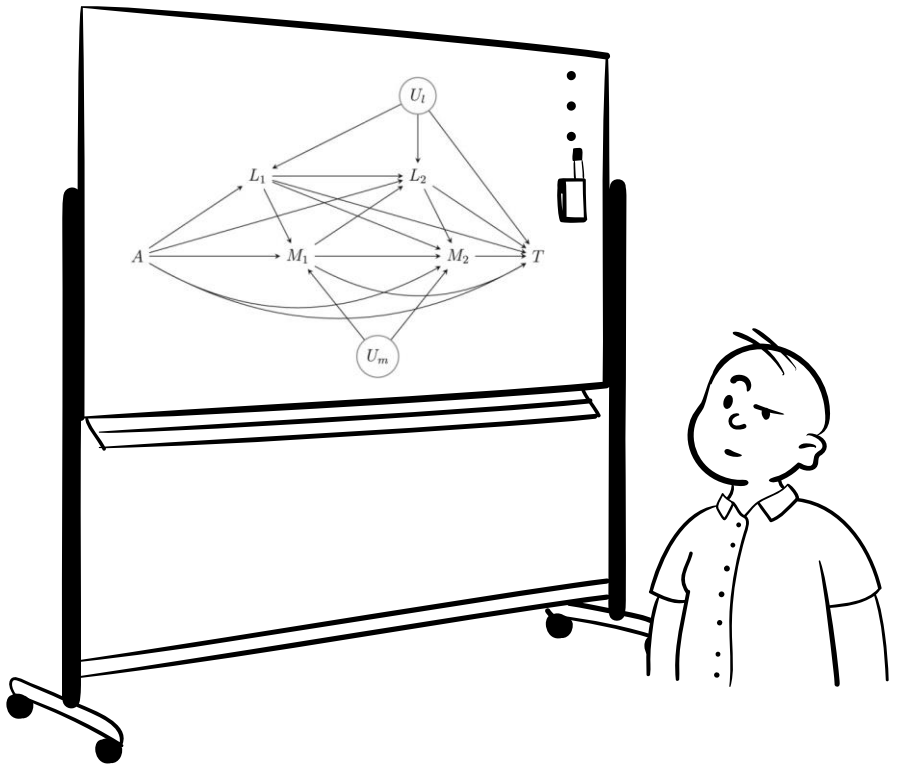
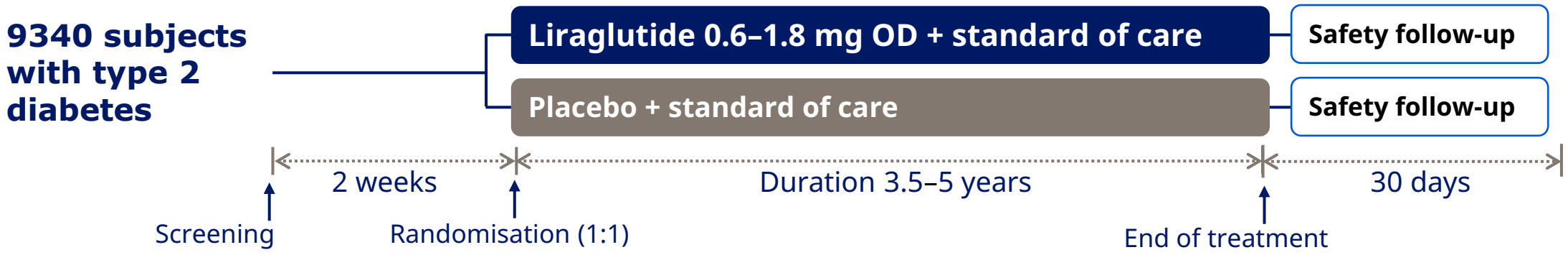


Mediation analysis for a cardiovascular outcome trial

Martin Linder
Novo Nordisk A/S

Motivating example

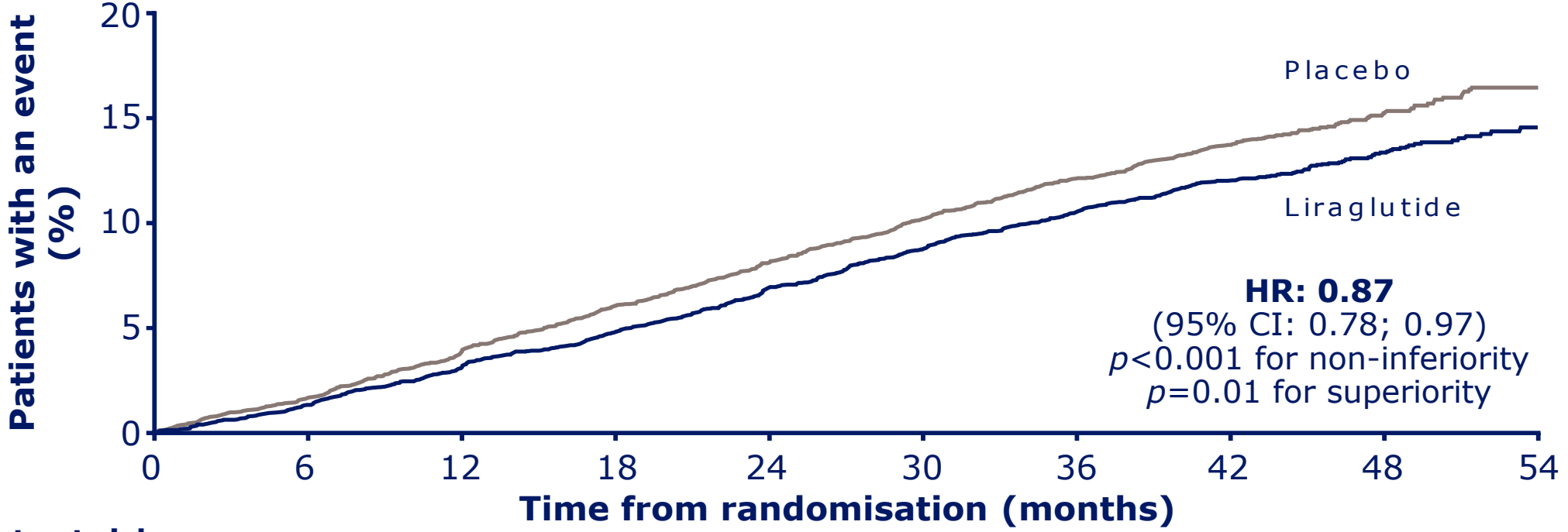
LEADER cardiovascular outcome trial



Primary endpoint

- Time from randomisation to first occurrence of a major adverse cardiovascular event (MACE; composite of cardiovascular death, myocardial infarction and stroke)

