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Effect of Semaglutide on Regression and Progression of Glycemia in People With Overweight or Obesity but Without Diabetes in the SELECT Trial

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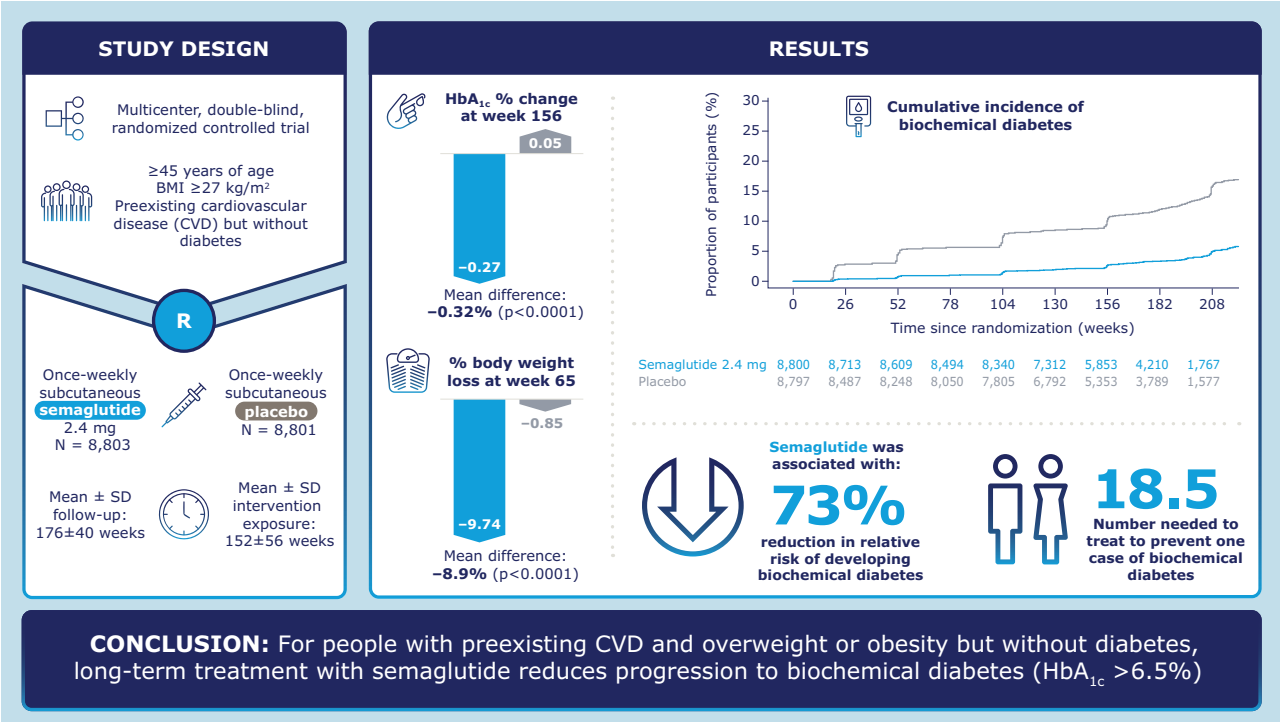

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Semaglutide reduces cardiovascular events in people with overweight or obesity without diabetes at high risk of cardiovascular events. We sought to determine whether improved glycemic control was also demonstrated in the trial participants.
- **What is the specific question(s) we wanted to answer?**
  Does ongoing semaglutide therapy increase regression to biochemical normoglycemia and reduce progression to biochemical diabetes?
- **What did we find?**
  Semaglutide 2.4 mg weekly increased regression to normoglycemia almost fourfold while reducing the risk of progression to diabetes by 73%. For prevention of one case of diabetes over 3 years, 18.5 individuals needed to be treated.
- **What are the implications of our findings?**
  People with established cardiovascular disease and overweight or obesity but without diabetes will experience improved glycemia, including a reduced risk of developing diabetes, while receiving semaglutide.

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OBJECTIVE

To determine whether semaglutide slows progression of glycemia in people with cardiovascular disease and overweight or obesity but without diabetes.

RESEARCH DESIGN AND METHODS

In a multicenter, double-blind trial, participants aged ≥45 years, with BMI ≥27 kg/m^2, and with preexisting cardiovascular disease but without diabetes (HbA_{1c} <6.5%) were randomized to receive subcutaneous semaglutide (2.4 mg weekly) or placebo. Major glycemic outcomes were HbA_{1c} and proportions achieving biochemical normoglycemia (HbA_{1c} <5.7%) and progressing to biochemical diabetes (HbA_{1c} ≧6.5%).

RESULTS

Of 17,604 participants, 8,803 were assigned to semaglutide and 8,801 to placebo. Mean ± SD intervention exposure was 152 ± 56 weeks and follow-up 176 ± 40 weeks. In both treatment arms mean nadir HbA_{1c} for participants was at 20 weeks. Thereafter, HbA_{1c} increased similarly in both arms, with a mean difference of −0.32 percentage points (95% CI −0.33 to −0.30; −3.49 mmol/mol [−3.66 to −3.32]) and with the difference favoring semaglutide throughout the study ($P < 0.0001$). Body weight plateaued at 65 weeks and was 8.9% lower with semaglutide. At week 156, a greater proportion treated with semaglutide were normoglycemic (69.5% vs. 35.8%; $P < 0.0001$) and a smaller proportion had biochemical diabetes by week 156 (1.5% vs. 6.9%; $P < 0.0001$). The number needed to treat was 18.5 to prevent a case of diabetes. Both regression and progression were dependent on glycemia at baseline, with the magnitude of weight reduction important in mediating 24.5% of progression and 27.1% of regression.

CONCLUSIONS

In people with preexisting cardiovascular disease and overweight or obesity but without diabetes, long-term semaglutide increases regression to biochemical normoglycemia and reduces progression to biochemical diabetes but does not slow glycemic progression over time.

