SUPPLEMENTAL MATERIAL

Definition of High CVD Risk in SUSTAIN 6 and PIONEER 6

Age 50 years or older with documented clinical evidence of cardiovascular disease (established cardiovascular disease), defined as meeting at least one of the below criteria.

- Prior myocardial infarction.
- Prior stroke or prior transient ischemic attack.
- Prior coronary, carotid or peripheral arterial revascularization.
- More than 50% stenosis on angiography or imaging of coronary, carotid or lower extremity arteries.
- History of symptomatic coronary heart disease, e.g. documented by positive exercise stress test or any cardiac imaging, or unstable angina with electrocardiogram changes.
- Asymptomatic cardiac ischemia documented by a positive nuclear imaging test, exercise test, stress echo or any cardiac imaging.
- Chronic heart failure New York Heart Association class II–III.
- Chronic renal impairment (SUSTAIN 6: estimated glomerular filtration rate [eGFR] below 60 mL/min/1.73 m^2 per Modification of Diet in Renal Disease; PIONEER 6: eGFR 30–59 mL/min/1.73 m^2 [eGFR was estimated using the CKD-Epidemiology Collaboration Creatinine equation in SUSTAIN 6 and PIONEER 6]).

Age 60 years or older with subclinical evidence of cardiovascular disease (cardiovascular risk factors), defined as meeting at least one of the below criteria.

- Persistent microalbuminuria (30–299 mg/g) or proteinuria.
- Hypertension and left ventricular hypertrophy by electrocardiogram or imaging.
- Left ventricular systolic or diastolic dysfunction by imaging.

- Ankle/brachial index less than 0.9.

Supplementary tables

Supplementary Table 1. Characteristics and CVD outcomes in patients stratified according to quartile of life-years free of new/recurrent CVD events gained with the addition of semaglutide to SoC

	Life-years free of new/recurrent CVD events gained with the addition of semaglutide to SoC			
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**
N	1,620	1,620	1,620	1,620
Age, years	70.8 (7.0)	70.5 (4.2)	64.0 (4.2)	58.2 (4.3)
Sex, female, *n* (%)	627 (38.7)	410 (25.3)	429 (26.5)	836 (51.6)
Diabetes duration, years	16.2 (9.1)	16.5 (8.5)	13.4 (7.5)	11.3 (7.0)
Current smoker, *n* (%)	136 (8.4)	183 (11.3)	276 (17.0)	160 (9.9)
BMI, kg/m^2	32.1 (6.7)	32.5 (6.5)	32.5 (6.2)	33.1 (6.0)
HbA_{1c}, mmol/mol	68 (15)	67 (16)	69 (18)	71 (19)
HbA_{1c}, %	8.4 (1.4)	8.3 (1.5)	8.5 (1.6)	8.6 (1.7)
SBP, mmHg	138 (18.9)	136.8 (17.5)	134.3 (16.8)	133.3 (15.8)
DBP, mmHg	75.8 (10.1)	75.2 (10.3)	76.6 (9.9)	78.7 (9.5)
Total cholesterol, mmol/L, geometric mean (CoV)	4.22 (24.37)	4.02 (26.94)	3.99 (27.68)	4.31 (29.41)
LDL-C, mmol/L	2.32 (0.86)	2.17 (0.90)	2.14 (0.88)	2.38 (1.01)
Non-HDL-C, mmol/L	3.17 (1.03)	3.04 (1.07)	3.04 (1.09)	3.34 (1.27)
Triglycerides, mmol/L	1.92 (1.11)	2.00 (1.43)	2.07 (1.63)	2.27 (1.97)
eGFR, mL/min/1.73 m^{2*}	71.1 (22.6)	63.8 (19.9)	77 (20.2)	88.3 (17.1)
10-year CVD risk with SoC	24.3	49.3	34.5	25.1
10-year CVD risk with the addition of semaglutide to SoC	20.8	40.8	27.7	19.9

Absolute risk reduction in 10-year CVD risk with the addition of semaglutide to SoC	3.5	8.6	6.8	5.3
Expected number of life-years free of new/recurrent CVD events from current age with SoC	12.9	8.2	13.1	18.3
Expected number of life-years free of new/recurrent CVD events from current age with the addition of semaglutide to SoC	13.3	9.7	15.1	21.1
Life-years free of new/recurrent CVD events gained with the addition of semaglutide to SoC	0.4	1.5	2.1	2.8

*Estimated using the CKD-EPI Creatinine equation.

