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ORIGINAL RESEARCH

Cardiovascular, Metabolic, and Safety Outcomes with Semaglutide by Baseline Age: Post Hoc Analysis of SUSTAIN 6 and PIONEER 6

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ABSTRACT

***Introduction*:** The high risk of cardiovascular events in people with type 2 diabetes increases with age. The cardiovascular effects of once-weekly subcutaneous and once-daily oral semaglutide versus placebo in people with type 2 diabetes at high cardiovascular risk were investigated in the SUSTAIN 6 and PIONEER 6 cardiovascular outcomes trials, respectively. It is unknown whether the effects of semaglutide are age dependent.

***Methods*:** This post hoc analysis evaluated cardiovascular, metabolic, and safety outcomes with semaglutide versus placebo in age subgroups (≤ 60; > 60 to ≤ 65; > 65 to ≤ 70; and > 70 years) pooled from SUSTAIN 6 and PIONEER 6. Major adverse cardiovascular events (composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke), changes from baseline in glycated hemoglobin A_{1c} (HbA_{1c}) and body weight, and adverse events were analyzed.

***Results*:** Semaglutide reduced major adverse cardiovascular events and its components versus placebo across age subgroups (most hazard ratios < 1.0; $p_{interaction} > 0.05$). The treatment difference in HbA_{1c} reduction was greater in those aged ≤ 60 years than in older subgroups ($p_{interaction} = 0.01$). Reductions in body weight with semaglutide versus placebo were consistent

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across age subgroups ($p_{interaction}$ = 0.124). Serious adverse events or severe hypoglycemic episodes did not differ between semaglutide and placebo across age subgroups.

Conclusion: Semaglutide consistently reduced major adverse cardiovascular events and body weight versus placebo across age subgroups; its safety profile did not differ with age. These results suggest that relaxing HbA_{1c} targets based solely on age may not always be required for people with type 2 diabetes.

Trial Registration: SUSTAIN 6 (NCT01720446) and PIONEER 6 (NCT02692716) are registered at ClinicalTrials.gov.

Keywords: Cardiovascular; Glucagon-like peptide 1 receptor agonist; Metabolic; Safety; Type 2 diabetes

Key Summary Points
Why carry out this study?
The management of type 2 diabetes requires specific considerations in relation to age.
The aim of this post hoc pooled analysis was to evaluate cardiovascular, metabolic, and safety outcomes with semaglutide in age subgroups from SUSTAIN 6 and PIONEER 6.
What was learned from the study?
Regardless of age, semaglutide reduced major adverse cardiovascular events versus placebo.
With semaglutide, changes from baseline in glycated hemoglobin A_{1c} were similar across age subgroups and reduction in body weight was consistent across age subgroups.
Safety profiles did not differ between semaglutide and placebo, regardless of age.

INTRODUCTION

The management of type 2 diabetes (T2D) requires specific considerations in relation to age. For example, the risk of cardiovascular events associated with T2D is higher in older (≥ 65 years) than in younger adults (< 65 years) [1–3]. Furthermore, the risk of adverse events (AEs), particularly hypoglycemia, is higher in older than in younger adults [4]. This is partly due to the presence of comorbidities [4], meaning that polypharmacy is more common in older versus younger adults, consequently increasing the risk of drug–drug interactions. It is, therefore, important to avoid treatments associated with hypoglycemia and problematic, symptomatic hypotension in this older population [5]. Functional characteristics (e.g., physical and/or cognitive impairment) are also a consideration in this age subgroup [5].

The American Diabetes Association (ADA) advocates a glycemic target for nonpregnant adults with diabetes of < 7.0% (53 mmol/mol) whilst glycated hemoglobin A_{1c} (HbA_{1c}) targets between 7.0% (53 mmol/mol) and 7.5% (58 mmol/mol) are recommended for adults ≥ 65 years with few comorbidities and intact functional and cognitive statuses [6]. For those with a complex health status (e.g., multiple comorbidities, cognitive impairment, or functional decline), an even less stringent glycemic target of HbA_{1c} < 8.0% (64 mmol/mol) is recommended, as comorbidities may affect the ability to self-manage and the ability to prevent hypoglycemia [6]. De-escalation and/or simplification of glucose-lowering therapies is also recommended to minimize the risk of hypoglycemia in adults ≥ 65 years [6]. However, the evidence base for assessing the risks versus the benefits of therapeutic interventions is either not available or of low quantity and quality in adults ≥ 65 years. This is due to the relatively low proportions of adults reported in this age group in clinical trials (between 25% and 33.8% of total participants) [7, 8].

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) improve glycemic control and reduce body weight in people with T2D, with cardiovascular event reduction also shown for some medications in this class versus placebo [9]. Semaglutide, a glucagon-like peptide 1 analogue available as once-weekly (OW) subcutaneous (s.c.) and once-daily (OD) oral formulations, reduces HbA_{1c} and body weight in people with

T2D versus a range of comparators, with a safety profile similar to that of other GLP-1RAs [10–14]. The cardiovascular effects of OW s.c. and OD oral semaglutide were investigated in SUSTAIN 6 and PIONEER 6, respectively [15, 16]. In these pre-approval cardiovascular outcomes trials (CVOTs), major adverse cardiovascular events (MACE, a composite of cardiovascular death, nonfatal myocardial infarction [MI], and nonfatal stroke) were reduced with semaglutide versus placebo in people with T2D at high cardiovascular risk (statistical superiority in SUSTAIN 6 and noninferiority in PIONEER 6, although both were powered for noninferiority) [15, 16].

