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Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes
The CAROLINA Randomized Clinical Trial

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IMPORTANCE Type 2 diabetes is associated with increased cardiovascular risk. In placebo-controlled cardiovascular safety trials, the dipeptidyl peptidase-4 inhibitor linagliptin demonstrated noninferiority, but it has not been tested against an active comparator.

OBJECTIVE This trial assessed cardiovascular outcomes of linagliptin vs glimepiride (sulfonylurea) in patients with relatively early type 2 diabetes and risk factors for or established atherosclerotic cardiovascular disease.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind, active-controlled, noninferiority trial, with participant screening from November 2010 to December 2012, conducted at 607 hospital and primary care sites in 43 countries involving 6042 participants. Adults with type 2 diabetes, glycated hemoglobin of 6.5% to 8.5%, and elevated cardiovascular risk were eligible for inclusion. Elevated cardiovascular risk was defined as documented atherosclerotic cardiovascular disease, multiple cardiovascular risk factors, aged at least 70 years, and evidence of microvascular complications. Follow-up ended in August 2018.

INTERVENTIONS Patients were randomized to receive 5 mg of linagliptin once daily (n = 3023) or 1 to 4 mg of glimepiride once daily (n = 3010) in addition to usual care. Investigators were encouraged to intensify glycemic treatment, primarily by adding or adjusting metformin, α-glucosidase inhibitors, thiazolidinediones, or insulin, according to clinical need.

MAIN OUTCOMES AND MEASURES The primary outcome was time to first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke with the aim to establish noninferiority of linagliptin vs glimepiride, defined by the upper limit of the 2-sided 95.47% CI for the hazard ratio (HR) of linagliptin relative to glimepiride of less than 1.3.

RESULTS Of 6042 participants randomized, 6033 (mean age, 64.0 years; 2414 [39.9%] women; mean glycated hemoglobin, 7.2%; median duration of diabetes, 6.3 years; 42% with macrovascular disease; 59% had undergone metformin monotherapy) were treated and analyzed. The median duration of follow-up was 6.3 years. The primary outcome occurred in 356 of 3023 participants (11.8%) in the linagliptin group and 362 of 3010 (12.0%) in the glimepiride group (HR, 0.98 [95.47% CI, 0.84-1.14]; $P < .001$ for noninferiority), meeting the noninferiority criterion but not superiority ($P = .76$). Adverse events occurred in 2822 participants (93.4%) in the linagliptin group and 2856 (94.9%) in the glimepiride group, with 15 participants (0.5%) in the linagliptin group vs 16 (0.5%) in the glimepiride group with adjudicated-confirmed acute pancreatitis. At least 1 episode of hypoglycemic adverse events occurred in 320 (10.6%) participants in the linagliptin group and 1132 (37.7%) in the glimepiride group (HR, 0.23 [95% CI, 0.21-0.26]).

CONCLUSIONS AND RELEVANCE Among adults with relatively early type 2 diabetes and elevated cardiovascular risk, the use of linagliptin compared with glimepiride over a median 6.3 years resulted in a noninferior risk of a composite cardiovascular outcome.

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When choosing medications to manage type 2 diabetes, cardiovascular safety, glucose-lowering potency, hypoglycemia risk, effect on body weight, and cost are important considerations.[1-3] Most guidelines state that metformin should be first-line therapy followed by various options for second-line treatment if sufficient glycemic control is not achieved after metformin monotherapy.[1-3] Sulfonylureas and dipeptidyl peptidase-4 (DPP-4) inhibitors are the most commonly used second-line glucose-lowering treatments in many countries.[4] Sulfonylureas are used mainly based on their low cost, well-established glucose-lowering action, and a long-standing experience in clinical practice. However, sulfonylureas are associated with increased risk of hypoglycemia[1,3,5-7] and modest weight gain.[1,5] In addition, there is an ongoing controversy regarding their long-term cardiovascular safety, based on early data from the University Group Diabetes Program in the 1960s[8] and multiple observational and smaller studies indicating conflicting results.[9,10]

Linagliptin is a selective, once-daily, DPP-4 inhibitor approved for glycemic management of type 2 diabetes, with low risk of hypoglycemia and weight neutrality.[11] To date, no head-to-head trial has compared the long-term effect of these agents on cardiovascular morbidity and mortality or glucose-lowering efficacy in patients with type 2 diabetes.

The Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes (CAROLINA) examined the effect of treatment with the DPP-4 inhibitor linagliptin vs the commonly used sulfonylurea glimepiride on cardiovascular safety in patients with relatively early type 2 diabetes and cardiovascular risk factors or established atherosclerotic cardiovascular disease using a noninferiority design.

Key Points

Question What is the effect of linagliptin compared with glimepiride on major cardiovascular events in patients with relatively early type 2 diabetes and elevated cardiovascular risk?

Findings In this randomized noninferiority clinical trial that included 6033 participants followed up for a median of 6.3 years, the use of linagliptin compared with glimepiride added to usual care resulted in rates of the composite outcome (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) of 11.8% vs 12.0%. The upper limit of the 95.47% CI of the hazard ratio was 1.14, which met the noninferiority criterion of a hazard ratio of less than 1.3.

Meaning Compared with glimepiride, the use of linagliptin demonstrated noninferiority with regard to the risk of major cardiovascular events over a median of 6.3 years in patients with relatively early type 2 diabetes and elevated cardiovascular risk.

Methods

The study protocol was approved by the institutional review board or independent ethics committee from each site, and all patients provided written informed consent; the trial protocol is available is Supplement 1 and the statistical analysis plan in Supplement 2.

The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonisation and was approved by local authorities.

Trial Oversight

An independent, unmasked data monitoring committee regularly reviewed trial data. Investigator-reported cardiovascular outcome events, deaths, pancreatitis, and pancreatic cancer were prospectively captured and centrally adjudicated by clinical events committees masked to treatment assignment.

Trial Design

The trial design has been previously published.[12] In brief, this was a multicenter, randomized, double-blind, active-controlled clinical trial conducted at 607 centers across 43 countries, aimed to continue until at least 631 participants had an adjudication-confirmed primary outcome event.