Time to first MACE – primary analysis

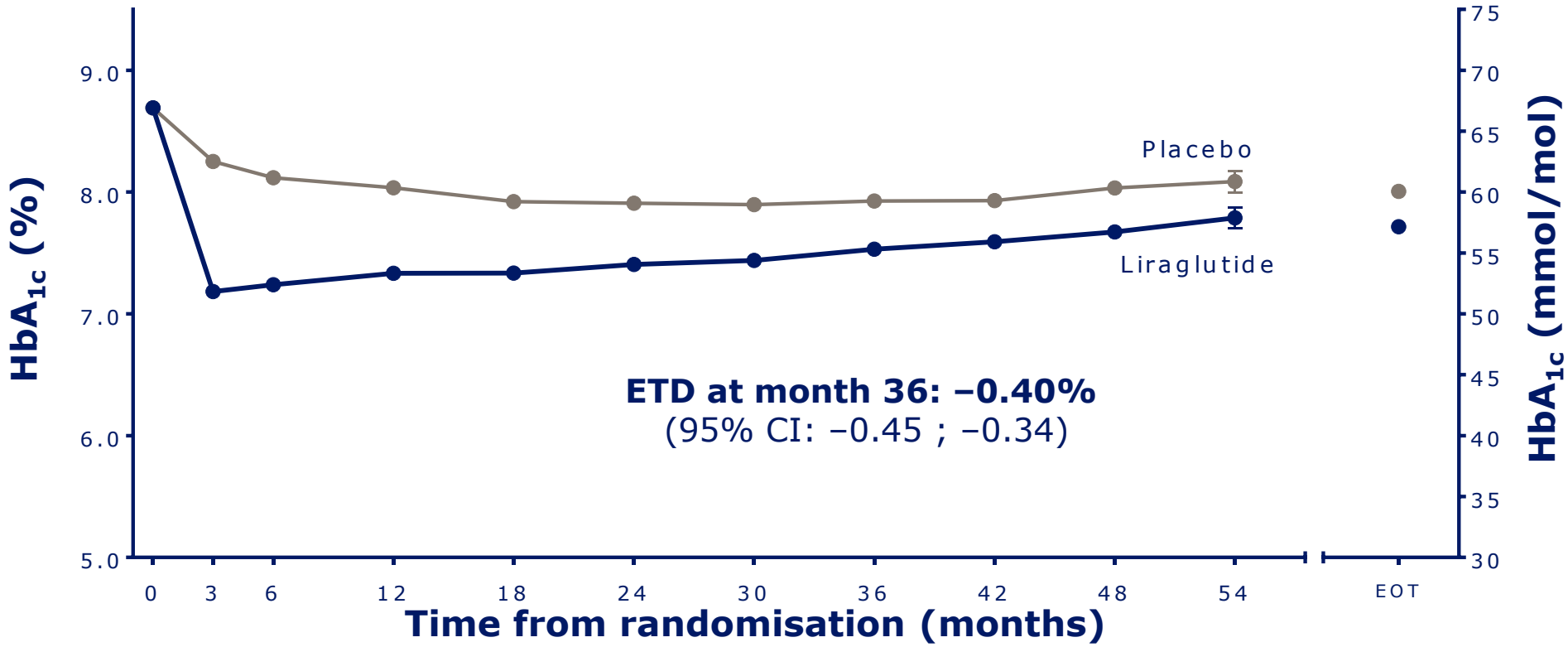


Patients at risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months
CI, confidence interval; CV, cardiovascular; HR, hazard ratio
Marso SP et al. *N Engl J Med* 2016; 375:311-322