The aim of this post hoc pooled analysis was to evaluate cardiovascular, metabolic, and safety outcomes with semaglutide in age subgroups from SUSTAIN 6 and PIONEER 6. The similarity in trial designs, populations, and outcome measures in SUSTAIN 6 and PIONEER 6 supports the scientific validity of post hoc analyses of pooled data from these trials.

METHODS

Trial Designs

The trial designs for SUSTAIN 6 (NCT01720446; registered at ClinicalTrials.gov) and PIONEER 6 (NCT02692716; registered at ClinicalTrials.gov) have been reported previously [15, 16]. In both trials, adults with T2D at high risk of a cardiovascular event were enrolled. High risk of a cardiovascular event was defined as age ≥ 50 years and established cardiovascular disease or chronic kidney disease (CKD), or ≥ 60 years of age with cardiovascular risk factors.

In SUSTAIN 6, participants received OW s.c. semaglutide 0.5 mg or 1.0 mg (median follow-up of 2 years), while in PIONEER 6, participants received OD oral semaglutide 14 mg (median observation time of 15.9 months). In both trials, the comparator was dose-matched placebo and treatments were in addition to standard of care (for glycemia and cardiovascular risk factors).

The primary endpoint in both trials was time to first 3-point MACE. When changes in HbA_{1c} and body weight were analyzed, scheduled visits that occurred at different weeks in SUSTAIN 6 and PIONEER 6 were combined according to the visits closest in time, as follows: weeks 14 and 16, weeks 26 and 30, weeks 38 and 44, weeks 50 and 56, weeks 62 and 68, and weeks 80 and 83.

Both trials were approved by independent ethics committees and institutional review boards at each participating center and conducted in compliance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. All participants provided written informed consent prior to any trial-related activities.

Subgroups

Four age subgroups, resembling quartiles that were derived using the default method in SAS® PROC RANK (SAS Institute, Cary, NC, USA) for age at baseline (as an integer), were investigated: ≤ 60 years (the lower limit being ≥ 50 because of the inclusion criteria of the two trials); > 60 to ≤ 65 years; > 65 to ≤ 70 years; and > 70 years.

Outcomes

We performed post hoc analyses for cardiovascular outcomes including time to first composite 3-point MACE, individual MACE components, metabolic outcomes (change from baseline in HbA_{1c} and reduction from baseline in body weight), and safety outcomes (severe hypoglycemic episodes and serious AEs). A serious AE was defined as an AE resulting in any of the following: death, life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity or a congenital anomaly/birth defect, or important medical event that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Hypoglycemic episodes were defined as severe (according to American Diabetes Association criteria [17]) or as confirmed on analysis of plasma glucose (with symptomatic hypoglycemia defined as < 56 mg/dL [3.1 mmol/L]).

Statistical Analysis

All events and measurements were collected during the "in-trial period" using the full analysis set (all randomized participants). Time to first cardiovascular event was analyzed using a Cox proportional hazards model with treatment (semaglutide, placebo), age subgroup, and baseline variables as fixed factors, stratified by trial (SUSTAIN 6, PIONEER 6) and cardiovascular risk group (established cardiovascular disease or cardiovascular risk factors). Furthermore, quadratic spline regression was applied using Cox proportional hazard regression to analyze treatment differences in time-to-first MACE by continuous baseline age. Metabolic outcomes (change from baseline in HbA_{1c} and reduction in body weight at pooled week 80/83) were based on a mixed model for repeated measurements with treatment by age subgroups and trial as fixed factors and baseline value as a covariate, all nested within visit.

Safety outcomes are based on the full analysis set. Episodes of severe hypoglycemia were analyzed using a negative binomial regression model with a log link and the logarithm of the observation time (100 years) as offset. Treatment by age subgroups and trial were included as fixed factors.

The interaction between treatment effect and age subgroups was evaluated using interaction p values, with $p < 0.05$ indicating that the treatment effect was not consistent across subgroups. No adjustment for multiple testing was performed.

RESULTS

Baseline Characteristics

SUSTAIN 6 and PIONEER 6 included 6480 participants, of whom 3239 were randomized to semaglutide, and 3241 to placebo. Demographics and baseline characteristics are shown in Table 1. Most demographics and baseline characteristics, including proportion of male participants, HbA_{1c}, diabetes duration, body weight, systolic blood pressure, and lipid levels, were significantly different across age groups regardless of treatment group ($p < 0.05$). An overview of concomitant medication use at baseline by age subgroup is displayed in Supplementary Table 1. More semaglutide-treated participants in the youngest subgroup were receiving metformin than in other subgroups, while the oldest subgroup was most likely to be treated with insulin. Additionally, there was a general tendency for greater use of antihypertensive and diuretic concomitant medications in the oldest subgroups compared with other ages in both treatment groups.

