ORIGINAL ARTICLE

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

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ABSTRACT

BACKGROUND

To assess potentially elevated cardiovascular risk related to new antihyperglycemic drugs in patients with type 2 diabetes, regulatory agencies require a comprehensive evaluation of the cardiovascular safety profile of new antidiabetic therapies. We assessed cardiovascular outcomes with alogliptin, a new inhibitor of dipeptidyl peptidase 4 (DPP-4), as compared with placebo in patients with type 2 diabetes who had had a recent acute coronary syndrome.

METHODS

We randomly assigned patients with type 2 diabetes and either an acute myocardial infarction or unstable angina requiring hospitalization within the previous 15 to 90 days to receive alogliptin or placebo in addition to existing antihyperglycemic and cardiovascular drug therapy. The study design was a double-blind, noninferiority trial with a prespecified noninferiority margin of 1.3 for the hazard ratio for the primary end point of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS

A total of 5380 patients underwent randomization and were followed for up to 40 months (median, 18 months). A primary end-point event occurred in 305 patients assigned to alogliptin (11.3%) and in 316 patients assigned to placebo (11.8%) (hazard ratio, 0.96; upper boundary of the one-sided repeated confidence interval, 1.16; P<0.001 for noninferiority). Glycated hemoglobin levels were significantly lower with alogliptin than with placebo (mean difference, −0.36 percentage points; P<0.001). Incidences of hypoglycemia, cancer, pancreatitis, and initiation of dialysis were similar with alogliptin and placebo.

CONCLUSIONS

Among patients with type 2 diabetes who had had a recent acute coronary syndrome, the rates of major adverse cardiovascular events were not increased with the DPP-4 inhibitor alogliptin as compared with placebo. (Funded by Takeda Development Center Americas; EXAMINE ClinicalTrials.gov number, NCT00968708.)

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Type 2 diabetes is associated with both microvascular and macrovascular complications.[1] The risk of cardiovascular disease is two to four times as high in people with diabetes as in people without diabetes.[1,2] Improved glycemic control can reduce the risk of many microvascular complications of diabetes,[3] but studies have not shown a favorable effect of glycemic control in reducing macrovascular events in patients with type 2 diabetes.[4,5] Concerns regarding adverse cardiovascular outcomes with antidiabetic agents[6,7] prompted the Food and Drug Administration (FDA) to issue guidance in December 2008 that included specific requirements for cardiovascular safety assessment before and after the approval of new antidiabetic therapies.[8] Regulatory agencies in other countries have adopted similar policies.

Alogliptin is a selective inhibitor of dipeptidyl peptidase 4 (DPP-4) that is approved for the treatment of type 2 diabetes.[9,10] By preventing the rapid degradation of glucagon-like peptide 1 (GLP-1) through inhibition of DPP-4, alogliptin enhances pancreatic insulin secretion and suppresses pancreatic glucagon secretion, thus reducing blood glucose levels.[10] During the clinical development program, no imbalance in cardiovascular events was noted among 4168 patients with type 2 diabetes who received alogliptin, 691 patients who received placebo, and 1169 patients who received active comparators.[11] Given the low cardiovascular-risk profile of the patient population and the low event rate, the cardiovascular safety in patients at high cardiovascular risk could not be assessed. We conducted the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial to determine whether alogliptin is noninferior to placebo with respect to major cardiovascular events in patients with type 2 diabetes who are at very high cardiovascular risk — those with recent acute coronary syndromes.

Methods

Study Design

The EXAMINE trial was a multicenter, randomized, double-blind trial. The details of the design have been published previously.[12] The content of the manuscript is consistent with the research protocol, which is available with the full text of this article at NEJM.org. The steering committee, consisting of academic members and three nonvoting representatives of the sponsor (Takeda Development Center Americas), designed and oversaw the conduct of the trial. An independent data and safety monitoring committee monitored the trial and had access to the unblinded data. The statistical analysis was performed by Pharmaceutical Product Development, a contract research organization, in collaboration with investigators at the academic centers and the sponsor, all of whom had full access to the final study data. The sponsor provided alogliptin at no cost and coordinated the data management. The chair of the steering committee (the first author) and other members of the committee who are academic authors wrote all drafts of the manuscript and vouch for the accuracy and completeness of the reported data. MedLogix Communications provided assistance with the figures, with funding from the sponsor. The appropriate national and institutional regulatory authorities and ethics committees approved the study design, and all participants provided written informed consent.

