Cardiovascular Mortality in Patients With Type 2 Diabetes and Recent Acute Coronary Syndromes From the EXAMINE Trial

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OBJECTIVE

We evaluated the risk of cardiovascular (CV) death in all Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study participants and in those who experienced an on-study, major nonfatal CV event.

RESEARCH DESIGN AND METHODS

The study randomly assigned 5,380 patients with type 2 diabetes to alogliptin or placebo within 15 to 90 days of an acute coronary syndrome (ACS). Deaths and nonfatal CV events (myocardial infarction [MI], stroke, hospitalized heart failure [HHF], and hospitalization for unstable angina [UA]) were adjudicated. Patients were monitored until censoring or death, regardless of a prior postrandomized nonfatal CV event. Time-updated multivariable Cox models were used to estimate the risk of death in the absence of or after each nonfatal event.

RESULTS

Rates of CV death were 4.1% for alogliptin and 4.9% for placebo (hazard ratio [HR] 0.85; 95% CI 0.66, 1.10). A total of 736 patients (13.7%) experienced a first nonfatal CV event (5.9% MI, 1.1% stroke, 3.0% HHF, and 3.8% UA). Compared with patients not experiencing a nonfatal event, the adjusted HR (95% CI) for death was 3.12 after MI (2.13, 4.58; $P < 0.0001$) 4.96 after HHF (3.29, 7.47; $P < 0.0001$), 3.08 after stroke (1.29, 7.37; $P = 0.011$), and 1.66 after UA (0.81, 3.37; $P = 0.164$). Mortality rates after a nonfatal event were comparable for alogliptin and placebo.

CONCLUSIONS

In patients with type 2 diabetes and a recent ACS, the risk of CV death was higher after a postrandomization, nonfatal CV event, particularly heart failure, compared with those who did not experience a CV event. The risk of CV death was similar between alogliptin and placebo.

Type 2 diabetes is associated with excess cardiovascular (CV) morbidity and mortality due to myocardial infarction (MI) and stroke (1,2). Heart failure is also a significant CV morbidity in patients with type 2 diabetes that is associated with an increased risk of death (3). Epidemiologic studies have demonstrated higher mortality rates in patients with diabetes experiencing an MI, stroke, heart failure, and end-stage kidney disease (4–6) as well as in patients with type 2 diabetes, chronic kidney disease, and/or vascular diseases (7). The relative effect of nonfatal CV events on survival in patients with type 2 diabetes and acute coronary syndromes (ACSs) is not well studied.

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The primary results of the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial showed that the dipeptidyl peptidase 4 (DPP-4) inhibitor alogliptin was comparable to placebo on risk of death and major nonfatal CV events (MI, stroke, and hospitalized heart failure [HHF]) in patients with type 2 diabetes at very high CV risk—those with recent ACS (8,9). Fatal outcomes in patients with type 2 diabetes and a first nonfatal MI, hospitalization for unstable angina (UA) or HHF, or stroke were compared with those of patients who did not have a major nonfatal CV event in the EXAMINE trial (9).

RESEARCH DESIGN AND METHODS

Study Design and Patients

The details, design, and primary results of EXAMINE have been published previously (8,9). Briefly, patients were eligible for enrollment if they had a diagnosis of type 2 diabetes, were receiving antihyperglycemic therapy (with the exception of a DPP-4 inhibitor or glucagon-like peptide 1 analog), and had a history of ACS within 15 to 90 days before randomization. Further criteria for type 2 diabetes included a glycated hemoglobin value between 6.5% (48 mmol/mol) and 11.0% (97 mmol/mol), inclusive, at screening, but if the antidiabetic regimen included insulin, the patient was required to have a glycated hemoglobin value between 7.0% (53 mmol/mol) and 11.0% (97 mmol/mol). ACSs were explicitly defined as diagnoses of acute MI or hospitalization with UA, with objective evidence of myocardial ischemia (8). Major exclusion criteria included a diagnosis of type 1 diabetes, unstable cardiac disorders, such as New York Heart Association Functional Classification IV heart failure, refractory angina, uncontrolled arrhythmias, critical valvular heart disease, severe uncontrolled hypertension, and dialysis within 14 days of screening.

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. Throughout the study, patients were required to receive standard of care for treatment of type 2 diabetes and CV risk factors according to regional guidelines. Outpatient visits were scheduled at screening and 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.

