

Semaglutide and cardiovascular outcomes by baseline and changes in adiposity measurements: a prespecified analysis of the SELECT trial



John Deanfield, A Michael Lincoff, Steven E Kahn, Scott S Emerson, Ildiko Lingvay, Benjamin M Scirica, Jorge Plutzky, Robert F Kushner, Helen M Colhoun, G Kees Hovingh, Signe Stensen, Peter E Weeke, Ole Kleist Jeppesen, Rafael Bravo, Chau-Chung Wu, Issei Komuro, Ferruccio Santini, Jøran Hjelmæsæth, Miguel Urina-Triana, Silvio Buscemi, Donna H Ryan



Summary

Background The SELECT trial found semaglutide reduced major adverse cardiovascular events (MACE) in patients with overweight or obesity with cardiovascular disease but without diabetes. We report a prespecified analysis of the SELECT trial on the relationships between baseline adiposity measures, treatment-induced adiposity changes, and subsequent MACE risk.

Methods Patients aged at least 45 years, with a BMI of at least 27 kg/m² were enrolled in 41 countries (804 sites) and randomised 1:1 to once-weekly semaglutide 2.4 mg or placebo. The primary outcome was time to first MACE (composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke). Adiposity measures included weight and waist circumference. In this analysis, risk of MACE occurring after 20 weeks was assessed between patients by adiposity changes in the first 20 weeks and, in a separate analysis, all in-trial MACE were assessed between patients by adiposity changes over 104 weeks. This trial is registered with ClinicalTrials.gov, NCT03574597.

Findings Semaglutide significantly reduced MACE incidence compared with placebo among 17 604 patients enrolled in SELECT, with consistent benefits across all baseline weight and waist circumference categories. In the semaglutide group, analyses for linear trends showed lower baseline bodyweight and waist circumference were associated with lower incidence of MACE—an average 4% reduction in risk per 5 kg lower bodyweight (hazard ratio [HR] 0.96 [95% CI 0.94–0.99]; $p=0.001$) and per 5 cm smaller waist circumference (0.96 [0.93–0.99]; $p=0.004$). In the placebo group, lower baseline waist circumference (0.96 [0.94–0.99]; $p=0.007$), but not bodyweight (0.99 [0.97–1.01]; $p=0.28$), was associated with a lower MACE risk and weight loss was paradoxically associated with increased MACE risk. In those receiving semaglutide there was no linear trend linking weight loss at week 20 to subsequent MACE risk, but greater waist circumference reduction at week 20 was associated with lower subsequent MACE risk, and waist circumference reduction by week 104 was associated with lower in-trial risk of MACE. An estimated 33% of the observed benefit on MACE was mediated through waist circumference reduction (HR 0.86 [95% CI 0.77–0.97] after adjustment for time-varying changes in waist circumference).

Interpretation The cardioprotective effects of semaglutide were independent of baseline adiposity and weight loss and had only a small association with waist circumference, suggesting some mechanisms for benefit beyond adiposity reduction.

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Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) were initially developed for glycaemic control in type 2 diabetes and some have also demonstrated efficacy in weight reduction and cardiovascular risk modification in non-diabetic populations.^{1–3} Obesity is a well established risk factor for cardiovascular morbidity and mortality, operating through haemodynamic, metabolic, and inflammatory pathways.⁴ Weight alone, however, does not distinguish between fat and lean muscle mass, nor does it capture differences between visceral and subcutaneous fat—each of which may have distinct

implications for cardiovascular risk.⁵ Visceral adiposity in particular has been causally implicated in adverse cardiovascular outcomes via the release of pro-inflammatory cytokines.⁶ Moreover, ectopic fat depots, such as epicardial and perivascular fat, might exert local pathogenic effects on heart and blood vessels.^{7–9} In trials with GLP-1RAs, the relationship between baseline adiposity phenotypes and their changes with treatment, with subsequent ischaemic major adverse cardiovascular events (MACE), remains undefined.¹⁰ This has important implications for clinical practice, particularly regarding patient stratification and the elucidation of mechanisms

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Institute of Cardiovascular Sciences, University College London, London, UK

(Prof J Deanfield MB BChir);

Department of Cardiovascular

Medicine, Cleveland Clinic,

Cleveland Clinic Lerner College

of Medicine of Case Western

Reserve University, Cleveland,

OH, USA (Prof A M Lincoff MD);

Department of Medicine, VA

Puget Sound Health Care

System, and University of

Washington, Seattle, WA, USA

(Prof S E Kahn MB ChB);

Department of Biostatistics,

University of Washington, WA,

USA (Prof S S Emerson MD PhD);

Department of Internal

Medicine and Endocrinology

and Peter O'Donnell Jr School

of Public Health, UT

Southwestern Medical Center,

Dallas, TX, USA

(Prof I Lingvay MD); TIMI Study

Group, Division of

Cardiovascular Medicine,

Brigham and Women's

Hospital, Harvard Medical

School, Boston, MA, USA

(B M Scirica MD MPH);

Department of Cardiovascular

Medicine, Brigham and

Women's Hospital, Harvard

Medical School, Boston, MA,

USA (J Plutzky MD);

Department of Medicine,

Feinberg School of Medicine,

Northwestern University,

Chicago, IL, USA

(Prof R F Kushner MD); Institute

of Genetics and Molecular

Medicine, University of

Edinburgh, Edinburgh, UK

(Prof H M Colhoun MD); Novo

Nordisk, Søborg, Denmark

(G K Hovingh MD PhD,

S Stensen MD PhD,

P E Weeke MD PhD,

O K Jeppesen MSc, R Bravo MD);

Department of Internal

Medicine, National Taiwan

University Hospital, Taipei,

Taiwan (Prof C-C Wu MD PhD);
International University of
Health and Welfare, Tokyo,
Japan (I Komuro MD PhD);
Obesity and Lipodystrophy
Centre, Endocrinology Unit,
University Hospital of Pisa,
Pisa, Italy
(Prof F Santini MD PhD);
Department of Endocrinology,
Obesity and Nutrition, Vestfold
Hospital Trust, Norway
(Prof J Hjelmæsæth MD PhD);
Department of Endocrinology,
Morbid Obesity and Preventive
Medicine, Institute of Clinical
Medicine, University of Oslo,
Norway (Prof J Hjelmæsæth);
Faculty of Health Sciences,
Simón Bolívar University,
Barranquilla, Colombia
(Prof M Urina-Triana MD PhD);
Department of Promozione
della Salute, Materno-Infantile,
Medicina Interna e Specialistica
di Eccellenza (PROMISE),
University of Palermo,
Palermo, Italy, and Unit of
Clinical Nutrition, Obesity and
Metabolic Diseases, University
Hospital Policlinico P Giaccone,
Palermo, Italy
(Prof S Buscemi MD PhD);
Pennington Biomedical
Research Center, Baton Rouge,
LA, USA (Prof D H Ryan MD)

Correspondence to:
Prof John Deanfield, Institute of
Cardiovascular Sciences,
University College London,
London WC1E 6BT, UK
j.deanfield@ucl.ac.uk

Research in context

Evidence before this study

Obesity-related cardiovascular disease is associated with substantial morbidity and mortality. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) were initially developed for glycaemic control in type 2 diabetes and some have been associated with significant weight loss and reductions in cardiovascular risk. Previous GLP-1RA cardiovascular outcome trials were conducted predominantly in cohorts with type 2 diabetes, where interpretation of cardiovascular benefits was confounded by concurrent glycaemic effects and potentially other cardiovascular disease mechanisms driven by diabetes. In searching PubMed, MEDLINE, and the Cochrane Library from database inception to April 1, 2024, using the terms “GLP-1 receptor agonist”, “CV outcomes”, “obesity”, “weight loss”, “adiposity”, and “MACE” for studies in patients without diabetes, only limited data are available. In the SELECT trial, in patients with obesity (BMI ≥ 27 kg/m²) and established cardiovascular disease but not diabetes, semaglutide resulted in a 20% reduction in major adverse cardiovascular events (MACE), while in the STEP-HFpEF trial, among patients with obesity (BMI ≥ 30 kg/m² and heart failure with preserved ejection fraction but not diabetes), semaglutide improved heart failure symptoms and physical function. Despite these findings, the relationship between baseline adiposity measures, semaglutide-induced weight loss patterns, and cardiovascular outcomes remained undefined.