Trial Participants

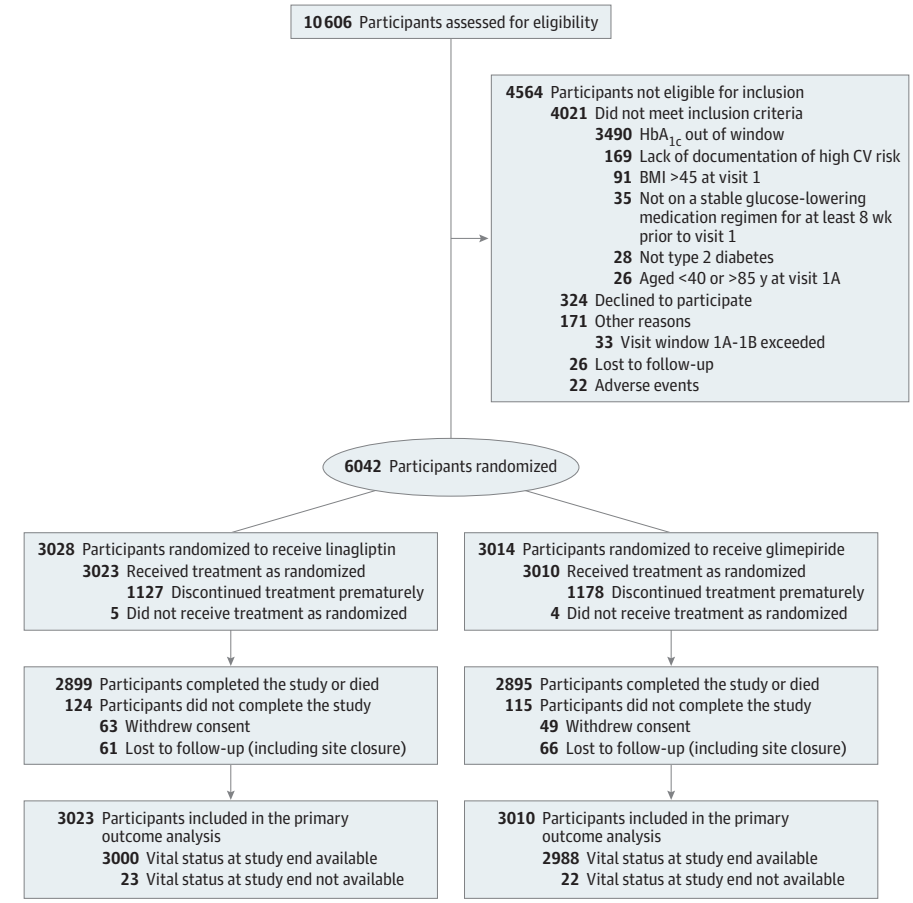
Adults with type 2 diabetes, glycated hemoglobin (HbA_{1c}) level of 6.5% to 8.5%, and high cardiovascular risk were eligible for inclusion. Participants naive to sulfonylurea or glinide therapy had to have a HbA_{1c} level of 6.5% to 8.5%, while participants who were currently treated with a sulfonylurea or glinide as monotherapy or in a dual combination with metformin or α-glucosidase inhibitor (who also were eligible for the trial) had to have an HbA_{1c} level of 6.5% to 7.5%. The sulfonylurea or glinide were discontinued at randomization. High cardiovascular risk was defined as (1) established atherosclerotic cardiovascular disease (documented ischemic heart disease, cerebrovascular disease, or peripheral artery disease), (2) multiple risk factors (at least 2 of the following: type 2 diabetes duration >10 years, systolic blood pressure >140 mm Hg [or receiving at least 1 blood pressure–lowering treatment], current smoker, low-density lipoprotein cholesterol ≥135 mg/dL [3.5 mmol/L], or receiving lipid-lowering treatment), (3) age at least 70 years, and (4) evidence of microvascular complications (impaired kidney function [estimated glomerular filtration rate of 30-59 mL/min/1.73 m^2], urine albumin/creatinine ratio ≥30 µg/mg, or proliferative retinopathy). Insulin therapy or previous exposure to DPP-4 inhibitors, glucagonlike peptide-1 receptor agonists, or thiazolidinediones were exclusion criteria, as was New York Heart Association class III to IV heart failure (eAppendix 3 and 4 in Supplement 3).

Information on race and ethnicity was captured by investigators based on self-classification by trial participants as reported in the electronic case record form (fixed categories) following written informed consent. This information was collected to allow for subgroup analysis, given some previous reports about potential heterogeneity of effects of sulfonylureas and incretin-based therapies on different genetic background,[13,14] and as required by regulatory bodies.[15]

Trial Procedures

Participants were randomized 1:1 using an interactive telephone- and web-based system in a block size of 4 to receive 5 mg of once-daily oral linagliptin or 1 to 4 mg of once-daily glimepiride (**Figure 1**). Treatment assignment was determined by a computer-generated random sequence with stratification by center. Glimepiride was started at 1 mg/d and

Figure 1. Enrollment, Randomization, and Follow-up of Participants in a Study of the Effect of Linagliptin vs Glimepiride on Cardiovascular Outcomes in Patients With Type 2 Diabetes



There were 19 participants (9 in the linagliptin group and 10 in the glimepiride group) identified to have been enrolled and treated at multiple sites. For these participants, treatment group allocation according to first randomization was used and only objective data (eg, selected baseline characteristics, serious adverse events, and trigger events sent for adjudication) were included in the analyses. Patients could meet more than 1 exclusion criteria. BMI indicates body mass index; CV, cardiovascular; HbA_{1c}, glycated hemoglobin.

uptitrated to a potential maximum dose of 4 mg/d every 4 weeks during the first 16 weeks. After the first 16 weeks, participants returned for follow-up study visits every 16 weeks until the end of the study. A final follow-up visit was scheduled 30 days after treatment cessation. Investigators were encouraged to monitor and use additional medication for glycemic control per local guidelines, particularly if HbA_{1c} was greater than 7.5% after the end of the titration phase. Recommended strategies were adjustments of background therapy or addition of pioglitazone, metformin, α-glucosidase inhibitor, or basal insulin. Investigators were also encouraged to manage all other cardiovascular risk factors in accordance with applicable guidelines and current standards of care. Participants who prematurely discontinued the study medication were followed up for ascertainment of cardiovascular events, mortality, adverse events, and other end points. Attempts were made to collect vital status and outcome event information on every randomized individual at study completion, in compliance with local law and regulations.

Trial Outcomes

The primary end point was time to first occurrence of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke (3-point major cardiovascular event [3P-MACE] composite). The original protocol included hospitalization for unstable angina in the primary end point (4-point major cardiovascular event [4P-MACE] composite); however, this was changed by a protocol amendment in April 2016, based on emerging evidence that a primary end point definition of 3P-MACE was preferred by regulators and consistent with other outcome trials of glucose-lowering therapies.[16,17] The steering committee and sponsor remained blinded to all trial data prior to database lock. Time to first occurrence of 4P-MACE was hierarchically evaluated as the first of the prespecified key secondary end points, followed by analyses of the proportion of patients receiving treatment and maintaining HbA_{1c} of less than or equal to 7.0% at the final follow-up visit who (1) were without the need for rescue medication, did not have any moderate/severe hypoglycemic episodes, and did not have greater than 2% weight gain or (2) were without the need for rescue medication and did not have greater than 2% weight gain between the end of titration and final visit.

Other secondary cardiovascular end points included individual components of 3P-MACE and 4P-MACE and time to any confirmed adjudicated cardiovascular events (cardiovascular death, including fatal stroke and fatal MI; nonfatal MI; nonfatal stroke; hospitalization for unstable angina; transient ischemic attack; hospitalization for HF; hospitalization for coronary revascularization procedures). Secondary diabetes-related end points included change in laboratory parameters from baseline

to final visit (eg, HbA_{1c}, fasting plasma glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides). In addition, we prespecified several tertiary cardiovascular end points (ie, occurrence of and time to first occurrence of each of the confirmed adjudicated end points), tertiary diabetes-related end points (eg, change of laboratory parameters from baseline to each planned week, hypoglycemia occurrence, change in weight and rescue medication use), and other end points (including noncardiovascular death and adverse events). All predefined outcomes and end point definitions are presented in Supplement 1, Supplement 3 (eAppendix 5), and Supplement 4.

Safety was assessed based on adverse events that occurred during treatment or within 7 days after the last dose of a study drug and coded using the Medical Dictionary for Drug Regulatory Activities version 21.0. Adverse events prespecified as being of special interest included hypersensitivity reactions, skin lesions, pancreatitis, pancreatic cancer, and hypoglycemia. Categories of hypoglycemia were analyzed as "any," "moderate or severe," "severe," or "leading to hospitalization" (for definitions of each categorization, see eAppendix 5 in Supplement 3).

