Ischemic cardiac outcomes and hospitalizations according to prior macrovascular disease status in patients with type 2 diabetes and recent acute coronary syndrome from the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care trial

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Background Concerns raised regarding adverse cardiovascular (CV) outcomes with new therapies for type 2 diabetes mellitus (T2DM) have led to several large-scale CV outcome trials. The EXAMINE trial confirmed noninferiority of the dipeptidyl dipeptidase 4 inhibitor alogliptin to placebo on major adverse cardiac event rates in a post–acute coronary syndrome (ACS) T2DM population. We present data on additional ischemic cardiac events and CV hospitalizations in EXAMINE.

Methods Patients with T2DM and an ACS event in the previous 15 to 90 days were randomly assigned to alogliptin or placebo on a background of standard treatment for diabetes. The incident rates of a 5-component composite end point of CV death, stroke, myocardial infarction, unstable angina, and coronary revascularization as well as CV hospitalization were calculated in all participants and according to macrovascular disease at baseline.

Results There were no significant differences between alogliptin (n = 2,701) and placebo (n = 2,679) in the event rate of the 5-component composite endpoint with median follow-up 533 days (21.0% vs 21.5%, hazard ratio [HR] 0.98 [0.87-1.10], *P* = .72). No differences were observed in terms of CV hospitalization (25.0% vs 25.4%, HR 0.98 [0.88-1.09], *P* = .70) or coronary revascularization (10.6% vs 10.2%, HR 1.05 [0.88-1.09], *P* = .60). No interactions were observed for treatment and prior macrovascular disease.

Conclusions EXAMINE demonstrates that there was no increase in the risk of cardiac ischemic events and CV hospitalizations with alogliptin in a high-risk post-ACS patient population. Because these are major driver of overall health care costs, these data suggest that there would be no adverse impact on health care resource utilization. (Am Heart J 2016;175:18-27.)

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Background

Patients with type 2 diabetes mellitus (T2DM) are at an increased risk for hospitalization for cardiovascular (CV) reasons including acute coronary syndrome (ACS), stroke, coronary revascularization, and heart failure exacerbation.[1-3] The total (direct and indirect) cost of diabetes in 2012 was estimated to be $245 billion in the United States, and CV hospitalizations have a major impact on overall health care costs for patients with diabetes mellitus (DM).[4] However, the effects of new antihyperglycemic agents for T2DM on CV ischemic events and CV hospitalizations are not well known. In fact, several studies have shown possible increase in adverse CV events with new glucose-lowering agents.[5-11] These concerns led the US Food and Drug Administration (FDA) and other authorities to mandate that all new medications for diabetes be tested for CV safety before and after approval.[12,13]

Alogliptin is a selective dipeptidyl peptidase 4 (DPP-4) inhibitor approved for the treatment of T2DM. Alogliptin exerts its antihyperglycemic effect by increasing insulin secretion and decreasing glucagon secretion from the pancreas through reducing degradation of glucagon-like peptide 1 via DPP-4 inhibition.[14] In the EXAMINE trial, alogliptin was noninferior to placebo for a composite of CV death, nonfatal myocardial infarction (MI), and nonfatal stroke in high-risk patients with T2DM and recent ACS.[15] Rates of all-cause mortality and CV death were also similar between the 2 groups.[15] Whether alogliptin affects the rate of CV hospitalization or cardiac ischemic outcomes such as unstable angina and coronary revascularization has not been previously reported. In addition, possible effect modification of a DPP-4 inhibitor, saxagliptin, has been reported suggesting that DPP-4 inhibitors may have differential effects in higher risk patient populations.[16,17] Currently, no data are available as to whether the safety of alogliptin is different between the highest risk patients with established macrovascular disease (coronary artery disease [CAD], cerebrovascular disease [CVD], or peripheral arterial disease [PAD]) and those without. In this report, we present data on CV hospitalizations and all cardiac ischemic events and investigate any interaction between the randomized treatment and prior macrovascular disease status in the EXAMINE trial.

Methods

Study design

The design and primary results of the EXAMINE trial (www.clinicaltrials.gov; NCT00968708) have been previously published.[15,18] The EXAMINE study was a multicenter, double-blind trial that randomized 5,380 post-ACS patients with T2DM to alogliptin versus placebo. Patients were enrolled from 898 centers in 49 countries from October 2009 to March 2013. An independent steering committee and data and safety monitoring committee provided oversight for the EXAMINE trial. An independent CV end points committee blinded to treatment allocation prospectively adjudicated all deaths and serious CV events, including coronary revascularization and CV hospitalizations. A contract research organization (Pharmaceutical Product Development Inc, Wilmington, DE) independently performed statistical analyses and served as a liaison with the data safety monitoring committee. The study design was approved by the national and international regulatory authorities, and informed consent was provided by all participants.

