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Semaglutide and cardiovascular risk reduction: a mediation analysis of the SELECT trial

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Abstract

Background and Aims In SELECT, subcutaneous semaglutide (target dose 2.4 mg) weekly in adults with pre-existing cardiovascular disease and body mass index ≥27 kg/m^2 without diabetes significantly reduced major adverse cardiovascular events (MACE) by 20% vs placebo. This analysis explored potential mediators of this cardiovascular benefit.

Methods Changes from randomization to 24 months in body weight, waist circumference, plasma high-sensitivity C-reactive protein (hsCRP), glycated haemoglobin (HbA_{1c}), lipids, blood pressure, estimated glomerular filtration rate, and urinary albumin-to-creatinine ratio were examined individually, and in combination, as potential mediators of MACE risk reduction, using the Vansteelandt repeated regression method (a counterfactual approach).

Results Semaglutide significantly ($P < .05$) improved all potential mediators investigated. Point estimates for % mediation were largest for waist circumference (64.0% [95% confidence interval (CI) 27.5, 179.6]), hsCRP (42.1% [17.9, 110.5]), HbA_{1c} (29.0% [−20.7, 120.5]), and body weight (19.5% [−33.0, 110.7]), examined separately, but all had wide CIs. Supplementary analyses suggested unreliability of estimates for body weight and waist circumference, potentially due to differing relationship of body weight and waist change to MACE between treatment arms. Multivariable analysis estimated joint mediation for all potential mediators combined to be 31.4% (95% CI −30.1, 143.6). When variables other than body weight and waist circumference were considered, % mediation was 46.0% (95% CI −6.0, 161.0).

Conclusions Mediation analyses could not fully ascribe the effects of semaglutide on MACE to known risk factors in SELECT with any certainty. Further investigation of potential additional biomarkers and mediators of semaglutide's cardiovascular protective effect are of interest.

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Structured graphical abstract

Key Question

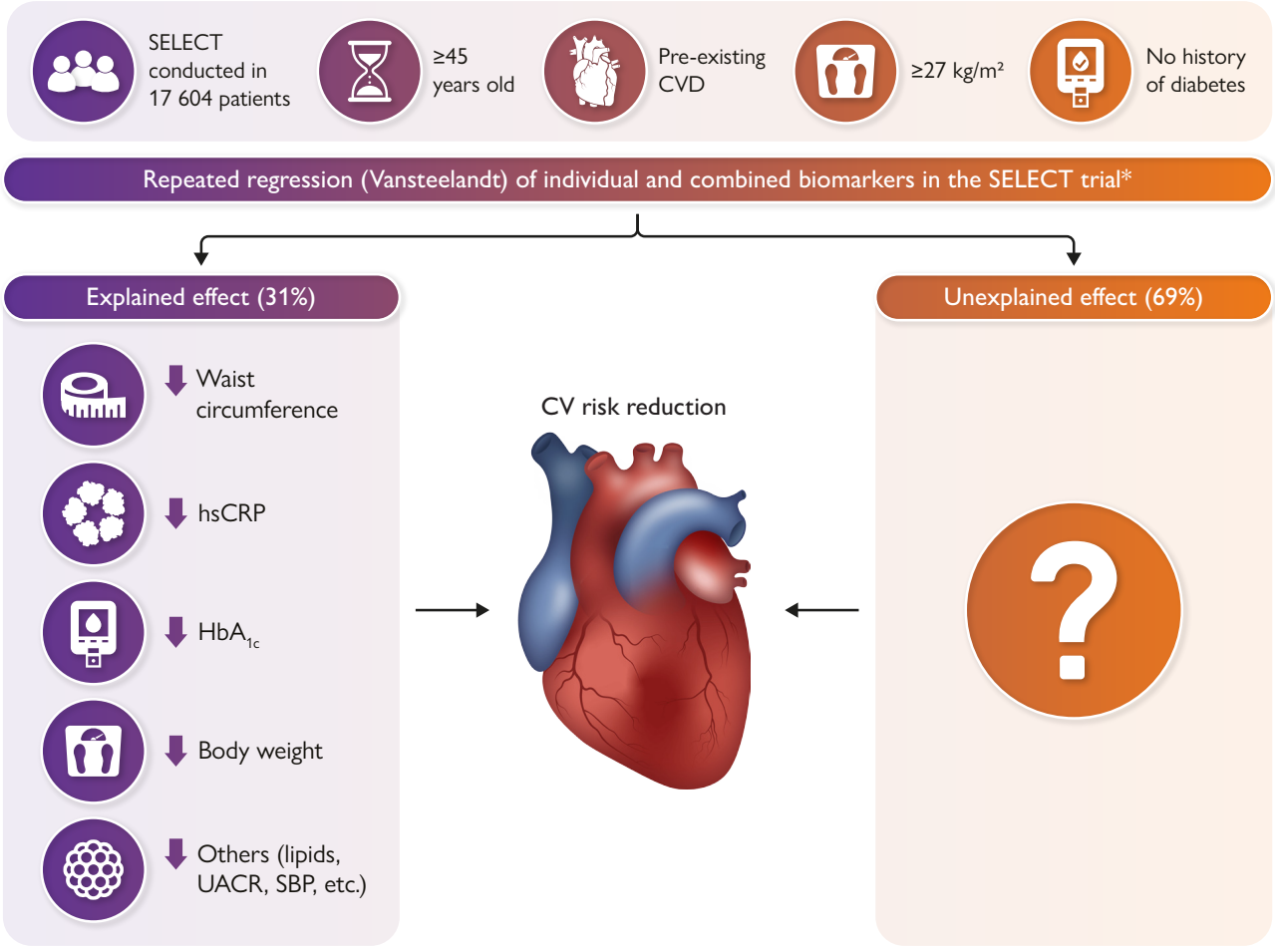
Which risk factors mediate the cardiovascular (CV) benefit of semaglutide in people with a body mass index ≥27 kg/m^2 and known CV disease, but without diabetes?

