Inference for Cumulative Incidences and Treatment Effects in Randomized Controlled Trials with Time-to-Event Outcomes under ICH E9 (E1)

Yuhao Deng

Beijing International Center for Mathematical Research (BICMR), Peking University

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Outline

1. Setup of Time-to-Event Data with Intercurrent Events
2. Estimands under the Five Strategies of ICH E9 (R1)
3. Identification, Estimation and Inference
4. Application to LEADER Trial
5. Discussion

This is joint work with

- Shasha Han (Chinese Academy of Medical Sciences & Peking Union Medical College, China)
- Henrik Ravn (Novo Nordisk, Denmark)
- Kajsa Kvist (Novo Nordisk, Denmark)
- Xiao-Hua Zhou (Peking University, China)

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Intercurrent Events

- Intercurrent events refer to the events "occurring after treatment initiation that affect either the interpretation of or the existence of the measurements associated with the clinical question of interest" (ICH, 2019).
- Two types of intercurrent events:
  1. Semi-competing risks – modifying the hazard of primary outcome event (e.g., Fine et al., 2001).
  2. Competing risks – preventing the primary outcome event from happening (e.g., Fine and Gray, 1999).

Estimands

- Several studies have studied the five strategies for binary and continuous outcomes (e.g., Ratitch et al., 2020; Ionan et al., 2023; Han and Zhou, 2023).
- Estimand: Average treatment effect by contrasting potential outcomes.
- Challenges when extending to time-to-event outcomes: Failure times possibly not observable because of censoring.
- Solution: To define estimands by contrasting distribution of failure times.
- Cumulative incidence on the risk scale is collapsible.

ICH E9 (R1)

- The International Conference on Harmonization (ICH) E9 (R1) addendum on *estimands and sensitivity analysis in clinical trials* to the guideline on *statistical principles for clinical trials* (ICH, 2019).
- Five strategies to address intercurrent events: treatment policy strategy, composite variable strategy, hypothetical strategy, while on treatment strategy, and principal stratum strategy.
- For simplicity, we only consider one intercurrent event in this talk.
- Strategies can be combined to deal with multiple intercurrent events.

Notations

- Consider a randomized controlled trial (RCT) with n individuals.
- W: binary treatment.
- $T(w)$: potential time to primary outcome event (if any).
- $R(w)$: potential time to intercurent event (if any).
- An upper limit for the monitoring time since treatment initiation is set to be t^*.
- If primary outcome events are prevented by intercurrent events, denote $T(w) = \infty$.
- If no intercurrent events happen until t^*, denote $R(w) = \infty$ or $R(w) > t^*$.

Forms of Estimands

- We use $\mu_w^k(t)$ to denote the cumulative incidence of the primary outcome event under treatment condition w and strategy k.
- Treatment effect

$$\tau^k(t) = \mu_1^k(t) - \mu_0^k(t).$$

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Treatment Policy Strategy

- The treatment policy strategy addresses intercurrent events by expanding the initial treatment conditions to a treatment policy (intention-to-treat).
- Treatments under comparison are now two treatment policies, the assignment of test drug plus the occurrence of intercurrents as natural versus the assignment of placebo plus the occurrence of intercurrents as natural.
- This strategy is valid only if primary outcome events cannot be prevented by intercurrent events.

$$\begin{aligned}\tau^{\text{tp}}(t) &:= \mu_1^{\text{tp}}(t) - \mu_0^{\text{tp}}(t) \\ &:= \Pr(T(1, R(1)) < t) - \Pr(T(0, R(0)) < t) \\ &= \Pr(T(1) < t) - \Pr(T(0) < t).\end{aligned}$$

Composite Variable Strategy

- The composite variable strategy addresses intercurrent events by expanding the outcome variables. It aggregates the intercurrent events and primary outcome variable as one composite outcome variable.
- The idea is not new in the notion of progression-free survival.
- One widely used composite outcome variable has the form $R(w) \wedge T(w) = \min\{T(w), R(w)\}$.

$$\begin{aligned}\tau^{\text{cv}}(t) &:= \mu_1^{\text{cv}}(t) - \mu_0^{\text{cv}}(t) \\ &:= \Pr(R(1) \wedge T(1) < t) - \Pr(R(0) \wedge T(0) < t).\end{aligned}$$

- Other form: quality-adjusted lifetime.

While On Treatment Strategy

- The while on treatment strategy considers the measure of outcome variables taken only up to the occurrence of intercurrent events.
- The failures of primary outcome events should not be counted in the cumulative incidence if intercurrent events occurred.

$$\begin{aligned}\tau^{\text{wo}}(t) &:= \mu_1^{\text{wo}}(t) - \mu_0^{\text{wo}}(t) \\ &:= \Pr(T(1) < t, R(1) \geq t) - \Pr(T(0) < t, R(0) \geq t).\end{aligned}$$

- The $\mu_w^{\text{wo}}(t)$ is also known as cause-specific cumulative incidence or subdistribution function.

While On Treatment Strategy

- The while on treatment strategy is closely related to the competing risks models.
- The hazards of $R(1)$ and $R(0)$ can be different, leading to vast difference in the underlying features of individuals who have not experienced primary outcome events between treatment conditions until any time $0 \leq t \leq t^*$.
- If the scientific question of interest is the impact of treatment on the primary outcomes, the while on treatment estimand is hard to interpret if systematic difference in the risks of intercurrent events between the treatment conditions under comparison are anticipated.

The Above Three Strategies under Multi-State Models

- Competing risks structure: Let the original status, intercurrent events status and primary outcome events status be three compartments.

$$F_1^w(t) = \Pr(T(w) < t, R(w) \geq t),$$
$$F_2^w(t) = \Pr(R(w) < t).$$

- $\mu_w^{\text{wo}}(t) = F_1^w(t)$ is the probability of being in the state of primary outcome events.
- $\mu_w^{\text{cv}}(t) = F_1^w(t) + F_2^w(t)$ is the probability of being in either state of intercurrent events or primary outcome events.
- $\mu_w^{\text{tp}}(t)$ is not valid.

The Above Three Strategies under Multi-State Models

- Semi-competing risks structure: Let the original status, intercurrent events status, direct primary outcome events status and indirect primary outcome events status be four compartments.

$$
\begin{aligned}
F_1^w(t) &= \Pr(T(w) < t, R(w) \geq t), \\
F_2^w(t) &= \Pr(R(w) < t), \\
F_3^w(t) &= \Pr(T(w) < t, R(w) < t).
\end{aligned}
$$

- $\mu_w^{\text{wo}}(t) = F_1^w(t)$ is the probability of being in the state of direct primary outcome events.
- $\mu_w^{\text{cv}}(t) = F_1^w(t) + F_2^w(t)$ is the probability of being in either state of intercurrent events, direct or indirect primary outcome events.
- $\mu_w^{\text{tp}}(t) = F_1^w(t) + F_3^w(t)$ is the probability of being in either state of direct or indirect primary outcome events.

