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Design of the liraglutide effect and action in diabetes: Evaluation of cardiovascular outcome results (LEADER) trial

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Background Diabetes is a multisystem disorder associated with a nearly twofold excess risk for a broad range of adverse cardiovascular outcomes including coronary heart disease, stroke, and cardiovascular death. Liraglutide is a human glucagon-like peptide receptor analog approved for use in patients with type 2 diabetes mellitus (T2DM).

Study Design To formally assess the cardiovascular safety of liraglutide, the Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial was commenced in 2010. LEADER is a phase 3B, multicenter, international, randomized, double-blind, placebo-controlled clinical trial with long-term follow-up. Patients with T2DM at high risk for cardiovascular disease (CVD) who were either drug naive or treated with oral antihyperglycemic agents or selected insulin regimens (human NPH, long-acting analog, or premixed) alone or in combination with oral antihyperglycemics were eligible for inclusion. Randomized patients are being followed for up to 5 years. The primary end point is the time from randomization to a composite outcome consisting of the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

Conclusions LEADER commenced in September 2010, and enrollment concluded in April 2012. There were 9,340 patients enrolled at 410 sites in 32 countries. The mean age of patients was 64.3 ± 7.2 years, 64.3% were men, and mean body mass index was 32.5 ± 6.3 kg/m². There were 7,592 (81.3%) patients with prior CVD and 1,748 (18.7%) who were high risk but without prior CVD. It is expected that LEADER will provide conclusive data regarding the cardiovascular safety of liraglutide relative to the current standard of usual care for a global population of patients with T2DM. (Am Heart J 2013;166:823-830.e5.)

Background

Diabetes mellitus affects nearly 350 million people worldwide,¹ including 26 million patients in the United

States,² and the prevalence continues to increase. Diabetes is a chronic disease associated with long-term vascular complications. Type 2 diabetes mellitus (T2DM) is a multisystem disorder that is also independently associated with a nearly twofold excess risk for a broad range of adverse cardiovascular outcomes including coronary heart disease (CHD), stroke, and cardiovascular death. Subgroups of individuals with diabetes at lower absolute risk of cardiovascular complications, including women, younger persons, nonsmokers, and persons with below average blood pressure, also have an elevated risk of micro- and macrovascular complications (including CHD), compared with persons without diabetes.³

Effective strategies to mitigate cardiovascular risk and prevent or reduce the occurrence of microvascular complications are the cornerstone of treatment for patients with diabetes.⁴ These measures include lifestyle management, smoking cessation, and individualized risk

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^mOn behalf of the LEADER Trial investigators.

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factor treatment for low-density lipoprotein cholesterol and blood pressure. Glycemic control significantly reduces the development and progression of microvascular complications. Although metformin is the mainstay of initial therapy, treatment with a glucagon-like peptide-1 (GLP-1) receptor agonist is now regularly used as an add-on approach to achieve glycemic control.⁵

Although available diabetes therapies clearly improve glycemic control, the cardiovascular safety of particular glucose-lowering agents is controversial. When cardiovascular safety concerns were identified in an agonist of the peroxisome proliferator-activated receptor gamma class,⁶ as well as in a separate federally funded study examining tight glycemic control in general,⁷ the United States Food and Drug Administration subsequently issued mandatory guidelines to manufacturers for evaluating the cardiovascular safety of emerging therapies to treat diabetes.⁸ Before new diabetes drug approval, manufacturers are now required to perform an integrated meta-analysis of completed studies to demonstrate an estimated relative risk with upper two-sided 95% confidence limits for major adverse cardiovascular events of <1.8 versus comparators. If the upper limit is 1.3 to 1.8, safety must subsequently be demonstrated in postmarketing cardiovascular outcome trials to rule out an upper confidence limit of 1.3.

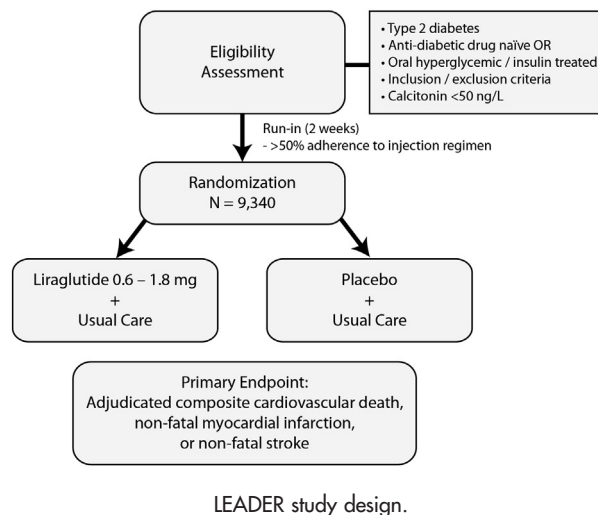
Glucagon-like peptide-1 and liraglutide. Native GLP-1 is an incretin hormone produced in the gut and secreted in response to food consumption.⁹ The main pharmacological effects of GLP-1 are stimulation of endogenous insulin in response to elevated glucose, suppression of elevated glucagon, and regulation of satiety/appetite^{10,11} and are all potentially beneficial or impaired in T2DM.