Key Finding

In the SELECT trial, allocation to semaglutide was associated with improvements in several risk (body weight, waist circumference, hsCRP, HbA_{1c} , lipids, blood pressure, eGFR, UACR) factors compared with placebo. However, the treatment effect on major adverse CV events could not be ascribed to these changes with certainty, body weight reduction explaining only 31% of risk reduction.

Take Home Message

These data suggest that other unidentified mechanisms could contribute to the CV benefit of semaglutide.



* The randomized, double-blind SELECT trial evaluated the impact of semaglutide versus placebo on cardiovascular events in patients aged ≥45 years with a BMI of ≥27 kg/m^2, with established CV disease and no history of diabetes

CVD, CV disease; **CV**, cardiovascular; **BMI**, body mass index; **hsCRP**, high-sensitivity C-reactive protein; **HbA_{1c}**, glycated haemoglobin; **eGFR**, estimated glomerular filtration rate; **UACR**, urinary albumin-to-creatinine ratio; **SBP**, systolic blood pressure.

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Keywords Semaglutide • Cardiovascular • Obesity • Mediation • Risk factor

Introduction

The Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial demonstrated that patients randomized to once-weekly subcutaneous semaglutide (a glucagon-like peptide-1 receptor agonist [GLP-1 RA]) at a target dose of 2.4 mg experienced 20% lower risk of major adverse cardiovascular (CV) events (MACE) compared with patients randomized to placebo (6.5% vs 8.0%; hazard ratio 0.80; 95% confidence interval [CI] 0.72, 0.90; $P < .001$).[1] SELECT was conducted in 17 604 patients aged 45 years or older who had pre-existing CV disease (CVD) and a body mass index (BMI) of 27 kg/m^2 or greater, but who did not have a history of diabetes.[1]

In SELECT allocation to semaglutide was associated with improvements in several risk factors for atherosclerosis: body weight and fat distribution, glycaemic control, blood pressure, high-sensitivity C-reactive protein (hsCRP), lipid levels, and kidney function compared with placebo. These risk factors have been well described as components of cardiometabolic and cardiorenal syndromes.[2] Whether the combined changes in these parameters could potentially explain the observed benefit on MACE risk is unclear.[1] Additional effects of semaglutide may contribute as well, as the effects of GLP-1 RAs on atherosclerosis may occur via many mechanisms (e.g. reduced lipid deposition, lower haemodynamic stress, improved endothelial function).[3–7] Mediation analyses use statistical modelling of the changes in potential mediators or biomarkers, and the relationship of these risk factors with the outcomes of interest, to examine if they account statistically for the treatment effect on clinical outcomes. It is important to note that such analyses cannot prove causality, not least because they rely on strong assumptions (such as the absence of unmeasured confounders), and these assumptions can be challenged. Furthermore they cannot differentiate between a biological mediator and biomarkers of the protective mechanism of action of the drug. However, mediation analyses are useful in suggesting whether studies of the drug's effect on other biological pathways beyond those already measured may be worthwhile.

Such analyses have been performed on data from trials of other GLP-1 RAs in people with diabetes and various states of CV risk. Mediation analyses from the LEADER trial, which examined the effect of liraglutide in people with type 2 diabetes and known CVD, identified effects on glycated haemoglobin (HbA_{1c}), and to a lesser extent urinary albumin-to-creatinine ratio (UACR), as potentially mediating the beneficial treatment effect of liraglutide on MACE in that trial.[8] In the REWIND trial, HbA_{1c} and UACR were also suggested as potentially mediating the effect of the GLP-1 RA dulaglutide on MACE in people with type 2 diabetes, with and without known CVD.[9] As diabetes was an exclusion criterion in the SELECT trial, the distribution of baseline HbA_{1c} differed from that observed in diabetes trials with semaglutide. Similarly, UACR was also different in SELECT from other semaglutide trials.

An initial analysis examined the effect of adjusting for body weight and waist circumference through the trial on the MACE treatment effect on the estimate in a Cox regression analysis. Adjusting for body weight had little effect but adjusting for waist circumference reduced the treatment effect estimate by a third.[10] Here we report the formal full pre-specified mediation analysis of the SELECT trial. We use the gold-standard Vansteeland counterfactual method, and explore the % of mediation of the MACE effect across not just weight and waist circumference but also other established CV risk factors singly and in combination.