Data presented are mean (SD) unless otherwise specified.

CKD, chronic kidney disease; CoV, coefficient of variance; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EPI, Epidemiology Collaboration; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation; SoC, standard of care.

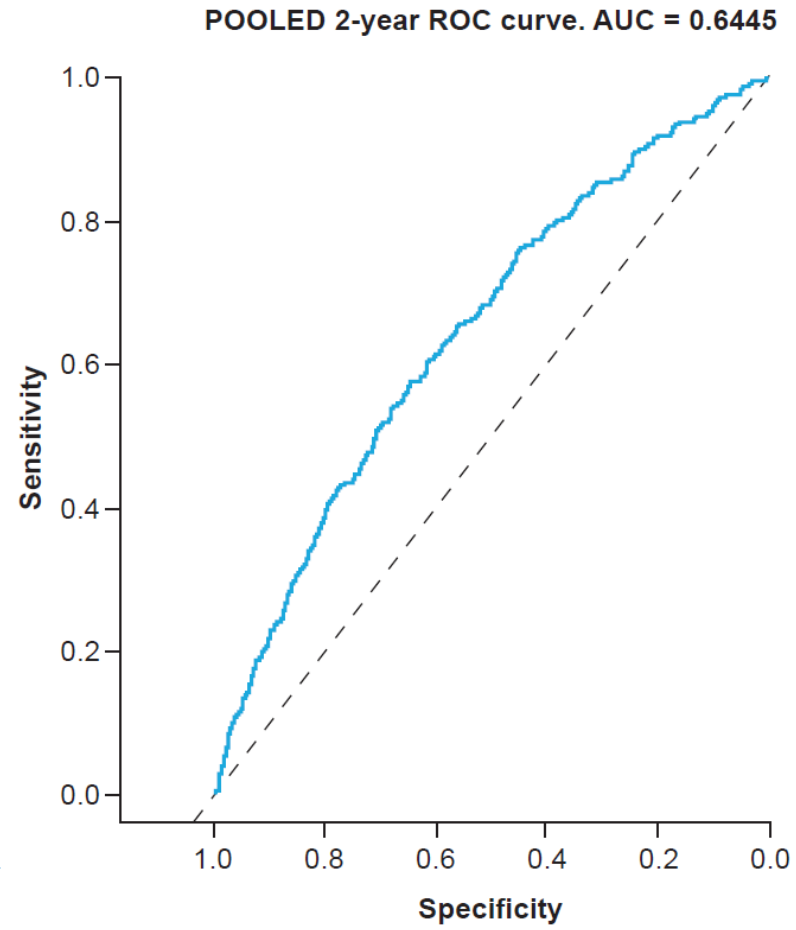
Supplementary Table 2. Assumptions used in the DIAL model

Assumption	Explanation
Lifetime prediction	
Proportional hazards	The model assumes proportional hazards for all predictors, meaning that hazard ratios are assumed to be constant over time. Since age is used as time scale, the assumption is made that hazard ratios are constant over age (e.g., the hazard ratio for male sex at age 50 years is the same as at age 80 years). The proportional hazards assumption is tested using Schoenfeld residuals, and visual inspection of hazard ratios plotted against age. If a hazard ratio for a predictor significantly changes with age, an interaction term between this predictor and age is included in the model
Linearity of the predictor-outcome relation	The model assumes a linear relationship between continuous predictors and the outcome. For all continuous predictors in relation to the outcome, it is assessed whether a logarithmic or quadratic transformation of the predictor substantially improves model fit. If the AIC decreases by ≥ 2 points, the transformation is included in the final model
Natural course of predictors	The model assumes that predictors follow a natural course over time (i.e., age) that matches the course of predictors in the derivation cohort. Model predictions are based on the current predictor levels of a patient. Predictor levels might change with age (e.g., a decrease in eGFR), but this happened during the follow-up period in the derivation cohort as well. As long as the change in predictor levels follows the same course over time as in the derivation cohort and the derivation cohort has substantial follow-up time, no adjustment is needed. However, for lifetime predictions, follow-up time is not sufficient, and these results should be interpreted with caution, especially in younger patients
Stationarity of baseline hazards	The model assumes that the baseline survival for each age interval is equal for all patients, during that interval. It assumes that the baseline survival for an age