Study participants

We enrolled patients who had T2DM, were receiving antidiabetic therapy (excluding DPP-4 inhibitors or glucagon-like peptide 1 analogs), and had had an ACS event within 15 to 90 days before randomization. Additional inclusion criteria included a glycated hemoglobin level between 6.5% and 11.0% at screening or 7.0% and 11.0% if the antidiabetic regimen included insulin. The qualifying ACS in EXAMINE included acute MI and unstable angina requiring hospitalization.[18] Patients with type 1 DM, unstable cardiac disorders (eg, 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 were excluded. The macrovascular disease in the present study was defined as the presence of established CAD, CVD, or PAD. Specifically, CAD included history of prior MI, unstable angina, stable chronic angina, and coronary revascularization. *Coronary revascularization* was defined as undergoing either percutaneous coronary intervention (PCI) with or without coronary stent placement or coronary artery bypass graft surgery (CABG). History of CAD, CVD, and PAD before the index ACS event was recorded by the physician investigator.

Study procedures and background therapy

Patients were randomly assigned to receive alogliptin or placebo, administered in a double-blind fashion, in addition to standard-of-care treatment for T2DM and CV risk factors according to regional guidelines. Given the renal clearance of alogliptin, the doses of alogliptin (and matching placebo) were adjusted according to renal function at the time of randomization and during the postrandomization period based on estimated glomerular filtration rate (eGFR).[18]

End points

The primary major adverse cardiac event (MACE) end point of the EXAMINE trial was a composite of CV death,

nonfatal MI, and nonfatal stroke. *Cardiovascular death* was defined as death from cardiac and cerebrovascular causes without another known cause.[15,18] The secondary MACE end point was the primary end point plus urgent revascularization due to unstable angina (defined as within 24 hours after hospital admission). In the present study, we investigated an exploratory extended MACE composite end point that combined the first occurrence of CV death, nonfatal MI, nonfatal stroke, unstable angina, and coronary revascularization. We also gathered data regarding hospitalizations for any reason and CV disorders such as MI, stroke, unstable angina, coronary revascularization, and heart failure.[19]

Statistical analysis

Baseline characteristics are presented as frequencies and percentages for categorical variables and as means with SD or medians with interquartile range for continuous variables. These characteristics were compared using χ^2 test for categorical variables and the Wilcoxon rank sum test or *t* test for continuous variables according to the distribution. We compared the outcomes for alogliptin versus placebo stratified by prior history of macrovascular disease, which was defined by having diagnosis of CAD, CVD, or PAD before the index ACS event. Data were summarized as the common event rates. Cox proportional hazard survival models were used to obtain unadjusted hazard ratios (HRs) for alogliptin versus placebo presented with 95% CIs. All statistical analyses were assessed at a 2-sided significance level of 0.05, and all CIs were reported as 2-sided values with a confidence level of 95%. The unadjusted interaction between macrovascular disease and the randomized treatment was tested at $\alpha = .05$ significance level. We performed all analyses for the intention-to-treat cohort. Analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

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Results

A total of 2,701 patients in alogliptin group and 2,679 in placebo group were included in this analysis by randomized treatment. A balanced distribution was observed between the 2 groups in terms of baseline characteristics and medications (Table I). There were 2,788 patients enrolled with a history of manifest clinical macrovascular disease before index hospitalization and 2,592 patients without a history of macrovascular disease. Patients with a prior history of macrovascular disease were significantly older, were more likely to be female and white, had a longer duration of diabetes, and had a higher body weight and body mass index. In addition, the macrovascular disease subgroup was more likely to have prior heart failure, hypertension, and impaired renal function ($P < .05$ for each comparison). Approximately 57% of patients with history of macrovascular disease had an MI as the index ACS event as opposed to unstable angina, whereas 99% of the index ACS event was an MI in patients without history of macrovascular disease (Table I).

Table II shows the rates of the composite primary and secondary end points and each component stratified by prior history of macrovascular disease. The event rates were generally higher in patients with a prior history of macrovascular disease compared to those without a history of macrovascular disease. There were no significant differences in any of the end points between alogliptin and placebo in either subgroup ($P > .10$), and no significant interactions were observed between the randomized treatment and prior macrovascular disease status for any end point (P for interaction > .10 for each comparison).

