EDITORIALS

Cardiac and Renovascular Complications in Type 2 Diabetes — Is There Hope?

Julie R. Ingelfinger, M.D., and Clifford J. Rosen, M.D.

According to the current posting on the website of the World Health Organization, the worldwide prevalence of diabetes mellitus among persons 18 years of age or older is 8.5% and increasing. Most of those affected have type 2 diabetes, which has been epidemic for several decades and is associated with many complications, including premature macrovascular and microvascular diseases affecting the eyes, heart, kidneys, and the circulation. We know that diabetes is associated with major morbidity and mortality, with an estimated 1.5 million deaths in 2012 being directly due to diabetes.[1]

Various approaches in the treatment of type 2 diabetes have been introduced recently, but whether these therapies alter cardiovascular and renal risk remains uncertain. Despite weight control (by diet and recently, in some patients, by gastric bypass) and the use of recently developed oral hypoglycemic agents and insulin, premature cardiovascular disease, kidney failure, retinal disease, and peripheral vascular disease develop in patients with type 2 diabetes. Three novel pharmacologic approaches have been approved in the past decade: first, glucagon-like peptide 1 (GLP-1) agonists, which stimulate insulin release; second, dipeptidyl peptidase 4 (DPP-4) inhibitors, which act along the same pathway and prevent the breakdown of GLP-1, also stimulating insulin release; and third, sodium–glucose cotransporter (SGLT) inhibitors (mainly inhibitors of type 2 [SGLT2]), which prevent the resorption of glucose by the proximal tubule. This action decreases the plasma glucose level and also depletes sodium and decreases the single-nephron glomerular filtration rate by means of tubuloglomerular feedback, by which glomerular filtration and resorption of electrolytes are coordinated, as well as altering the activity of the renin–angiotensin system mediated through the macula densa. SGLT2 inhibitors also tend to be associated with weight loss, and they frequently lower lipid and uric acid levels and decrease oxidative stress.

In the United States, three SGLT inhibitors — canagliflozin, dapagliflozin, and empagliflozin — have been approved by the Food and Drug Administration (FDA) for the treatment of type 2 diabetes. Approved GLP-1 agonists include liraglutide, exenatide, dulaglutide, and albiglutide, and approved DPP-4 inhibitors include sitagliptin, saxagliptin, alogliptin, and linagliptin. Additional agents in these classes are in various stages of trial and approval applications.

Notwithstanding government approval and current widespread use, the effectiveness and safety of these new agents are cause for reflection. Among the DPP-4 inhibitors studied recently, alogliptin (in the EXAMINE [Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care] trial),[2] saxagliptin (in the SAVOR-TIMI 53 [Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53] trial),[3] and sitagliptin (in TECOS [Trial Evaluating Cardiovascular Outcomes with Sitagliptin]),[4] were not associated with a lower rate of cardiovascular events than occurred with the control of diabetes with the use of other methods. Similar results were found with the GLP-1 agonist lixisenatide, which is now under review by the FDA, in the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial.[5]

Those trials were at least as large as the Lira-

glutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial of liraglutide, the results of which are now reported in the *Journal*.[6] Among the SGLT2 inhibitors that have been studied to date, only empagliflozin reached its end point of a lower rate of cardiovascular events, when added to standard therapy, as shown in the EMPA-REG OUTCOME trial in 2015.[7] A trial of pioglitazone, a thiazolidinedione, previously showed a lower rate of macrovascular events than were observed with matched placebo.[8] A number of other trials are in progress.[9]

In the EMPA-REG OUTCOME trial, patients with established cardiovascular disease and an estimated glomerular filtration rate (eGFR) of at least 30 ml per minute per 1.73 m^2 of body-surface area were randomly assigned to receive empagliflozin at a dose of 10 mg, empagliflozin at a dose of 25 mg, or placebo once daily in addition to standard-of-care therapy.[7] In the primary outcome of that trial, the rate of death due to cardiovascular causes was significantly lower in the pooled empagliflozin group than in the placebo group; there was no significant between-group difference in the risk of myocardial infarction or stroke. Furthermore, the pooled empagliflozin group and the placebo group had similar rates of hospitalization for unstable angina.[7]

The report from the EMPA-REG OUTCOME trial on the composite microvascular end point, now published in the *Journal*,[10] focuses on the renal microvascular outcomes — incident or worsening nephropathy, defined as progression to macroalbuminuria (urinary albumin-to-creatinine ratio, >300 mg of albumin per gram of creatinine), a doubling of the serum creatinine level (accompanied by an eGFR of ≤45 ml per minute per 1.73 m^2 [as calculated by the Modification of Diet in Renal Disease formula]), the initiation of renal-replacement therapy, or death from renal disease. This new report indicates that empagliflozin was associated with a slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care in patients at high cardiovascular risk.

In the randomized LEADER trial, 1.8 mg of daily liraglutide or placebo delivered subcutaneously was added to standard care in more than 9000 patients who were followed from 42 to 60 months, with a primary outcome of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The rate of death from any cause was lower in the liraglutide group than in the placebo group, whereas the rates of myocardial infarction, stroke, and hospitalization for heart failure were not significantly lower with liraglutide than with placebo. In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo.

Why do the EMPA-REG OUTCOME and LEADER trials show cardiovascular and microvascular benefit, whereas other trials have come close yet have not shown similar results? Are the differences due to the inclusion and exclusion criteria in the specific trials? Patients in the liraglutide trial had higher glycated hemoglobin levels (mean, 8.7%) than did those in most other studies. Patients were eligible if they either had not taken a hypoglycemic agent previously or had been treated with an oral hypoglycemic agent or insulin; in addition, eligible patients were 50 years of age or older and had at least one coexisting cardiovascular condition or were 60 years or older and had at least one cardiovascular risk factor, as determined by the investigator. Concomitant conditions in the participants in the two groups of the LEADER trial were similar. Participants in the LEADER trial had a lower prevalence of cardiovascular disease (72.4%) than did those in the EXAMINE trial (alogliptin), the SAVOR-TIMI 53 trial (saxagliptin), or TECOS (sitagliptin), all of which recruited patients with established cardiovascular disease, not just a risk factor for it.

