Effects of Liraglutide on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus With or Without History of Myocardial Infarction or Stroke

Post Hoc Analysis From the LEADER Trial

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BACKGROUND: The glucagon-like peptide-1 analog liraglutide reduced cardiovascular events and mortality in patients with type 2 diabetes mellitus in the LEADER trial (Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes). In a post hoc analysis, we evaluated the efficacy of liraglutide in those with and without a history of myocardial infarction (MI) and/or stroke.

METHODS: LEADER was a randomized trial of liraglutide (1.8 mg or maximum tolerated dose) versus placebo in 9340 patients with type 2 diabetes mellitus and high cardiovascular risk, with a median follow-up of 3.8 years. The primary outcome was a composite of cardiovascular death, nonfatal MI, or nonfatal stroke (major adverse cardiovascular events). Risk groups in this post hoc analysis were defined by history of MI/stroke, established atherosclerotic cardiovascular disease without MI/stroke, or cardiovascular risk factors alone.

RESULTS: Of the 9340 patients, 3692 (39.5%) had a history of MI/stroke, 3083 (33.0%) had established atherosclerotic cardiovascular disease without MI/stroke, and 2565 (27.5%) had risk factors alone. Major adverse cardiovascular events occurred in 18.8% of patients with a history of MI/stroke (incidence rate, 5.0 per 100 patient-years), 11.6% of patients with established atherosclerotic cardiovascular disease without MI/stroke (incidence rate, 3.0 per 100 patient-years), and 9.8% of patients with cardiovascular risk factors alone (incidence rate, 2.6 per 100 patient-years). Liraglutide reduced major adverse cardiovascular events in patients with a history of MI/stroke (322 of 1865 [17.3%] versus 372 of 1827 patients [20.4%]; hazard ratio, 0.85; 95% CI, 0.73–0.99) and in those with established atherosclerotic cardiovascular disease without MI/stroke (158 of 1538 [10.3%] versus 199 of 1545 patients [12.9%]; hazard ratio, 0.76; 95% CI, 0.62–0.94) compared with placebo. In patients with risk factors alone, the hazard ratio for liraglutide versus placebo was 1.08 (95% CI, 0.84–1.38, $P_{interaction}$=0.11). Similar results were seen for secondary outcomes across risk groups.

CONCLUSIONS: In this post hoc analysis of patients with type 2 diabetes mellitus and high cardiovascular risk, liraglutide reduced cardiovascular outcomes both in patients with a history of MI/stroke and in those with established atherosclerotic cardiovascular disease without MI/stroke. The cardiovascular effect appeared neutral in patients with cardiovascular risk factors alone.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01179048.

Key Words: cardiovascular system ■ diabetes mellitus, type 2 ■ glucagon-like peptide-1 ■ liraglutide ■ randomized controlled trial as topic

Clinical Perspective

What Is New?

- There is a spectrum of cardiovascular events in people with diabetes mellitus, with about twice the major adverse cardiovascular events rate in those with prior myocardial infarction/stroke versus those with risk factors alone.
- Liraglutide consistently lowered the primary and expanded major adverse cardiovascular event outcomes in people with diabetes mellitus and atherosclerotic cardiovascular disease regardless of prior myocardial infarction/stroke history.
- In people with diabetes mellitus with risk factors alone, liraglutide appeared safe but not superior to placebo.

What Are the Clinical Implications?

- Liraglutide is an effective antihyperglycemic agent for the reduction of cardiovascular events in people with diabetes mellitus who had a prior myocardial infarction or stroke or in those who have atherosclerotic cardiovascular disease but have not yet had a myocardial infarction or stroke.
- In people with type 2 diabetes mellitus who only have risk factors, liraglutide is safe but, in the short term, is not associated with reductions in major adverse cardiovascular events.

Despite optimal medical therapy, morbidity and mortality from cardiovascular disease remain significantly higher in patients with diabetes mellitus compared with age- and sex-matched individuals without diabetes mellitus.[1–3] In fact, patients with diabetes mellitus and a prior ischemic cardiovascular event are at an especially high risk of recurrent events.[4–6] Although strides have been made with respect to a reduction in macrovascular and microvascular events in diabetes mellitus,[7] the rise in the prevalence of diabetes mellitus poses a substantial cardiovascular burden worldwide.

The LEADER trial (Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes) demonstrated a 13% significant relative risk reduction in major adverse cardiovascular events (MACE) with liraglutide versus placebo, both as add-on to standard-of-care treatment, in patients with type 2 diabetes mellitus (T2DM) and high cardiovascular risk.[8]

Because the presence of myocardial infarction (MI) or stroke is one of the most important risk stratifiers in patients with diabetes mellitus and high cardiovascular risk,[1,9] it is important to evaluate the absolute and relative benefits of cardiovascular risk reduction approaches across the continuum of patients with diabetes mellitus with varying cardiovascular risk, ranging from history of MI/stroke to established atherosclerotic cardiovascular disease without a history of MI/stroke and cardiovascular risk factors alone.

METHODS

The subject-level analysis data sets for the research presented in the publication are available from the corresponding author on reasonable request.

The design of the LEADER trial (Clinicaltrials.gov NCT01179048) has been described previously.[8,10] Briefly, LEADER was a randomized, double-blind, multicenter, placebo-controlled, cardiovascular outcomes trial. The trial protocol was reviewed and approved by the institutional review board or ethics committee at each participating center. All patients provided written informed consent before participation.

Patients

In total, 9340 patients with T2DM with a glycohemoglobin level of ≥7.0% and high cardiovascular risk were randomly assigned to receive liraglutide 1.8 mg/d (or the maximum tolerated dose) or placebo, both as add-on to standard of care, and followed up for 3.5 to 5 years. Patients included were either >50 years of age with established cardiovascular disease, defined by the protocol as coronary artery disease, cerebrovascular disease, peripheral artery disease, New York Heart Association class II or III heart failure, or chronic kidney disease (estimated glomerular filtration rate <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$), or >60 years of age with at least 1 additional cardiovascular risk factor (microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle-brachial index <0.9).