CV Adjudication

CV death was defined as death from cardiac and cerebrovascular causes and any death without another known cause. All deaths not meeting these diagnoses were considered non-CV in nature. Deaths and the nonfatal CV events (MI, UA, heart failure, and stroke) were adjudicated by an independent CV end points committee blind to treatment assignment, according to prespecified criteria. An MI was defined by ischemic symptoms or new ischemic electrocardiographic changes accompanied by elevated cardiac biomarkers (troponin and/or creatine kinase-MB). Hospitalization for UA was defined by ischemic symptoms with evidence of ischemic electrocardiographic changes not accompanied by elevated cardiac biomarkers. HHF was defined as presentation to a hospital or acute heart failure center requiring hospitalization due to an unexpected exacerbation of heart failure that required treatment with parenteral diuretics, inotropes, mechanical fluid removal, or intraaortic balloon pump insertion for maintenance of hemodynamic compromise. A stroke was defined as a focal neurologic deficit lasting 24 h or longer, preferably with imaging confirmation of infarction of the brain or an intracranial hemorrhage not secondary to trauma.

Statistical Analyses

Baseline characteristics of the EXAMINE study population are presented according to the first nonfatal CV event as frequencies and percentages for categorical variables and as means with standard deviation or medians with interquartile range for continuous variables. These characteristics were compared using the χ^2 test for categorical variables and the Wilcoxon rank sum test or *t* test for continuous variables according to the distribution. Cox proportional hazards models were used to analyze the time to the occurrence of CV deaths for all randomized patients. The consistency of effects on CV mortality was explored in a variety of subgroups without adjustment for multiple comparisons. CV mortality was assessed and tabulated after a major nonfatal CV event (acute MI, HHF, and stroke) in the entire cohort and by treatment assignment. The adjusted association between the incidence of the first nonfatal event and the instantaneous risk (hazard) of death was assessed with the use of a time-dependent Cox proportional hazards model. The incidence of first stroke, MI, HHF, and UA were examined as a categorical time-dependent variable; at baseline, all patients were classified as not having any nonfatal events. The hazard ratios (HRs) were further adjusted by the baseline covariates of age, treatment assignment, sex, estimated glomerular filtration rate (eGFR), duration of diabetes, BMI, race, medical history of hypertension, MI, coronary revascularization, heart failure, peripheral arterial disease, index type of ACS, and time to postindex ACS before randomization. Data were stratified by baseline renal function and geographic region. All statistical analyses were assessed at a two-sided significance level of 5%, and all CIs are reported as two-sided values with a confidence level of 95%. We performed all analyses for the intention-to-treat cohort. Analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC).

RESULTS

General Mortality Findings

This analysis by randomized treatment included 2,701 patients in the alogliptin group and 2,679 in the placebo group. A total of 326 deaths occurred in the EXAMINE trial. Death from any cause occurred in 153 patients on alogliptin (5.7%) and 173 patients on placebo (6.5%) (HR 0.88; 95% CI 0.71, 1.09) (Fig. 1*A*). For CV causes of death, rates on alogliptin (112 [4.1%]) and placebo (130 [4.9%]) (HR 0.85; 95% CI 0.66, 1.10) were comparable (Fig. 1*B*). Sudden cardiac death, the most prevalent adjudicated cause of CV death, occurred in 59 patients on alogliptin (2.2%) versus 73 patients on placebo (2.7%) (HR 0.80; 95% CI 0.57, 1.12) (Fig. 1*C*).

When explored by subgroups, results for CV mortality showed heterogeneity for some of the baseline factors (Fig. 2). None of the interactions was associated with an increase in mortality on alogliptin versus placebo in any of the comparative subgroups. CV death rates were lower in women (HR 0.60; 95% CI 0.40, 0.91), patients with eGFR $\geq$60 mL/min/1.73 m^2