Added value of this study

This prespecified analysis of the SELECT trial, the largest cardiovascular outcomes trial of a GLP-1RA in patients without diabetes, provides several novel insights. First, we demonstrate that the cardiovascular benefits of semaglutide were independent of baseline adiposity measures. Second, we show that the magnitude of early weight loss did not predict subsequent cardiovascular benefit. Third, changes in waist circumference were associated with cardiovascular outcomes, but explained only a proportion (33%) of the observed benefit on MACE.

Implications of all the available evidence

Our findings, combined with existing evidence, suggest that semaglutide and perhaps other GLP-1RAs should be reconceptualised as disease-modifying treatments rather than solely medications for glycaemic control or weight loss. The independence of cardiovascular benefit from baseline adiposity and weight loss magnitude has important implications for clinical practice and health-care policy. Prescribing restrictions based on BMI thresholds or weight-loss targets may not be appropriate, as patients such as those included in our study (with overweight or obesity) might benefit regardless of weight-loss response. These results also suggest that future research should focus on the broader potential mechanisms of cardiovascular protection with GLP-1RAs.

underlying GLP-1RA-mediated cardiovascular protection.

The SELECT trial, including 17 604 participants, was the largest study of GLP-1RA therapy in patients with established cardiovascular disease and elevated BMI (≥ 27 kg/m²) who did not have diabetes. It demonstrated that semaglutide resulted in an 8·51% percentage points mean placebo-adjusted weight reduction and a 20% reduction in MACE.¹ We conducted a prespecified analysis of the trial to address two issues: first, the association between baseline adiposity measures—including both total body mass and central fat distribution—and MACE; and, second, the relationship between the magnitude and pattern of weight loss and subsequent cardiovascular benefit. These analyses aim to assist practitioners with patient selection, provide clinically relevant adiposity characteristics for treatment response, advance understanding of mechanisms for benefit, and inform health-care policy decisions. Such insights are crucial, as they could help reconceptualise GLP-1RAs from primarily weight-loss medications to disease-modifying treatments with broader therapeutic applications.

Methods

Study design and participants

The SELECT trial was a randomised, double-blind, multicentre, placebo-controlled, event-driven phase 3

trial in 41 countries (804 sites) which evaluated whether once-weekly subcutaneous semaglutide 2·4 mg, given as an adjunct to standard of care, was superior to placebo in reducing the risk of MACE in patients with established cardiovascular disease and overweight or obesity, but without diabetes.^{1,11,12} The protocol was approved by the Institutional Review Board and Ethics Committee at each participating centre.

Patients were eligible if they were aged 45 years or older, had a BMI of 27 kg/m² or above, and had established atherosclerotic cardiovascular disease, defined as one or more of the following: previous myocardial infarction, stroke, or symptomatic peripheral artery disease. Exclusion criteria included glycated haemoglobin (HbA_{1c}) of 48 mmol/mol or above ($\geq 6\cdot5\%$); history of type 1 or 2 diabetes; presence of end-stage kidney disease; or previous myocardial infarction, stroke, hospitalisation for unstable angina pectoris, or transient ischaemic attack within 60 days of screening; or New York Heart Association class IV heart failure. All patients provided written informed consent, consistent with the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (NCT03574597) and is completed with results.

Randomisation and masking

Patients were randomised in a 1:1 ratio with a block size of four to escalating doses of once-weekly subcutaneous

semaglutide over 16 weeks to a target dose of 2·4 mg, or to placebo. Injections were in the form of pre-filled pen-injectors (provided by Novo Nordisk, Søborg, Denmark), and each trial site was supplied with sufficient trial products on an ongoing basis controlled by an interactive web response system. Both investigators and participants were masked to treatment allocation.^{1,12}

If there were tolerability issues, investigators were permitted to extend dose-escalation intervals, pause treatment, or maintain the dose below 2·4 mg once-weekly. Investigators were instructed to follow evidence-based guidelines to optimise the management of underlying cardiovascular disease, and there was no lifestyle intervention to target weight reduction. Patients who developed diabetes during the study remained on their assigned treatment, with subsequent use of glucose-lowering therapies at the discretion of the investigator; however, initiation of an open-label GLP-1RA was not permitted. The pre-filled pen-injector for the investigational medical product and placebo were visually identical and packaged to maintain masking. Masking was permitted to be broken in the case of a medical emergency.

Procedures

After written informed consent was obtained, participants entered a 16-week period of dose escalation or injection with placebo. At the screening appointment, the investigator at each site orally directed the participant on how to use the injection device, and directions were provided in writing at the first dispensing visit. The semaglutide injection starting dose was 0·24 mg, rising to 0·5 mg, 1·0 mg, and 1·7 mg, with the target dose of 2·4 mg starting at week 17. Participants were instructed to inject semaglutide or placebo once weekly on the same day of the week, with a choice of thigh, abdomen, or upper arm as injection sites. All injections were taken at home (except from the first dose for some participants), and there was no dosing diary, but changes to dosing (date and dose) were recorded in the electronic case report file. The choice of injection site was decided by the participant, but the chosen site was requested to remain consistent throughout the trial, although changing between the left and right site of the body was permitted.

Outcomes

Bodyweight was measured at the time of random allocation, every 4 weeks until week 20, and every 13 weeks thereafter until the end of treatment. Waist circumference was measured at random allocation, week 20, and annually thereafter until the end of treatment (appendix p 2). The primary outcome of this prespecified analysis was MACE (defined as a composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, as adjudicated by a masked independent committee) in a time-to-first-event analysis, which was examined in relation to adiposity changes in

the treatment groups. Data from patients who withdrew from the trial, died from causes not included in the endpoint, or were lost to follow-up were censored at the time of withdrawal, death, or last contact with the investigator.