Risk Groups

In this post hoc analysis, we compared the incidence of the primary and secondary composite outcomes with liraglutide versus placebo in 3 mutually exclusive clinically relevant risk groups. Risk groups were defined according to those with and without atherosclerotic disease and degree of disease: (1) patients with a history of MI/stroke, (2) patients with established atherosclerotic cardiovascular disease without MI/stroke (≥50% coronary artery stenosis, percutaneous coronary intervention or coronary artery bypass graft [CABG] surgery, angina pectoris with a positive stress imaging test and/or asymptomatic ischemia [but no MI], transient ischemic attack, ≥50% intracranial or carotid artery stenosis, and ≥50% peripheral artery stenosis by imaging or ankle-brachial index <0.9), or (3) patients with cardiovascular risk factors alone (ie, those not meeting definitions for the former risk groups such as those with isolated chronic kidney disease, hypertension with left ventricular hypertrophy, New York Heart Association class II or III heart failure, and left ventricular systolic or diastolic dysfunction). This information was investigator-reported at randomization. The presence of stroke included both ischemic and hemorrhagic stroke.

Outcomes

The primary outcome was defined as the first occurrence of a MACE (defined as the composite of cardiovascular death,

nonfatal MI, or nonfatal stroke). A prespecified, key secondary expanded composite outcome included coronary revascularization, hospitalization for unstable angina, or heart failure in addition to MACE. Furthermore, prespecified secondary end points were time to first event of the individual components of the expanded composite outcomes and all-cause death. We also examined renal and metabolic outcomes in these 3 risk groups (see 'Detailed description of renal and metabolic outcomes and statistical considerations', page 1 in the online-only Data Supplement).

The cardiovascular and renal outcomes were adjudicated by an independent event adjudication committee of experts blinded to the randomization.[8] Furthermore, the event adjudication committee assessed whether MI/stroke was fatal or nonfatal, through which fatal events were linked to subsequent cardiovascular death. Serious and nonserious medical adverse events of special interest were reported by the investigator.

Statistical Analysis

The time from randomization to the first occurrence of the outcome was analyzed with a Cox proportional hazards model on all randomized subjects. The hazard ratios (HRs) and *P* values between risk groups were estimated with multivariable adjustment for prespecified baseline factors (sex, region, baseline age, diabetes duration, baseline antidiabetic medication, smoking history [never/prior/current], and estimated glomerular filtration rate at screening)[8] and for treatment allocation (liraglutide versus placebo). The treatment effect of liraglutide versus placebo within risk groups was estimated with a Cox proportional hazards regression model, with treatment, risk group, and the interaction of both as factors, and adjusted for the above prespecified baseline factors.[8] Furthermore, Kaplan-Meier curves were used to examine the association between treatment groups within risk groups and the outcome of interest. An interaction value of $P<0.05$ indicated a significant difference in the treatment HRs across the 3 risk groups. No adjustment for multiple testing was performed. All patients who underwent randomization were included in the analyses and followed up from the time of randomization until death or the end of follow-up. To evaluate any potential treatment interaction with prior cardiovascular disease, sensitivity analyses were conducted that were stratified by investigator-reported history of MI/stroke alone or including percutaneous coronary intervention or CABG or by carotid stenosis in addition to history of MI/stroke. Sensitivity analyses in relation to treatment differences were performed, with adjustment for all-cause death as a competing risk using the Fine and Gray regression method.[8,11] The number needed to treat was calculated from the predicted survival rates at 3 years after randomization.[12]

Serious and nonserious medical adverse events of special interest between the 3 treatment groups were summarized.

RESULTS

Baseline Characteristics

Of the 9340 patients, 3692 (39.5%) had a history of MI/stroke, 3083 (33.0%) had evidence of atherosclerotic cardiovascular disease without an MI/stroke, and 2565 (27.5%) had cardiovascular risk factors alone. The baseline demographics and cardiovascular histories of these 3 groups are detailed in Tables 1 and 2, respectively. Patients with a history of MI/stroke had a higher frequency of cardiovascular risk factors. Of patients with a history of MI/stroke, 76.0% had a history of MI, and 28.1% had a previous ischemic stroke; revascularization with percutaneous coronary intervention had been performed in 43.3%, and 24.5% had a history of CABG compared with 31.4% and 20.3%, respectively, in patients with atherosclerotic cardiovascular disease without an MI/stroke. More patients with a history of MI/stroke had evidence of left ventricular systolic dysfunction and heart failure. Median follow-up was 3.8 years.

Risk of Cardiovascular Events and Mortality According to Risk Groups Regardless of Treatment

Patients with a history of MI/stroke had the highest risk of MACE (694 events of 3692 [18.8%]), followed by patients with established atherosclerotic cardiovascular disease without a history of MI/stroke (357 of 3083 [11.6%]) and patients with cardiovascular risk factors alone (251 of 2565 [9.8%]). The adjusted HRs for MACE were 2.13 (95% CI, 1.84–2.47; $P<0.0001$) and 1.29 (95% CI, 1.10–1.52; $P=0.0021$) in patients with a history of MI/stroke and those with established atherosclerotic cardiovascular disease without MI/stroke, respectively, compared with patients with cardiovascular risk factors alone. Incidence rates of MACE were 5.0 per 100 person-years of observation (PYO) in patients with a history of MI/stroke, 3.0 per 100 PYO in patients with established atherosclerotic cardiovascular disease without MI/stroke, and 2.6 per 100 PYO in those with cardiovascular risk factors alone.

Similar results were obtained for expanded MACE when patients with MI/stroke (1052 of 3692 [28.5%]; HR, 2.27; 95% CI, 2.01–2.57; $P<0.0001$) and with established atherosclerotic cardiovascular disease without MI/stroke (597 of 3083 [19.4%]; HR, 1.52; 95% CI, 1.34–1.74; $P<0.0001$) were compared with those with cardiovascular risk factors alone (361 of 2565 [14.1%]). Incidence rates of expanded MACE were 7.5 per 100 PYO in patients with a history of MI/stroke, 5.1 per 100 PYO in patients with established atherosclerotic cardiovascular disease without MI/stroke, and 3.7 per 100 PYO in those with cardiovascular risk factors alone.