Methods

Trial design and participants

The current work reports a pre-specified mediation analysis of the SELECT trial (NCT03574597), the design and primary results of which have been reported previously.[1,11,12]

In brief, eligible patients were aged ≥45 years with a BMI of ≥27 kg/m^2, with established CVD and no history of diabetes. Additional exclusion criteria included prior myocardial infarction (MI), stroke, hospitalization for unstable angina pectoris, or a transient ischaemic attack within 60 days of screening; HbA_{1c} ≥6.5% (48 mmol/mol); New York Heart Association class IV heart failure; presence of end-stage kidney disease; or need for chronic or intermittent dialysis. Patients were randomized (1:1) to escalating doses of once-weekly subcutaneous semaglutide over 16 weeks to achieve a target dose of 2.4 mg, or placebo.[1,11]

Measurement of CV risk factors

The following risk factors were examined in this analysis: body weight; waist circumference; plasma levels of hsCRP, HbA_{1c}, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides; systolic and diastolic blood pressure (SBP and DBP); estimated glomerular filtration rate (eGFR); and UACR. These were measured at multiple time points across the trial, as shown in Supplementary data online, *Table S1*. Details of the methods used have been reported previously.[1,11,12]

Outcomes

The primary outcome of SELECT and the endpoint of this mediation analysis was 3-point MACE, defined as time to the first occurrence of a non-fatal MI or non-fatal stroke, or death from CV causes. The trial was designed to terminate when at least 1225 primary MACE endpoints had occurred.[1]

Statistical analyses

As pre-specified, the mediation analyses of MACE were performed using a repeated regression based on a counterfactual framework for causal inference. The statistical method was proposed by Vansteelandt *et al*., for the setting where the outcome is time to event (here it is time to MACE) and potential mediators are repeatedly measured during the trial.[13]

We evaluated mediation at the pre-specified time of 36 months since it was the expected minimum follow-up time among patients who completed the trial. Candidate mediators had been selected *a priori* based on an expectation that they would be affected by semaglutide and could plausibly have an effect on MACE or be markers of a process that has an effect on MACE. After unblinding, the treatment effect on each candidate was evaluated to confirm its viability as a potential mediator. Repeated values of the potential mediators up to at least 24 months were used in the mediation analysis. To illustrate the relationship of changes in mediators to each other, we first reported the partial Pearson correlation coefficients of the changes in risk factors from baseline to 24 months by treatment arm, controlling for the baseline value of all risk factors.

For the Vansteelandt repeated regression approach, first, the difference in MACE-free survival between semaglutide and placebo was estimated at 36 months as the 'total effect' (note that this is an absolute rather than relative treatment effect). The probability of MACE-free

survival in the semaglutide arm, had the semaglutide arm experienced the values of the mediator across follow-up observed in the placebo group (i.e. an unobserved counterfactual scenario), was also estimated as previously described (this is termed the adjusted semaglutide MACE-free survival).[13] The direct effect of semaglutide was then estimated as the difference between this adjusted semaglutide MACE-free survival and the placebo MACE-free survival.

The % mediation was then calculated as 100 × (1 − [direct effect] / [total effect]). Thus, were there a potential mediator that explained all of the treatment effects on MACE, the direct effect would approach zero and the % mediation would approach 100. Confidence intervals (CIs) for the total effect, direct effect, and percentage mediation were calculated using a bootstrap resampling procedure. Note that the CIs for % mediation may include values below 0% or above 100% since they reflect the uncertainty of the estimates.

Potential mediator values from one or more visits were included as covariates in the regression models. In addition, the baseline value of the corresponding mediator was included in all models as being a potential confounder. All planned mediator assessments before 36 months were included, except in the case of body weight, SBP, and DBP, where a subset of the assessments (weeks 12, 20, 39, 52, 78, 104, 130) was included in order to avoid convergence issues. If there was a missing mediator value for a patient still at risk of a first MACE, then the last observation was carried forward (LOCF) in the analysis.

As supplementary analyses, we also conducted a reversed counterfactual procedure in which the direct effect is estimated as the difference between arms in MACE-free survival had the placebo arm experienced the mediator values observed in the semaglutide arm. Whereas the main approach was based on the mediator-outcome association in the semaglutide arm, the reversed counterfactual approach was based on the corresponding association in the placebo arm. A large disparity between the estimated direct effects (and the resulting % mediation) under the two counterfactual scenarios can indicate a true treatment–mediator interaction (as could occur if there is a synergistic effect of receiving semaglutide and changing the level of the mediator), or it can be an artefact caused by hidden confounding or by a non-linear relationship between mediator and outcome.

As well as exploring each potential mediator, a combined analysis including multiple mediators in the same model was conducted. Note that mediators can be interrelated, such that you cannot assume that the total mediation increases when adding more mediators in the analyses.

In the main mediation analyses, data from randomization to the final follow-up visit were used in line with the intention-to-treat principle. Supplementary on-treatment analyses were performed using data from randomization to the first treatment discontinuation, defined as being off-treatment for five consecutive weeks.

For comparison of results across CV outcome studies, we also conducted supplementary mediation analyses using a Cox regression model with a time-dependent covariate, in the same way as in some other studies.[9,14] The direct effect was estimated as a log hazard ratio from a model including the updated mean of the mediator, calculated as the area under the curve divided by time as a time-dependent covariate, alongside treatment and baseline value of the mediator as fixed covariates. The total effect was estimated from a Cox regression model with treatment as a single fixed covariate. The % mediation was then calculated as 100 × (1 − [direct effect] / [total effect]), and its associated CI was estimated using a bootstrap resampling procedure.

All statistical analyses were performed with SAS software, version 9.4 TS1M5 (SAS Institute, Cary, NC, USA), based on individual-level data.