Yet, although there may have been differences among the participants that account for the positive results in the EMPA-REG OUTCOME and LEADER trials, such differences alone do not fully explain the results. We are left with differences that appear encouraging, yet are not a "home run" with regard to the management of diabetes. In the coming years, controlled and comparative effectiveness trials that uniformly combine newer agents with older agents may help to delineate an even more effective treatment plan for the millions of people whose lives are affected by type 2 diabetes.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Center for Clinical and Translational Research, Maine Medical Center Research Institute, Scarborough (C.J.R.).

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Von Willebrand Factor — A Rapid Sensor of Paravalvular Regurgitation during TAVR?

Firas E. Zahr, M.D., and Steven R. Lentz, M.D., Ph.D.

Von Willebrand factor is unique among coagulation factors by virtue of its highly multimeric structure, which allows it to function as an endogenous sensor of hemodynamic forces.[1] Under conditions of low shear stress (below the usual physiologic range), von Willebrand factor self-associates into compacted, high-molecular-weight (HMW) multimers that are unable to promote platelet adhesion. During physiologic shear stress (shear rate of 100 to 5000 sec^{-1}), von Willebrand factor undergoes partial unfolding and elongation, exposing binding sites for platelets and collagen and allowing the metalloprotease ADAMTS13 to regulate the size distribution of the HMW multimers by cleaving von Willebrand factor monomers within the A2 domain[1] (see Animation, available with the full text of the article by Van Belle et al.[2] in this issue of the *Journal* at NEJM.org).

Pathological conditions associated with supraphysiologic shear stress (shear rate >10,000 sec^{-1}) can cause excessive degradation of von Willebrand factor multimers by ADAMTS13, leading to acquired von Willebrand factor deficiency and major bleeding. This form of acquired von Willebrand factor deficiency occurs with congenital and valvular heart disease (e.g., Heyde's syndrome),[3] hypertrophic cardiomyopathy, circulatory-assist devices, and extracorporeal membrane-oxygenation systems. Alteration of the distribution of von Willebrand factor multimers in response to changes in shear stress is highly dynamic; loss of HMW multimers occurs rapidly after the onset of supraphysiologic shear stress, and the multimer distribution normalizes within minutes after restoration of normal blood flow.[4]

Van Belle et al. provide evidence that changes in von Willebrand factor function can be monitored during transcatheter aortic-valve replacement (TAVR) to predict the presence of paravalvular regurgitation.[2] TAVR has become an established therapy for patients with severe aortic stenosis who are at high risk for complications after surgical aortic-valve replacement, and it is undergoing evaluation for patients at intermediate or low surgical risk. Despite improvements in valve design, paravalvular regurgitation remains a procedural complication that is associated with high mortality at 1 year.[5] The incidence of moderate or severe paravalvular regurgitation on day 30 after TAVR was approximately 12% with the first-generation SAPIEN valve (Edwards

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Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

ABSTRACT

BACKGROUND

The cardiovascular effect of liraglutide, a glucagon-like peptide 1 analogue, when added to standard care in patients with type 2 diabetes, remains unknown.

METHODS

In this double-blind trial, we randomly assigned patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary hypothesis was that liraglutide would be noninferior to placebo with regard to the primary outcome, with a margin of 1.30 for the upper boundary of the 95% confidence interval of the hazard ratio. No adjustments for multiplicity were performed for the prespecified exploratory outcomes.

RESULTS

A total of 9340 patients underwent randomization. The median follow-up was 3.8 years. The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority). Fewer patients died from cardiovascular causes in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P=0.007). The rate of death from any cause was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (hazard ratio, 0.85; 95% CI, 0.74 to 0.97; P=0.02). The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events. The incidence of pancreatitis was nonsignificantly lower in the liraglutide group than in the placebo group.

CONCLUSIONS

In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo. (Funded by Novo Nordisk and the National Institutes of Health; LEADER ClinicalTrials.gov number, NCT01179048.)

From the University of Texas Southwestern Medical Center, Dallas (S.P.M.); Massachusetts General Hospital, Boston (G.H.D.); Novo Nordisk, Bagsvaerd, Denmark (K.B.-F., P.K., L.S.R., M.S.); Friedrich Alexander University of Erlangen, Erlangen (J.F.E.M.), and St. Josef Hospital, Ruhr University, Bochum (M.A.N.) — both in Germany; Cleveland Clinic, Cleveland (S.E.N.); London School of Hygiene and Tropical Medicine Medical Statistics Unit (S.P.) and Imperial College London (N.R.P.), London; George Washington University Medical Center, Washington, DC (W.M.S.); Lunenfeld–Tanenbaum Research Institute, Mt. Sinai Hospital, University of Toronto, Toronto (B.Z.); International Diabetes Center at Park Nicollet, Minneapolis (R.M.B.); and the University of North Carolina School of Medicine, Chapel Hill (J.B.B.). Address reprint requests to Dr. Buse at the University of North Carolina School of Medicine, CB7172, Chapel Hill, NC 27599, or at john_buse@med.unc.edu.