Study Patients

Patients were eligible for enrollment if they had received a diagnosis of type 2 diabetes mellitus, were receiving antidiabetic therapy (other than a DPP-4 inhibitor or GLP-1 analogue), and had had an acute coronary syndrome within 15 to 90 days before randomization. Further criteria for the diagnosis of type 2 diabetes included a glycated hemoglobin level of 6.5 to 11.0% at screening, or if the antidiabetic regimen included insulin, a glycated hemoglobin level of 7.0 to 11.0%. Acute coronary syndromes included acute myocardial infarction and unstable angina requiring hospitalization, as defined previously.[12] Major exclusion criteria were a diagnosis of type 1 diabetes, unstable cardiac disorders (e.g., New York Heart Association class IV heart failure, refractory angina, uncontrolled arrhythmias, critical valvular heart disease, or severe uncontrolled hypertension), and dialysis within 14 days before screening.

Study Drugs and Procedures

Patients were randomly assigned to receive alogliptin or placebo, administered in a double-blind fashion, in addition to standard-of-care treatment for type 2 diabetes mellitus. Through-

out the study, patients were required to receive standard-of-care treatment for type 2 diabetes and cardiovascular risk factors according to regional guidelines. Because alogliptin is cleared by the kidney, the doses of alogliptin (and matching placebo) were modified according to kidney function at the time of randomization and during the postrandomization period. The daily doses of the study drug were as follows: 25 mg in patients with an estimated glomerular filtration rate (GFR), calculated with the use of the Modification of Diet in Renal Disease formula, of at least 60 ml per minute per 1.73 m^2 of body-surface area; 12.5 mg in patients with an estimated GFR of 30 to less than 60 ml per minute per 1.73 m^2; and 6.25 mg in patients with an estimated GFR of less than 30 ml per minute per 1.73 m^2.

Outpatient visits were scheduled at the time of screening, at randomization, and at 1, 3, 6, 9, and 12 months after randomization during the first year of the study and every 4 months during subsequent years of participation. If patients declined to return for study visits, information was obtained during telephone contacts, but this was not the preferred approach nor was it recommended to the sites.

END POINTS

The primary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The principal secondary safety end point was the primary composite end point with the addition of urgent revascularization due to unstable angina within 24 hours after hospital admission (Table S1 in the Supplementary Appendix, available at NEJM.org).[12,13] Exploratory end points included death from cardiovascular causes and death from any cause. The consistency of effects with respect to the primary end point was explored in a variety of subgroups without adjustment for multiple comparisons. Additional safety end points included angioedema, hypoglycemia, pancreatitis, cancer, and the results of laboratory testing. An independent central adjudication committee adjudicated all suspected primary end-point events and other cardiovascular end points, as well as all deaths.

STATISTICAL ANALYSIS

Cox proportional-hazards models were used to analyze the time to the first occurrence of a primary or secondary end-point event among all randomly assigned patients, with stratification according to geographic region and renal function at baseline. Initial group sequential analyses were planned after 80, 100, 125, and 150 adjudicated primary end-point events occurred, with an O'Brien and Fleming–type spending function[14] used to preserve an overall alpha of 2.5% for ruling out a hazard ratio of more than 1.8. If each of the four initial group sequential analyses failed to rule out an upper boundary of 1.8, the trial would be stopped because of futility. If one of these analyses ruled out an upper boundary of 1.8, the trial was designed to continue and similar analyses were to be performed after 550 and 650 adjudicated primary end-point events occurred, with a separate alpha spending function used to maintain a 2.5% overall alpha for ruling out a hazard ratio of more than 1.3 (1.0% and 1.5% alpha spent after 550 and 650 events, respectively). Additional tests for statistical superiority of alogliptin with respect to the primary and secondary end points would be conducted if a hazard ratio of more than 1.3 was ruled out with the use of the same alpha spending function. If noninferiority was declared but the conditional power for superiority at 650 events on the basis of the 550-event interim analysis was 20% or lower, the study would be stopped. We calculated that with a sample of 5400 patients, the study would have 91% power to determine the noninferiority of alogliptin to placebo for the 1.8 (initial) and 1.3 margins, with the assumption of a true hazard ratio of 1.0 and overall one-sided significance levels of 2.5%.

