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Effects of semaglutide versus comparators on cardiovascular events across a continuum of baseline cardiovascular risk: combined analysis of the SUSTAIN and PIONEER trials

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BACKGROUND

- Fewer major adverse cardiovascular events (MACE) were observed with semaglutide vs placebo in cardiovascular outcomes trials (CVOTs) in subjects with type 2 diabetes (T2D) at high risk of cardiovascular (CV) events (once-weekly subcutaneous semaglutide in SUSTAIN 6; once-daily oral semaglutide in PIONEER 6).[1,2]
- To better understand the CV effect of semaglutide in a broader range of subjects with T2D, including those at lower CV risk, we conducted a *post hoc* analysis of semaglutide and comparator (placebo, sitagliptin, exenatide extended release, insulin glargine, dulaglutide, liraglutide, and empagliflozin) data from all phase 3a SUSTAIN and PIONEER trials across the continuum of baseline CV risk characterizing a broad T2D population.

METHODS

- Data from 18 phase 3a trials of semaglutide (once-daily oral, once-weekly subcutaneous) vs active comparators or placebo in subjects with T2D were combined.[1–18] Time to first adjudication-confirmed MACE (defined as death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) was analyzed.[1,2]
- CV risk was quantified using a CV risk score model derived from the LEADER (liraglutide vs placebo) CVOT,[19] which used the definitions of adjudicated endpoints and baseline factors common to the LEADER, SUSTAIN, and PIONEER trials, and applied a Cox proportional hazards stepwise model procedure to select potential baseline predictors for time-to-first MACE.
- This CV risk score was included as a linear effect modifier for pooled treatment groups (semaglutide vs comparators) in a Cox proportional hazards model stratified by trial program and trial type.

RESULTS

- Baseline characteristics differed between CVOTs and glycemic efficacy trials, especially regarding CV medical history (Table 1).
- The LEADER-derived CV risk score predicted risk of first MACE in the semaglutide data well, both when data from the glycemic efficacy trials and CVOTs were pooled (area under the curve [AUC]: 0.77) and when they were analyzed separately (AUC: 0.68 and 0.74, respectively).
- Relative (Figure 1) and absolute (Figure 2) risk of MACE were lower with semaglutide vs comparators across CV risk scores; the interaction p-value between CV risk score and treatment effect was nonsignificant (p=0.06).
- The shape of the hazard ratio curve across baseline CV risk score for each MACE component was similar to that of the composite MACE endpoint (Figure 3).

CONCLUSIONS

- Semaglutide reduced the risk of MACE vs comparators across the continuum of CV risk characterizing a broad T2D population.
- These results will help physicians to understand the CV benefits of the glucagon-like peptide-1 analog semaglutide in subjects with T2D across a broad continuum of CV risk.