*A complete list of the investigators in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Type 2 diabetes is a complex metabolic disorder that is characterized by hyperglycemia and associated with a high risk of cardiovascular, microvascular, and other complications.[1,2] Although glycemic control is associated with reductions in the risk of microvascular complications, the macrovascular benefits of glycemic control are less certain. Furthermore, concern has been raised about the cardiovascular safety of antihyperglycemic therapies.[3] Consequently, regulatory authorities have mandated cardiovascular safety assessments of new diabetes treatments.[4,5]

Liraglutide, an analogue of human glucagon-like peptide 1 (GLP-1),[6] has been approved for the treatment of type 2 diabetes. Its efficacy in lowering glucose levels has been established, and it has been associated with slight reductions in weight and blood pressure.[6-8] It has been associated with an increase in pulse rate.[7,8] To assess the long-term effects of liraglutide on cardiovascular outcomes and other clinically important events, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was initiated in 2010.[9]

Methods

Trial Design and Oversight

We performed this multicenter, double-blind, placebo-controlled trial at 410 sites in 32 countries. Detailed methods of the trial have been published previously,[9] and the trial protocol is available with the full text of this article at NEJM.org. The trial protocol was reviewed and approved by the institutional review board or ethics committee at each participating center. All the patients provided written informed consent before participation. Patients with type 2 diabetes who were at high risk for cardiovascular disease were randomly assigned, in a 1:1 ratio, to receive liraglutide or placebo. The minimum planned follow-up was 42 months, with a maximum of 60 months of receiving the assigned regimen and an additional 30 days of follow-up afterward.

The trial was overseen by a steering committee consisting of 11 academic investigators and 4 employees of the sponsor. The steering committee, in collaboration with the sponsor and regulatory authorities, was responsible for designing the trial protocol. An independent data and safety monitoring committee performed ongoing safety surveillance and had access to all the data in an unblinded fashion. The protocol for the treatment of risk factors and the concomitant use of medications was developed by a global expert panel (Table S1 in the Supplementary Appendix, available at NEJM.org). The data were gathered by the site investigators, and the sponsor performed site monitoring and data collection. The data were analyzed by Statogen Consulting and the sponsor.

All the authors had access to the final results and vouch for the fidelity of the trial to the protocol. The first and last authors wrote the first draft of the manuscript, which was revised and approved by all the authors, who also assume responsibility for the accuracy and completeness of its content and for the decision to submit the manuscript for publication. Editorial support, funded by the sponsor, was provided by an independent medical writer under the guidance of the authors.

Patients

Patients with type 2 diabetes who had a glycated hemoglobin level of 7.0% or more were eligible if they either had not received drugs for this condition previously or had been treated with one or more oral antihyperglycemic agents or insulin (human neutral protamine Hagedorn, long-acting analogue, or premixed) or a combination of these agents. The major inclusion criteria were the following: an age of 50 years or more with at least one cardiovascular coexisting condition (coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney disease of stage 3 or greater, or chronic heart failure of New York Heart Association class II or III) or an age of 60 years or more with at least one cardiovascular risk factor, as determined by the investigator (microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle–brachial index [the ratio of the systolic blood pressure at the ankle to the systolic blood pressure in the arm] of less than 0.9).[9] Major exclusion criteria were type 1 diabetes; the use of GLP-1–receptor agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, pramlintide, or rapid-acting insulin; a familial or personal history of multiple endocrine neoplasia type 2 or medullary thyroid cancer; and the occurrence of

an acute coronary or cerebrovascular event within 14 days before screening and randomization. The complete inclusion and exclusion criteria are listed in the Supplementary Appendix.

PROCEDURES

After a 2-week placebo run-in phase to establish whether patients were able to adhere to the injection regimen, patients were randomly assigned, in a 1:1 ratio, to receive either 1.8 mg (or the maximum tolerated dose) of liraglutide or matching placebo once daily as a subcutaneous injection in addition to standard care (Fig. S1 in the Supplementary Appendix). Randomization was stratified according to the estimated glomerular filtration rate (eGFR) at screening (<30 or ≥30 ml per minute per 1.73 m^2 of body-surface area), as calculated with the use of the Modification of Diet in Renal Disease equation. For patients who did not meet the recommended target for glycemic control (glycated hemoglobin level ≤7% or individualized target at the investigator's discretion) after randomization, the addition of any antihyperglycemic agents except for GLP-1–receptor agonists, DPP-4 inhibitors, or pramlintide was permitted. Patients were scheduled for follow-up visits at months 1, 3, and 6 and every 6 months thereafter.

OUTCOMES

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal (including silent) myocardial infarction, or nonfatal stroke. Prespecified exploratory outcomes included an expanded composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure), death from any cause, a composite renal and retinal microvascular outcome (nephropathy [defined as the new onset of macroalbuminuria or a doubling of the serum creatinine level and an eGFR of ≤45 ml per minute per 1.73 m^2, the need for continuous renal-replacement therapy, or death from renal disease] and retinopathy [defined as the need for retinal photocoagulation or treatment with intravitreal agents, vitreous hemorrhage, or the onset of diabetes-related blindness]), neoplasms, and pancreatitis — all of which were adjudicated in a blinded fashion by an external, independent event-adjudication committee. The definitions that were used for the clinical events and the members of the committee are listed in the Supplementary Appendix.

The glycated hemoglobin level was measured at randomization, at month 3, and then every 6 months thereafter. Other laboratory tests were performed at randomization, at months 6 and 12, and annually thereafter. Prespecified comparisons between groups were performed at 36 months, which was the last annual visit with laboratory testing that was prespecified for the entire trial population, given the minimum follow-up of 42 months.

STATISTICAL ANALYSIS

The statistical analysis plan is available with the protocol at NEJM.org. We based the required sample size for the trial on an assumed annual primary-event rate of 1.8% in each group. Uniform enrollment was projected over the period of 1.5 years. Assuming a withdrawal rate of less than 10%, a minimum exposure to the trial regimen of 42 months, a null hypothesis hazard ratio of 1.30 or more, 90% power, and a one-sided alpha level of 0.025, we calculated that 8754 patients would need to undergo randomization if we were to observe at least 611 primary outcomes.

