The importance of addressing multiple risk markers in type 2 diabetes: results from the LEADER and SUSTAIN 6 trials

Emilie H. Zobel, Bernt Johan von Scholten, Tine W. Hansen, Frederik Persson, Søren Rasmussen, Benjamin Wolthers, Peter Rossing

SUPPLEMENTARY MATERIAL

Table S1: Baseline characteristics of the participants from the LEADER trial by risk marker improvement subgroups

Baseline	**G0**	**G1**	**G2**	**G3**	**G4**	**Total**
Number of patients, n (%)[†]	802 (100)	2408 (100)	2656 (100)	1844 (100)	928 (100)	8638 (100)
Treated with liraglutide, n (%)	265 (33.0)	958 (39.8)	1321 (49.7)	1120 (60.7)	672 (72.4)	4336 (50.2)
Placebo, n (%)	537 (67.0)	1450 (60.2)	1335 (50.3)	724 (39.3)	256 (27.6)	4302 (49.8)
Age, years	64.0 ± 7.4	64.3 ± 7.0	64.1 ± 7.2	64.4 ± 7.2	64.4 ± 7.3	64.2 ± 7.2
Female, n (%)	241 (30.0)	780 (32.4)	945 (35.6)	718 (38.9)	393 (42.3)	3,077 (35.6)
HbA_{1c}, %	8.1 ± 1.1	8.5 ± 1.4	8.9 ± 1.5	8.9 ± 1.5	8.8 ± 1.4	8.7 ± 1.5
HbA_{1c}, mmol/mol	65.5 ± 12.4	69.4 ± 15.6	73.2 ± 16.9	73.2 ± 16.9	72.9 ± 15.8	71.2 ± 16.4
Body weight, kg	90.8 ± 20.8	91.5 ± 20.6	91.5 ± 20.8	92.2 ± 20.7	92.0 ± 21.8	91.7 ± 20.8
Diabetes duration, years, median (IQR)	11.2 (6.7–16.7)	11.3 (6.8–17.1)	11.2 (6.9–16.9)	11.3 (6.9–16.9)	12.2 (7.2–18.4)	11.4 (6.9–17.1)
Current smoker, n (%)	96 (12.0)	321 (13.3)	278 (10.5)	212 (11.5)	114 (12.3)	1021 (11.8)
SBP, mmHg	132 ± 16	133 ± 17	136 ± 18	139 ± 18	141 ± 18	136 ± 18
LDL-C, mg/dL	85.0 ± 32.2	84.9 ± 33.7	90.0 ± 35.7	92.7 ± 36.9	100.6 ± 40.4	89.8 ± 36.0
LDL-C, mmol/L	2.2 ± 0.8	2.2 ± 0.9	2.3 ± 0.9	2.4 ± 1.0	2.6 ± 1.0	2.3 ± 0.9
eGFR (CKD-EPI), mL/min/1.73m^2	81.9 ± 21.5	80.3 ± 21.9	79.4 ± 21.6	78.5 ± 21.9	77.5 ± 22.2	80.3 ± 21.7
UACR, median (IQR)	11.8 (3.5–64.3)	11.8 (3.8–53.1)	14.3 (4.6–61.6)	17.1 (5.6–64.0)	21.3 (7.5–88.8)	14.7 (4.5–63.0)
Established CVD, n (%)	659 (82.2)	1938 (80.5)	2135 (80.4)	1501 (81.4)	767 (82.7)	7000 (81.0)
Presence of CVD risk factor, n (%)[‡]	143 (17.8)	470 (19.5)	521 (19.6)	343 (18.6)	161 (17.4)	1638 (19.0)
Lipid-lowering treatment, n (%)	622 (77.6)	1843 (76.5)	2032 (76.5)	1384 (75.1)	678 (73.1)	6559 (75.9)
RAAS treatment, n (%)	654 (81.5)	1941 (80.6)	2137 (80.5)	1485 (80.5)	736 (79.3)	6953 (80.5)
Metformin treatment, n (%)	609 (75.9)	1914 (79.5)	2054 (77.3)	1401 (76.0)	699 (75.3)	6677 (77.3)
Insulin treatment, n (%)	375 (46.8)	1115 (46.3)	1141 (43.0)	810 (43.9)	417 (44.9)	3858 (44.7)
Aspirin treatment, n (%)	517 (64.5)	1537 (63.8)	1695 (63.8)	1146 (62.1)	581 (62.6)	5476 (63.4)

Presented data are mean ± standard deviation, unless stated otherwise. Participants were categorized according to number of risk markers with an improvement at year 1 [none (group G0), 1 (G1), 2 (G2), 3 (G3) and ≥4 (G4)]. Parameters in bold are risk markers that were evaluated in this post-hoc analysis. SGLT-2 inhibitors were not marketed prior to randomization in the LEADER trial, hence none of the participants received this medication at baseline.

