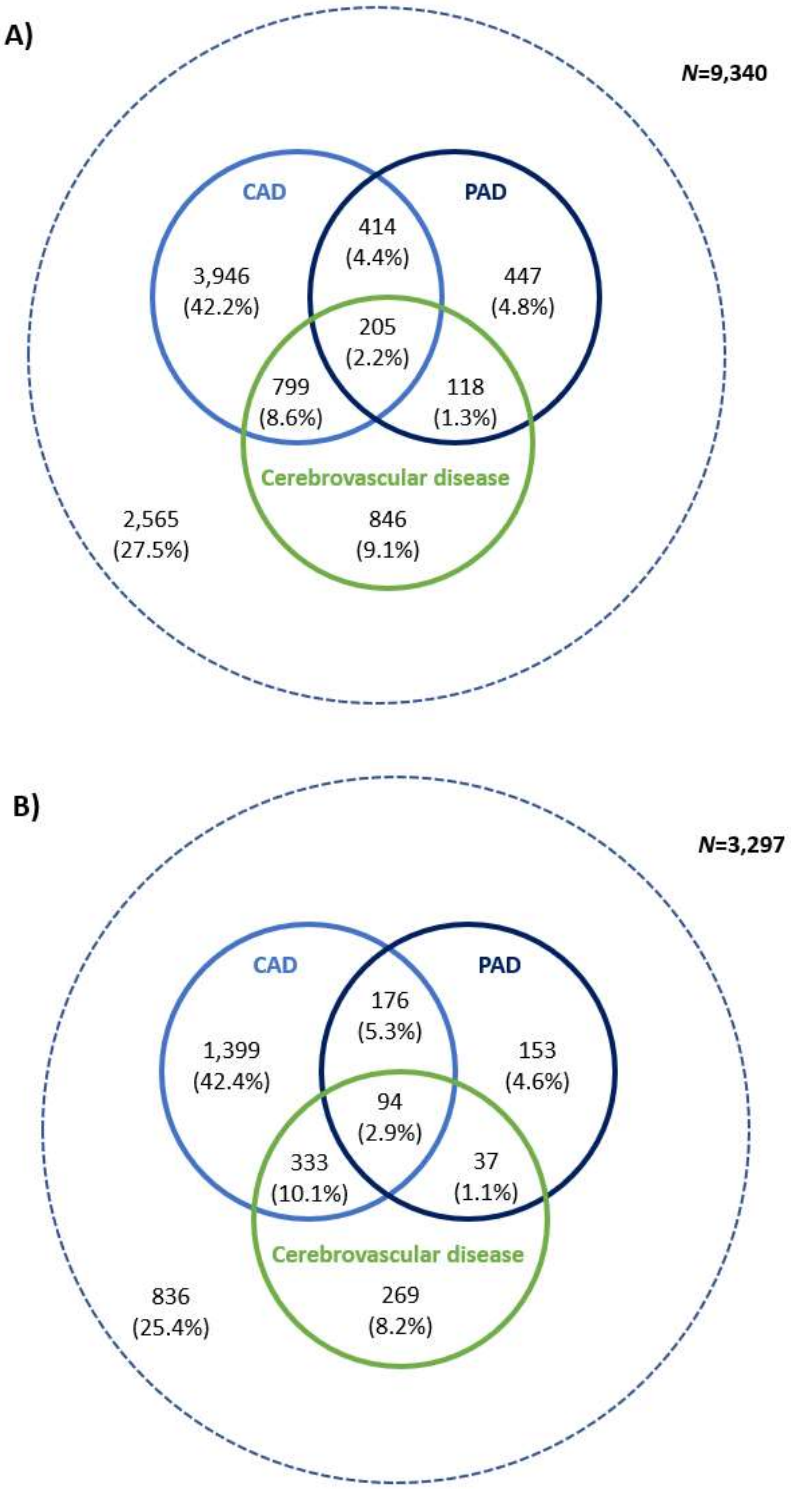
Cardiovascular efficacy of liraglutide and semaglutide in individuals with diabetes and peripheral artery disease

Subodh Verma, Mohammed Al-Omran, Lawrence A. Leiter, C. David Mazer, Søren Rasmussen, Hans A. Saevereid, Maria Sejersten Ripa, Marc P. Bonaca

SUPPLEMENTARY MATERIAL

Supplementary Figure S1: Venn diagram of number (%) of patients according to PAD, CAD and cerebrovascular disease. A) LEADER; B) SUSTAIN 6.