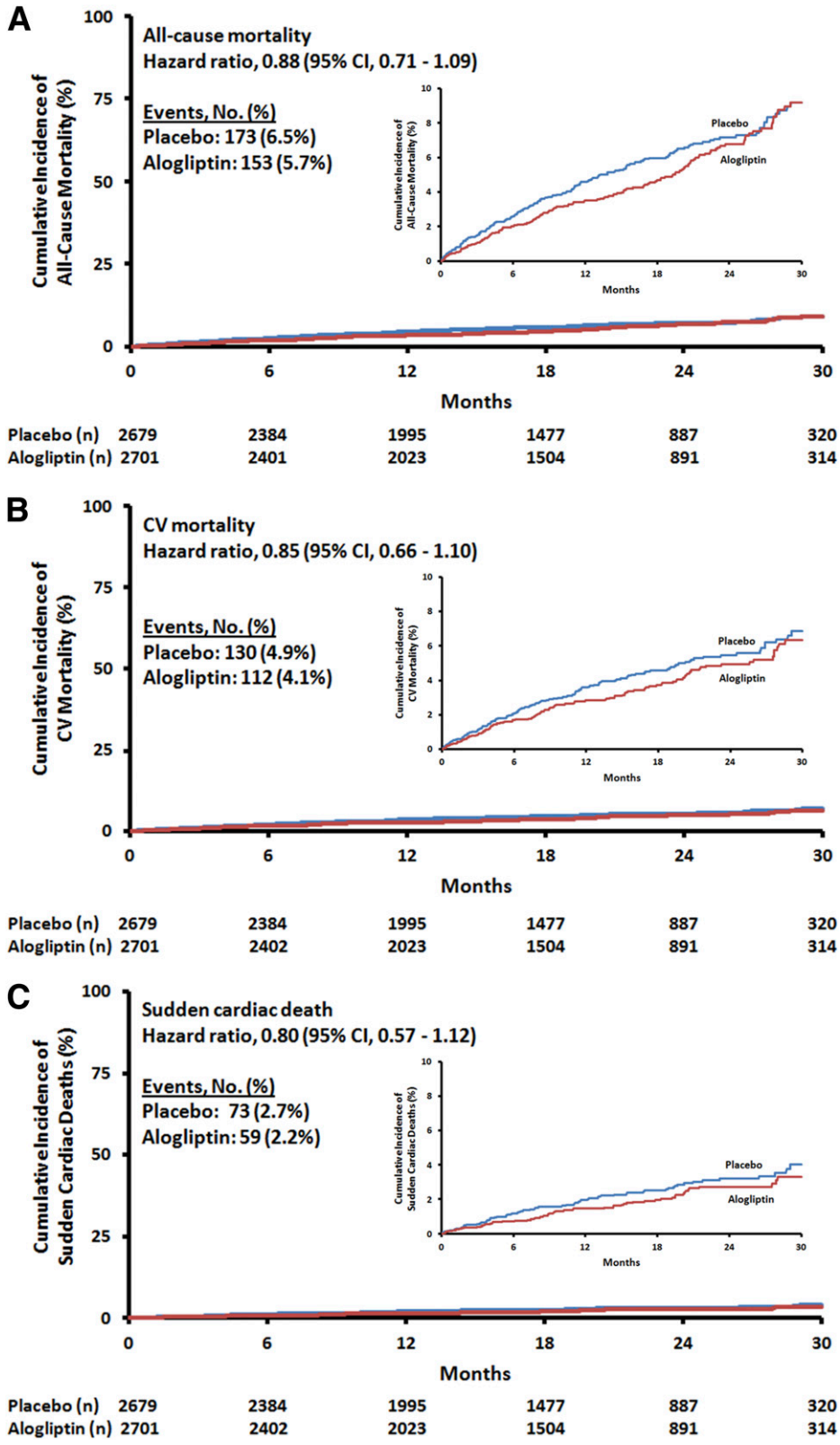

Figure 1—Time to all-cause mortality (*A*), CV mortality (*B*), and sudden death (*C*) on alogliptin and placebo in the EXAMINE trial. Insets show magnified versions of the larger figure for each panel.

(HR 0.67; 95% CI 0.46, 0.98), and those with a history of type 2 diabetes for less than 5 years (HR 0.61; 95% CI 0.37, 1.00) on alogliptin versus placebo. Death rates for alogliptin and placebo did not differ according to age, race, BMI, type of ACS, or baseline glycated hemoglobin level (Fig. 2).

