A NOVEL ESTIMAND FOR RCTS WITH RESCUE MEDICATION

THE LINK WITH MEDIATION ANALYSIS

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Joint work with Stijn Vansteelandt and An Vandebosch

DISCLAIMER

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CANAGLIFLOZIN PHASE 3 MONOTHERAPY STUDY[1]

- Patients with diabetes type 2
- 584 patients received CANA 100 or 300 mg or placebo once daily
- Primary endpoint: change from baseline in haemoglobin A1c (HbA1c) at week 26

[1] K Stenlöf e.a. “Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise”. In: *Diabetes, Obesity and Metabolism* 15.4 (2013), p. 372–382.

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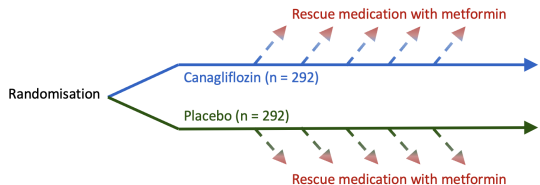
Rescue medication

- Glycaemic rescue therapy with metformin
- Initiated based on the observed fasting plasma glucose (FPG) value
- Large imbalance in use of rescue medication (20% more in control arm)
- Intention-to-treat / treatment policy effect typically leads to reduced treatment effect



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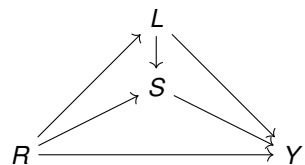
ESTIMANDS

Notation

- R: CANA 100 mg (1) or placebo (0)
- Y: Change from baseline in HbA1c at week 26
- S: Switched to rescue medication during trial (1) or not (0)
- L: Fasting plasma glucose (FPG) (determines switching)
- Counterfactuals: e.g. $Y(R = r)$: potential outcome under treatment $R = r$



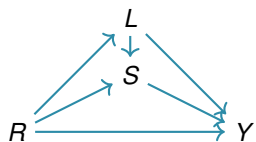
- Both S and L are mediators between R and Y
- Assumption: switching happens at one pre-specified time point in the trial

TREATMENT POLICY ESTIMAND

Treatment policy estimand

- Total effect of the treatment on the outcome:
  combined effect of randomized and rescue treatment
- The intercurrent event is considered irrelevant
- Comparing outcomes under treatment with those under control:

$$E[Y(R = 1) - Y(R = 0)]$$



HYPOTHETICAL ESTIMANDS ARE PRONE TO EXTRAPOLATION

Hypothetical estimand

Treatment effect if patients had no access to rescue medication

$$E[Y(R = 1, S = 0) - Y(R = 0, S = 0)]$$

Corresponds to a controlled direct effect from mediation analysis

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Corresponds to a controlled direct effect from mediation analysis

- Of limited use for policy making if rescue medication is needed for ethical reasons
- The hypothetical estimand cannot always be identified
  - Deterministic switching
  - Protocols often state strict guidelines about when patients are allowed to start rescue therapy, e.g. observed FPG values above a certain threshold
  - Violates the positivity assumptions: $P(S = 0|L, R = r) > 0$
- Inverse probability weights are often very unstable
- Imputation strategies are prone to extrapolation

BALANCED ESTIMAND

BALANCED ESTIMAND[2]

- To lessen the extent of extrapolation,
  we propose to evaluate the treatment effect if rescue medication were balanced across arms

Balanced estimand

Treatment effect, had patients on the control been switched to rescue medication
if and only if they would have been switched when randomised to active treatment

[2] Hege Michiels e.a. “A novel estimand to adjust for rescue treatment in randomized clinical trials”. In: *Statistics in Medicine* 40.9 (2021), p. 2257–2271.

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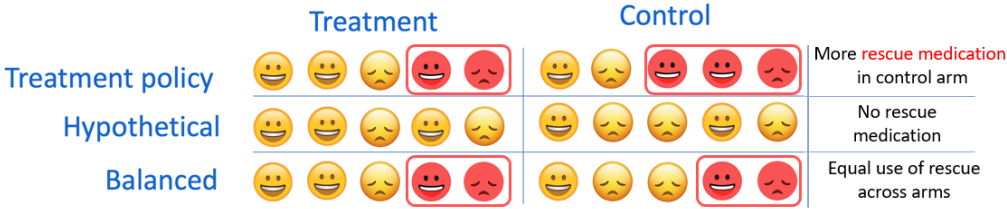