For each group sequential analysis, the statistical analysis plan specified that the upper boundary of a one-sided repeated confidence interval for the hazard ratio (alogliptin to placebo) would be calculated with the use of the critical value obtained from the appropriate spending function and compared with the appropriate noninferiority margins.[14,15] Each analysis was to be conducted by an independent statistician and reviewed by the data and safety monitoring committee. The first group sequential analysis, performed after 83 adjudicated primary end-point events had occurred, showed that the upper boundary of the one-sided repeated confidence interval for the hazard ratio was 1.51. This information was communicated to the data and safety monitoring

Table 1. Baseline Characteristics of the Patients, According to Study Group.*

Characteristic	Placebo (N=2679)	Alogliptin (N=2701)
Median age — yr	61.0	61.0
Age ≥65 yr — no. (%)	934 (34.9)	973 (36.0)
Male sex — no. (%)	1823 (68.0)	1828 (67.7)
Duration of diabetes — yr		
Median	7.3	7.1
Range	2.8–13.7	2.6–13.8
Glycated hemoglobin — %	8.0±1.1	8.0±1.1
Body weight — kg		
Median	80.0	80.2
Range	35.5–196.3	36.0–185.0
Body-mass index†		
Median	28.7	28.7
Range	15.6–68.3	15.7–55.9
Race or ethnic group — no. (%)‡		
White	1943 (72.5)	1966 (72.8)
Black	115 (4.3)	101 (3.7)
Asian	542 (20.2)	547 (20.3)
Native American	54 (2.0)	56 (2.1)
Other	25 (0.9)	31 (1.1)
Region of world — no. (%)		
United States and Canada	426 (15.9)	427 (15.8)
Western Europe, Australia, New Zealand, and Middle East	303 (11.3)	313 (11.6)
Central and South America and Mexico	693 (25.9)	700 (25.9)
Eastern Europe and Africa	753 (28.1)	755 (28.0)
Asia and Pacific Islands	504 (18.8)	506 (18.7)
Cardiovascular risk factors and history — no. (%)		
Current smoker	383 (14.3)	351 (13.0)
Hypertension	2240 (83.6)	2229 (82.5)
Myocardial infarction§	2345 (87.5)	2389 (88.4)
Percutaneous coronary intervention§	1683 (62.8)	1689 (62.5)
Coronary-artery bypass grafting§	341 (12.7)	347 (12.8)
Congestive heart failure	744 (27.8)	757 (28.0)
Stroke	193 (7.2)	195 (7.2)
Peripheral arterial disease	252 (9.4)	262 (9.7)
Estimated glomerular filtration rate¶		
Median — ml/min/1.73 m^2	71.2	71.1
≥60 ml/min/1.73 m^2 — no. (%)	1886 (70.4)	1929 (71.4)
<60 ml/min/1.73 m^2 — no. (%)	793 (29.6)	772 (28.6)
Index ACS — no. (%)		
Myocardial infarction	2068 (77.2)	2084 (77.2)
Unstable angina requiring hospitalization	605 (22.6)	609 (22.5)
Missing data	6 (0.2)	8 (0.3)
Time between index ACS and randomization — days		
Median	46	44
Interquartile range	31–64	30–65

* Plus–minus values are means ±SD. There were no significant differences between the two groups for any baseline characteristic. ACS denotes acute coronary syndrome.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race or ethnic group was self-reported.
§ Values include the index event of the acute coronary syndrome.
¶ The estimated glomerular filtration rate was calculated with the use of the Modification of Diet in Renal Disease formula.

committee by the independent statistician, and after the assessment by that committee, the analysis was submitted to the regulatory authorities for review. To protect the overall statistical validity and integrity of the study, persons associated with this analysis were not involved in subsequent preparation and review of blinded data, nor were they involved in ongoing study conduct or communication with those involved in study conduct.

The study then continued to the next group sequential analysis, which was performed after 550 adjudicated primary end-point events had occurred, to rule out a hazard ratio of more than 1.3. This analysis resulted in a hazard ratio of 0.96 and an upper boundary of the one-sided repeated confidence interval of 1.17, findings that indicated noninferiority but not superiority of alogliptin to placebo, and the conditional power for superiority at 650 events was less than 20%; therefore, the data and safety monitoring committee recommended to the steering committee that the study be stopped. On March 9, 2013, the steering committee accepted the recommendation, and the sponsor agreed to stop enrollment in the study and proceed with a timely and orderly study closeout. The final date for evaluation of vital status was June 18, 2013.