The primary and exploratory analyses for the outcomes in the time-to-event analyses were based on a Cox proportional-hazards model with treatment as a covariate. The primary hypothesis was that liraglutide would be noninferior to placebo with regard to the primary outcome, with a margin of 1.30 for the upper boundary of the 95% confidence interval of the hazard ratio. We used a hierarchical testing strategy for the liraglutide group versus the placebo group, first testing for noninferiority and subsequently for superiority. Noninferiority was established for the primary outcome if the upper limit of the two-sided 95% confidence interval of the hazard ratio was less than 1.30, and superiority was established if the upper limit was less than 1.00. In addition, prespecified sensitivity analyses were conducted (see the protocol). For exploratory outcomes, no adjustments of P values for multiplicity were performed. All the patients who underwent randomization were included in the primary and exploratory analyses, and data from the patients who completed or discontin-

ued the trial without having an outcome were censored from the day of their last visit; events occurring after that visit were not included. Two-sided P values are presented throughout. We estimated the mean differences between the trial groups in the glycated hemoglobin level, weight, systolic and diastolic blood pressure, and pulse using a mixed model for repeated measurements, with adjustment for baseline covariates.

RESULTS

OVERVIEW OF TRIAL CONDUCT

A total of 9340 patients underwent randomization from September 2010 through April 2012; 4668 patients were randomly assigned to receive liraglutide and 4672 to receive placebo. The planned closeout of follow-up of the patients was from August 2014 through December 2015. The vital status was known in 99.7% of the patients. A total of 96.8% of the patients completed a final visit, died, or had a primary outcome. The median time of exposure to liraglutide or placebo was 3.5 years. The mean percentage of time that patients received the trial regimen was 84% for liraglutide and 83% for placebo. The median follow-up was 3.8 years in each group. The median daily dose of liraglutide was 1.78 mg (interquartile range, 1.54 to 1.79), including periods during which the patients did not receive liraglutide. The screening, randomization, and follow-up of the patients are shown in Figure S2 in the Supplementary Appendix.

The demographic and clinical characteristics of the patients were similar in the two groups (Table S2 in the Supplementary Appendix). Of the 9340 patients, the majority (7598 [81.3%]) had established cardiovascular disease (6764 patients [72.4%]), chronic kidney disease of stage 3 or higher (2307 [24.7%]), or both (1473 [15.8%]). At baseline, the mean duration of diabetes was 12.8 years, and the mean glycated hemoglobin level was 8.7%.

CARDIOVASCULAR OUTCOMES

The primary composite outcome occurred in fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority) (Table 1 and Fig. 1A). Death from cardiovascular causes occurred in fewer patients in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P=0.007) (Fig. 1B). The rate of death from any cause was also lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (hazard ratio, 0.85; 95% CI, 0.74 to 0.97; P=0.02). The frequencies of nonfatal myocardial infarction and nonfatal stroke were lower in the liraglutide group than in the placebo group, although the differences were not significant (Fig. 1C and 1D and Table 1). The magnitude of the differences was similar in sensitivity analyses with alternative censoring, including the per-protocol analysis (Fig. S3 in the Supplementary Appendix). Findings for the remaining adjudicated cardiovascular outcomes and the expanded composite outcome are provided in Table 1, and Figure S4 in the Supplementary Appendix.

Subgroup analyses are shown in Figure 2. Significant interactions were observed for an eGFR of 60 ml or more per minute per 1.73 m^2 versus an eGFR of less than 60 ml per minute per 1.73 m^2, with a benefit favoring the lower eGFR, and for the presence versus absence of established cardiovascular disease at baseline, with benefit for those with cardiovascular disease at baseline. Additional subgroup analyses regarding the eGFR are provided in Table S3 in the Supplementary Appendix.

GLYCEMIC CONTROL

Changes in the glycated hemoglobin values over time are shown in Figure S5A in the Supplementary Appendix. The prespecified analysis at 36 months showed a mean difference between the liraglutide group and the placebo group of −0.40 percentage points (95% CI, −0.45 to −0.34). Changes in the use of diabetes medication during the trial are shown in Table S4 in the Supplementary Appendix.

CARDIOVASCULAR RISK FACTORS

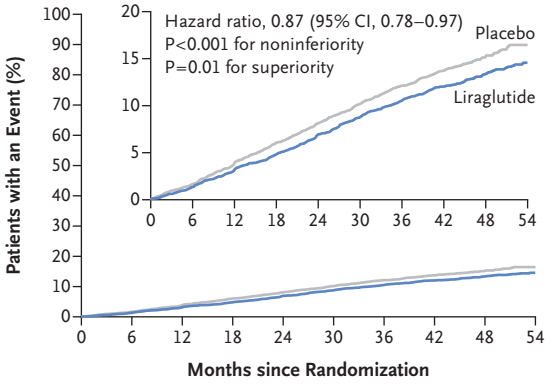
There were significant mean differences between the liraglutide group and the placebo group in the change from baseline to 36 months in the following variables: weight loss was 2.3 kg (95% CI, 2.5 to 2.0) higher in the liraglutide group, the systolic blood pressure was 1.2 mm Hg (95% CI, 1.9 to 0.5) lower in the liraglutide group, the diastolic blood pressure was 0.6 mm Hg (95%