[†]Calculated as a percentage of the overall total (all other percentages were calculated out of the risk marker improvement subgroups).

[‡]Presence of CVD risk factor was defined as 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, or ankle/brachial index less than 0.9.

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; IQR, interquartile range; LDL-C, low-density lipoprotein-cholesterol; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; SGLT-2, sodium-glucose cotransporter-2; UACR, urinary albumin-to-creatinine ratio.

Table S2: Baseline characteristics of the participants from the SUSTAIN 6 trial by risk marker improvement subgroups

Baseline	**G0**	**G1**	**G2**	**G3**	**G4**	**Total**
Number of patients, n (%)[†]	253 (100)	754 (100)	884 (100)	671 (100)	478 (100)	3040 (100)
Treated with semaglutide, n (%)	57 (22.5)	244 (32.4)	406 (45.9)	430 (64.1)	387 (81.0)	1524 (50.1)
Placebo, n (%)	196 (77.5)	510 (67.6)	478 (54.1)	241 (35.9)	91 (19.0)	1516 (49.9)
Age, years	64.8 ± 7.2	64.6 ± 7.5	64.5 ± 7.2	64.4 ± 7.4	64.6 ± 7.1	64.5 ± 7.3
Female, n (%)	79 (31.2)	281 (37.3)	333 (37.7)	273 (40.7)	220 (46)	1186 (39)
HbA_{1c}, %	8.3 ± 1.3	8.6 ± 1.4	8.7 ± 1.6	8.8 ± 1.5	8.8 ± 1.4	364 (12.0)
HbA_{1c}, mmol/mol	67.7 ± 14.2	69.9 ± 15.3	72.0 ± 17.1	72.4 ± 15.9	72.6 ± 15.2	8.7 ± 1.5
Body weight, kg	92.3 ± 20.6	92.0 ± 20.9	91.1 ± 20.0	92.8 ± 21.2	92.6 ± 21.0	92.0 ± 20.7
Diabetes duration, years, median (IQR)	12.4 (7.3–17.8)	13.3 (8.2–18.9)	12.9 (7.9–18.4)	12.8 (7.8–18.6)	12.7 (7.9–18.2)	12.9 (7.9–18.5)
Current smoker, n (%)	29 (11.5)	92 (12.2)	98 (11.1)	89 (13.3)	56 (11.7)	364 (12.0)
SBP, mmHg	129 ± 14	133 ± 16	135 ± 17	138 ± 17	142 ± 17	136 ± 17
LDL-C, mg/dL	83.3 ± 33.2	82.6 ± 31.8	88.2 ± 34.8	92.3 ± 38.7	102.9 ± 43.9	89.6 ± 37.1
LDL-C, mmol/L	2.2 ± 0.9	2.1 ± 0.8	2.3 ± 0.9	2.4 ± 1.0	2.7 ± 1.1	2.3 ± 1.0
eGFR (CKD-EPI), mL/min/1.73m^2	78.6 ± 22.7	77.0 ± 22.3	77.0 ± 21.8	75.3 ± 23.5	72.7 ± 23.9	76.1 ± 22.8
UACR, median (IQR)	11.9 (3.3–68.9)	14.9 (4.4–79.2)	15.2 (4.5–74.8)	18.3 (5.6–106)	24.1 (7.2–117)	16.8 (4.9–89.7)
Established CVD, n (%)	214 (84.6)	621 (82.4)	728 (82.4)	558 (83.2)	389 (81.4)	2510 (82.6)
Presence of CVD risk factor, n (%)[‡]	39 (15.4)	133 (17.6)	156 (17.6)	113 (16.8)	89 (18.6)	530 (17.4)
Lipid-lowering treatment, n (%)	198 (78.3)	588 (78.0)	696 (78.7)	502 (74.8)	345 (72.2)	2329 (76.6)
RAAS treatment, n (%)	203 (80.2)	607 (80.5)	746 (84.4)	547 (81.5)	387 (81.0)	2490 (81.9)
Metformin treatment, n (%)	187 (73.9)	572 (75.9)	673 (76.1)	486 (72.4)	334 (69.9)	2252 (74.1)
Insulin treatment, n (%)	112 (44.3)	383 (50.8)	409 (46.3)	301 (44.9)	214 (44.8)	1419 (46.7)

SGLT-2 inhibitors treatment, n (%)	1 (0.4)	0 (0.0)	2 (0.2)	1 (0.1)	1 (0.2)	5 (0.2)
Aspirin treatment, n (%)	165 (65.2)	485 (64.3)	569 (64.4)	430 (64.1)	287 (60.0)	1936 (63.7)

Presented data are mean ± standard deviation, unless stated otherwise. Patients were categorized according to number of risk markers with an improvement at year 1 [none (group G0), 1 (G1), 2 (G2), 3 (G3) and ≥4 (G4)]. Parameters in bold are risk markers that were evaluated in this post-hoc analysis.