Results

Potential mediators at baseline and change during follow-up

Of 17 604 randomized participants in SELECT, 8803 were assigned to receive semaglutide and 8801 to placebo. The baseline characteristics have been reported previously.[1] The mean age was 62 years, 72% were male, 72% had a BMI ≥30 kg/m^2, 66.4% had prediabetes defined as HbA_{1c} between 5.7%–6.4%, and 68% had a history of a prior MI. The mean follow-up time was 39.8 months, and the assigned regimen was received for 82.5% of potential treatment time in the semaglutide arm and 87.7% of potential treatment time in the placebo arm. By 24 months, approximately 77% of patients in the semaglutide arm were receiving the maximum dose of 2.4 mg.[1] As reported previously, randomization to semaglutide was associated with significant improvements ($P < .05$) in the 12 potential mediators examined (see Supplementary data online, *Figure S1*).[1] As shown by the partial correlation coefficients (PCC) of the change in potential mediators by 24 months, there was a notable correlation in the change between some mediators (see Supplementary data online, *Table S2*). For example, PCC were >[absolute] 0.2 for the correlation between change in body weight and waist circumference, HbA_{1c}, hsCRP, and triglycerides in the semaglutide arm, and between change in body weight and waist circumference, HbA_{1c}, and triglycerides in the placebo arm (see Supplementary data online, *Table S2*). Correlations differed somewhat between arms, e.g. a correlation of 0.3 vs 0.1 for the correlation in change in hsCRP and waist circumference in the semaglutide vs placebo arm.

Estimates of % mediation from counterfactual analysis

For the mediation analysis, the proportion of missing values that were imputed by LOCF at each visit ranged from 8% to 23%. These proportions were very similar in the two treatment arms (see Supplementary data online, *Table S3*). *Table 1* shows the estimated % mediation of the effect of semaglutide on MACE at 36 months by potential mediators evaluated separately. The largest point estimates for % mediation were for waist circumference (64.0% [95% CI 27.5, 179.6]), hsCRP (42.1% [95% CI 17.9, 110.5]), HbA_{1c} (29.0% [95% CI −20.7, 120.5]), and body weight (19.5% [95% CI −33.0, 110.7]), but with wide CIs (*Table 1*) several of which encompass 100%. The survival curves underlying these estimates are shown in *Figure 1* for the four potential mediators with the largest point estimates. Survival curves for the other mediators are shown in Supplementary data online, *Figure S2*.

Estimates of % mediation from reverse counterfactual analysis

The estimated % mediation at 36 months was markedly lower for waist circumference when using the reversed counterfactual approach compared with the main approach but with wide overlapping CIs for both (*Figure 1*). This pattern of lower point estimates for mediation in the reverse counterfactual analysis was also seen for HbA_{1c} and triglycerides, whereas for HDL cholesterol, the % mediation was higher in the reverse counterfactual

Table 1 Time from randomization to first EAC-confirmed MACE adjusted for each of the 12 potential mediators (full analysis set)

	Probability of not having had a MACE at 36 months			Estimated total effect[d] (95% CI)	Estimated direct effect[e] (95% CI)	Estimated % mediation[f] (95% CI)
	Semaglutide[a]	Adjusted semaglutide[b]	Placebo[c]			
Body weight	0.941	0.939	0.929	0.012 (0.004, 0.019)	0.009 (−0.001, 0.019)	19.5 (−33.0, 110.7)
Waist circumference	0.941	0.934	0.930	0.012 (0.004, 0.020)	0.004 (−0.004, 0.013)	64.0 (27.5, 179.6)
HbA_{1c}	0.941	0.938	0.929	0.012 (0.004, 0.019)	0.008 (−0.001, 0.018)	29.0 (−20.7, 120.5)
hsCRP	0.941	0.936	0.929	0.013 (0.005, 0.020)	0.007 (−0.001, 0.016)	42.1 (17.9, 110.5)
DBP	0.941	0.941	0.929	0.012 (0.004, 0.019)	0.012 (0.005, 0.020)	−1.8 (−10.6, 4.0)
SBP	0.941	0.940	0.929	0.012 (0.004, 0.019)	0.010 (0.002, 0.018)	14.3 (−6.1, 51.7)
Total cholesterol	0.941	0.940	0.929	0.012 (0.005, 0.020)	0.011 (0.003, 0.019)	7.6 (−10.8, 36.1)
HDL cholesterol	0.941	0.940	0.930	0.012 (0.004, 0.019)	0.011 (0.003, 0.018)	9.3 (−8.4, 42.3)
LDL cholesterol	0.942	0.940	0.930	0.012 (0.005, 0.020)	0.011 (0.003, 0.018)	10.9 (0.8, 36.0)
Triglycerides	0.942	0.939	0.929	0.012 (0.005, 0.020)	0.010 (0.002, 0.018)	18.6 (−0.5, 65.5)
eGFR	0.941	0.940	0.929	0.012 (0.005, 0.020)	0.011 (0.004, 0.019)	6.9 (2.1, 21.3)
UACR	0.942	0.940	0.930	0.012 (0.005, 0.020)	0.010 (0.003, 0.018)	14.6 (5.2, 39.0)

Probabilities of no event were estimated using Vansteelandt mediation analysis for repeatedly measured mediators.[13] All probabilities were adjusted for the baseline value of the corresponding mediator. The variables hsCRP, UACR, and lipids were log-transformed before analysis. Treatment effects were evaluated as the difference in probabilities of no event. Percentiles based on 1000 bootstrap replicates were used to calculate CIs.
CI, confidence interval; DBP, diastolic blood pressure; EAC, event adjudication committee; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio.
[a]The probability of surviving MACE-free by 36 months in the semaglutide arm.
[b]The estimated probability of surviving MACE-free by 36 months in the semaglutide arm had the placebo arm values of the mediator been observed in the semaglutide arm.
[c]The probability of surviving MACE-free by 36 months in the placebo arm.
[d]The difference in probability of surviving MACE-free between the semaglutide and placebo arms is shown as the estimated total effect.
[e]The difference between the adjusted semaglutide probability and the placebo probability is shown as the estimated direct effect.
[f]The % mediation was calculated as 100 × (1 − [direct effect] / [total effect]).

analysis (see Supplementary data online, *Figure S2*). For body weight, the estimated % mediation was similar for the two approaches, but the CI was considerably wider when using the reversed counterfactual approach.