Liraglutide is an analog of human GLP-1 approved for use in patients with T2DM. Liraglutide has 97% homology with human GLP-1 and is administered subcutaneously once daily. Its glucose-lowering efficacy has been established, and its use results in hemoglobin A1c (HbA1c) reductions of 1.0 to 1.5% in addition to moderate weight loss across a wide range of patient types.¹² To formally assess the cardiovascular safety of liraglutide, the Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial (clinicaltrials.gov NCT01179048) was commenced in 2010. This article reports the study design and baseline characteristics of the study population.

Study design

Objective. The primary objective of LEADER is to assess the effect of treatment with liraglutide compared to placebo (for at least 3.5 years and up to 5 years) on the incidence of cardiovascular events, as defined by the primary end point of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke in adult patients with T2DM. The primary analysis will be noninferiority testing. If the prespecified noninferiority criteria are met, then superiority testing will be per-

Figure 1



formed. Noninferiority of liraglutide versus placebo will be assessed by inspecting the upper range of the two-sided 95% CI, and noninferiority will be established if that upper range is <1.3. Only if noninferiority is established for the primary outcome will the data then be used to test for evidence of a lower outcome hazard with liraglutide over placebo. Superiority will be established if the hazard ratio of the upper range of the two-sided 95% CI is <1.0. This approaches a closed testing procedure, and therefore, no adjustment of the significance level is required.

Patient population. LEADER is a phase 3B, multicenter, international, randomized, double-blind, placebo-controlled clinical trial with long-term follow-up (Figure 1). Male and female patients with T2DM, who were either drug naïve or treated with oral antihyperglycemic agents or selected insulin regimens (human NPH, long-acting analog, or premixed) alone or in combination with oral antihyperglycemics were eligible for inclusion.

LEADER enrolled 2 distinct populations of high-risk patients either with or without prior cardiovascular disease (CVD): (1) patients with prior CVD were ≥ 50 years old and had one or more of the following cardiovascular comorbidities (detailed criteria are shown in Table 1): concomitant CVD, cerebrovascular disease, peripheral vascular disease, chronic renal failure, or chronic heart failure; (2) patients without prior CVD were ≥ 60 years old at screening and had one or more cardiovascular risk factors shown in Table 1. Enrollment of approximately 400 patients with moderate (30-59 mL/min per 1.73 m²) and 200 patients with severe (<30 mL/min per 1.73 m²) reductions in baseline estimated glomerular filtration rate (eGFR) as estimated using the Modification of Diet in Renal Disease (MDRD)

Table I. LEADER Inclusions and Exclusions

Inclusion criteria

- Type 2 diabetes
- Anti-diabetic drug naïve or treated with one or more oral anti-diabetic drugs or treated with human NPH insulin or long-acting insulin analogue or premixed insulin, alone or in combination with OAD(s)
- HbA1c $\geq 7.0\%$
- Prior CVD cohort: age ≥ 50 and ≥ 1 of the following criteria.
 - Prior MI
 - Prior stroke or TIA
 - Prior coronary, carotid or peripheral arterial revascularization
 - $>50\%$ stenosis of coronary, carotid, or lower extremity arteries
 - History of symptomatic CHD documented by Positive exercise stress test or any cardiac imaging or Unstable angina with ECG changes
 - Asymptomatic cardiac ischemia Documented by positive nuclear imaging test, exercise test or dobutamine stress echo
 - Chronic heart failure NYHA class II-III
 - Chronic renal failure, eGFR <60 mL/min per 1.73m^2 MDRD eGFR <60 mL/min per Cockcroft-Gault formula
- No Prior CVD group: Age ≥ 60 y and ≥ 1 of the following criteria.
 - Microalbuminuria or proteinuria
 - Hypertension and left ventricular hypertrophy by ECG or imaging
 - Left ventricular systolic or diastolic dysfunction by imaging
 - Ankle-brachial index <0.9

Exclusion criteria

- Type 1 diabetes
- Calcitonin ≥ 50 ng/L
- Use of a GLP-1 receptor agonist (exenatide, liraglutide or other) or pramlintide or any DPP-4 inhibitor within the 3 months prior to screening
- Use of insulin other than human NPH insulin or long-acting insulin analogue or premixed insulin within 3 months prior to screening. Short-term use of other insulin during this period in connection with intercurrent illness is allowed, at Investigators discretion
- Acute decompensation of glycemic control
- An acute coronary or cerebrovascular event in the previous 14 d
- Currently planned coronary, carotid, or peripheral artery revascularization
- Chronic heart failure (NYHA class IV)
- Current continuous renal replacement therapy
- End-stage liver disease
- History of solid organ transplant or awaiting solid organ transplant
- Malignant neoplasm
- Family or personal history of multiple endocrine neoplasia type 2 (MEN2) or familial medullary thyroid carcinoma (FMTC)
- Personal history of non-familial medullary thyroid carcinoma

equation was also prespecified. Exclusion criteria are listed in Table I.