The prevalence of type 2 diabetes continues to increase worldwide and is typically preceded by prediabetes, a high-risk condition often diagnosed based on glycated hemoglobin (HbA_{1c}) (1–3). The pathogenesis of dysglycemia involves the combination of insulin resistance, frequently in the setting of obesity, and an inability of the β-cell

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to release adequate amounts of insulin in the face of this change in insulin sensitivity, reflecting β-cell dysfunction (4). It is the progression of the β-cell impairment that in most instances drives the evolution of diabetes from prediabetes and deterioration of glycemic control in diabetes, an observation that has been made in different racial and ethnic groups (5,6).

Reducing the risk of developing diabetes has been studied using approaches that included lifestyle and medications (7–17). The glucose-lowering agents studied have been available for decades and have different mechanisms of action: insulin sensitizers such as thiazolidinediones and metformin, insulin secretagogues including nateglinide, and endogenous insulin replacement with the basal insulin glargine. The weight loss medication orlistat and angiotensin receptor blocker valsartan have also been evaluated. The outcome of these "prevention studies," which typically lasted a few years and were performed in large cohorts in different populations, has ranged in reductions of progression from 72% with thiazolidinediones (7–9) to 58% with intensive lifestyle intervention (10–12), 37% with orlistat (13), 31% with metformin (10,14), 20% with insulin glargine (15), and 14% with valsartan (16). Nateglinide was associated with a slightly increased risk of progression to diabetes (17).

Weight loss typically improves insulin sensitivity and represents an attractive approach to reduce β-cell workload (4). Such an effect could be beneficial if maintained long-term. Furthermore, with weight loss in combination with an approach to enhance insulin release, it should be possible to slow the progression of dysglycemia. Such a benefit has been suggested for glucagon-like peptide 1 receptor agonists (GLP-1RA) in an extension study of individuals with prediabetes who had been treated with liraglutide for weight reduction (18) and in a pooled analysis of three weight reduction studies with semaglutide (19). It has also been implied from a nonrandomized study of bariatric surgery (20).

The Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity (SELECT) trial evaluated whether it was possible to decrease cardiovascular (CV) events in individuals with overweight or obesity but without diabetes at enrollment (21). In this high-risk cohort, which included people at increased risk of developing diabetes, the primary outcome of three-point major adverse CV events (MACE) was reduced by 20% (22).

In this prespecified secondary analysis of SELECT, we expanded on the previously reported secondary end points of glycemic status at 52 and 104 weeks (22) by evaluating glycemia through 156 weeks to ask the following questions. First, are the patterns of glycemia in those treated with semaglutide 2.4 mg weekly similar to those in participants receiving placebo? Second, is it possible for semaglutide to improve glucose metabolism sufficiently to normalize glycemia in people with prediabetes, and if so, is this related to glycemia at baseline as well as the change in weight during the study? And finally, does semaglutide treatment reduce the progression of prediabetes to diabetes, and how does this relate to glycemia and body size at baseline as well as the magnitude of weight change?

RESEARCH DESIGN AND METHODS

Study Design

SELECT was a multicenter, randomized, double-blind, event-driven superiority trial that examined the effect of weekly 2.4 mg semaglutide compared with placebo for the prevention of major adverse CV events in individuals with overweight or obesity who had established CV disease (CVD). The rationale, study design, participant baseline characteristics, and primary outcome results have previously been published (21–23). The protocol was approved by national and institutional regulatory and ethics authorities. The study was registered at ClinicalTrials.gov, clinical trial reg. no. NCT03574597. All participants provided written informed consent, consistent with the Declaration of Helsinki.

Participants

A total of 17,604 participants enrolled; 8,803 were assigned to receive semaglutide and 8,801 placebo. Details on the inclusion and exclusion criteria have previously been published (21). Briefly, participants had to be age ≥45 years and have overweight or obesity and established CVD. Women with a history of gestational diabetes mellitus were eligible. Potential participants were excluded if they had previously been diagnosed with diabetes; if HbA_{1c} level was ≥6.5% (≥48 mmol/mol), measured at screening; and in the case of treatment in the previous 90 days with any glucose-lowering medication, New York Heart Association class IV heart failure, or end-stage renal disease or dialysis.

Study Interventions and Participant Management

Participants were randomly assigned 1:1 to receive once-weekly semaglutide 2.4 mg or placebo subcutaneously. The dose of semaglutide was titrated sequentially every 4 weeks until the target dose was achieved at 16 weeks. Participants who did not tolerate dose escalation could be managed through extending dose

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*A list of the SELECT Trial Investigators can be found in the supplementary material of Lincoff et al. N Engl J Med 2023;389:2221–2232. DOI: 10.1056/NEJMoa2307563.

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See accompanying articles, pp. 1322 and 1360.

escalation intervals, treatment pauses, or maintaining the dose at <2.4 mg weekly. The assigned treatment was to be continued throughout the trial unless a participant became or planned to become pregnant, developed pancreatitis, or had a calcitonin level ≥100 ng/L.

Investigators were instructed to follow evidence-based guidelines to optimize the management of underlying CVD. There was no lifestyle intervention targeting weight reduction. Participants 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 forbidden.

Procedures, Calculations, and Assays

Body weight and height were measured with light clothing and without shoes. Waist circumference was measured with the participant in a standing position (23).

BMI was calculated as weight in kilograms divided by the square of height in meters. To assess the possible impact of differential weight change on glycemic outcomes, we categorized individuals into five subgroups based on weight change from baseline to week 65: weight gain or loss <2% and losses of 2% to <5%, 5% to <10%, 10% to <15%, and ≥15%.

Blood samples for HbA_{1c} measurement were drawn at baseline, at weeks 20 and 52, and annually thereafter. HbA_{1c} was determined in a central laboratory using a Premier Hb9210 analyzer (Trinity Biotech, Bray, Ireland). This measure was calibrated against hemolysate.

Outcomes

Based on American Diabetes Association HbA_{1c} criteria, three glycemic control categories were defined biochemically: normoglycemia, <5.7% (<39 mmol/mol); prediabetes, 5.7% to <6.5% (39 to <48 mmol/mol); and diabetes, ≥6.5% (≥48 mmol/mol) (2). Data were also examined using the International Expert Committee's categorization of a "very high-risk subdiabetic group," defined according to HbA_{1c} 6.0% to <6.5% (42 to <48 mmol/mol) (3).

