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Cardiovascular risk reduction with once-weekly semaglutide in subjects with type 2 diabetes: a post hoc analysis of gender, age, and baseline CV risk profile in the SUSTAIN 6 trial

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Abstract

Background: The SUSTAIN 6 trial demonstrated that once-weekly semaglutide (0.5 and 1.0 mg) significantly reduced major adverse cardiovascular (CV) events (MACE) vs placebo in subjects with type 2 diabetes (T2D) and high CV risk. The effects of gender, age and baseline CV risk on outcomes are important considerations for further study.

Methods: Subjects were grouped according to gender, age (50–65 years and > 65 years), and CV risk profile at baseline (prior myocardial infarction [MI] or stroke vs no prior MI or stroke, and established CV disease [CVD] vs CV risk factors alone, including subjects with chronic kidney disease). Time to MACE and its individual components (CV death, nonfatal MI, nonfatal stroke), hospitalization for unstable angina or heart failure, and revascularization (coronary and peripheral) were analyzed for all subgroups. Additional analyses were performed for gender and age to investigate change from baseline in HbA_{1c} and body weight, as well as tolerability.

Results: A total of 3297 subjects were included. The majority of subjects (60.7%) were male; 43% were > 65 years of age; 41.5% had a history of MI or stroke; and 76.8% had established CVD. Compared with placebo, semaglutide reduced the risk of the first occurrence of MACE and each MACE component consistently across all subgroups (gender, age, and baseline CV risk profile). Revascularizations, HbA_{1c} and body weight were also reduced consistently across all subgroups compared with placebo. Gastrointestinal adverse events in all treatment groups were more common among women than men, but rates of premature treatment discontinuation were similar for both genders.

Conclusions: In this post hoc analysis of SUSTAIN 6, once-weekly semaglutide vs placebo reduced the risk of MACE in all subjects included in the trial, regardless of gender, age, or baseline CV risk profile.

Trial registry Clinicaltrials.gov, Identifying number: NCT01720446, Date of registration: October 29, 2012

Keywords: Semaglutide, Cardiovascular events, Gender, Age, Baseline cardiovascular risk, Type 2 diabetes, SUSTAIN 6, Cardiovascular outcome trial

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Background

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in people with type 2 diabetes (T2D) [1, 2], and diabetes itself confers a substantial independent risk of coronary heart disease, stroke, and death from other vascular causes [3]. Current diabetes guidelines recommend multifactorial CV risk management and the preferential use of a glucagon-like peptide-1 receptor agonist (GLP-1RA) or sodium–glucose cotransporter-2 inhibitor with proven CV benefits as a first choice add-on to metformin in patients with T2D and established atherosclerotic CVD [2, 4]. Semaglutide is a GLP-1 analogue approved as a once-weekly, subcutaneous treatment for T2D [5, 6]. The phase 3 SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) clinical trial program evaluated the efficacy and safety of semaglutide in subjects with T2D in a range of patient populations across the continuum of diabetes care [7–14]. In the SUSTAIN 6 CV outcomes trial (CVOT), once-weekly semaglutide (0.5 or 1.0 mg) added to standard of care significantly reduced the occurrence of a first major adverse CV event (MACE: CV death, nonfatal myocardial infarction [MI], or nonfatal stroke) vs placebo over 2 years in 3297 subjects with T2D and high CV risk [12]. Given the increasing emphasis on individualized patient care in the management of T2D [4], this post hoc analysis assessed the effects of gender, age, and baseline CV risk on the reduction of CV risk in the SUSTAIN 6 trial.

Methods

SUSTAIN 6 study design

The design of SUSTAIN 6 (clinicaltrials.gov NCT01720446) has been described previously [12]. In brief, SUSTAIN 6 was a randomized, double-blind, placebo-controlled, parallel-group trial to evaluate once-weekly semaglutide 0.5 or 1.0 mg vs volume-matched placebo over a 104-week treatment period plus a 5-week follow-up period. The trial was conducted in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki [15, 16]. The protocol was approved by local ethics committees and institutional review boards. Written informed consent was obtained from all subjects before trial commencement.