Statistical Analysis

The primary aim of the study was to evaluate whether linagliptin was noninferior to glimepiride for the time to 3P-MACE, defined by the upper limit of the multiplicity-adjusted 2-sided 95.47% CI for the hazard ratio (HR) of linagliptin relative to glimepiride of less than 1.3.[15] This margin (ie, an upper limit of the 2-sided 95% CI <1.3) was deemed able to demonstrate a reassuring point estimate of overall cardiovascular risk between study groups in the context of a noninferiority assessment by the US Food and Drug Administration. A 5-step hierarchical testing strategy was prespecified, in which each subsequent test would be performed in case of significant prior results. If noninferiority was achieved for the primary outcome, the subsequent tests were (1) superiority test of 3P-MACE, (2) superiority test of 4P-MACE, (3) superiority test of the second key secondary end point (ie, proportion of patients receiving treatment and maintaining HbA_{1c} ≤7.0% at the final visit who were without the need for rescue medication following the end of titration, did not have moderate/severe hypoglycemic episodes, and did not have >2% weight gain), and (4) superiority test of the third key secondary end point (ie, proportion of patients receiving treatment and maintaining HbA_{1c} ≤7.0% at the final visit who were, from the end of titration, without the need for rescue medication and did not have >2% weight gain). Not adjusted for interim analyses, a total of 631 individuals with an adjudication-confirmed 3P-MACE would provide 90.9% power to demonstrate noninferiority (noninferiority margin, 1.3) of linagliptin vs glimepiride at the overall 1-sided α level of 2.5% assuming an HR of 1.0, and 80% power for superiority assuming an HR of 0.80. The 95.47% bound for the CI reflected an O'Brien-Fleming α-spending adjustment for the 2 interim analyses of the primary outcome,[18] in addition to Bonferroni adjustment, to control for type I error for the change from 4P-MACE to 3P-MACE after the first interim analysis. The interim analyses were planned to be performed after 190 and 411 participants experienced a primary outcome event. Outcomes were analyzed in all randomized patients treated with at least 1 dose of the study drug (treated set) using the intention-to-treat principle. Patients were analyzed according to their randomized treatment group. Additional sensitivity analyses are described in eAppendix 6 in Supplement 3. Time-to-event outcomes were analyzed using a Cox proportional hazards model, with treatment assignment as a factor in the model. Proportional hazards assumptions were explored by plotting log(−log [survival function]) against the log of time × treatment group and checked for parallelism. Further, Schoenfeld residuals were plotted against time and log(time). For all Cox proportional hazards analyses, the proportional hazard assumption was met. Subgroup analyses included additional factors for subgroup and treatment by subgroup interaction.

In addition, Kaplan-Meier estimates are presented. Censoring was applied the day a participant was last known to be free of the specific outcome event. Because of declining numbers of participants at risk, Kaplan-Meier plots were truncated at 6.5 years after randomization. Logistic regression models with randomized treatment as the factor and χ^2 tests were used to analyze noncardiovascular key secondary efficacy end points. For continuous parameters, the change from baseline over time was evaluated with a restricted maximum likelihood–based mixed-model repeated-measures approach (2-sided significance threshold $P < .05$; eAppendix 6 in Supplement 3). As prespecified, data were included up to the planned week that could theoretically be achieved by all patients. The prespecified approach for handling missing data are described in the statistical analysis plan (Supplement 2). The approach varied according to the statistical analysis employed (eg, censoring in Cox models and Kaplan-Meier plots for time-to-event analysis and mixed models for continuous variables). Specifically, we defined the censoring date for the time-to-event analysis as the last date a patient was known to be free of an end point event, including any start dates of adverse event/outcome events, onset dates of adjudicated-confirmed events, date of percutaneous coronary intervention/coronary artery bypass grafting, or date of trial completion (defined as the latest of date of the last clinic visit, telephone call, or contact if lost to follow-up). Except for the prespecified 5-step hierarchical testing strategy, there was no adjustment for multiple comparisons and, therefore, the results of subgroup analyses and other end points should be interpreted as exploratory. Safety assessments were conducted using descriptive statistics for adverse events, except for analyses of hypoglycemia, which was analyzed using a Cox proportional hazards model (2-sided P value threshold < .05). Analyses were conducted using SAS version 9.4 (SAS Institute).

Results

Trial Participants

Participants were screened from November 2010 through December 2012, with final follow-up on August 21, 2018. A total of 6042 participants were randomized, of whom 6033 received at least 1 dose of the study medication and were included in the primary outcome analysis (Figure 1).

Baseline clinical characteristics were well balanced between groups (**Table 1**), with 42% of all participants having prevalent atherosclerotic cardiovascular disease at the time of screening.

Table 1. Baseline Participant Characteristics in a Study of the Effect of Linagliptin vs Glimepiride on Cardiovascular Outcomes in Patients With Type 2 Diabetes

Characteristic	No. (%) Linagliptin (n = 3023)	Glimepiride (n = 3010)
Age, mean (SD), y	63.9 (9.5)	64.2 (9.5)
Sex		
Men	1838 (60.8)	1781 (59.2)
Women	1185 (39.2)	1229 (40.8)
Race	(n = 3014)	(n = 3000)
White	2217 (73.6)	2190 (73.0)
Asian	531 (17.6)	530 (17.7)
Black	155 (5.1)	169 (5.6)
American Indian/Alaska Native	106 (3.5)	108 (3.6)
Hawaiian/Pacific Islander	5 (0.2)	3 (0.1)
Ethnicity	(n = 3014)	(n = 3000)
Not Hispanic/Latino	2495 (82.8)	2487 (82.9)
Hispanic/Latino	519 (17.2)	513 (17.1)
Region		
Europe	1422 (47.0)	1399 (46.5)
North America, New Zealand, or Australia	618 (20.4)	622 (20.7)
Asia	465 (15.4)	468 (15.5)
South America and Mexico	454 (15.0)	454 (15.1)
Africa (Tunisia and South Africa)	64 (2.1)	67 (2.2)
Smoking status	(n = 3014)	(n = 3000)
Never smoker	1356 (45.0)	1442 (48.1)
Previous smoker	1051 (34.9)	977 (32.6)
Current smoker	607 (20.1)	581 (19.4)
Cardiovascular risk entry criteria		
Vascular disease	1051 (34.8)	1038 (34.5)
Microvascular-related organ damage	258 (8.5)	254 (8.4)
Age ≥70 y	566 (18.7)	592 (19.7)
Multiple cardiovascular risk factors	1132 (37.4)	1111 (36.9)
Missing cardiovascular risk group category or all entries "no"	16 (0.5)	15 (0.5)
History of heart failure	(n = 3014)	(n = 3000)
Yes	122 (4.1)	149 (5.0)
No	2892 (95.6)	2851 (95.0)
Atherosclerotic cardiovascular disease	(n = 3014)	(n = 3000)
Any	1272 (42.2)	1250 (41.7)
Coronary artery disease	968 (32.1)	937 (31.2)
Cerebrovascular disease	371 (12.3)	356 (11.9)
Peripheral artery disease	207 (6.9)	200 (6.7)
History of hypertension	3014 (100)	3000 (100)
Yes	2720 (90.2)	2698 (89.6)
No	294 (9.8)	302 (10.1)
Microvascular disease	3014 (100)	3000 (1000)
Any	847 (28.1)	881 (29.4)
Diabetic neuropathy	515 (17.1)	495 (16.5)
Diabetic nephropathy	352 (11.7)	372 (12.4)
Diabetic retinopathy	212 (7.0)	236 (7.9)
eGFR (MDRD), mL/min/1.73 m^2	(n = 3011)	(n = 3000)
Mean (SD)	76.5 (19.7)	77.0 (19.8)
≥90	693 (23.0)	722 (24.1)
60-89	1726 (57.3)	1740 (58.0)
30-59	576 (19.1)	525 (17.5)
15-29	13 (0.4)	13 (0.4)
<15	3 (0.1)	0