CV Mortality Findings After Nonfatal Major CV Events

The first nonfatal CV event was MI in 316 patients (5.9%), HHF in 159 (3.0%),

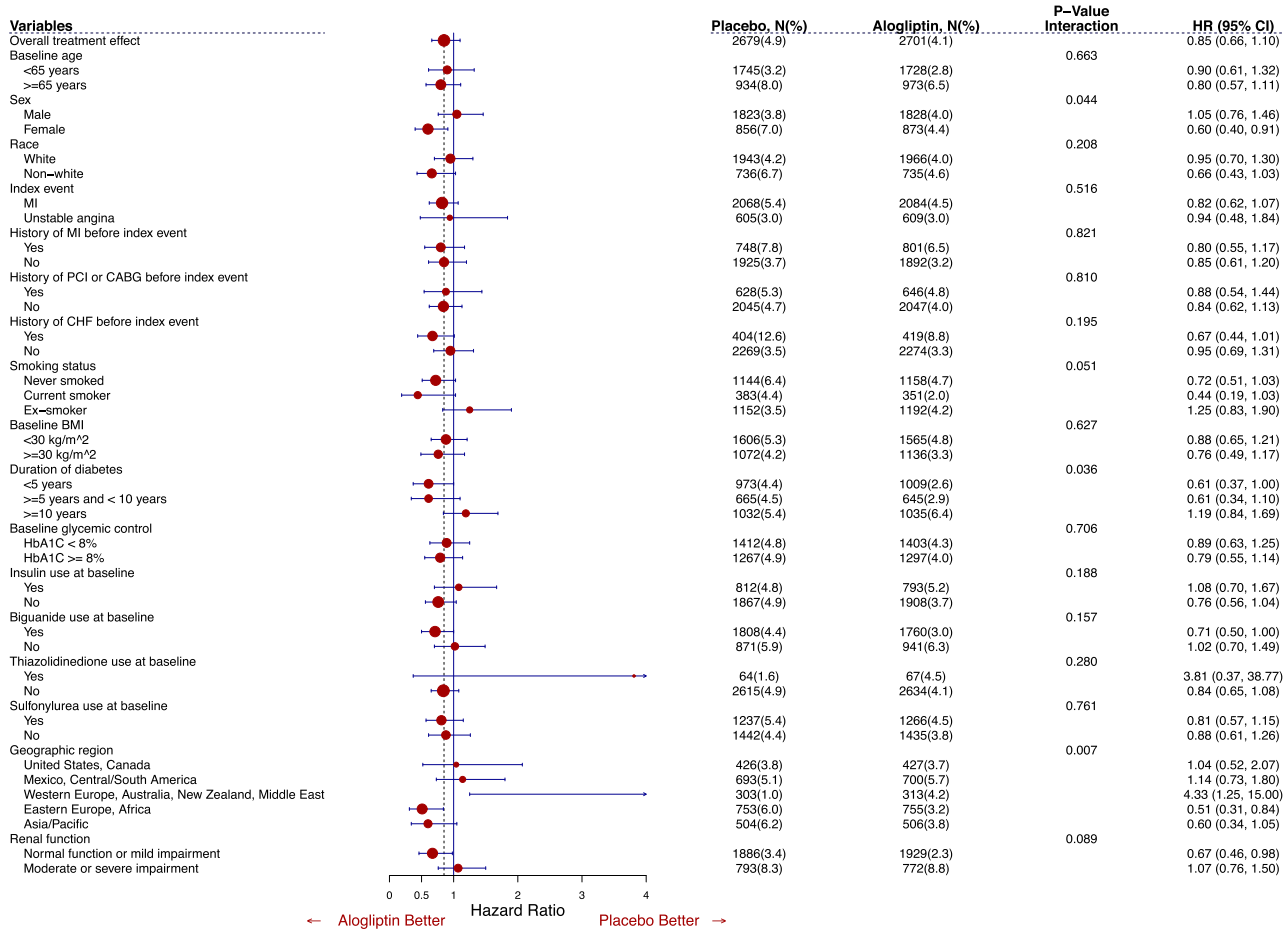

Figure 2—CV mortality according to prespecified subgroups in the EXAMINE trial. CABG, coronary artery bypass graft; CHF, congestive heart failure; PCI, percutaneous coronary intervention.

nonfatal stroke in 57 (1.1%), and hospitalization for UA in 204 (3.8%) during a median follow-up of 18.8 months. There were 4,644 patients (86.3%) who did not experience any of the major nonfatal CV events, and of these, 233 (5.0%) died, with 172 of these (74%) of CV causes.

The baseline characteristics of patients according to those without a nonfatal CV event and those with a first type of major nonfatal CV events are reported in Table 1. Several characteristics were different for patients with no nonfatal event versus those with nonfatal CV events, including age, duration of diabetes, BMI, likelihood of having coronary revascularization, rates of peripheral artery disease, and eGFR. Patients with an HHF event were older, had a longer duration of diabetes, were more likely to have had coronary revascularization, had reduced eGFR, and were more likely to have a history of congestive heart failure compared with the other groups.

Mortality rates after a first CV event were higher in patients who had experienced an HHF first, followed by stroke and MI, compared with those who did not experience any major CV event (Table 2). By the end of follow-up, the rate of death was highest in those who had an admission for heart failure, followed by those with a stroke and MI, versus those who had none of these events during follow-up. The rates of CV death for those with hospitalization for UA were comparable to those patients who did not have a nonfatal event after randomization (Fig. 3). Compared with patients who did not experience a nonfatal event, the adjusted HR for CV death was 3.12 (95% CI 2.13, 4.58; $P < 0.0001$) after MI, 4.96 (95% CI 3.29, 7.47; $P < 0.0001$) after HHF, 3.08 (95% CI 1.29, 7.37; $P = 0.011$) after stroke, and 1.66 (95% CI 0.81, 3.37; $P = 0.164$) after admission for UA. Mortality rates in patients who did not have a postrandomization nonfatal CV event were comparable on alogliptin and placebo (4.5% and 5.8%; adjusted HR 0.81; 95% CI 0.63, 1.05). Subsequent mortality rates after HHF were 22.7% in patients randomized to alogliptin and 34.1% in patients randomized to placebo (adjusted HR 1.02; 95% CI 0.51, 2.02).