Table 1. Primary and Secondary Outcomes.*

Outcome	Liraglutide (N=4668)	Incidence Rate	Placebo (N=4672)	Incidence Rate	Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*no. of events/ 100 patient-yr*	*no. of patients (%)*	*no. of events/ 100 patient-yr*		
Primary composite outcome†	608 (13.0)	3.4	694 (14.9)	3.9	0.87 (0.78–0.97)	0.01
Expanded composite outcome‡	948 (20.3)	5.3	1062 (22.7)	6.0	0.88 (0.81–0.96)	0.005
Death from any cause	381 (8.2)	2.1	447 (9.6)	2.5	0.85 (0.74–0.97)	0.02
Death from cardiovascular causes	219 (4.7)	1.2	278 (6.0)	1.6	0.78 (0.66–0.93)	0.007
Death from noncardiovascular causes	162 (3.5)	0.9	169 (3.6)	1.0	0.95 (0.77–1.18)	0.66
Myocardial infarction§	292 (6.3)	1.6	339 (7.3)	1.9	0.86 (0.73–1.00)	0.046
Fatal§	17 (0.4)	0.1	28 (0.6)	0.2	0.60 (0.33–1.10)	0.10
Nonfatal	281 (6.0)	1.6	317 (6.8)	1.8	0.88 (0.75–1.03)	0.11
Silent§	62 (1.3)	0.3	76 (1.6)	0.4	0.86 (0.61–1.20)	0.37
Stroke§	173 (3.7)	1.0	199 (4.3)	1.1	0.86 (0.71–1.06)	0.16
Fatal§	16 (0.3)	0.1	25 (0.5)	0.1	0.64 (0.34–1.19)	0.16
Nonfatal	159 (3.4)	0.9	177 (3.8)	1.0	0.89 (0.72–1.11)	0.30
Transient ischemic attack§	48 (1.0)	0.3	60 (1.3)	0.3	0.79 (0.54–1.16)	0.23
Coronary revascularization	405 (8.7)	2.3	441 (9.4)	2.5	0.91 (0.80–1.04)	0.18
Hospitalization for unstable angina pectoris	122 (2.6)	0.7	124 (2.7)	0.7	0.98 (0.76–1.26)	0.87
Hospitalization for heart failure	218 (4.7)	1.2	248 (5.3)	1.4	0.87 (0.73–1.05)	0.14
Microvascular event	355 (7.6)	2.0	416 (8.9)	2.3	0.84 (0.73–0.97)	0.02
Retinopathy	106 (2.3)	0.6	92 (2.0)	0.5	1.15 (0.87–1.52)	0.33
Nephropathy	268 (5.7)	1.5	337 (7.2)	1.9	0.78 (0.67–0.92)	0.003

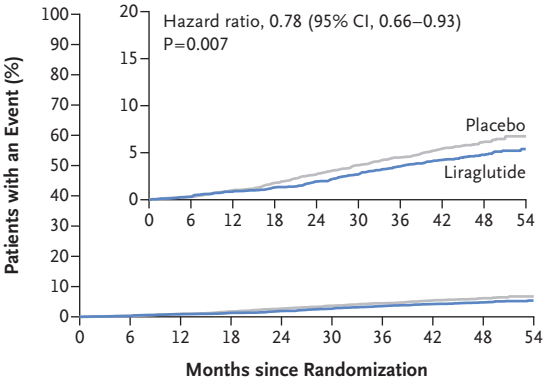
* Hazard ratios and P values were estimated with the use of a Cox proportional-hazards model with treatment as a covariate.
† The primary composite outcome in the time-to-event analysis consisted of the first occurrence of death from cardiovascular causes (181 patients in the liraglutide group vs. 227 in the placebo group), nonfatal (including silent) myocardial infarction (275 vs. 304), or nonfatal stroke (152 vs. 163). The P value is for superiority.
‡ The expanded composite outcome included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure.
§ This analysis was not prespecified.

A Primary Outcome



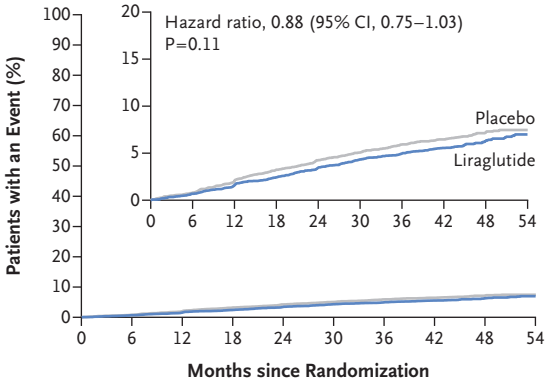
No. at Risk										
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

B Death from Cardiovascular Causes



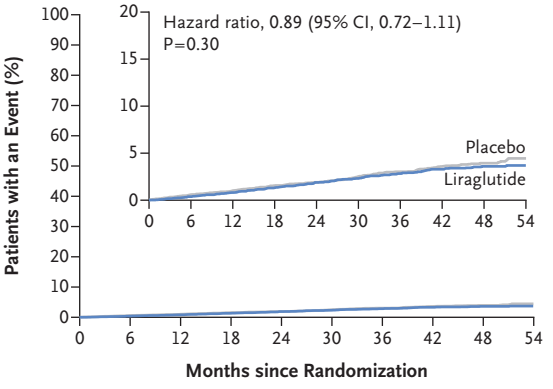
No. at Risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

C Nonfatal Myocardial Infarction



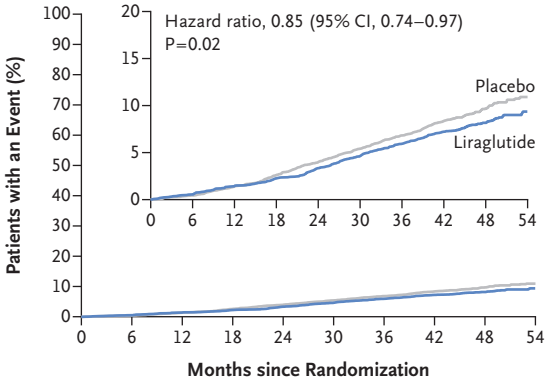
No. at Risk										
Liraglutide	4668	4609	4531	4454	4359	4263	4181	4102	1619	440
Placebo	4672	4613	4513	4407	4301	4202	4103	4020	1594	424

D Nonfatal Stroke



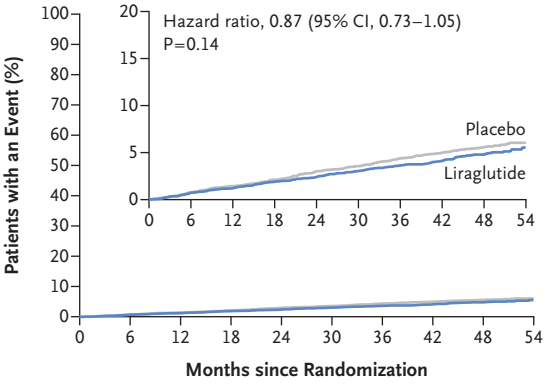
No. at Risk										
Liraglutide	4668	4624	4564	4504	4426	4351	4269	4194	1662	465
Placebo	4672	4622	4558	4484	4405	4314	4228	4141	1648	445

E Death from Any Cause



No. at Risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

F Hospitalization for Heart Failure



No. at Risk										
Liraglutide	4668	4612	4550	4483	4414	4337	4258	4185	1662	467
Placebo	4672	4612	4540	4464	4372	4288	4187	4107	1647	442

Figure 1 (facing page). Primary and Exploratory Outcomes.
The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. The insets show the same data on an enlarged y axis.