RESULTS

STUDY PATIENTS

We recruited 5380 patients from 898 centers in 49 countries (Fig. S1 in the Supplementary Appendix) from October 2009 through March 2013. At the date of the last patient visit (June 18, 2013), information on vital status was available for all but 25 patients (9 in the alogliptin group [0.3%] and 16 in the placebo group [0.6%]). The two study groups were well balanced with respect to baseline characteristics (Table 1) and nonstudy medications (Table 2). In the alogliptin group, on the basis of the estimated GFR at baseline, 71.4% of the patients received 25 mg daily, 25.7% received 12.5 mg daily, and 2.9% received 6.25 mg daily. The rate of premature discontinuation of the study drug was similar in the alogliptin and placebo groups (20.9% and 22.6% of patients, respectively). The median duration of exposure to alogliptin was 533 days (interquartile range, 280 to 751).

Changes in glycated hemoglobin levels over time are shown in Figure 1. By the end of the study period, the mean change from baseline was −0.33% in the alogliptin group and 0.03% in the placebo group, and the least-squares mean difference between the alogliptin group and the placebo group was −0.36 percentage points (95% confidence interval [CI], −0.43 to −0.28; P<0.001). The change from baseline in body weight was 1.09 kg with alogliptin and 1.04 kg with placebo, and the least-squares mean difference between the alogliptin group and the placebo group was 0.06 kg (95% CI, −0.25 to 0.36; P=0.71). No significant differences in lipoprotein levels were observed between the two study groups (Table S2 in the Supplementary Appendix).

Table 2. Exposure to Study Drugs and Proportions of Patients Receiving Nonstudy Medications.*

Variable	Placebo (N=2679)	Alogliptin (N=2701)
Receipt of study drug — no. (%)	2676 (99.9)	2698 (99.9)
Premature discontinuation of study drug — no. (%)	606 (22.6)	564 (20.9)
Because of adverse event, including death	275 (10.3)	270 (10.0)
Because patient declined to continue drug	192 (7.2)	169 (6.3)
Other reason	139 (5.2)	125 (4.6)
Duration of exposure to study drug		
Median (interquartile range) — days	520 (273–744)	533 (280–751)
>1 Year of exposure to study drug — no. (%)	1787 (66.7)	1836 (68.0)
Medications administered at baseline — no. (%)		
Antiplatelet agents	2602 (97.1)	2630 (97.4)
Aspirin	2433 (90.8)	2448 (90.6)
Thienopyridine	2165 (80.8)	2155 (79.8)
Beta-blockers	2203 (82.2)	2208 (81.7)
Statins	2420 (90.3)	2446 (90.6)
Antidiabetic agents	2649 (98.9)	2676 (99.1)
Insulin	812 (30.3)	793 (29.4)
Metformin	1805 (67.4)	1757 (65.0)
Thiazolidinediones	64 (2.4)	67 (2.5)
Sulfonylureas	1237 (46.2)	1266 (46.9)
Calcium-channel blockers	611 (22.8)	586 (21.7)
Diuretics	1009 (37.7)	1005 (37.2)
Renin–angiotensin system–blocking agents	2210 (82.5)	2201 (81.5)

* Diuretics included loop diuretics and thiazide diuretics. Renin–angiotensin system–blocking agents included angiotensin-converting–enzyme inhibitors and angiotensin II–receptor blockers.