Supplementary analysis estimating % mediation using on-treatment data

The supplementary analyses showed similar % mediation at 36 months in the on-treatment counterfactual analysis as in the intention-to-treat counterfactual analysis for potential mediators in general; exceptions were HbA_{1c}, for which the point estimate for % mediation increased from 29.0% to 43.0%; SBP, which decreased from 14.3% to 5.5%; and triglycerides, which decreased from 18.6% to 9.5% but all with wide overlapping CIs (*Table 1* and Supplementary data online, *Table S4*).

Estimates of % mediation from multivariable counterfactual analysis

We examined the joint % mediation estimated when several risk factors were included together in different models (*Table 2*). When only body weight and waist circumference were included, the % mediation from these two factors was estimated as 12.3% (95% CI −42.6, 92.6), which was lower than for each one separately. When only variables other than body weight and waist

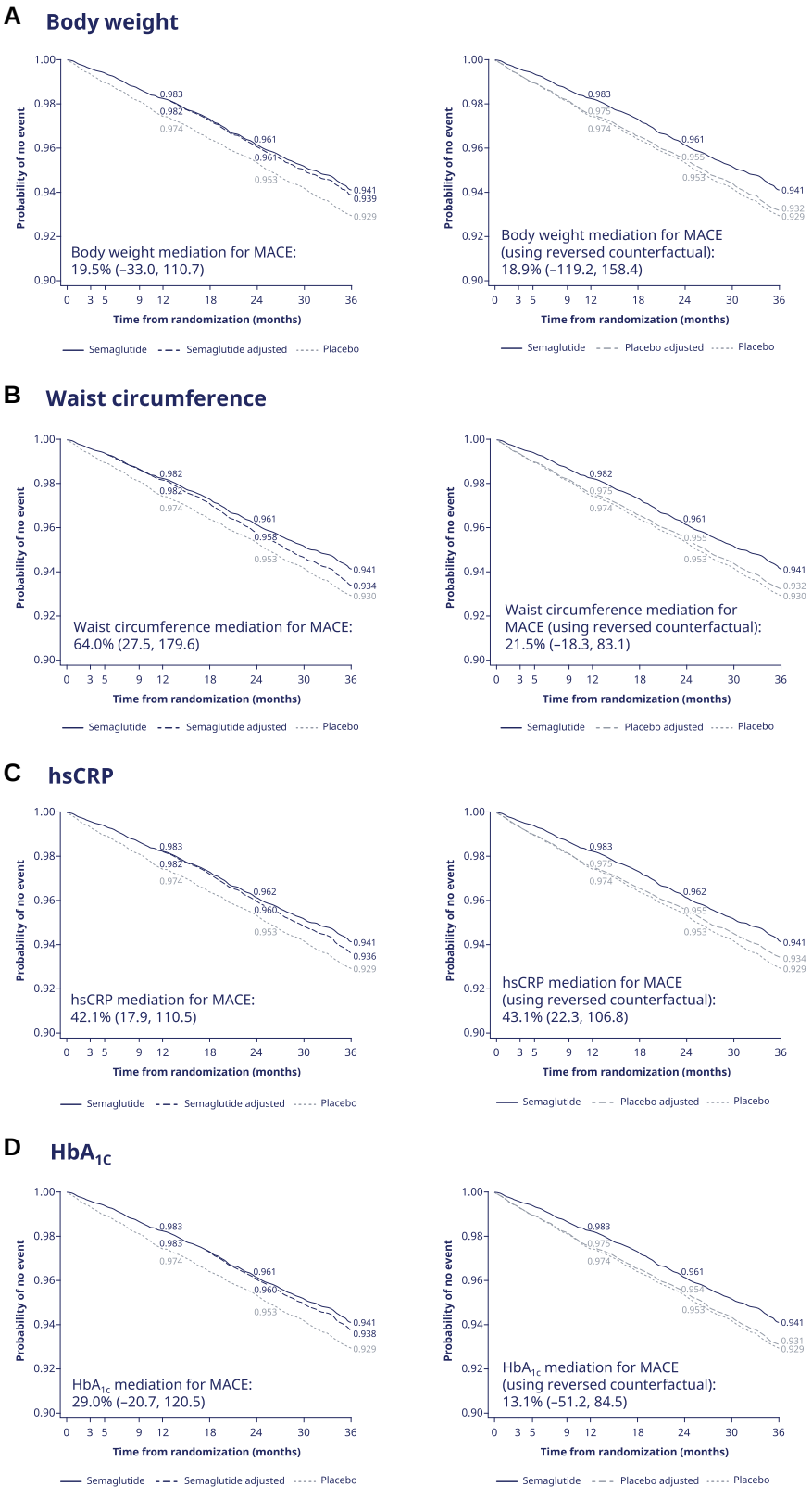

Figure 1 Counterfactual and reverse counterfactual survival curves for first EAC-confirmed MACE for the four potential mediators with the largest effect evaluated separately. Mediation analyses used the Vansteelandt repeated regression approach.[13] Data shown are the estimated % mediation and the corresponding 95% CIs at 36 months. The solid blue and dotted grey lines show the observed survival curves for semaglutide and placebo. The dashed blue line in the left-hand figures shows the survival curve for semaglutide, which has