CONCLUSIONS

The EXAMINE trial showed that the DPP-4 inhibitor alogliptin resulted in rates of mortality that were similar to rates with placebo among patients with type 2 diabetes and a high burden of CV disease and risk. There were similar rates of sudden cardiac death on alogliptin versus placebo, the most commonly adjudicated cause of death in the trial. Most of the CV deaths in EXAMINE occurred in patients who did not have a postrandomization, nonfatal CV event first. However, for those patients with a HHF, the subsequent mortality due to CV causes was more than fourfold higher than for patients who did not have a nonfatal CV event. For those patients with an initial

Table 1—Baseline characteristics according to first event type

Characteristics	No CV event (*N* = 4,644)	Nonfatal MI (*N* = 316)	HHF (*N* = 159)	Nonfatal stroke (*N* = 57)	UA (*N* = 204)
Age (years)	61.0 (54.0, 68.0)	63.00 (56.0, 70.0)†	64.0 (57.0, 71.0)†	63.0 (56.0, 65.0)	59.0 (52.0, 66.0)
Male sex	68.3 (3,172/4,644)	63.3 (200/316)	61.0 (97/159)	80.7 (46/57)*	66.7 (136/204)
Diabetes duration (years)	6.8 (2.5, 13.1)	10.2 (5.2, 15.9)†	9.9 (3.8, 19.5)†	8.9 (3.7, 12.6)	9.3 (3.3, 16.3)†
Baseline glycated hemoglobin (%)	7.9 (7.2, 8.7)	7.9 (7.2, 8.6)	7.9 (7.3, 8.7)	8.1 (7.2, 8.6)	8.0 (7.3, 8.8)
BMI (kg/m^2)	28.7 (25.5, 32.5)	29.5 (26.5, 33.4)**	29.0 (24.6, 34.2)	29.1 (25.3, 32.1)	29.7 (26.3, 33.1)*
Race					
White	72.4 (3,361/4,644)	77.9 (246/316)*	62.3 (99/159)**	71.9 (41/57)	79.4 (162/204)
Black	3.6 (169/4,644)	5.1 (16/316)*	8.2 (13/159)**	7.0 (4/57)	6.9 (14/204)
Asian	20.8 (964/4,644)	14.2 (45/316)*	27.0 (43/159)**	19.3 (11/57)	12.8 (26/204)
Native American	2.1 (98/4,644)	2.5 (8/316)*	1.3 (2/159)**	1.8 (1/57)	0.5 (1/204)
CV risk factors and history					
Current smoker	13.8 (642/4,644)	12.7 (40/316)	8.8 (14/159)	14.0 (8/57)*	14.7 (30/204)
Hypertension	81.9 (3,801/4,644)	92.1 (291/316)†	87.4 (139/159)	89.5 (51/57)	91.7 (187/204)†
MI	87.8 (4,078/4,644)	91.8 (290/316)*	95.6 (152/159)**	86.0 (49/57)	80.9 (165/204)**
Percutaneous coronary intervention	61.8 (2,868/4,644)	66.8 (211/316)	59.1 (94/159)	61.4 (35/57)	80.4 (164/204)†
Coronary artery bypass graft	11.3 (525/4,644)	19.9 (63/316)†	25.2 (40/159)†	19.3 (11/57)	24.0 (49/204)†
Congestive heart failure	26.4 (1,227/4,644)	32.3 (102/316)*	64.1 (102/159)†	26.3 (15/57)	27.0 (55/204)
Stroke	2.5 (117/4,644)	3.5 (11/316)	2.5 (4/159)	10.5 (6/57)†	3.4 (7/204)
Peripheral arterial disease	8.3 (387/4,644)	18.7 (59/316)†	22.6 (36/159)†	12.3 (7/57)	12.3 (25/204)
eGFR (mL/min/1.73 m^2)	72.2 (57.5, 86.0)	62.9 (48.8, 77.3)†	55.6 (38.1, 70.3)†	70.0 (57.1, 77.8)	74.1 (61.1, 86.7)

Continuous variables are shown as the median (quartile 1, quartile 2) and categorical variables as % (*n*/*N*). *$P < 0.05$. **$P < 0.01$. †$P < 0.001$ for comparisons of groups with nonfatal events vs. those with no CV event.

MI or stroke, subsequent rates of CV mortality also were much higher than for patients without a CV event.