Subsequent discussion of these glycemic categories refers to a single laboratory-based end point and not a clinical diagnosis. As a surrogate for the development of diabetes, we used the time to the first measurement of HbA_{1c} ≥6.5%.

Data Management and Statistical Analyses

Descriptive figures for HbA_{1c} and weight are provided for the available data. Measurements for time-to-event variables were censored from the time of their last data collection. Reasons for missing measurements at specific times might have been prior withdrawal of consent (0.8% vs. 1.1% for semaglutide and placebo arms by the end of the study, respectively), loss to follow-up (2.2% vs. 2.1% by the end of the study), or death (Kaplan-Meier estimates of mortality of 0.8% vs. 1.2% at 52 weeks, 2.3% vs. 2.6% at 104 weeks, and 3.8% vs. 4.3% at 156 weeks) (22). Further, 4,814 (27.3%) participants had follow-up for <3 years due to administrative censoring at the time of study closure.

Statistical analyses were based on the intention-to-treat principle and included all randomized participants irrespective of adherence to semaglutide or placebo or changes to background medications. Continuous end points were analyzed using an ANCOVA model with treatment as a fixed factor and the baseline value of the end point as a covariate. Missing data at a given time point was imputed using multiple imputation (24) by treatment arm under a missing-at-random assumption based on a linear regression model with baseline value as a covariate fitted to participants with an observation at the given time point. Estimated means are provided with SEs, and estimated treatment differences are provided with 95% CIs. Binary end points were analyzed using logistic regression with treatment and baseline value as a covariate, where missing data were again imputed using multiple imputation. Time-to-event end points were analyzed with a Cox proportional hazards model with treatment as a fixed factor, and subgroup analyses also included the subgroup and interaction with treatment. CIs were not adjusted for multiplicity and should therefore not be used to infer definitive treatment effects. Mediation analysis was performed using the method of Vansteelandt et al. (25) to explore as outcomes the time to the first HbA_{1c} measurement <5.7% or ≥6.5% with body weight as mediator, including visits at 0, 12, 20, 39, 52, 78, 104, 130, and 156 weeks.

Data Availability

Data will be shared with bona fide researchers who submit a research proposal approved by the independent review board. Individual participant data will be shared in data sets in a de-identified and anonymized format. Information about data access request proposals can be found at novonordisk-trials.com.

RESULTS

Baseline Characteristics of the Cohort

Table 1 lists characteristics of the whole cohort at baseline, when participants were subdivided on glycemic control (HbA_{1c} <5.7%, 5.7% to <6.5%, 5.7% to <6.0%, and 6.0% to <6.5%). The majority of participants were between 55 and 75 years of age, with a predominance of males and White race. The average BMI was consistent with obesity, and participants were on average normotensive with a normal estimated glomerular filtration rate and relatively normal lipid profiles. Characteristics of those receiving semaglutide or placebo within the whole cohort or any glycemic category are presented in Supplementary Tables 1–5.

Change in Glycemia and Body Weight Over Time

Mean ± SD duration of follow-up was 176 ± 40 weeks, ranging from 0 to 240 weeks, with mean exposure to study medication being 152 ± 56 weeks. Figure 1*A* illustrates the change in mean glycemia over time over 208 weeks. The nadir in mean HbA_{1c} was reached at 20 weeks in both treatment groups, at which time semaglutide had reduced mean HbA_{1c} to 5.45 ± 0.00% vs. 5.77 ± 0.00% with placebo, resulting in a mean difference of −0.31 percentage points (%-points) (95% CI −0.32, −0.30; $P <$ 0.0001). Thereafter, a slight, gradual, parallel increase in HbA_{1c} over time was seen in both treatment groups. After 156 weeks, mean HbA_{1c} was reduced to 5.51 ± 0.01% with semaglutide vs. 5.83 ± 0.01% with placebo, resulting in a mean difference of −0.32 %-points (−0.33, −0.30; $P <$ 0.0001). Compared with the week 20 measurements,