Hypothetical Strategy

- The hypothetical strategy envisions a hypothetical clinical trial condition where the occurrence of intercurrent events is restricted in certain ways.
- We use $T'(w)$ to denote the time to the primary outcome event in the hypothetical scenario.

$$\begin{aligned}\tau^{\text{hp}}(t) &:= \mu_1^{\text{hp}}(t) - \mu_0^{\text{hp}}(t) \\ &:= \Pr(T'(1) < t) - \Pr(T'(0) < t).\end{aligned}$$

- How to envision the hypothetical scenario?
- We only consider the competing risks structure here.

Hypothetical Strategy

- There can be many hypothetical scenarios envisioned by manipulating the hazard specific to intercurrent events

$$d\Lambda_2(t;w) := \Pr(t \leq R(w) < t + dt \mid T(w) \geq t, R(w) \geq t),$$

  while assuming the hazard specific to primary outcome events

$$d\Lambda_1(t;w) := \Pr(t \leq T(w) < t + dt \mid T(w) \geq t, R(w) \geq t)$$

  is unchanged.
- Let $d\Lambda_2'(t;w)$ and $d\Lambda_1'(t;w)$ be the hazards specific to intercurrent events and primary outcome events in the hypothetical scenario respectively, with $d\Lambda_1'(t;w) = d\Lambda_1(t;w)$, $w = 1, 0$.

Hypothetical Strategy: Scenario I

- The intercurrent events when individuals were assigned to test drugs were only permitted if such intercurrent events would have occurred if these individuals were assigned to placebo.
- In this hypothetical scenario, when assigned to placebo, individuals would be equally likely to experience intercurrent events as they are assigned to placebo in the real-world trial; when assigned to test drug, the hazard of intercurrent events would be identical to that assigned to placebo in the real-world trial.
- That is, $d\Lambda_2'(t;0) = d\Lambda_2'(t;1) = d\Lambda_2(t;0)$.

Hypothetical Strategy: Scenario II

- The intercurrent events are absent in the hypothetical scenario for all individuals.
- In this hypothetical scenario, $d\Lambda_2'(t;0) = d\Lambda_2'(t;1) = 0$.
- This hypothetical scenario leads to an estimand called the marginal cumulative incidence.

Principal Stratum Strategy

- The principal stratum strategy aims to stratify the population into subpopulations based on the joint potential occurrences of intercurrent events under the two treatment assignments $(R(1), R(0))$.
- We are interested in a principal stratum comprised of individuals who would never experience intercurrent events regardless of receiving which treatment $\{R(1) = R(0) = \infty\}$.

$$\begin{aligned}\tau^{\text{ps}}(t) &:= \mu_1^{\text{ps}}(t) - \mu_0^{\text{ps}}(t) \\ &:= \Pr(T(1) < t \mid R(1) = R(0) = \infty) \\ &\quad - \Pr(T(0) < t \mid R(1) = R(0) = \infty).\end{aligned}$$

Principal Stratum Strategy

- However, the target population is impossible to identify, not only because values of $R(1)$ and $R(0)$ are never observed simultaneously, but also due to the problem of censoring so whether $R(w) = \infty$ is unknown even under the treatment w.
- The target population would get smaller with increasing t^* except if there is an upper limit, which is smaller than t^* alomst surely, for the occurrence time of intercurrent events.
- Typically, untestable assumptions are attended to identify the principal stratum estimand.

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Observed Data

- Before describing the observed data structure, we update our notations to account for censoring.
- Each individual has two potential censoring times $C(1)$ and $C(0)$.
- Because of censoring, we are only able to partially observe potential primary outcome events through

$$\Delta^T(w) = \mathrm{I}\{T(w) \leq C(w)\}, \ \tilde{T}(w) = \min\{T(w), C(w)\},$$

and potential intercurrent events through

$$\Delta^R(w) = \mathrm{I}\{R(w) \leq C(w)\}, \ \tilde{R}(w) = \min\{R(w), C(w)\}.$$

- Observed data (under causal consistency):

$$\tilde{T} = \tilde{T}(W), \Delta^T = \Delta^T(W), \tilde{R} = \tilde{R}(W), \Delta^R = \Delta^R(W).$$

Assumptions

- Assumption 1: Randomization

$$W \perp (T(1), T(0), R(1), R(0)).$$

- Assumption 2: Independent censoring

$$C(w) \perp (T(w), R(w)) \mid W = w, \ \ w = 1, 0.$$

- Assumption 3: Positivity

$$\Pr(W = w) > 0, \ \Pr(C(w) > t^*) > 0, \ \ w = 1, 0.$$

- Assumption 4: Principal ignorability (required only for principal stratum strategy)

$$T(w) \perp R(1 - w) \mid R(w), \ \ w = 1, 0.$$

Treatment Policy Strategy: Identification

- Under Assumptions 1–3, the hazard function of the potential primary outcome event can be identified through

$$\begin{aligned} d\Lambda(t; w) &:= \Pr(t \leq T(w) < t + dt \mid T(w) \geq t) \\ &= \Pr(t \leq \tilde{T} < t + dt, \Delta^T = 1 \mid \tilde{T} \geq t, W = w). \end{aligned}$$

- Next, we can identify $\tau^{\text{tp}}(t)$ as

$$\tau^{\text{tp}}(t) = \exp\{-\Lambda(t; 0)\} - \exp\{-\Lambda(t; 1)\}.$$

Treatment Policy Strategy: Estimation

- To estimate this quantity, we need data $(\tilde{T}, \Delta^T, W)$.
- We write the event process and at-risk process of the primary outcome event as follows,

$$N(t; w) = \sum_{i=1}^{n} \mathrm{I}\{\tilde{T}_i \leq t, \Delta_i^T = 1, W_i = w\},$$

$$Y(t; w) = \sum_{i=1}^{n} \mathrm{I}\{\tilde{T}_i \geq t, W_i = w\}.$$

- The cumulative hazard function $\Lambda(t; w)$, $w = 1, 0$ is then consistently and unbiasedly estimated by the Nelson-Aalen estimator

$$\widehat{\Lambda}(t; w) = \int_0^t \frac{dN(s; w)}{Y(s; w)}.$$

Treatment Policy Strategy: Inference

- We shall estimate $\mu_w^{\text{tp}}(t)$ and $\tau^{\text{tp}}(t)$ by plug-in estimators.
- The pointwise asymptotic variances of $\widehat{\mu}_w^{\text{tp}}(t)$ and $\widehat{\tau}^{\text{tp}}(t)$ are

$$\text{avar}\{\widehat{\mu}_w^{\text{tp}}(t)\} = \exp\{-2\Lambda(t;w)\} \cdot \text{E}\left\{\int_0^t \frac{d\Lambda(s;w)}{Y(s;w)}\right\},$$

$$\text{avar}\{\widehat{\tau}^{\text{tp}}(t)\} = \text{avar}\{\widehat{\mu}_1^{\text{tp}}(t)\} + \text{avar}\{\widehat{\mu}_0^{\text{tp}}(t)\}.$$

