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Total Cardiovascular Events Analysis of the EXAMINE Trial in Patients with Type 2 Diabetes and Recent Acute Coronary Syndrome

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Abstract

Background: Alogliptin, a dipeptidyl-peptidase 4 inhibitor, is approved for the treatment of patients with type 2 diabetes. EXAMINE was a randomized-controlled clinical trial designed to demonstrate the cardiovascular safety of alogliptin. In the trial, 5380 patients with established T2DM who had a recent ACS event (between 15-90 days) were randomized to treatment with either alogliptin or placebo.

Hypothesis: To better understand and describe the cardiovascular (CV) safety of alogliptin, we analyzed data from the EXAMINE randomized clinical trial to determine whether treatment with alogliptin affected recurrent and total CV

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events.

Methods: Poisson regression analysis was performed to compare the total number of occurrences of CV death, MI, stroke, unstable angina, and coronary revascularization between all patients randomized to alogliptin versus placebo groups.

Results: Patients with recurrent CV events were older and more likely to have renal disease and history of heart failure. There were 1100 first CV events and an additional 666 recurrent events over a median of 18 months of follow-up. There were no significant differences with regard to the total number of events in patients treated with alogliptin (n=873) or placebo (n=893; p=0.52). Furthermore, there were no differences in the types of events seen in patients treated with alogliptin or placebo.

Conclusion: Alogliptin did not increase the risk of either first or recurrent CV events when compared to placebo in patients with type 2 diabetes and recent ACS. These data support the CV safety of alogliptin in patients who are at increased risk of future CV events.

Word Count: 245

Alogliptin, a dipeptidyl-peptidase 4 inhibitor, is approved for the treatment of patients with type 2 diabetes (T2DM). The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study was a randomized, double-blind, placebo-controlled, multinational trial of alogliptin in patients with T2DM that were enrolled 15 to 90 days after an acute coronary syndrome (ACS). In the EXAMINE trial, there was neither an increase nor decrease in the risk of time to first CV death, MI, or stroke (MACE).(1) To better understand and describe the cardiovascular safety of alogliptin by providing a comprehensive picture of total CV events, we sought to determine the number of initial, recurrent and total CV events (CV death, MI, stroke, unstable angina and coronary revascularization) which occurred in the EXAMINE trial.

Methods

The full details of the EXAMINE trial have been previously published (clinicaltrials.gov: NCT00968708).(2) In brief, patients were eligible for the trial if they had established T2DM, were being treated with pharmacotherapies for T2DM (with the exception of a DPP-IV inhibitor or GLP-1 agonist), had a HbA1c level between 6.5% and 11.0% (7.0-10.0% if on insulin), and had a recent ACS event (either a myocardial infarction or unstable angina within 15-90 days of randomization). Patients with type 1 diabetes, end stage renal disease who had received hemodialysis within 14 days of screening, or unstable cardiovascular disorders (NYHA Class IV heart failure, refractory angina, uncontrolled arrhythmias, critical valvular heart disease, severe uncontrolled hypertension) were not eligible for the study.

Eligible patients with T2DM and recent ACS were randomly assigned to treatment with either alogliptin or placebo. Patients with a GFR ≥60 milliliters per minute per 1.73 m^2 of body surface area were treated with 25mg of alogliptin or matching placebo. Alogliptin is cleared via renal excretion so patients with a GFR of 30 to <60 milliliters per minute per 1.73 m^2 of body surface area were treated with 12.5 mg of alogliptin/placebo and 6.25 mg of alogliptin/placebo was used in patients with a GFR <30 milliliters per minute per 1.73 m^2 of body surface area. During the course of the trial, patients were to continue with evidence-based therapies for their T2DM and risk factors for cardiovascular disease prescribed by their health care providers. Hemoglobin A1c was not blinded during the study and clinicians were encouraged to treat patients based on regional guidelines; however, treatment with GLP-1 agonists or DPP-4 inhibitors during the course of the trial were prohibited. Treatment allocation was blinded to patients and investigators throughout the course of the study. National regulatory authorities and institutional ethics committees at each site approved the study design and all participants provided written informed consent.