Treatment regimen. After eligibility assessment and informed consent, patients completed a minimum 2-week run-in period consisting of a daily single-blind subcutaneous injection of placebo. Patients demonstrating $\geq 50\%$ adherence to the regimen and willingness to continue with the injection protocol throughout the trial then underwent randomization, which was carried out for all subjects using the interactive voice/web response system. Subjects meeting all inclusion/exclusion criteria were randomized in a 1:1 manner to receive a double-blind, once-daily maximum dose of liraglutide 1.8 mg or

Table II. Standard of Care Guidelines for LEADER

Blood glucose

- HbA1c $\leq 7.0\%$ (individualized depending on patient).
- If $>7.0\%$, additional HbA1c measurement after 3 m. If HbA1c still $>7.0\%$, treatment should be intensified to achieve target if appropriate.

Therapy

- Lifestyle modifications and metformin are considered foundational therapy in most countries
- Intensification:
 - Add-on therapy: thiazolidinediones, sulfonylureas, α -glucosidase inhibitors, according to local labels (dipeptidyl peptidase-4 inhibitors and other incretin based therapies are not allowed)
 - Insulin therapy should be based on local practice, including basal, basal/bolus, premix, and mealtime bolus (SIT)

Blood pressure

- Target: 130/80 mm Hg

Antihypertensive therapy

- First line: ACE inhibitors or ARBs
- Based on individual patient needs: Ca²⁺-blockers, diuretics, others

Lipid targets and therapy

- LDL <100 mg/dL (<70 mg/dL in patients with previous cardiovascular events)
- Statins recommended for all patients
- Second line therapy at investigator discretion

Antiplatelet therapy

- Aspirin or clopidogrel (if aspirin intolerant) for patients with prior cardiovascular events (MI, cerebrovascular accident, or revascularization)

equivalent placebo as an add-on to their standard-of-care treatment. Liraglutide was administered at 0.6 mg daily for 1 week, 1.2 mg for an additional week, and a potential maximum dosage thereafter of 1.8 mg based on tolerance, as determined by the investigator.

For patients with suboptimal glucose control after randomization, concomitant use and dosage of insulin, sulfonylureas, glimepiride, thiazolidinediones, and α -glucosidase inhibitors is permitted at the discretion of the investigator, but use of other GLP-1 agonists, dipeptidyl peptidase-4 inhibitors, and pramlintide is not.

Concomitant use of premixed insulin. Continued use of premixed insulin, including injection frequency and timing, during the trial is permitted at the investigator's discretion. A 20% reduction in insulin dosage when starting randomized therapy is recommended for patients with HbA1c $\leq 8\%$.

The LEADER global expert panel (GEP) and national study leaders in participating countries developed a protocol for the treatment of risk factors and concomitant use of medications. Guidelines were finalized during a series of workshops using consensus practice recommendations in 2010.¹³⁻¹⁶ Table II contains a list of the finalized standard of care guidelines endorsed by the LEADER steering committee.

Planned follow-up. After randomization, patients were initially seen at 1, 3, and 6 months. Thereafter, patients are seen every 6 months for up to 5 years. During each study visit, patients are assessed for clinical events, study drug compliance, and concomitant medication

usage. Blood, urine specimens, and electrocardiograms were collected at randomization and then yearly for the duration of the study.

End points. The primary end point is the time from randomization to a composite outcome consisting of the first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke. Comprehensive descriptions for each component of the primary composite end point are listed in the online Appendix Supplementary Table I. Secondary end points include the first occurrence of an expanded composite cardiovascular outcome, including cardiovascular death, nonfatal MI, nonfatal stroke, revascularization, hospitalization for unstable angina, or hospitalization for chronic heart failure. Additional end points include time from randomization to the occurrence of noncardiovascular or all-cause death, each individual component of the expanded composite cardiovascular outcome, composite microvascular outcomes, and each individual component of composite microvascular outcomes.

Safety end points. Additional end points are being assessed to support the secondary efficacy and safety objectives (online Appendix Supplementary Table II). Hypoglycemia is defined according to American Diabetes Association criteria¹⁷ as (1) severe: requiring the assistance of another person to administer resuscitative actions, carbohydrate, or glucagon; (2) documented symptomatic: typical symptoms of hypoglycemia accompanied by a measured plasma glucose concentration ≤ 70 mg/dL; (3) asymptomatic: measured plasma glucose concentration ≤ 70 mg/dL in the absence of symptoms; (4) probable symptomatic: unmeasured plasma glucose concentration in the presence of typical symptoms of hypoglycemia; and (5) relative hypoglycemia: typical symptoms of hypoglycemia and interpreted by the patient as a hypoglycemic episode with a measured plasma glucose concentration ≥ 70 mg/dL. An independent, event adjudication committee (EAC) blinded to treatment arm will adjudicate serious adverse events, including pancreatitis or severe persistent abdominal pain leading to suspicion of pancreatitis, neoplasm, and thyroid disease resulting in thyroidectomy (online Appendix Supplementary Table II).

Calcitonin monitoring. Blood samples were collected at screening to assess baseline levels of calcitonin in a central laboratory; patients with values ≥ 50 ng/L were excluded. Calcitonin levels are measured at prespecified time intervals in all subjects throughout the study. An independent calcitonin-monitoring committee (CMC) consisting of thyroid experts blinded to treatment provides ongoing surveillance to monitor longitudinal changes in calcitonin levels. Any value ≥ 20 ng/L is reported to the CMC for review and consideration of additional diagnostic procedures. For any level ≥ 20 ng/L, testing is repeated within 4 weeks. If the level is

confirmed, a medical event of special interest is reported, and the CMC provides guidance on individualized follow-up and/or subsequent monitoring to site investigators. All medical events of special interest, including development of neoplasm or thyroid disease resulting in thyroidectomy, are reviewed and adjudicated by the EAC.