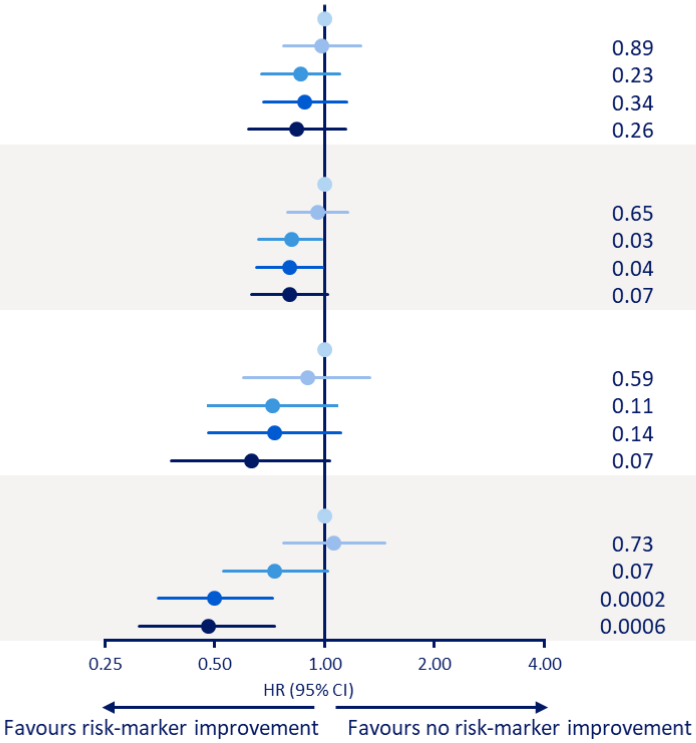
[†]Calculated as a percentage of the overall total (all other percentages were calculated out of the risk marker improvement subgroups).

[‡]Presence of CVD risk factor was defined as 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, or ankle/brachial index less than 0.9

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; IQR, interquartile range; LDL-C, low-density lipoprotein-cholesterol; MDRM, Modification of Diet in Renal Disease; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; SGLT-2, sodium-glucose cotransporter-2; UACR, urinary albumin-to-creatinine ratio.

Figure S1: Outcomes according to number of risk marker improvements[†] among persons with type 2 diabetes in the LEADER trial

	Number of people with event/subgroup total (%)	IR	HR (95% CI)[‡]	*P*-value	*P*-value$_{\text{test for trend}}$[§]
MACE					
G0 (reference)	92/802 (11.5)	3.0	1		
G1	274/2408 (11.4)	3.0	0.98 (0.77–1.26)	0.89	
G2	300/2656 (11.3)	2.9	0.86 (0.67–1.10)	0.23	0.08
G3	217/1844 (11.8)	3.0	0.88 (0.68–1.15)	0.34	
G4	103/928 (11.1)	2.9	0.84 (0.62–1.14)	0.26	
Expanded MACE					
G0 (reference)	149/802 (18.6)	4.9	1		
G1	448/2408 (18.6)	4.8	0.96 (0.79–1.16)	0.65	
G2	458/2656 (17.2)	4.5	0.81 (0.66–0.98)	0.03	0.004
G3	315/1844 (17.1)	4.4	0.80 (0.65–0.99)	0.04	
G4	157/928 (16.9)	4.4	0.80 (0.63–1.02)	0.07	
CV death					
G0 (reference)	34/802(4.2)	1.1	1		
G1	103/2408 (4.3)	1.1	0.90 (0.60–1.33)	0.59	
G2	108/2656 (4.1)	1.0	0.72 (0.48–1.08)	0.11	0.02
G3	80/1844 (4.3)	1.1	0.73 (0.48–1.11)	0.14	
G4	33/928 (3.6)	0.9	0.63 (0.38–1.03)	0.07	
Nephropathy					
G0 (reference)	55/802 (6.9)	1.8	1		
G1	192/2408 (8.0)	2.1	1.06 (0.77–1.46)	0.73	
G2	179/2656 (6.7)	1.7	0.73 (0.53–1.02)	0.07	<0.0001
G3	93/1844 (5.0)	1.3	0.50 (0.35–0.72)	0.0002	
G4	48/928 (5.2)	1.3	0.48 (0.31–0.73)	0.0006	