Incidence rates for time to the first of the individual components of the primary and secondary outcomes in the 3 groups (history of MI/stroke versus established atherosclerotic cardiovascular disease without MI/stroke versus cardiovascular risk factors alone) were as follows: cardiovascular death (1.9 versus 1.1 versus 1.1 per 100 PYO), nonfatal MI (2.3 versus 1.5 versus 1.0 per 100 PYO), nonfatal stroke (1.3 versus 0.8 versus 0.7 per 100 PYO), coronary revascularization (3.3 versus 2.4 versus

Table 1. Baseline Demographics and Characteristics by History of Myocardial Infarction and/or Stroke and Cardiovascular Disease

	Overall			With Prior MI/Stroke (n=3692)		CVD Without MI or Stroke (n=3083)		Cardiovascular Risk Factors Alone (n=2565)	
	With Prior MI/Stroke (n=3692)	CVD Without MI or Stroke (n=3083)	Cardiovascular Risk Factors Alone (n=2565)	Placebo (n=1827)	Liraglutide (n=1865)	Placebo (n=1545)	Liraglutide (n=1538)	Placebo (n=1300)	Liraglutide (n=1265)
Male, n (%)	2693 (72.9)	1922 (62.3)	1388 (54.1)	1333 (73.0)	1360 (72.9)	952 (61.6)	970 (63.1)	707 (54.4)	681 (53.8)
Age (SD), y	63.4 (7.5)	64.3 (7.4)	65.5 (6.4)	63.6 (7.5)	63.3 (7.5)	64.4 (7.5)	64.2 (7.3)	65.5 (6.3)	65.5 (6.6)
BMI (SD), kg/m^2	32.0 (5.9)	32.4 (6.1)	33.4 (6.9)	31.9 (6.0)	32.0 (5.9)	32.4 (6.2)	32.4 (6.1)	33.3 (6.7)	33.4 (7.0)
Diabetes mellitus duration (SD), y	12.6 (8.1)	13.0 (8.0)	12.9 (7.9)	12.7 (8.2)	12.4 (8.0)	13.2 (8.1)	12.9 (7.8)	13.2 (8.0)	12.7 (7.7)
HbA_{1c} (SD), %	8.7 (1.5)	8.6 (1.5)	8.8 (1.6)	8.7 (1.5)	8.8 (1.6)	8.6 (1.5)	8.6 (1.5)	8.7 (1.5)	8.8 (1.6)
HbA_{1c} (SD), mmol/mol	71.9 (16.8)	70.4 (16.1)	72.2 (17.2)	71.5 (16.4)	72.4 (17.1)	70.3 (15.9)	70.6 (16.3)	71.7 (16.6)	72.8 (17.7)
Smoking status, n (%)									
Current smoker	516 (14.0)	343 (11.1)	271 (10.6)	254 (13.9)	262 (14.0)	167 (10.8)	176 (11.4)	142 (10.9)	129 (10.2)
Never smoker	1251 (33.9)	1345 (43.6)	1274 (49.7)	624 (34.2)	627 (33.6)	660 (42.7)	685 (44.5)	636 (48.9)	638 (50.4)
Previous smoker	1925 (52.1)	1395 (45.2)	1020 (39.8)	949 (51.9)	976 (52.3)	718 (46.5)	677 (44.0)	522 (40.2)	498 (39.4)
SBP (SD), mm Hg	134.7 (17.7)	135.9 (17.6)	137.5 (17.8)	134.8 (17.8)	134.7 (17.7)	136.2 (17.6)	135.7 (17.6)	137.1 (17.7)	137.9 (17.9)
DBP (SD), mm Hg	77.0 (10.2)	76.7 (10.2)	77.7 (10.3)	76.8 (10.2)	77.2 (10.2	76.6 (10.0)	76.9 (10.4)	77.7 (10.2)	77.6 (10.5)
Heart rate (SD), bpm	71.9 (11.4)	72.3 (11.2)	74.0 (11.4)	71.6 (11.7)	72.1 (11.2)	72.4 (11.3)	72.2 (11.1)	74.0 (11.1)	74.1 (11.7)
eGFR from the MDRD equation (SD), mL·min^{-1}·1.73 m^{-2}	81.5 (27.6)	82.3 (26.4)	76.4 (27.8)	81.5 (27.8)	81.6 (27.4)	82.6 (26.0)	81.9 (26.8)	76.9 (27.3)	76.0 (28.2)
Renal function									
Severe (<30 mL·min^{-1}·1.73 m^{-2}), n (%)	76 (2.1)	41 (1.3)	107 (4.2)	34 (1.9)	42 (2.3)	17 (1.1)	24 (1.6)	56 (4.3)	51 (4.0)
Moderate (30–59 mL·min^{-1}·1.73 m^{-2}), n (%)	727 (19.7)	567 (18.4)	640 (25.0)	353 (19.3)	374 (20.1)	279 (18.1)	288 (18.7)	303 (23.3)	337 (26.6)
Mild (60–89 mL·min^{-1}·1.73 m^{-2}), n (%)	1549 (42.0)	1322 (42.9)	1036 (40.4)	777 (42.5)	772 (41.4)	651 (42.1)	671 (43.6)	547 (42.1)	489 (38.7)
Normal (≥90 mL·min^{-1}·1.73 m^{-2}), n (%)	1340 (36.3)	1153 (37.4)	782 (30.5)	663 (36.3)	677 (36.3)	598 (38.7)	555 (36.1)	394 (30.3)	388 (30.7)
Total cholesterol (SD), mg/dL	165.1 (43.6)	169.9 (46.5)	177.8 (45.0)	166.0 (44.5)	164.3 (42.6)	169.3 (47.1)	170.4 (45.9)	176.7 (43.7)	178.9 (46.4)
LDL cholesterol (SD), mg/dL	86.9 (35.7)	89.6 (36.7)	95.0 (36.1)	87.6 (35.9)	86.2 (35.4)	89.0 (35.9)	90.1 (37.5)	94.7 (36.0)	95.4 (36.2)
HDL cholesterol (SD), mg/dL	43.6 (11.6)	45.6 (12.3)	47.7 (12.9)	43.8 (11.4)	43.5 (11.7)	45.6 (12.5)	45.6 (12.1)	47.6 (12.7)	47.8 (13.0)
Triglycerides (SD), mg/dL	183.2 (133.3)	183.2 (150.3)	183.9 (140.5)	183.7 (143.0)	182.8 (123.0)	183.3 (171.2)	183.1 (126.0)	180.3 (141.2)	187.5 (139.8)
Antihypertensive therapy, n (%)	3473 (94.1)	2854 (92.6)	2304 (89.8)	1712 (93.7)	1761 (94.4)	1421 (92.0)	1433 (93.2)	1169 (89.9)	1135 (89.7)
Diuretics, n (%)	1533 (41.5)	1207 (39.2)	1166 (45.5)	767 (42.0)	766 (41.1)	619 (40.1)	588 (38.2)	567 (43.6)	599 (47.4)
Lipid-lowering drugs, n (%)	3073 (83.2)	2364 (76.7)	1642 (64.0)	1500 (82.1)	1573 (84.3)	1173 (75.9)	1191 (77.4)	842 (64.8)	800 (63.2)
Platelet aggregation inhibitors, n (%)	2937 (79.6)	2252 (73.0)	1137 (44.3)	1450 (79.4)	1487 (79.7)	1108 (71.7)	1144 (74.4)	563 (43.3)	574 (45.4)
Antithrombotic medications, n (%)	300 (8.1)	160 (5.2)	163 (6.4)	151 (8.3)	149 (8.0)	80 (5.2)	80 (5.2)	83 (6.4)	80 (6.3)
Blood glucose-lowering drugs, excluding insulin, n (%)	3234 (87.6)	2755 (89.4)	2253 (87.8)	1605 (87.8)	1629 (87.3)	1385 (89.6)	1370 (89.1)	1139 (87.6)	1114 (88.1)
Insulin treatment, n (%)	1697 (46.0)	1338 (43.4)	1134 (44.2)	851 (46.6)	846 (45.4)	697 (45.1)	641 (41.7)	583 (44.8)	551 (43.6)
Insulin-naive, n (%)	1995 (54.0)	1745 (56.6)	1431 (55.8)	976 (53.4)	1019 (54.6)	848 (54.9)	897 (58.3)	717 (55.2)	714 (56.4)

