **<180-day** strategy was artificially censored when cumulative days covered by a dispensing reached 180 days (ID1)
- A clone assigned to the **≥ 180 -day** strategy was artificially censored on the date on which their exposure deficit made it impossible to accumulate 180 covered days by Day 360 (ID2)
 - ID2 has single 60-day dispensing $\rightarrow$ 120-day deficit; censored on day 360-120=240
- Individuals who experienced events (ID3) or censoring (ID4) before definitive treatment strategy assignment contributed data to both strategies

Weighting:

- **Selection from artificial censoring:** Inverse-probability-of-censoring weights (IPCW) were estimated using pre-index and time-varying predictors of adherence to the assigned treatment strategy and RCC
 - At each interval, IPCW upweighted individuals who remained uncensored to represent all individuals who were alive and event free at the start of that interval, assuming censoring of initiators occurred at random conditional on measured covariates
- **Confounding:** A tPS was estimated using pre-index covariates. Stabilized treatment weights used to estimate the average treatment effect among the treated (ATT), defined here as canagliflozin initiators
- ATT and IPCW product truncated at 1st and 99th percentiles for analysis

RESULTS/CONCLUSIONS

- Application of this methodology yielded an adjusted RCC HR of 0.88 (95% CI: 0.75, 1.04) comparing the treatment strategies of interest
 - See full results in **C-408: Risk of RCC Following at Least 180 Days of Exposure to Canagliflozin in U.S. Patients with T2D**
- **Ad hoc** examination of baseline and post-index covariate balance among individuals surviving to Day 360 showed weighting improved balance on demographics, health characteristics, medical product use, healthcare utilization, and risk scores (**Figure 2**)
 - Residual imbalance observed for initiation of GLP-1RA and insulin in the 1st year of follow-up with SMDs of 0.092 and -0.102, respectively

LIMITATIONS

- The study design did not use IPCW to account for censoring due to other potentially informative end-of-follow-up criteria, including CKD and dialysis
- Limited duration of follow-up prevented evaluation of longer duration treatment strategies and more complex strategies
- Diagnostics for IPCW performance are the subject of ongoing research. Individuals lost to follow-up or experiencing events are not represented in **Figure 2**, nor were balance assessments conducted in a time-varying manner (Gaber et al. 2024: [10.1002/cam4.70461](https://doi.org/10.1002/cam4.70461); Jackson 2019: [10.1093/aje/kwz136](https://doi.org/10.1093/aje/kwz136))
- Interpretation of our findings as a hypothetical target trial depends on meeting standard causal identifiability criteria
 - In particular, conditional exchangeability is unlikely to be met when using administrative data due to unmeasured or mismeasured covariates
 - Model misspecification is also possible for both propensity score and outcome models