Treatment Policy Strategy: Testing

- The null and alternative hypotheses are

$$H_0^{\text{tp}} : \Lambda(t;1) = \Lambda(t;0),\ \forall\ t < t^*$$
$$\text{vs}\quad H_1^{\text{tp}} : \Lambda(t;1) \neq \Lambda(t;0),\ \exists\ t < t^*.$$

- For any left-continuous weight function $\omega(t)$, the test statistic

$$U^{\text{tp}} = \int_0^{t^*} \omega(s) \frac{Y(s;1)dN(s;0) - Y(s;0)dN(s;1)}{Y(s;1) + Y(s;0)}.$$

- Under the null,

$$n^{-1/2} U^{\text{tp}} \to_d N\left(0, \text{E} \int_0^{t^*} \omega(t)^2 \frac{Y(s;1)Y(s;0)\{dN(s;1) + dN(s;0)\}}{n\{Y(s;1) + Y(s;0)\}^2}\right).$$

Composite Variable Strategy: Identification

- Under Assumptions 1–3, the hazard function of the composite outcome variable $T(w) \wedge R(w)$ can be identified through

$$\begin{aligned} d\Lambda_{12}(t; w) &:= \Pr(t \leq T(w) \wedge R(w) < t + dt \mid T(w) \wedge R(w) \geq t) \\ &= \Pr(t \leq \tilde{T} \wedge \tilde{R} < t + dt, \Delta^T \vee \Delta^R = 1 \\ &\qquad \mid \tilde{T} \wedge \tilde{R} \geq t, W = w). \end{aligned}$$

- Next, $\tau^{\text{cv}}(t)$ is identified as

$$\tau^{\text{cv}}(t) = \exp\{-\Lambda_{12}(t; 0)\} - \exp\{-\Lambda_{12}(t; 1)\}.$$

Composite Variable Strategy: Estimation

- To estimate this quantity, we need data $(\tilde{T} \wedge \tilde{R}, \Delta^T \vee \Delta^R, W)$.
- We write the event process and at-risk process of the composite outcome event as follows,

$$N_{12}(t; w) = \sum_{i=1}^{n} \mathrm{I}\{\tilde{T}_i \wedge \tilde{R}_i \leq t, \Delta_i^T \vee \Delta_i^R = 1, W_i = w\},$$

$$Y_{12}(t; w) = \sum_{i=1}^{n} \mathrm{I}\{\tilde{T}_i \wedge \tilde{R}_i \geq t, W_i = w\}.$$

The cumulative hazard function $\Lambda_{12}(t; w)$ is estimated by

$$\widehat{\Lambda}_{12}(t; w) = \int_0^t \frac{dN_{12}(s; w)}{Y_{12}(s; w)}.$$

Composite Variable Strategy: Inference

- The pointwise asymptotic variances of the plug-in estimators of $\mu_w^{\text{cv}}(t)$ and $\tau^{\text{cv}}(t)$ are given by

$$\text{avar}\{\widehat{\mu}_w^{\text{cv}}(t)\} = \exp\{-2\Lambda_{12}(t;w)\} \cdot \text{E}\left\{\int_0^t \frac{d\Lambda_{12}(s;w)}{Y_{12}(s;w)}\right\},$$

$$\text{avar}\{\widehat{\tau}^{\text{cv}}(t)\} = \text{avar}\{\widehat{\mu}_1^{\text{cv}}(t)\} + \text{avar}\{\widehat{\mu}_0^{\text{cv}}(t)\}.$$

Composite Variable Strategy: Testing

- The null and alternative hypotheses are

$$H_0^{\text{cv}} : \Lambda_{12}(t;1) = \Lambda_{12}(t;0),\ \forall\ t < t^*$$
$$\text{vs}\quad H_1^{\text{cv}} : \Lambda_{12}(t;1) \neq \Lambda_{12}(t;0),\ \exists\ t < t^*.$$

- For any left-continuous weight function $\omega(t)$, the test statistic

$$U^{\text{cv}} = \int_0^{t^*} \omega(s) \frac{Y_{12}(s;1)dN_{12}(s;0) - Y_{12}(s;0)dN_{12}(s;1)}{Y_{12}(s;1) + Y_{12}(s;0)}.$$

- Under the null,

$$n^{-1/2} U^{\text{cv}} \to_d N\left(0, \text{E}\int_0^{t^*} \omega(t)^2 \frac{Y_{12}(s;1)Y_{12}(s;0)\{dN_{12}(s;1) + dN_{12}(s;0)\}}{n\{Y_{12}(s;1) + Y_{12}(s;0)\}^2}\right).$$

While On Treatment Strategy: Identification

- Under Assumptions 1–3, the hazard functions specific to primary outcome events and intercurrent events can be identified through

$$d\Lambda_1(t;w) = \Pr(t \le \tilde{T} < t + dt, \Delta^T = 1 \mid \tilde{T} \ge t, \tilde{R} \ge t, W = w),$$
$$d\Lambda_2(t;w) = \Pr(t \le \tilde{R} < t + dt, \Delta^R = 1 \mid \tilde{T} \ge t, \tilde{R} \ge t, W = w).$$

- In fact,

$$d\Lambda_1(t;w) + d\Lambda_2(t;w) = d\Lambda_{12}(t;w).$$

- Next, $\tau^{\text{wo}}(t)$ is identified as

$$\tau^{\text{wo}}(t) = \int_0^t \exp\{-\Lambda_{12}(s;1)\} d\Lambda_1(s;1) - \int_0^t \exp\{-\Lambda_{12}(s;0)\} d\Lambda_1(s;0).$$

While On Treatment Strategy: Estimation

- To estimate these quantities, we need data $(\tilde{T} \wedge \tilde{R}, \Delta^T, \Delta^R, W)$.
- We write the event processes and at-risk process as follows,

$$N_1(t; w) = \sum_{i=1}^{n} \mathrm{I}\{\tilde{T}_i \leq t, \Delta_i^T = 1, W_i = w\},$$

$$N_2(t; w) = \sum_{i=1}^{n} \mathrm{I}\{\tilde{R}_i \leq t, \Delta_i^R = 1, W_i = w\},$$

$$Y_{12}(t; w) = \sum_{i=1}^{n} \mathrm{I}\{\tilde{T}_i \geq t, \tilde{R}_i \geq t, W_i = w\}.$$

- The cumulative hazard function $\Lambda_j(t; w)$, $j = 1, 2$, is consistently and unbiasedly estimated by

$$\widehat{\Lambda}_j(t; w) = \int_0^t \frac{dN_j(t; w)}{Y_{12}(t; w)}.$$

While On Treatment Strategy: Inference

- The pointwise asymptotic variances of the plug-in estimators of $\mu_w^{\text{wo}}(t)$ and $\tau^{\text{wo}}(t)$ are given by

$$\text{avar}\{\widehat{\mu}_w^{\text{wo}}(t)\} = \text{E}\int_0^t \left[\{e^{-\Lambda_{12}(s;w)} - \mu_w^{\text{wo}}(t) + \mu_w^{\text{wo}}(s)\}^2 \frac{d\Lambda_1(s;w)}{Y_{12}(s;w)} + \{\mu_w^{\text{wo}}(t) - \mu_w^{\text{wo}}(s)\}^2 \frac{d\Lambda_2(s;w)}{Y_{12}(s;w)}\right],$$

$$\text{avar}\{\widehat{\tau}^{\text{wo}}(t)\} = \text{avar}\{\widehat{\mu}_1^{\text{wo}}(t)\} + \text{avar}\{\widehat{\mu}_0^{\text{wo}}(t)\}.$$

- No simple form for hypothesis testing.