BMI indicates body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycohemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDRD, Modified Diet in Renal Disease; MI, myocardial infarction; SBP, systolic blood pressure; and SD, standard deviation.

Table 2. Cardiovascular History and Complications at Screening by a History of Myocardial Infarction and/or Stroke and Cardiovascular Disease

	Overall, n (%)								
	With Prior MI/Stroke (n=3692)	CVD Without MI or Stroke (n=3083)	Cardiovascular Risk Factors Alone (n=2565)	With Prior MI/Stroke (n=3692), n (%)		CVD Without MI or Stroke (n=3083), n (%)		Cardiovascular Risk Factors Alone (n=2565), n (%)	
				Placebo (n=1827)	Liraglutide (n=1865)	Placebo (n=1545)	Liraglutide (n=1538)	Placebo (n=1300)	Liraglutide (n=1265)
Myocardial infarction	2807 (76.0)	0 (0)	0 (0)	1373 (75.2)	1434 (76.9)	0 (0)	0 (0)	0 (0)	0 (0)
Arrhythmia	643 (17.4)	494 (16.0)	302 (11.8)	314 (17.2)	329 (17.6)	244 (15.8)	250 (16.3)	163 (12.5)	139 (11.0)
Heart failure	766 (20.7)	506 (16.4)	395 (15.4)	387 (21.2)	379 (20.3)	243 (15.7)	263 (17.1)	202 (15.5)	193 (15.3)
NYHA class I	202 (5.5)	104 (3.4)	42 (1.6)	100 (5.5)	102 (5.5)	47 (3.0)	57 (3.7)	22 (1.7)	20 (1.6)
NYHA class II	447 (12.1)	341 (11.1)	303 (11.8)	223 (12.2)	224 (12.0)	168 (10.9)	173 (11.2)	155 (11.9)	148 (11.7)
NYHA class III	106 (2.9)	58 (1.9)	50 (1.9)	56 (3.1)	50 (2.7)	25 (1.6)	33 (2.1)	25 (1.9)	25 (2.0)
Ischemic heart disease	2795 (75.7)	2264 (73.4)	0 (0)	1386 (75.9)	1409 (75.5)	1131 (73.2)	1133 (73.7)	0 (0)	0 (0)
Stable angina	639 (17.3)	1178 (38.2)	0 (0)	306 (16.7)	333 (17.9)	604 (39.1)	574 (37.3)	0 (0)	0 (0)
Asymptomatic (silent) cardiac ischemia	289 (7.8)	555 (18.0)	0 (0)	147 (8.0)	142 (7.6)	271 (17.5)	284 (18.5)	0 (0)	0 (0)
Unstable angina	283 (7.7)	497 (16.1)	0 (0)	139 (7.6)	144 (7.7)	240 (15.5)	257 (16.7)	0 (0)	0 (0)
Non–ST-segment–elevation MI	599 (16.2)	0 (0)	0 (0)	302 (16.5)	297 (15.9)	0 (0)	0 (0)	0 (0)	0 (0)
ST-segment–elevation MI	869 (23.5)	0 (0)	0 (0)	437 (23.9)	432 (23.2)	0 (0)	0 (0)	0 (0)	0 (0)
PCI performed	1599 (43.3)	969 (31.4)	0 (0)	790 (43.2)	809 (43.4)	476 (30.8)	493 (32.1)	0 (0)	0 (0)
CABG performed	906 (24.5)	625 (20.3)	0 (0)	438 (24.0)	468 (25.1)	311 (20.1)	314 (20.4)	0 (0)	0 (0)
Left ventricular systolic dysfunction	619 (16.8)	250 (8.1)	130 (5.1)	308 (16.9)	311 (16.7)	112 (7.2)	138 (9.0)	58 (4.5)	72 (5.7)
Left ventricular diastolic dysfunction	580 (15.7)	487 (15.8)	514 (20.0)	317 (17.4)	263 (14.1)	225 (14.6)	262 (17.0)	257 (19.8)	257 (20.3)
Hypertension	3356 (90.9)	2815 (91.3)	2340 (91.2)	1662 (91.0)	1694 (90.8)	1403 (90.8)	1412 (91.8)	1185 (91.2)	1155 (91.3)
Ischemic stroke	1038 (28.1)	0 (0)	0 (0)	526 (28.8)	512 (27.5)	0 (0)	0 (0)	0 (0)	0 (0)
Transient ischemic attack	265 (7.2)	302 (9.8)	0 (0)	146 (8.0)	119 (6.4)	164 (10.6)	138 (9.0)	0 (0)	0 (0)
Hemorrhagic stroke	103 (2.8)	0 (0)	0 (0)	50 (2.7)	53 (2.8)	0 (0)	0 (0)	0 (0)	0 (0)
Intracranial artery stenosis	80 (2.2)	30 (1.0)	0 (0)	37 (2.0)	43 (2.3)	9 (0.6)	21 (1.4)	0 (0)	0 (0)
Carotid artery stenosis	342 (9.3)	357 (11.6)	0 (0)	162 (8.9)	180 (9.7)	170 (11.0)	187 (12.2)	0 (0)	0 (0)
Peripheral artery disease in lower extremities	404 (10.9)	763 (24.7)	0 (0)	205 (11.2)	199 (10.7)	395 (25.6)	368 (23.9)	0 (0)	0 (0)
>50% stenosis of the coronary, carotid, or other arteries	1294 (35.0)	1084 (35.2)	0 (0)	650 (35.6)	644 (34.5)	541 (35.0)	543 (35.3)	0 (0)	0 (0)