The rates of all-cause mortality, CV mortality, and non-CV mortality, whether after a nonfatal CV event or not, were comparable in patients randomized to alogliptin and placebo. The number of deaths in patients randomized to alogliptin was nominally lower than those randomized to placebo, but in none of these analyses were the findings statistically significant. Because EXAMINE had a median duration of ~18 months, these mortality findings do not rule out longer-term benefits (or risks) of alogliptin in patients with type 2 diabetes and high degrees of CV risk. Other major trials of the DPP-4 inhibitors in patients with type 2 diabetes and CV disease or elevated risk that are of longer duration support the findings of our analysis in EXAMINE. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR TIMI 53) trial (10), with ~2 years of median follow-up, death from any cause occurred in 4.9% of patients randomized to saxagliptin versus 4.2% on placebo (HR 1.11, $P = 0.15$), and this finding was driven primarily by rates of death from CV causes (3.2% on saxagliptin vs. 3.4% on placebo). Similarly, in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) (11), with ~3 years of median duration, rates of all-cause mortality occurred in 7.5% of patients randomized to sitagliptin versus 7.3% randomized to placebo (HR 1.01, $P = 0.875$) with CV death rates of 5.2% on sitagliptin versus 5.0% on placebo.

The noninferiority of alogliptin to placebo with respect to CV death was heterogeneous in three subgroups ($P < 0.05$ for the interaction). This included sex, the duration of diabetes, and geographic region of study conduct. Given the number of subgroup tests performed, these findings may have been due to chance. The number of events contributing to these differences was fairly small, and the CIs were wide, particularly for geographic region. Nevertheless, these results do raise questions about whether differences according to these subgroups influenced the effects of the randomly assigned drug on CV mortality.

Table 2—Mortality rates after first nonfatal event type

Characteristics	No CV event (*N* = 4,644)	Nonfatal MI (*N* = 316)	HHF (*N* = 159)	Nonfatal stroke (*N* = 57)	UA (*N* = 204)
All-cause mortality	5.0 (233/4,644)	11.1 (35/316)	27.0 (43/159)	10.5 (6/57)	4.4 (9/204)
Rate per 100 PYs (95% CI)	3.2 (2.8, 3.7)	6.5 (4.5, 9.0)	16.3 (11.8, 22.0)	5.8 (2.1, 12.6)	2.4 (1.1, 4.6)
CV death	3.7 (172/4,644)	8.2 (26/316)	20.1 (32/159)	8.8 (5/57)	3.4 (7/204)
Rate per 100 PYs (95% CI)	2.4 (2.1, 2.8)	4.8 (3.1, 7.0)	12.1 (8.3, 17.1)	4.8 (1.6, 11.2)	1.9 (0.8, 3.9)
Sudden cardiac death	2.0 (94/4,644)	4.4 (14/316)	12.0 (19/159)	3.5 (2/57)	1.5 (3/204)
Rate per 100 PYs (95% CI)	1.3 (1.1, 1.6)	2.6 (1.4, 4.3)	7.2 (4.3, 11.2)	1.9 (0.2, 7.0)	0.8 (0.2, 2.3)
Non-CV death	1.3 (61/4,644)	2.9 (9/316)	6.9 (11/159)	1.8 (1/57)	1.0 (2/204)
Rate per 100 PYs (95% CI)	0.9 (0.7, 1.1)	1.7 (0.8, 3.2)	4.2 (2.1, 7.5)	1.0 (0.0, 5.4)	0.5 (0.1, 1.9)

Categorical data are shown as % (*n*/*N*). PYs, patient-years.