See Online for appendix

	<30 kg/m ² (n=5024)	≥30 to <35 kg/m ² (n=7474)	≥35 to <40 kg/m ² (n=3346)	≥40 kg/m ² (n=1760)
Age group, years				
<55	999 (19·9%)	1706 (22·8%)	883 (26·4%)	563 (32·0%)
≥55 to <65	1869 (37·2%)	2849 (38·1%)	1308 (39·1%)	699 (39·7%)
≥65 to <75	1653 (32·9%)	2322 (31·1%)	949 (28·4%)	438 (24·9%)
≥75 to <85	478 (9·5%)	578 (7·7%)	203 (6·1%)	59 (3·4%)
≥85	25 (0·5%)	19 (0·3%)	3 (<0·1%)	1 (<0·1%)
Sex				
Female	1047 (20·8%)	1919 (25·7%)	1105 (33·0%)	801 (45·5%)
Male	3977 (79·2%)	5555 (74·3%)	2241 (67·0%)	959 (54·5%)
Region				
Asia	911 (18·1%)	881 (11·8%)	293 (8·8%)	116 (6·6%)
Europe	1880 (37·4%)	2954 (39·5%)	1305 (39·0%)	553 (31·4%)
North America	1040 (20·7%)	1814 (24·3%)	897 (26·8%)	650 (36·9%)
Other	1193 (23·7%)	1825 (24·4%)	851 (25·4%)	441 (25·1%)
Race				
American Indian or Alaska Native	15 (0·3%)	17 (0·2%)	8 (0·2%)	4 (0·2%)
Asian	730 (14·5%)	550 (7·4%)	128 (3·8%)	39 (2·2%)
Black or African American	161 (3·2%)	232 (3·1%)	138 (4·1%)	140 (8·0%)
Native Hawaiian or Other Pacific Islander	3 (<0·1%)	3 (<0·1%)	1 (<0·1%)	1 (<0·1%)
White	3870 (77·0%)	6430 (86·0%)	2966 (88·6%)	1525 (86·6%)
Other	195 (3·9%)	180 (2·4%)	69 (2·1%)	30 (1·7%)
Not reported	50 (1·0%)	62 (0·8%)	36 (1·1%)	21 (1·2%)
Ethnicity				
Not Hispanic or Latino	4345 (86·5%)	6643 (88·9%)	3008 (89·9%)	1615 (91·8%)
Glycaemic status				
HbA _{1c} <5·7%	1895 (37·7%)	2522 (33·7%)	1002 (29·9%)	486 (27·6%)
HbA _{1c} ≥5·7%	3129 (62·3%)	4951 (66·2%)	2342 (70·0%)	1274 (72·4%)
Prediabetes	3019 (60·1%)	4814 (64·4%)	2292 (68·5%)	1237 (70·3%)
Normoglycaemic	2005 (39·9%)	2660 (35·6%)	1052 (31·4%)	523 (29·7%)
Bodyweight in kg, mean (SD)	83·0 (9·4)	94·1 (11·2)	107·5 (12·8)	126·1 (19·3)
BMI in kg/m ² , mean (SD)	28·6 (0·9)	32·2 (1·4)	37·1 (1·4)	44·5 (4·3)
Waist circumference in cm, mean (SD)	101·8 (8·9)	109·7 (9·1)	119·3 (10·0)	130·7 (13·6)
Waist circumference to height ratio, mean (SD)	0·60 (0·05)	0·64 (0·05)	0·70 (0·05)	0·78 (0·07)
Blood pressure in mm Hg, mean (SD)				
Systolic	129·7 (15·7)	130·9 (15·1)	132·2 (15·5)	132·6 (15·2)
Diastolic	78·3 (9·9)	79·4 (9·9)	79·9 (10·1)	80·6 (10·0)
Lipids in mg/dL, mean (SD)				
HDL-C	46·3 (12·3)	45·5 (11·6)	44·7 (11·5)	45·3 (11·3)
LDL-C	84·0 (36·1)	84·2 (35·5)	87·4 (37·0)	90·1 (35·6)
Triglycerides	148·9 (90·6)	159·2 (95·0)	167·8 (94·7)	156·2 (83·4)
Total cholesterol	158·6 (42·8)	160·0 (42·2)	163·9 (43·6)	165·1 (42·7)

(Table 1 continues on next page)

	<30 kg/m ² (n=5024)	≥30 to <35 kg/m ² (n=7474)	≥35 to <40 kg/m ² (n=3346)	≥40 kg/m ² (n=1760)
(Continued from previous page)				
eGFR level in mL/min per 1.73 m ² , mean (SD)	81.9 (17.4)	82.2 (17.0)	82.9 (17.7)	84.4 (18.4)
Albuminuria in mg/g, geometric mean (SD)*	9.27 (167.6)	9.2 (161.8)	10.4 (185.1)	11.09 (202.3)
hsCRP <2.0 mg/dL	3159 (62.9%)	4196 (56.1%)	1401 (41.9%)	483 (27.4%)
hsCRP ≥2.0 mg/dL	1827 (36.4%)	3235 (43.3%)	1916 (57.3%)	1268 (72.0%)
Hypercholesterolaemia†	4976 (99.0%)	7408 (99.1%)	3306 (98.8%)	1733 (98.5%)
Cardiovascular inclusion criteria				
Myocardial infarction only	3485 (69.4%)	5169 (69.2%)	2201 (65.8%)	1051 (59.7%)
Stroke only	811 (16.1%)	1243 (16.6%)	641 (19.2%)	439 (24.9%)
PAD only	180 (3.6%)	311 (4.2%)	166 (5.0%)	120 (6.8%)
Myocardial infarction and stroke	214 (4.3%)	282 (3.8%)	126 (3.8%)	61 (3.5%)
Myocardial infarction and PAD	164 (3.3%)	234 (3.1%)	100 (3.0%)	35 (2.0%)
Stroke and PAD	43 (0.9%)	51 (0.7%)	27 (0.8%)	9 (0.5%)
Myocardial infarction, stroke, and PAD	24 (0.5%)	31 (0.4%)	8 (0.2%)	4 (0.2%)
Other	103 (2.1%)	153 (2.0%)	77 (2.3%)	41 (2.3%)

Data are n (%) unless otherwise specified. eGFR=estimated glomerular filtration rate. HbA_{1c}=glycated haemoglobin. HDL-C=high-density lipoprotein-cholesterol. hsCRP=high-sensitivity C-reactive protein. LDL-C=low-density lipoprotein-cholesterol. PAD=peripheral artery disease. UACR=urine albumin-creatinine ratio. Data included in this table have been previously published.¹³ Data are reproduced here under the Creative Commons license CC BY 4.0. Selected data from the original publication are included here; no changes have been made to the data presented here versus the original. *Based on UACR. †Defined as serum LDL-C ≥1.8 mmol/L (≥70 mg/dL) or treated with lipid-lowering medications. Baseline is defined as the eligible assessment associated with the randomisation visit, if taken before or at the date of first dose. If missing or taken after the date of first dose, the assessment from the screening visit is used.

Table 1: Baseline characteristics and demographics by baseline BMI category

before week 20 and allowing greater variation in changes in adiposity, although this approach ignores temporal relationships between changes in adiposity and the first MACE (appendix pp 3–4). A time-varying, covariate-adjusted Cox proportional hazards model was used to estimate the extent to which changes in adiposity measures (bodyweight and waist circumference, using for each the observed value which was carried forward each day until a new value was obtained at a subsequent trial visit or otherwise left unchanged) might be mediators or markers of the effect of semaglutide treatment on MACE reduction throughout the post-random assignment period. This model compares the estimated treatment effect when the time-varying covariate is included with the estimated effect from the unadjusted analysis, where the percentage attenuation between the estimates reflects the extent to which changes in adiposity might mediate changes in the risk of MACE. Serious adverse events were summarised by weight loss and change in waist circumference by the proportion of patients with an event by system organ class. 95% CIs were not adjusted for multiplicity, so should not be used to infer definitive treatment effects. A two-sided significance level of 5% was considered significant. Statistical analyses were performed using SAS version 9.4.

Role of the funding source

The funder, along with the Academic Steering Committee (AML, DHR, HMC, JD, SSE, SEK, RFK, IL, JP, KB-F, GKH, SH-L, and CWT), was responsible for the study design and contributed to data collection, analysis, preparation, and review of the manuscript in collaboration with the authors.

Results

Baseline characteristics by BMI category are shown in table 1.¹³ Higher BMI categories were associated with younger age, female sex, and non-Asian nationality. Across BMI categories from lowest to highest, there was an increase in prediabetes prevalence and blood pressure. Inflammatory burden, assessed by high-sensitivity C-reactive protein (≥2.0 mg/L), showed a marked increase from 36.4% in the 1827 patients in the lowest BMI category to 72.0% in the 1268 patients in the highest BMI category. Previous myocardial infarction was the most common of the cardiovascular inclusion criteria at baseline. The mean duration of exposure was 33.3 months (SD 14.4) for semaglutide and 35.1 months (13.0) for placebo, with permanent premature discontinuation of the study drug occurring in 2351 (26.7%) of 8803 patients and 2078 (23.6%) of 8801 patients allocated to semaglutide and placebo, respectively. Patients were followed up for MACE, adverse events, and other events for an average of 39.8 months (SD 9.4), and 17 061 (96.9%) completed the trial (attended the follow-up visit or died).