Estimated mean HbA_{1c}



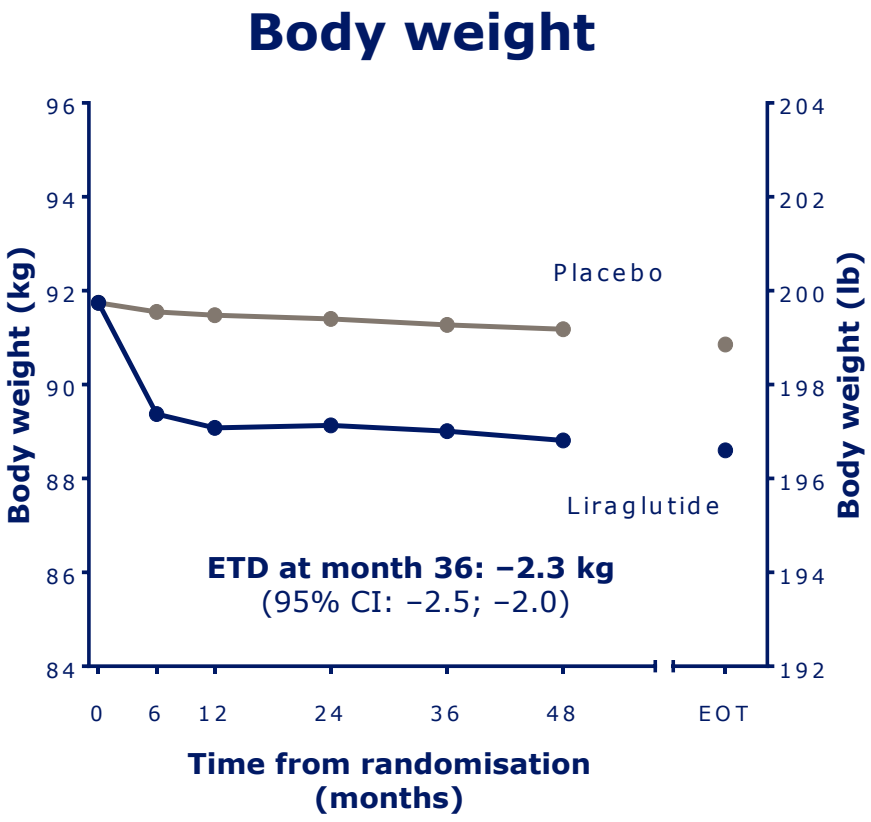
Number of patients at each visit

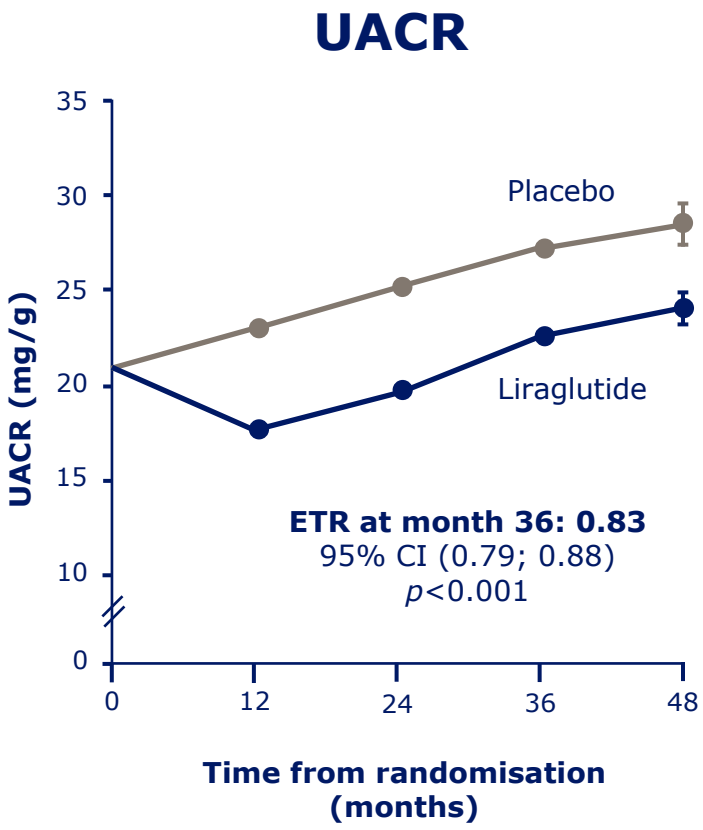
Liraglutide	4668	4402	4355	4295	4135	4034	3877	3810	2349	809	101	3705
Placebo	4672	4413	4355	4235	4030	3905	3742	3640	2303	756	87	3561

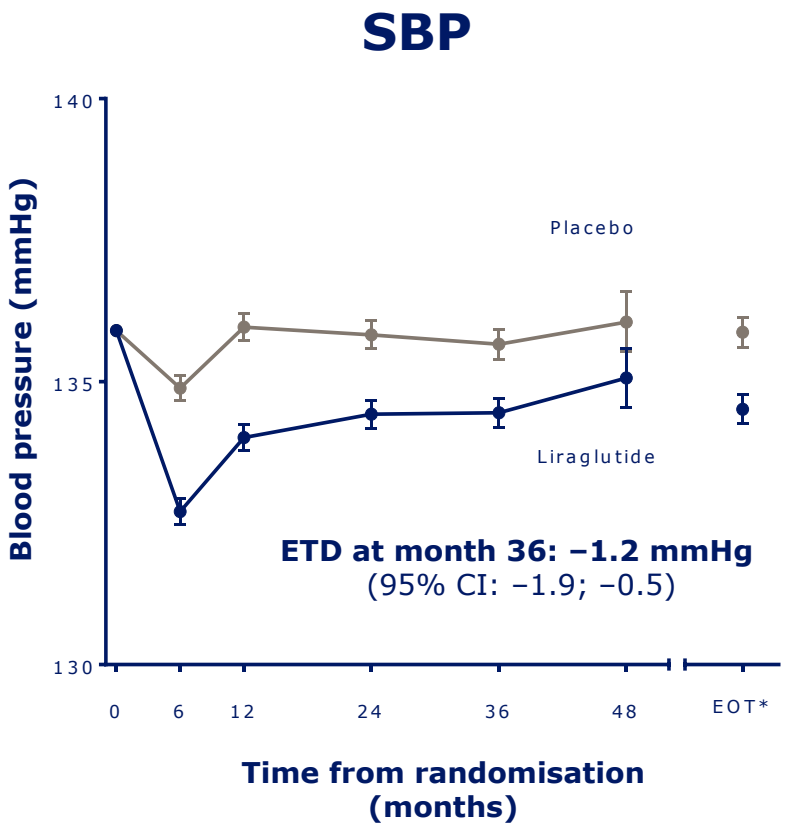
CI, confidence interval; EOT, end of trial; ETD, estimated treatment difference; HbA_{1c}, glycosylated haemoglobin

Marso SP et al. *N Engl J Med* 2016;375:311–322

Estimated mean body weight, urinary albumin-to-creatinine ratio (UACR) and systolic blood pressure (SBP)



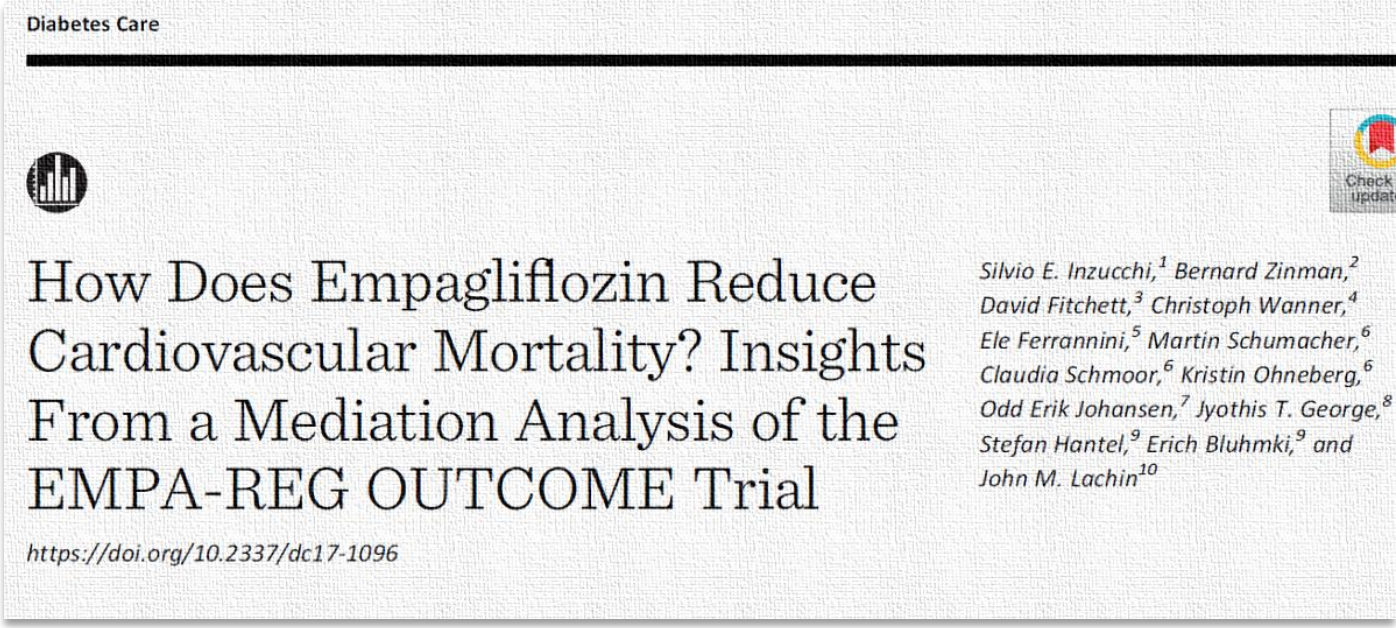




Data are estimated mean values from randomisation to EOT
CI, confidence interval; EOT, end of trial; ETD, estimated treatment difference
Marso SP et al. *N Engl J Med* 2016;375:311–322

Why do we need to perform mediation analyses?

