FACULTY
OF SCIENCES

August 25, 2025

ISCB 2025

Can Treatment Effect Testing in Trials with Intercurrent Events Be Nearly Assumption-Free?

Joint work with Kelly Van Lancker and Stijn Vansteelandt

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Introduction

- Aim: Test for causal effect of binary randomized treatment A on an outcome $Y(t)$, planned to be measured at fixed visit times $t = 0, 1, \ldots, \tau$.

Introduction

- Aim: Test for causal effect of binary randomized treatment A on an outcome $Y(t)$, planned to be measured at fixed visit times $t = 0, 1, \ldots, \tau$.
- Complicated in the presence of intercurrent events (ICEs) such as
  - treatment switching
  - rescue therapy
  - truncation by death
  - ...

COMMON APPROACHES

Compare treated and untreated patients

- in terms of their last recorded ICE-free outcomes: Last Observation Carried Forward (LOCF).
- who reached the end of the study without ICE: Per Protocol (PP).
- in terms of ratio of (recurrent event) outcome and survival time: While-Alive Estimand.
  (Schmidli et al., 2023)
- who would have reached the end of the study without ICE under either treatment or control: Principal Stratification (PS).
  - Truncation by death: Survivor Average Causal Effect (SACE).

  (Robins, 1986; Frangakis and Rubin, 2004)
- under a hypothetical scenario where the ICE does not occur: Hypothetical Estimands.

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Current Medical Research and Opinion

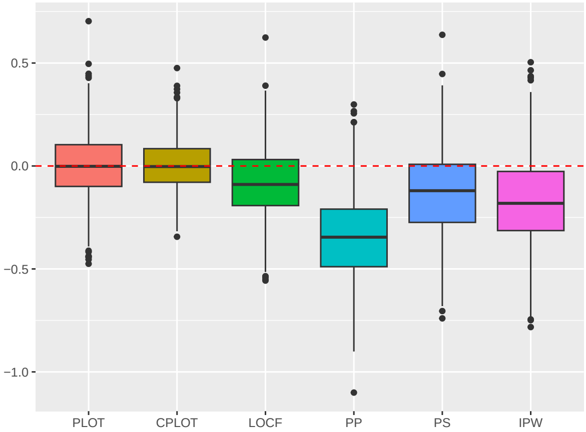
ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: www.tandfonline.com/journals/icmo20

Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: findings from the 52-week CANTATA-M study

Kaj Stenlöf, William T. Cefalu, Kyoung-Ah Kim, Esteban Jodar, Maria Alba, Robert Edwards, Cindy Tong, William Canovatchel & Gary Meininger

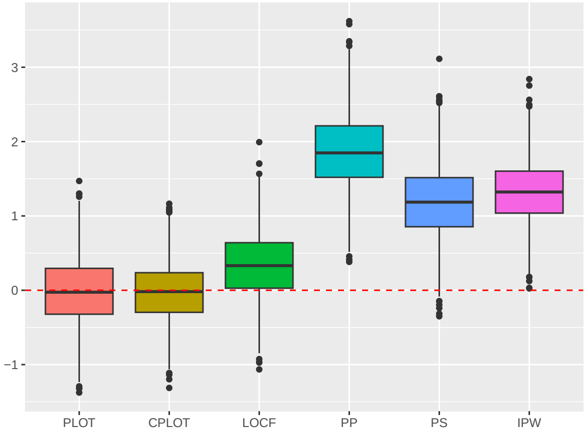
Example 1: Switching to rescue medication

- Patients (deterministically) switch to rescue medication at the first time t their blood sugar level $Z(t)$ exceeds a threshold.
- Treatment does not affect the outcome but it does affect $Z(t)$ for $t > 0$.



Example 2: Truncation by death

- Treatment does not affect outcome, but only survival time.
- Outcome at time t is normal with mean $\alpha_0 + \alpha_1 t + \alpha_2 L + \alpha_3 U$, with L an observed and U an unobserved common cause of outcome and survival.



Proposal

- T last time point before an ICE (dropout, rescue medication, etc.)
- Potential outcomes $Y^a(t)$ and T^a, under treatment $a = 0, 1$

Proposal:

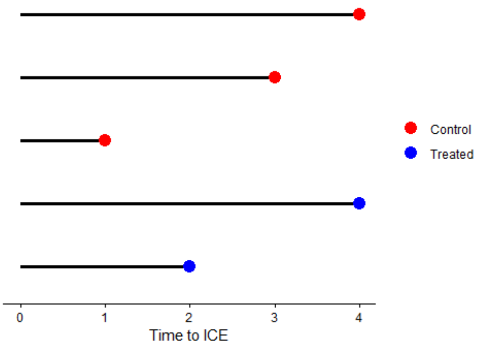
- Contrast the outcome of a treated individual with the outcome of an untreated individual at the last time $M = \min(T^1, T^{*0})$ both were observed prior to an ICE.