Table 1—Baseline characteristics of the SELECT cohort by glycemic status

	All, *n* = 17,604	HbA_{1c} <5.7% (<39 mmol/mol), *n* = 5,905	HbA_{1c} 5.7% to <6.5% (39 to <48 mmol/mol), *n* = 11,696	HbA_{1c} 5.7% to <6.0% (39 to <42 mmol/mol), *n* = 6,086	HbA_{1c} 6.0% to <6.5% (42 to <48 mmol/mol), *n* = 5,610
Age (years)	61.6 ± 8.9	61.0 ± 9.1	61.9 ± 8.7	61.7 ± 8.8	62.1 ± 8.6
Age distribution (years)					
<55	4,151 (23.6)	1,599 (27.1)	2,551 (21.8)	1,401 (23.0)	1,150 (20.5)
55 to <65	6,725 (38.2)	2,149 (36.4)	4,574 (39.1)	2,363 (38.8)	2,211 (39.4)
65 to <75	5,362 (30.5)	1,707 (28.9)	3,655 (31.3)	1,848 (30.4)	1,807 (32.2)
75 to <85	1,318 (7.5)	436 (7.4)	882 (7.5)	458 (7.5)	424 (7.6)
≥85	48 (0.3)	14 (0.2)	34 (0.3)	16 (0.3)	18 (0.3)
Male sex	12,732 (72.3)	4,275 (72.4)	8,455 (72.3)	4,408 (72.4)	4,047 (72.1)
Race					
White	14,791 (84.0)	5,034 (85.2)	9,755 (83.4)	5,120 (84.1)	4,635 (82.6)
Black	671 (3.8)	228 (3.9)	442 (3.8)	214 (3.5)	228 (4.1)
Asian	1,447 (8.2)	446 (7.6)	1,001 (8.6)	501 (8.2)	500 (8.9)
Other	526 (3.0)	160 (2.7)	366 (3.1)	190 (3.1)	176 (3.1)
Not reported	169 (1.0)	37 (0.6)	132 (1.1)	61 (1.0)	71 (1.3)
Ethnicity					
Hispanic or Latino	1,822 (10.3)	755 (12.8)	1,067 (9.1)	594 (9.8)	473 (8.4)
Not Hispanic or Latino	15,611 (88.7)	5,112 (86.6)	10,496 (89.7)	5,430 (89.2)	5,066 (90.3)
Not reported	171 (1.0)	38 (0.6)	133 (1.1)	62 (1.0)	71 (1.3)
Region					
Asia	2,201 (12.5)	722 (12.2)	1,479 (12.6)	757 (12.4)	722 (12.9)
Europe	6,692 (38.0)	1,889 (32.0)	4,802 (41.1)	2,437 (40.0)	2,365 (42.2)
North America	4,401 (25.0)	1,717 (29.1)	2,683 (22.9)	1,423 (23.4)	1,260 (22.5)
Other	4,310 (24.5)	1,577 (26.7)	2,732 (23.4)	1,469 (24.1)	1,263 (22.5)
Weight (kg)	96.68 ± 17.66	95.56 ± 17.10	97.23 ± 17.91	96.30 ± 17.32	98.25 ± 18.47
BMI (kg/m^2)	33.34 ± 5.04	32.84 ± 4.82	33.59 ± 5.13	33.23 ± 4.94	33.97 ± 5.29
BMI (kg/m^2)					
<30	5,024 (28.5)	1,895 (32.1)	3,129 (26.8)	1,747 (28.7)	1,382 (24.6)
30 to <35	7,474 (42.5)	2,522 (42.7)	4,951 (42.3)	2,637 (43.3)	2,314 (41.2)
35 to <40	3,346 (19.0)	1,002 (17.0)	2,342 (20.0)	1,117 (18.4)	1,225 (21.8)
40 to <45	1,174 (6.7)	330 (5.6)	844 (7.2)	403 (6.6)	441 (7.9)
≥45	586 (3.3)	156 (2.6)	430 (3.7)	182 (3.0)	248 (4.4)
Waist circumference (cm)	111.3 ± 13.1	109.9 ± 12.7	112.0 ± 13.2	111.2 ± 13.1	113.0 ± 13.3
Systolic BP (mmHg)	131.0 ± 15.4	130.4 ± 15.4	131.3 ± 15.4	131.0 ± 15.5	131.6 ± 15.4
Diastolic BP (mmHg)	79.3 ± 10.0	79.3 ± 10.0	79.3 ± 10.0	79.4 ± 10.0	79.2 ± 9.9
HbA_{1c}					
%	5.78 ± 0.34	5.42 ± 0.20	5.97 ± 0.22	5.80 ± 0.08	6.15 ± 0.18
mmol/mol	39.7 ± 3.68	35.7 ± 2.13	41.7 ± 2.44	39.9 ± 0.88	43.7 ± 1.95
eGFR ($mL/min/1.73\ m^2$)	82.5 ± 17.4	83.2 ± 17.6	82.1 ± 17.3	82.1 ± 17.5	82.2 ± 17.1
Lipids (mg/dL)					
Total cholesterol	160.9 ± 42.8	162.3 ± 43.7	160.1 ± 42.3	160.6 ± 42.3	159.6 ± 42.3
LDL cholesterol	85.4 ± 36.0	86.4 ± 36.6	84.9 ± 35.7	85.5 ± 36.1	84.2 ± 35.3
HDL cholesterol	45.6 ± 11.8	47.3 ± 12.9	44.7 ± 11.1	45.5 ± 11.5	43.7 ± 10.5
Triglycerides	157.6 ± 92.8	150.9 ± 93.0	161.0 ± 92.6	156.1 ± 87.5	166.3 ± 97.4

Data are mean ± SD or *n* (%). BP, blood pressure; eGFR, estimated glomerular filtration rate.

statistically significant increases in mean HbA_{1c} by week 156 were 0.07 %-points and 0.06 %-points in the semaglutide and placebo arms, respectively ($P < 0.0001$ in each arm), with no statistically significant differences between arms in the magnitude of the increase ($P = 0.09$).

When treatment arms were subdivided by baseline HbA_{1c}, the greatest absolute HbA_{1c} decline was observed in those with the highest HbA_{1c}. In each glycemic category, the nadir in mean HbA_{1c} again occurred at 20 weeks with the estimated difference over time between semaglutide and placebo being