(continued)

Table 1. Baseline Participant Characteristics in a Study of the Effect of Linagliptin vs Glimepiride on Cardiovascular Outcomes in Patients With Type 2 Diabetes (continued)

Characteristic	No. (%) Linagliptin (n = 3023)	Glimepiride (n = 3010)
UACR, mg/g	(n = 3007)	(n = 2988)
Median (Q1, Q3)	9.7 (5.3, 31.8)	9.7 (5.3, 30.1)
<30	2228 (74.1)	2234 (74.8)
30-300	645 (21.4)	630 (21.1)
>300	134 (4.4)	124 (4.1)
BMI, mean (SD)	30.2 (5.2) (n = 3012)	30.0 (5.1) (n = 2997)
Glycated hemoglobin, mean (SD), %	7.2 (0.6) (n = 3013)	7.2 (0.6) (n = 3000)
Fasting plasma glucose, mean (SD), mg/dL	140 (31) (n = 3008)	140 (30) (n = 2993)
Diabetes duration, median (Q1, Q3), y	6.3 (3.0, 11.1) (n = 3001)	6.2 (2.9, 10.9) (n = 2982)
Diabetes duration ≤5 y	(n = 3014)	(n = 3000)
Yes	1224 (40.6)	1212 (40.4)
No	1790 (59.4)	1788 (59.6)
Blood pressure	(n = 3014)	(n = 2998)
Systolic	136 (16)	136 (16)
Diastolic	79 (10)	79 (9)
Heart rate, mean (SD), beats/min	71 (11) (n = 3014)	71 (10) (n = 2998)
Total cholesterol, mean (SD), mg/dL	177 (43) (n = 2893)	177 (45) (n = 2866)
LDL cholesterol, mean (SD), mg/dL	95 (35) (n = 2794)	95 (36) (n = 2763)
HDL cholesterol, mean (SD), mg/dL	48 (13) (n = 2889)	49 (13) (n = 2854)
Triglycerides, median (Q1, Q3), mg/dL	144 (106-200) (n = 2893)	142 (105-196) (n = 2866)
Glucose-lowering therapy	(n = 3014)	(n = 3000)
Metformin	2510 (83.3)	2510 (83.7)
Sulfonylurea	869 (28.8)	846 (28.2)
α-Glucosidase inhibitor	97 (3.2)	92 (3.1)
Glinide	28 (0.9)	38 (1.3)
No. of glucose-lowering therapies	(n = 3014)	(n = 3000)
0	274 (9.1)	272 (9.1)
1	1984 (65.8)	1982 (66.1)
2	736 (24.4)	725 (24.2)
3	20 (0.7)	21 (0.7)
Blood pressure-lowering medications	(n = 3014)	(n = 3000)
≥1	2662 (88.3)	2682 (89.4)
ACE inhibitors	1330 (44.1)	1342 (44.7)
ARBs	956 (31.7)	928 (30.9)
β-Blockers	1193 (39.6)	1159 (38.6)
Calcium-channel antagonists	891 (29.6)	885 (29.5)
Diuretics	1099 (36.5)	1137 (37.9)
Select cardiovascular medications	(n = 3014)	(n = 3000)
Acetylsalicylic acid	1410 (46.8)	1413 (47.1)
Statins	1913 (63.5)	1987 (66.2)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease study equation[19]; UACR, urinary albumin-to-creatinine ratio.

SI conversion factors: To convert cholesterol to mmol/L, multiply values by 0.0259; triglycerides to mmol/L, multiply by 0.0113; and glucose to mmol/L, multiply by 0.0555.

Median (quartile [Q] 1, Q3) follow-up was 6.3 (5.9, 6.6) years in both the linagliptin and glimepiride groups. Median (Q1, Q3) study medication exposure was 5.9 years in the linagliptin group and 5.9 (3.4, 6.4) years in the glimepiride group (eAppendix 7 in Supplement 3). Cumulative participant-years of follow-up was 18 336 for the linagliptin group and 18 212 for the glimepiride group. Overall, 96.0% of participants completed the study, with 38.2% prematurely discontinuing the study drug (incidence rate per 100 years at risk of 7.6 in the linagliptin group and 8.0 in the glimepiride group). Vital status was available for 99.3% of participants at the end of the study (Figure 1).

Primary End Point

The primary 3P-MACE end point occurred in 356 of 3023 participants (11.8%) treated with linagliptin (2.1 per 100 person-years) and 362 of 3010 (12.0%) treated with glimepiride (2.1 per 100 person-years), meeting the criterion for noninferiority (HR, 0.98 [95.47% CI, 0.84-1.14], P <.001 for noninferiority; **Table 2** and **Figure 2**A). The subsequent testing for superiority according to the prespecified testing procedure was not statistically significant (P = .76). Overall, the HR for 3P-MACE was consistent across prespecified subgroups (eAppendix 8 in Supplement 3).

Key Secondary End Points

Because the result of the test for superiority was null, findings for the key secondary outcomes are presented descriptively. Post hoc analytic results can be found in eAppendix 9 and eTable 3 in Supplement 3. The secondary 4P-MACE outcome occurred in 398 of 3023 participants (13.2%) in the

Table 2. Primary End Point, Key Secondary Outcomes, and Other Secondary or Tertiary Cardiovascular End Points in a Study of the Effect of Linagliptin vs Glimepiride on Cardiovascular Outcomes in Patients With Type 2 Diabetes