Hypothetical Strategy I: Identification

- The estimand of hypothetical scenario I can be identified as

$$\tau^{\text{hs,I}}(t) = \int_0^t \exp\{-\Lambda_1(s;1) - \Lambda_2(s;0)\} d\Lambda_1(s;1) - \int_0^t \exp\{-\Lambda_1(s;0) - \Lambda_2(s;0)\} d\Lambda_1(s;0).$$

- Note that $\mu_0^{\text{hs,I}}(t)$ is identical to $\mu_0^{\text{wo}}(t)$ in the while on treatment strategy.
- Within the mediation analysis framework, $\tau^{\text{hs,I}}(t)$ represents the natural direct effect under sequential ignorability assuming no common causes for potential intercurrent events and primary outcome events.

Hypothetical Strategy I: Estimation, Inference

- We need data $(\tilde{T} \wedge \tilde{R}, \Delta^T, \Delta^R, W)$.
- The pointwise asymptotic variances of the plug-in estimators of cumulative incidences and treatment effects are

$$\begin{aligned}
\mathrm{avar}\{\widehat{\mu}_w^{\mathrm{hp,I}}(t)\} &= \mathrm{E}\int_0^t \{e^{-\Lambda_1(s;w)-\Lambda_2(s;0)} - \mu_w^{\mathrm{hp,I}}(t) + \mu_w^{\mathrm{hp,I}}(s)\}^2 \frac{d\Lambda_1(s;w)}{Y_{12}(s;w)} \\
&\quad + \mathrm{E}\int_0^t \{\mu_w^{\mathrm{hp,I}}(t) - \mu_w^{\mathrm{hp,I}}(s)\}^2 \frac{d\Lambda_2(s;0)}{Y_{12}(s;0)}, \\
\mathrm{avar}\{\widehat{\tau}^{\mathrm{hp,I}}(t)\} &= \mathrm{E}\int_0^t \{e^{-\Lambda_1(s;1)-\Lambda_2(s;0)} - \mu_1^{\mathrm{hp,I}}(t) + \mu_1^{\mathrm{hp,I}}(s)\}^2 \frac{d\Lambda_1(s;1)}{Y_{12}(s;1)} \\
&\quad + \mathrm{E}\int_0^t \{e^{-\Lambda_1(s;0)-\Lambda_2(s;0)} - \mu_0^{\mathrm{hp,I}}(t) + \mu_0^{\mathrm{hp,I}}(s)\}^2 \frac{d\Lambda_1(s;0)}{Y_{12}(s;0)} \\
&\quad + \mathrm{E}\int_0^t \{\mu_1^{\mathrm{hp,I}}(t) - \mu_0^{\mathrm{hp,I}}(t) - \mu_1^{\mathrm{hp,I}}(s) + \mu_0^{\mathrm{hp,I}}(s)\}^2 \frac{d\Lambda_2(s;0)}{Y_{12}(s;0)}.
\end{aligned}$$

Hypothetical Strategy II: Identification

- The estimand of hypothetical scenario II can be identified as

$$\tau^{\text{hs,II}}(t) = \int_0^t \exp\{-\Lambda_1(s;1)\} d\Lambda_1(s;1) - \int_0^t \exp\{-\Lambda_1(s;0)\} d\Lambda_1(s;0).$$

- Of note, $\tau^{\text{hs,II}}(t)$ evaluates the contrast of the marginal distributions of $T(1)$ and $T(0)$ with intercurrent events viewed as independent censoring.
- Within the mediation analysis framework, $\tau^{\text{hs,II}}(t)$ represents the controlled direct effect on the primary outcome event where the hazard specific to intercurrent events is controlled at zero under sequential ignorability.

Hypothetical Strategy II: Estimation, Inference

- We need data $(\tilde{T} \wedge \tilde{R}, \Delta^T, \Delta^R, W)$.
- The pointwise asymptotic variances of the plug-in estimators of cumulative incidences and treatment effects are

$$\text{avar}\{\widehat{\mu}_w^{\text{hp,II}}(t)\} = \exp\{-2\Lambda_1(t;w)\} \cdot \text{E} \int_0^t \frac{d\Lambda_1(t;w)}{Y_{12}(t;w)},$$

$$\text{avar}\{\widehat{\tau}^{\text{hp,II}}(t)\} = \text{avar}\{\widehat{\mu}_1^{\text{hp,II}}(t)\} + \text{avar}\{\widehat{\mu}_0^{\text{hp,II}}(t)\}.$$

Hypothetical Strategy: Testing

- The null and alternative hypotheses are

$$H_0^{\text{hp}} : \Lambda_1(t;1) = \Lambda_1(t;0),\ \forall\ t < t^*$$
$$\text{vs}\quad H_1^{\text{hp}} : \Lambda_1(t;1) \neq \Lambda_1(t;0),\ \exists\ t < t^*.$$

- For any left-continuous weight function $\omega(t)$, the test statistic

$$U^{\text{hp}} = \int_0^{t^*} \omega(s) \frac{Y_{12}(s;1)dN_1(s;0) - Y_{12}(s;0)dN_1(s;1)}{Y_{12}(s;1) + Y_{12}(s;0)}.$$

- Under the null,

$$n^{-1/2} U^{\text{hp}} \to_d N\left(0, \text{E}\int_0^{t^*} \omega(t)^2 \frac{Y_{12}(s;1)Y_{12}(s;0)\{dN_1(s;1) + dN_1(s;0)\}}{n\{Y_{12}(s;1) + Y_{12}(s;0)\}^2}\right).$$

Principal Stratum Strategy: Identification

- Assumption 4 states that the potential time to the primary outcome event $T(w)$ can be correlated with $R(w)$ but should not have cross-world reliance on $R(1-w)$.
- Therefore, the distribution of $T(w)$ is identical in the group $\{R(w)=\infty\}$ and the principal stratum $\{R(1)=R(0)=\infty\}$.

$$
\begin{aligned}
\mu^{\text{ps}}(t) &= \Pr(T(w)<t \mid R(1)=\infty, R(0)=\infty) \\
&= \Pr(T(w)<t \mid R(w)=\infty) \\
&= \frac{\Pr(T(w)<t, R(w)=\infty)}{\Pr(R(w)=\infty)} = \frac{\Pr(T(w)<t, R(w)\geq t)}{\Pr(R(w)>t^*)} \\
&= \frac{\int_0^t \exp\{-\Lambda_{12}(s;w)\} d\Lambda_1(s;w)}{1-\int_0^{t^*} \exp\{-\Lambda_{12}(s;w)\} d\Lambda_2(s;w)}.
\end{aligned}
$$