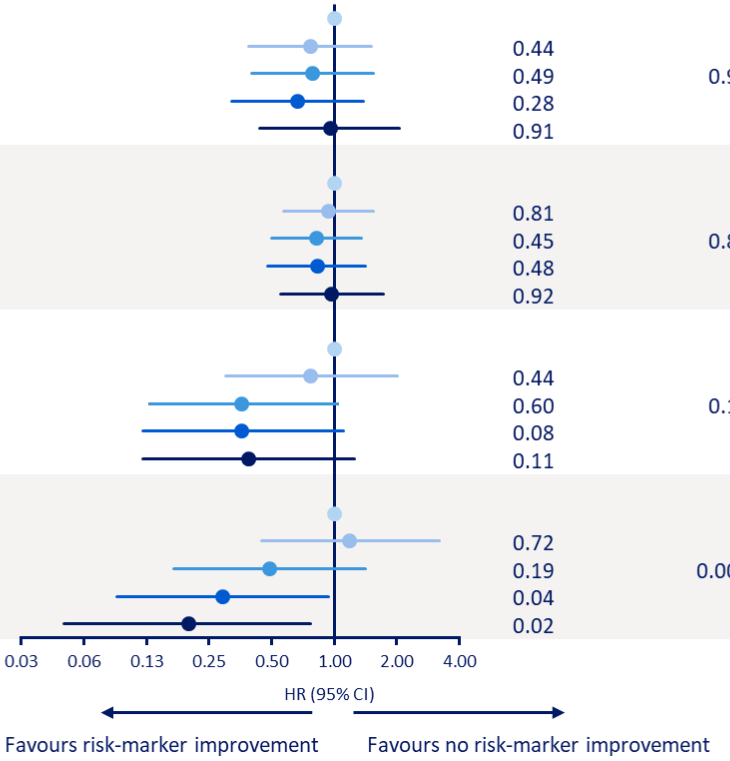
Hazard ratios show risk for outcomes according to number of risk markers with a clinically relevant improvement among persons with type 2 diabetes. *Post hoc* analysis of data from the LEADER trial including 8638 persons with type 2 diabetes followed for a median of 3.8 years. Participants were categorised according to number of risk markers with an improvement at year 1 [none (group G0), 1 (G1), 2 (G2), 3 (G3) and ≥4 (G4)] and investigated subsequent risk of outcome. N is number of events in each group.

[†]Adjusted by baseline variables; [‡]compared G1−G4 to G0 (the reference group); [§]test for trend was evaluated in a Cox regression model with number of risk marker improvements as a continuous variable adjusted for treatment and baseline levels of the risk markers.

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IR, incidence rate per 100 patient years of observation; MACE, major adverse cardiovascular events.

Figure S2: Outcomes according to number of risk marker improvements[†] among persons with type 2 diabetes in the SUSTAIN 6 trial

	Number of people with event/subgroup total (%)	IR	HR (95% CI)[‡]	*P*-value	*P*-value$_{\text{test for trend}}$[§]
MACE					
G0 (reference)	12/253 (4.7)	2.6	1		
G1	31/754 (4.1)	2.2	0.77 (0.39–1.51)	0.44	
G2	36/884 (4.1)	2.1	0.79 (0.40–1.54)	0.49	0.95
G3	22/671 (3.3)	1.7	0.67 (0.32–1.39)	0.28	
G4	24/478 (5.0)	2.5	0.96 (0.44–2.06)	0.91	
Expanded MACE					
G0 (reference)	22/253 (8.7)	4.8	1		
G1	63/754 (8.4)	4.5	0.94 (0.57–1.55)	0.81	
G2	67/884 (7.6)	3.9	0.82 (0.50–1.36)	0.45	0.80
G3	50/671 (7.5)	3.8	0.83 (0.48–1.41)	0.48	
G4	42/478 (8.8)	4.4	0.97 (0.55–1.72)	0.92	
CV death					
G0 (reference)	6/253 (2.4)	1.3	1		
G1	16/754 (2.1)	1.1	0.77 (0.30–2.01)	0.44	
G2	10/884 (1.1)	0.6	0.36 (0.13–1.04)	0.60	0.10
G3	8/671 (1.2)	0.6	0.36 (0.12–1.11)	0.08	
G4	8/478 (1.7)	0.8	0.39 (0.12–1.26)	0.11	
Nephropathy					
G0 (reference)	5/253 (2.0)	1.1	1		
G1	21/754 (2.8)	1.5	1.19 (0.45–3.20)	0.72	
G2	14/884 (1.6)	0.8	0.49 (0.17–1.42)	0.19	0.0004
G3	8/671 (1.2)	0.6	0.29 (0.09–0.94)	0.04	
G4	6/478 (1.3)	0.6	0.20 (0.05–0.77)	0.02	