In terms of cardiac ischemic endpoints, the event rates of coronary revascularization either with PCI or CABG did not differ between alogliptin and placebo groups (10.6% vs 10.2%, HR 1.05, 95% CI 0.89-1.23, $P = .60$) (Table III, Figure 1). The findings in each component of coronary revascularization including overall PCI, PCI with stent, PCI without stent, and CABG ($P > .05$ for each comparison) were consistent with the overall coronary revascularization results. Similarly, the event rates of hospitalization for unstable angina were similar between the randomized treatment groups (4.0% vs 4.4%, HR 0.91, 95% CI 0.70-1.19, $P = .49$). The rates of a composite endpoint of CV death, MI, stroke, unstable angina, and revascularization were high but comparable between the alogliptin and placebo groups (21.0% vs 21.5%, HR 0.98, 95% CI 0.87-1.10, $P = .72$) (Figure 2). Similar results were observed for other combinations of the 5 end points (Table III). With regard to noninferiority, the upper limits of 95% CI for most of the end points were below the noninferiority margin of 1.3 for the HR, which was prespecified for the primary end point in the main trial (Table III).

A total of 676 patients (25.0%) in alogliptin group and 680 (25.4%) in placebo had at least 1 hospitalization for CV diagnoses (HR 0.98, 95% CI 0.88-1.09, $P = .70$) (Figure 3). The median length of in-hospital stay among these patients who had at least 1 CV hospitalization was 8 days for both randomized treatment groups (interquartile range 4-17 days in alogliptin group and 4-18 days for placebo, $P = .78$). In addition, the event rates of any hospitalization (33.9% vs 35.5%, HR 0.94, 95% CI 0.86-1.03, $P = .22$) and the median length of stay among hospitalized patients (9 days [4-22] vs 9 days [4-21], $P = .68$) were not different between the 2 treatment groups (Table III).

In patients with a history of macrovascular disease before the index ACS event, event rates for CV events

Table I. Baseline characteristics of patients stratified by prior history of macrovascular disease status