Principal Stratum Strategy: Estimation, Inference

- We need data $(\tilde{T} \wedge \tilde{R}, \Delta^T, \Delta^R, W)$.
- The pointwise asymptotic variances of the plug-in estimators of $\mu_w^{\text{ps}}(t)$ and $\tau^{\text{ps}}(t)$ are given by

$$\begin{aligned}\text{avar}\{\widehat{\mu}_w^{\text{ps}}(t)\} = \text{E} \int_0^t \Bigg[&\{1 - e^{-\Lambda_{12}(t;w)}\}^2 \frac{d\Lambda_1(s;w)}{Y_{12}(s;w)} \\ &+ \{e^{-\Lambda_{12}(t;w)} - e^{-\Lambda_{12}(s;w)}\}^2 \frac{d\Lambda_2(s;w)}{Y_{12}(s;w)} \Bigg] \\ &\cdot \left[1 - \int_0^{t^*} e^{-\Lambda_{12}(s;w)} d\Lambda_2(s;w)\right]^{-2},\end{aligned}$$

$$\text{avar}\{\widehat{\tau}^{\text{ps}}(t)\} = \text{avar}\{\widehat{\mu}_1^{\text{ps}}(t)\} + \text{avar}\{\widehat{\mu}_0^{\text{ps}}(t)\}.$$

- No simple form for hypothesis testing.

A Comparison

Table: A comparison of five strategies

Strategy	Data	Hypothesis testing	Practical interpretation
Treatment policy	$\tilde{T}, \Delta^T$	Available	Effect on primary outcomes with intercurrent events as natural
Composite variable	$\tilde{T} \wedge \tilde{R}$, $\Delta^T \vee \Delta^R$	Available	Effect on composed primary outcomes and intercurrent events
While on treatment	$\tilde{T} \wedge \tilde{R}$, Δ^T, Δ^R	Not simple	Effect on primary outcomes counted up to intercurrent events
Hypothetical	$\tilde{T} \wedge \tilde{R}$, Δ^T, Δ^R	Available	Effect on primary outcomes after adjusting the hazard of intercurrent events
Principal stratum	$\tilde{T} \wedge \tilde{R}$, Δ^T, Δ^R	Not simple	Effect on primary outcomes in a subpopulation determined by the potential occurrences of intercurrent events

Artificial Example

- Suppose that the hazard specific to the potential primary outcome event is $\lambda_1(t; w) = a_w t$.
- Suppose that the hazard specific to the intercurrent event is $\lambda_2(t; w) = c_w$.
- Suppose the intercurrent event would neither prevent nor modify the hazard of the primary outcome event.
- Therefore, the marginal distribution of the potential primary outcome event $T(w) \sim \mathit{Weibull}(2, \sqrt{2/a_w})$.

Artificial Example

Table: Comparison of estimands under the five strategies

k	Cumulative incidence $\mu_w^k(t)$, $0 \leq t \leq t^*$
tp	$1 - e^{-a_w t^2/2}$
cv	$1 - e^{-a_w t^2/2 - c_w t}$
wo	$1 - e^{-a_w t^2/2 - c_w t} - e^{c_w^2/2a_w}\sqrt{2\pi c_w^2/a_w}\{\Phi(\sqrt{a_w}(t + c_w/a_w)) - \Phi(c_w/\sqrt{a_w})\}$
hp	$1 - e^{-a_w t^2/2 - c'_w t} - e^{c_w'^2/2a_w}\sqrt{2\pi c_w'^2/a_w}\{\Phi(\sqrt{a_w}(t + c'_w/a_w)) - \Phi(c'_w/\sqrt{a_w})\}$
ps	$\frac{1-e^{-a_w t^2/2 - c_w t} - e^{c_w^2/2a_w}\sqrt{2\pi c_w^2/a_w}\{\Phi(\sqrt{a_w}(t+c_w/a_w)) - \Phi(c_w/\sqrt{a_w})\}}{1-e^{c_w^2/2a_w}\sqrt{2\pi c_w^2/a_w}\{\Phi(\sqrt{a_w}(t^*+c_w/a_w)) - \Phi(c_w/\sqrt{a_w})\}}$

Remark: $\Phi(\cdot)$ denotes the cdf of standard normal distribution.

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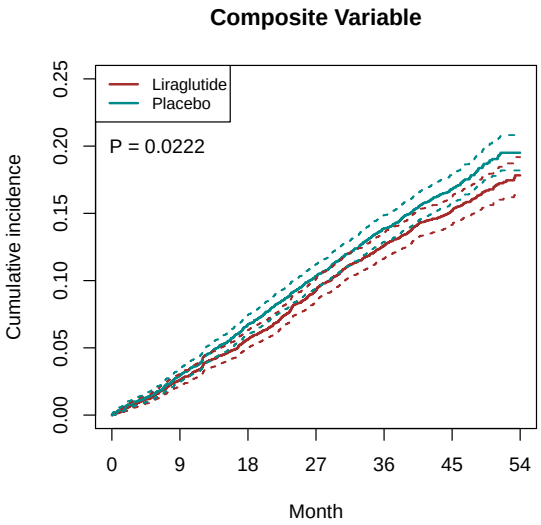
LEADER Trial

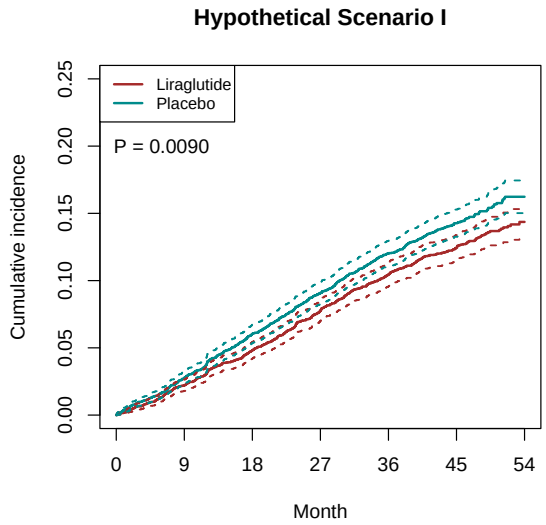
- The LEADER Trial was conducted at 410 clinical research sites in 32 countries as part of a large global phase 3a clinical development program (Marso et al., 2016).
- A target sample including 9340 patients was randomly assigned to liraglutide (a glucagon-like peptide-1 receptor against) or placebo for assessment of the long-term efficacy of liraglutide in preventing cardiovascular outcomes.
- However, a substantial number of patients died due to other reasons before the measurement of primary outcome events.
- We conduct two analyses to evaluate the effect of liraglutide on cardiovascular outcomes.