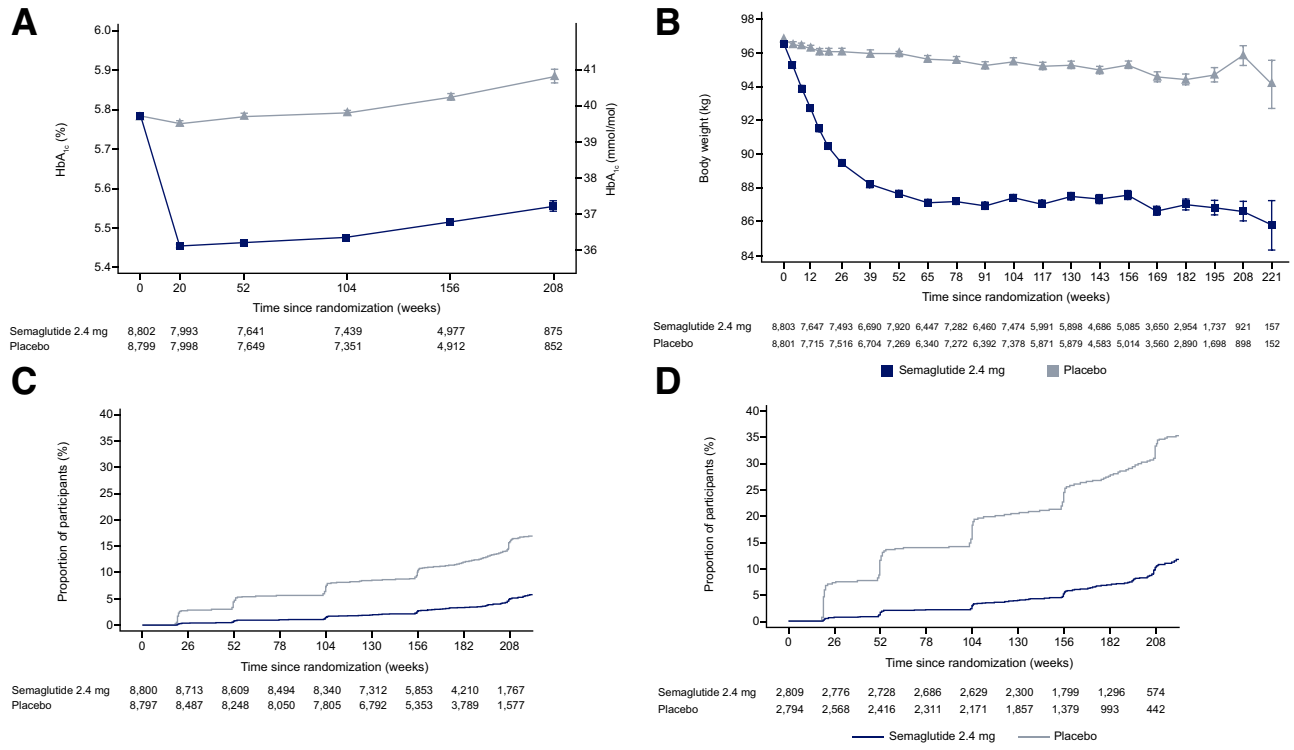

Figure 1—Changes over time in glycemia and body weight, and time-to-event analysis for progression to diabetes in all participants. The change over time in HbA_{1c} is illustrated in *A* and that in body weight in *B*. The cumulative incidence of diabetes, defined according to HbA_{1c} ≥6.5% (≥48 mmol/mol), in all participants is illustrated in *C* and for those with HbA_{1c} 6.0% to <6.5% (42 to <48 mmol/mol) at baseline in *D*. The number of participants sampled at each time point is provided. Error bars represent the SEM.

−0.22 %-points (95% CI −0.24, −0.20) in those with baseline HbA_{1c} <5.7% ($P < 0.0001$) (Supplementary Fig. 1*A*), −0.31 %-points (−0.34, −0.29) with baseline HbA_{1c} 5.7% to <6.0% ($P < 0.0001$) (Supplementary Fig. 1*B*), and −0.44 %-points (−0.47, −0.40) with baseline HbA_{1c} 6.0% to <6.5% ($P < 0.0001$) (Supplementary Fig. 1*C*), all at week 156. As in the entire cohort, in each glycemic category there was evidence of a progressive decline in glycemic control over time.

Body weight change over time in individuals in the two intervention groups is shown in Fig. 1*B*. Mean weight declined by 9.74 ± 0.09% with semaglutide, reaching a plateau of 87.2 ± 0.08 kg after 65 weeks and remaining stable thereafter. At the same time point, mean weight decreased by 0.85 ± 0.08% to 95.8 ± 0.08 kg with placebo and remained lower throughout the study. The difference in body weight averaged −8.89 %-points (95% CI −9.12, −8.66; $P < 0.0001$) between treatment groups at week 65 and remained stable throughout the study.

At week 65, 90.1% of participants receiving semaglutide experienced weight reduction vs. 55.0% with placebo (odds ratio 7.50; 95% CI 6.82, 8.25; $P < 0.0001$). Among semaglutide participants, 15.5% either gained weight or lost <2% of their body weight, 13.1% lost 2% to <5%, 25.5% lost 5% to <10%, 22.8% lost 10% to <15%, and 23.1% lost ≥15%. In the placebo group, the proportion of participants in each of these weight change categories was 63.1%, 19.3%, 12.6%, 3.7%, and 1.3%, respectively (Supplementary Fig. 2).

Effect of the Interventions to Attain Normoglycemia

At baseline, 33.5% of participants had HbA_{1c} <5.7%. Figure 2*A* illustrates, for 20 weeks and each annual time point in the first 3 years, the proportions of participants whose HbA_{1c} measurements corresponded to normoglycemia at that visit. Importantly, each individual was classified based on their HbA_{1c} at that time point and did not necessarily have normoglycemia at each time point. At each time point, the proportions were greater with semaglutide (20 weeks, 76.1% vs. 38.0%; 52 weeks, 74.3% vs. 37.2%; 104 weeks, 73.9% vs. 38.4%; and 156 weeks, 69.5% vs. 35.8% [$P <$ 0.0001 for each time point]). These differences were present despite some participants permanently discontinuing their assigned treatment prematurely (52 weeks, 12.0% vs. 8.2% for the semaglutide and placebo groups, respectively [22]; 104 weeks, 18.0% vs. 14.1%; and 156 weeks, 24.3% vs. 21.0%).

At baseline, 66.4% of participants had prediabetes (HbA_{1c} ≥5.7%). At 156 weeks, the proportion who were normoglycemic was highest among those with baseline HbA_{1c} 5.7% to <6.0%, being 71.4% for semaglutide vs. 28.1% for placebo (Fig. 2*B*); the proportion was lowest among those who were the most dysglycemic (HbA_{1c} 6.0% to <6.5%): 47.3% vs. 9.3%, respectively (Fig. 2*C*). There was heterogeneity in response to semaglutide based on baseline glycemia as well as race, ethnicity, and region but not age, sex, baseline body weight, or baseline BMI (Supplementary Table 6).

Effect of the Interventions on Diabetes Development

Figure 1*C* illustrates the cumulative incidence of diabetes in all participants based on at least one diagnostic HbA_{1c} of