CAD, coronary artery disease; *N,* number of patients; PAD, peripheral artery disease.

Supplementary Table S1: Demographics and baseline characteristics of LEADER trial participants by history of PAD.

	PAD at baseline (*N*=1184)	No PAD at baseline (*N*=8156)
Age (years), mean (SD)	65.4 (7.4)	64.1 (7.2)
Sex, female	439 (37.1)	2898 (35.5)
HbA1c, %, mean (SD)	8.7 (1.5)	8.7 (1.5)
Duration of diabetes, years, mean (SD)	14.0 (8.4)	12.6 (7.9)
Weight, kg, mean (SD)	88.2 (19.4)	92.3 (21.2)
Body mass index, kg/m^2, mean (SD)	31.4 (5.5)	32.7 (6.4)
Systolic blood pressure, mmHg, mean (SD)	136.5 (18.1)	135.8 (17.7)
Diastolic blood pressure, mmHg, mean (SD)	75.9 (10.1)	77.3 (10.2)
LDL-C, mmol/L, mean (SD)	2.4 (1.0)	2.3 (0.9)
HDL-C, mmol/L, mean (SD)	1.2 (0.3)	1.2 (0.3)
Current or previous smoker	776 (65.5)	4694 (57.6)
Renal impairment		
Normal	403 (34.0)	2872 (35.2)
Mild	469 (39.6)	3438 (42.2)
Moderate or severe	312 (26.4)	1846 (22.6)
eGFR, mL/min/1.73m^2, mean (SD)	78.7 (27.0)	80.6 (27.4)
History of hypertension	1075 (90.8)	7436 (91.2)
History of arrhythmia	211 (17.8)	1228 (15.1)
History of ischemic stroke	132 (11.1)	906 (11.1)
History of myocardial infarction	311 (26.3)	2496 (30.6)
History of heart failure, NYHA class II–III	197 (16.6)	1108 (13.6)
Prior CABG	212 (17.9)	1319 (16.2)
History of PCI	286 (24.2)	2282 (28.0)
PAD history		
PAD diagnosed by:		
Ankle-brachial index <0.9	488 (41.2)	—
Ultrasonography	345 (29.1)	—
Angiography	309 (26.1)	—
PAD severity		
Claudication	649 (54.8)	—
>50% stenosis of the peripheral	284 (24.0)	—
arteries	295 (24.9)	—
Prior revascularization		
Medications at baseline		
Insulin	578 (48.8)	3591 (44.0)
Statins or other lipid-lowering therapy	859 (72.6)	6220 (76.3)
Antiplatelet agents	808 (68.2)	5518 (67.7)
Antithrombotic medication	90 (7.6)	533 (6.5)
Antihypertensive therapy	1061 (89.6)	7570 (92.8)

Data are *N* (%), unless otherwise stated. Data for cardiovascular history and complications are from the screening visit. Renal impairment and eGFR data are based on eGFR calculated using the Modification of Diet in Renal Disease equation.

CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; *N*, number of patients; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SD, standard deviation.

Supplementary Table S2: Demographics and baseline characteristics of SUSTAIN 6 participants by history of PAD.