- Key opinion leaders speculate on the mode of action
- EMA and other regulatory agencies ask for evidence that the reduction in cardiovascular risk is independent of other differences between the treatment arms
- Competitors publish results of mediation analyses of their outcome trials



Scientific question

To what extent is the effect of liraglutide on MACE mediated through HbA_{1c}*?

* Replace with body weight, UACR or systolic blood pressure.

Acknowledgement

- Novo Nordisk consulted two experts in mediation analysis:
  - **Stijn Vansteelandt**, Professor, Ghent University, Department of Applied Mathematics, Computer Science and Statistics
  - **Aksel Karl Georg Jensen**, Post-doc, University of Copenhagen, Department of Public Health, Section of Biostatistics
- They independently presented similar proposals for analysis
- We decided to adopt Vansteelandt's proposal
- Method described in
  - Vansteelandt S, Linder M, Vandenberghe S, Steen J, Madsen J. **Mediation analysis of time to-event endpoints accounting for repeatedly measured mediators subject to time-varying confounding**. *Stat Med* 2019;38:4828–4840. https://doi.org/10.1002/sim.8336

Simplified model

Simplified model for LEADER

Once measured mediator and no intermediate confounding

- For each patient i, define the treatment variable as

$$A_i = \begin{cases} 1, & \text{if randomised to liraglutide} \\ 0, & \text{if randomised to placebo} \end{cases}$$

- Let the mediator M_i be change in HbA_{1c} from randomisation to 6 months
- Let the baseline covariate C_i be HbA_{1c} at randomisation
- Define the outcome as

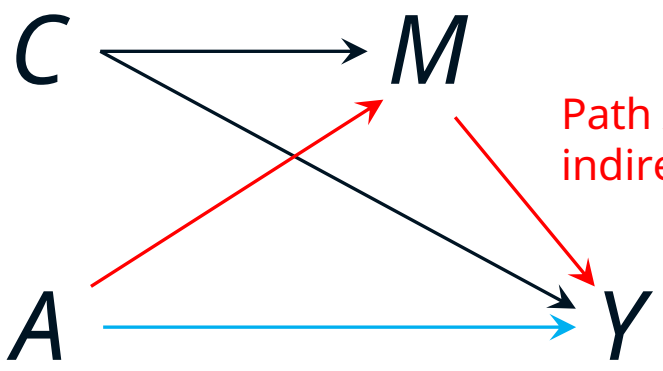
$$Y_{t,i} = \begin{cases} 1, & \text{if a MACE occurred between 6 and } t \text{ months} \\ 0, & \text{otherwise} \end{cases}$$

- Patients with events (or censored) before 6 months are excluded from the population

For the moment, we ignore the issue this causes with respect to assumptions

Causal diagram

Directed acyclic graph (DAG)



Path $A \rightarrow M \rightarrow Y$ corresponds to the indirect effect (mediated effect)

Path $A \rightarrow Y$ corresponds to the direct effect (remaining effect)

Composite counterfactuals

Let $Y(1, m)$ and $Y(0, m)$ be the potential outcomes if liraglutide or placebo, respectively, is given and the value of HbA_{1c} (the mediator) had been fixed to *m*.

Let $M(1)$ and $M(0)$ be the potential HbA_{1c} values if liraglutide or placebo, respectively, is given.

Combined, we can define composite counterfactuals $Y(1, M(1))$, $Y(0, M(0))$, $Y(1, M(0))$ and $Y(0, M(1))$.

For example, $Y(1, M(0))$ may be viewed as the outcome which would have occurred if the patient received liraglutide *but* HbA_{1c} *were set to the value that it would have taken if the patient received placebo*.

Note that only $Y\big(1, M(1)\big)$ or $Y\big(0, M(0)\big)$ can be observed.

Effect decomposition

Total effect

Expected difference in outcome if the treatment of patients changed from placebo to liraglutide

$$E[Y(1, M(1))] - E[Y(0, M(0))]$$

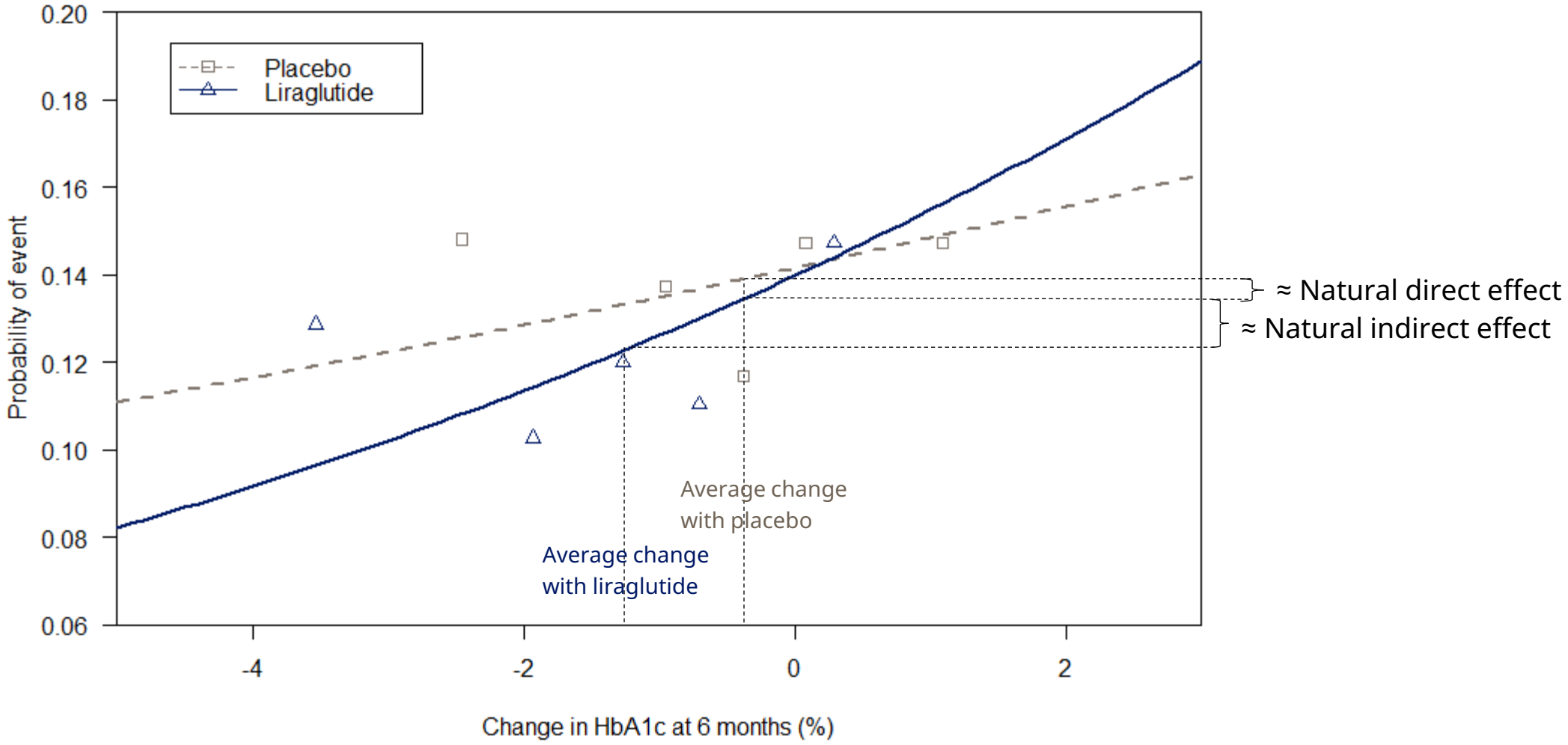
$$= \underbrace{E[Y(1, M(1))] - E[Y(1, M(0))]}_{\text{Natural indirect effect}} + \underbrace{E[Y(1, M(0))] - E[Y(0, M(0))]}_{\text{Natural direct effect}}$$