Time to First MACE

Semaglutide consistently reduced MACE across all age subgroups versus placebo with all hazard ratios [HRs] < 1.0 (≤ 60 years HR [95% CI], 0.56 [0.37;0.84]; > 60 to ≤ 65 years HR, 0.84 [0.56;1.26]; > 65 to ≤ 70 years HR, 0.76 [0.50;1.14]; and > 70 years HR, 0.93 [0.63;1.36], $p_{interaction} = 0.33$; Fig. 1) and with age as continuous variable (most HRs < 1.0; Supplementary Fig. 1). Reductions in the individual MACE components (cardiovascular death, nonfatal MI, and nonfatal stroke) with semaglutide were also consistent across age subgroups (most HRs < 1.0, all $p_{interaction} > 0.05$; Fig. 2).

Metabolic Outcomes

The change from baseline in HbA_{1c} with semaglutide was similar in all age groups. A clinically small but statistically significant heterogeneity in HbA_{1c} reduction was observed between age subgroups. The estimated treatment differences (ETDs, semaglutide versus placebo) for subgroups were − 0.9%-points (≤ 60 years), − 0.8%-points (> 60 to ≤ 65 years and > 65 to ≤ 70 years), and − 0.7%-points (> 70 years; Fig. 3a, $p_{interaction} = 0.012$). Reductions in body weight with semaglutide versus placebo were consistent across age subgroups ($p_{interaction} = 0.124$; Fig. 3b).

Table 1 Demographics and baseline characteristics by age subgroup

Age subgroup, years	Semaglutide					Placebo				
	Overall	≤ 60	> 60 to ≤ 65	> 65 to ≤ 70	> 70	Overall	≤ 60	> 60 to ≤ 65	> 65 to ≤ 70	> 70
Number of participants, *n*	3239	831	900	752	756	3241	832	820	791	798
Age*, years	65.3	56.4	63.0	67.8	75.1	65.5	56.2	63.1	68.0	75.1
Sex, *n* (%)										
Male*	2097 (64.7)	558 (67.1)	545 (60.6)	481 (64.0)	513 (67.9)	2081 (64.2)	539 (64.8)	503 (61.3)	516 (65.2)	523 (65.5)
HbA_{1c}*, %	8.4	8.8	8.5	8.3	8.1	8.4	8.9	8.5	8.3	8.0
Diabetes duration*, years	14.4	11.5	13.6	15.4	17.6	14.3	11.6	13.8	15.1	17.0
Body weight*, kg	91.7	94.9	91.4	92.6	87.6	91.3	94.1	90.3	91.4	89.5
BMI*, kg/m^2	32.5	33.2	32.7	32.8	31.4	32.5	33.3	32.5	32.6	31.8
Systolic BP*, mmHg	136	133	135	137	138	136	133	135	137	137
LDL-cholesterol*, mmol/L[a]	2.2	2.3	2.3	2.2	2.1	2.3	2.4	2.3	2.2	2.1
HDL-cholesterol*, mmol/L[a]	1.1	1.1	1.1	1.1	1.2	1.1	1.1	1.1	1.1	1.1
Total cholesterol*, mmol/L[a]	4.3	4.4	4.4	4.2	4.1	4.3	4.5	4.3	4.2	4.1
Triglycerides*, mmol/L[b]	2.1	2.4	2.1	2.0	1.8	2.1	2.3	2.1	2.0	1.8
eGFR*, mL/min/1.73 m^2	75.0	85.1	78.5	70.8	63.8	75.1	85.9	78.4	72.4	63.1
Prior CV events, *n* (%)										
MI*	1091 (33.7)	346 (41.6)	279 (31.0)	221 (29.4)	245 (32.4)	1131 (34.9)	343 (41.2)	280 (34.1)	243 (30.7)	265 (33.2)
Stroke*	363 (11.2)	103 (12.4)	89 (9.9)	84 (11.2)	87 (11.5)	412 (12.7)	125 (15.0)	99 (12.1)	81 (10.2)	107 (13.4)
TIA*	190 (5.9)	50 (6.0)	48 (5.3)	31 (4.1)	61 (8.1)	192 (5.9)	51 (6.1)	43 (5.2)	47 (5.9)	51 (6.4)
No prior MI, stroke, or TIA*	1820 (56.2)	388 (46.7)	532 (59.1)	457 (60.8)	443 (58.6)	1776 (54.8)	379 (45.6)	462 (56.3)	481 (60.8)	454 (56.9)