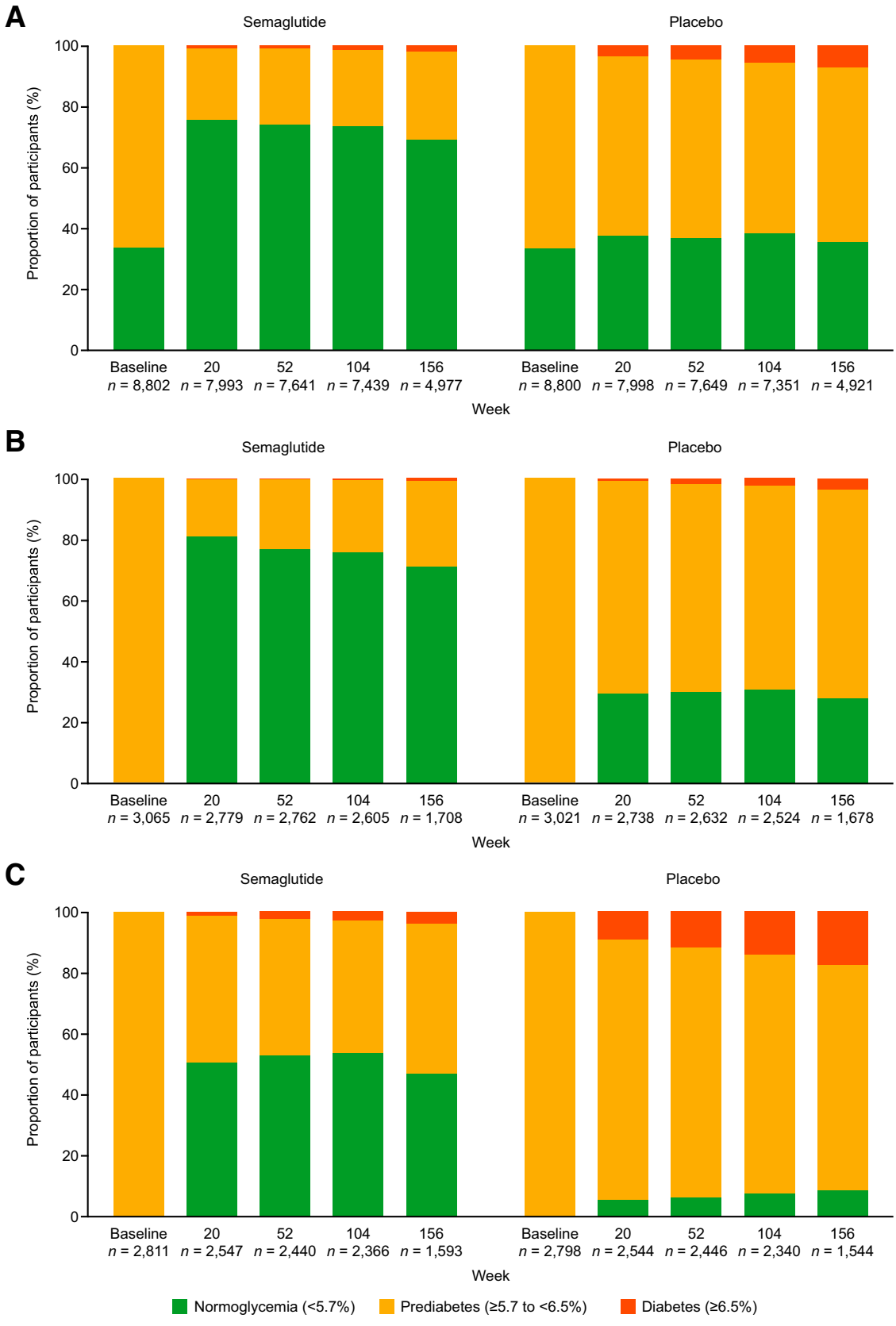

Figure 2—Bar graphs of glucose tolerance status at baseline, and 20, 52, 104, and 156 weeks, using observed data from the in-trial period. *A*: All participants. *B*: Subgroup with baseline HbA_{1c} 5.7% to <6.0% (39 to <42 mmol/mol). *C*: Subgroup with baseline HbA_{1c} 6.0% to <6.5% (42 to <48 mmol/mol). Normoglycemia was defined according to HbA_{1c} <5.7% (<39 mmol/mol) and diabetes according to HbA_{1c} ≥6.5% (≥48 mmol/mol). The number of participants sampled at each time point is provided. Participants who had died or who withdrew consent are excluded from the time of that occurrence. There were seven participants with HbA_{1c} 6.0% to <6.5% (42 to <48 mmol/mol) who were randomized in error.

≥6.5% during follow-up. In this instance, once an individual reached this outcome they could not subsequently be reclassified. The estimated proportions were significantly lower with semaglutide versus placebo (20 weeks, 0.5% vs. 3.2%, respectively; 52 weeks, 0.8% vs. 4.5%; 104 weeks, 1.3% vs. 5.5%; and 156 weeks, 1.5% vs. 6.9% [$P < 0.0001$ for each time point]). These differences represented a hazard ratio of 0.27 (95% CI 0.24, 0.31; $P < 0.0001$) for semaglutide versus placebo in the time from randomization to first HbA_{1c} ≥6.5% and yielded a number needed to treat for 156 weeks of 18.5 to prevent one case of diabetes. Figure 1*D* illustrates the cumulative incidence of diabetes in participants with baseline HbA_{1c} 6.0% to <6.5%. Again, semaglutide reduced the risk of progression to diabetes, with the difference representing a hazard ratio of 0.23 (0.19, 0.26; $P < 0.0001$) in this subgroup. There was heterogeneity in the response to semaglutide based on baseline glycemia but not age, sex, race, ethnicity, region, baseline body weight, or baseline BMI (Supplementary Fig. 3).

Within glycemic categories, in which a participant was classified based on HbA_{1c} at a particular time point, for whom it could differ at other time points, the proportions with HbA_{1c} ≥6.5% were lowest among those who were normoglycemic at baseline, intermediate among those with baseline HbA_{1c} 5.7% to <6.0% (Fig. 2*B*), and highest among those who were the most dysglycemic (HbA_{1c} 6.0% to <6.5%) (Fig. 2*C*). At 156 weeks, among those with normal baseline HbA_{1c}, diabetes had developed in 9 of 1,676 (0.5%) participants receiving semaglutide and in 18 of 1,690 (1.1%) participants receiving placebo, whereas in the intermediate-glycemia subgroup (HbA_{1c} 5.7% to <6.0%) the proportion was 0.8% with semaglutide and 3.5% with placebo. In the most dysglycemic subgroup at baseline (HbA_{1c} 6.0% to <6.5%), diabetes had developed in 3.5% of participants receiving semaglutide vs. 17.0% receiving placebo.