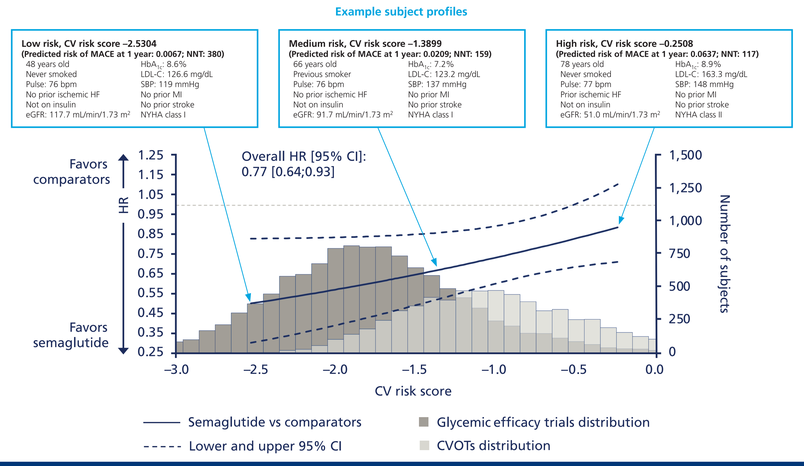
REFERENCES

(**1**) Marso et al. *N Engl J Med* 2016;375:1834–44; (**2**) Husain et al. *N Engl J Med* 2019;381:841–51; (**3**) Sorli et al. *Lancet Diabetes Endocrinol* 2017;5:251–60; (**4**) Ahrén et al. *Lancet Diabetes Endocrinol* 2017;5:341–54; (**5**) Ahmann et al. *Diabetes Care* 2018;41:258–66; (**6**) Aroda et al. *Lancet Diabetes Endocrinol* 2017;5:355–66; (**7**) Rodbard et al. *J Clin Endocrinol Metab* 2018;103:2291–301; (**8**) Kaku et al. *Diabetes Obes Metab* 2018;20:1202–12; (**9**) Seino et al. *Diabetes Obes Metab* 2018;20:378–88; (**10**) Aroda et al. *Diabetes Care* 2019;42:1724–32; (**11**) Rodbard et al. *Diabetes Care* 2019;42:2272–81; (**12**) Rosenstock et al. *JAMA* 2019;321:1466–80; (**13**) Pratley et al. *Lancet* 2019;394:39–50; (**14**) Mosenzon et al. *Lancet Diabetes Endocrinol* 2019;7:515–27; (**15**) Pieber et al. *Lancet Diabetes Endocrinol* 2019;7:528–39; (**16**) Zinman et al. *Diabetes Care* 2019;42:2262–71; (**17**) Yamada et al. Presented at The Asian Association for the Study of Diabetes, Shanghai, China, 23–25 May 2019; (**18**) Yabe et al. Presented at the Asian Association for the Study of Diabetes, Shanghai, China, 23–25 May 2019; (**19**) Marso et al. *N Engl J Med* 2016;375:311–22.

Semaglutide reduced the risk of MACE vs comparators across the continuum of CV risk characterizing a broad T2D population

FIGURE 1: RELATIVE RISK OF MACE

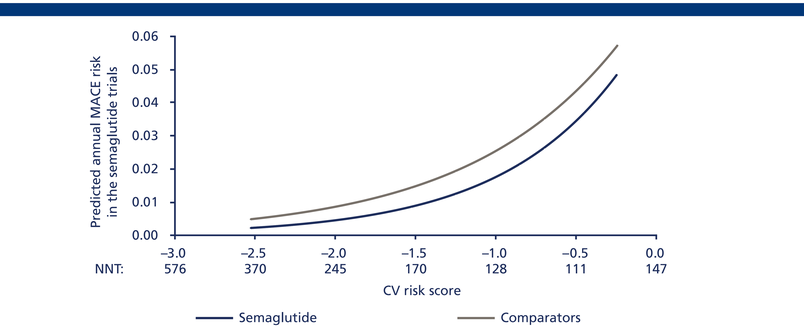
Lower relative risk of MACE with semaglutide vs comparators across the continuum of CV risk characterizing a broad T2D population



Hazard ratio for treatment effect (semaglutide vs comparator) and 95% CI estimated using a Cox proportional hazards model including effects of treatment, CV risk score, and interaction between both. The x-axis shows the CV risk score derived from subjects' baseline characteristics in the semaglutide trials. Dashed gray line represents a hazard ratio of 1.00. Underlying histograms: distribution of subjects in the glycemic efficacy trials or CVOTs across baseline CV risk scores (histogram data for 439 subjects not shown, as these subjects had a CV risk score of <–3.0 or >0.0). Real subject profile examples, chosen at the 5-, 50-, and 95-percentiles of risk-score distribution, show all the factors identified (using LEADER) to significantly affect CV risk. bpm, beats per minute; CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HF, heart failure; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction; NNT, number needed to treat to avoid one MACE during 1 year; NYHA, New York Heart Association; SBP, systolic blood pressure; T2D, type 2 diabetes

FIGURE 2: ABSOLUTE RISK OF MACE

Lower absolute risk of MACE with semaglutide vs comparators across the continuum of CV risk characterizing a broad T2D population



Absolute yearly MACE probabilities, estimated using a Cox proportional hazards model including effects of treatment, CV risk score, and interaction between both (with no stratification). The x-axis shows the CV risk score derived from subjects' baseline characteristics in the semaglutide trials. Data on graph cut off at the 5- and 95-percentile of whole dataset. *CV*, cardiovascular; MACE, major adverse cardiovascular events; NNT, number needed to treat to avoid one MACE during 1 year; T2D, type 2 diabetes