Expected difference in outcome if patients received liraglutide but their HbA_{1c} values changed to what they "naturally" would have been with placebo

Expected difference in outcome if the treatment of patients changed from placebo to liraglutide but their HbA_{1c} values were held fixed

Effect decomposition

Visualised using crude approximation



Curves fitted by logistic regression on treatment, change in HbA_{1c}, treatment-HbA_{1c} change interaction and baseline HbA_{1c}, and evaluated at mean baseline values. Points depict observed proportions of patients with events within quintiles of change in HbA_{1c}.

Assumptions

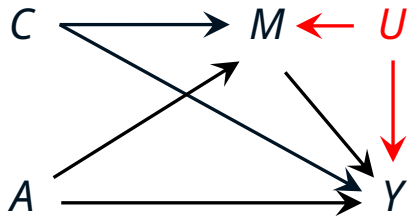
Assumptions
Consistency

- Observed values of mediator and outcome are the same as corresponding potential values
  - $Y = Y(a, m)$ if $A = a$ and $M = m$
  - $M = M(a)$ if $A = a$
  - $Y\big(a, M(a)\big) = Y(a, m)$ if $M(a) = m$
- In other words (?) …
  - The risk of MACE is not related to *how* liraglutide is given to patients or *how* a change in HbA_{1c} is achieved

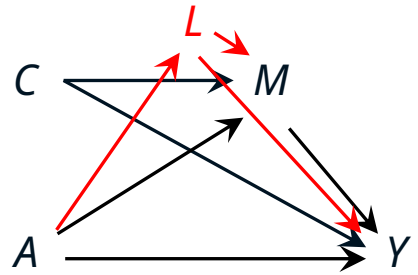
Assumptions
Conditional exchangeability

- No uncontrolled confounding
  - No unmeasured treatment-outcome confounder
    - $Y(a,m) \perp\!\!\!\perp A \mid C$ for a = 0,1 and all levels of m
  - No unmeasured treatment-mediator confounder
    - $M(a) \perp\!\!\!\perp A \mid C$ for a = 0,1

Solved by randomisation



  - No unmeasured mediator-outcome confounder
    - $Y(a,m) \perp\!\!\!\perp M \mid A = a, C$ for a = 0,1 and all levels of m
    - Includes factors not affected by treatment
  - No mediator-outcome confounders affected by treatment
    - $Y(1,m) \perp\!\!\!\perp M(0) \mid C$ and $Y(0,m) \perp\!\!\!\perp M(1) \mid C$ for all levels of m



Will later be relaxed

- In other words…
  - There are no hidden characteristics associated to both HbA_{1c} change and MACE

Assumptions
Positivity

- Common support
  - Both treatments may be observed with positive probability at all covariate levels
    - $0 < P(A = 1|C) < 1$
  - Same range of mediator values across treatments and covariate levels
    - $f_{M|C,A=1}(m) > 0$ if and only if $f_{M|C,A=0}(m) > 0$
- In other words…
  - For each liraglutide patient, there are some placebo patients with similar baseline characteristics and HbA_{1c} changes (and vice versa)

Solved by randomisation

Problem if strong effect of treatment on mediator

Estimation using simplified model

Counterfactual survival curves

Define counterfactual survival probabilities as

$$S_{a,a^*}(t) = 1 - E\left[Y_t\left(a, M(a^*)\right)\right]$$

For example, $S_{1,0}(t)$ is the survival probability if patients received liraglutide *but the HbA_{1c} values were set to the levels that they would have taken if the patients received placebo.*

We can identify $S_{1,0}(t)$ by

$$\begin{aligned} S_{1,0}(t) &= 1 - E\left[E\left[E(Y_t|A=1,C,M)|A=0,C\right]\right] \\ &= E\left[E\left[P(T>t|A=1,C,M)|A=0,C\right]\right] \end{aligned}$$

where T is the time to event.

Estimation of $S_{1,0}(t)$
Step 1

$$E\left[E\left[P(T > t|A = 1, C, M)\right]|A = 0, C\right]$$

Fit a Cox regression model among liraglutide patients for T on M and C.

Make a prediction $\hat{Q}(t)$ for each patient in both arms using observed values of M and C.

```
proc phreg data=ds;
   where trt eq 1 and tte gt ady1;
   model tte*cnsr(1) = hba1c0 hba1c1;
   id usubjid;
   baseline covariates=ds(where=(tte gt ady1))
            timelist=1099
            survival=Q
            out=Qdata;
run;
```

Estimation of $S_{1,0}(t)$
Step 2

$$E\left[E[P(T > t|A = 1, C, M)|A = 0, C]\right]$$

Fit a logistic regression model among placebo patients for $\hat{Q}(t)$ on C.