Continued

circumference were included in the analysis, the % mediation was 46.0% (95% CI −6.0, 161.0). Since including too many variables causes convergence issues in such models, in this multivariable model we included only one of the blood pressure variables (SBP) and one of the lipid variables (LDL cholesterol). When body weight and waist circumference were added to this latter model, the % mediation was lower at 31.4% (95% CI −30.1, 143.6).

Supplementary analysis estimating % mediation using a non-counterfactual time-dependent Cox regression analysis

The results of the Cox model adjustment for time-dependent mean potential mediators are shown in *Table 3*. Using this method, the % mediation for each potential mediator was lower than using the Vansteelandt method, but the largest effects continued to be seen for waist circumference, hsCRP, and HbA_{1c}; CIs were narrower using this approach. In Cox regressions including multiple time-dependent mediators, the % mediation was highest for the model that included HbA_{1c}, hsCRP, SBP, LDL cholesterol, eGFR, and UACR at 32.8%. As with the counterfactual method, the % mediation fell when body weight and waist circumference were added to the model. We further performed the same time-dependent type of Cox regression separately by treatment arm (see Supplementary data online, *Table S5*). This analysis found no significant association between time-updated body weight and lower MACE incidence in either treatment arm. A lower time-updated waist circumference was significantly associated with lower MACE incidence only in the semaglutide arm, while a lower time-updated hsCRP was significantly associated with lower MACE incidence in both arms.

Discussion

In SELECT, the 20% reduction in MACE with semaglutide vs placebo was accompanied by significant improvements across multiple known CV risk factors.[1] Here we investigated to what extent changes in these risk factors might mediate semaglutide's effect on MACE. Our primary analysis method was the Vansteeland counterfactual approach but we also conducted a supplementary analysis using a time updated Cox regression model. Among the CV risk factors evaluated, change in waist circumference (64.0%), hsCRP (42.1%), HbA_{1c} (29.0%), and body weight (19.5%) showed the largest contribution in the counterfactual mediation analysis with each considered separately, but CIs were wide and all overlapped 100%. While the CIs that encompass 100% of mediation mean that it is possible that such risk factors may explain the entirety of the drug effect on MACE, the point estimates for the most likely value of the % mediation are well below 100%, consistent with alternative factors mediating at least some of the effect. In the Cox regression approach the same risk factors showed the highest mediation although the point estimates were generally lower but with narrower CIs that did not overlap 100%. Thus neither of these analyses show with any confidence that the most immediate candidate mediators, body weight or waist circumference change, or other factors, could account for all the MACE effect with any certainty when considered separately (*Structured Graphical Abstract*).

Change in plasma hsCRP level was associated with the second largest point estimate for % mediation after waist circumference. hsCRP levels are reported as being higher in patients living with obesity, which may involve various factors, including interleukin-6 which is produced in adipose tissue and induces CRP gene expression.[15] CRP is a biomarker of systemic inflammation and also of total body fat mass.[16] Higher BMI is associated with higher hsCRP levels[16] and non-pharmacological weight loss is associated with a fall in hsCRP.[17] The large point estimate for mediation of the MACE effect in SELECT by hsCRP could partly reflect mediation of the effect of semaglutide on MACE being through change in total body fat mass, or for part of the effect of semaglutide being a direct anti-inflammatory effect; we cannot differentiate between these two explanations.

SELECT was the first trial of a GLP-1 RA conducted in people with known CVD but without diabetes to show a reduction in CV outcomes,[1] and as such this represents the first mediation analysis in such a population without diabetes at baseline. In the LEADER trial of liraglutide, which included only patients with known CVD, and the REWIND trial of dulaglutide, which included patients both with and without CVD, all participants had type 2 diabetes. In those trials, HbA_{1c} change was estimated to account for up to 83% (using the Vansteelandt method in LEADER) and 36% (using the time-updated Cox regression method in REWIND) of treatment effects on MACE.[8,9] When considered separately in our analysis, the estimate for HbA_{1c} using the Vansteelandt method was 29%. Using the time-updated Cox regression approach yielded a % mediation of just 13% for HbA_{1c}. Overall, these data suggest that glucose lowering may have mediated some of the effect on MACE, but with considerable uncertainty regarding how much. In LEADER and REWIND, UACR was considered the only other mediator of the MACE effect with good support (33% and 29%, respectively).[8,9] In SELECT, the % mediation estimate for UACR was considerably lower than this (14.6%), which might be expected given the higher prevalence of baseline normoalbuminuria in people in SELECT (84%)[11] than in the LEADER (63%)[18] and REWIND (65%)[19] trials in people with diabetes. A mediation through UACR is consistent with either a kidney effect or an effect on endothelial dysfunction. Higher levels of baseline albuminuria were observed in the