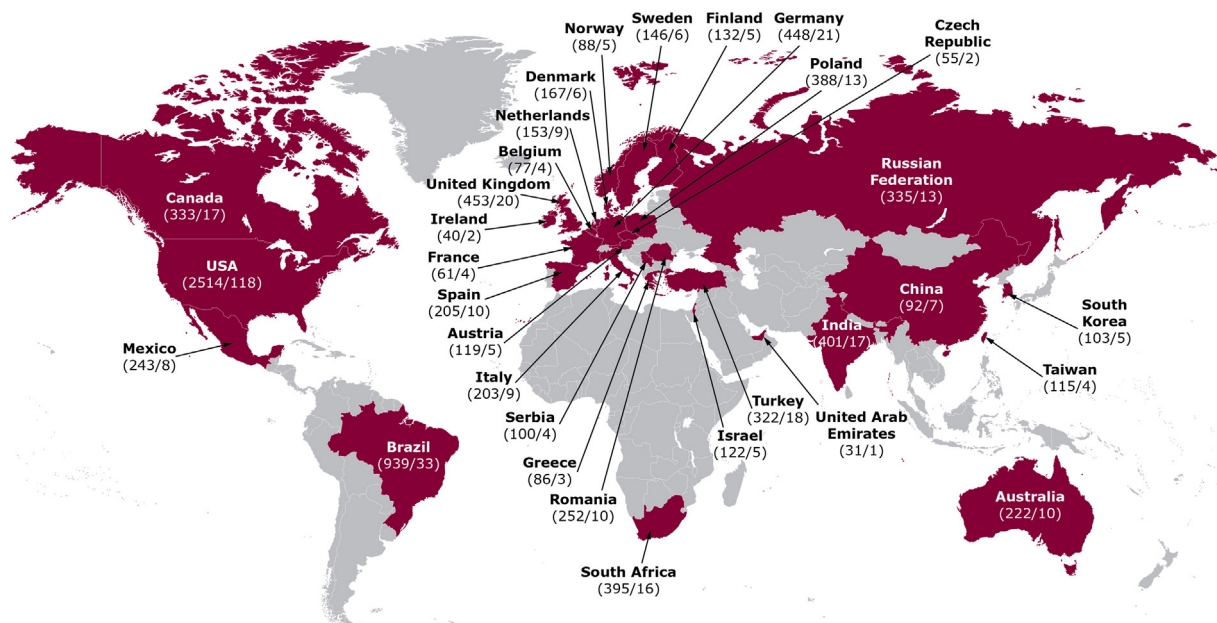
Study organization, event adjudication, and data monitoring. LEADER is overseen by a steering committee composed of experts in endocrinology, cardiology, gastroenterology, thyroid disease, nephrology, biostatistics, and employees of the study sponsor (Novo Nordisk). The steering committee independently oversees all aspects of the trial. The GEP consists of principal investigators from enrolling countries and designated employees of the sponsor and provides advice and active implementation assistance for operational issues.

Several end points will be adjudicated by the EAC based on several efficacy end points, including death, acute coronary syndrome (MI and hospitalization for unstable angina), cerebrovascular events (stroke and transient ischemic attack), coronary revascularization procedures, hospitalization for heart failure, nephropathy, and diabetic retinopathy.

The EAC consists of experts in cardiology, neurology, gastroenterology, endocrinology, oncology, pathology, nephrology, and ophthalmology and will meet throughout the duration of the trial. A chairperson oversees 4 separate subcommittees consisting of 16 primary adjudicators. The cardiovascular subcommittee includes 2 cardiologists and 2 neurologists. The microvascular subcommittee includes 2 nephrologists and 2 ophthalmologists. The pancreatitis subcommittee includes 3 gastroenterologists. The neoplasm subcommittee includes 3 oncologists and 2 endocrinologists. In case of thyroid disease resulting in a thyroidectomy, adjudicators include 1 endocrinologist and 1 oncologist who will review both the local pathology report and the report of an external pathologist who has reviewed the pathology specimen independently.

An independent, external data-monitoring committee (DMC) was established to perform ongoing safety surveillance and consists of permanent members who are recognized experts in cardiology, endocrinology, gastroenterology, and statistics. The DMC has access to complete unblinded data and meets at predefined intervals and on an ad hoc basis as required to evaluate all relevant safety information. After each meeting, the DMC will issue a recommendation on trial continuation, modification, or termination. The DMC can recommend to terminate the trial prematurely in case there is evidence for an excess number of deaths in the liraglutide group (significance level determined at $P < .01$), an excess number of major adverse cardiovascular events in the liraglutide group (significance level determined at $P <$

Figure 2



Enrollment of LEADER trial participants by country. Data presented are number of randomized participants/number of trial sites that randomized participants by country. In total, 9,340 participants were randomized across 410 active LEADER trial sites. There were 7 sites that screened but did not enroll or randomize any participants.

.01), or clear evidence of benefit for the primary end point in the liraglutide arm (significance level determined at $P < .001$).