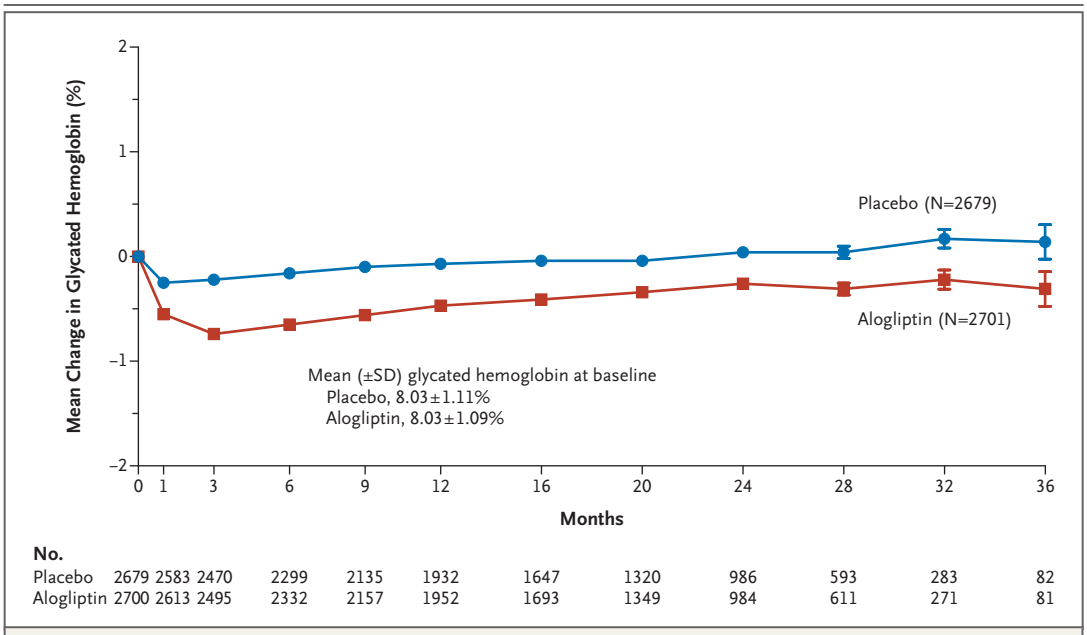

Figure 1. Least-Squares Mean Change from Baseline in Glycated Hemoglobin Levels over Time, According to Study Group.

Data at 40 months were truncated owing to the small numbers of patients (eight per group). I bars indicate standard errors.

PRIMARY AND SECONDARY END POINTS

An additional 71 patients had a primary end-point event after the 550-event interim analysis and just before the database was locked. For this complete analysis, the primary end point occurred at similar rates in the alogliptin and placebo groups (in 11.3% and 11.8% of patients, respectively, after a median exposure of 18 months; hazard ratio, 0.96; upper boundary of the one-sided repeated CI, 1.16; P<0.001 for noninferiority; P = 0.32 for superiority) (Table 3 and Fig. 2A). In the analysis of the components of the primary end point, the hazard ratios were consistent with the hazard ratio for the composite end point. The analysis of the principal secondary end point of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization due to unstable angina showed no significant difference between the alogliptin group and the placebo group (12.7% and 13.4% of patients, respectively; hazard ratio, 0.95; upper boundary of the one-sided repeated CI, 1.14) (Table 3, and Fig. S2 in the Supplementary Appendix). Hazard ratios for death from any cause and death from cardiovascular causes (including deaths that occurred as primary end-point events and deaths that occurred after a nonfatal primary end-point event) were consistent with the hazard ratio for the primary composite end point (Table 3 and Fig. 2B and 2C).

The subgroup analyses of the primary end point showed between-group heterogeneity in subgroups defined according to some of the baseline factors (Fig. S3 in the Supplementary Appendix). Subgroups in which there was nominally significant between-group heterogeneity included former smokers, patients who had had diabetes for at least 10 years, patients who were receiving insulin at baseline, patients who were not receiving biguanides at baseline, patients with moderate or severe renal impairment at baseline, and patients residing in North America or the region that included western Europe, Australia, New Zealand, and the Middle East.

ADVERSE EVENTS

The alogliptin and placebo groups did not differ significantly with respect to the incidence of serious adverse events (33.6% and 35.5%, respectively; P=0.14) (Table S3 in the Supplementary Appendix). The incidence of hypoglycemia was similar in the two study groups. The incidences

Table 3. Major Safety End Points.

End Point	Placebo (N=2679)	Alogliptin (N=2701)	Hazard Ratio for Alogliptin Group (95% CI)	P Value*
	no. (%)			
Primary end point†	316 (11.8)	305 (11.3)	0.96 (≤1.16)‡	0.32
Components of primary end point				
Death from cardiovascular causes	111 (4.1)	89 (3.3)	0.79 (0.60–1.04)	0.10
Nonfatal myocardial infarction	173 (6.5)	187 (6.9)	1.08 (0.88–1.33)	0.47
Nonfatal stroke	32 (1.2)	29 (1.1)	0.91 (0.55–1.50)	0.71
Principal secondary end point§	359 (13.4)	344 (12.7)	0.95 (≤1.14)‡	0.26
Other end points				
Death from any cause	173 (6.5)	153 (5.7)	0.88 (0.71–1.09)	0.23
Death from cardiovascular causes¶	130 (4.9)	112 (4.1)	0.85 (0.66–1.10)	0.21