Statistical analysis

Cumulative change in bodyweight and waist circumference were calculated from baseline to each visit week, and treatment groups were compared by difference in means. Missing values for each visit week were multiply imputed under missing-at-random models that used data from each treatment group separately (appendix pp 2–3). Risk of MACE was summarised both within and between treatment groups according to baseline adiposity measurements and changes after random assignment by incidence rates per 100 person-years of observation. Cox proportional hazards models used categorisations for descriptive assessment of trends, and linear continuous modelling for statistical inference of trends. Quadratic terms were used to detect non-linearity of effects. The association between changes in adiposity during the first 20 weeks of the trial and subsequent risk of MACE by treatment group was assessed with a landmark approach, where the risk of MACE occurring after 20 weeks was compared between patients by changes in adiposity during the first 20 weeks of the trial. A further analysis considered the risk of MACE throughout the trial period by changes in adiposity up to death or visit week 104, whichever occurred first, thereby gaining precision from the inclusion of MACE

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The primary analysis of SELECT showed no interaction between sex, age, region, race, ethnicity, BMI, cardiovascular disease, history of heart failure, estimated glomerular filtration rate, or HbA_{1c}, and treatment effect of semaglutide.¹ Figure 1 provides incidence rates for MACE within categories of baseline weight and waist circumference for each treatment group, with hazard ratios (HRs). Results based on BMI and the ratio of waist circumference to height demonstrated similar patterns to those for weight and waist circumference. Treatment with semaglutide reduced the incidence of MACE, with no heterogeneity in treatment effect across measures of body habitus at baseline. Within each treatment group, the risk of MACE was lower in patients with lower baseline adiposity measures. For baseline weight, there was a significant linear trend towards 4% lower risk per 5 kg lower baseline weight in the semaglutide group (HR 0.96 [95% CI 0.94–0.99]; $p=0.001$), but not in the placebo group (HR 0.99 [95% CI 0.97–1.01]; $p=0.28$). For baseline waist circumference, significant linear trends towards a 4% lower risk per 5 cm smaller baseline waist circumference were observed in both the semaglutide (HR 0.96 [95% CI 0.93–0.99]; $p=0.004$) and placebo (HR 0.96 [95% CI 0.94–0.99]; $p=0.007$) groups.

Only weight and waist circumference are presented in the subsequent analyses of change in adiposity measures and MACE, as patterns for BMI and waist circumference to height ratio closely follow their corresponding numerators (data not shown).

Effects of semaglutide on bodyweight, waist circumference, and other adiposity outcomes using a missing-at-random by baseline values imputation scheme have been previously reported.^{1,11} Average change in bodyweight and waist circumference over time for each treatment group over 208 weeks are shown in the appendix (p 14). For the missing-at-random last observation carried forward imputation analysis, mean change in bodyweight at 20 weeks was -6.4% and -0.8% in the semaglutide and placebo groups, respectively, for an estimated treatment difference of -5.6% (95% CI -5.7 to -5.4 ; appendix p 7). Mean change in waist circumference at 20 weeks was -5.0 cm and -1.1 cm in the semaglutide and placebo groups, respectively, for an estimated treatment difference of -3.9 cm (95% CI -4.1 to -3.7). There was a significantly greater ($p<0.0001$) correlation between percentage of weight loss and change in waist circumference in the semaglutide group than in the placebo group (correlation coefficients 0.68 vs 0.53 at week 104 and 0.67 vs 0.52 at week 208 for semaglutide vs placebo, respectively;

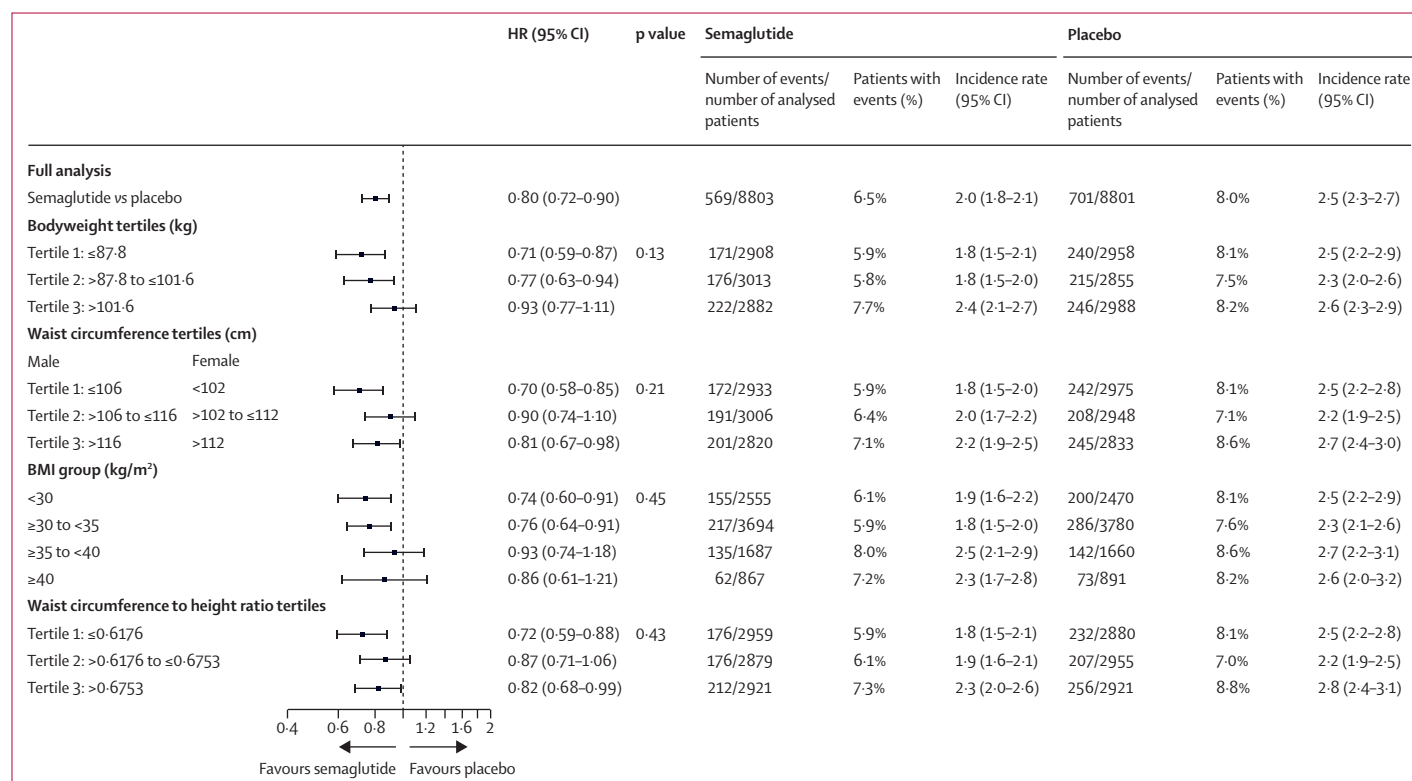


Figure 1: Forest plot of adiposity subgroups at baseline for primary MACE endpoint

Data are from the in-trial period. For the full analysis set analysis, the HR and CI are adjusted for the group sequential design using the likelihood ratio ordering. For the subgroup analyses, estimated HRs and corresponding CIs are calculated in a Cox proportional hazards model with interaction between treatment group and the relevant subgroup as a fixed factor. p value represents the p value for test of no interaction effect. HR=hazard ratio. MACE=major adverse cardiovascular events.

appendix p 5). Sensitivity analyses for semaglutide effect on change in bodyweight and waist circumference conducted using alternative imputation strategies are shown in the appendix (pp 7–8), and the joint distribution of changes in adiposity measures at week 104 are presented (p 9).