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Statistical considerations

Sample size calculation. The required sample size was estimated on the basis of time to first primary outcome using a log-rank test that included the full analysis set and an intention-to-treat principle. The primary event rate was estimated to be 1.8% in both the liraglutide and placebo groups, with uniform enrollment over 1.5 years, and a maximum follow-up period of 5 years. The noninferiority margin was set at 1.3 for the upper bound of the 2-sided 95% CI. It was also estimated that patients who permanently stop randomized treatment and are lost to follow-up would not exceed 10% in total. Finally, the power to reject the null hypothesis (ie, that the upper bound of

the 2-sided CI would exceed 1.3) was set at 90%. Given these assumptions, 8,754 randomized subjects were required with an accrual of no <611 events with a minimum follow-up of 42 months after last subject randomized.

Analysis of the primary end point. Only outcomes confirmed by the blinded EAC will be analyzed. Subjects who complete or discontinue the trial without having an outcome will be censored for the relevant analyses on the last day of follow-up. The primary end point will be analyzed for the full analysis set and performed using Cox regression, including only treatment group as a covariate. The Cox regression model will be used to estimate the hazard ratio (liraglutide to placebo) and the 2-sided 95% CI. The objective of the LEADER trial is to assess the cardiovascular safety of liraglutide. Safety will be established if the two-sided 95% confidence limit is less than the prespecified upper bound of 1.3, as established by the United States Food and Drug Administration. If safety is established, then formal superiority testing will be performed. Noninferiority of liraglutide versus placebo will be assessed and established if the upper limit is <1.3 . If noninferiority is established for the primary outcome, the data will be used to test for evidence of a lower outcome hazard with liraglutide versus placebo. Superiority with respect to the hazard ratio will be established if the upper range

Table III. Baseline characteristics of all randomized subjects and by presence of existing CVD

Clinical demographics	Previous CVD (n = 7,592)	No previous CVD (n = 1,748)	Total (N = 9,340)
Age, y	63.9 ± 7.6	65.8 ± 5.2	64.3 ± 7.2
Gender (male)	5,048 (66.5)	955 (54.6)	6,003 (64.3)
Ethnicity			
Hispanic or Latino	908 (12.0)	227 (13.0)	1,135 (12.2)
Not Hispanic or Latino	6,684 (88.0)	1,521 (87.0)	8,205 (87.8)
Race			
White	5,974 (78.7)	1,263 (72.3)	7,237 (77.5)
Asian	753 (9.9)	169 (9.7)	922 (9.9)
Black	535 (7.0)	240 (13.7)	775 (8.3)
Other	330 (4.3)	76 (4.3)	406 (4.3)
Weight, kg	92.3 ± 20.9	89.6 ± 21.4	91.8 ± 21.0
Body mass index, kg/m ²	32.5 ± 6.3	32.4 ± 6.3	32.5 ± 6.3
Hypertension	6,888 (90.7)	1,520 (87.0)	8,408 (90.0)
Hyperlipidemia	6,135 (80.8)	1,056 (60.4)	7,191 (77.0)
Smoking			
Current	927 (12.2)	203 (11.6)	1,130 (12.1)
Previous	3,670 (48.3)	667 (38.2)	4,337 (46.4)
Coronary artery disease	5,288 (69.7)	17 (1.0)	5,303 (56.8)
Congestive heart failure	1,562 (20.6)	37 (2.1)	1,599 (17.1)
Peripheral artery disease	1,394 (18.4)	250 (14.3)	1,644 (17.6)
Diabetes duration, y	12.8 ± 8.1	12.3 ± 7.5	12.7 ± 8.0
HbA1c, %	8.7 ± 1.5	8.8 ± 1.6	8.7 ± 1.5
Glucose-lowering therapy			
None/diet	405 (5.3)	99 (5.7)	504 (5.4)
Oral antihyperglycemics*			
1	1,539 (20.3)	378 (21.6)	1,917 (20.5)
2	2,131 (28.1)	555 (31.8)	2,686 (28.8)
≥3	257 (3.4)	71 (4.1)	328 (3.5)
Insulin†	3,260 (42.9)	645 (36.9)	3,905 (41.8)
Aspirin use	5,807 (76.5)	716 (41.0)	6,523 (69.8)
Laboratory Evaluation			
Total cholesterol, mg/dL	168.5 ± 45.4	178.8 ± 43.8	170.4 ± 45.3
LDL cholesterol, mg/dL	88.0 ± 35.5	96.5 ± 34.6	89.5 ± 35.5
HDL, mg/dL	44.9 ± 12.1	48.0 ± 12.7	45.5 ± 12.3
Triglycerides, mg/dL	183.5 ± 141.1	177.8 ± 135.0	182.5 ± 140.0
Creatinine, mg/dL	1.0 ± 0.5	0.8 ± 0.2	1.0 ± 0.4
eGFR, mL/min/1.73m ²			
<30	177 (2.3)	0	177 (1.9)
30-60	1,854 (24.4)	0	1,854 (19.9)
60-90	2,942 (38.8)	918 (52.5)	3,860 (41.3)
>90	2,619 (34.5)	828 (47.4)	3,447 (36.9)
Lipase U/L	48.2 ± 45.6	44.9 ± 34.6	47.5 ± 43.7
Amylase U/L	66.5 ± 36.8	64.7 ± 33.7	66.2 ± 36.3

Data presented as number (percentage of group) or mean ± SD.