CABG indicates coronary artery bypass graft; CVD, cardiovascular disease; MI, myocardial infarction; NYHA, New York Heart Association; and PCI, percutaneous coronary intervention.

1.0 per 100 PYO), hospitalization for unstable angina (1.0 versus 0.7 versus 0.2 per 100 PYO), and hospitalization for heart failure (1.7 versus 1.1 versus 1.0 per 100 PYO). All-cause death was also higher in patients with history of MI/stroke compared with patients with established atherosclerotic cardiovascular disease without MI/stroke or those with cardiovascular risk factors alone (incidence rates, 2.9 versus 1.9 versus 2.0 per 100 PYO, respectively).

Effects of Liraglutide on Cardiovascular Events and Mortality in Patients With a History of MI and/or Stroke

The primary composite end point occurred in 322 of 1865 patients (17.3%) with an incidence rate of 4.6 per 100 PYO in the liraglutide group compared with 372 of the 1827 patients (20.4%) with an incidence rate of 5.4

per 100 PYO in the placebo group (HR, 0.85; 95% CI, 0.73–0.99). Time to the first of the individual components of the 3-point MACE was consistently numerically reduced with liraglutide, including cardiovascular death (HR, 0.80; 95% CI, 0.63–1.02), nonfatal MI (HR, 0.83; 95% CI, 0.67–1.03), and nonfatal stroke (HR, 0.95; 95% CI, 0.71–1.27; Figures 1 and 2). All-cause death was numerically reduced by 10% (HR, 0.90; 95% CI, 0.74–1.09; Figure 2). Liraglutide treatment significantly reduced the key secondary expanded end point (7.1 events per 100 PYO) compared with the placebo group (8.0 events per PYO; HR, 0.88; 95% CI, 0.78–0.99; Figure 2).

Effects of Liraglutide on Cardiovascular Events in Patients With a History of Established Atherosclerotic Cardiovascular Disease Without MI/Stroke

The primary composite end point occurred in 158 of the 1538 patients (10.3%) with an incidence rate of 2.7 PYO in the liraglutide group compared with 199 of the 1545 patients (12.9%) with an incidence rate of 3.4 per 100 PYO in the placebo group (HR, 0.76; 95% CI, 0.62–0.94). Individual components of 3-point MACE were consistently reduced with liraglutide, including cardiovascular death (HR, 0.59; 95% CI, 0.41–0.84), nonfatal MI (HR, 0.91; 95% CI, 0.68–1.22), and nonfatal stroke (HR, 0.68; 95% CI, 0.45–1.03; (Figures 1 and 2). All-cause death was reduced by 34% (HR, 0.66; 95% CI, 0.51–0.86; Figure 2 and Figure I in the online-only Data Supplement). Liraglutide treatment also showed consistent reduction of the key expanded secondary end point (incidence rate, 4.4 per 100 PYO) compared with placebo (incidence rate, 5.7 per 100 PYO; HR, 0.74; 95% CI, 0.63–0.87; Figure 2).

Effects of Liraglutide on Cardiovascular Events in Patients With Cardiovascular Risk Factors Alone

In patients with cardiovascular risk factors alone, the primary composite end point occurred in 128 of 1265 patients (10.1%) with an incidence rate of 2.6 per 100 PYO in the liraglutide group compared with 123 of the 1300 patients (9.5%) with an incidence rate of 2.5 per 100 PYO in the placebo group (HR, 1.08; 95% CI, 0.84–1.38). The HRs for liraglutide versus placebo for time to the first of the individual components of the 3-point MACE were as follows: 0.99 (95% CI, 0.67–1.46) for cardiovascular death, 1.00 (95% CI, 0.67–1.49) for nonfatal MI, and 1.12 (95% CI, 0.68–1.82) for nonfatal stroke (Figures 1 and 2). The HR for all-cause death was 0.95 (95% CI, 0.72–1.27; Figure 2). Liraglutide treatment showed a similar trend for the key secondary expanded end point (incidence rate, 3.9 per 100 PYO)