Table 1 continued

Age subgroup, years	Semaglutide					Placebo				
	Overall	≤ 60	> 60 to ≤ 65	> 65 to ≤ 70	> 70	Overall	≤ 60	> 60 to ≤ 65	> 65 to ≤ 70	> 70
Prior heart failure*	569 (17.6)	185 (22.3)	149 (16.6)	118 (15.7)	117 (15.5)	596 (18.4)	196 (23.6)	141 (17.2)	120 (15.2)	139 (17.4)
Other comorbidities, *n* (%)										
Hypertension	2799 (86.4)	700 (84.2)	782 (86.9)	659 (87.6)	658 (87.0)	2756 (85.0)	702 (84.4)	698 (85.1)	679 (85.8)	677 (84.8)
Hypotension	7 (0.2)	1 (0.1)	2 (0.2)	2 (0.3)	2 (0.3)	6 (0.2)	2 (0.2)	2 (0.2)	2 (0.3)	0
Dyslipidemia*	1042 (32.2)	294 (35.4)	305 (33.9)	244 (32.4)	199 (26.3)	1085 (33.5)	300 (36.1)	290 (35.4)	258 (32.6)	237 (29.7)
Retinopathy*	964 (29.8)	258 (31.0)	274 (30.4)	205 (27.3)	227 (30.0)	903 (27.9)	250 (30.0)	242 (29.5)	199 (25.2)	212 (26.6)
Neuropathy	1267 (39.1)	301 (36.2)	360 (40.0)	310 (41.2)	296 (39.2)	1251 (38.6)	320 (38.5)	301 (36.7)	304 (38.4)	326 (40.9)
eGFR ≥ 90 mL/min/1.73 m^{2}*	1032 (31.9)	455 (55.0)	362 (40.2)	167 (22.2)	48 (6.4)	1021 (31.6)	456 (55.0)	325 (39.7)	183 (23.1)	57 (7.2)

Data are shown as mean values unless otherwise stated. eGFR based on Chronic Kidney Disease-Epidemiology Collaboration

BMI body mass index, *BP* blood pressure, *CV* cardiovascular, *eGFR* estimated glomerular filtration rate, HbA_{1c} glycated hemoglobin A_{1c}, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *MI* myocardial infarction, *TIA* transient ischemic attack

*$p < 0.05$ for significant differences between age subgroups regardless of treatment group

[a]To convert cholesterol values from mmol/L to mg/dL, multiply mmol/L by 38.7

[b]To convert triglyceride values from mmol/L to mg/dL, multiply mmol/L by 88.6

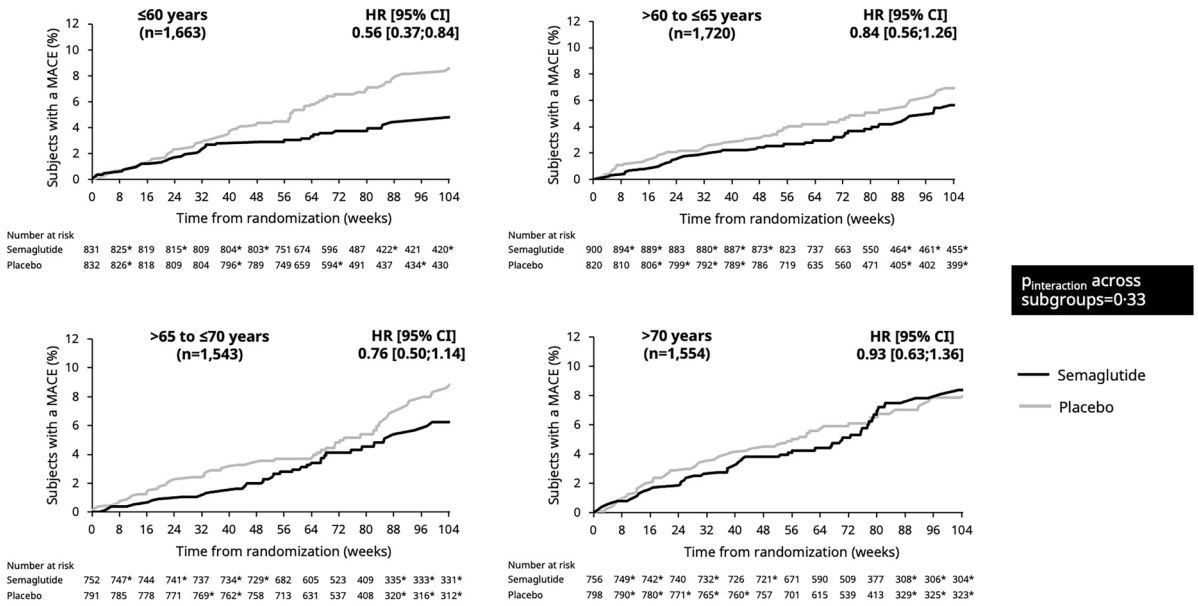

Fig. 1 Time to first MACE across age subgroups. *Risk values were not available for the week denoted and so data values for the closest relevant timepoint values have been included. Analysis of CV outcomes was based on a Cox proportional hazards model with treatment (semaglutide, placebo) by age subgroups (≤ 60 years, $n = 1663$; > 60 to ≤ 65 years, $n = 1720$; > 65 to ≤ 70 years, $n = 1543$; > 70 years, $n = 1554$; overall, $n = 6480$) and baseline variables as fixed factors, stratified by trial (SUSTAIN 6, PIONEER 6) and CV risk group (established CV disease vs risk factors). No adjustment for multiple testing was performed. Age division based on quartiles of age as integer at baseline. *CI* confidence interval, *CV* cardiovascular, *HR* hazard ratio, *MACE* major adverse cardiovascular events