Make a prediction $\hat{Q}_m(t)$ for each patient in both arms using observed value of C.

(Ignore warnings about applying logistic regression for non-binary response.)

```
data input;
   merge ds Q1data;
   by usubjid;
   if trt eq 0 then Qtemp = Q;
   else Qtemp = .;
run;

proc genmod data=input;
   model Qtemp = hba1c0 / dist=normal link=logit;
   output out=Qmdata pred=Qm;
run;
```

Estimation of $S_{1,0}(t)$
Step 3

$$E\left[E\left[P(T > t|A = 1, C, M)|A = 0, C\right]\right]$$

Estimate the survival probability $S_{1,0}(t)$ by the average of $\hat{Q}_m(t)$ across all patients.

```
proc summary data= Qmdata;
   var Qm;
   output out=finsum N=N mean=Survival;
run;
```

$S_{1,1}(t)$ and $S_{0,0}(t)$ are calculated using the same approach

Estimation of indirect and direct effects

Estimate of natural indirect effect:

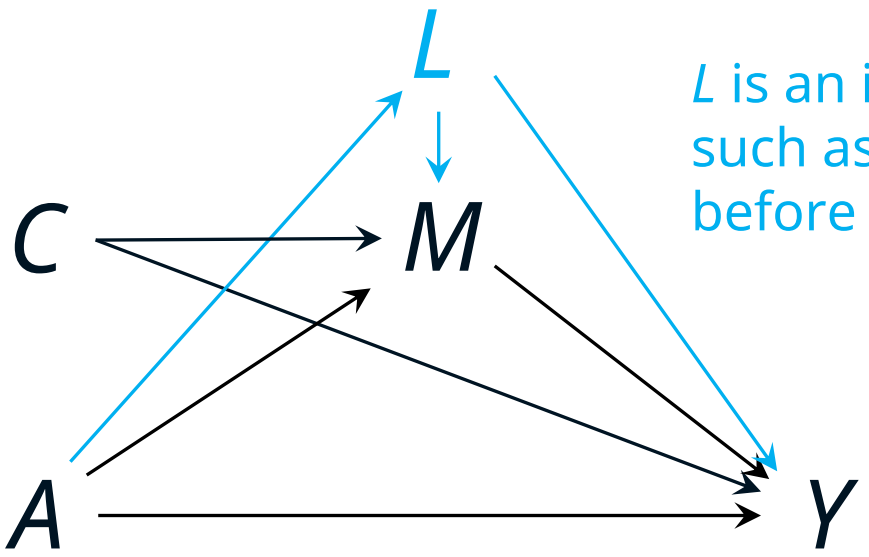
$$\hat{E}\left[Y_t\left(1, M(0)\right)\right] - \hat{E}\left[Y_t\left(1, M(1)\right)\right] = \hat{S}_{1,1}(t) - \hat{S}_{1,0}(t)$$

Estimate of natural direct effect:

$$\hat{E}\left[Y_t\left(0, M(0)\right)\right] - \hat{E}\left[Y_t\left(1, M(0)\right)\right] = \hat{S}_{1,0}(t) - \hat{S}_{0,0}(t)$$

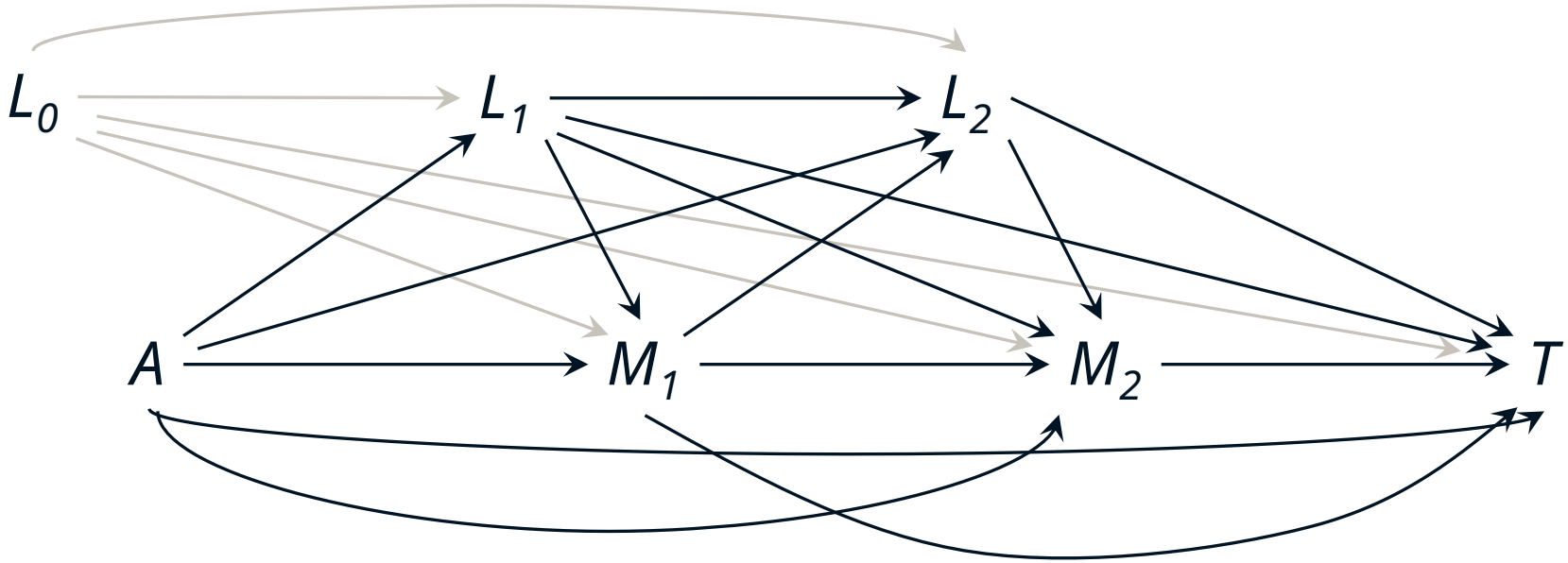
Fully complex model

Intermediate confounding



L is an intermediate confounder, such as an indicator for no event before 6 months

Intermediate confounding and repeatedly measured mediator



A: Treatment (1=liraglutide, 0=placebo)

T: Outcome (time to MACE)