*Not used in combination with insulin.

†Either used alone or in combination with concomitant oral antihyperglycemics.

of the two-sided 95% CI is <1. This approach is a closed testing procedure, and therefore, no adjustment of the significance level is required.^{18,19}

Exploratory subgroup analyses. The effect of sex, age (<60 or ≥60 years), body mass index (≤30 or >30 kg/m²), HbA1c (≤8.3 or >8.3%), duration of diabetes (≤11 or >11 years), region (Europe, North America, Asia, or other), race (white, black, Asian, or other), cardiovascular risk, chronic heart failure, severe chronic renal failure, severe-to-moderate chronic renal failure, and use of concomitant glucose medication and/or insulin on the primary composite end point will be explored separately

as a main effect and interaction with treatment by adding each to the original model.

There will be 2 populations analyzed. The full analysis set includes all randomized subjects with evaluation by intention-to-treat, and subjects will be evaluated as randomized. A sensitivity analysis will be performed using the per-protocol analysis set that includes only data from follow-up of subjects exposed to treatment plus 30 days. Subjects exposed to treatment in the per-protocol analysis will include those with a maximum accumulated drug holiday of ≤120 days during the study. Subjects accumulating >120 days will be

considered as having discontinued study drug on the 121st day.

Enrolled population

Enrollment for LEADER commenced in September 2010 and concluded in April 2012. Patients were enrolled at 410 sites in 32 countries (Figure 2). Baseline demographics of the enrolled population are shown in Table III. Of the 9,340 patients, 7,592 (81.3%) had prior CVD and 1,748 (18.7%) did not. There were 1,854 patients with moderate and 177 with severe reductions in screening eGFR.

Discussion

There remains a compelling need to develop novel, effective, and safe glucose-lowering therapies for patients with T2DM. Liraglutide is associated with a reduction in HbA1c ranging from 1.0 to 1.5%.²⁰ Current dosing of liraglutide was derived from clinical data aiming to improve gastrointestinal tolerability while maintaining efficacy. From this perspective, a starting dose of 0.6 mg daily is suggested, increasing to 1.2 or 1.8 mg based on clinical response.

Prior studies have investigated the perceived beneficial effects of GLP-1 receptor agonists on cardiovascular risk. The mechanism of action behind these effects remains to be clarified. However, there appear to be a number of direct and indirect effects of treatment possibly explaining this reduction in risk, such as significant weight and systolic blood pressure reduction and, potentially, direct effects on cardiac myocytes and endothelium.²¹ A decrease in systolic blood pressure of 2.1 mm Hg with liraglutide 1.2 mg and 3.6 mm Hg with 1.8 mg, together with a sustained mean weight loss of approximately 2 kg, has been reported.²² In addition, data from 5 long-term phase 3 trials suggested no adverse impact of liraglutide treatment on lipid profiles with respect to cardiovascular risk and favorable changes in triglycerides and free fatty acids. Others have reported decreases in levels of cardiovascular risk markers such as plasminogen-activator inhibitor-1 and B-natriuretic peptide after treatment.²³⁻²⁵ However, liraglutide is associated with an approximate 1-2 beat/min increase in heart rate.

Conclusions

LEADER is a phase 3B randomized, double-blind clinical trial to evaluate the cardiovascular safety of liraglutide in patients with T2DM at heightened risk for cardiovascular complications. It is expected that LEADER will provide conclusive data regarding the cardiovascular safety of liraglutide relative to standard of care for a global population of patients with T2DM.

Disclosures

Conflicts of interest: Dr Bergenstal has served on a scientific advisory board, consulted or performed clinical research with Abbott Diabetes Care, Amylin, Bayer, Becton Dickinson, Boehringer Ingelheim, Bristol-Myers Squibb/AstraZeneca, Intuity, Calibra, DexCom, Eli Lilly, Halozyme, Helmsley Trust, Hygieia, Johnson & Johnson, Medtronic, Merck, NIH, Novo Nordisk, ResMed, Roche, Sanofi, and Takeda. His employer, nonprofit Park Nicollet Institute, contracts for his services, and no personal income goes to Dr Bergenstal. He has inherited stock in Merck.

Dr Buse is an investigator and/or consultant without any direct financial benefit under contracts between his employer and the following companies: Abbott, Amylin, Andromeda, AstraZeneca, Bayhill Therapeutics, BD Research Laboratories, Boehringer-Ingelheim, Bristol-Myers Squibb, Catabasis, Cebix, Diartis, Elcylex, Eli Lilly, Exsulin, Genentech, GI Dynamics, GlaxoSmithKline, Halozyme, Hoffman-LaRoche, Johnson & Johnson, LipoScience, Medtronic, Merck, Metabolic Solutions Development Company, Metabolon, Novan, Novartis, Novo Nordisk, Orexigen, Osiris, Pfizer, Rhythm, Sanofi, Spherix, Takeda, Tolerex, TransPharma, Veritas, and Verva.

Dr Brown Frandsen is a full-time employee of and holds stock in Novo Nordisk A/S.