The primary endpoint of the EXAMINE trial was the time to the first incidence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. For the purposes of this analysis in which we sought to better understand the total burden of cardiovascular events in patients with T2DM following a recent ACS, we evaluated a broader composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularization (either PCI or CABG). Heart failure has been the topic of a prior analysis and publication

and was not included in this analysis.(3) All clinical endpoints evaluated in the trial were adjudicated by a clinical events committee using prespecified definitions based on the guidelines from the Food and Drug Administration.(4) Fatal events were counted as a single event, such that, if a patient experienced an MI and then had CV death with the cause of death adjudicated as being due to the MI, the event was considered 1 fatal MI event.

Comparisons between baseline characteristics were made with the chi-square test (categorical) and Kruskal-Wallis (continuous). Poisson regression analysis was performed to compare the total number of occurrences of CV death, MI, stroke, unstable angina, and coronary revascularization between all patients in the alogliptin and placebo groups. All statistical analyses were performed by independent academic statisticians using SAS Version 9.4 (Cary, NC) at the Baim Institute for Clinical Research (Boston, MA).

Results

Of the 5380 patients randomized in the EXAMINE trial following an ACS event, 1100 patients had at least one post-randomization cardiovascular event over a median follow-up period of 18 months (Table 1). Over this follow-up period, in the 1100 patients with a cardiovascular event during the trial, 380 patients had an additional cardiovascular event (resulting in a total of 666 recurrent cardiovascular events) **(Table 1)**. The majority of patients randomized in the trial did not have an additional cardiovascular event (79.6%, n=4280) while 13.4% (n=720) had a single recurrent cardiovascular event and 7.1% (n=380) had multiple recurrent cardiovascular events. Patients with recurrent CV events

were older, had type 2 diabetes for a longer duration, had higher prevalence of heart failure, peripheral arterial disease, prior stroke, and were more likely to have renal disease **(Table 1).**

In the patients who had multiple cardiovascular events during followup, the burden of recurrent events was high with the mean number of cardiovascular events being 1.6±1.2 events per patient **(Table 2).** There were a considerable number of patients who had multiple events including 12 patients who had ≥6 events **(Figure 1).** In the 2701 patients treated with alogliptin, there were 545 initial events and 328 recurrent events and in the 2679 patients treated with placebo there were 555 initial events and 338 recurrent events **(Figure 2A)**. There was no difference in the number or type of cardiovascular events that occurred during followup in the alogliptin or placebo groups (p=0.52, Poisson) (**Figure 2B).**

Predictors for multiple cardiovascular events included having myocardial infarction or revascularization prior to the index ACS that led to study entry. **(Table 3).**

Discussion

In this analysis of the EXAMINE trial, we found that the burden of cardiovascular events is high and recurrent events are common in patients with diabetes and recent ACS. While clinical effectiveness studies including both randomized controlled clinical trials and observational studies traditionally focus on the incidence of the first cardiovascular event, this underestimates the true burden of cardiovascular events since it does not take into account those

patients who have multiple recurrent events.(5, 6) Secondly, we found that those patients with recurrent events are at increased risk of mortality and the presence of known cardiovascular disease (prior MI or revascularization) identifies patients with diabetes in whom recurrent events are more common.(7) In those patients with these characteristics, intensive medical therapy and close clinical monitoring should be considered in an attempt to minimize the risk of future cardiovascular events and death. Importantly, alogliptin did not increase nor decrease the risk of initial or recurrent cardiovascular events in patients with diabetes even after accounting for all the initial and recurrent events which occurred during the study.

During clinical trial follow-up, data on all cardiovascular events of interest are collected, although when performing comparative effectiveness analyses, the reporting is typically performed by analyzing only the first occurrence of a cardiovascular event. However, patients, clinicians, and payers have considerable interest in the total burden of cardiovascular events.(8, 9) Prior studies have found that intensive lipid control with high dose statins and more potent anti-platelet therapies can reduce the overall burden of cardiovascular events.(10, 11) These studies highlight the importance of assessing recurrent events to provide an overall picture of benefit.

The EXAMINE trial was designed to demonstrate the cardiovascular safety of alogliptin, a DPP-4 inhibitor, as required by guidance from the United States Food and Drug Administration. (12) This current analysis of all ischemic cardiovascular events which occurred in the EXAMINE trial allows for a more complete assessment of the overall cardiovascular safety of alogliptin and