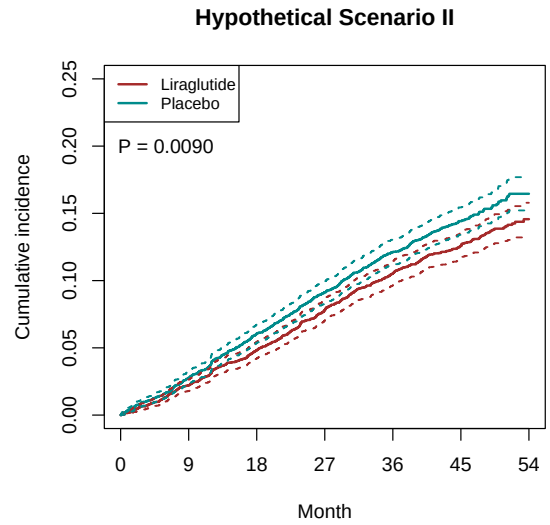
Endpoint I (MACE)

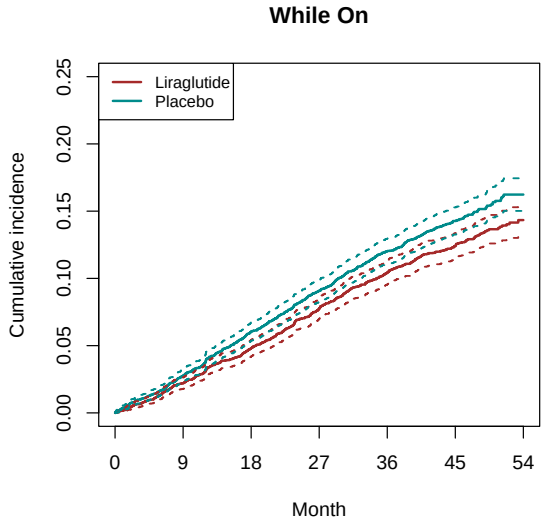
- In Endpoint I, we consider the occurrence of major adverse cardiovascular events (MACE, including non-fatal cardiovascular events and cardiovascular death) as the primary outcome event, and non-cardiovascular death (NCVD) as the intercurrent event.
- Of the individuals taking liraglutide, 608 had major adverse cardiovascular events and 137 died due to non-cardiovascular reasons.
- Of the individuals taking placebo, 694 had major adverse cardiovascular events and 133 died due to non-cardiovascular reasons.