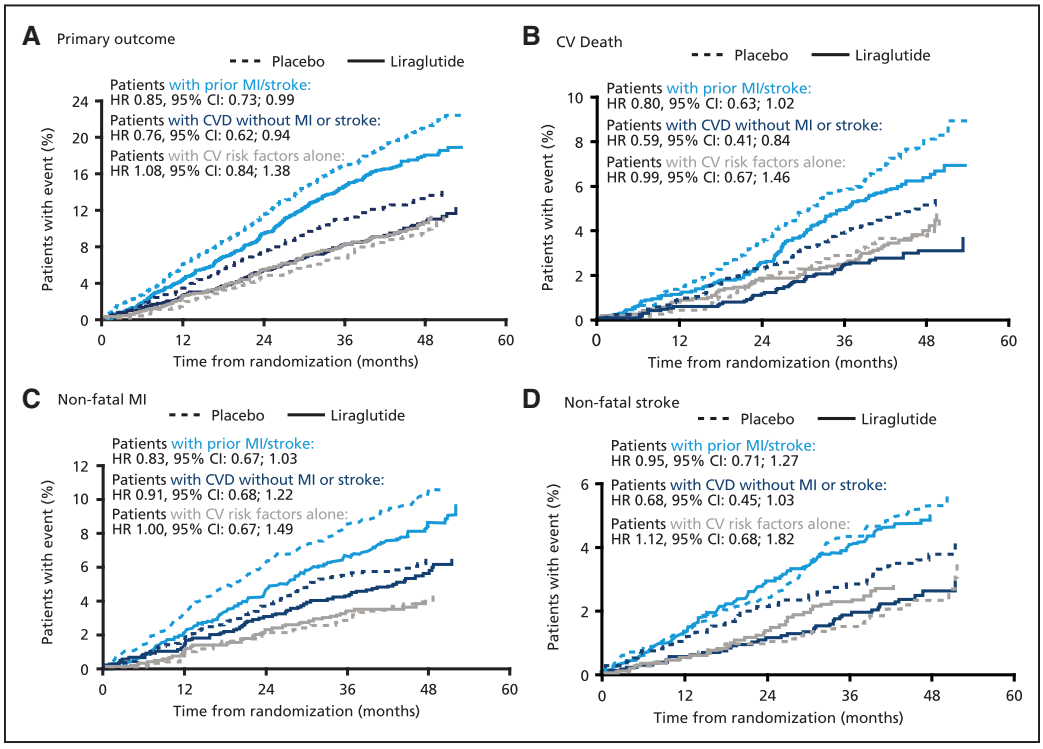

Figure 1. Occurrence of the primary composite outcome (A), cardiovascular (CV) death (B), nonfatal myocardial infarction (MI; C), and nonfatal stroke (D), stratified by history of MI and/or stroke, established cardiovascular disease (CVD) without MI/stroke, or cardiovascular risk factors alone. Primary composite end point (cardiovascular death, nonfatal MI, or nonfatal stroke) from randomization to follow-up. The *x* axis was truncated at 54 months because <10% of patients remained in the trial after this time point. HR indicates hazard ratio between treatment groups (liraglutide vs placebo).

compared with the placebo group (incidence rate, 3.5 per 100 PYO; HR, 1.12; 95% CI, 0.91–1.38; Figure 2).

Comparing the Cardiovascular Effects of Liraglutide Across Risk Groups

No statistically significant interactions were found across risk groups for the primary end point ($P_{interaction}$=0.11), cardiovascular death ($P_{interaction}$=0.19), nonfatal MI ($P_{interaction}$=0.71), or nonfatal stroke ($P_{interaction}$=0.28), indicating no statistical differences across the subgroups in these post hoc analyses (Figures 1 and 2). The interaction for the expanded key secondary end point was significant ($P_{interaction}$=0.01). Liraglutide appeared to reduce cardiovascular outcomes consistently in patients with history of MI/stroke and in those with evidence of established atherosclerotic cardiovascular disease without MI/stroke. However, in patients with cardiovascular risk factors alone, liraglutide seemed more neutral with respect to the primary and expanded composite end point.

Analyses of Number Needed to Treat

The number needed to treat to prevent a first MACE with liraglutide compared with placebo over 3 years was 39 in patients with a history of MI/stroke and 44 in patients with established atherosclerotic cardiovascular disease without MI/stroke. The number needed to treat for liraglutide to prevent 1 cardiovascular death was 82 and 63 in these respective risk groups.

Sensitivity Analysis

In separate subanalyses based on the total LEADER population, we stratified by history of MI/stroke alone. Liraglutide reduced cardiovascular outcomes regardless of baseline history of MI and/or stroke for the primary end point ($P_{interaction}$=0.56) and for the key secondary expanded composite end point ($P_{interaction}$=0.90). Furthermore, the treatment effect of liraglutide on nonfatal MI ($P_{interaction}$=0.39) or nonfatal stroke ($P_{interaction}$=0.64) was also similar in patients with and without a history of MI/stroke. Liraglutide reduced rates of cardiovascular mortality similarly in patients with and without a history of MI/stroke ($P_{interaction}$=0.79; Figure I in the online-only Data Supplement). After stratification by known cerebrovascular or coronary artery disease, defined as those with a history of CABG, percutaneous coronary intervention, or carotid revascularization in addition to MI/stroke, results were similar with comparable relative risk re-