* P values for testing the superiority of alogliptin to placebo were calculated with the use of a Cox regression analysis.
† The primary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
‡ The parenthetical value is the upper boundary of the one-sided repeated CI, at an alpha level of 0.01.
§ The secondary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization due to unstable angina within 24 hours after hospital admission.
¶ Included are deaths that occurred as primary end-point events and deaths that occurred after a nonfatal primary end-point event.

of acute and chronic pancreatitis were similar in the two groups; no cases were fatal. There were no significant between-group differences in the incidence of cancer, and there were no reports of pancreatic cancer. The incidence of angioedema was low and did not differ significantly between the study groups. The proportion of patients with serum aminotransferase values three times the upper limit of the normal range at any time was similar in the alogliptin and placebo groups. Changes in estimated GFR according to baseline kidney function and incidences of initiation of dialysis were similar in the two study groups (Table S3 and S4 in the Supplementary Appendix).

DISCUSSION

This trial showed that treatment with the DPP-4 inhibitor alogliptin resulted in rates of major cardiovascular events that were similar to rates with placebo among patients with type 2 diabetes and substantial cardiovascular disease and cardiovascular risk. The results of analyses of the individual components of the primary end point (death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke) and of analyses of deaths from any cause and all deaths from cardiovascular causes were consistent with those of the primary composite end point. The similar rates of the primary end point in the alogliptin and placebo groups were observed in the context of modestly better glycemic control in patients who received alogliptin. This finding is not surprising in light of other trials that showed no effects of larger reductions in glycated hemoglobin levels on similar end points over a period of 5 years.[4,5] However, the EXAMINE trial had a median duration of 18 months, and thus the results do not rule out longer-term benefits or risks of alogliptin with respect to cardiovascular end points.

Although DPP-4 inhibitors are in widespread clinical use for the treatment of type 2 diabetes,[16] their cardiovascular safety has not been established. The primary safety analysis in our trial determined the effects of alogliptin as compared with placebo on a composite of major cardiovascular events that were adjudicated by an independent committee whose members were unaware of the study-group assignments. As compared with other cardiovascular safety studies of various antidiabetic therapies,[17-19] the EXAMINE trial included patients at considerably higher cardiovascular risk, with event rates of