At 20 weeks, changes in adiposity in the semaglutide group represent 71% of the weight loss and 68% of the decrease in waist circumference that were observed at 104 weeks (appendix pp 7–8). Of the total 1270 first MACE, 142 (11.2%) had occurred within the first 20 weeks (52 in the semaglutide group and 90 in the placebo group; table 2), and incidence rates between patients receiving semaglutide and placebo had already diverged (HR 0.58 [95% CI 0.41–0.81]). These earliest events are omitted from the analyses of MACE after week 20 but are included in the analyses of in-trial MACE conditioning on week 104 adiposity changes.

In the placebo group, there was no linear trend in subsequent MACE risk by the amount of weight loss at week 20 (HR 0.99 [95% CI 0.88–1.11]; $p=0.84$), but there were non-linear effects (HR 0.98 [95% CI 0.97–1.00]; $p=0.007$) driven by the higher incidence rates of MACE in the patients with 5% or greater weight loss (figure 2A, appendix pp 10–11). In the semaglutide group, there was no linear (HR 0.95 [95% CI 0.86–1.05]; $p=0.31$) or non-linear (HR 1.00 [95% CI 1.00–1.01]; $p=0.54$) trend in subsequent MACE risk of weight loss at

week 20 (figure 2B, appendix pp 10–11). The HR for the interaction of linear effects for semaglutide versus placebo was 0.96 (95% CI 0.83–1.12; $p=0.62$). Among patients who lost weight by week 20, the incidence of MACE was lower in the semaglutide group compared with placebo, but patients receiving semaglutide had similar incidence rates whether they lost 5% or more or less than 5% weight. There was no difference in incidence of MACE in the small number of patients receiving semaglutide who gained weight at week 20 (488 [5.5%] of 8803) compared with the larger number who gained weight while receiving placebo (3433 [39.0%] of 8801; table 2). Analyses between weight loss at week 104 and risk of MACE throughout the study showed similar overall patterns (appendix pp 12–13, 15). Patients receiving placebo with the greatest weight loss at week 104 had the highest incidence of in-trial MACE, whereas the patients receiving semaglutide who lost the most weight at week 104 had the lowest incidence of MACE. In the placebo group there was no linear trend in the risk of MACE on trial by amount of weight lost at week 104, but with semaglutide, there was a linear trend towards lower risk of in-trial MACE by weight lost over this period.

In the semaglutide group there was a linear trend towards decreased subsequent MACE by waist circumference change at week 20 (HR 0.91 [95% CI 0.84–0.98]; $p=0.02$). This was not seen in the

	Semaglutide			Placebo			Semaglutide:placebo
	n	First MACE, n per 100 person-years of follow-up	Incidence rate (95% CI)	n	First MACE, n per 100 person-years of follow-up	Incidence rate (95% CI)	HR (95% CI)
Incidence of MACE after week 20 by categories of percent change in weight at 20 weeks							
All	8803	569/286.5	2.0 (1.8–2.1)	8801	701/283.0	2.5 (2.3–2.7)	0.80 (0.72–0.90)
Before 20 weeks	8803	52/33.6	1.5 (1.1–2.0)	8801	90/33.5	2.7 (2.1–3.2)	0.58 (0.41–0.81)
After 20 weeks	8721	517/253.0	2.0 (1.9–2.2)	8681	611/249.5	2.4 (2.3–2.6)	0.83 (0.74–0.94)
Weight loss at 20 weeks							
Weight loss ≥5%	5346	313/156.2	2.0 (1.8–2.2)	841	73/23.5	3.1 (2.4–3.8)	0.65 (0.50–0.84)
Weight loss ≥0% to <5%	2887	169/83.1	2.0 (1.7–2.3)	4407	292/127.3	2.3 (2.0–2.6)	0.89 (0.73–1.07)
Weight gain	488	35/13.7	2.6 (1.7–3.4)	3433	246/98.6	2.5 (2.2–2.8)	1.02 (0.71–1.44)
Incidence of MACE after week 20 by categories of change in waist circumference at 20 weeks							
All	8803	569/286.5	2.0 (1.8–2.1)	8801	701/283.0	2.5 (2.3–2.7)	0.80 (0.72–0.90)
Before 20 weeks	8803	52/33.6	1.5 (1.1–2.0)	8801	90/33.5	2.7 (2.1–3.2)	0.58 (0.41–0.81)
After 20 weeks	8721	517/253.0	2.0 (1.9–2.2)	8681	611/249.5	2.4 (2.3–2.6)	0.83 (0.74–0.94)
Change in waist circumference at 20 weeks							
≥8 cm decrease	2219	116/64.5	1.8 (1.5–2.1)	556	36/16.2	2.2 (1.5–2.9)	0.81 (0.56–1.20)
≥4 cm to <8 cm decrease	2692	150/78.7	1.9 (1.6–2.2)	1294	94/36.8	2.6 (2.0–3.1)	0.75 (0.58–0.97)
≥0 cm to <4 cm decrease	2941	185/84.9	2.2 (1.9–2.5)	4162	277/119.7	2.3 (2.0–2.6)	0.94 (0.78–1.13)
Waist circumference increase	827	61/23.7	2.6 (1.9–3.2)	2627	199/75.6	2.6 (2.3–3.0)	0.98 (0.73–1.30)
Data from the in-trial period. Missing data for bodyweight and waist circumference were imputed using a missing-at-random assumption with 500 imputations for patients while still in trial, and for patients who died or withdrew from the trial, the last observed/imputed observation was carried forward to the week in question. There were 42 patients in each treatment group with missing waist circumference at baseline who did not have MACE before week 20. In both treatment groups they had five first MACE after week 20. HR=hazard ratio. MACE=major adverse cardiovascular events.							
Table 2: Joint distribution of changes in adiposity measures at week 20 and risk of cardiovascular events after week 20							

placebo group (HR 0.94 [95% CI 0.86–1.02]; $p=0.13$; figure 3, appendix pp 10–11). The HR for the interaction of linear effects for semaglutide versus placebo was 0.97 (95% CI 0.87–1.07; $p=0.52$). The non-linear trends for waist circumference were HR 1.00 (95% CI 1.00–1.01; $p=0.21$) versus 1.00 (1.00–1.00; $p=0.77$). There were numerically lower rates of subsequent MACE in patients

receiving semaglutide compared with placebo for all categories of decrease in waist circumference. At week 104, there were similar findings for the association between waist circumference change and MACE throughout the study (appendix pp 12–13, 17). There was no linear trend in the risk of in-trial MACE in the placebo group by change in waist circumference by week 104, but