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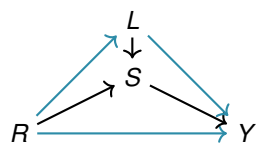
BALANCED ESTIMAND

Treatment effect, had patients on placebo been switched to rescue medication if and only if they would have been switched when randomised to CANA 100 mg:

$$E[Y(1, S(1)) - Y(0, S(1))] = E[Y(1) - Y(0, S(1))]$$

with $Y(r, S(1))$: potential outcome under treatment $R = r$ with switching as under active

- Corresponds to a natural direct effect from mediation analysis
- Distinguishes effect of randomised treatment from rescue
- Variant of hypothetical estimand
- Preserves one observed arm, bringing it closer to reality
- Use of rescue medication is balanced across arms
- More realistic scenario where patients can switch



Identification of the balanced estimand

$E[Y(1)]$ CAN BE IDENTIFIED FROM THE OBSERVED DATA

$E[Y(1)]$

Expected outcome had all patients been randomised to CANA 100 mg

Identified as the average outcome in experimental group:

$$E[Y(1)] = E[Y(1)|R = 1] = E[Y|R = 1],$$

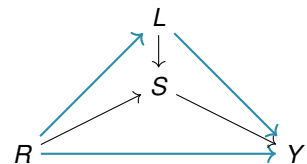
assuming $R \perp\!\!\!\perp Y(1)$ (implied by randomization)

IDENTIFICATION OF $E[Y(0, S(1))]$ IS CHALLENGING

$E[Y(0, S(1))]$

Expected outcome had all patients been randomised to placebo and switched to rescue medication if they would have been switched when randomised to CANA 100 mg

- Cannot be identified without untestable assumptions
  - Potential outcome $Y(0, S(1))$ is never observed
- Post-treatment confounding
- Existing methods do not identify paths of interest
- L possibly high-dimensional
- Avoiding to model the joint density of $L(0)$ and $L(1)$



Identification of $E[Y(0, S(1))]$

Inverse probability weighting (IPW) estimator

$$E\left(Y(0, S(1))\right) = E\left(Y\frac{P(S(1)|L(0), R=1)}{P(S(0)|L(0), R=0)}\middle| R=0\right) = E\left(Y\frac{P(S|L(0), R=1)}{P(S|L(0), R=0)}\middle| R=0\right)$$

(Assuming randomised treatment and cross-worlds independence)

- $P(S=1|L(0), R=0)$
  - $P(S=1|L, R=0)$
  - Probability to initiate rescue medication when assigned to placebo, **given the observed FPG**
  - Can be estimated based on observed data
- $P(S=1|L(0), R=1)$
  - Probability to initiate rescue medication when assigned to CANA 100 mg, **given the FPG values that would have been observed under placebo**
  - FPG values under placebo not observed for patients in CANA 100 mg group
  - How to estimate this probability?

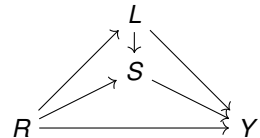
Sensitivity analysis for $P(S = 1|L(0), R = 1)$

1. Estimate probability to switch under placebo
   e.g. $P(S = 1|L(0), R = 0) = \text{expit}(\omega_1 + \omega_2 L(0))$
   - ω_2: effect of FPG on switching in the placebo group
2. Estimate probability to switch under CANA 100 mg
   $P(S = 1|L(0), R = 1) = \text{expit}(\lambda_1 + \rho\hat{\omega}_2 L(0))$
   - $\rho \leq 1$: sensitivity parameter
   - $\rho\hat{\omega}_2$: effect of FPG under placebo on switching in the CANA 100 mg group
   - Parameter λ_1 can be estimated by solving estimating equations, extracting information from the marginal probability of switching under CANA 100 mg: $P(S = 1|R = 1)$

IDENTIFICATION ASSUMPTIONS

- No unmeasured confounders (implied by randomisation):

$$R \perp\!\!\!\perp Y(r)$$
$$R \perp\!\!\!\perp \{Y(0,s), S(1), L(0)\}$$



  - L is only common cause of switching S and outcome Y
    "Potential decision to switch can be fully attributed to the observed FPG values"
    This implies
    - Cross-world independence assumption: $Y(0,s) \perp\!\!\!\perp S(1)|L(0)$
    - Ignorability assumption: $Y(0,s) \perp\!\!\!\perp S|L, R = 0$