Outcome	Linagliptin (n = 3023)		Glimepiride (n = 3010)		Incidence Rate/100 Patient-Years Difference, Linagliptin – Glimepiride (95% CI)	HR[a]/Odds Ratio[b] (95% CI)
	No. (%)	Rate/100 Patient-Years	No. (%)	Rate/100 Patient-Years		
Primary End Point						
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (3P-MACE)	356 (11.8)	2.1	362 (12.0)	2.1	0.0 (−0.4 to 0.3)	0.98 (0.84 to 1.14)[a,c,d]
Cardiovascular death[c]	129 (4.3)		125 (4.2)			
Nonfatal myocardial infarction	141 (4.7)		138 (4.6)			
Nonfatal stroke[c]	86 (2.8)		101 (3.4)			
Key Secondary End Points						
Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina pectoris (4P-MACE)	398 (13.2)	2.3	401 (13.3)	2.4	0.0 (−0.4 to 0.3)	0.99 (0.86 to 1.14)[a]
Receiving treatment and maintaining HbA_{1c} ≤7.0% at final visit [onwards from titration] without the need for rescue medication, without any moderate/severe hypoglycemic episodes, and without >2% weight gain[c]	481 (16.0)		305 (10.2)			1.68 (1.44 to 1.96)[b]
Receiving treatment and maintaining HbA_{1c} ≤7.0% at final visit [onwards from titration] without the need for rescue medication and without >2% weight gain[c]	524 (17.4)		422 (14.1)			1.29 (1.12 to 1.48)[b]
Other Secondary or Tertiary Cardiovascular End Points						
All-cause mortality	308 (10.2)	1.7	336 (11.2)	1.8	−0.2 (−0.4 to 0.1)	0.91 (0.78 to 1.06)[a]
Cardiovascular mortality	169 (5.6)	0.9	168 (5.6)	0.9	0.0 (−0.2 to 0.2)	1.00 (0.81 to 1.24)[a]
Noncardiovascular mortality	139 (4.6)	0.8	168 (5.6)	0.9	−0.2 (−0.4 to 0.0)	0.82 (0.66 to 1.03)[a]
Nonfatal myocardial infarction	145 (4.8)	0.8	142 (4.7)	0.8	0.0 (−0.2 to 0.2)	1.01 (0.80 to 1.28)[a]
Fatal or nonfatal myocardial infarction	153 (5.1)	0.9	148 (4.9)	0.9	0.0 (−0.2 to 0.2)	1.03 (0.82 to 1.29)[a]
Nonfatal stroke	91 (3.0)	0.5	104 (3.5)	0.6	−0.1 (−0.2 to 0.1)	0.87 (0.66 to 1.15)[a]
Fatal or nonfatal stroke	104 (3.4)	0.6	120 (4.0)	0.7	−0.1 (−0.3 to 0.1)	0.86 (0.66 to 1.12)[a]
Transient ischemic attack	25 (0.8)	0.1	33 (1.1)	0.2	0.0 (−0.1 to 0.0)	0.75 (0.45 to 1.26)[a]
Hospitalization for unstable angina	60 (2.0)	0.3	56 (1.9)	0.3	0.0 (−0.1 to 0.1)	1.07 (0.74 to 1.54)[a]
Coronary revascularization procedure	202 (6.7)	1.2	189 (6.3)	1.1	0.1 (−0.2 to 0.3)	1.06 (0.87 to 1.29)[a]
Hospitalization for heart failure	112 (3.7)	0.6	92 (3.1)	0.5	0.1 (−0.1 to 0.3)	1.21 (0.92 to 1.59)[a]
Investigator-reported heart failure events[e]	166 (5.5)	1.0	155 (5.2)	0.9	0.1 (−0.1 to 0.3)	1.06 (0.85 to 1.32)[a]
Hospitalization for heart failure or cardiovascular death	236 (7.8)	1.3	234 (7.8)	1.3	0.0 (−0.2 to 0.2)	1.00 (0.84 to 1.20)[a]
Any adjudicated-confirmed cardiovascular event[f]	518 (17.1)	3.1	535 (17.8)	3.2	−0.1 (−0.5 to 0.3)	0.96 (0.85 to 1.09)[a]

Abbreviations: 3P-MACE, 3-point major adverse cardiovascular event; 4P-MACE, 4-point major adverse cardiovascular event; HbA_{1c}, glycated hemoglobin.

[a] Hazard ratio (HR) based on Cox regression analyses in participants treated with ≥1 dose of the study drug.

[b] Odds ratio based on logistic regression for second and third secondary outcomes in participants treated with ≥1 dose of study drug.

[c] Number of events for individual components of composite outcomes. In the glimepiride group, 2 participants had 2 primary outcomes on the same date.

[d] 95.47% CI for the primary end point, adjusted for multiplicity because of 2 interim analyses and change of the primary end point.

[e] Analysis based on 6014 participants (3014 in the linagliptin group and 3000 in the glimepiride group).

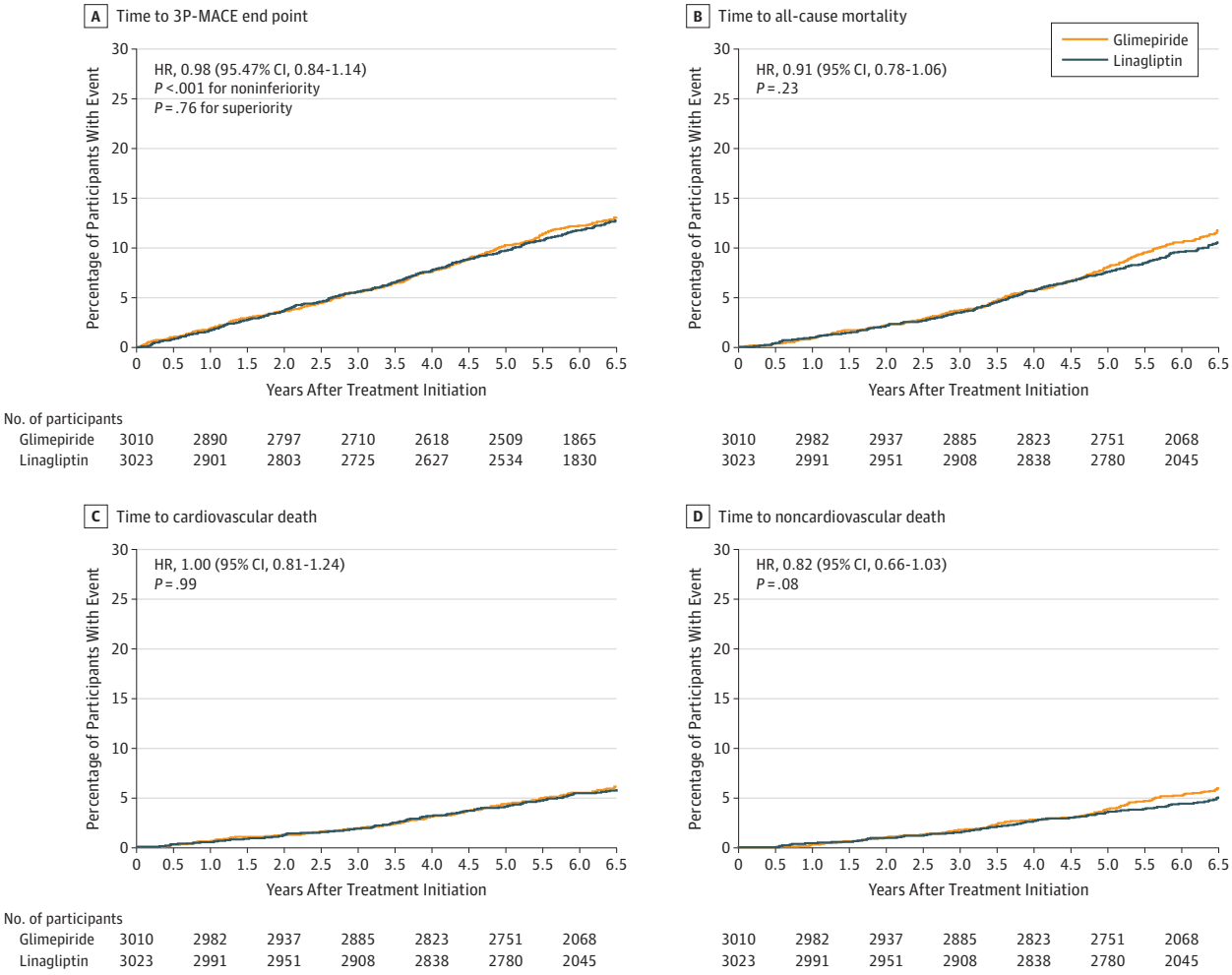
[f] Any adjudicated-confirmed cardiovascular event includes the following components: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina pectoris, transient ischemic attack, hospitalization for heart failure, hospitalization for coronary revascularization (coronary artery bypass grafting, percutaneous coronary intervention).

linagliptin group and 401 of 3010 (13.3%) in the glimepiride group (Table 2). The second key secondary end point of the proportion of patients receiving treatment and maintaining HbA_{1c} less than or equal to7.0% at the final visit who were (following the end of titration) without the need for rescue medication, without any moderate/severe hypoglycemic episodes, and without greater than 2% weight gain occurred in 481 of 3023 participants (16.0%) in the linagliptin group and 305 of 3010 (10.2%) in the glimepiride group (Table 2; eAppendix 9 in Supplement 3). The third key secondary end point of the proportion of patients receiving treatment and maintaining HbA_{1c} less than or equal to 7.0% at the final visit who were (following the end of titration) without the need for rescue medication and did not have greater than 2% weight gain occurred in 524 of 3023 participants (17.4%) in the linagliptin group and in 422 of 3010 (14.1%) in the glimepiride group (Table 2; eAppendix 9 Supplement 3).

