Potential kidney protection with liraglutide and semaglutide – exploratory mediation analysis

Johannes F. E. Mann, MD; John B. Buse, MD; Thomas Idorn, MD; Lawrence A. Leiter, MD; Richard E. Pratley, MD; Søren Rasmussen, PhD; Tina Vilsbøll, MD; Benjamin Wolthers MD; Vlado Perkovic, MD

Corresponding author: Johannes F.E. Mann, MD.
KfH Kidney Centre, 15, Isoldenstrasse, München, 80804, Germany. Email: *prof.j.mann@gmail.com*

Supplementary appendix

Supplementary table S1: Demographics and baseline characteristics of patients in LEADER and SUSTAIN 6

	LEADER		SUSTAIN 6	
	Liraglutide (n=4,668)	Placebo (n=4,672)	Semaglutide (n=1,648)	Placebo (n=1,649)
Age, years	64.2 (7.2)	64.4 (7.2)	64.7 (7.2)	64.6 (7.5)
Female, %	35.5	36.0	38.5	40.0
HbA$_{1c}$, % [mmol/mol]	8.7 (1.6) [72]	8.7 (1.5) [72]	8.7 (1.5) [72]	8.7 (1.5) [72]
Systolic blood pressure, mmHg	135.9 (17.8)	135.9 (17.7)	136.0 (17.5)	135.3 (16.82)
Diastolic blood pressure, mmHg	77.2 (10.3)	77.0 (10.1)	77.0 (10.0)	77.1 (10.4)
Heart rate, beats/min	72.7 (11.3)	72.5 (11.4)	72.1 (11.1)	72.0 (10.8)
LDL cholesterol, mmol/L	2.3 (0.9)	2.3 (0.9)	2.3 (1.0)	2.33 (1.0)
HDL cholesterol, mmol/L	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.8 (0.3)
Body weight, kg	91.9 (21.2)	91.6 (20.8)	92.3 (20.7)	91.7 (20.6)
BMI, kg/m^2	32.5 (6.3)	32.5 (6.3)	32.8 (6.3)	32.8 (6.2)
eGFR, mL/min/1.73m^2	80.2 (27.5)	80.6 (27.2)	75.9 (25.9)	76.4 (27.2)
Normal kidney function or mild impairment (≥60 mL/min/1.73m^2), %	76.1	77.7	71.5	71.5
Moderate to severe kidney impairment (<60 mL/min/1.73m^2), %	23.9	22.3	28.5	28.5
Albuminuria status				
Microalbuminuria (UACR 30–300 mg/g), n (%)	1,223 (26.2)	1,233 (26.4)	472 (29.2)	412 (25.4)
Macroalbuminuria (UACR >300 mg/g), n (%)	461 (9.9)	505 (10.8)	196 (12.1)	224 (13.8)
History of cardiovascular disease				
Myocardial infarction	1,434 (30.7)	1,373 (29.4)	530 (32.2)	542 (32.9)
Stroke	512 (11.0)	526 (11.3)	178 (10.8)	205 (12.4)
Revascularization	142 (3.0)	153 (3.3)	58 (3.5)	54 (3.3)
>50% artery stenosis	1,187 (25.4)	1,191 (25.5)	567 (34.4)	600 (36.4)
Heart failure NYHA II–III	653 (14.0)	652 (14.0)	285 (17.3)	289 (17.5)
Duration of diabetes, years	12.8 (8)	12.9 (8.1)	14.2 (8.2)	13.6 (8.0)
Insulin-naïve, %	56.3	54.4	52.5	53.4
Current or previous smoker, %	58.2	59	54.3	55.1

Data are mean (SD) unless otherwise stated.
BMI, body mass index; eGFR, estimated glomerular filteration rate; HbA$_{1c}$, glycated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; NYHA, New York Heart Association; SD, standard deviation; UACR, urinary albumin-to-creatinine ratio.

Supplementary table S2: Vansteelandt modelling for mediation of time to first kidney outcome with liraglutide versus placebo for additional mediators in LEADER

Variable	Estimated probability of no event at 36 months				
	Liraglutide	**Placebo**	**Total treatment effect liraglutide – placebo (95% CI)**	**Direct treatment effect liraglutide – placebo (95% CI)**	**Percentage mediation, % (95% CI)**
Diastolic blood pressure	0.958	0.940	0.018 (0.009; 0.027)	0.018 (0.009, 0.027)	None* −0.4 (−4.0; 3.2)
Haemoglobin	0.958	0.940	0.018 (0.009; 0.028)	0.017 (0.008, 0.027)	4.2 (1.2; 11.6)
Heart rate	0.958	0.940	0.018 (0.009; 0.027)	0.020 (0.010, 0.029)	None* −10.2 (−30.7; 2.7)
LDL cholesterol	0.958	0.940	0.018 (0.009; 0.028)	0.018 (0.009, 0.028)	None* −0.1 (−1.6; 1.1)
Total cholesterol	0.958	0.940	0.018 (0.009; 0.027)	0.018 (0.009, 0.028)	None* −0.6 (−6.6; 1.4)
White blood cell count	0.958	0.940	0.018 (0.008; 0.027)	0.018 (0.009, 0.027)	0.1 (−6.3; 0.5)

95% CI calculated using bootstrap (N=1,000).
*A negative percentage of mediation is a numerical result from the analysis, and it is interpreted as no mediation.
CI, confidence interval; LDL, low-density lipoprotein.

Supplementary table S3: Vansteelandt modelling for mediation of time to first kidney outcome with semaglutide versus placebo for additional mediators in SUSTAIN 6

Variable	Estimated probability of no event at 24 months				Percentage mediation, %
	Semaglutide	Placebo	Total treatment effect semaglutide – placebo	Direct treatment effect semaglutide – placebo	
Diastolic blood pressure	0.966	0.939	0.027	0.025	6.8
Haemoglobin	0.963	0.938	0.025	0.022	11.4
Heart rate	0.964	0.940	0.024	0.026	None* (–8.1)
LDL cholesterol	0.966	0.939	0.027	0.024	11.1
Total cholesterol	0.965	0.938	0.026	0.024	9.1
White blood cell count	0.946	0.937	0.027	0.026	1.9

*A negative percentage of mediation is a numerical result from the analysis, and it is interpreted as no mediation.
LDL, low-density lipoprotein.