CI, 0.2 to 1.0) higher in the liraglutide group, and the heart rate was 3.0 beats per minute (95% CI, 2.5 to 3.4) higher in the liraglutide group (Fig. S5B, S5C, and S5D in the Supplementary Appendix). The use of cardiovascular medications at baseline and during the trial is shown in Table S4 in the Supplementary Appendix.

MICROVASCULAR OUTCOMES

The incidence of a composite outcome of renal or retinal microvascular events was lower in the liraglutide group than in the placebo group (hazard ratio, 0.84; 95% CI, 0.73 to 0.97; P=0.02), a difference that was driven by a lower rate of nephropathy events in the liraglutide group (1.5 vs. 1.9 events per 100 patient-years of observation; hazard ratio, 0.78; 95% CI, 0.67 to 0.92; P=0.003) (Table 1). The incidence of retinopathy events was nonsignificantly higher in the liraglutide group than in the placebo group (0.6 vs. 0.5 events per 100 patient-years; hazard ratio, 1.15; 95% CI, 0.87 to 1.52; P=0.33).

SAFETY AND ADVERSE EVENTS

Adverse events are listed in Table 2. The overall rates of benign or malignant neoplasms were higher in the liraglutide group than in the placebo group, but the difference was not significant (Fig. S6 in the Supplementary Appendix). There were 13 patients with pancreatic cancer in the liraglutide group and 5 in the placebo group. Additional data regarding pancreatic cancer are provided in Table S5 in the Supplementary Appendix. There were fewer patients with prostate cancer in the liraglutide group than in the placebo group (26 vs. 47) and also fewer patients with leukemia (5 vs. 14) (Fig. S6 in the Supplementary Appendix). Medullary thyroid carcinoma occurred in no patient in the liraglutide group and in 1 in the placebo group. Calcitonin levels over time were similar in the two groups (data not shown).

Acute pancreatitis occurred in 18 patients in the liraglutide group and in 23 in the placebo group. The mean levels of serum amylase and lipase were higher in the liraglutide group than in the placebo group (Fig. S7 in the Supplementary Appendix). Acute gallstone disease was more common with liraglutide than with placebo (in 145 vs. 90 patients), including severe events (in 40 vs. 31). During the trial, fewer patients in the liraglutide group were treated with hypoglycemic medications (insulin, sulfonylurea, and glinides) than in the placebo group (Table S4 in the Supplementary Appendix). Severe hypoglycemia occurred in 114 patients in the liraglutide group and in 153 in the placebo group (rate ratio, 0.69; 95% CI, 0.51 to 0.93). Similarly, the rate ratio for confirmed hypoglycemia (plasma glucose level, <56 mg per deciliter [3.1 mmol per liter]) was 0.80 (95% CI, 0.74 to 0.88). Additional details regarding severe hypoglycemia are provided in Table S6 in the Supplementary Appendix.

Adverse events leading to the permanent discontinuation of the trial regimen were more common with liraglutide than with placebo (Table 2). This result appears to have been driven by gastrointestinal disorders in the liraglutide group.

DISCUSSION

In the present trial, patients in the liraglutide group had a lower risk of the primary composite outcome — first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in the time-to-event analysis — and lower risks of death from cardiovascular causes, death from any cause, and microvascular events than did those in the placebo group. The number of patients who would need to be treated to prevent one event in 3 years was 66 in the analysis of the primary outcome and 98 in the analysis of death from any cause.[10] There has been concern about the risk of hospitalization for heart failure with various agents that have been used to treat diabetes mellitus, including DPP-4 inhibi-