	PAD at baseline (*N*=460)	No PAD at baseline (*N*=2837)
Age (years), mean (SD)	65.8 (7.2)	64.5 (7.4)
Sex, female	156 (33.9)	1139 (40.1)
HbA1c, %, mean (SD)	8.7 (1.5)	8.7 (1.5)
Duration of diabetes, years, mean (SD)	15.3 (8.4)	13.7 (8.0)
Weight, kg, mean (SD)	90.6 (19.3)	92.3 (20.8)
Body mass index, kg/m^2, mean (SD)	32.1 (5.7)	32.9 (6.3)
Systolic blood pressure, mmHg, mean (SD)	136.9 (17.1)	135.4 (17.1)
Diastolic blood pressure, mmHg , mean (SD)	76.3 (9.9)	77.2 (10.0)
LDL-C, mmol/L, mean (SD)	2.3 (1.0)	2.3 (1.0)
HDL-C, mmol/L, mean (SD)	1.2 (0.3)	1.2 (0.3)
Current or previous smoker	301 (65.4)	1502 (52.9)
Renal impairment		
Normal	128 (27.8)	862 (30.4)
Mild	200 (43.5)	1168 (41.2)
Moderate or severe	130 (28.3)	797 (28.1)
eGFR, mL/min/1.73m^2, mean (SD)	76.3 (25.6)	76.1 (26.7)
History of hypertension	427 (92.8)	2632 (92.8)
History of ischemic stroke	50 (10.9)	333 (11.7)
History of myocardial infarction	141 (30.7)	931 (32.8)
History of heart failure, NYHA class II–III	93 (20.2)	481 (17.0)
Prior CABG	97 (21.1)	480 (16.9)
History of PCI	131 (28.5)	881 (31.1)
PAD history		
PAD diagnosed by:		
Ankle-brachial index <0.9	132 (28.7)	—
Ultrasonography	190 (41.3)	—
Angiography	122 (26.5)	—

PAD severity		
Claudication	254 (55.2)	—
>50% stenosis of the peripheral arteries	150 (32.6)	—
Prior revascularization	112 (24.3)	—
Medications at baseline		
Insulin	231 (50.2)	1320 (46.5)
Statins or other lipid-lowering therapy	355 (77.2)	2166 (76.3)
Antiplatelet agents	368 (80.0)	2041 (71.9)
Antithrombotic medication	35 (7.6)	160 (5.6)
Antihypertensive therapy	426 (92.6)	2656 (93.6)

Data are *N* (%), unless otherwise stated. Data for cardiovascular history and complications are from the screening visit. Renal impairment and eGFR data are based on eGFR calculated using the Modification of Diet in Renal Disease equation.

CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; *N*, number of patients; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SD, standard deviation.

Supplementary Table S3: Risk of CV events and mortality by history of PAD at baseline and randomized treatment group, adjusted for baseline variables.

	LEADER HRs; liraglutide versus placebo			**SUSTAIN 6 HRs; semaglutide versus placebo**		
Endpoint	PAD at baseline	No PAD at baseline	$P_{interaction}$	PAD at baseline	No PAD at baseline	$P_{interaction}$
MACE	0.76 [0.58–1.00]	0.89 [0.79–1.00]	0.30	0.59 [0.32–1.09]	0.76 [0.58–0.99]	0.47
Nonfatal MI	0.53 [0.34–0.84]	0.95 [0.80–1.13]	0.02	0.86 [0.37–1.99]	0.71 [0.47–1.09]	0.70
Nonfatal stroke	1.06 [0.61–1.85]	0.87 [0.69–1.10]	0.51	—	—	—
CV death	0.91 [0.61–1.35]	0.75 [0.61–0.91]	0.40	—	—	—
Expanded MACE	0.84 [0.67–1.05]	0.88 [0.80–0.97]	0.67	0.54 [0.35–0.82]	0.80 [0.65–0.98]	0.10
All-cause death	0.93 [0.67–1.29]	0.82 [0.71–0.96]	0.50	—	—	—

Data are HR [95% CI] for GLP-1 analog versus placebo, unless otherwise stated. Some adjusted data are not shown because of convergence issues arising due to few events.

CI, confidence interval; CV, cardiovascular; GLP-1, glucagon-like peptide-1; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; PAD, peripheral artery disease.

Supplementary Table S4: Changes from baseline in HbA1c, blood pressure and body weight in LEADER trial participants by history of PAD and randomized treatment group.