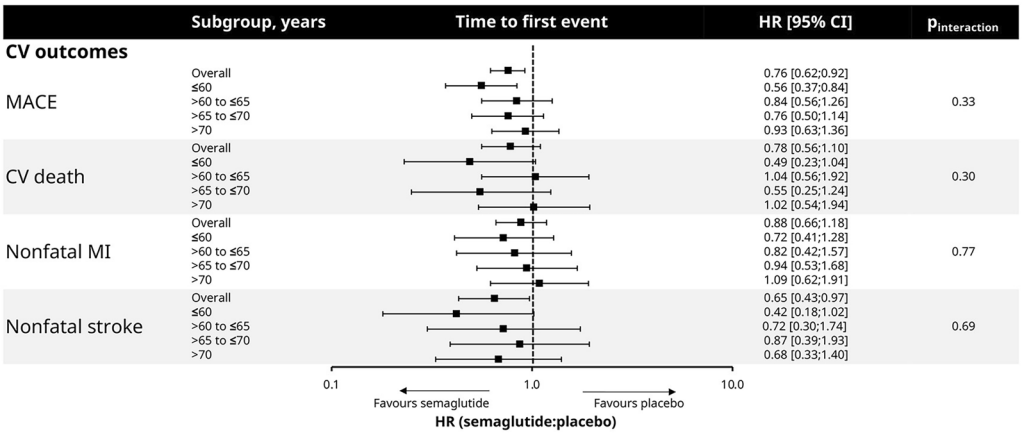

Fig. 2 Individual MACE components across age subgroups. Analysis of CV outcomes was based on a Cox proportional hazards model with treatment (semaglutide, placebo) by age subgroups (overall, $n = 6480$; ≤ 60 years, $n = 1663$; > 60 to ≤ 65 years, $n = 1720$; > 65 to ≤ 70 years, $n = 1543$; > 70 years, $n = 1554$) and baseline variables as fixed factors, and stratified by trial (SUSTAIN 6, PIONEER 6) and CV risk group (established CV disease vs risk factors). Age division was based on quartiles of age as integers at baseline. *CI* confidence interval, *CV* cardiovascular, *HR* hazard ratio, *MACE* major adverse cardiovascular events, *MI* myocardial infarction