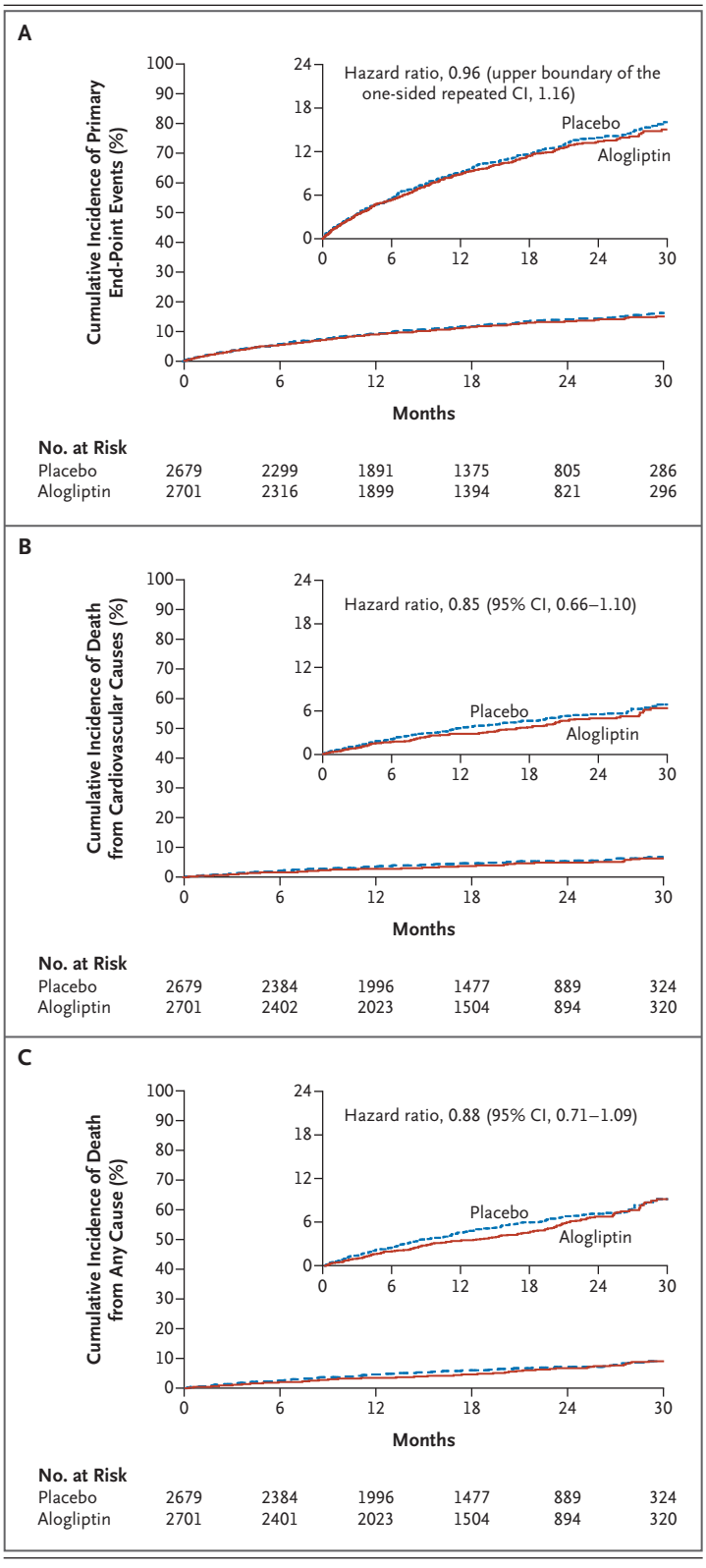

Figure 2. Cumulative Kaplan–Meier Estimates of the Time to the First Adjudicated Occurrence of a Primary End-Point Event or Other Safety End Point.

Panel A shows the time to the first occurrence of a primary end-point event — death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. After a median exposure of 18 months, the rates of the primary composite end point were similar in the alogliptin and placebo groups (11.3% and 11.8%, respectively). Data at 40 months were truncated owing to the small numbers of patients (eight per group). Panel B shows the time to death from cardiovascular causes, and Panel C, the time to death from any cause. In each panel, the inset shows the same data on an enlarged y axis.

more than 11% during the median follow-up period of 18 months. This trial showed no increase in cardiovascular risk with alogliptin in this population during this median follow-up period. Hence, for patients with elevated cardiovascular risk, including those with a recent acute coronary syndrome, who are likely candidates for the drug in clinical practice, it is reassuring that alogliptin does not increase cardiovascular morbidity or mortality over a median period of 18 months.

There has been considerable speculation that DPP-4 inhibitors may exert beneficial effects on the cardiovascular system.[20,21] Recent meta-analyses of the clinical trial data have shown a lower risk of major cardiovascular events with DPP-4 inhibitors than with other classes of antidiabetic agents.[11,22] However, the studies were limited by their short duration (<6 months in most cases), low event numbers, nonuniform and incomplete ascertainment of cardiovascular end points, and comparisons of the DPP-4 inhibitors with both placebo and active agents, some of which have been associated with increased risk of cardiovascular disease and death from cardiovascular causes.[7,23,24] In our trial, the rates of major adverse cardiovascular events were neither significantly increased nor significantly decreased with alogliptin, as compared with placebo, among patients who received appropriate standard-of-care treatment for type 2 diabetes and acute coronary syndromes.

The EXAMINE trial successfully adhered to the recommendations of the 2008 FDA guidance on the evaluation of new therapies for type 2

diabetes.[8] The nuances of the EXAMINE trial required a close interaction among the members of the steering committee, members of the data and safety monitoring committee, and representatives of the sponsor.[12,25] The integrity of the trial was preserved during enrollment and follow-up as well as during the months of study closeout because data were collected only by persons who were unaware of the results of interim analyses.

The noninferiority of alogliptin to placebo with respect to the primary end point was heterogeneous in six subgroups ($P<0.05$ for interaction). These findings may have been due to chance, given the large number of tests performed. Although the number of events contributing to these differences was small and the confidence intervals were large, these results raise questions as to whether differences among populations of patients or practice patterns influenced the effects of the randomly assigned study drugs. Further analyses will be required.

In conclusion, among patients with type 2 diabetes and a recent acute coronary syndrome, treatment with alogliptin resulted in rates of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke that were similar to those with placebo. These data can be used to help guide clinicians in choosing among the many available antidiabetic agents when treating patients with type 2 diabetes and very high cardiovascular risk.

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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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