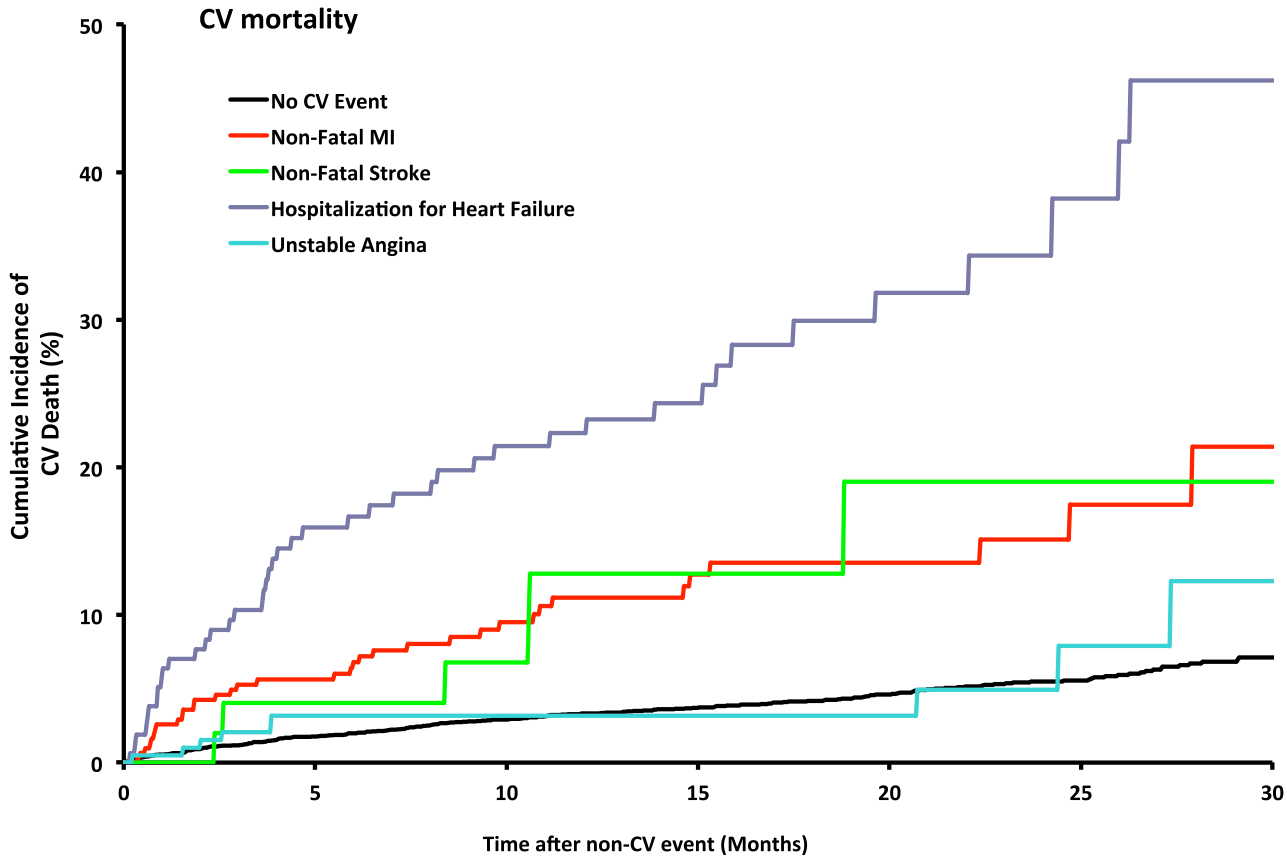

Figure 3—Kaplan-Meier curves representing the increase in instantaneous risk (hazard) of CV death with the incidence of corresponding nonfatal CV events vs. no incidence of a nonfatal CV event. Time of follow-up starts at randomization for the "no CV event" group (172 CV deaths) and at the time of the corresponding first nonfatal CV event for nonfatal MI (26 CV deaths), stroke (5 CV deaths), HHF (32 CV deaths), and hospitalization for UA (7 CV deaths).

The severity of CV disease in EXAMINE was high, most deaths occurred in those patients who did not experience a nonfatal CV event first, and most were due to CV causes, as has been the case with other studies (7,11–13). The rates of all-cause and death from CV causes in EXAMINE were higher than those observed in SAVOR TIMI 53 (10) and TECOS (11) and similar to those in the Evaluation of LIXisenatide in Acute coronary syndrome (ELIXA) trial (14). This is likely explained by the requirement of a recent ACS for inclusion into EXAMINE and ELIXA, whereas the acuity of CV disease was less in the other trials of incretin-based therapies (9–11,14). MI accounted for the highest proportion of the nonfatal CV events in EXAMINE, consistent with a cohort of patients with recent ACS and type 2 diabetes. The numbers of patients with heart failure and UA hospitalizations were similar, but stroke was relatively infrequent in this trial. There were also few deaths occurring after an initial stroke in the trial. However, because CV diseases will develop in approximately half of all patients with type 2 diabetes during their lifetime (15), our findings do apply to a broader population with type 2 diabetes.

Although the development of heart failure in EXAMINE was lower than that of MI, the subsequent rate of death was much greater in those with HHF than other types of CV events. As previously noted by us (16) and others in recent studies of heart failure outcomes in patients with type 2 diabetes (3,7,17), the finding of a substantially higher mortality rate for patients progressing to HHF demonstrate that heart failure should be a standard CV outcome, along with MI and stroke, in studies of patients with type 2 diabetes. This observation has not yet led into a concerted effort for reducing the incidence of heart failure in patients with type 2 diabetes; however, there is evidence from the recently completed Empaglifozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) (18) in patients with type 2 diabetes and the Systolic Blood Pressure Intervention Trial (SPRINT) (19) in patients without type 2 diabetes that reductions in the primary end points were driven by reductions in HHF and death from CV causes. In both trials, the prominent use of drugs that reduce plasma volume appears to be the most likely reason for success in the studies at reducing heart failure– related mortality.