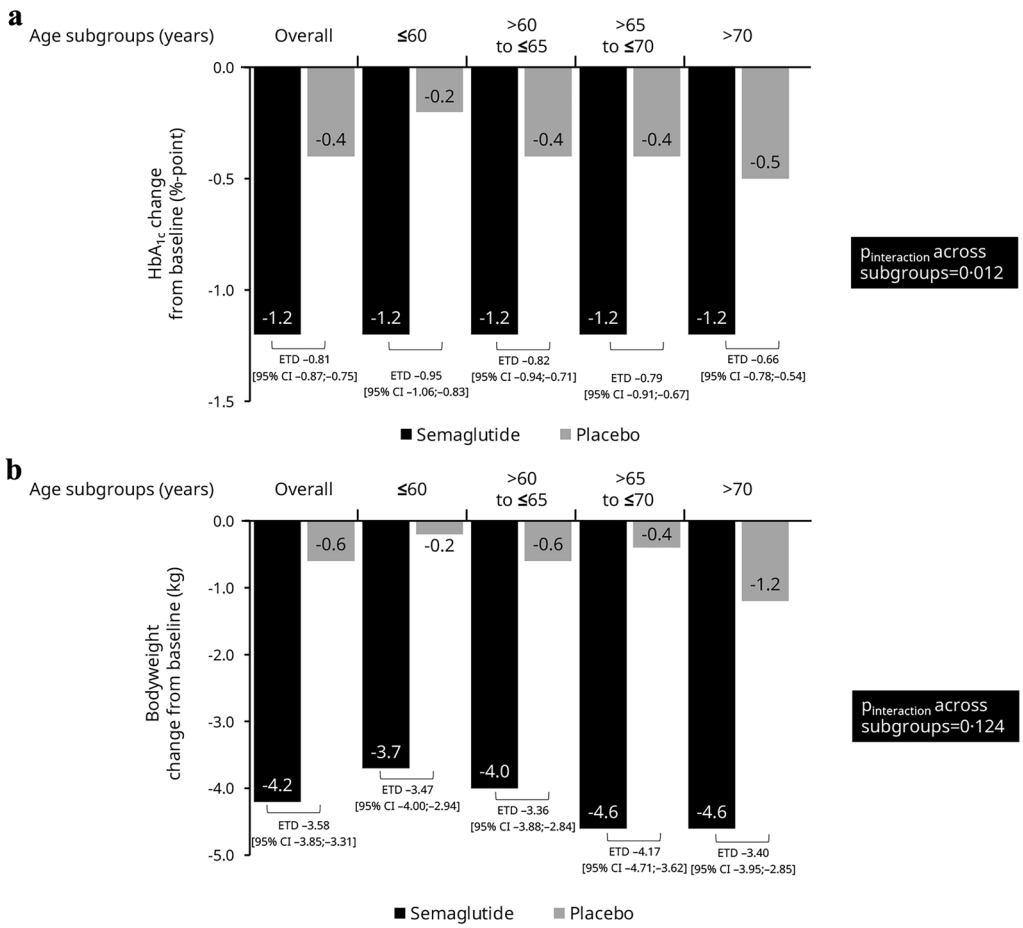

Fig. 3 Change from baseline in **a** $_{1c}HbA_{1c}$ and **b** body weight. Analysis of change in HbA_{1c} and body weight was based on a mixed model for repeated measurements with treatment by age subgroups (overall, $n = 6480$; ≤ 60 years, $n = 1663$; > 60 to ≤ 65 years, $n = 1720$; > 65 to ≤ 70 years, $n = 1543$; > 70 years, $n = 1554$) and trial as fixed factors, and baseline values as covariates, all nested within visit. No adjustment for multiple testing was performed. Age division was based on quartiles of age as integers at baseline. Change in HbA_{1c} and body weight was assessed at pooled week 80/83. *CI* confidence interval, *ETD* estimated treatment difference, *HbA*$_{1c}$ glycated hemoglobin A_{1c}

Safety

An overview of safety outcomes is shown in Table 2. The rate of serious AEs did not differ between semaglutide and placebo across age subgroups. Gastrointestinal AEs were the most common serious AEs with semaglutide and occurred at similar rates across all age subgroups. In adults treated with semaglutide, there was no apparent difference in the rates of severe hypoglycemia between the older and other age subgroups (e.g., 1.2% in > 70 years and 1.1% in ≤ 60 years). Conversely, in the placebo group, the older subgroup had more severe hypoglycemic episodes than in younger age groups (e.g., 2.5% in > 70 years versus 1.0% in ≤ 60 years). Additionally, there were no differences in the occurrence of serious AEs of interest in this analysis, including falls, fractures, diarrhea, and hypotension, across the various age groups for either semaglutide or placebo (Table 2).

Table 2 Safety outcomes

Age subgroup, years	Semaglutide					Placebo				
	Overall	≤ 60	> 60 to ≤ 65	> 65 to ≤ 70	> 70	Overall	≤ 60	> 60 to ≤ 65	> 65 to ≤ 70	> 70
Number of participants, *n*	3239	831	900	752	756	3241	832	820	791	798
Serious AEs	889 (27.4)	200 (24.1)	232 (25.8)	215 (28.6)	242 (32.0)	998 (30.8)	242 (29.1)	230 (28.0)	241 (30.5)	285 (35.7)
Severe hypoglycemic episodes[a]	51 (1.6)	9 (1.1)	22 (2.4)	11 (1.5)	9 (1.2)	45 (1.5)	8 (1.0)	8 (1.0)	9 (1.1)	20 (2.5)
Serious AEs of interest										
Cardiac disorders	301 (9.3)	72 (8.7)	83 (9.2)	70 (9.3)	76 (10.1)	344 (10.6)	78 (9.4)	93 (11.3)	76 (9.6)	97 (12.2)
Acute MI	50 (1.5)	11 (1.3)	12 (1.3)	14 (1.9)	13 (1.7)	64 (2.0)	19 (2.3)	13 (1.6)	16 (2.0)	16 (2.0)
Unstable angina	48 (1.5)	12 (1.4)	12 (1.3)	14 (1.9)	10 (1.3)	56 (1.7)	11 (1.3)	19 (2.3)	15 (1.9)	11 (1.4)
Congestive cardiac failure	45 (1.4)	11 (1.3)	14 (1.6)	9 (1.2)	11 (1.5)	44 (1.4)	11 (1.3)	13 (1.6)	9 (1.1)	11 (1.4)
Falls	22 (0.7)	0	6 (0.7)	7 (0.9)	9 (1.2)	30 (0.9)	3 (0.4)	5 (0.6)	7 (0.9)	15 (1.9)
Fractures[b]	48 (1.5)	10 (1.2)	15 (1.7)	8 (1.1)	15 (2.0)	63 (1.9)	11 (1.3)	13 (1.6)	22 (2.8)	17 (2.1)
Gastrointestinal disorders	103 (3.2)	19 (2.3)	26 (2.9)	26 (3.5)	32 (4.2)	74 (2.3)	20 (2.4)	15 (1.8)	20 (2.5)	19 (2.4)
Diarrhea	12 (0.4)	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)	3 (0.1)	2 (0.2)	1 (0.1)	0	0
Hypotension	7 (0.2)	1 (0.1)	2 (0.2)	1 (0.1)	3 (0.4)	9 (0.3)	3 (0.4)	1 (0.1)	2 (0.3)	3 (0.4)
Ischemic stroke	24 (0.7)	5 (0.6)	5 (0.6)	6 (0.8)	8 (1.1)	31 (1.0)	8 (1.0)	6 (0.7)	8 (1.0)	9 (1.1)

Data are shown as *n* (%). All serious AEs of interest were categorized using MedDRA coding, events from SUSTAIN 6 were coded according to MedDRA version 18.0, PIONEER 6 were coded according to MedDRA version 20.1

ADA American Diabetes Association, *AE* adverse event, *HLGT* high level group term, *HLT* high level term, *MedDRA* Medical Dictionary for Regulatory Activities, *MI* myocardial infarction, *NEC* not elsewhere classified

[a]ADA classification; a severe event characterized by altered mental and/or physical status requiring assistance

[b]Adverse events with an HLGT of "Bone and joint injuries" are included except for those with HLT of "Bone and joint injuries NEC"

DISCUSSION

In this post hoc analysis of SUSTAIN 6 and PIONEER 6, treatment with semaglutide versus placebo reduced cardiovascular outcomes and body weight, with a similar safety profile, across all age subgroups.