Other Secondary and Tertiary Cardiovascular End Points

Death from any cause was not significantly different between participants in the linagliptin (308 of 3023 [10.2%]) and glimepiride (336 of 3010 [11.2%]) groups (HR, 0.91 [95% CI,

Figure 2. Time to Occurrence of End Points Based on Cox Regression Analyses in Patients Treated With at Least 1 Dose of the Study Drug



A, Composite end point of cardiovascular death, first nonfatal myocardial infarction, or first nonfatal stroke (3-point major cardiovascular event [3P-MACE] outcome). Median (quartile [Q] 1, Q3) follow-up was 6.2 (5.8, 6.6) years in the linagliptin group and 6.2 (5.6, 6.5) years in the glimepiride group. The 95.47% CI for the primary end point was adjusted for multiplicity due to 2 interim analyses and change of the primary end point. B, Median (Q1, Q3) follow-up was 6.3 (5.9, 6.6) years in the linagliptin group and 6.3 (5.9, 6.6) years in the glimepiride group. C, Median (Q1, Q3) follow-up was 6.3 (5.9, 6.6) years in the linagliptin group and 6.3 (5.9, 6.6) years in the glimepiride group. D, Median (Q1, Q3) follow-up was 6.3 (5.9, 6.6) years in the linagliptin group and 6.3 (5.9, 6.6) years in the glimepiride group. 3P-MACE indicates 3-point major adverse cardiovascular event.

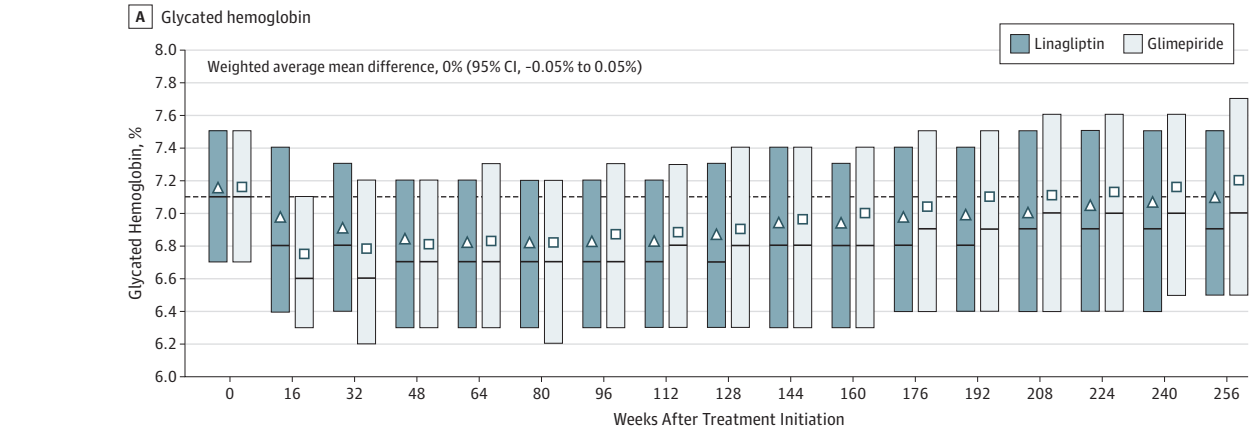
0.78-1.06]; Figure 2B), with an HR for cardiovascular death of 1.00 (95% CI, 0.81-1.24; Figure 2C) and an HR for noncardiovascular death of 0.82 (95% CI, 0.66-1.03; Figure 2D; eAppendix 9 in Supplement 3). The distribution of causes of noncardiovascular death in the linagliptin group (139 of 3023 participants [4.6%]) and the glimepiride group (168 of 3010 participants [5.6%]) is provided in eAppendix 10 in Supplement 3. Adjudication-confirmed hospitalizations for HF, alone or included in composite outcomes with cardiovascular mortality or investigator-reported HF events, were not significantly different between groups (Table 2; eAppendix 9 in Supplement 3).

Secondary and Tertiary Diabetes-Related and Other End Points

The mean (SD) dose of glimepiride over the trial duration was 2.9 (1.1) mg daily (eAppendix 11 in Supplement 3), with 49% of participants using the highest 4-mg dose at week 16 and 61% at week 256. Initially, the effect on adjusted mean change in HbA_{1c} favored glimepiride over linagliptin, but overall there was no significant difference between the groups (weighted mean treatment difference in adjusted means until week 256, 0% [95% CI, −0.05% to 0.05%]; **Figure 3**A). Introduction of additional glucose-lowering therapies occurred in similar proportions across study groups, with a pattern of shorter time to introduction in the linagliptin group compared with the glimepiride group (eAppendix 12 in Supplement 3).

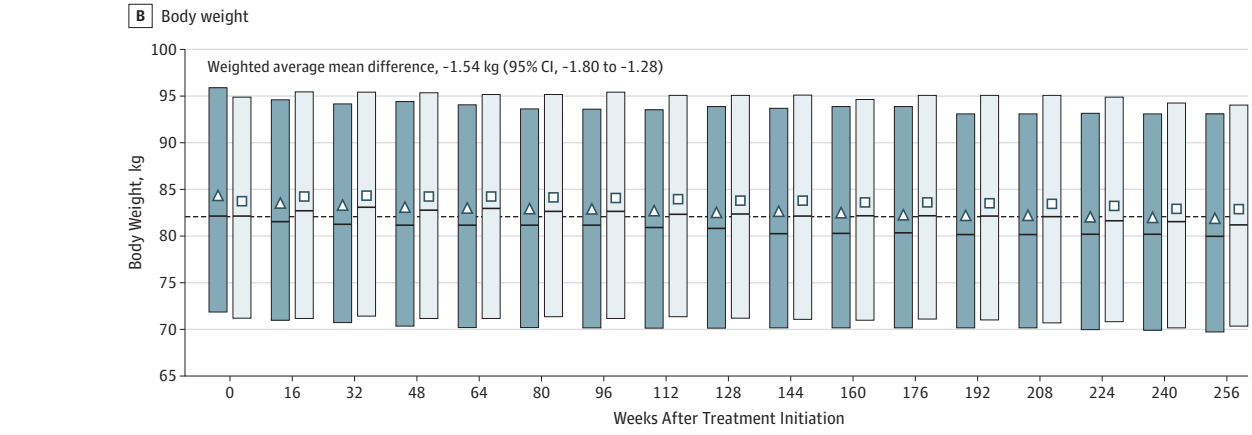
Modest weight gain was observed in the glimepiride group early in the study and maintained thereafter, with a weighted mean between-group difference of −1.54 kg (95% CI, −1.80 to −1.28; Figure 3B). Fasting plasma glucose, blood pressure, and lipid levels over time were not significantly different between groups (eAppendix 13 and 14 in Supplement 3).