Pairwise Last Observation Time (PLOT) estimand

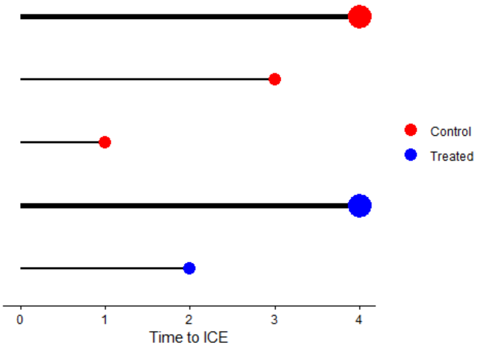
$$E\left\{Y^1(M) - Y^{*0}(M)\right\}$$

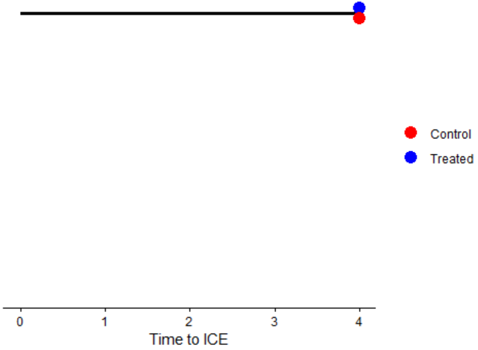
- Comparing at time M:
  - Entire population
  - Not hypothetical

Comparing treated and untreated at time M



COMPARING TREATED AND UNTREATED AT TIME M





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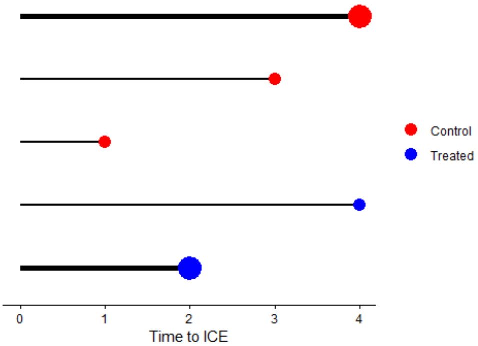

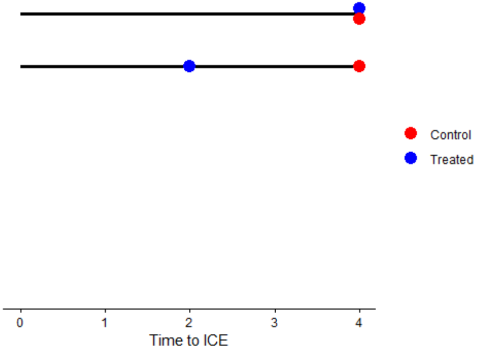

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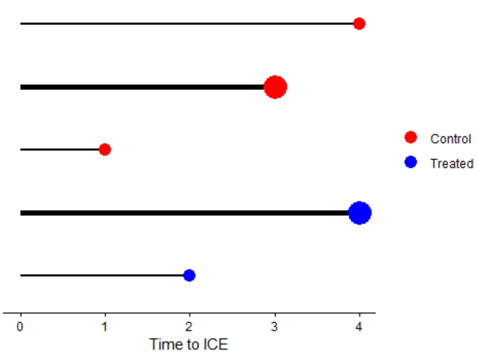

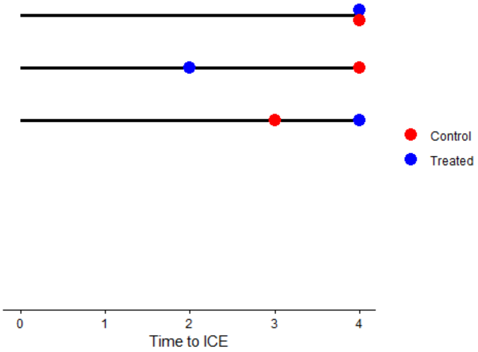

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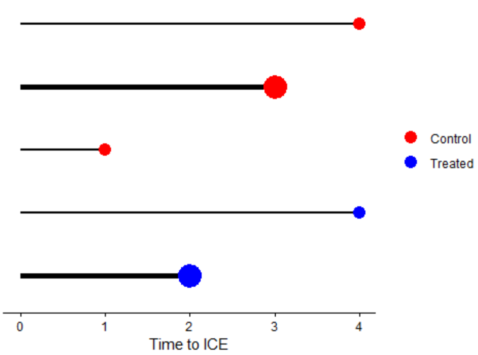