provides additional evidence supporting the safety of alogliptin for use in the treatment of patients with type 2 diabetes and cardiovascular disease. We found that 7.1% of the patients enrolled in the EXAMINE trial had multiple cardiovascular events following the initial ACS event. Prior studies have found that a small proportion of patients account for the majority of health care expenditures in the United States.(13) In the EXAMINE study, those patients with recurrent/multiple events were older, had diabetes for a prolonged period of time, or had heart failure or prior atherothrombotic disorders (peripheral arterial disease, stroke). Prior ischemic events with either a coronary revascularization or myocardial infarction were independent predictors of having multiple cardiovascular events in our population of patients with diabetes. Identification of patient characteristics associated with a higher likelihood of recurrent events over the short and intermediate term following an ACS are needed to allow for the development of strategies to identify these high risk patients. Prior efforts to identify patients who are high risk of readmission following a heart failure admission with intensification of followup and therapy have been successful in reducing readmission rates.(14) Thus, it is possible that the design of interventions to increase the intensity of therapies in patients with diabetes who are at high risk for additional events could have the potential to improve outcomes while minimizing costs and result in reduced overall healthcare costs.

These data should be considered in the light of several potential limitations. First, the EXAMINE trial had a median followup time of 18 months which is relatively short given the duration of time in which patients live with

diabetes. Thus, it is possible that differences between therapies could emerge over a longer followup period. Secondly, in this analysis we did not assess events such as total hospitalizations, serious adverse events or total health care expenditures which are also important when considering the overall burden related to diabetes. Finally, there could be differences between patients who died and were censored because of the occurrence of a fatal event or concomitant treatments among patients who experienced a nonfatal event during the trial; however, we found no overall differences in the total number of cardiovascular events, including death, in patients treated with alogliptin or placebo, making this concern unlikely to be relevant.

In conclusion, patients with diabetes and recent ACS commonly have high burdens of recurrent events and these events seem to concentrated in a minority of patients. Alogliptin did not increase nor decrease the risk of either first or recurrent cardiovascular events when compared to placebo in patients with T2DM and recent ACS. These data support the CV safety of alogliptin in patients with diabetes and increased risk of future CV events. Further studies are needed to identify pharmacotherapies and interventions that can reduce the continued burden of cardiovascular disease in high risk populations of patients with diabetes and ACS.

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Figure Legends

Figure 1 – Number of cardiovascular events per patient during follow-up of the EXAMINE trial.

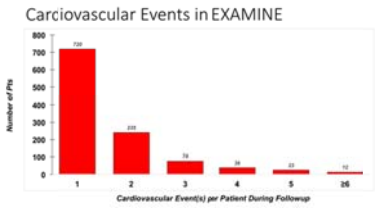

Figure 2 – Incidence of cardiovascular (A) and number and type of cardiovascular events (B) in patients treated with alogliptin or placebo.

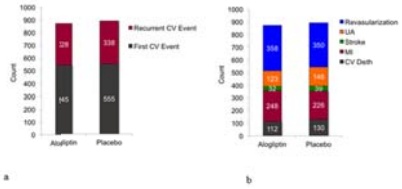

Table 1 – Baseline Characteristics stratified by number of post-randomization cardiovascular events.