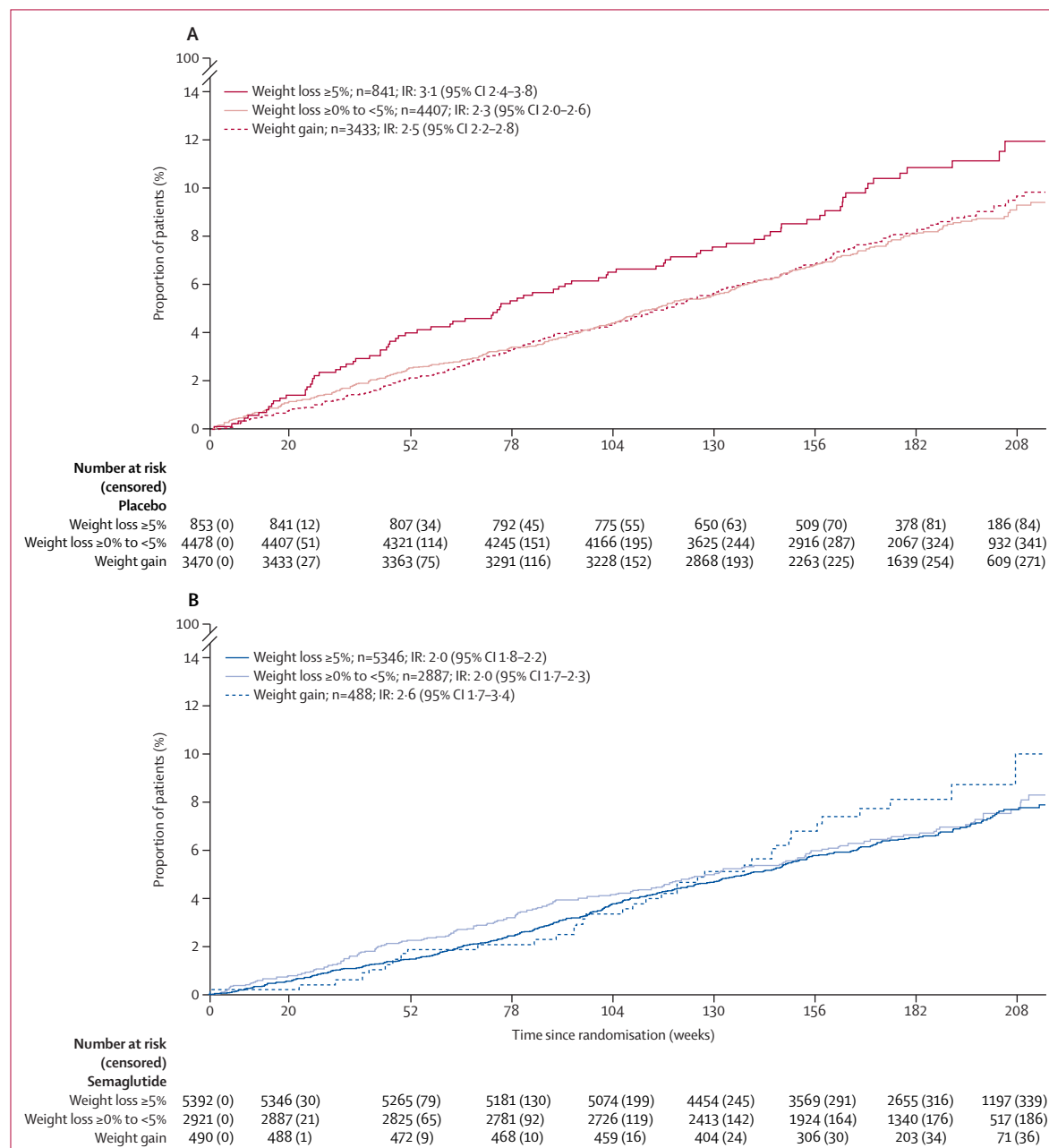


Figure 2: Cumulative incidence plots showing time from randomisation to first MACE by bodyweight loss at week 20 in (A) the placebo group and (B) the semaglutide group

Data from the in-trial period. Cumulative incidence estimates are based on time from randomisation to first MACE, with non-cardiovascular death modelled as competing risk using the Aalen-Johansen estimator. Patients without events of interest were censored at the end of their in-trial observation period. Missing data for bodyweight at week 20 were imputed using a missing-at-random assumption with 500 imputations for patients while still in trial; for patients who died or withdrew from the trial, the last observed or imputed observation was carried forward to week 20. IR=incidence rate. MACE=major adverse cardiovascular events.

there was a linear trend towards lower incidence of MACE with greater decrease in waist circumference at week 104 in the semaglutide group (appendix p 13).

There was no evidence that the semaglutide effect on MACE was mediated by time-varying weight loss, as the unadjusted HR of 0.80 (95% CI 0.72–0.90) for the risk

of MACE with semaglutide versus placebo was not attenuated (HR 0.81 [95% CI 0.71–0.93]; data not shown) after adjustment for weight loss as a time-varying covariate. In contrast, an early change in waist circumference was estimated to mediate or mark 33% of the semaglutide reduction in the later risk of MACE,

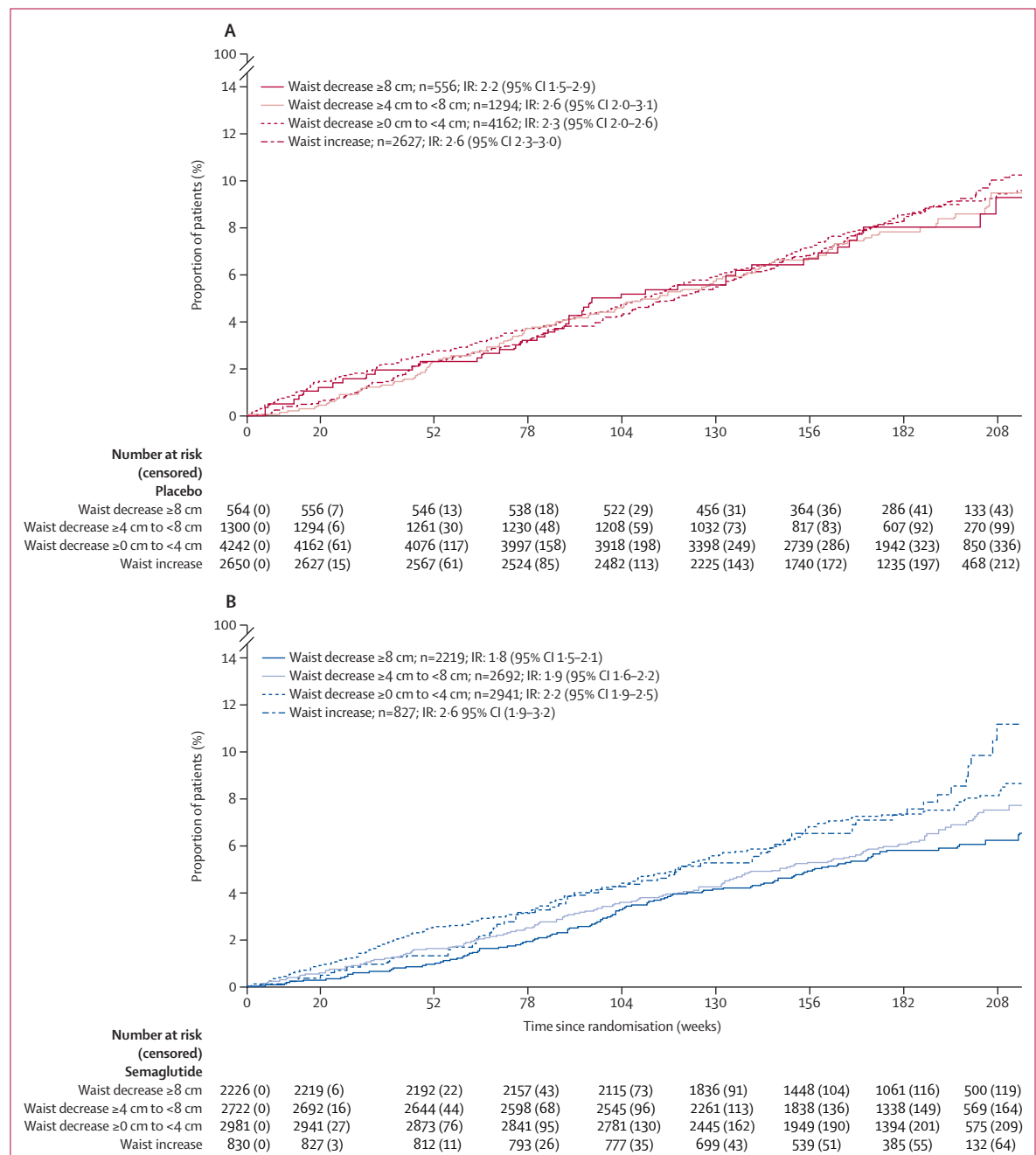


Figure 3: Cumulative incidence plots showing time from randomisation to first MACE by change in waist circumference at week 20 in (A) the placebo group and (B) the semaglutide group

Data from the in-trial period. Cumulative incidence estimates are based on time from randomisation to first MACE with non-cardiovascular death modelled as competing risk using the Aalen-Johansen estimator. Patients without events of interest were censored at the end of their in-trial observation period. Missing data for waist circumference at week 20 were imputed using a missing-at-random assumption with 500 imputations for patients while still in trial; for patients who died or withdrew from the trial, the last observed or imputed observation was carried forward to week 20. IR=incidence rate. MACE=major adverse cardiovascular events.

with attenuation of the HR to 0·86 (95% CI 0·77–0·97; data not shown).