The effect of semaglutide versus placebo on MACE consistently favored semaglutide across age groups for the composite endpoint and its three components. Furthermore, HRs generally decreased with decreasing age. This suggests that younger participants experienced a greater treatment effect of semaglutide versus placebo than older participants, despite having a higher risk of MACE based on the trial inclusion criteria for established CV disease or CKD for people aged < 60 years, while people aged ≥ 60 years needed only to have cardiovascular risk factors [15, 16].

This analysis is consistent with a meta-analysis of eight GLP-1RAs CVOTs (including SUSTAIN 6 and PIONEER 6), which showed that GLP-1RAs reduced MACE irrespective of age [9]. Specifically, that analysis showed that GLP-1RAs, versus placebo, reduced the risk of MACE both in people with T2D aged < 65 years and in those aged ≥ 65 years ($p_{interaction}$ between age subgroups, 0.78) [9]. The meta-analysis included only two age groups, unlike the present analysis that spans four age subgroups, and therefore provides a more comprehensive overview.

Statistically significant heterogeneity in HbA_{1c} reduction was observed, with a larger ETD for semaglutide versus placebo in the youngest age subgroup (≤ 60 years) compared with other age subgroups. However, this difference was small and of limited clinical significance. Despite HbA_{1c} being significantly greater in older people than in younger people at baseline, this was corrected for and the actual change from baseline in HbA_{1c} was similar in all age subgroups with semaglutide, and always greater than with placebo. It should be noted that the actual change from baseline in HbA_{1c} in those receiving placebo was greater in older versus younger people and is likely to contribute to the heterogeneity observed in ETDs across the subgroups.

There was no difference in serious AEs across age subgroups for both semaglutide and placebo. However, this was not specifically analyzed in this combined analysis of SUSTAIN 6 and PIONEER 6; therefore, this hypothesis requires further study to substantiate. The rate of severe hypoglycemia was lower with semaglutide than placebo in most age subgroups. Furthermore, in the placebo groups, the highest incidence of severe hypoglycemia occurred in the oldest subgroup. Additional glucose-lowering medications were used to maintain glucose control according to local guidelines in those who received placebo, suggesting that semaglutide allows target HbA_{1c} values to be achieved without the need for additional glucose-lowering medications or at the expense of hypoglycemia.

Results from this analysis are consistent with observations from a previous post hoc analysis of SUSTAIN 1–5, in which OW s.c. semaglutide (0.5 mg and 1.0 mg) had similar efficacy (HbA_{1c} and body weight reduction) and safety profiles in non-elderly (< 65 years) and elderly (≥ 65 years) people with T2D [17]. Semaglutide 1.0 mg (versus comparators) decreased mean HbA_{1c} from baseline by 1.5–1.9% (versus 0–0.9%) in those aged < 65 years, and by 1.2–1.8% (versus 0.2–1.0%) in those aged ≥ 65 years. Similarly, body weight was reduced by − 4.6 to − 6.4 kg (vs + 1.1 to − 2.1 kg) in those aged < 65 years, and − 4.1 to − 6.7 kg (vs + 1.5 to − 1.7 kg) in those aged ≥ 65 years. Similar proportions of people experienced AEs across age subgroups and there was no increased risk of severe or blood glucose-confirmed hypoglycemia with semaglutide versus comparators, between age subgroups [18]. Again, however, this previous analysis included only two age groups, unlike the present analysis that spans four age subgroups and indicates consistent metabolic and safety outcomes with semaglutide for older adults including for those in the higher age range (subgroups > 65 to ≤ 70 and > 70 years, which have not been included in previous analyses).

Our findings are particularly relevant to the management of T2D in older adults with long-duration diabetes, as semaglutide reduces MACE, improves HbA_{1c}, and reduces body weight without increasing serious AEs. As a result, HbA_{1c} targets may not need to be adjusted for older adults, as is currently advised by the ADA [6], when using glucose-lowering treatment with a

low intrinsic risk of hypoglycemia. Furthermore, there is suggestion that tight glycemic control in older adults has benefits on microvascular complications and minimizes the risk of other geriatric syndromes [19]. However, taken together, the above highlights the importance of individualized treatment approaches.

Despite recommendations that medications that improve cardiovascular and kidney outcomes in people with T2D should not differ for older adults (unless the person is assessed as frail) [5], the particular challenges of managing T2D in this population can mean that treatment is not always intensified and, in some cases, the paternalistic practice of treatment de-escalation is used [20, 21]. This strategy denies older adults from receiving MACE-reduction benefits associated with GLP-1RAs. Additionally, lower HbA_{1c} targets when achieved with GLP-1RAs are not harmful in older adults, unless accompanied by increased risk of hypoglycemia.