Subgroup	No. of Patients	Liraglutide	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
		no. of events/no. of patients (%)			
Primary analysis	9340	608/4668 (13.0)	694/4672 (14.9)	0.87 (0.78–0.97)	
Sex					0.84
Female	3337	183/1657 (11.0)	209/1680 (12.4)	0.88 (0.72–1.08)	
Male	6003	425/3011 (14.1)	485/2992 (16.2)	0.86 (0.75–0.98)	
Age					0.27
<60 yr	2321	140/1197 (11.7)	166/1124 (14.8)	0.78 (0.62–0.97)	
≥60 yr	7019	468/3471 (13.5)	528/3548 (14.9)	0.90 (0.79–1.02)	
Geographic region					0.20
Europe	3296	207/1639 (12.6)	252/1657 (15.2)	0.82 (0.68–0.98)	
North America	2847	212/1401 (15.1)	216/1446 (14.9)	1.01 (0.84–1.22)	
Asia	711	24/360 (6.7)	37/351 (10.5)	0.62 (0.37–1.04)	
Rest of the world	2486	165/1268 (13.0)	189/1218 (15.5)	0.83 (0.68–1.03)	
Race					0.32
White	7238	494/3616 (13.7)	543/3622 (15.0)	0.90 (0.80–1.02)	
Black	777	47/370 (12.7)	59/407 (14.5)	0.87 (0.59–1.27)	
Asian	936	40/471 (8.5)	56/465 (12.0)	0.70 (0.46–1.04)	
Other	389	27/211 (12.8)	36/178 (20.2)	0.61 (0.37–1.00)	
Ethnic group					0.30
Hispanic	1134	68/580 (11.7)	86/554 (15.5)	0.74 (0.54–1.02)	
Non-Hispanic	8206	540/4088 (13.2)	608/4118 (14.8)	0.89 (0.79–1.00)	
Body-mass index					0.15
≤30	3574	241/1743 (13.8)	261/1831 (14.3)	0.96 (0.81–1.15)	
>30	5757	367/2920 (12.6)	431/2837 (15.2)	0.82 (0.71–0.94)	
Glycated hemoglobin					0.58
≤8.3%	4768	289/2340 (12.4)	333/2428 (13.7)	0.89 (0.76–1.05)	
>8.3%	4572	319/2328 (13.7)	361/2244 (16.1)	0.84 (0.72–0.98)	
Duration of diabetes					0.42
≤11 yr	4429	265/2216 (12.0)	316/2213 (14.3)	0.82 (0.70–0.97)	
>11 yr	4892	340/2441 (13.9)	376/2451 (15.3)	0.90 (0.78–1.04)	
Risk of CVD					0.04
≥50 yr of age and established CVD	7598	536/3831 (14.0)	629/3767 (16.7)	0.83 (0.74–0.93)	
≥60 yr of age and risk factors for CVD	1742	72/837 (8.6)	65/905 (7.2)	1.20 (0.86–1.67)	
Chronic heart failure					0.53
Yes	1305	112/653 (17.2)	119/652 (18.3)	0.94 (0.72–1.21)	
No	8035	496/4015 (12.4)	575/4020 (14.3)	0.85 (0.76–0.96)	
Antidiabetic therapy					0.73
1 Oral antidiabetic agent	1818	99/922 (10.7)	125/896 (14.0)	0.75 (0.58–0.98)	
>1 Oral antidiabetic agent	2997	191/1515 (12.6)	196/1482 (13.2)	0.95 (0.78–1.16)	
Insulin with oral antidiabetic agent	3422	223/1674 (13.3)	259/1748 (14.8)	0.89 (0.74–1.06)	
Insulin without oral antidiabetic agent	737	71/361 (19.7)	86/376 (22.9)	0.86 (0.63–1.17)	
None	366	24/196 (12.2)	28/170 (16.5)	0.73 (0.42–1.25)	
Renal function					
Severe or moderate disease					0.01
<60 ml/min/1.73 m^2	2158	172/1116 (15.4)	223/1042 (21.4)	0.69 (0.57–0.85)	
≥60 ml/min/1.73 m^2	7182	436/3552 (12.3)	471/3630 (13.0)	0.94 (0.83–1.07)	
Severe disease					0.93
<30 ml/min/1.73 m^2	224	25/117 (21.4)	26/107 (24.3)	0.89 (0.51–1.54)	
≥30 ml/min/1.73 m^2	9116	583/4551 (12.8)	668/4565 (14.6)	0.87 (0.77–0.97)	

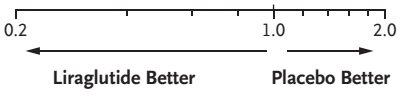


Figure 2 (facing page). Primary Composite Outcomes in Various Demographic and Clinical Subgroups.

Prespecified Cox proportional-hazard regression analyses were performed for subgroups of patients with respect to the primary outcome (first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). P values signify tests of homogeneity for between-group differences with no adjustment for multiple testing. The percentages of patients with a first primary outcome between the randomization date and the date of last follow-up are shown. Race and ethnic group were self-reported. There were missing data for the body-mass index (the weight in kilograms divided by the square of the height in meters) in 5 patients in the liraglutide group and 4 in the placebo group and for the duration of diabetes in 11 patients in the liraglutide group and 8 in the placebo group. Renal function was assessed by means of the estimated glomerular filtration rate, as calculated by the Modification of Diet in Renal Disease equation. CVD denotes cardiovascular disease.

tors.[11] In the present trial, there were fewer hospitalizations for heart failure among patients in the liraglutide group than among those in the placebo group, although the difference was not significant.

Sensitivity analyses suggested that our findings were robust to baseline adjustment and alternative censoring. Cardiovascular benefits were observed in the context of generally acceptable levels of cardiovascular risk-factor management at baseline and during the trial. There were fewer add-on therapies for diabetes medications, lipid-lowering medications, and diuretics in patients in the liraglutide group than in those in the placebo group. Subgroup analyses suggest a greater benefit of liraglutide with respect to the primary outcome in patients with an eGFR of less than 60 ml per minute per 1.73 m^2 and possibly in patients with a history of cardiovascular disease. A sensitivity analysis of data for patients with an eGFR of less than 60 ml per minute per 1.73 m^2 did not support a clinically meaningful interaction (Table S3 in the Supplementary Appendix).

The pattern of cardiovascular benefits that were associated with liraglutide in our trial appears to differ from that with the sodium–glucose cotransporter 2 inhibitor empagliflozin in the previously reported EMPA-REG OUTCOME trial.[12] The time to benefit emerged earlier in that trial than in the present trial, and the heterogeneity of the direction and magnitude of the effects on the components of the primary composite outcome in that trial contrasts with the consistency of the effect in the present trial. Although these differences may reflect patient populations or chance, the observed benefits in that trial may be more closely linked to hemodynamic changes, whereas in the present trial, the observed benefits are perhaps related to the modified progression of atherosclerotic vascular disease.[13]

It should be noted that in the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial,[14] the GLP-1–receptor agonist lixisenatide, which is shorter-acting than and structurally dissimilar to liraglutide, did not show any cardiovascular benefit in patients with diabetes and a recent acute coronary syndrome. There are a number of other trials regarding cardiovascular outcomes in high-risk cohorts of patients with type 2 diabetes in which similar magnitude effects on glycemic control have been shown but without significant benefits with respect to rates of cardiovascular events or death.[15-20] These include trials with insulin,[16] thiazolidinediones,[15,18] and DPP-4 inhibitors.[17,19,20] Our trial had greater statistical power and included patients with a higher baseline glycated hemoglobin level than did most previous studies. However, no obvious single explanation in terms of either the study designs or the included populations is apparent to explain the divergent findings across this body of medical literature.