Dr Daniels is a consultant for Genzyme (Sanofi), Exilixis, and Novo Nordisk.

Dr Mann is an investigator and/or consultant receiving honoraria from Abbott, Bayer, Boehringer-Ingelheim, Novo-Nordisk, Roche, and Vifor.

Dr Marso reports no personal conflicts of interest during the previous 12 months. All compensation for his research activities, including research grants and consulting fees from The Medicines Company, Novo Nordisk, Abbott Vascular, Amylin Pharmaceuticals, Volcano Corporation, St. Jude Medical, and Terumo Medical, are paid directly to the Saint Luke's Hospital Foundation of Kansas City.

Dr Moses is a full-time employee of and holds stock in Novo Nordisk A/S.

Dr Nissen reports that the Cleveland Clinic Center for Clinical Research receives funding to perform clinical trials from Amgen, Pfizer, Novartis, Takeda, Resverlogix, Ethicon, Orexigen, Vivus, and Eli Lilly. Dr Nissen is involved in these clinical trials but receives no personal remuneration for his participation. Dr Nissen consults for many pharmaceutical companies, including Novo Nordisk, but requires them to donate all honoraria or consulting fees directly to charity so that he receives neither income nor a tax deduction.

Dr Nauck has received research grants payable to his institution, the Diabeteszentrum Bad Lauterberg, from Berlin-Chemie/Menarini, Eli Lilly, Merck, Sharp & Dohme, Novartis Pharma, AstraZeneca, Boehringer Ingelheim,

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Dr Pocock reports receiving honoraria for serving on independent data monitoring committees for the EXSCEL, TECOS, and ACE trials.

Dr Poulter has received financial support from several pharmaceutical companies that manufacture either blood pressure-lowering or lipid-lowering agents, or both, for consultancy fees, research projects and staff, and for arranging and speaking at educational meetings. He holds neither stock nor shares of stock in any such companies.

Dr Steen Ravn is a full-time employee of and holds stock in Novo Nordisk A/S.

Dr Steinberg has served as a legal consultant for Eli Lilly, Amylin, and Novo Nordisk.

Dr Zinman has received honoraria from Novo Nordisk for scientific advisory board meetings and presentations. His institution has received research support from Novo Nordisk.

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Appendix

Supplementary Table I. Definitions Used for Clinical Events

Event	Definition
Cardiovascular death (occurring from any of the following):	<p>Sudden, unexpected cardiac cause:</p> <ul style="list-style-type: none"> • Cardiac arrest (symptomatic myocardial ischemia, new ST elevation or left bundle branch block, and/or angiographic or autopsy evidence of new thrombus) <p>CV cause</p> <ul style="list-style-type: none"> • Sudden cardiac death by acute MI, heart failure, stroke, other cardiovascular causes, or no documented nonvascular cause <p>Sudden cardiac cause: Unexpected occurrence in a previously stable patient and including:</p> <ul style="list-style-type: none"> • Absence of new or worsening symptoms • Within 60 min of new/worsening symptom onset • Attributed to identified arrhythmia on ECG or witnessed by emergency medical technicians • Unsuccessful resuscitation from cardiac arrest or resuscitation but death within 24 h without noncardiac etiology • Other cause with information on clinical status within the week preceding death <p>Acute MI:</p> <ul style="list-style-type: none"> • Occurring up to 30 days after documented acute MI and no conclusive evidence of other cause • Occurring before biomarker confirmation of myocardial necrosis with adjudication based on clinical presentation and ECG evidence <p>Other cardiovascular cause</p> <ul style="list-style-type: none"> • MI occurring directly from cardiovascular procedures <p>Heart failure or cardiogenic shock Occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death. New or worsening signs or symptoms without evidence of another cause including:</p> <ul style="list-style-type: none"> • Requiring initiation or increase in treatment for heart failure or occurring in a patient on maximal therapy • Signs/symptoms requiring continuous intravenous therapy or oxygen administration • Confinement to bed for heart failure symptoms • Pulmonary edema sufficient to cause tachypnea and distress not occurring in an acute MI or as the consequence of arrhythmia without worsening heart failure • Cardiogenic shock not occurring in an acute MI or from an arrhythmia in the absence of worsening heart failure. Cardiogenic shock: systolic blood pressure <90 mm Hg >1 h, unresponsive to fluids or heart rate correction, secondary to cardiac dysfunction and associated with >1 of the following: <ul style="list-style-type: none"> • Cool, clammy skin or • Oliguria (urine output <30 mL/h) • Altered sensorium • Cardiac index <2.2 L min⁻¹ m⁻² • SBP ≥90 mm Hg from positive inotropic or vasopressor agents alone and/or with mechanical support in <1 h, and after randomization. • Occurring before and continuing after randomization not included • Sudden death during admission for worsening heart failure. <p>Cerebrovascular event:</p> <ul style="list-style-type: none"> • Intracranial hemorrhagic or nonhemorrhagic stroke occurring up to 30 d and based on clinical signs and symptoms, neuroimaging or autopsy, and no conclusive evidence of other cause of death <p>Other cardiovascular cause</p>
Myocardial infarction	<p>Presumed cardiovascular cause</p> <p>Not attributed to cardiovascular or noncardiovascular are presumed cardiovascular deaths Any of the following based European Society of Cardiology/American College of Cardiology Foundation)/American Heart Association/World Heart Federation criteria²⁵:</p> <ul style="list-style-type: none"> • Spontaneous MI: Rise and/or fall in cardiac biomarkers with >1 value >ULN and evidence of: <ul style="list-style-type: none"> ○ Ischemia ○ New ischemia on ECG ST-T changes or left bundle branch block[†] ○ Pathological Q waves on ECG[†] ○ New loss of viable myocardium or regional wall motion abnormality on imaging • ST-elevation MI: At the J point in 2 contiguous leads (≥0.2 mV in men or ≥0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in other leads)