The findings from this post hoc analysis of SUSTAIN 6 and PIONEER 6 reinforce the recommendation in the guidelines that GLP-1RAs should be used to reduce the risk of MACE across the spectrum of age, and offer an alternative approach to treatment de-escalation, as is currently advised by the ADA in adults ≥ 65 years [6], which should lead to better outcomes for older adults [1, 18, 22]. Glucose-lowering therapies that cause hypoglycemia in the older population should be avoided, as semaglutide offers an alternative with a low intrinsic risk of hypoglycemia. By prescribing GLP-1RAs, it may be possible to reduce the risk of cardiovascular events, maintain glycemic control, and avoid complications/comorbidities with a low risk of hypoglycemia even in elderly people; these data may help overcome the treatment inertia that this population can experience [23] and suggest that de-escalation recommendations may require refinement, considering the availability of new medications with a lower risk of hypoglycemia.

Limitations of this analysis include the relatively short durations of SUSTAIN 6 and PIONEER 6 trials compared with CVOTs such as LEADER (trial duration 60 months) [24], making it difficult to draw long-term conclusions. Data for HbA_{1c} and body weight were combined for visits that occurred at different weeks in the two trials, with a variation of up to 6 weeks. This could introduce variability, as both HbA_{1c} and body weight can change over short periods in response to treatment and different phases of the treatment response may be observed in different weeks. Safety findings were based on analysis of serious AEs only and do not incorporate other AEs that may be meaningful to an elderly population, such as non-serious gastrointestinal AEs. Additionally, differences between trial populations and real-world practice in terms of age, evident by the low numbers of participants aged ≥ 65 years included in clinical trials, may affect the ability to extrapolate clinical trial results to a real-world population. It is also important to note that during the time of these trials, sodium–glucose cotransporter 2 inhibitors (SGLT2is) were not considered standard of care; therefore, the number of participants treated with SGLT2is within this post hoc analysis is low, and higher number of patients were treated with α-glucosidase inhibitors, sulfonylureas, and other drugs that do not reflect current real-world practice. As SGLT2is also have proven benefits on metabolic and CV outcomes [25], this should be taken into consideration when interpreting these results. Furthermore, very elderly and frail people may not have been randomized in SUSTAIN 6 and PIONEER 6 (although they were not specifically excluded); hence, these findings may not be applicable to all people with T2D and high cardiovascular risk. While the inclusion of four age subgroups is an extension of previous analyses [9, 18], it limits the number of cardiovascular events within each subgroup, reducing statistical power. This analysis is not powered to determine whether there are significant treatment effects within each subgroup; $p_{\text{interaction}} < 0.05$ suggests a lack of heterogeneity in treatment effect between subgroups. Finally, there are inherent limitations with post hoc compared with prospective analyses from randomized clinical trials; hence, these findings should be interpreted as hypothesis generating. However, the similarity in trial designs, populations, and outcome measures in SUSTAIN 6 and PIONEER 6 supports the scientific validity of post hoc analyses of pooled data from these trials. In addition, the high retention rates

(98.0–99.7% completing the trials) and recording of vital status (known for 99.6–100% of the participants at the end of the trials) support the validity of the data and the good conduct of the original trials [15, 16]. Further studies investigating the effects of semaglutide, including those on sarcopenia and its sequelae, across the spectrum of ages would be of interest.

CONCLUSIONS

Treatment with semaglutide reduced cardiovascular events and body weight versus placebo irrespective of age. There were no differences in serious AEs or severe hypoglycemia across the age subgroups. Results from this post hoc analysis raise the possibility that relaxing HbA_{1c} targets based solely on age may not always be required for people with T2D when treated with GLP-1RAs.

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Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Stephen Bain has received honoraria, teaching and research sponsorship/grants from the following: AstraZeneca, Boehringer Ingelheim, BMS, Eli Lilly, GSK, Merck Sharp & Dohme, Novo Nordisk, Pfizer, Sanofi, and Takeda. Stephen Bain is an Editorial Board member of *Diabetes Therapy*. Stephen Bain was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Nicolas Belmar, Søren Hoff, and Søren Rasmussen are employees of Novo Nordisk, and Søren Hoff and Søren Rasmussen are shareholders in Novo Nordisk. Mansoor Husain has received research grants from AstraZeneca, Merck, and Novo Nordisk, and advisory/consultancy fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, and Roche. Tina Vilsbøll has served on scientific advisory panels, been part of speakers' bureaus, served as a consultant to and/or received research support from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Gilead, GSK, Mundipharma, MSD/Merck, Novo Nordisk, Sanofi, and Sun Pharmaceuticals. Mark Petrie has received grants or contracts from AstraZeneca, Boehringer Ingelheim, Boston Scientific, Medtronic, Novartis, Novo Nordisk, Pharmacosmos, Roche, and SQ Innovation Inc; consulting fees and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis AG, Corvia Medical, Novartis, Novo Nordisk, Pharmacosmos, Siemens, Takeda, and Vifor; has participated in a Data Safety Monitoring Board or advisory board

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