Characteristics	History of macrovascular disease before index hospitalization		No history of macrovascular disease before index hospitalization		
	Alogliptin (n = 1394)	Placebo (n = 1394)	Alogliptin (n = 1307)	Placebo (n = 1285)	*P* value MVD vs non-MVD
Age	62 ± 10 (1394)	62 ± 10 (1394)	59 ± 10 (1307)	59 ± 10 (1285)	<.001
Age ≥65 y	41.2% (575/1394)	39.7% (554/1394)	30.5% (398/1307)	29.6% (380/1285)	<.001
Male	65.5% (913/1394)	65.9% (919/1394)	70.0% (915/1307)	70.4% (904/1285)	<.001
Duration of diabetes (y)	8.8 (3.9-15.3)	8.7 (3.9-15.2)	5.6 (1.3-11.2)	5.8 (2.0-11.5)	<.001
Baseline HbA1c concentration	8.0 ± 1.1 (1394)	8.1 ± 1.1 (1394)	8.0 ± 1.1 (1306)	8.0 ± 1.1 (1285)	.82
Body weight (kg)	84.3 ± 19.3 (1394)	84.8 ± 18.9 (1394)	80.1 ± 19.0 (1307)	79.3 ± 18.7 (1285)	<.001
BMI (kg/m^2)	30.1 ± 5.5 (1394)	30.3 ± 5.6 (1393)	28.7 ± 5.2 (1307)	28.7 ± 5.8 (1285)	<.001
Race					<.001
American Indian or Alaska Native	1.5% (21/1394)	1.3% (18/1394)	2.7% (35/1307)	2.8% (36/1285)	
Asian	15.8% (220/1394)	14.3% (199/1394)	25.0% (327/1307)	26.7% (343/1285)	
Black or African American	3.7% (52/1394)	4.9% (68/1394)	3.7% (49/1307)	3.7% (47/1285)	
Native Hawaiian or other Pacific Islander	0.3% (4/1394)	0.1% (1/1394)	0.2% (2/1307)	0.3% (4/1285)	
White	78.0% (1088/1394)	79.1% (1103/1394)	67.2% (878/1307)	65.4% (840/1285)	
Multiracial	0.6% (9/1394)	0.4% (5/1394)	1.2% (16/1307)	1.2% (15/1285)	
Cardiovascular risk factors and history					
Current smoker	11.7% (163/1394)	13.3% (185/1394)	14.4% (188/1307)	15.4% (198/1285)	.03
Hypertension	85.2% (1188/1394)	86.0% (1199/1394)	59.4% (776/1307)	61.6% (792/1285)	<.001
MI	52.9% (738/1394)	49.1% (685/1394)	0	0	–
PCI	37.8% (527/1394)	36.8% (513/1394)	0	0	–
CABG	15.3% (213/1394)	15.1% (211/1394)	0	0	–
Congestive heart failure	21.5% (300/1394)	21.9% (305/1394)	3.2% (42/1307)	3.3% (43/1285)	<.001
Transient ischemic attack	4.8% (67/1394)	4.4% (62/1394)	0	0	–
PAD	14.3% (200/1394)	13.3% (186/1394)	0	0	–
Renal function eGFR (mL/min/1.73 m^2)	67.8 ± 21.3 (1394)	69.1 ± 21.7 (1394)	74.1 ± 20.8 (1307)	73.1 ± 21.2 (1285)	<.001
eGFR <60 mL/min/1.73 m^2	33.8% (471/1394)	32.9% (459/1394)	23.0% (301/1307)	26.0% (334/1285)	<.001
eGFR ≥60 mL/min/1.73 m^2	66.2% (923/1394)	67.1% (935/1394)	77.0% (1006/1307)	74.0% (951/1285)	
Index ACS event					<.001
MI	57.0% (791/1387)	57.5% (798/1389)	99.0% (1293/1306)	98.9% (1270/1284)	
Unstable angina	43.0% (596/1387)	42.5% (591/1389)	1.0% (13/1306)	1.1% (14/1284)	
Time from index ACS event to randomization (d)	47.4 ± 22.2 (1387)	48.8 ± 22.1 (1389)	47.8 ± 21.9 (1306)	47.2 ± 21.8 (1284)	.33
NYHA CHF class					<.001
I	22.0% (111/505)	16.9% (81/480)	25.1% (63/251)	28.8% (76/264)	
II	54.7% (276/505)	60.4% (290/480)	59.0% (148/251)	57.2% (151/264)	
III	22.0% (111/505)	21.7% (104/480)	14.7% (37/251)	12.1% (32/264)	
IV	1.4% (7/505)	1.0% (5/480)	1.2% (3/251)	1.9% (5/264)	
Baseline BNP concentration (pg/mL)	71.2 (29.1-174.5)	68.0 (26.5-158.6)	79.4 (32.1-185.0)	81.8 (33.0-177.5)	<.001
Baseline concomitant cardiovascular medications					
Renin-angiotensin system–blocking agents	81.7% (1139/1394)	83.5% (1164/1394)	81.3% (1062/1307)	81.4% (1046/1285)	.22
ACE inhibitor	59.3% (827/1394)	59.6% (831/1394)	65.3% (854/1307)	63.1% (811/1285)	<.001
ARB	24.7% (345/1394)	26.0% (363/1394)	17.5% (229/1307)	19.7% (253/1285)	<.001
β-Blockers	83.0% (1157/1394)	82.1% (1145/1394)	80.4% (1051/1307)	82.3% (1058/1285)	.25
Diuretics					
All	44.7% (623/1394)	44.0% (614/1394)	29.2% (382/1307)	30.7% (395/1285)	<.001
Thiazide	18.9% (263/1394)	19.8% (276/1394)	9.5% (124/1307)	10.8% (139/1285)	<.001
Loop diuretic	21.4% (298/1394)	19.9% (278/1394)	14.1% (184/1307)	14.0% (180/1285)	<.001
MRAs	13.1% (183/1394)	12.2% (170/1394)	12.9% (169/1307)	12.3% (158/1285)	.96

Data are shown as median (interquartile range), mean ± SD, or percentage (number).
Abbreviations: *MVD*, Macrovascular disease; *BMI*, body mass index; *NYHA*, New York Heart Association; *CHF*, congestive heart failure; *BNP*, brain natriuretic peptide; *ACE*, angiotensin-converting enzyme; *ARB*, angiotensin II receptor blocker; *MRA*, mineralocorticoid receptor antagonist.