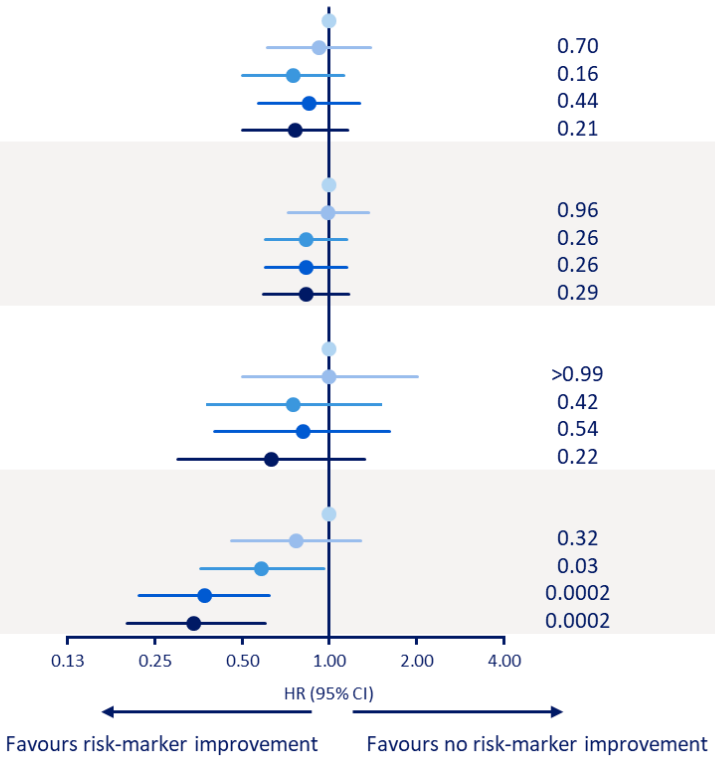
Hazard ratios show risk for outcomes according to number of risk markers with a clinically relevant improvement among persons with type 2 diabetes. *Post hoc* analysis of data from the SUSTAIN 6 trial including 3040 persons with type 2 diabetes followed for a median of 2.1 years. Participants were categorised according to number of riskmarkers with an improvement at year 1 [none (group G0), 1 (G1), 2 (G2), 3 (G3) and ≥4 (G4)] and investigated subsequent risk of outcome. N is number of events in each group.

[†]Adjusted by baseline variables; [‡]compared G1−G4 to G0 (the reference group); [§]test for trend was evaluated in a Cox regression model with number of risk marker improvements as a continuous variable adjusted for treatment and baseline levels of the risk markers.

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IR, incidence rate per 100 patient years of observation; MACE, major adverse cardiovascular events.

Figure S3: Outcomes according to number of risk marker improvements[†] among persons with type 2 diabetes (liraglutide/semaglutide treatment only)

	Number of people with event/subgroup total (%)	IR	HR (95% CI)[‡]	*P*-value	*P*-value$_{\text{test for trend}}$[§]
MACE					
G0 (reference)	32/322 (9.9)	2.9	1		
G1	113/1202 (9.4)	2.8	0.92 (0.61–1.39)	0.70	
G2	145/1727 (8.4)	2.5	0.75 (0.50–1.12)	0.16	0.16
G3	144/1550 (9.3)	2.8	0.85 (0.57–1.27)	0.44	
G4	83/1059 (7.8)	2.4	0.76 (0.50–1.16)	0.21	
Expanded MACE					
G0 (reference)	49/322 (15.2)	4.4	1		
G1	184/1202 (15.3)	4.5	0.99 (0.72–1.37)	0.96	
G2	241/1727 (14.0)	4.1	0.83 (0.60–1.15)	0.26	0.07
G3	208/1550 (13.4)	4.0	0.83 (0.60–1.15)	0.26	
G4	138/1059 (13.0)	4.1	0.83 (0.59–1.17)	0.29	
CV death					
G0 (reference)	10/322 (3.1)	0.9	1		
G1	42/1202 (3.5)	1.0	1.00 (0.50–2.01)	>0.99	
G2	53/1727 (3.1)	0.9	0.75 (0.38–1.50)	0.42	0.09
G3	50/1550 (3.2)	1.0	0.81 (0.40–1.61)	0.54	
G4	25/1059 (2.4)	0.7	0.63 (0.30–1.32)	0.22	
Nephropathy					
G0 (reference)	22/322 (6.8)	2.0	1		
G1	67/1202 (5.6)	1.6	0.77 (0.46–1.28)	0.32	
G2	93/1727 (5.4)	1.6	0.58 (0.36–0.96)	0.03	<0.0001
G3	60/1550 (3.9)	1.2	0.37 (0.22–0.62)	0.0002	
G4	37/1059 (3.5)	1.1	0.34 (0.20–0.60)	0.0002	