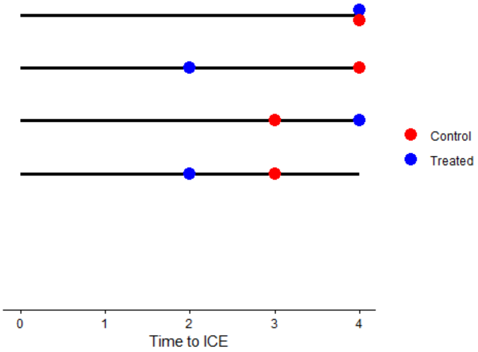

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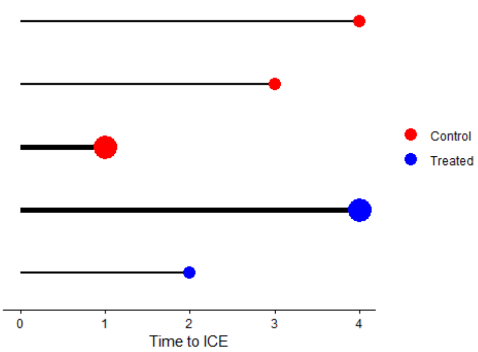

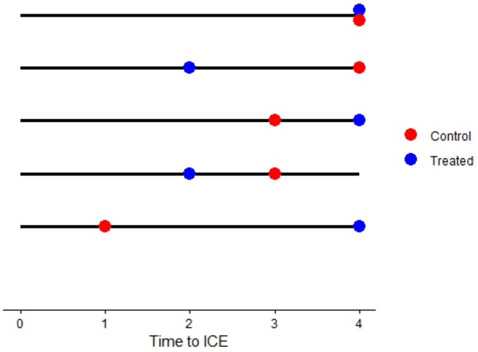

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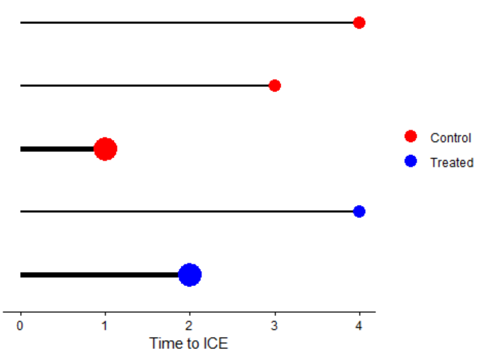

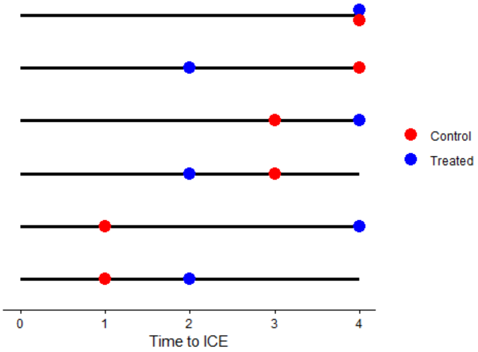

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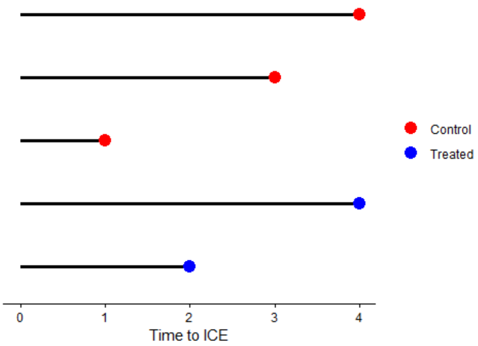
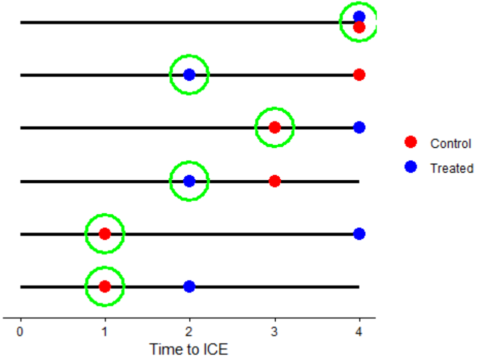