The prespecified primary microvascular outcome in our trial was a composite of nephropathy and retinopathy outcomes. The benefit with liraglutide was driven by lower rates of renal outcomes, such as new-onset persistent macroalbuminuria in particular. There was a higher rate of retinopathy events with liraglutide than with placebo, although the difference was not significant. With moderate differences in glycemic control between the trial groups over a median 3.8 years of follow-up, the achievement of

Table 2. Selected Adverse Events Reported during the Trial.*

Event	Liraglutide (N=4668)	Placebo (N=4672)	P Value
	no. of patients (%)		
Adverse event			
Any adverse event	2909 (62.3)	2839 (60.8)	0.12
Serious adverse event	2320 (49.7)	2354 (50.4)	0.51
Confirmed hypoglycemia†	2039 (43.7)	2130 (45.6)	0.06
Severe adverse event	1502 (32.2)	1533 (32.8)	0.51
Severe hypoglycemia†	114 (2.4)	153 (3.3)	0.02
Acute gallstone disease	145 (3.1)	90 (1.9)	<0.001
Cholelithiasis	68 (1.5)	50 (1.1)	0.09
Acute cholecystitis	36 (0.8)	21 (0.4)	0.046
Hypothyroidism	44 (0.9)	33 (0.7)	0.21
Hyperthyroidism	13 (0.3)	8 (0.2)	0.27
Diabetic foot ulcer	181 (3.9)	198 (4.2)	0.38
Allergic reaction	59 (1.3)	44 (0.9)	0.14
Injection-site reaction	32 (0.7)	12 (0.3)	0.002
Adverse event leading to permanent discontinuation of trial regimen			
Any adverse event	444 (9.5)	339 (7.3)	<0.001
Serious adverse event	192 (4.1)	245 (5.2)	0.01
Severe adverse event	164 (3.5)	188 (4.0)	0.20
Nausea	77 (1.6)	18 (0.4)	<0.001
Vomiting	31 (0.7)	2 (<0.1)	<0.001
Diarrhea	27 (0.6)	5 (0.1)	<0.001
Increased lipase level‡	15 (0.3)	11 (0.2)	0.43
Abdominal pain	11 (0.2)	3 (0.1)	0.03
Decreased appetite	11 (0.2)	2 (<0.1)	0.01
Abdominal discomfort	10 (0.2)	0	0.002
Pancreatitis or neoplasm§			
Acute pancreatitis	18 (0.4)	23 (0.5)	0.44
Chronic pancreatitis	0	2 (<0.1)	0.16
Any benign neoplasm	168 (3.6)	145 (3.1)	0.18
Any malignant neoplasm	296 (6.3)	279 (6.0)	0.46
Pancreatic carcinoma	13 (0.3)	5 (0.1)	0.06
Medullary thyroid carcinoma	0	1 (<0.1)	0.32

* Serious adverse events and nonserious medical events of special interest were identified by search in the *Medical Dictionary for Regulatory Activities*, version 18.0. Permanent discontinuation of the treatment regimen was indicated by the investigator in the adverse-event form. P values were calculated by means of Pearson's chi-square test.

† Confirmed hypoglycemia was defined a plasma glucose level of less than 56 mg per deciliter (3.1 mmol per liter). Severe hypoglycemia was defined as hypoglycemia for which the patient required assistance from a third party.

‡ Increased lipase levels were those that were reported by the investigator as adverse events.

§ Events of pancreatitis and neoplasms were adjudicated by the event-adjudication committee. This committee interpreted neoplastic growth as clonal disorders that grow in an autonomous manner. The abnormality of clonal disorder may not always have been identified nor could autonomous growth always be determined, but both were considered to be fundamental aspects of neoplastic growth.

renal microvascular benefits is surprising. It is uncertain whether this finding relates to the direct effects of liraglutide on kidney function.[21,22]

More patients in the liraglutide group than in the placebo group permanently discontinued the trial regimen owing to adverse events (difference, 2.2 percentage points). There has been considerable interest in a potential association between the use of GLP-1–receptor agonists and pancreatitis and pancreatic cancer, although there is no consistent preclinical, pharmacovigilance, or epidemiologic evidence to date.[23-25] Higher levels of lipase and amylase were observed in the liraglutide group, a finding that is similar to results in other studies.[24] Blinded medications were to be stopped only in relation to confirmed pancreatitis as evaluated by the investigator. There were 1.5 episodes of pancreatitis per 1000 patient-years of observation in both regimens combined, and there were numerically fewer acute or chronic pancreatitis events with liraglutide than with placebo. There were more episodes of gallstone disease with liraglutide, a finding that has been reported previously.[26]

An excess in adjudicated cancers of pancreatic origin was observed in the liraglutide group, although the finding was not significant; there were small overall numbers and no between-group difference in the number of overall cancers. Among rodents receiving liraglutide, higher rates of thyroid C-cell tumors and hyperplasia have been observed than were observed among control animals.[27] In the present trial, no episodes of C-cell hyperplasia or medullary thyroid carcinoma were observed in patients in the liraglutide group. Randomized trials of this type, despite their size, are not powered to determine the effect of drugs on cancer risk and can therefore neither confirm nor exclude such a possibility.

Many patients in each group were treated with sulfonylureas or insulin at baseline, but fewer patients in the liraglutide group than in the placebo group added insulin during the trial. There was a 31% lower rate of severe hypoglycemia and a 20% lower rate of the combination of severe and confirmed hypoglycemia (plasma glucose level, <56 mg per deciliter) in the liraglutide group than in the placebo group.

A limitation of our trial is that patients were followed for only 3.5 to 5.0 years, so the safety and efficacy data are restricted to that time period. Also, because our trial recruited a population of patients who were at high risk for cardiovascular events and who had a baseline glycated hemoglobin level of 7% or more, the observed benefits and risks may not apply to patients at lower risk. Furthermore, no adjustments were made for multiplicity of exploratory outcomes.

In conclusion, among patients with type 2 diabetes who were at high risk for cardiovascular events while they were taking standard therapy, those in the liraglutide group had lower rates of cardiovascular events and death from any cause than did those in the placebo group.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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