(continued on next page)

Supplementary Table I. (continued)

- **Non-ST-elevation MI:** At the J point in 2 contiguous leads (≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads absent on ECG)
- **PCI-Related MI:** Elevations of cardiac biomarkers >99 th percentile upper reference limit in patients with normal baseline troponin values **OR**

○ In patients with elevated cardiac biomarkers before PCI, a $\geq 20\%$ increase in a second biomarker sample within 24 h of PCI and documented decreasing values before suspected recurrent MI

• **Coronary artery bypass grafting-related mi:** Normal baseline troponin values with elevated cardiac biomarkers >99 th percentile URL

○ In patients with elevated cardiac biomarkers before CABG, a $\geq 20\%$ increase in a second biomarker sample within 72 h of CABG and documented decreasing values before suspected recurrent MI and either new pathological Q waves in at least 2 contiguous leads on ECG or new left bundle branch block, angiographically documented new graft or native coronary artery occlusion, or loss of viable myocardium on imaging

• **Silent MI:**

○ No evidence of acute MI **AND**

New pathological Q waves, evidence a regional loss of viable myocardium on imaging, evidence of healed or healing MI on autopsy

Stroke: Acute neurologic dysfunction documented by CT, MRI, or autopsy and attributed to a vascular cause and determined to *not* be due to readily identifiable cause,

Transient ischemic attack <24 h

Micro-hemorrhage: Rounded <5 to 10 mm foci of susceptibility artifact on MRI .
(occurrence not included in the primary event)

Transient ischemic attack: Neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

Ischemic stroke: Acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue

Hemorrhagic stroke: Acute episode of focal or global cerebral, spinal, or retinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage with documentation of cerebral hemorrhage on imaging or autopsy

Undetermined stroke: Insufficient information to categorize

Cerebrovascular events (stroke and TIA)

Classification of cerebrovascular events (stroke and TIA)

* ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy [LVH] and left bundle branch block [LBBB]): (1) ST elevation New ST elevation at the J point in 2 contiguous leads with the cutoff points: ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads. (2) ST depression and T-wave changes New horizontal or down-sloping ST depression ≥ 0.05 mV in 2 contiguous leads; and/or T inversion ≥ 0.1 mV in 2 contiguous leads with prominent R wave or R/S ratio >1 .
† Pathological Q waves: (1) Any Q wave in leads V2-V3 ≥ 0.02 s or QS complex in leads V2 and V3 Q wave ≥ 0.03 s and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any 2 leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF).

Supplementary Table II. Other efficacy and safety end points

Time from randomization to first occurrence of a composite microvascular outcome:

- Retinal photocoagulation
- Vitreous hemorrhage
- Diabetes-related blindness
- New or worsening nephropathy (defined as new onset of macroalbuminuria, or doubling of serum creatinine level and eGFR ≤ 45 mL/min per 1.73m², or the need for continuous renal-replacement therapy (in the absence of an acute reversible cause)
- Death due to renal disease

Diabetic foot ulcers

Change from baseline to the last assessment during the treatment period in:

- Weight and waist circumference
- HbA1c
- Blood lipids: total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides
- Blood pressure and pulse rate
- eGFR rate (MDRD and chronic kidney disease-EPI formulas)
- Laboratory parameters:
 - Lipase
 - Amylase
 - Calcitonin
 - Anti liraglutide antibodies
 - ALT
 - Bilirubin (total)
 - Calcium (total)
 - Sodium
 - Potassium
 - Urinary albumin to creatinine ratio

Change from baseline to assessment at 3 y during the treatment period in:

- Weight and waist circumference
- HbA1c
- Blood lipids: total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides
- Blood pressure and pulse rate
- eGFR rate (MDRD and chronic kidney disease-EPI formulas)
- Incidence of hypoglycemic episodes

Incidence of serious adverse events and medical events of special interest:

- Neoplasm
- Pancreatitis
- Acute, severe and persistent abdominal pain leading to a suspicion of pancreatitis
- Acute gallstone disease (biliary colic or acute cholecystitis)
- First confirmed episode of calcitonin concentration increase ≥ 20 ng/L
- Thyroid disease
- Severe hypoglycemic event
- Immunogenicity event (antibody formation, allergic reactions, immune complex disease and injection site disorders)
- Adverse events leading to treatment discontinuation

Patient reported outcome assessed by EQ-5D questionnaire (in a subset of subjects only)

Supplementary Table III. Principal Investigators by Country**Steering Committee****J. Buse (Chair) S. Marso (Co-chair)**

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Supplementary Table III. (continued)

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Supplementary Table III. (continued)

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