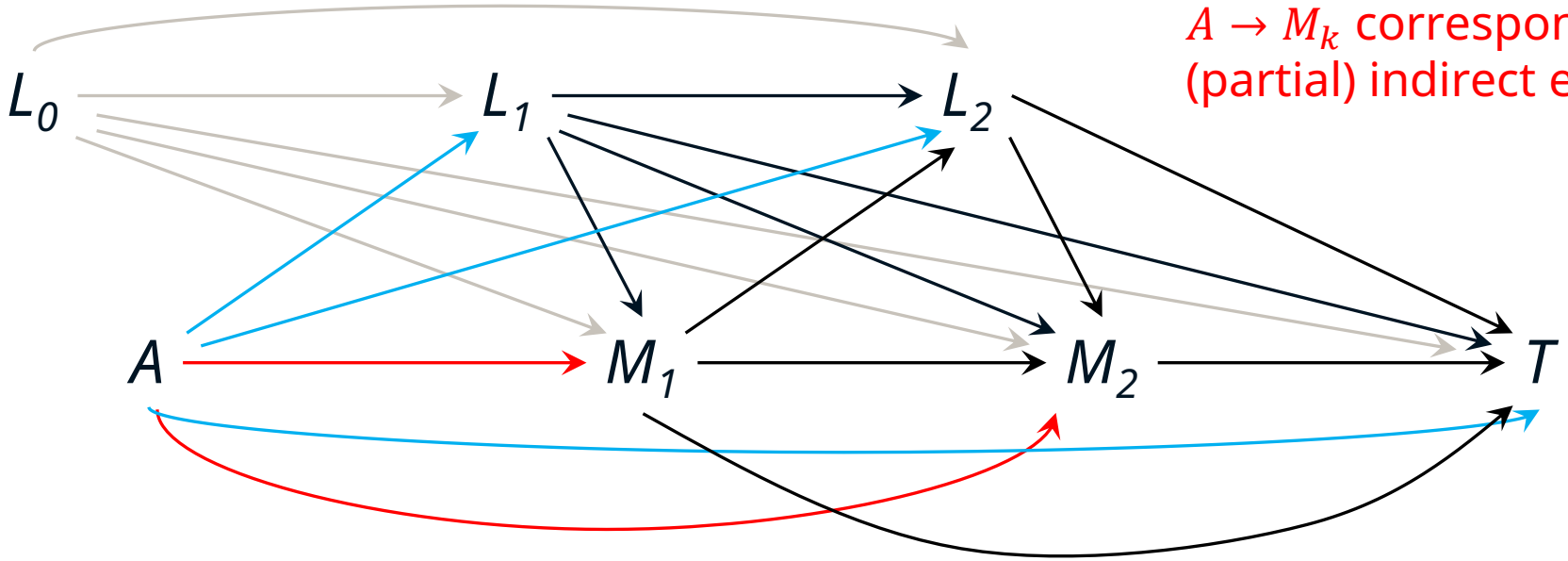
M_1, M_2,...: Mediator (HbA_{1c} values at visits 1,2,...)

L_0: Baseline covariates (HbA_{1c} at randomization)

L_1, L_2,...: Intermediate confounders

Intermediate confounding and repeatedly measured mediator

Path-specific effects



Paths starting through edges $A \to M_k$ correspond to the (partial) indirect effect

Paths starting through edges $A \to L_k$ or $A \to T$ correspond to the direct effect

A: Treatment (1=liraglutide, 0=placebo)

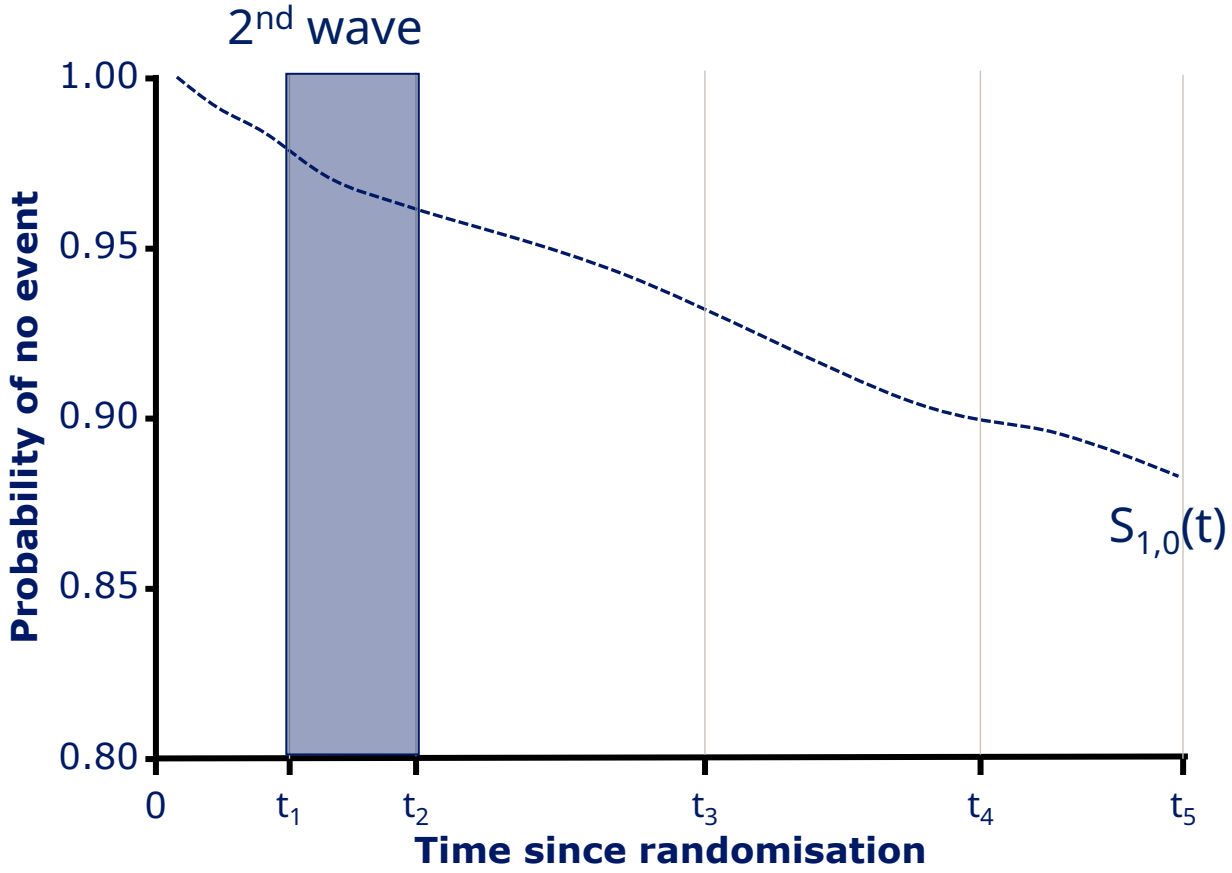
T: Outcome (time to MACE)

M_1, M_2,...: Mediator (HbA_{1c} values at visits 1,2,...)