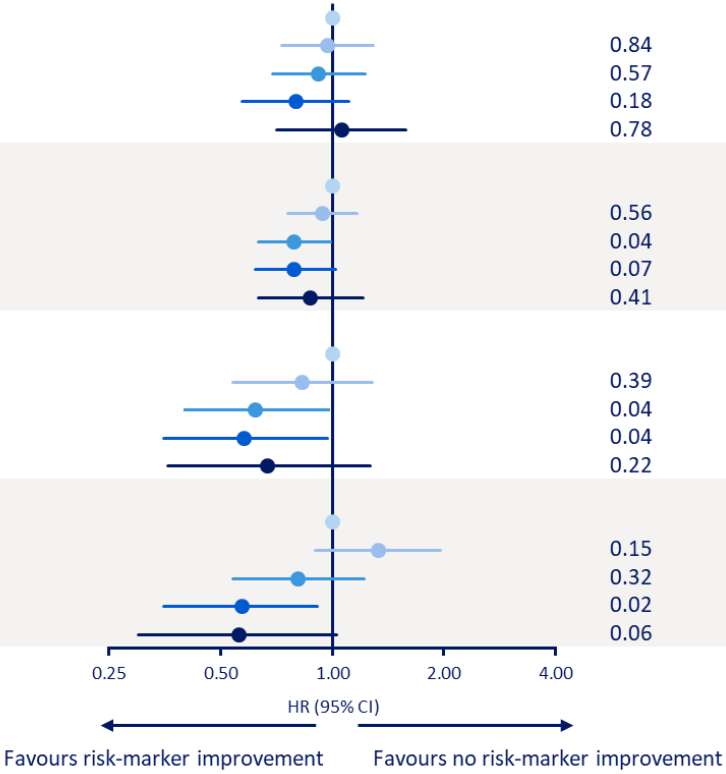
Hazard ratios show risk for outcomes according to number of risk markers with a clinically relevant improvement among persons with type 2 diabetes. *Post hoc* analysis of data from the LEADER and SUSTAIN 6 trials included 5,860 persons with type 2 diabetes. Participants were categorized according to number of risk markers with an improvement at year 1 [none (group G0), 1 (G1), 2 (G2), 3 (G3) and ≥4 (G4)].

[†]Adjusted by baseline variables; [‡]compared G1−G4 to G0 (the reference group); [§]test for trend was evaluated in a Cox regression model with number of risk marker improvements as a continuous variable adjusted for baseline levels of the risk markers.

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IR, incidence rate per 100 patient years of observation; MACE, major adverse cardiovascular events.

Figure S4: Outcomes according to number of risk marker improvements[†] among persons with type 2 diabetes (placebo treatment only)

	Number of people with event/subgroup total (%)	IR	HR (95% CI)[‡]	*P*-value	*P*-value$_{\text{test for trend}}$[§]
MACE					
G0 (reference)	72/733 (9.8)	3.0	1		
G1	192/1960 (9.8)	2.9	0.97 (0.73–1.29)	0.84	
G2	191/1813 (10.5)	3.1	0.92 (0.69–1.23)	0.57	0.45
G3	95/965 (9.8)	2.9	0.80 (0.57–1.11)	0.18	
G4	44/347 (12.7)	3.8	1.06 (0.71–1.58)	0.78	
Expanded MACE					
G0 (reference)	122/733 (16.6)	5.0	1		
G1	327/1960 (16.7)	5.0	0.94 (0.76–1.17)	0.56	
G2	284/1813 (15.7)	4.6	0.79 (0.63–0.99)	0.04	0.047
G3	157/965 (16.3)	4.8	0.79 (0.62–1.02)	0.07	
G4	61/347 (17.6)	5.3	0.87 (0.63–1.21)	0.41	
CV death					
G0 (reference)	30/733 (4.1)	1.2	1		
G1	77/1960 (3.9)	1.2	0.83 (0.54–1.28)	0.39	
G2	65/1813 (3.6)	1.1	0.62 (0.40–0.98)	0.04	0.028
G3	38/965 (3.9)	1.2	0.58 (0.35–0.97)	0.04	
G4	16/347 (4.6)	1.4	0.67 (0.36–1.27)	0.22	
Nephropathy					
G0 (reference)	38/733 (5.2)	1.6	1		
G1	146/1960 (7.4)	2.2	1.33 (0.90–1.96)	0.15	
G2	100/1813 (5.5)	1.6	0.81 (0.54–1.22)	0.32	<0.0001
G3	41/965 (4.2)	1.3	0.57 (0.35–0.91)	0.02	
G4	17/347 (4.9)	1.5	0.56 (0.30–1.03)	0.06	