Table II. Risk of composite primary and secondary end points and components, stratified by prior history of macrovascular disease

	Event rate								
	Macrovascular disease (+)				Macrovascular disease (–)				
End point	Alogliptin	Placebo	HR (95% CI)	*P*	Alogliptin	Placebo	HR (95% CI)	*P*	*P* value for interaction between treatment and subgroup
Primary MACE end point	14.7% (205/1394)	14.2% (198/1394)	1.04 (0.86-1.27)	.66	7.7% (100/1307)	9.2% (118/1285)	0.83 (0.63-1.08)	.17	.18
Secondary MACE end point	16.6% (232/1394)	16.2% (226/1394)	1.04 (0.86-1.25)	.70	8.6% (112/1307)	10.4% (133/1285)	0.83 (0.64-1.06)	.14	.15
CV death	5.1% (71/1394)	5.5% (77/1394)	0.90 (0.65-1.24)	.51	3.1% (41/1307)	4.1% (53/1285)	0.77 (0.51-1.17)	.22	.54
Nonfatal MI	9.5% (133/1394)	8.4% (117/1394)	1.16 (0.90-1.48)	.26	4.2% (55/1307)	4.6% (59/1285)	0.92 (0.63-1.33)	.64	.30
Nonfatal stroke	1.1% (16/1394)	1.9% (26/1394)	0.62 (0.33-1.16)	.13	1.1% (14/1307)	0.9% (11/1285)	1.23 (0.56-2.70)	.61	.17
Urgent revascularization due to unstable angina	2.5% (35/1394)	2.2% (30/1394)	1.20 (0.74-1.95)	.47	1.1% (14/1307)	1.4% (18/1285)	0.79 (0.39-1.59)	.50	.31

Primary MACE composite comprises CV death, nonfatal MI, and nonfatal stroke. Secondary MACE composite comprises CV death, nonfatal MI, nonfatal stroke, and urgent revascularization due to unstable angina. Event rate is counting the first occurrence of each type of the events.

were 1.5 to 2 times higher versus those without a prior history of macrovascular disease. There was no effect modification in the subgroup analysis of the composite end point of CV death, MI, stroke, unstable angina, or revascularization when stratified by prior history of macrovascular disease (Table IV) (*P* for interaction = .69). The results were comparable for the other combinations of the CV end points shown in Table IV. No effect modification by alogliptin versus placebo was observed in terms of unstable angina, coronary revascularization either with PCI or CABG, and hospitalization for CV reason or any reason (*P* for interaction > .05) (Table IV).

Discussion

The current analysis from the EXAMINE trial demonstrates several additional findings in patients with T2DM who are post-ACS. The overall event rates of any cardiac ischemic end points including coronary revascularization with either PCI or CABG were not different between alogliptin and placebo group. There were also no differences in the rate of all-cause and CV hospitalization as well as length of in-hospital stay among hospitalized patients between the randomized treatment groups. Much higher event rates of MACE, CV rehospitalization, and coronary revascularization were observed in patients with a history of macrovascular disease before the index ACS event than in those patients without known macrovascular disease. The effects of alogliptin compared to placebo on CV events were similar between patients with and without history of macrovascular disease before the ACS event. These new data demonstrate that alogliptin does not increase the risk of cardiac ischemic events or CV hospitalization in a high-risk post-ACS patient population and that the effects of alogliptin are not different in the "highest risk" subgroup of patients who had known macrovascular disease before the ACS event. In addition, although CV hospitalization has a major impact on the overall health care utilization in diabetic patient population, use of alogliptin should not put additional burden on the costs associated with diabetes care according to our findings.[20]

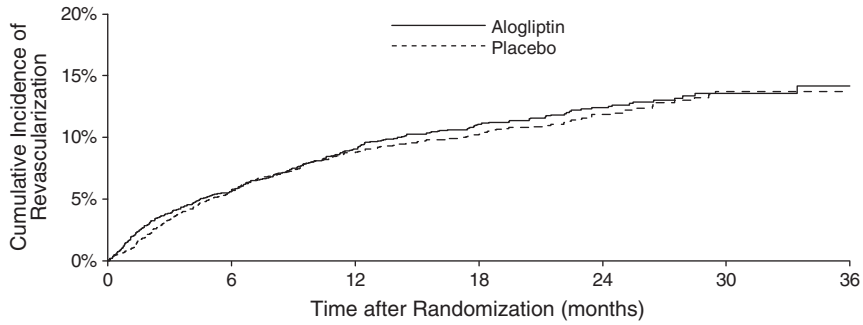
Type 2 diabetes mellitus increases the risk of developing CV disease by 2- to 4-fold.[21,22] Patients with DM also have an elevated risk of CV hospitalization, longer length of stay, and higher total charges per hospitalization than patients without T2DM.[23] Therefore, therapies to lower blood glucose levels might have been expected to reduce the risk of CV hospitalization and cardiac ischemic event. However, such reductions have not been consistently observed in prior studies that achieved improved glycemic control. In terms of the effects of DPP-4 inhibitors, 2 meta-analyses that collected results from glycemic control studies (which were not specifically designed to evaluate CV outcomes) showed favorable effects on CV outcomes,[24,25] which disappeared when data from EXAMINE and SAVOR-TIMI 53 were included.[26] On the other hand, past studies on other antidiabetic agents have shown conflicting results with regard to CV safety with some reporting increased risk of CV death.[6] Based on these reports, the FDA and corresponding regulatory authorities in other parts of the world have