There were no substantial differences in serious adverse events in patients treated with semaglutide according to the strata of change in weight or waist circumference (tables 3 and 4). Patients in the placebo group with a 5% or greater bodyweight loss had higher rates of mortality compared with patients receiving placebo who had weight loss of 0% up to 5% or weight gain. There was a small increase in cardiovascular-related deaths but a larger increase in non-cardiovascular-related deaths and overall mortality

in this placebo cohort with the highest weight loss (table 3).

Discussion

In the SELECT trial, semaglutide was superior to placebo for MACE reduction at all levels of baseline weight or waist circumference from early in the study. We now show that early in-trial weight loss, however, was not related to the cardiovascular benefit after 20 weeks. By contrast, there was a linear relationship between waist circumference (a measure of central adiposity) and treatment effects of semaglutide. However, mediation analyses estimated that

	Semaglutide			Placebo		
	Weight loss ≥5% (n=5392)	Weight loss ≥0% to <5% (n=2921)	Weight gain (n=490)	Weight loss ≥5% (n=853)	Weight loss ≥0% to <5% (n=4478)	Weight gain (n=3470)
Serious adverse events						
Any events	1825 (33·8%)	942 (32·2%)	174 (35·5%)	339 (39·7%)	1580 (35·3%)	1285 (37·0%)
Cardiac disorders	615 (11·4%)	329 (11·3%)	64 (13·1%)	120 (14·1%)	575 (12·8%)	489 (14·1%)
Non-cardiac disorders	1648 (30·6%)	845 (28·9%)	155 (31·6%)	310 (36·3%)	1405 (31·4%)	1157 (33·3%)
Hospitalisations						
Any events	1665 (30·9%)	846 (29·0%)	154 (31·4%)	312 (36·6%)	1447 (32·3%)	1181 (34·0%)
Cardiac disorders	564 (10·5%)	295 (10·1%)	56 (11·4%)	108 (12·7%)	523 (11·7%)	448 (12·9%)
Non-cardiac disorders	1497 (27·8%)	758 (26·0%)	138 (28·2%)	286 (33·5%)	1278 (28·5%)	1049 (30·2%)
Mortality						
EAC-confirmed all-cause death	213 (4·0%)	137 (4·7%)	25 (5·1%)	62 (7·3%)	227 (5·1%)	169 (4·9%)
Cardiovascular death	86 (1·6%)	51 (1·7%)	9 (1·8%)	23 (2·7%)	91 (2·0%)	58 (1·7%)
Non-cardiovascular, non-renal	85 (1·6%)	58 (2·0%)	9 (1·8%)	32 (3·8%)	96 (2·1%)	68 (2·0%)
Undetermined cause	42 (0·8%)	28 (1·0%)	7 (1·4%)	7 (0·8%)	40 (0·9%)	43 (1·2%)

Data are n (%). Adverse events that were not classified as cardiac disorders in the system organ class are classified as non-cardiac disorders. Missing data for bodyweight at week 20 were imputed using a missing-at-random assumption with 500 imputations for patients while still in trial; for patients who died or withdrew from the trial, the last observed or imputed observation was carried forward to week 20. EAC=event adjudication committee.

Table 3: Adverse events reported in patients with weight changes at week 20

	Waist circumference change (semaglutide)				Waist circumference change (placebo)			
	Decrease ≥8 cm (n=2226)	Decrease ≥4 cm to <8 cm (n=2722)	Decrease ≥0 cm to <4 cm (n=2981)	Increase (n=830)	Decrease ≥8 cm (n=564)	Decrease ≥4 cm to <8 cm (n=1300)	Decrease ≥0 cm to <4 cm (n=4242)	Increase (n=2650)
Serious adverse events								
Any events	752 (33·8%)	899 (33·0%)	973 (32·6%)	298 (35·9%)	206 (36·5%)	493 (37·9%)	1499 (35·3%)	987 (37·2%)
Cardiac disorders	232 (10·4%)	320 (11·8%)	348 (11·7%)	103 (12·4%)	65 (11·5%)	174 (13·4%)	550 (13·0%)	386 (14·6%)
Non-cardiac disorders	682 (30·6%)	815 (29·9%)	860 (28·8%)	273 (32·9%)	191 (33·9%)	444 (34·2%)	1333 (31·4%)	886 (33·4%)
Hospitalisations								
Any events	698 (31·4%)	809 (29·7%)	874 (29·3%)	270 (32·5%)	190 (33·7%)	458 (35·2%)	1358 (32·0%)	916 (34·6%)
Cardiac disorders	219 (9·8%)	292 (10·7%)	309 (10·4%)	91 (11·0%)	57 (10·1%)	164 (12·6%)	492 (11·6%)	359 (13·5%)
Non-cardiac disorders	631 (28·3%)	726 (26·7%)	774 (26·0%)	249 (30·0%)	174 (30·9%)	411 (31·6%)	1200 (28·3%)	811 (30·6%)
Mortality								
EAC-confirmed all-cause death	75 (3·4%)	105 (3·9%)	156 (5·2%)	36 (4·3%)	25 (4·4%)	61 (4·7%)	241 (5·7%)	128 (4·8%)
Cardiovascular death	26 (1·2%)	41 (1·5%)	60 (2·0%)	19 (2·3%)	9 (1·6%)	18 (1·4%)	95 (2·2%)	49 (1·8%)
Non-cardiovascular, non-renal	36 (1·6%)	44 (1·6%)	59 (2·0%)	11 (1·3%)	14 (2·5%)	32 (2·5%)	102 (2·4%)	47 (1·8%)
Undetermined cause	13 (0·6%)	20 (0·7%)	37 (1·2%)	6 (0·7%)	2 (0·4%)	11 (0·8%)	44 (1·0%)	32 (1·2%)

Data are n (%). Adverse events that were not classified as cardiac disorders in the system organ class are classified as non-cardiac disorders. Missing data for waist circumference at week 20 were imputed using a missing-at-random assumption with 500 imputations for patients while still in trial; for patients who died or withdrew from the trial, the last observed or imputed observation was carried forward to week 20. EAC=event adjudication committee.

Table 4: Adverse events reported in patients with waist circumference changes at week 20

waist circumference reduction accounted for no more than 33% of the MACE effect. These findings suggest that the cardioprotective effects of semaglutide extend beyond its impact on adiposity, with important implications for clinical practice and understanding of the mechanisms responsible for the benefits from GLP1-RAs.