Impact of Baseline Phenotypic Characteristics and Weight Loss on Glycemia Regression and Progression

Table 2 lists the proportions of participants who achieved HbA_{1c} <5.7% in the treatment groups based on magnitudes of weight change. These proportions are provided for participants with

Table 2—Participants with regression to normoglycemia and progression to diabetes at 156 weeks by the degree of weight loss and baseline glycemia

	Regression to normoglycemia			Progression to diabetes		
	Baseline HbA_{1c} 5.7% to <6.5% (39 to <48 mmol/mol), *n* = 11,696	Baseline HbA_{1c} 5.7% to <6.0% (39 to <42 mmol/mol), *n* = 6,086	Baseline HbA_{1c} 6.0% to <6.5% (42 to <48 mmol/mol), *n* = 5,610	Baseline HbA_{1c} <6.5% (<48 mmol/mol), *n* = 17,594*	Baseline HbA_{1c} 5.7% to <6.0% (39 to <42 mmol/mol), *n* = 6,086	Baseline HbA_{1c} 6.0% to <6.5% (42 to <48 mmol/mol), *n* = 5,610
Semaglutide						
All	4,717/5,877 (80.3)	2,725/3,065 (88.9)	1,992/2,812 (70.8)	306/8,799 (3.5)	49/3,065 (1.6)	207/2,809 (7.4)
Weight gain or loss <2%	583/949 (61.4)	384/489 (78.5)	199/460 (43.3)	130/1,402 (9.3)	22/489 (4.5)	93/459 (20.3)
Weight loss 2% to <5%	587/804 (73.0)	341/413 (82.6)	246/391 (62.9)	62/1,173 (5.3)	13/413 (3.1)	42/391 (10.7)
Weight loss 5% to <10%	1,226/1,589 (77.2)	727/847 (85.8)	499/742 (67.3)	72/2,423 (3.0)	11/847 (1.3)	44/742 (5.9)
Weight loss ≥10%†					3/1,316 (0.2)	
Weight loss 10% to <15%	1,169/1,341 (87.2)	658/694 (94.8)	511/647 (79.0)	30/2,002 (1.5)		21/646 (3.3)
Weight loss ≥15%	1,152/1,194 (96.5)	615/622 (98.9)	537/572 (93.9)	12/1,799 (0.7)		7/571 (1.2)
Placebo						
All	2,160/5,819 (37.1)	1,629/3,021 (53.9)	531/2,798 (19.0)	1,059/8,795 (12.0)	196/3,021 (6.5)	778/2,794 (27.8)
Weight gain or loss <2%	1,239/3,790 (32.7)	977/2,007 (48.7)	262/1,783 (14.7)	757/5,687 (13.3)	157/2,007 (7.8)	554/1,780 (31.1)
Weight loss 2% to <5%	431/1,091 (39.5)	307/532 (57.7)	124/559 (22.2)	186/1,659 (11.2)	22/532 (4.1)	145/558 (26.0)
Weight loss 5% to <10%	353/697 (50.6)	258/367 (70.3)	95/330 (28.8)	90/1,060 (8.5)	13/367 (3.5)	62/330 (18.8)
Weight loss ≥10%†					4/115 (3.5)	
Weight loss 10% to <15%	101/174 (58.0)	67/89 (75.3)	34/85 (40.0)	20/286 (7.0)		11/85 (12.9)
Weight loss ≥15%	36/67 (53.7)	20/26 (76.9)	16/41 (39.0)	6/103 (5.8)		6/41 (14.6)

Data are from the in-trial period and are presented as the number of events/the number of participants contributing to the analysis (percentage of participants meeting the response criteria). Regression was defined as the time from randomization to first HbA_{1c} <5.7% (<39 mmol/mol) in participants with HbA_{1c} ≥5.7% (≥39 mmol/mol) at baseline. Progression was defined as the time from randomization to first HbA_{1c} ≥6.5% (≥48 mmol/mol) in participants with HbA_{1c} <6.5% (<48 mmol/mol) at baseline. *Seven participants were randomized with HbA_{1c} ≥6.5%; six were assessed as having prediabetes and one was considered normoglycemic by the investigator. In addition, three participants were assessed as having prediabetes by the investigator, but without an HbA_{1c} value at baseline. †For the baseline HbA_{1c} 5.7% to <6.0% subcategory, the weight loss 10% to <15% and ≥15% subgroups have been combined due to the small number of events.

baseline HbA_{1c} ≥5.7%, stratified into two subgroups based on baseline glycemic category. In the whole cohort and two subgroups, the proportion of participants who became normoglycemic increased with increasing weight loss. In each category of weight loss, the proportion who achieved normoglycemia was greater among those receiving semaglutide. With use of the method of Vansteelandt et al. (25), 27.1% of the effect to induce regression to normoglycemia in all participants with HbA_{1c} ≥5.7% at baseline was mediated through weight change (Supplementary Table 7).

Table 2 also lists the proportions of participants who developed diabetes (HbA_{1c} ≥6.5%) in the treatment groups based on magnitudes of weight change and by baseline glycemia. In the whole cohort and the two prediabetes subgroups, the proportion of participants who developed diabetes decreased with increasing weight loss. Within each category of weight loss, diabetes developed in a smaller proportion of participants receiving semaglutide. In the mediation analysis, 34.5% of the effect to prevent progression to diabetes in all participants was mediated through weight change (Supplementary Table 7).

CONCLUSIONS

In this prespecified analysis of the SELECT trial, we demonstrated that with use of semaglutide there was increased regression to normoglycemia and reduced progression to diabetes in people with overweight or obesity and preexisting CVD. The analyses presented here represent data that extend to 156 weeks of the interventions. Despite the administrative censoring leading to decreased sample sizes at 156 weeks, we see the persistence of the statistically significant trends observed at 52 and 104 weeks for both regression and progression of glycemia (22). Our observation is the first to examine these outcomes in a long-term study using a GLP-1RA and is likely due to the two well-recognized effects of this medication class, namely, weight loss that would be expected to improve insulin sensitivity and the effect of the medication to improve islet secretory responses (26).