A total of 3297 subjects with T2D ($HbA_{1c} \geq 7\%$) were randomized to receive once-weekly semaglutide 0.5 or 1.0 mg or placebo for 104 weeks. Subjects were ≥ 50 years of age with established CVD (defined as previous CV, cerebrovascular, or peripheral vascular disease), chronic heart failure (New York Heart Association class II or III), or chronic kidney disease (CKD) of stage 3 or higher, or were ≥ 60 years of age with at least one CV risk factor (microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction or ankle–brachial index < 0.9). All subjects treated with semaglutide followed a fixed dose-escalation regimen, with a starting dose of 0.25 mg for 4 weeks that escalated to 0.5 mg for 4 weeks until the maintenance dose (0.5 or 1.0 mg) was reached.

The primary composite outcome (MACE) was the first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke. Other outcomes included time to first hospitalization for unstable angina and heart failure, time to first revascularization (coronary or peripheral), and changes in HbA_{1c} and weight. All outcomes were collected after 104 weeks of treatment.

Statistical analysis

This post hoc analysis examined the effect of gender, age (subjects aged 50–65 and > 65 years), and CV risk profile at baseline on time to first occurrence of MACE, the individual components of MACE (CV death, nonfatal MI, or nonfatal stroke), hospitalization for unstable angina or heart failure, and revascularization. Additional analyses were performed by gender and age to investigate changes from baseline in HbA_{1c} and body weight, adverse events (AEs), and hypoglycemia, as defined by the American Diabetes Association (ADA) [17].

For comparison of outcomes between men and women, estimated hazard ratios (HRs) and associated confidence intervals (CIs) were determined by a Cox proportional hazards model with an interaction between treatment (semaglutide, placebo) and gender as a fixed factor. Efficacy and safety were assessed by age group using post hoc subgroup analyses of subjects ≤ 65 and > 65 years. Post-baseline responses for time to first occurrence of MACE, CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina or heart failure, revascularization, and change from baseline in HbA_{1c} and body weight were analyzed using a mixed model for repeated measurements with interaction between subgroup, randomized treatment, and baseline value as covariate. No adjustment for multiplicity was performed. A significance level for interaction of 5% was considered significant. To investigate more general linear and non-linear effects of age at baseline, individual outcomes and AEs were modelled as a function of age, controlling for randomized treatment and CVD at baseline via negative-binomial log regression (see "Post hoc analysis by age"). Analyses were based on pooled data using semaglutide 0.5 mg and 1.0 mg doses for MACE and its components, hospitalization due to angina or heart failure, revascularization, and AEs. HbA_{1c} and body weight were reported separately for both semaglutide doses following the statistical methods used in the primary SUSTAIN 6 trial [12].

CV risk profile subgroups

To assess the effect of baseline CV risk profiles on outcomes, two separate subgroup analyses were performed: (1) for subjects who had experienced a prior MI or stroke compared with those who had not, and (2) for those with established CVD, defined as prior stroke, ischemic heart disease (including MI), peripheral arterial disease, ≥ 50% arterial stenosis in any artery, coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft), or heart failure vs those with CV risk factors alone and no manifestations of CVD as defined above. The risk classification in the latter subgroup comparison differs from the prespecified group of evidence of CVD in SUSTAIN 6, in which subjects with CKD stage 3 or higher were included [12]. In this post hoc analysis, however, subjects with CKD were included in the CV risk factor alone group to reflect the usual definition of established CVD used in clinical practice. Statistical analyses were carried out using Cox proportional hazards models for time to first MACE with treatment, and treatment by subgroup interaction, if applicable, as fixed factor(s). No adjustment for multiplicity was performed. A significance level for interaction of 5% was considered significant.