Table III. Cardiac ischemic end points and cardiovascular hospitalizations according to treatment allocation

End point	Event rate			
	Alogliptin (n = 2701)	Placebo (n = 2679)	HR (95% CI)	*P*
CV death or nonfatal MI	10.4% (280/2701)	10.8% (290/2679)	0.96 (0.82-1.13)	.64
CV death, nonfatal MI, or unstable angina	13.4% (362/2701)	14.7% (393/2679)	0.91 (0.79-1.05)	.19
CV death, nonfatal MI, unstable angina, or revascularization	20.2% (546/2701)	20.6% (552/2679)	0.98 (0.87-1.11)	.77
CV death, nonfatal MI, or nonfatal stroke	11.3% (305/2701)	11.8% (316/2679)	0.96 (0.82-1.13)	.63
CV death, nonfatal MI, nonfatal stroke, or unstable angina	14.3% (387/2701)	15.6% (419/2679)	0.91 (0.79-1.05)	.19
CV death, nonfatal MI, nonfatal stroke, unstable angina, or revascularization	21.0% (567/2701)	21.5% (575/2679)	0.98 (0.87-1.10)	.72
Unstable angina	4.0% (108/2701)	4.4% (117/2679)	0.91 (0.70-1.19)	.49
Revascularization (PCI or CABG)	10.6% (286/2701)	10.2% (272/2679)	1.05 (0.89-1.23)	.60
PCI	8.8% (238/2701)	8.2% (221/2679)	1.07 (0.89-1.29)	.44
With stent	7.6% (204/2701)	7.7% (205/2679)	0.99 (0.81-1.20)	.91
Without stent	2.0% (53/2701)	1.3% (36/2679)	1.47 (0.96-2.24)	.08
CABG	2.0% (55/2701)	2.3% (61/2679)	0.89 (0.62-1.28)	.53
Hospitalization for CV reason	25.0% (676/2701)	25.4% (680/2679)	0.98 (0.88-1.09)	.70
Length of stay				
Median (Q1, Q3)	8 (4, 17)	8 (4, 18)		.78
Hospitalization for any reason	33.9% (915/2701)	35.5% (950/2679)	0.94 (0.86-1.03)	.22
Length of stay				
Median (Q1, Q3)	9 (4, 22)	9 (4, 21)		.68

Note that most of the 95% CIs for the HRs are below the noninferiority margin of 1.3. Event rate is counting the first occurrence of each type of the events.

Figure 1

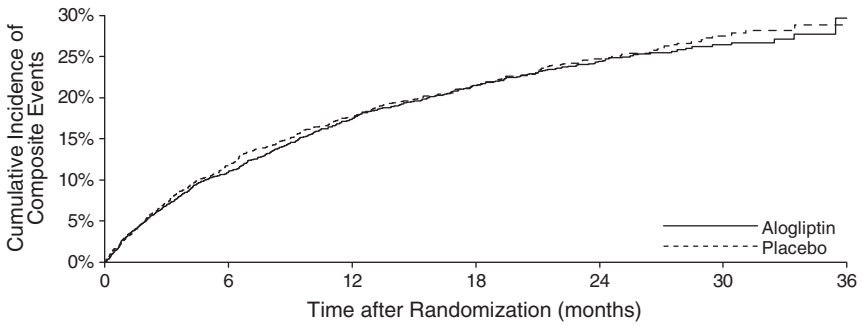


Cumulative Kaplan-Meier estimates of the time to the first adjudicated occurrence of coronary revascularization either with PCI or CABG.