Figure 1 Continued
been adjusted to estimate the probability of no event in the unobserved counterfactual scenario that the semaglutide arm mediator values were as if treated with placebo. The dashed grey line in the right-hand figures shows the survival curve for placebo, which has been adjusted for the reversed counterfactual scenario that the placebo arm mediator values were as if treated with semaglutide. All curves were adjusted for the baseline value of the corresponding mediator. The variable hsCRP was log-transformed before analysis. Percentiles based on 1000 bootstrap replicates were used to calculate CIs. CI, confidence interval; EAC, event adjudication committee; HbA_{1c}, glycated haemoglobin; hsCRP, high-sensitivity C-reactive protein; MACE, major adverse cardiovascular event

Table 2 Estimated % mediation for potential mediators evaluated jointly (full analysis set)

Probability of not having had a MACE at 36 months			Estimated total effect[d] (95% CI)	Estimated direct effect[e] (95% CI)	Estimated % mediation[f] (95% CI)	Reversed counterfactual estimated % mediation[g] (95% CI)
Semaglutide[a]	Adjusted semaglutide[b]	Placebo[c]				
Body weight, waist circumference, HbA_{1c}, hsCRP, SBP, LDL cholesterol, eGFR, UACR						
0.943	0.939	0.930	0.012 (0.005, 0.020)	0.008 (−0.003, 0.019)	31.4 (−30.1, 143.6)	52.6 (−55.1, 192.6)
HbA_{1c}, hsCRP, SBP, LDL cholesterol, eGFR, UACR						
0.942	0.937	0.930	0.012 (0.005, 0.020)	0.007 (−0.004, 0.016)	46.0 (−6.0, 161.0)	60.4 (1.2, 165.0)
Body weight, waist circumference						
0.942	0.940	0.930	0.012 (0.004, 0.020)	0.011 (0.000, 0.020)	12.3 (−42.6, 92.6)	12.2 (−121.1, 134.7)

Probabilities of no event were estimated using Vansteelandt's mediation analysis for repeatedly measured mediators.[13] All probabilities were adjusted for the baseline value of the corresponding mediator. The variables hsCRP, UACR, and lipids were log-transformed before analysis. Treatment effects were evaluated as the difference in probabilities of no event. Percentiles based on 1000 bootstrap replicates were used to calculate CIs.

CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio.

[a]The probability of surviving MACE-free by 36 months in the semaglutide arm.

[b]The estimated probability of surviving MACE-free by 36 months in the semaglutide arm had the placebo arm values of the mediator been observed in the semaglutide arm.

[c]The probability of surviving MACE-free by 36 months in the placebo arm.

[d]The difference in probability of surviving MACE-free between the semaglutide and placebo arms is shown as the estimated total effect.

[e]The difference between the adjusted semaglutide probability and the placebo probability is shown as the estimated direct effect.

[f]The % mediation was calculated as 100 × (1 − [direct effect] / [total effect]).

[g]The % mediation was calculated as 100 × (1 − [direct effect] / [total effect]), where the direct effect was the difference between arms in MACE-free survival had the placebo arm experienced the mediator values observed in the semaglutide arm.

FLOW trial, so whether greater mediation by UACR will be observed in FLOW will be of interest, though no interaction between baseline albuminuria and MACE effect was observed in FLOW.[20] Some mediation via lipid changes and SBP was also suggested by the examination of each risk factor separately.

A key goal of our analysis was to evaluate the joint mediation of all risk factors considered together. As shown, there is a correlation in the within-person change in risk factors; thus, the % mediation attributable to each cannot be fully separated and point estimates must then be interpreted with this in mind. When risk factors other than body weight or waist were combined together the % mediation was not much increased above the largest single risk factor estimate. Surprisingly, when body weight and waist change were added to these multivariable models, the % mediation explained actually fell. Indeed, the % mediation in a model that included only body weight and waist circumference was lower than for either separately; this was the case with both counterfactual and Cox models. This suggests that there may be unmeasured confounders of the association between waist circumference and body weight change with MACE. That this may be the case is further suggested by the reversed counterfactual analysis, giving very different point estimates for mediation by waist circumference than the counterfactual analysis, or in the case of body weight change, having much wider CIs. The treatment arm-specific supplementary analyses using Cox regression likewise suggested that the strength of association of time-updated waist circumference and MACE differed in the two treatment arms, and there was no significant association of time-updated bodyweight with MACE in either arm. We also noted that the correlation of body weight and waist circumference change differed by treatment arm. A previous subgroup analysis from SELECT that concluded that about a third of the MACE effect was attributable to waist circumference change showed that in the placebo group, weight loss of >5% by week 20 was associated with increased MACE.[10] Taken together, these observations are consistent with unintentional weight loss driven by comorbid conditions or frailty acting as a confounding factor. The same confounding factors are likely also occurring in those receiving semaglutide; however, unintentional weight loss driven by comorbid conditions is likely being masked by the efficacy of semaglutide in the treatment arm. Thus, while it remains possible that a greater % of mediation is due to waist circumference or weight change than the point estimates we have obtained here, our analyses cannot convincingly show that the effect of semaglutide on MACE in SELECT is totally accounted for by body weight or waist circumference change or change in the other CV risk factors measured.