Our study is limited by the lack of formal assessment of type of MI (ST segment elevation vs. non-ST segment elevation) and type of heart failure (reduced systolic function vs. preserved systolic function) at baseline. However, all CV events were formally adjudicated by an independent end points committee blinded to treatment assignment. In addition, our analysis is unique considering that patients randomized with type 2 diabetes had an ACS just before randomization, making the population at high risk for future events in the trial.

In conclusion, mortality, including CV mortality, in the EXAMINE trial was comparable for alogliptin versus placebo over 18 months of follow-up. The occurrence of an additional nonfatal CV event (i.e., postrandomization, after the index ACS) during the trial was common and increased the risk of death, particularly after an admission to the hospital for heart failure. Hence, the potential to reduce mortality through aggressive use of evidence-based secondary preventive therapies remains substantial and should be considered a standard in the clinical management of high CV risk patients with type 2 diabetes.

Duality of Interest. W.B.W., F.Z., C.R.M., G.L.B., W.C.C., S.R.H., and R.M.B. have received personal fees from Takeda Development Center. S.K., C.A.W., and P.R.F. are full-time employees of Takeda Development Center. L.L. is an employee of Harvard Clinical Research Group. C.P.C. is an employee of the Harvard Clinical Research Institute. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. W.B.W. is chair of the EXAMINE steering committee. F.Z., C.R.M., G.L.B., S.E.N., W.C.C., S.R.H., and R.M.B. are members of the EXAMINE steering committee. W.B.W. wrote the initial and subsequent drafts of the manuscript after reviews and edits from coauthors. S.K., F.Z., C.R.M., C.A.W., L.L., G.L.B., S.E.N., W.C.C., S.R.H., R.M.B., P.R.F., and C.P.C. reviewed and edited the manuscript. All authors take full responsibility for the work as a whole, including the study design and the decision to submit and publish the manuscript. W.B.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990-2010. N Engl J Med 2014;370:1514–1523
2. Vaur L, Gueret P, Lievre M, Chabaud S, Passa P; DIABHYCAR Study Group (type 2 DIABetes, Hypertension, CARdiovascular Events and Ramipril) study. Development of congestive heart failure in type 2 diabetic patients with microalbuminuria or proteinuria: observations from the DIABHYCAR (type 2 DIABetes, Hypertension, CArdiovascular Events and Ramipril) study. Diabetes Care 2003;26:855–860
3. McMurray JJV, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. Lancet Diabetes Endocrinol 2014;2:843–851
4. Sprafka JM, Burke GL, Folsom AR, McGovern PG, Hahn LP. Trends in prevalence of diabetes mellitus in patients with myocardial infarction and effect of diabetes on survival. The Minnesota Heart Survey. Diabetes Care 1991;14:537–543
5. Icks A, Claessen H, Morbach S, Glaeske G, Hoffmann F. Time-dependent impact of diabetes on mortality in patients with stroke: survival up to 5 years in a health insurance population cohort in Germany. Diabetes Care 2012;35:1868–1875
6. Hoffmann F, Haastert B, Koch M, Giani G, Glaeske G, Icks A. The effect of diabetes on incidence and mortality in end-stage renal disease in Germany. Nephrol Dial Transplant 2011;26:1634–1640
7. Jhund PS, McMurray JJV, Chaturvedi N, et al. Mortality following a cardiovascular or renal event in patients with type 2 diabetes in the ALTITUDE trial. Eur Heart J 2015;36:2463–2469
8. White WB, Pratley R, Fleck P, et al. Cardiovascular safety of the dipetidyl peptidase-4 inhibitor alogliptin in type 2 diabetes mellitus. Diabetes Obes Metab 2013;15:668–673
9. White WB, Cannon CP, Heller SR, et al.; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327–1335
10. Scirica BM, Bhatt DL, Braunwald E, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317–1326
11. Green JB, Bethel MA, Armstrong PW, et al.; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232–242
12. Dormandy JA, Charbonnel B, Eckland DJ, et al.; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279–1289
13. Frye RL, August P, Brooks MM, et al.; BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 2009;360:2503–2515
14. Pfeffer MA, Claggett B, Diaz R, et al.; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247–2257
15. Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation 2006;113:791–798
16. Zannad F, Cannon CP, Cushman WC, et al.; EXAMINE Investigators. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. Lancet 2015;385:2067–2076
17. Scirica BM, Braunwald E, Raz I, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation 2014;130:1579–1588
18. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
19. Wright JT Jr, Williamson JD, Whelton PK, et al.; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103–2116