We demonstrated a beneficial effect of semaglutide on HbA_{1c} by an average of −0.32 %-points compared with placebo; however, after reaching a nadir at 20 weeks, glycemic control deteriorated slightly over time at a similar rate in both groups (0.07 %-points with semaglutide and 0.06 %-points with placebo). This observation is consistent with those with long-term liraglutide administration in people with type 2 diabetes (27), with the basis being a progressive decline in β-cell function (28). Although weight reduction with semaglutide was far greater than observed with liraglutide and would be expected to produce a greater reduction in glycemia, the randomized treatment did not appear to slow the rate of progression over time in the semaglutide group compared with the placebo group. In those with the highest HbA_{1c}, the rate of glycemic deterioration was greatest, an observation likely due to less residual β-cell function in this group. Discontinuation of semaglutide by approximately one-quarter of participants might explain part of the subsequent rise in HbA_{1c}. We also cannot rule out that tachyphylaxis of the semaglutide effect on glycemia might also play a role in the observed increases beyond week 20. Nevertheless, use of semaglutide reduced the risk of development of diabetes by 73%, with treatment of 18.5 participants required for 156 weeks to prevent a case of diabetes.

In SELECT we used the semaglutide dose approved for weight management in obesity, which is higher than that approved for treating hyperglycemia. The changes in glycemia and weight over time demonstrated a glycemia nadir at 20 weeks, whereas maximum weight loss was attained at 65 weeks. Subsequently, weight remained stable, but as noted HbA_{1c} increased. This pattern is consistent with previous observations in people with type 2 diabetes (27,29,30) and is compatible with the glucose-lowering effect not being solely the result of the weight change. Furthermore, the time course of glycemic versus weight changes is in keeping with the effect of GLP-1RA to rapidly increase insulin release and reduce glucagon secretion through a direct effect on the islet, while decreasing weight due to a central effect to reduce appetite (26).

Weight reduction with semaglutide varied from no change to a marked reduction, with nearly one-quarter of participants losing ≥15% of their baseline body weight. Increasing gradations of weight loss were associated with a greater ability of semaglutide to induce regression to normoglycemia and prevent progression to diabetes, highlighting the importance of obesity as a risk factor for diabetes (31). Mediation analyses suggested that approximately one-third of the effect of semaglutide to induce regression and prevent progression was due to its effect on weight. In those who did not lose weight or lost <2%, a beneficial effect of semaglutide was still observed, which may be due to the effect of semaglutide to modulate islet function, and this mechanism may potentially contribute to the remaining effect on glycemia.

We observed some heterogeneity in the response to semaglutide. For both regression and progression, the beneficial effect of semaglutide was related to baseline glycemia and the magnitude of weight reduction, suggesting that the impact of semaglutide on islet function is vital but that its perceived effect on insulin sensitivity mediated through weight loss is also important. These observations are compatible with β-cell dysfunction and insulin resistance being important in diabetes pathogenesis, the β-cell being the more important determinant of glucose tolerance (4–6). As regards progression to diabetes, we observed no other heterogeneity with semaglutide, implying a consistent beneficial clinical effect.

Our longitudinal data indicate that our results are not due solely to the variability of the HbA_{1c} measurement about a static process. In the placebo group, the proportion with diabetes due to disease progression increased over time, particularly in those with HbA_{1c} ≥6.0% to <6.5% (Fig. 2*C*). With semaglutide, the proportion with diabetes in this glycemic subgroup was lower at all time points but increased over time. Progression while on glucose-lowering therapy is also indicated by the increasing proportion in the prediabetes category over time (Fig. 2*A*). Thus, we believe a single HbA_{1c} measurement is sensitive for categorizing glucose tolerance over time. However, for clinically diagnosing diabetes we agree with the recommendation of time-separated duplicate measurements that would have greater specificity (32).

It is of interest to assess our findings in the context of those from diabetes prevention studies. Intensive lifestyle interventions and several glucose-lowering medication classes are effective. All these interventions purportedly "rest" the β-cell either by improving insulin sensitivity and reducing β-cell secretory demand or by replacing insulin and reducing the need for endogenous insulin (7–12,14,15). In many of these studies, diabetes was

diagnosed based on elevated fasting or 2-h glucose, the latter glucose concentration frequently reached before diagnostic thresholds for fasting glucose or HbA_{1c} (33). Thus, direct comparisons are limited. From the Diabetes Prevention Program (DPP), in a secondary analysis with an HbA_{1c} threshold of 6.5% for diabetes, the diabetes incidence rate reported among those with baseline HbA_{1c} 6.0% to <6.5% who received placebo was ~21 cases per 100 participant-years, and this was reduced by ~55% with an intensive lifestyle intervention and ~50% with metformin (34). In our study, in the same baseline glycemic range, the proportion of participants progressing to diabetes at week 156 was 3.5% with semaglutide and 17.0% with placebo. One reason for this difference may be cohort enrichment in the DPP with a requirement that randomized participants have a fasting plasma glucose ≥95 mg/dL (5.3 mmol/L) (10).

There are some limitations to our study. First, although we examined the trajectory of HbA_{1c} over time, we did not have the necessary measurements to determine whether the progressive loss of glycemic control was due to changes in insulin sensitivity and/or β-cell function. Given the recent report of progressive loss of β-cell function over 4 years during liraglutide treatment of people with type 2 diabetes (28), a similar mechanism is possible in SELECT. Second, although approximately one-quarter of participants discontinued treatment, we do not believe that adherence affected our findings substantively given the large number of participants who remained on their assigned treatment throughout the study. Third, we have not evaluated any long-term effect of semaglutide to induce regression of glycemia and change the natural history of the disease, as we did not examine its legacy effects after discontinuation. Similarly, in most diabetes prevention studies, glucose-lowering medications were not stopped. For remission of diabetes, this period should be a minimum of 3 months (35), which would be appropriate for studies examining whether interventions change the natural history of the disease. However, given we observed variable degrees of weight change, it is possible those with the greatest weight loss would have a more sustained effect.

In conclusion, we have demonstrated that the beneficial effect of semaglutide on glycemia extends beyond type 2 diabetes, positively impacting rates of regression to normoglycemia and progression to diabetes in those with prediabetes. These effects were modulated by weight loss, with greater benefit in those with the greatest degree of weight reduction. Notably, we also observed a benefit of semaglutide in inducing regression and reducing progression in those who did not experience any weight loss. Thus, in people with overweight or obesity and CVD, semaglutide would be expected to positively impact glycemia in addition to CV outcomes.

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