Figure 1. Visual representation of cloning and artificial censoring

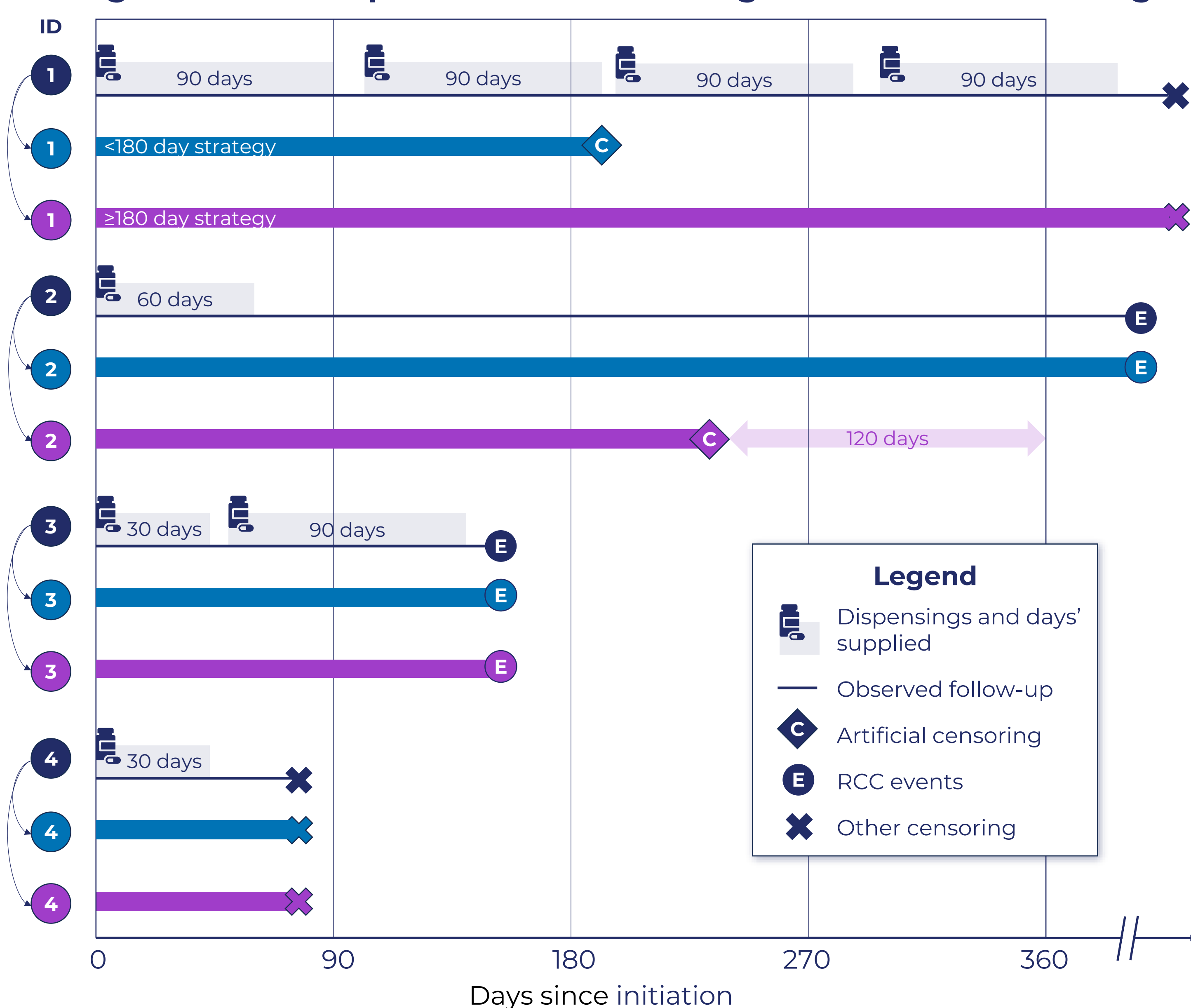
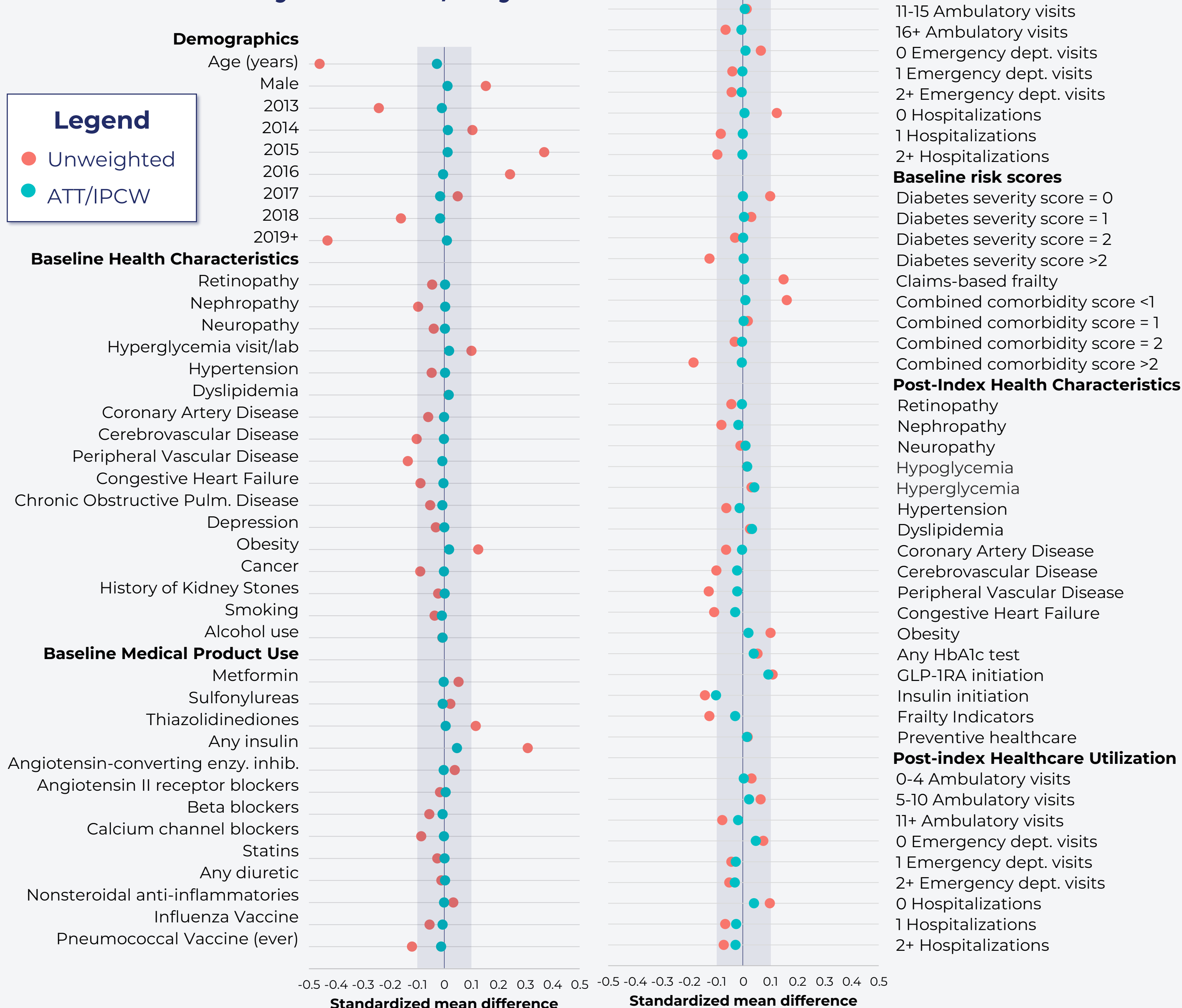


Figure 2. Characteristics of CANA and SITA ≥ 180 -day adherers, Day 360



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