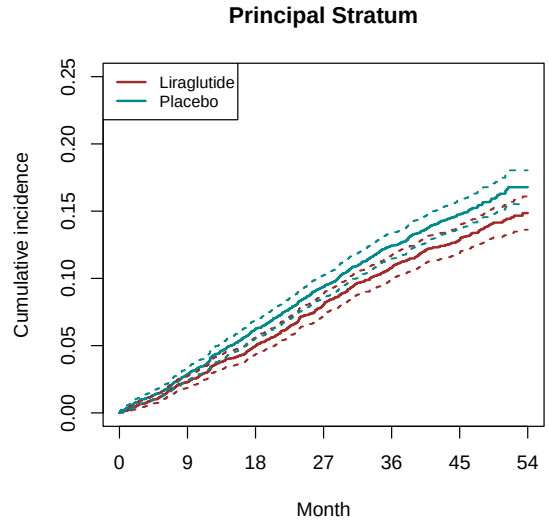
Endpoint I: Cumulative Incidences



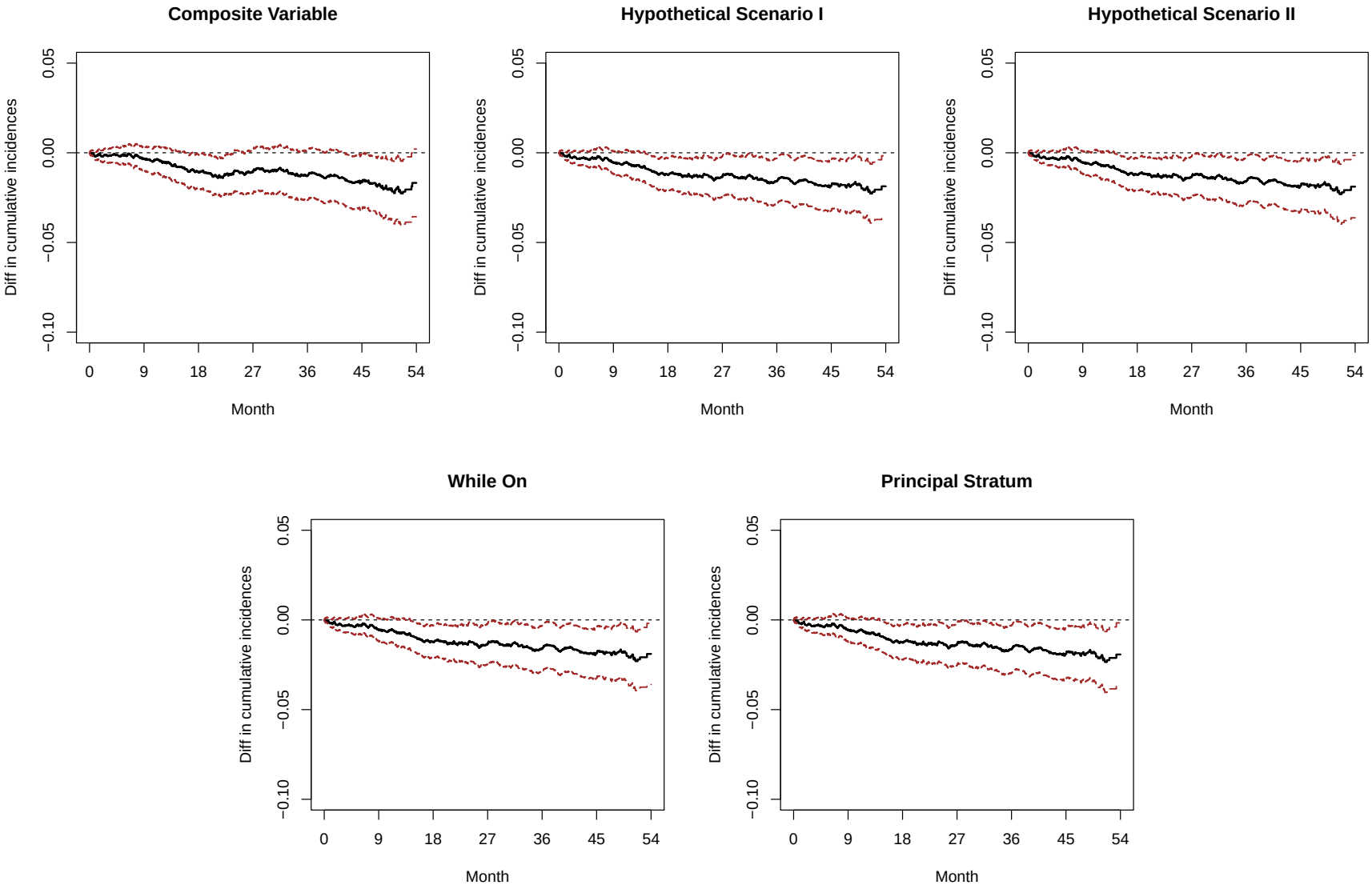








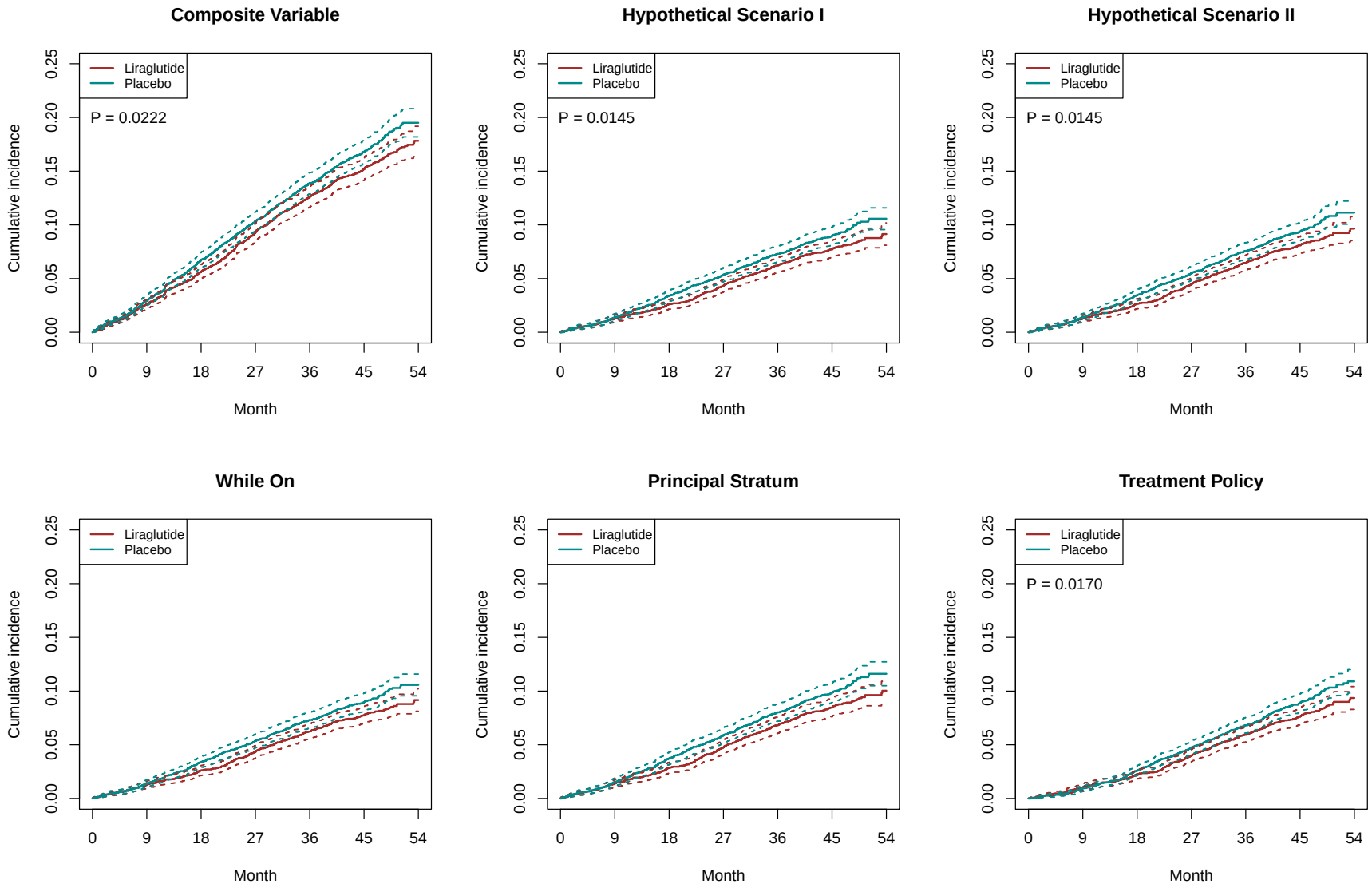
Endpoint I: Treatment Effects



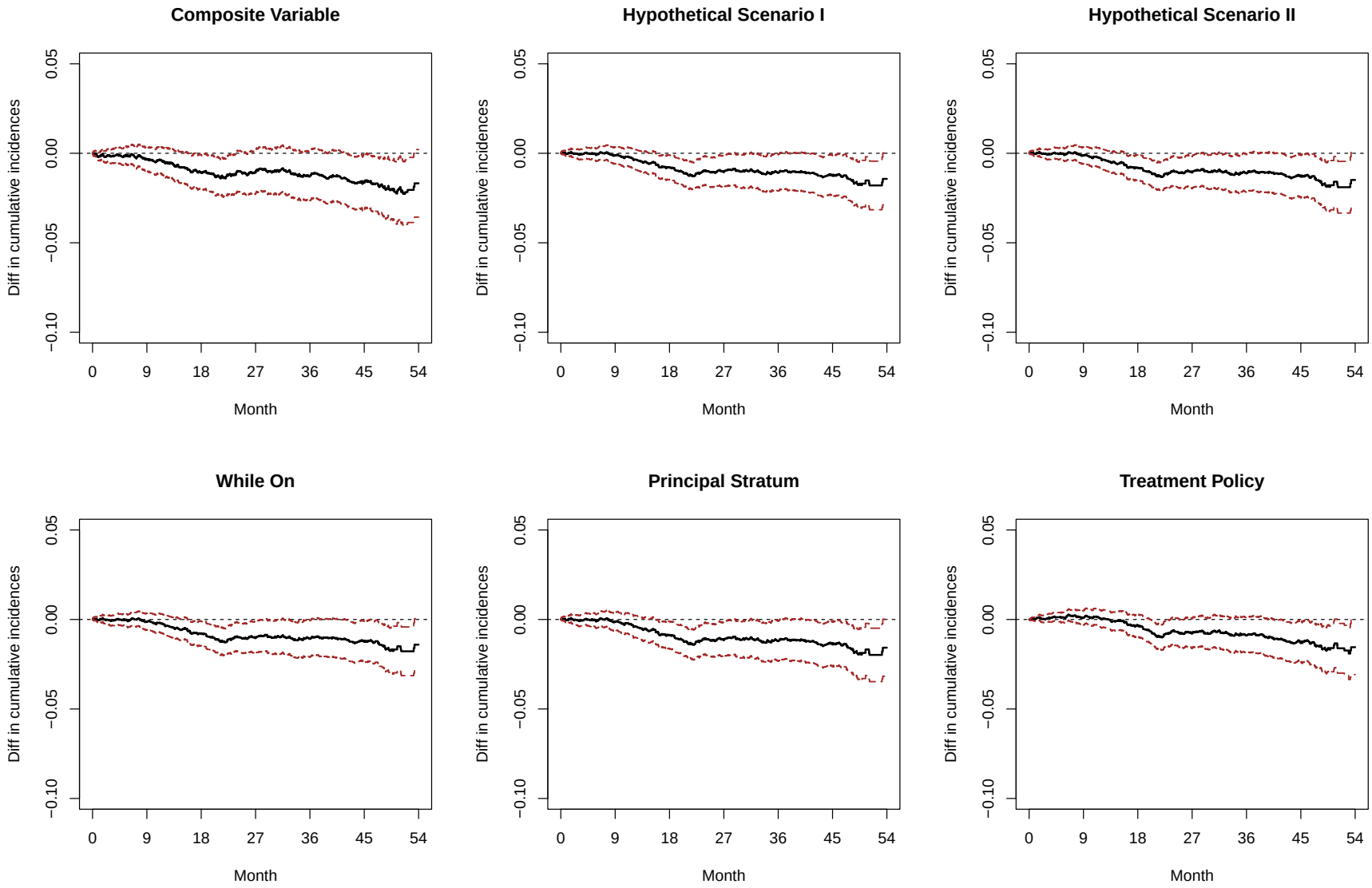
Endpoint II (All-Cause Death)