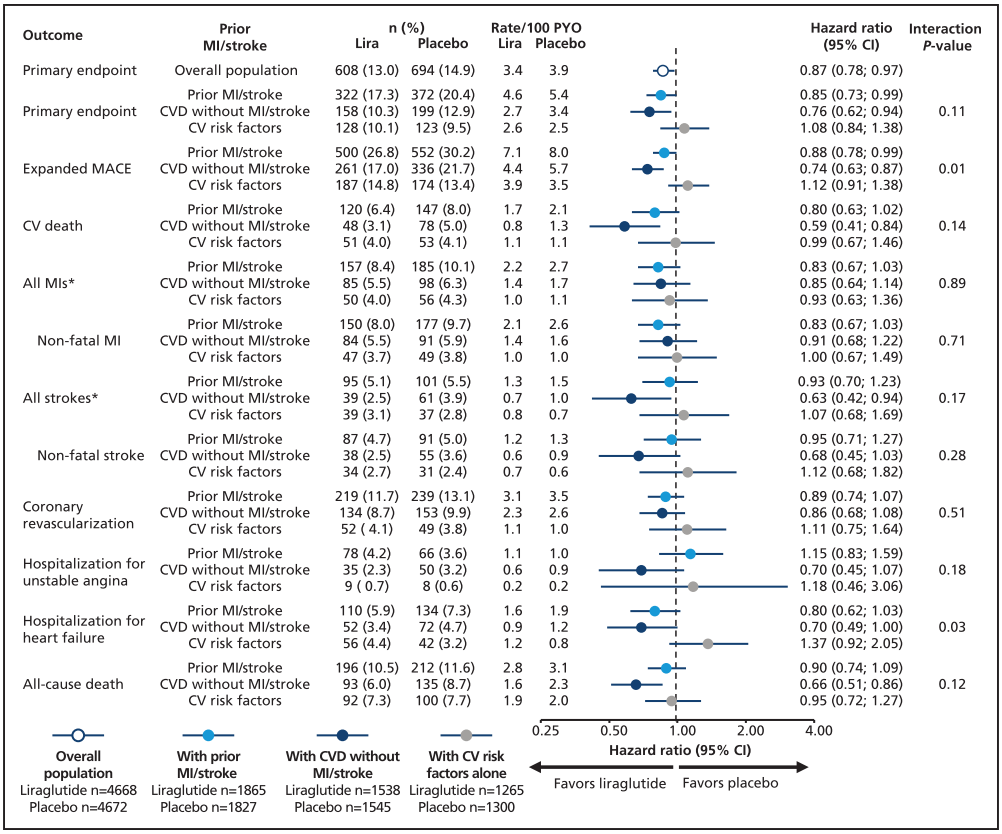

Figure 2. Occurrence of cardiovascular outcomes stratified by history of myocardial infarction (MI)/stroke, established cardiovascular (CV) disease (CVD) without MI/stroke, or cardiovascular risk factors alone.

N refers to the number of patients with an event (as a proportion of the full analysis set). Lira indicates liraglutide; MACE, major adverse cardiovascular event; and PYO, person-years of observation. *Including fatal and nonfatal events.

ductions for the primary and expanded key secondary end points with liraglutide. Greater absolute risk reductions were noted in patients with a history of MI/stroke and/or coronary/cerebral revascularization procedures. Furthermore, for individual components of the expanded composite end point, consistency in risk reductions was observed (Figure II in the online-only Data Supplement).

Finally, sensitivity analyses taking into account all-cause death as a competing risk factor showed similar results for the treatment differences (Figure III in the online-only Data Supplement).

Efficacy of Liraglutide on Nephropathy Outcomes, Glycohemoglobin, Weight, and Systolic Blood Pressure According to Risk Groups

The composite renal outcome was consistently reduced in patients with MI/stroke (HR, 0.71; 95% CI, 0.54–0.94) and in those with established atherosclerotic cardiovascular disease without a history of MI/stroke (HR, 0.66; 95% CI, 0.49–0.90) and numerically lower in those with cardiovascular risk factors alone (HR, 0.92; 95% CI, 0.71–1.19; $P_{interaction}$=0.23).

Similar effects of liraglutide across risk groups were observed within efficacy parameters: differences in glycohemoglobin reduction resulting from treatment with liraglutide versus placebo from baseline to the 3-year visit were –0.40% (95% CI, –0.50 to –0.31) in patients with a history of MI/stroke, –0.43% (95% CI, –0.53 to –0.33) in those with established atherosclerotic cardiovascular disease without a history of MI/stroke, and –0.34% (95% CI, –0.45 to –0.23) in those with cardiovascular risk factors alone ($P_{interaction}$=0.48). Differences in weight reduction resulting from treatment were also consistent in all risk groups: –2.23 kg (95% CI, –2.67 to –1.79), –2.16 kg (95% CI, –2.64 to –1.69), and –2.43 kg (95% CI, –2.95 to –1.91), respectively ($P_{interaction}$=0.74). Furthermore, no differences in treatment effects of liraglutide on systolic blood pressure were seen across groups ($P_{interaction}$=0.83).

Adverse Events

Adverse events are listed in Table I in the online-only Data Supplement. Overall, adverse event percentages were 64.9% in patients with a history of MI/stroke, 61.1% in those with established atherosclerotic cardiovascular disease without MI/stroke, and 57.3% in those with cardiovascular risk factors alone. The proportion of patients with any adverse events was similar between the liraglutide and placebo groups in patients with a history of MI/stroke (65.0% versus 64.8%), in patients with established atherosclerotic cardiovascular disease without MI/stroke (62.2% versus 60.0%), and in patients with cardiovascular risk factors alone (58.6% versus 56.1%). Similar results were obtained for severe adverse events and serious adverse events. However, compared with patients on placebo, more patients on liraglutide permanently discontinued treatment because of adverse events: for patients with a history of MI/stroke, 10.8% versus 8.3%; for those with established atherosclerotic cardiovascular disease without MI/stroke, 8.3% versus 6.3; and for those with cardiovascular risk factors alone, 9.3% versus 7.0%, respectively. The most frequently reported adverse events were gastrointestinal symptoms, which are well-known side effects of glucagon-like peptide-1 receptor agonists.