Figure 3. Glycated Hemoglobin (HbA_{1c}) and Weight Over Time by Treatment Groups



No. of participants

Glimepiride	3000	2920	2808	2731	2668	2600	2541	2498	2467	2401	2361	2300	2271	2223	2196	2165	2146
Linagliptin	3013	2924	2806	2719	2653	2593	2518	2467	2426	2393	2382	2333	2288	2247	2235	2190	2184
Total in follow-up analysis	6033	6021	5995	5979	5953	5929	5901	5879	5856	5826	5787	5752	5702	5662	5629	5592	5551



No. of participants

Glimepiride	2998	2933	2814	2740	2682	2621	2572	2534	2498	2434	2398	2341	2291	2257	2229	2193	2178
Linagliptin	3014	2936	2822	2741	2674	2620	2546	2522	2466	2433	2426	2378	2326	2280	2280	2236	2221
Total in follow-up analysis	6033	6021	5995	5979	5953	5929	5901	5879	5856	5826	5787	5752	5702	5662	5629	5592	5551

Weighted average mean difference for panels A and B based on mixed-model repeated measures, including treatment, week repeated within participants, week × treatment interaction, continuous baseline HbA_{1c} and weight, and baseline HbA_{1c} × week and weight × week interaction for patients who received at least 1 dose of a study drug and had a baseline and at least 1 postbaseline measurement. The squares and triangles indicate the unadjusted mean, the solid lines indicate the median (quartile [Q] 1, Q3), and the dashed lines indicate the median value at baseline. A, Median (Q1, Q3) follow-up was 6.1 (5.2, 6.4) years in the linagliptin group and 6.1 (4.8, 6.4) years in the glimepiride group. B, Median (Q1, Q3) follow-up was 6.1 (5.2, 6.5) years in the linagliptin group and 6.1 (4.9, 6.4) years in the glimepiride group.

Frequencies of adverse events, serious adverse events, and adverse events leading to discontinuation of study medication were comparable between groups (**Table 3**). Overall, the number of participants with at least 1 hospitalization was 1245 (41.2%) in the linagliptin group and 1303 (43.3%) in the glimepiride group. There was no between-group imbalance in adjudication-confirmed pancreatitis or pancreatic cancer.

Incidence of hypoglycemic events was lower in the linagliptin group than in the glimepiride group across all predefined hypoglycemia severity categories (Table 3). Rates of investigator-reported hypoglycemia were 2.3 events per 100 participant-years in the linagliptin group and 11.1 per 100 participant-years in the glimepiride group (incidence rate difference, −8.7 [95% CI, −9.4 to −8.0]; HR, 0.23 [95% CI, 0.21-0.26]; $P < .001$); rates of moderate or severe hypoglycemic events were 1.4 per 100 participant-years in the linagliptin group and 8.4 per 100 participant-years in the glimepiride group (incidence rate difference, −7.0 [95% CI, −7.6 to −6.5]; HR, 0.18 [95% CI, 0.15-0.21]; $P < .001$; **Figure 4**). Rates of severe hypoglycemic events were 0.07 per 100 participant-years in the linagliptin group and 0.45 per 100 participant-years in the glimepiride group (incidence rate difference, −0.4 [95% CI, −0.5 to −0.3]; HR, 0.15 [95% CI, 0.08-0.29]; $P < .001$; Table 3), and hospitalization due to hypoglycemia rates were 0.01 per 100 patient-years in the linagliptin group vs 0.18 per 100 patient-years in the glimepiride group (incidence rate difference, −0.2 [95% CI, −0.2 to −0.1]; HR, 0.07 [95% CI, 0.02-0.31]; $P < .001$; Table 3). Hypoglycemia risk was increased

Table 3. Adverse Events of Participants in a Study of the Effect of Linagliptin vs Glimepiride on Cardiovascular Outcomes in Patients With Type 2 Diabetes

Adverse Events[a]	Linagliptin (n = 3023) No. (%)	Linagliptin (n = 3023) Rate/100 Patient-Years	Glimepiride (n = 3010) No. (%)	Glimepiride (n = 3010) Rate/100 Patient-Years
Any adverse events[b]	2821 (93.6)	121.9	2855 (95.2)	144.5
Serious adverse events	1403 (46.4)	12.8	1448 (48.1)	13.5
Adverse events leading to study medication discontinuation[b]	414 (13.7)	2.8	448 (14.9)	3.1
Any hospitalization	1245 (41.2)	9.2	1303 (43.3)	9.8
Hypersensitivity reactions[c]	404 (13.4)	3.0	346 (11.5)	2.6
Angioedema events with concomitant ACE inhibitor/ARB use at baseline[d]	42 (1.9)	0.4	41 (1.9)	0.4
Pemphigoid[b]	5 (0.2)	<0.1	0	0.0
Skin lesions[b]	9 (0.3)	<0.1	4 (0.1)	<0.1
Adjudication-confirmed acute pancreatitis	15 (0.5)	0.1	16[e] (0.5)	0.1
Adjudication-confirmed chronic pancreatitis	3 (0.1)	<0.1	0 (0.0)	0.0
All cancers	280 (9.3)	1.6	303 (10.1)	1.7
Colorectal cancer	32 (1.1)	0.2	30 (1.0)	0.2
Adjudication-confirmed pancreatic cancer	16 (0.5)	0.1	24 (0.8)	0.1
Gastric cancer	9 (0.3)	0.1	5 (0.2)	<0.1
Thyroid cancer	1 (<0.1)	<0.1	3 (0.1)	<0.1
Hypoglycemic adverse events[b]				
≥1 Investigator-reported episode of hypoglycemia	320 (10.6)	2.3	1132 (37.7)	11.1
≥1 Investigator-reported episode of symptomatic hypoglycemia with plasma glucose ≤70 mg/dL or severe hypoglycemia	195 (6.5)	1.4	927 (30.9)	8.4
≥1 Investigator-reported episode of severe hypoglycemia[f]	10 (0.3)	0.1	65 (2.2)	0.5
≥1 Episode of hospitalized hypoglycemia	2 (0.1)	<0.1	27 (0.9)	0.2

[a] Adverse events are classified based on Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 and include adverse events from participants treated with ≥1 dose of study medication until 7 days after the last intake of study medication, with the exception of pancreatitis, cancers, and hospitalizations, which include all events in patients treated with ≥1 dose of study drug until study end.

[b] Data set used for analysis of specific adverse events and hypoglycemia was based on 3014 participants in the linagliptin and 3000 in the glimepiride group.

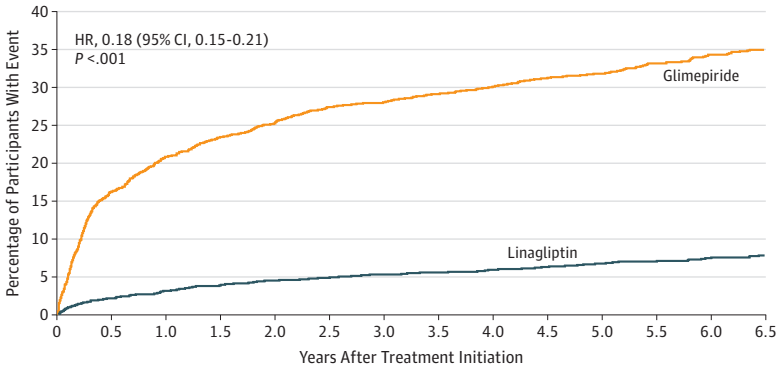
[c] Based on 276 MedDRA 21.0 preferred terms.