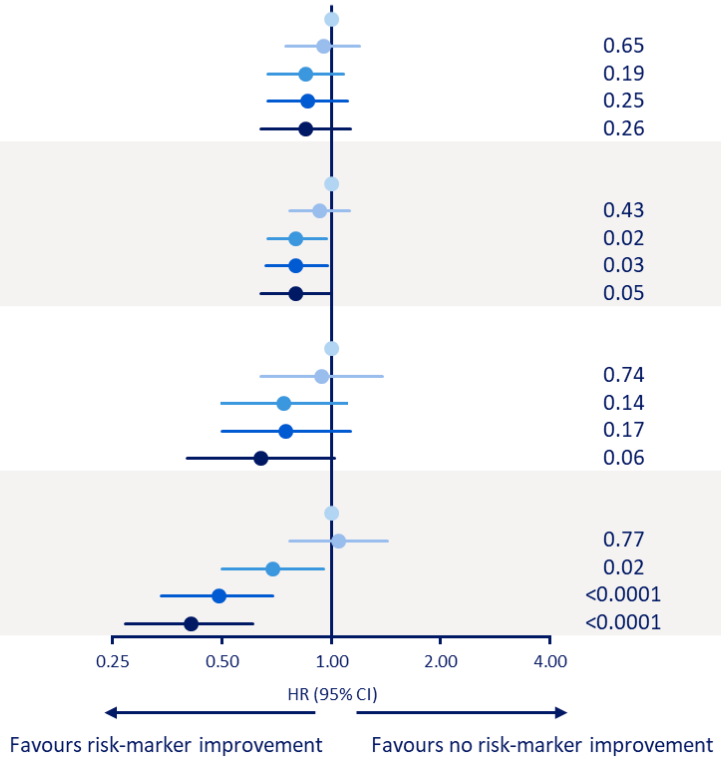
Hazard ratios show risk for outcomes according to number of risk markers with a clinically relevant improvement among persons with type 2 diabetes. Post-hoc analysis of data from the LEADER and SUSTAIN 6 trials included 5,818 persons with type 2 diabetes. Participants were categorized according to number of riskmarkers with an improvement at year 1 [none (group G0), 1 (G1), 2 (G2), 3 (G3) and ≥4 (G4)].

[†]Adjusted by baseline variables; [‡]compared G1−G4 to G0 (the reference group); [§]test for trend was evaluated in a Cox regression model with number of risk marker improvements as a continuous variable adjusted for baseline levels of the risk markers.

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IR, incidence rate per 100 patient years of observation; MACE, major adverse cardiovascular events.

Figure S5: Outcomes according to number of risk marker improvements[†] among persons with type 2 diabetes (with missing response data imputed)

	Number of people with event/subgroup total (%)	IR	HR (95% CI)[‡]	*P*-value	*P*-value$_{\text{test for trend}}$[§]
MACE					
G0 (reference)	98/1014 (9.7)	2.9	1		
G1	247/3129 (9.5)	2.8	0.95 (0.75–1.20)	0.65	
G2	341/3558 (9.6)	2.8	0.86 (0.67–1.08)	0.19	0.11
G3	246/2550 (9.7)	2.9	0.86 (0.67–1.11)	0.25	
G4	128/1427 (9.0)	2.8	0.85 (0.64–1.13)	0.26	
Expanded MACE					
G0 (reference)	164/1014 (16.2)	4.8	1		
G1	498/3129 (15.9)	4.7	0.93 (0.77–1.12)	0.43	
G2	533/3558 (15.0)	4.4	0.80 (0.67–0.97)	0.02	0.0062
G3	376/2550 (14.7)	4.4	0.80 (0.66–0.98)	0.03	
G4	200/1427 (14.0)	4.3	0.80 (0.64–1.00)	0.05	
CV death					
G0 (reference)	35/1014 (3.5)	1.0	1		
G1	115/3129 (3.7)	1.1	0.94 (0.64–1.38)	0.74	
G2	123/3558 (3.5)	1.0	0.74 (0.50–1.10)	0.14	0.0165
G3	92/2550 (3.6)	1.1	0.75 (0.50–1.13)	0.17	
G4	41/1427 (2.9)	0.9	0.64 (0.40–1.02)	0.06	
Nephropathy					
G0 (reference)	58/1014 (5.7)	1.7	1		
G1	207/3129 (6.6)	2.0	1.05 (0.77–1.43)	0.77	
G2	194/3558 (5.5)	1.6	0.69 (0.50–0.95)	0.02	<0.0001
G3	108/2550 (4.2)	1.3	0.49 (0.34–0.69)	<0.0001	
G4	54/1427 (3.8)	1.2	0.41 (0.27–0.61)	<0.0001	