- In Endpoint I, the primary outcome event is the death event (CVD+NCVD) and the intercurrent event is the occurrence of non-fatal major adverse cardiovascular events (MACE).
- Of the individuals taking liraglutide, 381 individuals died and 364 experienced non-fatal major cardiovascular events.
- Of the individuals taking placebo, 447 died and 380 experienced non-fatal major cardiovascular events.

Endpoint II: Cumulative Incidences

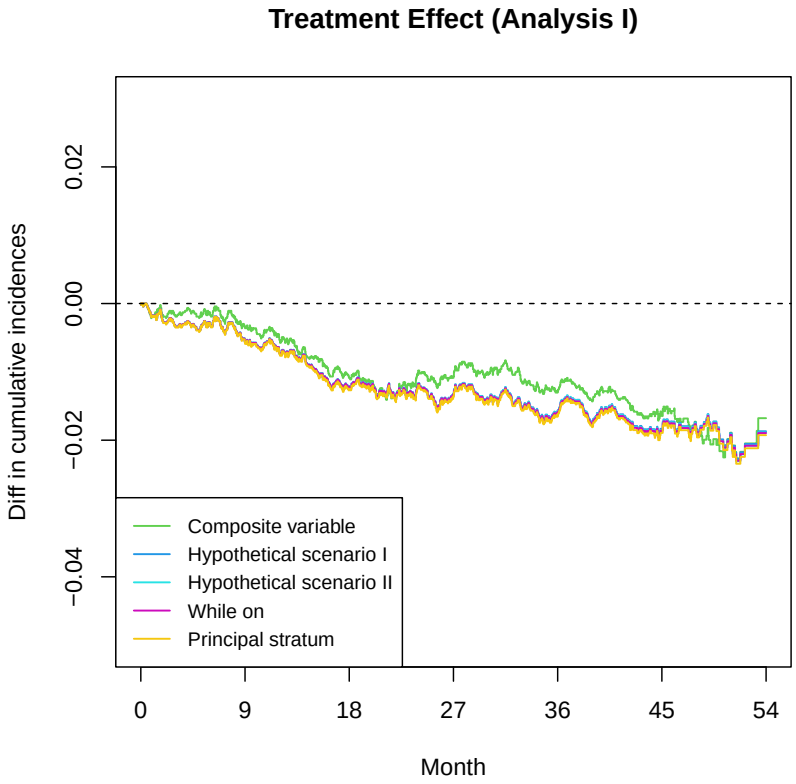


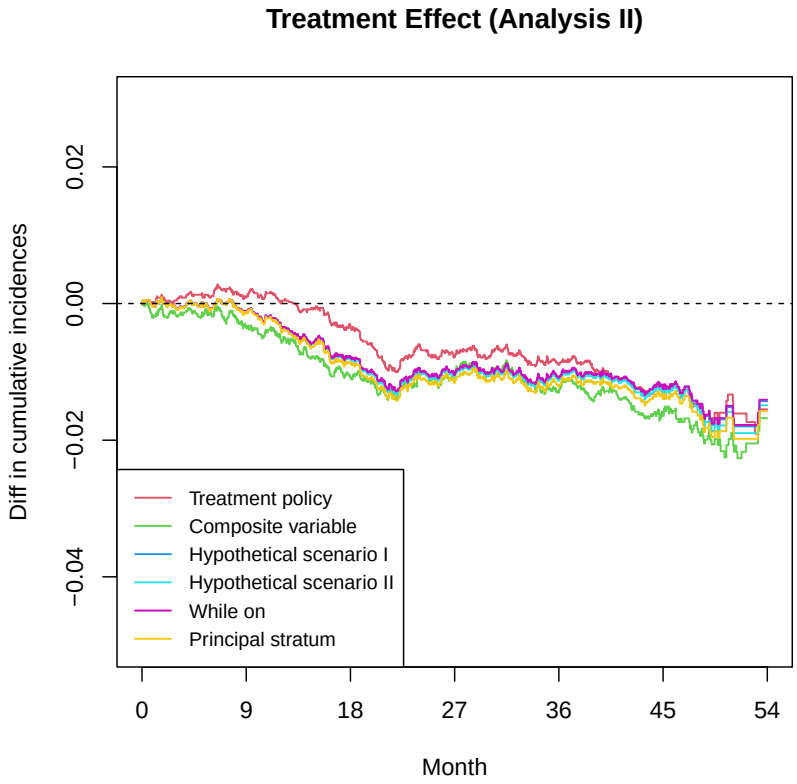
Endpoint II: Treatment Effects



Summary

- Analysis results can vary across strategies.
- They are answering different questions!





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Concluding Remarks

- The presence of intercurrent events has posed challenges in the statistical analysis for clinical trials with time-to-event outcomes.
- In this talk, we construct the causal estimands and provide their estimators under the five strategies in ICH E9 (R1) addendum.
- These strategies address different scientific questions and may require different data to investigate.
- Appropriate choices of strategies depend on the specific scientific question that practitioners want to answer.
- Multiple strategies can be used to deal with multiple intercurrent events.

Extension to Obervational Studies

- In estimation, we have focused on completely randomized clinical trials where covariates are naturally balanced between treatment groups of contrast.
- With imbalanced covariates, we could use semi-parametric models like proportional hazards and additive hazards models to estimate the hazard functions.
- Alternatively, we might employ propensity-score-based methods, such as generalized (weighted) Nelson-Aalen estimators or propensity score matching.
- Things would be more complicated if there are time-varying covariates or treatment discontinuation.

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- The data that support the findings of this study belongs to Novo Nordisk A/S. Restrictions apply to the availability of these data, which were used under license for this study.
- The R codes will be available on GitHub soon.

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Welcom for discussion!