	interval (e.g., between 60 years and 61 years) is equal for patients currently within that interval (i.e., patients who just turned 60 years old) as well as patients entering that interval in the future (e.g., 50-year old patients who will turn 60 in 10 years). It is assumed that the baseline survivals are stationary over time (i.e., baseline survival for a 60-year old patient now is equal to baseline survival for a 60-year old patient in the future)
Treatment effects	
Equal relative treatment effect	It is assumed that relative treatment effects (i.e., the hazard ratios derived from meta-analyses) are equal for all patients for whom a treatment is recommended. This assumption is made since subgroup analyses from trials and meta-analyses mostly have not identified significant differences in relative treatment effects between eligible patients with varying characteristics. Also, subgroup analyses are underpowered for the detection of heterogeneity in relative treatment effects
Constant treatment effect over time	It is assumed that the relative treatment effects remain constant over time, so that therapy benefits continue to accrue over lifetime exposure. In other words, it is assumed that the hazard ratios found in actual trials or meta-analyses are equal to hazard ratios that would have been found in trials with lifelong follow-up
Additive benefits	It is assumed that benefits of individual therapies are additive when used simultaneously
Adequate adherence	It is assumed that patients remain adherent to the prescribed therapies for their remaining lifetimes
No effect on non-CV mortality	It is assumed that semaglutide has no effect on non-CV mortality

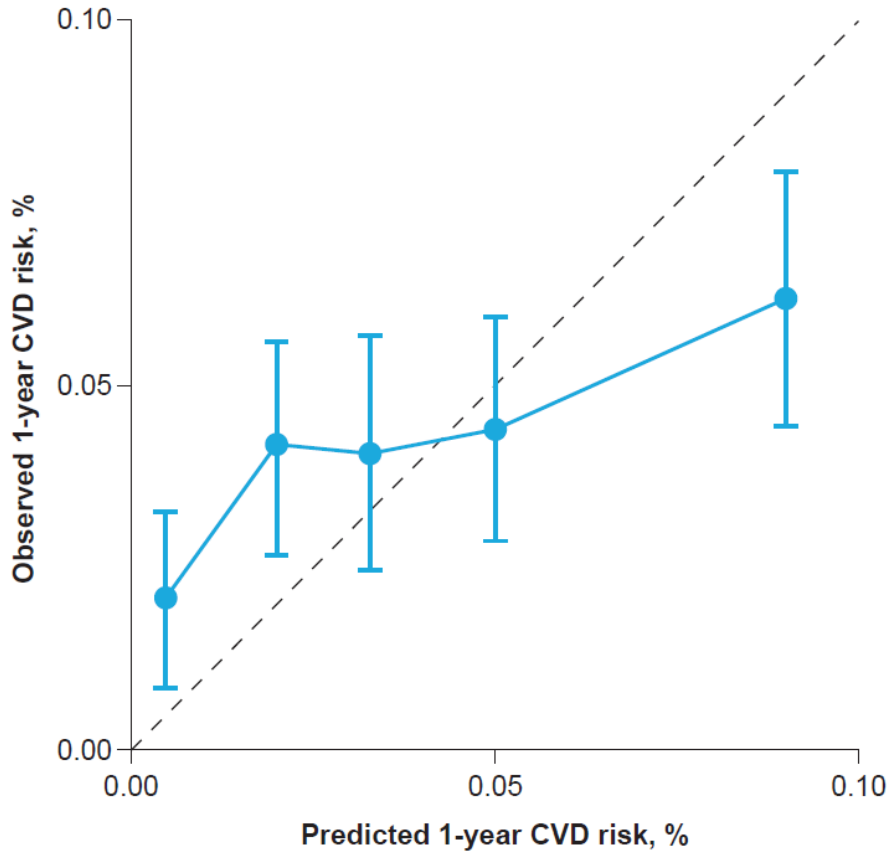
AIC, Akaike Information Criterion; CV, cardiovascular; eGFR, estimated glomerular filtration rate.

Supplementary figures



Supplementary Figure 1. Observed versus predicted 2-year risk in a repeater operator curve.

AUC, area under the curve; ROC, repeater operator curve.



Supplementary Figure 2. Observed versus predicted 1-year risk of CVD (DIAL model) in the POOLED cohort.

Observed versus predicted 1-year risk of CVD from the DIAL model in quintiles of risk in the POOLED cohort.

CVD, cardiovascular disease; DIAL, Diabetes Lifetime-perspective prediction.