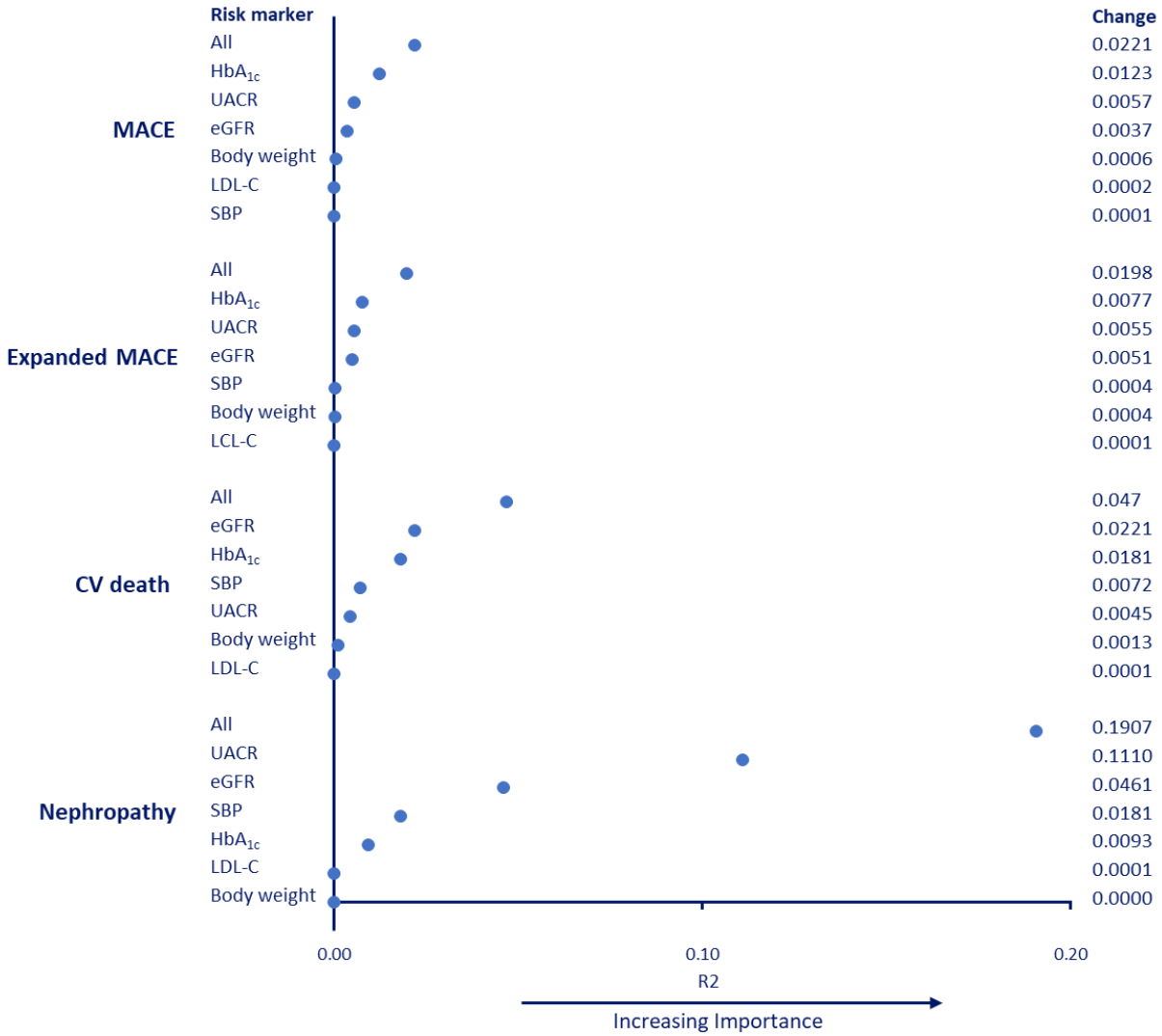


A sensitivity analysis imputing missing values (single imputation) at year 1 for those subjects with a least one measurement at year 1 was performed using the participant-wise predicted values from a random slope model for each risk marker independently, with baseline value and treatment by a linear time interaction as fixed effects. After the imputation, the clinically relevant improvements were derived for each risk marker and participants were categorized according to number of risk markers with an improvement at year 1 [none (group G0), 1 (G1), 2 (G2), 3 (G3) and ≥4 (G4)]. Post-hoc analysis of data from the LEADER and SUSTAIN 6 trials included 5,818 persons with type 2 diabetes. Hazard ratios show risk for outcomes according to number of risk markers with a clinically relevant improvement among persons with type 2 diabetes.

[†]Adjusted by baseline variables; [‡]compared G1−G4 to G0 (the reference group); [§]test for trend was evaluated in a Cox regression model with number of risk marker improvements as a continuous variable adjusted for treatment and baseline levels of the risk markers.

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IR, incidence rate per 100 patient years of observation; MACE, major adverse cardiovascular events.

Figure S6: Relative importance of risk markers for outcomes in the LEADER and SUSTAIN 6 trials



Relative importance provided an estimate of how important each risk marker improvement was in terms of predicting each of the outcomes after year 1. We calculated the R2 for the 'all' model from the Cox regression model for each endpoint with all six risk marker improvements (yes versus no) adjusted for the continuous baseline levels of the six risk markers stratified by trial. Furthermore the contribution to the R2 as 'change' from each parameter was calculated from the Cox regression model with the improvement (yes versus no) for each of the parameters, adjusted for the parameter in question at baseline and stratified by trial.CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; LDL-C, low-density lipoprotein-cholesterol; MACE, major adverse coronary event; UACR, urinary albumin-to-creatinine ratio.