announced in 2008 that a CV safety assessment is required for new antidiabetic drugs before and after approval.[12] The EXAMINE and SAVOR-TIMI 53 trials were the first to investigate CV safety of DPP-4 inhibitors according to the FDA guidance.[15,27] Neither of these 2 trials showed an increase nor a decrease in MACE among diabetic patients with a recent ACS event in EXAMINE or with a history of (or at a high risk for developing) CV event in SAVOR-TIMI 53. A more recent trial, TECOS, has also shown neutral effects of sitagliptin on major adverse CV events in T2DM patients with established CV disease.[28] In the present study, addition of a prospectively adjudicated end point of unstable angina on the prespecified composite end point of CV death, MI, and stroke did not demonstrate significant differences in the event rates between alogliptin and placebo groups. Another composite end point that is more specific to cardiac ischemia including CV death, MI, unstable angina, and coronary revascularization was also not different between the 2 randomized treatment groups. In addition, analysis of a 5-component composite end point that encompasses a wide spectrum of CV events such as CV death, MI, stroke, unstable angina, and coronary revascularization revealed that the event rates were essentially identical between the 2 groups. Our findings in the EXAMINE trial are consistent with those from SAVOR-TIMI 53 trial which did not find any signal of increased risk of hospitalization for unstable angina or hospitalization for coronary revascularization.[16] The present analysis adds to the body of knowledge by demonstrating that alogliptin does not increase the event rates of other cardiac ischemic outcomes such as coronary revascularization and CV events that require hospitalization.

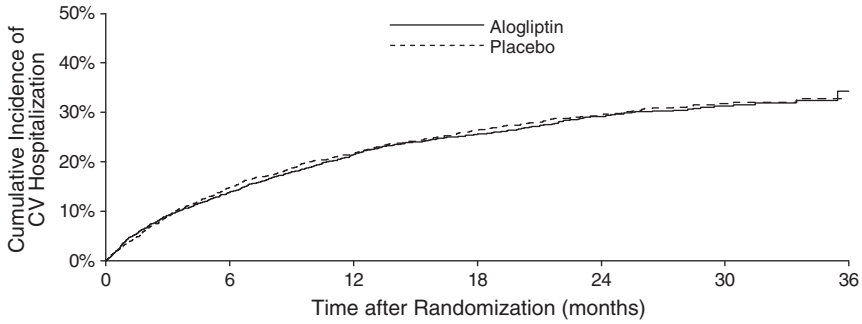
It has been reported that the cost of hospital inpatient care for people with diabetes in the United States has risen from $58 billion in 2007 to $76 billion in 2012.[4]

Figure 2



Cumulative Kaplan-Meier estimates of the time to the first adjudicated occurrence of a composite of CV death, MI, stroke, unstable angina, or revascularization.

Figure 3



Cumulative Kaplan-Meier estimates of the time to the first adjudicated occurrence of CV hospitalization.

Hospitalization drives up health care costs for the care of patients with T2DM, and CV hospitalizations are especially expensive. For example, a recent study reported that the costs for hospitalization were approximately $13,000 for PCI and $24,000 for CABG.[29] The estimated cost for hospitalization was $17,654 for heart failure and $ 19,349 for an MI treated with PCI.[30,31] As such, CV hospitalization is a substantial public health burden. The data from the present study would be reassuring for patients with T2DM and health care professionals who treat these patients as it did not show any evidence of increased risk of hospitalization for CV reason or for any other reason. These data lend more evidence to support that there would be no adverse impact on health care costs from adding alogliptin on background standard care for T2DM.

Possible effect modification of DPP-4 inhibitor in several higher risk patient populations, such as patients with advanced age or impaired renal function, has been reported from the SAVOR-TIMI 53 trial.[16,17] In the present analysis from the EXAMINE trial, however, there was no difference in MACE, cardiac ischemic event, CV hospitalization, or combination of these end points in a subset of patients who are at highest risk for CV events because of preexisting macrovascular disease before the index ACS event. These data provide further support that alogliptin can be safely administered in these highest risk patients with diabetes and prior macrovascular disease who developed an ACS.

This study has strengths as the EXAMINE trial met the regulatory goals required by the FDA.[12] This large-scale, randomized, placebo-controlled trial involved multiple nations and regions and patients with various stages of T2DM who were treated with different background therapy for diabetes and CV disease according to local guidelines.[15] The quality is enhanced by the high event rates and prespecified outcomes that were prospectively adjudicated. The present study also has limitations. The post hoc nature of this analysis should be taken into consideration when interpreting the data. Specifically, assessment of noninferiority in the present analysis needs careful interpretation as we did not prespecify a noninferiority margin for each additional end point but applied the noninferiority margin of HR of 1.3 that was originally determined for the primary end point in the main trial. Patients with a prior history of macrovascular disease were a subgroup of this trial, which may not have had the