POSITIVITY ASSUMPTION

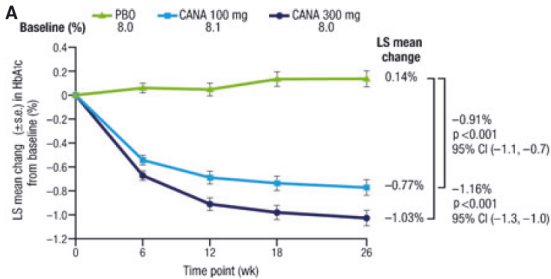
$$E\left(Y(0, S(1))\right) = E\left(Y \frac{P(S|L(0), R=1)}{P(S|L(0), R=0)} \middle| R=0\right)$$

- If $P(S=1|L(0), R=0) = 0$, then also $P(S=1|L(0), R=1) = 0$
  "Patients who are guaranteed not to switch on control, must also be guaranteed not to switch on treatment"
- If $P(S=1|L(0), R=0) = 1$, then also $P(S=1|L(0), R=1) = 1$
  "Patients who are guaranteed to switch on control, must also be guaranteed to switch on treatment"

Data analysis

CANAGLIFLOZIN MONOTHERAPY STUDY[3]

PRIMARY (PUBLISHED) ANALYSIS

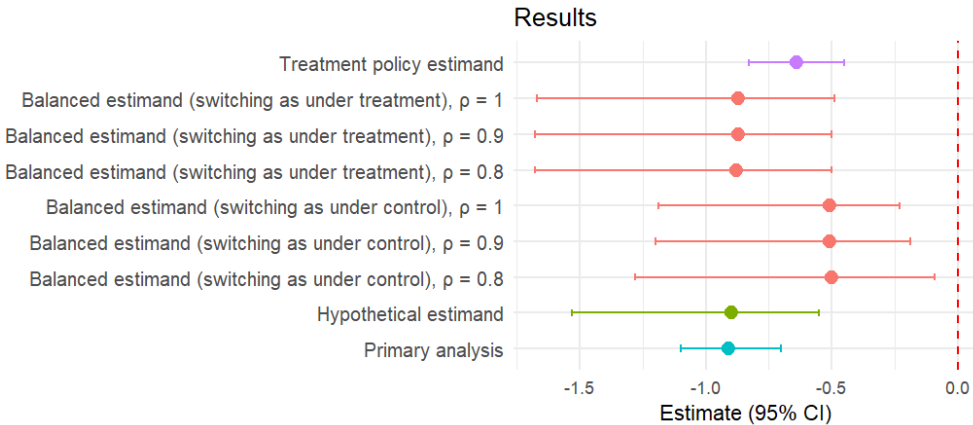


- Missing values were imputed using last-observation-carried-forward approach
- For patients who received rescue therapy, last value prior to initiation of rescue was used
- Difference in mean changes was -0.91% [-1.1; -0.7] for CANA 100 mg relative to placebo

[3] K Stenlöf e.a. “Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise”. In: *Diabetes, Obesity and Metabolism* 15.4 (2013), p. 372–382.

CANAGLIFLOZIN MONOTHERAPY STUDY

RESULTS ON PRIMARY ENDPOINT



Conclusions

Balanced estimand

- Less ambitious than hypothetical estimand
- The estimand allows to decide on the effectiveness of a treatment
- Corresponds to natural direct effect from mediation analysis

Novel IPW estimator

- We developed a novel inverse-probability-weighting estimator and sensitivity analysis to account for post-treatment confounding
- The estimator relies on the assumption of no unmeasured confounders between switching and the outcome
  - This assumption may well be met in the Canagliflozin trial as switching is based on measured confounders
  - The hypothetical estimand also needs this assumption
- The positivity assumption of the balanced estimand is a relaxation of the one needed for the hypothetical estimand

A NOVEL ESTIMAND FOR RCTS WITH RESCUE MEDICATION

VLAIO PROJECT HBC.2019.2155

Michiels, H., Sotto, C., Vandebosch, A., Vansteelandt, S. (2021). A novel estimand to adjust for rescue treatment in randomized clinical trials. *Statistics in Medicine, 40*(9).

APPENDICES

CANAGLIFLOZIN MONOTHERAPY STUDY

BALANCED ESTIMAND

- Baseline variables were included
- Assumption: switching happened at one pre-specified time point
  - Longitudinal FPG (variable *L*) was summarized
  - Average before week 26 for non-switchers
  - Average before initiation of rescue for switchers
- Missing values were imputed using multiple imputations[4]
- Variance of estimators: Multiple imputation Boot pooled sample method[5]

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[4] Donald B Rubin. *Multiple imputation for nonresponse in surveys*. Deel 81. John Wiley & Sons, 2004.