Results

Post hoc analysis by gender

Among 3297 subjects in the SUSTAIN 6 study population, 2002 were male and 1295 were female (Table 1A). There were no clear differences in subject demographics or key baseline characteristics between men and women, with the exception of weight (men tended to be heavier) and smoking status (51.7 vs 26.1% and 56.1 vs 23.0% of men vs women had a history of smoking in the semaglutide and placebo groups, respectively). Similar proportions of male and female subjects completed the trial and treatment. MACE occurred in lower proportions of subjects treated with semaglutide vs placebo in both men and women, and this overall benefit was independent of gender ($p = 0.45$ for interaction) (Fig. 1). The same pattern was noted across the individual MACE components of CV death, nonfatal MI and nonfatal stroke; lower or similar proportions of both men and women experienced events with semaglutide vs placebo, and p-values for interaction were nonsignificant ($p = 0.46$, $p = 0.34$ and $p = 0.74$, respectively, for each endpoint) (Fig. 1). Gender had no apparent effect on first hospitalization for unstable angina ($p = 0.35$ for interaction) or heart failure ($p = 0.55$ for interaction), or time to first revascularization procedure ($p = 0.50$ for interaction; Fig. 2).

Post hoc analysis by age

In the SUSTAIN 6 study, 1879 subjects were 50–65 years of age and 1418 were > 65 years (Table 1B). There were no clear differences in subject demographics or key baseline characteristics between groups. Duration of diabetes was greater in subjects > 65 years compared with those ≤ 65 years (16.4 vs 12.6 years for the semaglutide group and 15.2 vs 12.4 years for the placebo group). Similar proportions of subjects in each age group completed the trial and treatment. HRs for time to first confirmed MACE were all below 1.0 for subjects treated with semaglutide vs placebo, irrespective of age ($p = 0.92$ for interaction, Fig. 1). Results were consistent for the individual components of MACE across age groups (Fig. 1; $p = 0.35$, $p = 0.42$, and $p = 0.45$ for interaction, respectively, for CV death, nonfatal MI, and nonfatal stroke). Age had no apparent effect on first hospitalization due to unstable angina ($p = 0.16$ for interaction), heart failure ($p = 0.26$ for interaction) or revascularization procedures ($p = 0.97$ for interaction; Fig. 2). A series of regression analyses were conducted to assess more general linear and nonlinear trends for the incidence of MACE by age; since no significant effects were found, these have not been reported further (see Additional file 1).

Post hoc analysis by CV risk

Pooled key baseline characteristics, CV risk factors, and manifestation of CVD at baseline for the two CV subgroups [subjects with prior MI or stroke vs no prior MI or stroke and subjects with established CVD vs risk factors only (including CKD)] are shown in Table 1C. In total, 1367 subjects had a history of MI or stroke (vs 1930 without prior history) and 2533 had established CVD (vs 764 with CV risk factors only).

Hazard ratios for time to first confirmed MACE were all below 1.0 in subjects treated with semaglutide vs placebo, irrespective of baseline CV risk profile (Fig. 3). Similar results were observed across the individual components of MACE, with the exception of CV death in subjects with a prior MI or stroke or with established CVD ($p = 0.22$ for interaction between subjects with prior MI or stroke vs no prior MI or stroke; $p = 0.52$ for interaction between subjects with established CVD vs risk factors only) (Fig. 2).

In the SUSTAIN 6 trial, there was no difference in hospitalization for angina or heart failure between semaglutide and placebo [12], and this result was independent of baseline CV risk profile (Fig. 2). The between-group interaction for unstable angina in subjects with prior MI or stroke compared with no prior MI or stroke was significant ($p = 0.02$ for interaction), with

Table 1 Baseline characteristics and demographics of subjects in the SUSTAIN 6 trial