Obesity represents a complex pathophysiological state with multiple potential mechanisms for harm.^{4,5} Although some adverse effects are related directly to weight burden, such as sleep apnoea or musculoskeletal complications,^{4,14,15} others are likely to be mediated through the effects of obesity on different pathways, including glycaemic control, lipids, blood pressure, and inflammation.^{4,16} The relationship between BMI and adverse cardiovascular outcomes is already present from adolescence, largely due to emergence of coronary risk factors such as diabetes and hypertension.^{17,18} As a result, obesity-related complications may vary in their relationship to weight and adipose tissue size distribution as well as in their response to weight change. In heart failure with preserved ejection fraction, which is causally related to obesity, the magnitude of weight loss has been shown to predict the extent of improvement in patient-reported outcomes and exercise performance with semaglutide treatment.¹⁹ In contrast, we demonstrate that, in individuals with atherosclerotic cardiovascular disease and overweight or obesity, although baseline adiposity was positively associated with MACE risk, semaglutide consistently reduced MACE incidence relative to placebo across the full spectrum of baseline adiposity. Importantly, the observed treatment effect was only modestly attenuated by on-treatment weight reduction.

Cardiovascular outcomes were similar among semaglutide-treated patients who did or did not lose at least 5% of their baseline bodyweight. In the 5·5% of patients in the semaglutide group who gained weight, semaglutide appeared to have less treatment effect on MACE, although the extent to which non-adherence to study drug contributed is unknown. Comparison between the effect of semaglutide and placebo on MACE is complicated by the paradoxical relationship between weight change and cardiovascular outcome which was observed among patients receiving placebo. The few patients in the placebo group who lost at least 5% of their baseline bodyweight had the highest MACE rates, suggesting that substantial weight loss may have been unintentional in some of those patients and driven by comorbid conditions that also influenced the risk of MACE.²⁰ Furthermore, weight loss may result from reductions in both fat and muscle mass, and the degree of each may differ between individuals as well as between drivers of weight loss. Future studies could usefully include formal measures of body composition.

MACE outcomes were more closely associated with changes in waist circumference than with overall bodyweight, suggesting that reduction in central adiposity may contribute to the cardiovascular benefits of semaglutide. This is consistent with substantial evidence

indicating that visceral fat—more accurately reflected by waist circumference than by total bodyweight—exerts greater adverse metabolic and inflammatory effects than peripheral fat. Moreover, the stronger correlation between changes in waist circumference and bodyweight in the semaglutide group compared with the placebo group suggests that weight loss induced by semaglutide preferentially targets visceral adiposity.

Despite the association between the benefit of semaglutide on MACE and the magnitude of waist circumference decrease, this mediated or marked only 33% of the semaglutide treatment effect. Several potential mechanisms might explain the cardiovascular benefits of semaglutide on MACE beyond adiposity reduction. Direct effects on endothelial function and other atherosclerotic pathways have been demonstrated. Furthermore, recent data suggest a role for GLP-1 receptor signalling in the brain, which may modulate systemic inflammation as well as other downstream effects on inflammatory pathways.²¹ The effects on blood pressure control and lipid levels may also be important.²² These pleiotropic effects of GLP-1RAs on multiple organ systems indicate a complex network of beneficial mechanisms that might be independent of adipose tissue reductions reflected by weight or waist circumference change. Furthermore, adipose tissue biology undoubtedly changes before the mass of adipose tissue is measurably reduced, and this may in part mediate the earliest effects of semaglutide on MACE.⁴ The temporal dissociation between weight loss and MACE reduction observed in our study supports the hypothesis that these and other mechanisms may play a key role in vascular protection.

Strengths of our study include its scale and duration, as well as the inclusion of patients with a broad range of BMIs, representing most patients seen in a typical cardiovascular practice.²³ We made comprehensive, repeated adiposity measures with a standardised protocol and methodology and had robust outcome adjudication. However, several limitations merit discussion. Although conducted in 41 countries, the study population was predominantly White and male. This might limit generalisability to other demographic groups in which relationships between adiposity measures and cardiovascular outcomes differ. Although SELECT was a randomised comparison between semaglutide and placebo, analysis of MACE outcomes according to post-randomisation changes in weight or waist circumference within the treatment groups is subject to confounding and therefore cannot prove causation or define mechanisms. In our study, we were interested both in associations between adiposity measures and cardiovascular events and in the degree to which early changes in adiposity while on treatment might be prognostic for later decreases in the risk of MACE. Our analyses based on changes in adiposity by week 20 and subsequent risk of MACE examined temporal relationships, but of necessity made no use of the earliest observed differences in risk of MACE across treatment

groups. The additional analyses of associations between cumulative weight loss at week 104 and the risk of MACE benefit from using all the MACE endpoints and the greater precision in characterising individual cumulative weight changes, but cannot consider temporal relationships between the timing of changes in adiposity and the timing of MACE (appendix pp 15–16).

Our findings have substantial implications for both clinical practice and health-care policy. Most patients who are treated for cardiovascular disease have a BMI of at least 27 kg/m², suggesting that many patients may benefit from semaglutide to reduce adverse cardiovascular outcomes. The early cardiovascular benefits of semaglutide in SELECT were not related to weight change and only modestly related to waist circumference change. This is in keeping with studies of other drug classes and different GLP1-RAs, which have shown cardiovascular outcome benefit in association with little or no weight loss.²⁴ Therefore, for the clinician and patient, it should not be assumed that lack of substantial weight loss on semaglutide would preclude the opportunity for improved cardiovascular outcome. Furthermore, the demonstration of cardiovascular benefits across a broad range of adiposity levels, coupled with the independence from weight loss magnitude, suggests that current prescribing restrictions, which are largely based on BMI thresholds, need to be reconsidered.

In conclusion, our findings from the longest and largest trial of GLP-1RAs in patients with atherosclerotic cardiovascular disease demonstrate that semaglutide resulted in improved cardiovascular outcomes, independent of baseline adiposity and over a wide range of treatment-induced weight loss. This supports the reconceptualisation of GLP-1RAs as potential cardiovascular disease-modifying agents, with implications for clinical practice and health-care policy.

Contributors

JD, AML, SEK, SSE, IL, JP, RFK, HMC, GKH, and DHR designed the study. IL, C-CW, FS, MU-T, and SB were study investigators and enrolled patients. JD, AML, SEK, SSE, SS, PEW, OKJ, and RB collected and assembled the data and performed the data analysis. JD, SSE, and OKJ verified the data. JD, AML, SEK, SSE, IL, BMS, JP, RFK, HMC, GKH, SS, PEW, OKJ, RB, C-CW, IK, FS, JH, MU-T, SB, and DHR prepared the manuscript. AML, Christoffer W Tornøe, DHR, GKH, HMC, IL, JD, JP, Kirstine Brown-Frandsen, RFK, SSE, Søren Hardt-Lingberg, and SEK were members of the Academic Steering Committee. All authors had access to all the data, contributed to data interpretation, reviewed the manuscript and provided revisions, and had final approval of the manuscript. All authors vouch for the accuracy and integrity of the analyses.

Declaration of interests

JD declares having received consulting honoraria from Aegerion, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis, Novo Nordisk, Pfizer, Sanofi, and Takeda; and research grants from Aegerion, Alzheimer's Research UK, British Heart Foundation, Colgate, Medical Research Council (UK), MSD, National Institute for Health and Care Research, Pfizer, Public Health England, and Roche. AML declares having received consulting honoraria from Akebia, Alnylam, Amgen, Ardelyx, Becton Dickinson, Brainstorm Cell, Eli Lilly, Endologix, Fibrogen, GlaxoSmithKline, Intarcia, Medtronic, Neovasc, Novo Nordisk, Provention Bio, and ReCor; and research funding to his institution from

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Structure Therapeutics, Tenvie, Wondr Health, and Zealand Pharma; and stock options from Calibrate, Epitomee, Scientific Intake, and Xeno Bioscience.

Data sharing

Data will be shared with researchers who submit a research proposal approved by the independent review board. Individual participant data will be shared in datasets in a de-identified and anonymised format. Information about data access request proposals can be found online.

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