[5] Michael Schomaker en Christian Heumann. "Bootstrap inference when using multiple imputation". In: *Statistics in medicine* 37.14 (2018), p. 2252–2266.

SENSITIVITY PARAMETER ρ

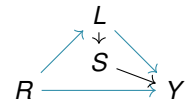
- Probability to switch under placebo
  $P(S = 1|L(0), R = 0) = \text{expit}(\omega_1 + \omega_2 L(0))$
- Probability to switch under CANA 100 mg
  $P(S = 1|L(0), R = 1) = \text{expit}(\lambda_1 + \rho\hat{\omega}_2 L(0))$

ρ

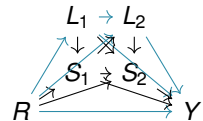
- Expresses to what extent the association between switching and FPG values under placebo is weaker in the CANA 100 mg group than in the placebo group
- Needs to be specified and can be used as sensitivity parameter
- Correlation between $L(0)$ and $L(1)$ under certain data generating mechanisms
- $\rho = 0$: switching in CANA 100 mg group is independent of $L(0)$
- $\rho = 1$: effect of $L(0)$ on switching is the same in both treatment arms
- Varying ρ over $[0.8, 1]$ will often be a good choice

BALANCED ESTIMAND: FUTURE RESEARCH

- Setting without direct effect of R on S was considered
  - At first glance it seems like it would be sufficient to correct for S, leading to a more simple estimator for the balanced estimand
  - However, this is not sufficient since necessary assumptions have been violated
    - Shows that violation of identification assumptions often happens subtly



- Extension to the setting with switching at multiple time points is challenging
  - Balanced estimand becomes complex: $E\left(Y^{1L_1^1 S_1^0 L_2^{1L_1^1 S_1^{0L_1^0}} S_2^0} - Y^0\right)$
  - Identification requires information on the joint distribution of $L_1(0)$ and $L_1(1)$, while these are never jointly observed and can be high-dimensional



- Interventional effects (VanderWeele et al. 2014) assume L and S to be independent, which is unrealistic in this setting

PRINCIPAL STRATIFICATION ESTIMAND

Principal stratification estimand [6]

Treatment effect for patients who would never need rescue medication (regardless of the assigned treatment):

$$E[Y(1) - Y(0)|S(1) = S(0) = 0]$$

- Effect for non-identifiable and selective subgroup of the population
- Identification relies on strong assumptions
  - Some of these assumptions are often inevitably violated (Vansteelandt and Van Lancker 2024)

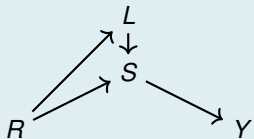
[6] Constantine E Frangakis en Donald B Rubin. "Principal stratification in causal inference". In: *Biometrics* 58.1 (2002), p. 21–29.

BALANCED ESTIMAND HAS RELEVANCE FOR TESTING THE H_0

Important to always protect the null hypothesis of no treatment effect (Vansteelandt 2023)

Null hypothesis

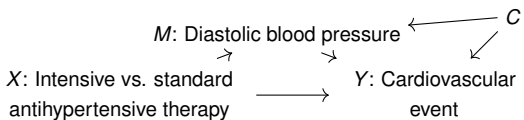
Treatment only affects outcome through the use of rescue treatment



- Treatment policy estimand will not evaluate to 0
  - Combined effect of randomized and rescue treatment
- Balanced and hypothetical estimand lead to effect estimate of 0
- Principal stratification estimands also have this property,
  but can equal zero even when the treatment is beneficial or harmful for some patients

CONTROLLED VS. NATURAL DIRECT EFFECTS

- Controlled direct effects (Robins and Greenland 1992)
  - E.g. Fixing the diastolic blood pressure at 60 mmHg: $E[Y(1,60) - Y(0,60)]$
  - Limitations (VanderWeele and Vansteelandt 2009)
    - Often not realistic to force the mediator to be the same for all subjects in the population
    - Indirect effects cannot be defined similarly
    - Even if the treatment has no effect on the mediator, the direct effect may differ from the total effect
- Natural direct effects
  - Fixing the mediator to the natural value it would have been under $X = x$
  - E.g. Fixing the diastolic blood pressure to the value it would have been under control: $E[Y(1, M(0) - Y(0, M(0)]$
  - Total effect can be decomposed into natural direct and indirect effect
  - Requires cross-worlds assumption (Pearl 2001) for identification



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