Conditional Pairwise Last Observation Time (CPLOT)

Estimand

Conditional Pairwise Last Observation Time (CPLOT) estimand

$$E\left[E\left\{Y^1(M) - Y^{*0}(M) | L = L^*\right\}\right] \qquad \text{with} \quad M = \min(T^1, T^{*0})$$

- Pairs of random, independent individuals with the same baseline covariates L, one treated but the other not.
- Generally different from PLOT estimand (non-collapsibility).
- When individuals with the same covariates are being considered, then the time at which both are ICE-free will tend to be larger.
- We view this estimand as being preferable by ‘truncating’ fewer measurements.

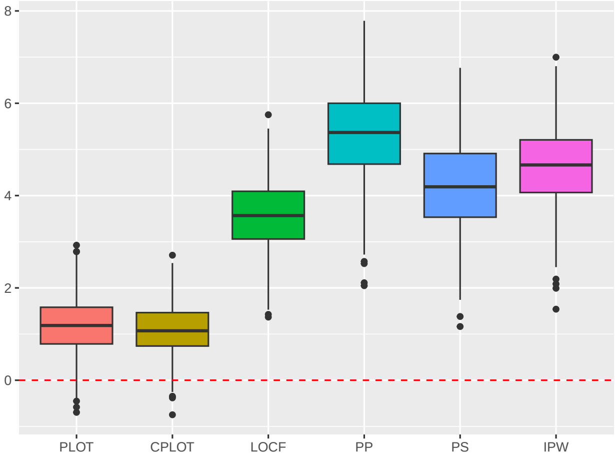
Identification, estimation and inference

- Straightforward identification and estimation of PLOT estimand without assumptions.
- Not straightforward for CPLOT estimand because of the curse of dimensionality.
- Express estimand using data from a single subject (without assumptions), and use standard debiased machine learning techniques for estimation and inference.
- The nuisance parameters include:

$$P(A=1),\ P(T>s|A,L),\ E\{Y(s)|A,L,T>s\},\ E\{Y(s)|A,L,T\geq s\},$$

  for all $s \leq \tau$.
- Asymptotic normality, with variance given by the variance of the influence functions.

Can treatment effect testing in trials with ICEs be nearly assumption-free?



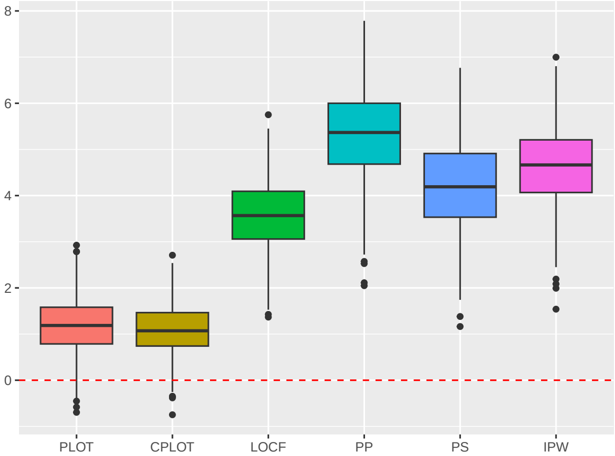
Can treatment effect testing in trials with ICEs be nearly assumption-free?

- Comparing outcomes at selected time points may yield nonzero estimands under the null.

$$E\left\{Y^1(\min(T^1, T^{*0})) - Y^{*0}(\min(T^1, T^{*0}))\right\} = E\left\{Y^1(\min(T^1, T^{*0})) - Y^0(\min(T^{*1}, T^0))\right\}$$

- Standard causal inference framework:
  (1) Estimand, (2) Assumptions to identify the estimand from observable data, (3) Estimator.
- We started from observable data and constructed estimands that make clever use of it.
- Then, we investigated the assumptions for valid treatment effect testing.
- We prove that our proposal works under essentially the same assumptions as competitive methods and even relax some assumptions.

Can treatment effect testing in trials with ICEs be nearly assumption-free?



KEY TAKEAWAYS

- New estimands for treatment effect testing that avoid hypothetical thinking.
- Asymptotically valid inference for the entire population.
- Weaker assumptions than alternative methods.

QUESTIONS?

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