https://novoposters.com/acc2020/Semaglutide/husain/

- Poster summary slides
- Animated poster

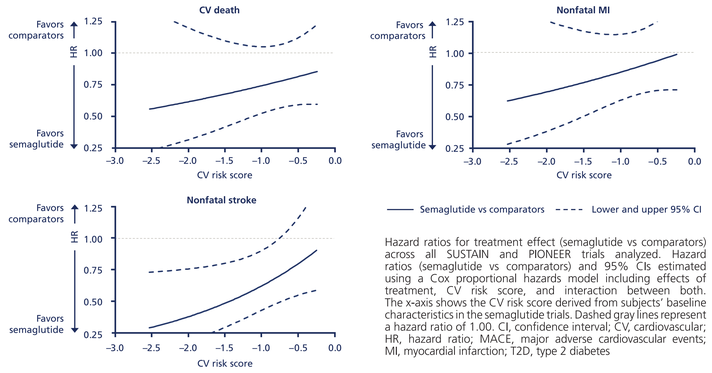
TABLE 1: BASELINE CHARACTERISTICS

	CVOTs*		Glycemic efficacy trials†	
	Semaglutide n=3,239	Placebo n=3,241	Semaglutide n=7,269	Comparator‡ n=3,896
CV risk score	–1.0 (0.6)	–0.9 (0.6)	–1.7 (0.6)	–1.7 (0.6)
Age, years	65.3 (7.2)	65.5 (7.4)	57.5 (10.4)	57.5 (10.6)
HbA_{1c}, %	8.4 (1.5)	8.4 (1.6)	8.2 (0.9)	8.2 (0.9)
Smoking status, n (%)				
Current smoker	388 (12.0)	367 (11.3)	1,254 (17.3)	667 (17.1)
Never smoked	1,473 (45.5)	1,457 (45.0)	3,946 (54.3)	2,153 (55.3)
Previous smoker	1,378 (42.5)	1,417 (43.7)	2,069 (28.5)	1,076 (27.6)
LDL-C, mg/dL	2.2 (0.9)	2.3 (0.9)	2.7 (0.9)	2.7 (0.9)
Pulse rate, bpm	71.6 (11.1)	71.5 (11.1)	74.2 (10.5)	74.3 (10.5)
SBP, mmHg	135.7 (17.5)	135.5 (17.2)	132.2 (14.7)	132.3 (15.1)
Heart failure, n (%)	564 (17.4)	586 (18.1)	349 (4.8)	212 (5.4)
NYHA Class I§	91 (2.8)	97 (3.0)	155 (2.1)	93 (2.4)
NYHA Class II	404 (12.5)	419 (12.9)	177 (2.4)	115 (3.0)
NYHA Class III	69 (2.1)	70 (2.2)	17 (0.2)	4 (0.1)
Prior ischemic heart disease, n (%)	1,403 (43.3)	1,430 (44.1)	850 (11.7)	491 (12.6)
Prior MI, n (%)	1,091 (33.7)	1,131 (34.9)	307 (4.2)	185 (4.7)
Prior stroke, n (%)	363 (11.2)	412 (12.7)	199 (2.7)	117 (3.0)
Insulin use, n (%)	1,740 (53.7)	1,722 (53.1)	869 (12.0)	374 (9.6)
eGFR,‖ mL/min/1.73 m²	75.0 (21.8)	75.1 (22.1)	94.8 (17.1)	94.3 (17.9)

Data are mean (standard deviation) unless otherwise stated. *SUSTAIN 6 and PIONEER 6. †SUSTAIN 1–5, SUSTAIN Japanese trials, PIONEER 1–5 and PIONEER 7–10. ‡Placebo, sitagliptin, exenatide extended release, insulin glargine, dulaglutide, liraglutide, and empagliflozin. §NYHA Class I was not measured in the PIONEER 6 trial. ‖eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration formula. bpm, beats per minute; CV, cardiovascular; CVOT, cardiovascular outcomes trial; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NYHA, New York Heart Association; SBP, systolic blood pressure

FIGURE 3: INDIVIDUAL MACE COMPONENTS

Lower relative risk of each MACE component with semaglutide vs comparators across the continuum of CV risk characterizing a broad T2D population



Hazard ratios for treatment effect (semaglutide vs comparators) across all SUSTAIN and PIONEER trials analyzed. Hazard ratios (semaglutide vs comparators) and 95% CIs estimated using a Cox proportional hazards model including effects of treatment, CV risk score, and interaction between both. The x-axis shows the CV risk score derived from subjects' baseline characteristics in the semaglutide trials. Dashed gray lines represent a hazard ratio of 1.00. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; T2D, type 2 diabetes

ACKNOWLEDGMENTS AND DISCLOSURES

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