L_0: Baseline covariates (HbA_{1c} at randomization)

L_1, L_2,...: Intermediate confounders

Estimation of $S_{1,0}(t)$
General strategy



Estimate $S_{1,0}(t)$ in *waves*, corresponding to the time intervals between the scheduled visits.

Estimation of $S_{1,0}(t), t_1 < t \leq t_2$, accounting for $L_1 = I\{T > t_1\}$

Outline

$$S_{1,0}(t) = E[\underbrace{E[P(T > t | T > t_1, A = 1, L_0, M_1) | T > t_1, A = 0, L_0]}_{Q^1(t), \text{ estimated by Cox regression}} P(T > t_1 | A = 1, L_0)]$$

$$= E[\underbrace{E[Q^1(t) | T > t_1, A = 0, L_0]}_{Q_m^1(t), \text{ estimated by logistic regression}} P(T > t_1 | A = 1, L_0)]$$

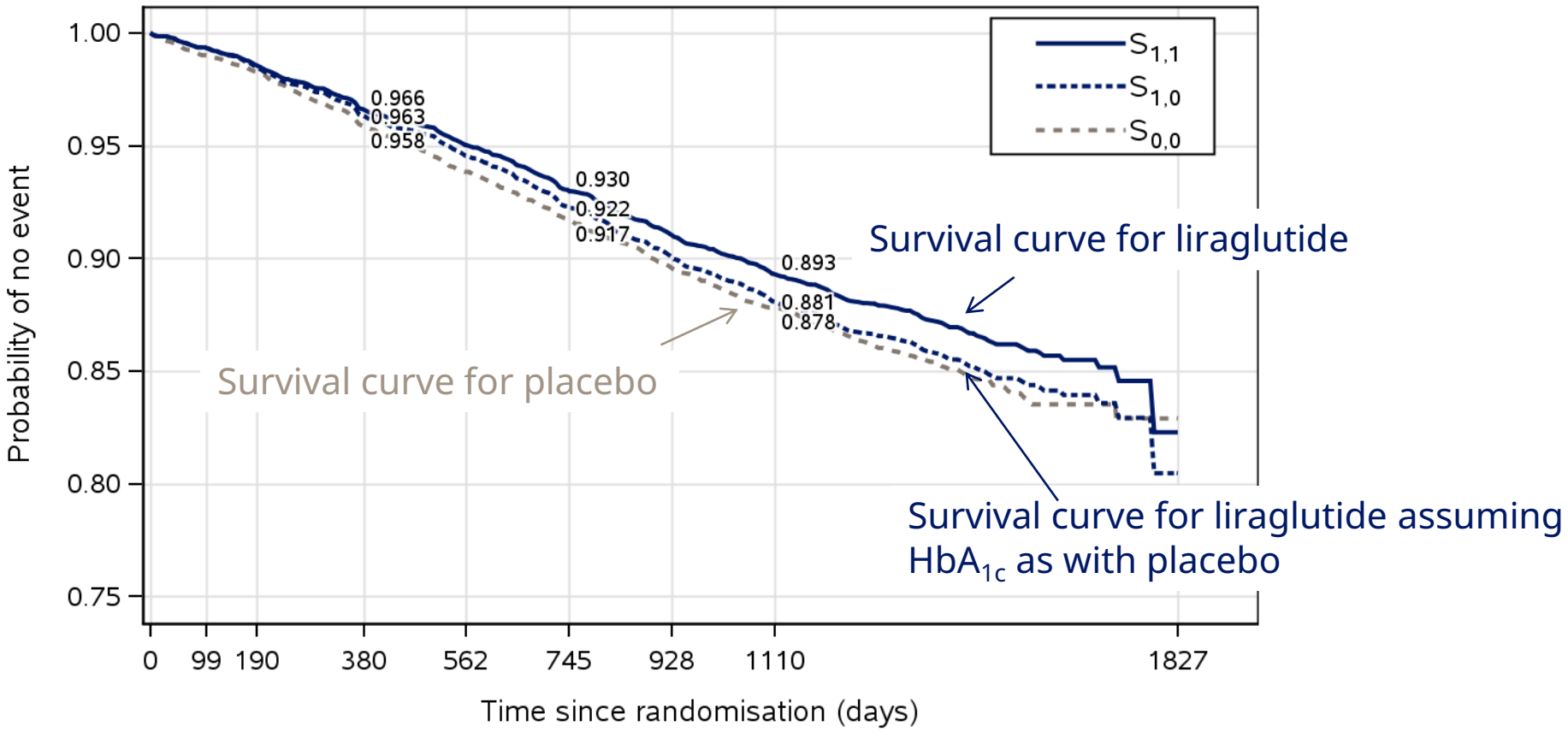
$$= E[Q_m^1(t) \underbrace{P(T > t_1 | A = 1, L_0)}_{Q^0(t_1), \text{ estimated by Cox regression}}]$$

$$= \underbrace{E[Q_m^1(t) Q^0(t_1)]}_{\text{Estimated by } \frac{1}{n}\sum_{i=1}^n \hat{Q}_i^0(t) = \frac{1}{n}\sum_{i=1}^n \hat{Q}_{m,i}^1(t)\hat{Q}_i^0(t_1)}$$

LEADER Results

MACE mediated by HbA_{1c}

Estimated survival curves



MACE mediated by HbA_{1c}

Effect estimates at 3 years (1110 days)

	Estimate	95% CI
Probability of no event within 3 years		
Liraglutide	0.893	
Placebo	0.878	
Liraglutide with HbA_{1c} as in placebo	0.881	
Total effect	0.015	[0.003, 0.028]
Direct effect	0.003	[-0.013, 0.020]
Proportion mediated (%)	82.0	[11.4, 510.1]

CI: Confidence interval (calculated based on 1000 bootstrap samples)

Conclusion

From paper in Diabetes Care 2020

In summary, these mediation analyses have identified HbA_{1c} as a potential mediator of the CV effects of liraglutide. We did not identify any mediation effects for less well-studied but possible candidate mediators, which are also risk factors for CV events, including weight and hypoglycemia. Similar to all other mediation analyses, we cannot necessarily infer causality, and whether HbA_{1c} is a marker of an unmeasured factor or a true mediator remains a key question. Based on existing evidence, we consider it unlikely that HbA_{1c} is a true mediator of the CV benefit observed with liraglutide, and this finding warrants further investigation.

(Could possibly be nuanced)

Buse JB et al. *Diabetes Care* 2020;43:1546–1552