Other potentially cardioprotective actions of semaglutide not necessarily captured by the conventional CVD risk factors measured in SELECT and analysed here have been suggested, but remain speculative at present. For example, semaglutide reduces steatohepatitis and whether this mediates some of the CVD effects in SELECT is unclear.[21] In mouse models of atherosclerosis, semaglutide reduced plaque size.[22] In conjunction with this reduction, circulating inflammatory markers (including tumour necrosis factor-alpha, interferon-gamma, and osteopontin) were reduced, as was the expression of inflammation-associated genes in plaque. Changes in these and other pro-inflammatory markers may not be fully captured by hsCRP measurements.

Table 3 Time-adjusted estimated % mediation for each of the 12 potential mediators individually, and for potential mediators evaluated jointly (full analysis set) using Cox regression

	Semaglutide/ placebo Estimated HR (95% CI)	Estimated % mediation (95% CI)
Unadjusted	0.801 (0.717, 0.895)	–
Body weight	0.818 (0.718, 0.931)	9.1 (−23.5, 49.3)
Waist circumference	0.860 (0.764, 0.968)	32.0 (12.6, 73.9)
HbA_{1c}	0.825 (0.729, 0.933)	13.0 (−11.7, 45.4)
hsCRP	0.858 (0.767, 0.961)	31.0 (16.1, 65.4)
DBP	0.801 (0.717, 0.895)	−0.2 (−2.0, 1.2)
SBP	0.815 (0.728, 0.912)	7.8 (−3.3, 23.9)
Total cholesterol	0.807 (0.720, 0.903)	2.9 (−9.5, 17.7)
HDL cholesterol	0.800 (0.715, 0.895)	−0.6 (−10.4, 8.2)
LDL cholesterol	0.813 (0.726, 0.911)	6.7 (−5.0, 22.6)
Triglycerides	0.807 (0.720, 0.905)	3.1 (−10.4, 20.9)
eGFR	0.798 (0.714, 0.892)	−1.7 (−9.9, 5.1)
UACR	0.818 (0.730, 0.915)	9.1 (−0.5, 25.4)
Body weight, waist circumference, HbA_{1c}, hsCRP, SBP, LDL cholesterol, eGFR, UACR	0.853 (0.743, 0.979)	28.0 (−8.4, 87.3)
HbA_{1c}, hsCRP, SBP, LDL cholesterol, eGFR, UACR	0.862 (0.758, 0.980)	32.8 (2.7, 90.1)
Body weight, waist circumference	0.814 (0.714, 0.927)	6.9 (−27.0, 46.4)

Cox regression analysis including treatment and baseline value of mediator as fixed covariates, and updated mean of the mediator as a time-dependent covariate. The % mediation was calculated as 100 × (1 − [direct effect] / [total effect]), where the direct and total effects were entered as log HR.
CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio.

An increase in the endocrine activity of epicardial fat with anti-thrombotic properties with semaglutide in samples taken from patients during cardiac surgery has been reported.[23] Extensive changes in the plasma proteome with semaglutide have been reported from the STEP 1 and 2 trials, such as ANGPT2 (involved in vascular remodelling and angiogenesis), CD93 (involved in CV homeostasis), and MSR1 (involved in lipid metabolism and immune function).[24] Further studies in SELECT will examine proteomic changes and their impact on CVD in more detail.

The strengths of this study are the randomized allocation of semaglutide, the lengthy follow-up, the range of potential mediators that were measured, and the substantial 20% reduction in MACE. Limitations include the fact that SELECT was not powered with respect to any mediation analysis, and the frequency of measurements—were these available more frequently, then % mediation estimates may have been more precise. A further limitation is that missingness in covariates (not all data could be collected due to the COVID-19 pandemic), while not very large and of equal magnitude in the treatment arms, nonetheless also introduces less precision in mediation estimates (see Supplementary data online, *Table S3*). When the outcome is time to event, there is a potential issue of competing risks. For example, it is possible that some patients died due to non-CV causes before the benefit of a change in the mediator on the risk of MACE could be observed, and the frequency of this could be different in the two treatment arms. Indeed, an analysis of causes of mortality in SELECT demonstrated a reduction in COVID-19 deaths and deaths from infection with semaglutide compared with placebo, and these non-CV deaths were a competing risk for CV death in the placebo group.[25] Finally, and most importantly, all mediation analyses inherently rely on strong assumptions, including the untestable assumption that there is no unmeasured confounding factor, i.e. a hidden factor that affects both the potential mediator and the risk of MACE. When the mediators of interest include body weight and body fat distribution, this problem is especially an issue given that the relationship of body weight change to outcomes varies by the cause of the change. Such confounding could lead to an over- or underestimation of the % mediation. These limitations emphasize that all mediation analyses are exploratory, and the results should therefore be interpreted with caution.

In conclusion, mediation analyses could not fully explain the effects of semaglutide on MACE to known risk factors in SELECT with any certainty. These findings highlight that further investigations of potential additional biomarkers and mediators of semaglutide's cardioprotective effect are worthwhile.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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G. Kees Hovingh declares being an employee of and stakeholder in Novo Nordisk.

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Data Availability

An authorized researcher can request access to clinical study data by submitting a research proposal for review and approval by Novo Nordisk and an internal independent review panel. Requests are usually considered after the research is finished and the main results have been published. If the research supports a regulatory application, requests will be considered after the product and its intended use are approved in both the EU and the USA. Participants clinical data will be anonymized, following an approved internal process, before data are shared to external third parties. For details on how to request access to clinical data, visit novonordisk-trials.com.

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Ethical Approval

All applicable regulatory and ethical authorities approved the SELECT protocol, and all participants provided written informed consent prior to study-related activities.

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