	PAD at baseline (*N*=1184)			No PAD at baseline (*N*=8156)			$P_{interaction}$
	Liraglutide (*N*=573)	Placebo (*N*=611)	Estimated treatment contrast [95% CI]	Liraglutide (*N*=4095)	Placebo (*N*=4061)	Estimated treatment contrast [95% CI]	
HbA1c, %	−1.05	−0.71	−0.34 [−0.51; −0.18]	−1.18	−0.77	−0.40 [−0.46; −0.34]	0.51
Systolic blood pressure, mmHg	−0.88	−0.46	−0.42 [−2.46; 1.62]	−1.52	−0.21	−1.31 [−2.07; −0.54]	0.43
Diastolic blood pressure, mmHg	−1.52	−2.04	0.52 [−0.62; 1.66]	−0.69	−1.28	0.59 [0.16; 1.02]	0.92
Body weight, kg	−2.44	−0.71	−1.74 [−2.52; −0.96]	−2.78	−0.44	−2.34 [−2.63; −2.05]	0.16

Data are estimated means for changes from baseline to the 3-year visit, unless otherwise stated.

CI, confidence interval; HbA1c, glycated hemoglobin; *N*, number of patients; PAD, peripheral artery disease.

Supplementary Table S5: Changes from baseline in HbA1c, blood pressure and body weight in SUSTAIN 6 trial participants by history of PAD and randomized treatment group.

	PAD at baseline (*N*=460)			No PAD at baseline (*N*=2837)			$P_{interaction}$
	Semaglutide (*N*=230)	Placebo (*N*=230)	Estimated treatment contrast [95% CI]	Semaglutide (*N*=1418)	Placebo (*N*=1419)	Estimated treatment contrast [95% CI]	
HbA1c, %	−1.27	−0.19	−1.08 [−1.32; −0.84]	−1.25	−0.44	−0.81 [−0.91;−0.72]	0.047
Systolic blood pressure, mmHg	−2.80	−2.41	−0.39 [−2.99; 2.22]	−4.67	−2.49	−2.18 [−3.23; −1.13]	0.21
Diastolic blood pressure, mmHg	−1.92	−1.66	−0.26 [−1.76; 1.25]	−1.40	−1.56	0.17 [−0.44; 0.77]	0.61
Body weight, kg	−4.81	−0.96	−3.85 [−4.91; −2.79]	−4.13	−0.56	−3.57 [−4.00; −3.14]	0.63

Data are estimated means for changes from baseline to the 2-year visit, unless otherwise stated.

CI, confidence interval; HbA1c, glycated hemoglobin; *N*, number of patients; PAD, peripheral artery disease.

Supplementary Table S6: Serious adverse events and non-serious medical events of special interest in LEADER trial participants by history of PAD.

	PAD at baseline			No PAD at baseline		
	Liraglutide (*N*=573)	Placebo (*N*=611)	Total (*N*=1184)	Liraglutide (*N*=4095)	Placebo (*N*=4061)	Total (*N*=8156)
Person-years of observation	2137	2267	4404	15685	15474	31159
Events	396 (69.1)	403 (66.0)	799 (67.5)	2513 (61.4)	2436 (60.0)	4949 (60.7)
Serious adverse events	324 (56.5)	347 (56.8)	671 (56.7)	1996 (48.7)	2007 (49.4)	4003 (49.1)
Medical events of special interest	333 (58.1)	346 (56.6)	679 (57.3)	2045 (49.9)	1967 (48.4)	4012 (49.2)
Severity						
Severe	226 (39.4)	244 (39.9)	470 (39.7)	1276 (31.2)	1289 (31.7)	2565 (31.4)
Moderate	245 (42.8)	257 (42.1)	502 (42.4)	1544 (37.7)	1430 (35.2)	2974 (36.5)
Mild	176 (30.7)	172 (28.2)	348 (29.4)	1059 (25.9)	1030 (25.4)	2089 (25.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	3 (<0.1)	3 (<0.1)	6 (<0.1)