DISCUSSION

In this post hoc analysis of the LEADER trial including patients with T2DM and high cardiovascular risk, we have shown that patients with a history of MI/stroke had a nearly 2-fold greater risk of MACE relative to those without. In addition, we have demonstrated a consistent level of benefit on all cardiovascular end points, including cardiovascular death, associated with the use of liraglutide compared with placebo in patients with a history of MI/stroke at baseline and in those with established cardiovascular disease without MI/stroke. Similar observations were made when patients were further stratified by baseline history of coronary or cerebral revascularization. In patients with cardiovascular risk factors alone, the estimated HRs—although no significant interaction between risk groups was found for the primary outcome and no correction for multiplicity was performed—may suggest that liraglutide had a neutral effect on cardiovascular outcomes. This is consistent with previous analyses of the LEADER trial; however, subgroups in analyses are overlapping.[8,13] Taken together, these data indicate that the cardiovascular benefits of liraglutide are observed across a clinically relevant continuum of risk in T2DM with atherosclerosis or prior ischemic events. The lack of apparent cardiovascular benefit in patients with T2DM and cardiovascular risk factors alone may suggest either a threshold effect or that a longer duration of therapy is required to demonstrate cardiovascular efficacy. However, it could also be a random finding resulting from multiplicity issues in post hoc analyses. The finding is in line with other trials that also showed a greater effect of intervention on cardiovascular outcomes for patients at higher cardiovascular risk.[14–19] The renal composite outcome, glycohemoglobin, weight, and systolic blood pressure were reduced with liraglutide treatment independently of risk group.

Patients recruited into the LEADER trial were categorized as being either >50 years of age with established cardiovascular or chronic kidney disease or >60 years of age with 1 additional cardiovascular risk factor (microalbuminuria or proteinuria, hypertension and left ven-

tricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle-brachial index <0.9). Hence, although this type of enrollment strategy was effective in identifying patients with T2DM at high risk of developing cardiovascular events during the trial, it was not ideally suited to provide practical information to help physicians decide whether the benefits of liraglutide may be seen in patients with or without a history of atherosclerotic cardiovascular disease treated within a duration of time similar to that of the LEADER trial. Clinicians often base decisions on risk reduction therapies on the presence or absence of prior MI/stroke or other established atherosclerotic cardiovascular disease (secondary prevention) or on evidence of risk factors alone (primary prevention)[1,9]; hence, the assessment of cardiovascular effects based on these categories is important. When we examine the outcomes on the basis of the presence of MI/stroke, there is no heterogeneity with respect to the relative benefits of liraglutide on cardiovascular outcomes; however, a more neutral result is observed in those with cardiovascular risk factors alone. There is, of course, a large overlap between the >60 years of age enrollment stratum and the subgroup of patients with cardiovascular risk factors alone, and the present finding of neutrality is in concordance with the previous subgroup analysis of LEADER, in which an actual interaction between the 2 recruitment strata was detected, suggesting a differential treatment effect of liraglutide in these subgroups.[8]

Recently, the EXSCEL trial (Exenatide Study of Cardiovascular Event Lowering) reported cardiovascular outcomes with exenatide, an exendin-4–based glucagon-like peptide-1 receptor agonist.[17] Similar to LEADER, this trial recruited a patient population with T2DM, established cardiovascular disease, and multiple risk factors. Although the primary outcome and mortality showed directional consistency with LEADER, the primary outcome was not significant with respect to superiority. In keeping with subgroup analyses in LEADER, the HR for the primary outcome was 0.90 (95% CI, 0.82–1.00) in EXSCEL patients with a prior cardiovascular event, defined as clinical manifestation of coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral artery disease, versus an HR of 0.99 (95% CI, 0.77–1.28) in those without a history of a cardiovascular event. In line with this trend, the subgroup analysis for SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) showed an HR of 0.72 (95% CI, 0.55–0.93) for patients with established cardiovascular disease and an HR of 1.00 (95% CI, 0.41–2.46) for those with cardiovascular risk factors alone ($P_{interaction}$=0.49).[20] For EXSCEL, SUSTAIN-6, and LEADER, the group without established cardiovascular disease, as defined by the inclusion criteria, contributed a smaller proportion of primary events because of their lower absolute risk.[8,18,20]

In the CANVAS program (Canagliflozin Cardiovascular Assessment Study), the cardiovascular outcomes trial investigating the sodium-glucose cotransporter-2 inhibitor canagliflozin,[21] patients with T2DM were enrolled who were ≥50 years of age and had ≥2 cardiovascular risk factors or were ≥30 years of age and with a history of cardiovascular event defined as stroke, MI, hospitalization for unstable angina, CABG, peripheral revascularization, and carotid or peripheral vascular disease or amputation resulting from vascular disease. Overall, patients enrolled in the CANVAS program were at a lower risk than patients in LEADER. This is manifested by seemingly lower event rates in the 2 cardiovascular risk cohorts in CANVAS compared with the LEADER population stratified by MI/stroke (for MACE: 1.6 versus 2.8 per 100 patient-years for the lower-risk groups and 3.7 versus 5.0 per 100 patient-years for the higher-risk groups, respectively). Canagliflozin reduced cardiovascular outcomes primarily in patients with prior cardiovascular disease, with a neutral outcome for MACE observed in those in the primary prevention subgroup, although consistent benefits were seen with respect to heart failure and renal end points.[21]

There are limitations to these analyses of the LEADER data. First, we do not have the time from the self-reported pretrial MI/stroke to randomization. Because the first year after the event is usually considered a higher-risk period for recurrent events,[5] efficacy of liraglutide in this cohort would have been interesting to evaluate. Second, there was a lack of detail in the collection of information of history of cardiovascular disease before enrollment; for example, baseline assessments of cardiovascular disease were lacking. In addition, because of the lower number of patients within the subgroups of interest compared with the overall trial population, there is limited statistical power to determine the effects of liraglutide within these subgroups.

CONCLUSIONS

In this clinically relevant post hoc analysis of the LEADER trial, we demonstrate similar relative risk reductions yet higher absolute risk reductions of liraglutide on cardiovascular events in patients with a history of MI/stroke. Liraglutide exerts a consistent benefit in patients with established atherosclerotic cardiovascular disease with and without a history of MI/stroke; however, it appears to be neutral in patients with cardiovascular risk factors alone. The reason for no apparent cardiovascular benefit in patients with cardiovascular risk factors alone could be that the baseline risk was lower, and establishing any potential effect might require a longer treatment period or larger sample size. Nevertheless, all patients with T2DM regardless of risk group benefit from liraglutide treatment in regard to reduced renal outcomes, improved glycemic control, weight reduction, and better blood pressure control. These data may

provide clinicians with important information to help identify appropriate patients who would most benefit from liraglutide therapy in their practice.

ARTICLE INFORMATION

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