Table IV. Risk of cardiac ischemic events and cardiovascular hospitalizations stratified by prior history of macrovascular disease

	Event rate								
	Macrovascular disease (+)				Macrovascular disease (–)				
End point	Alogliptin	Placebo	HR (95% CI)	*P*	Alogliptin	Placebo	HR (95% CI)	*P*	*P* value for interaction between treatment and subgroup
CV death or nonfatal MI	13.7% (191/1394)	13.0% (181/1394)	1.06 (0.87-1.31)	.55	6.8% (89/1307)	8.5% (109/1285)	0.80 (0.60-1.06)	.12	.11
CV death, nonfatal MI, or unstable angina	17.8% (248/1394)	18.3% (255/1394)	0.97 (0.82-1.16)	.76	8.7% (114/1307)	10.7% (138/1285)	0.81 (0.63-1.04)	.10	.23
CV death, nonfatal MI, unstable angina, or revascularization	24.0% (334/1394)	23.8% (332/1394)	1.01 (0.87-1.18)	.87	16.2% (212/1307)	17.1% (220/1285)	0.95 (0.79-1.15)	.62	.60
CV death, nonfatal MI, or nonfatal stroke	14.7% (205/1394)	14.2% (198/1394)	1.04 (0.86-1.27)	.66	7.7% (100/1307)	9.2% (118/1285)	0.83 (0.63-1.08)	.17	.18
CV death, nonfatal MI, nonfatal stroke, or unstable angina	18.8% (262/1394)	19.5% (272/1394)	0.96 (0.81-1.14)	.66	9.6% (125/1307)	11.4% (147/1285)	0.83 (0.66-1.06)	.13	.33
CV death, nonfatal MI, nonfatal stroke, unstable angina, or revascularization	24.8% (346/1394)	24.9% (347/1394)	1.00 (0.86-1.16)	.97	16.9% (221/1307)	17.7% (228/1285)	0.96 (0.79-1.15)	.63	.69
Unstable angina	5.5% (76/1394)	6.0% (84/1394)	0.92 (0.68-1.26)	.60	2.4% (32/1307)	2.6% (33/1285)	0.96 (0.59-1.56)	.86	.93
Revascularization (PCI or CABG)	11.2% (156/1394)	10.2% (142/1394)	1.11 (0.88-1.39)	.37	9.9% (130/1307)	10.1% (130/1285)	1.00 (0.78-1.28)	1.00	.50
PCI	9.3% (129/1394)	8.2% (115/1394)	1.13 (0.88-1.45)	.34	8.3% (109/1307)	8.2% (106/1285)	1.03 (0.79-1.35)	.83	.60
With stent	7.7% (108/1394)	7.5% (105/1394)	1.03 (0.79-1.35)	.83	7.3% (96/1307)	7.8% (100/1285)	0.96 (0.72-1.27)	.77	.69
Without stent	2.4% (34/1394)	1.5% (21/1394)	1.61 (0.93-2.77)	.09	1.5% (19/1307)	1.2% (15/1285)	1.28 (0.65-2.53)	.47	.60
CABG	2.2% (30/1394)	2.4% (33/1394)	0.94 (0.57-1.54)	.81	1.9% (25/1307)	2.2% (28/1285)	0.88 (0.51-1.51)	.65	.85
Hospitalization for CV reason	29.4% (410/1394)	29.5% (411/1394)	0.98 (0.86-1.13)	.80	20.4% (266/1307)	20.9% (269/1285)	0.99 (0.83-1.17)	.88	.96
Hospitalization for any reason	38.5% (536/1394)	40.9% (570/1394)	0.91 (0.81-1.03)	.13	29.0% (379/1307)	29.6% (380/1285)	0.99 (0.86-1.15)	.94	.37

Event rate is counting the first occurrence of each type of the events.

statistical power to detect small differences in the event rates between alogliptin and placebo. The EXAMINE trial had a median follow-up period of 18 months; therefore, we cannot determine whether there is any difference in the event rates over the long term.

Conclusions

These new data from the EXAMINE trial demonstrate that alogliptin does not increase the risk of cardiac ischemic event or CV hospitalization in high-risk patients with T2DM who experienced a recent ACS event. These findings were confirmed when patients were stratified by existence of established macrovascular disease before the index ACS event. Because CV hospitalization and coronary revascularization are main drivers of overall health care costs associated with T2DM care, these data suggest that there would be no unfavorable impact on health care resource utilization and costs by addition of alogliptin on standard therapy for T2DM.

Declaration of interests

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Final approval of the manuscript: All authors

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