[d] Based on 2216 participants in the linagliptin group and 2195 participants in the glimepiride group with angiotensin-converting enzyme or angiotensin-receptor blocker use at baseline.

[e] 1 participant (0.1%) died from pancreatitis.

[f] Requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Figure 4. Moderate or Severe Hypoglycemia Over Time by Treatment Groups



No. of participants

Glimepiride	3000	2382	2145	1999	1882	1779	1691	1607	1539	1473	1411	1325	957	344
Linagliptin	3014	2763	2596	2499	2386	2298	2234	2140	2072	2001	1932	1850	1333	526

Median (quartile 1, quartile 3) follow-up was 5.9 (2.8, 6.5) years in the linagliptin group and 4.3 (0.8, 6.2) years in the glimepiride group. Moderate or severe hypoglycemia was defined as time to the first occurrence of symptomatic investigator-defined hypoglycemic adverse event with plasma glucose ≤70 mg/dL or a severe hypoglycemic adverse event. Analysis based on hypoglycemic adverse events occurring between first study drug intake until 7 days after receiving the study drug for the final time. Severe hypoglycemia was defined as an event requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Hazard ratio (HR) for hypoglycemia derived by Cox regression model analyses in patients treated with ≥1 dose of the study drug.

across the entire dose range for the glimepiride group (eAppendix 15 in Supplement 3). A consistently lower hypoglycemia risk was observed in the linagliptin group than in the glimepiride group across all subgroups analyzed (eAppendix 16 in Supplement 3).

Discussion

In this long-term, multicenter, double-blind, randomized, active comparator trial of individuals with relatively early type

2 diabetes at elevated cardiovascular risk, linagliptin was noninferior to glimepiride for the combined 3P-MACE end point.

Currently, 4 large cardiovascular outcome trials have established the cardiovascular safety of DPP-4 inhibitors vs placebo in patients with type 2 diabetes at a high cardiovascular risk,[20-23] including the Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (CARMELINA).[23] In 2009, when the current trial was designed, sulfonylureas were the most commonly used second-line glucose-lowering agents after metformin, followed by DPP-4 inhibitors, but no head-to-head cardiovascular outcome trial existed for those 2 classes of medications. The current study demonstrates noninferior cardiovascular safety effects for linagliptin vs glimepiride when used predominantly as a second-line glucose-lowering treatment option after metformin.

The current study reaffirms clinical recommendations to choose an oral agent after metformin based on proven cardiovascular benefit,[1,2] which none of the agents studied provide. However, when additional glucose-lowering therapy is required, a DPP-4 inhibitor, such as linagliptin, is an option with a low risk of hypoglycemia and weight gain.

Limitations

This study has several limitations. First, because the trial recruited participants with relatively early type 2 diabetes and insulin treatment was an exclusion criterion, the results may not necessarily be applicable to patients with more advanced disease. While there was no statistically significant heterogeneity in the effects on the 3P-MACE outcome in subgroups based on diabetes duration or cardiovascular risk at baseline, the study may have been underpowered to test for interactions. Second, inherent for many long-term trials is the early termination of study medication, which could have influenced the results. However, medication exposure was comparable between study groups, and annualized discontinuation rates are in line with most of the contemporary cardiovascular outcome trials of glucose-lowering therapies, all of which were of shorter duration.[17,18,20,21,24] Furthermore, analyses limited to events that were occurring while patients were receiving study medication yielded results consistent with the primary analysis.

Conclusions

Among adults with relatively early type 2 diabetes and elevated cardiovascular risk, the use of linagliptin compared with glimepiride over a median of 6.3 years resulted in a noninferior risk of a composite cardiovascular outcome.

ARTICLE INFORMATION

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Author Contributions: Drs Rosenstock and Marx had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Rosenstock, Kahn, Johansen, Zinman, Woerle, Baanstra, Meinicke, McGuire, Marx.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Johansen, Espeland, Pfarr, Keller, Marx.
Critical revision of the manuscript for important intellectual content: Rosenstock, Kahn, Johansen, Zinman, Espeland, Woerle, Mattheus, Baanstra, Meinicke, George, von Eynatten, McGuire, Marx.
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Obtained funding: Johansen, Zinman.
Administrative, technical, or material support: Woerle.
Supervision: Rosenstock, Johansen, Zinman, Woerle, Baanstra, Meinicke, George, von Eynatten, Marx.

Conflict of Interest Disclosure: Dr Rosenstock reported serving on scientific advisory boards and received honoraria and consulting fees from Eli Lilly, Sanofi, Novo Nordisk, Janssen, AstraZeneca, Boehringer Ingelheim, and Intarcia and receiving grants/research support from Merck, Pfizer, Sanofi, Novo Nordisk, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Genentech, Janssen, Lexicon, Boehringer Ingelheim, and Intarcia. Dr Kahn reported receiving personal fees from Boehringer Ingelheim, Elcelyx, Eli Lilly, Intarcia, Janssen, Merck, Neurimmune, and Novo Nordisk. Dr Johansen is employed by Boehringer Ingelheim, Norway. Dr Zinman reported receiving grant support from Boehringer Ingelheim, AstraZeneca, and Novo Nordisk and consulting fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novo Nordisk, and Sanofi Aventis. Dr Espeland reported receiving consulting fees from Boehringer Ingelheim during the conduct of the study and grants from the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute on Aging outside the submitted work. Dr Woerle is a former employee of Boehringer Ingelheim, Germany, and is now employed by Nestle. Mr Pfarr, Mrs Mattheus, and Drs Keller, Meinicke, George, and von Eynatten are employed by Boehringer Ingelheim, Germany. Mr Baanstra is employed by Boehringer Ingelheim, the Netherlands. Dr McGuire reported receiving personal fees from Boehringer-Ingelheim, Janssen Research and Development LLC, Sanofi-Aventis Group, Merck Sharp & Dohme, Eli Lilly USA, Novo Nordisk, GlaxoSmithKline, AstraZeneca, Lexicon, Eisai, Esperion, Pfizer, Metavant, and Applied Therapeutics. Dr Marx is funded by the German Research Foundation SFB TRR 219 (projects M-03 and M-05); reported giving lectures for and receiving honoraria from Amgen, Boehringer Ingelheim, Sanofi-Aventis, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Lilly, Novo Nordisk; receiving unrestricted research grants from Boehringer Ingelheim; serving as an advisor for Amgen, Bayer, Boehringer Ingelheim, Sanofi-Aventis, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Novo Nordisk; serving in trial leadership for Boehringer Ingelheim and Novo Nordisk; and declining all personal compensation from pharmaceutical and device companies.

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Group Information: The trial was designed by independent academic investigators along with clinician scientists employed by Boehringer Ingelheim, the latter as nonvoting members of the steering committee that oversaw the trial. Investigators and committee members are listed in eAppendix 1 and 2 in Supplement 3. Site monitoring, data management, and data analysis

were conducted by Boehringer Ingelheim. Members of Leuven Biostatistics and Statistical Bioinformatics Centre, Belgium, conducted an independent statistical analysis of the cardiovascular and mortality outcomes (eAppendix 2 in Supplement 3).

Data Sharing Statement: See Supplement 5.

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