A. Post hoc analysis by gender

	Semaglutide		Placebo	
	Male	**Female**	**Male**	**Female**
Subject demographics				
Full analysis set, N	1013	635	989	660
Trial completers, n (%)	959 (94.7)	602 (94.8)	926 (93.6)	623 (94.4)
Treatment completers, n (%)	773 (76.3)	481 (75.7)	788 (79.7)	514 (77.9)
Baseline characteristics[a]				
Age, years	64.6 (7.3)	64.8 (7.1)	64.6 (7.6)	64.6 (7.5)
Body weight, kg	96.7 (20.5)	85.4 (19.0)	95.8 (21.0)	86.0 (18.4)
BMI, kg/m^2	32.3 (5.9)	33.7 (6.6)	32.1 (6.0)	33.9 (6.3)
Diabetes duration, years	13.9 (8.1)	14.5 (8.4)	13.5 (8.0)	13.8 (8.1)
HbA_{1c}, %	8.6 (1.4)	8.8 (1.6)	8.6 (1.4)	8.8 (1.6)
Smoking status (never/previous/current), %	33.5/51.7/14.8	65.4/26.1/8.5	30.1/56.1/13.7	66.8/23.0/10.2

B. Post hoc analysis by age

	Semaglutide		Placebo	
	≤ 65 years	**> 65 years**	**≤ 65 years**	**> 65 years**
Subject demographics				
Full analysis set, N	950	698	929	720
Trial completers, n (%)	899 (94.6)	662 (94.8)	875 (94.2)	674 (93.6)
Treatment completers, n (%)	745 (78.4)	509 (72.9)	745 (80.2)	557 (77.4)
Baseline characteristics[b]				
Age, years	59.7 (4.1)	71.4 (4.7)	59.2 (4.3)	71.6 (4.5)
Females, %	38.4	38.7	40.9	38.9
Body weight, kg	94.0 (21.1)	90.0 (19.8)	93.0 (21.4)	90.5 (19.3)
BMI, kg/m^2	33.3 (6.4)	32.2 (5.9)	33.1 (6.4)	32.4 (5.8)
Diabetes duration, years	12.6 (7.2)	16.4 (8.9)	12.4 (7.4)	15.2 (8.5)
HbA_{1c}, %	8.9 (1.6)	8.4 (1.2)	8.9 (1.6)	8.4 (1.3)
Smoking status (never/previous/current), %	47.0/37.1/16.0	44.1/48.4/7.5	45.3/39.0/15.7	44.2/47.9/7.8

C. Post hoc analyses by CV risk profile at baseline

	Semaglutide		Placebo		Semaglutide		Placebo	
	Prior MI/ stroke	**No prior MI/ stroke**	**Prior MI/ stroke**	**No prior MI/ stroke**	**Established CVD**	**CV risk factors**	**Established CVD**	**CV risk factors**
Full analysis set, N	673	975	694	955	1262	386	1271	378
Baseline characteristics								
Age, years	63.8 (7.5)	65.2 (6.9)	63.6 (7.9)	65.3 (7.2)	64.2 (7.3)	66.1 (6.5)	64.2 (7.7)	66.0 (6.7)
Female, n (%)	208 (30.9)	427 (43.8)	225 (32.4)	435 (45.5)	445 (35.3)	190 (49.2)	463 (36.4)	197 (52.1)
Diabetes duration, years	13.7 (8.5)	14.5 (8.0)	13.3 (8.1)	13.8 (8.0)	14.0 (8.4)	14.8 (7.6)	13.3 (7.9)	14.6 (8.2)
BMI, kg/m^2	32.6 (6.0)	33.0 (6.4)	32.7 (6.2)	32.8 (6.2)	32.8 (6.1)	32.8 (6.5)	33.0 (6.2)	32.3 (6.1)
HbA_{1c}, %	8.8 (1.6)	8.7 (1.4)	8.7 (1.5)	8.7 (1.4)	8.7 (1.5)	8.7 (1.4)	8.7 (1.5)	8.7 (1.5)
CV risk factors								
Systolic blood pressure, mmHg	134.6 (17.7)	136.9 (17.3)	134.9 (17.1)	135.5 (16.6)	135.5 (17.5)	137.5 (17.5)	134.9 (16.6)	136.5 (17.4)