Data are *N* (%), unless otherwise stated. A serious adverse event was defined as an incident at any dose resulting in: death; a life-threatening experience; in-patient hospitalization or prolongation of existing hospitalization; a perisistent or significant disability or incapacity; or a congential anomaly or birth defect. Important medical events that did not result in death, were not life-threatening, or did not require hospitalization could be considered a serious adverse events when there was appropriate medical judgement that they could jeopardize the patient and could require medical or surgical intervention to prevent one of the outcomes listed in the definition. Predefined medical events of special interest included: acute coronary syndrome; cerebrovascular events; heart failure;

revascularization procedures; nephropathy (defined as new onset of macroalbuminuria or doubling of serum creatinine level and creatinine clearance per MDRD ≤45 mL/min/1.73m^2 or the need for continuous renal-replacement therapy [in the absence of an acute reversible cause] or death due to renal disease); diabetic foot ulcers; diabetic retinopathy (defined as the need for retinal photocoagulation or vitreous hemorrhage or diabetes-related blindness); neoplasms; pancreatitis or acute, severe and persistent abdominal pain leading to a suspicion of pancreatitis; acute gallstone disease; first confirmed episodes of calcitonin concentration increase ≥20 ng/L; thyroid disease; severe hypoglycemic events; immunogenicity events; adverse events leading to treatment discontinuation; medication errors; and suspected transmission of an infectious agent via a trial product.

MDRD, Modification of Diet in Renal Disease Study equation; *N,* number of patients; PAD, peripheral artery disease.

Supplementary Table S7: Serious adverse events and non-serious medical events of special interest in SUSTAIN 6 trial participants by history of PAD.

	PAD at baseline			No PAD at baseline		
	Semaglutide (*N*=230)	Placebo (*N*=230)	Total (*N*=460)	Semaglutide (*N*=1418)	Placebo (*N*=1419)	Total (*N*=2837)
Person-years of observation	1381	1380	2761	3369	2486	5855
Events	112 (48.7)	117 (50.9)	229 (49.8)	616 (43.4)	592 (41.7)	1208 (42.6)
Serious adverse events	71 (30.9)	85 (37.0)	156 (33.9)	379 (26.7)	435 (30.7)	814 (28.7)
Medical events of special interest	97 (42.2)	105 (45.7)	202 (43.9)	511 (36.0)	479 (33.8)	990 (34.9)
Severity						
Severe	48 (20.9)	53 (23.0)	101 (22.0)	209 (14.7)	213 (15.0)	422 (14.9)
Moderate	55 (23.9)	69 (30.0)	124 (27.0)	343 (24.2)	337 (23.7)	680 (24.0)
Mild	49 (21.3)	52 (22.6)	101 (22.0)	273 (19.3)	254 (17.9)	527 (18.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data are *N* (%), unless otherwise stated. A serious adverse event was defined as an incident at any dose resulting in: death; a life-threatening experience; in-patient hospitalization or prolongation of existing hospitalization; a perisistent or significant disability or incapacity; or a congential anomaly or birth defect. Important medical events that did not result in death, were not life-threatening, or did not require hospitalization could be considered a serious adverse events when there was appropriate medical judgement that they could jeopardize the patient and could require medical or surgical intervention to prevent one of the outcomes listed in the definition. Predefined medical events of special interest included: neoplasms; pancreatitis or clinical suspicion of pancreatitis; acute gallstone

disease; thyroid disease; cardiac arrhythmia; acute renal failure; severe hypoglycemic episodes; immunogenicity events; medication errors concerning trial products; suspected transmission of an infectious agent via a trial product; adverse events leading to treatment discontinuation; fatal events; acute coronary syndrome; cerebrovascular events; coronary revascularization procedures; peripheral arterial revascularization procedures, heart failure requiring hospital admission; nephropathy (defined as new onset of persistent macroalbuminuria [>300 mg/g/24 hours], or persistent doubling of serum creatinine level and creatinine clearance per MDRD ≤45 mL/min/1.73m^2, or the need for continuous renal-replacement therapy [in the absence of an acute reversible cause], or death due to renal disease); and diabetic retinopathy (defined as the need for retinal photocoagulation, or treatment with intravitreal agents, or vitreous hemorrhage, or diabetes-related blindness).

MDRD, Modification of Diet in Renal Disease Study equation; *N*, number of patients; PAD, peripheral artery disease.