Table 1 (continued)

C. Post hoc analyses by CV risk profile at baseline

	Semaglutide		Placebo		Semaglutide		Placebo	
	Prior MI/ stroke	No prior MI/ stroke	Prior MI/ stroke	No prior MI/ stroke	Established CVD	CV risk factors	Established CVD	CV risk factors
Diastolic blood pressure, mmHg	76.8 (9.9)	77.1 (10.1)	76.7 (10.4)	77.4 (9.8)	76.7 (10.0)	77.9 (9.8)	77.0 (10.2)	77.5 (9.6)
Total cholesterol, mmol/L [mean (CoV)]	4.2 (26.8)	4.4 (25.5)	4.2 (27.9)	4.3 (26.5)	4.3 (26.9)	4.4 (23.6)	4.2 (27.6)	4.4 (25.4)
eGFR, mL/ min/1.73 m^2 [mean (CoV)]	72.1 (39.2)	70.1 (41.4)	73.8 (39.8)	69.0 (44.6)	72.9 (38.7)	64.9 (44.8)	73.9 (39.7)	61.7 (49.2)
Current smoker, n (%)	106 (15.8)	98 (10.1)	109 (15.7)	93 (9.74)	170 (13.5)	34 (8.8)	167 (13.1)	35 (9.3)
Manifestation of CVD								
Prior MI, n (%)	530 (78.8)	–	542 (78.1)	–	530 (42.0)	–	542 (42.6)	–
Ischemic heart disease, n (%)	571 (84.8)	417 (42.8)	589 (84.9)	417 (43.7)	988 (78.3)	–	1006 (79.2)	–
Prior stroke, n (%)	191 (28.4)	–	210 (30.3)	–	191 (15.1)	–	210 (16.5)	–
Peripheral arterial disease, n (%)	87 (12.9)	139 (14.3)	89 (12.8)	138 (14.5)	226 (17.9)	–	227 (17.9)	–
≥ 50% arterial stenosis, n (%)	327 (48.6)	240 (24.6)	361 (52.0)	239 (25.0)	567 (44.9)	–	600 (47.2)	–
Percutaneous coronary intervention, n (%)	327 (48.6)	163 (16.7)	342 (49.3)	180 (18.8)	490 (38.8)	–	522 (41.1)	–
Coronary artery bypass graft, n (%)	182 (27.0)	106 (10.9)	182 (26.2)	107 (11.2)	288 (22.8)	–	289 (227)	–
Heart failure, n (%)	187 (27.8)	194 (19.9)	185 (26.7)	211 (22.1)	381 (30.2)	–	396 (31.2)	–

Data presented as mean (SD) unless otherwise indicated. Data were pooled for semaglutide groups and placebo groups in each SUSTAIN 6 subgroup

BMI body mass index, *CoV* coefficient of variation, *CV* cardiovascular, *CVD* cardiovascular disease, *eGFR* estimated glomerular filtration rate, *MI* myocardial infarction, *SD* standard deviation

[a] Numbers are based on an in-trial analysis comprising events with onset on or after the day of randomization and until end of trial

[b] Data were pooled for semaglutide groups and placebo groups in each SUSTAIN 6 subgroup

a significant reduction in hospitalization for unstable angina for semaglutide vs placebo in subjects with no prior MI or stroke ($p = 0.03$). No significant interactions were noted for hospitalization for heart failure between the various risk groups (Fig. 2; $p = 0.59$ for interaction between subjects with prior MI or stroke vs no prior MI or stroke and $p = 0.93$ for interaction between subjects with established CVD vs CV risk factors only).

Semaglutide reduced time to first revascularization vs placebo in the overall study; this result was observed regardless of baseline CV risk profile, with no significant differences between subgroups ($p = 0.25$ for interaction between subjects with prior MI or stroke vs no prior MI or stroke and $p = 0.27$ for interaction between subjects with established CVD vs CV risk factors only).

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