Characteristics	No Event (N=4280)	1 Event (N=720)	Multiple Events (N=380)	p-value
Alogliptin	50.4% (2156/4280)	48.6% (350/720)	51.3% (195/380)	0.62
Age; Median (Q1,Q3)	60 (54,68)	62 (55,70)	62 (55,68)	<0.001
Male	68.4% (2926/4280)	66.3% (477/720)	65.3% (248/380)	0.28
Duration of diabetes (years); Median (Q1,Q3)	6.7 (2.5,13.0)	9.2 (3.5,15.3)	9.9 (4.8,16.2)	<0.001
Baseline HbA1c concentration; Median (Q1,Q3)	7.9 (7.2,8.7)	7.9 (7.2,8.7)	8.0 (7.3,8.8)	0.42
BMI (kg/m^2); Median (Q1,Q3)	28.7 (25.6,32.4)	28.7 (25.3,32.8)	29.3 (26.0,33.8)	0.01
Race				<0.001
American Indian or Alaska Native	2.1% (91/4280)	2.2% (16/720)	0.8% (3/380)	
Asian	20.4% (872/4280)	23.1% (166/720)	13.4% (51/380)	
Black or African American	3.6% (153/4280)	5.8% (42/720)	5.5% (21/380)	
Native Hawaiian or Other Pacific Islander	0.2% (10/4280)	0.1% (1/720)	0.0% (0/380)	
White	72.8% (3116/4280)	67.9% (489/720)	80.0% (304/380)	
Multiracial	0.9% (38/4280)	0.8% (6/720)	0.3% (1/380)	
Region of world				<0.001
United States, Canada	15.1% (647/4280)	16.3% (117/720)	23.4% (89/380)	
Western Europe, Australia, New Zealand and Middle East	10.9% (467/4280)	11.1% (80/720)	18.2% (69/380)	
Central and South America, Mexico	26.7% (1141/4280)	24.4% (176/720)	20.0% (76/380)	
Eastern Europe and Africa	28.4% (1216/4280)	26.8% (193/720)	26.1% (99/380)	
Asia, Pacific Islands	18.9% (809/4280)	21.4% (154/720)	12.4% (47/380)	
Cardiovascular Risk Factors and History				
Current smoker	13.8% (592/4280)	12.5% (90/720)	13.7% (52/380)	0.32
Hypertension	81.4% (3484/4280)	89.2% (642/720)	90.3% (343/380)	<0.001
Myocardial infarction*	0.0% (0/4280)	19.0% (137/720)	59.7% (227/380)	<0.001
PCI*	0.0% (0/4280)	28.6% (206/720)	66.6% (253/380)	<0.001
CABG*	0.0% (0/4280)	8.1% (58/720)	15.3% (58/380)	<0.001
Congestive Heart Failure	26.6% (1137/4280)	34.9% (251/720)	29.7% (113/380)	<0.001
Cerebrovascular Accident	6.1% (262/4280)	12.1% (87/720)	10.3% (39/380)	<0.001
Peripheral Arterial Disease	8.6% (369/4280)	11.7% (84/720)	16.1% (61/380)	<0.001
Renal function eGFR ($mL/min/1.73\ m^2$)				
Mean±SD (N)	72.0±21.0 (4280)	65.9±22.1 (720)	68.1±22.7 (380)	<0.001
Median (Q1,Q3)	72.4 (58.1,86.1)	65.8 (50.7,80.8)	67.3 (53.2,84.7)	
Range (min,max)	(4.2,186.1)	(5.0,136.1)	(13.7,169.6)	
eGFR < 60 $mL/min/1.73\ m^2$	27.0% (1157/4280)	39.7% (286/720)	32.1% (122/380)	<0.001
eGFR >= 60 $mL/min/1.73\ m^2$	73.0% (3123/4280)	60.3% (434/720)	67.9% (258/380)	
Index ACS event				0.07
Myocardial infarction	76.7% (3273/4267)	79.7% (574/720)	80.5% (305/379)	
Unstable angina	23.3% (994/4267)	20.3% (146/720)	19.5% (74/379)	
Time from index ACS event to randomization (days)				
Mean±SD (N)	48.5±22.1 (4267)	45.5±21.5 (720)	44.2±21.2 (379)	<0.001
Median (Q1,Q3)	45.0 (30.0,65.0)	41.0 (28.0,61.0)	41.0 (27.0,59.0)	
Range (min,max)	(8.0,141.0)	(10.0,97.0)	(10.0,101.0)	

Table 2 – Number of events per patient with alogliptin or placebo during followup of the EXAMINE trial.

Endpoints	Alogliptin (N=2701)	Placebo (N=2679)	p-value	Total (N=5380)
Number of events per patient				
Mean±SD (N)	1.6±1.1 (545)	1.6±1.2 (555)	0.54	1.6±1.2 (1100)
Median (Q1,Q3)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)		1.0 (1.0, 2.0)
Range (min,max)	(1.0, 11.0)	(1.0, 14.0)		(1.0, 14.0)
CV Death	4.1% (112/2701)	4.9% (130/2679)	0.21	4.5% (242/5380)
Death	5.7% (153/2701)	6.5% (173/2679)	0.223	6.1% (326/5380)
Number of non-fatal events per patient				
Mean±SD (N)	1.6±1.1 (462)	1.7±1.3 (449)	0.91	1.7±1.2 (911)
Median (Q1,Q3)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)		1.0 (1.0, 2.0)
Range (min,max)	(1.0, 11.0)	(1.0, 14.0)		(1.0, 14.0)

Table 3 – Predictors of recurrent cardiovascular events in patients with diabetes.

Predictors	Odds Ratio [95% CI]	P-value
Central and South America, Mexico (as compared to United States/Canada)	1.04 [0.76-1.43]	0.81
Western Europe, Australia, New Zealand and Middle East (as compared to United States/Canada)	1.26 [0.89-1.79]	0.19
Eastern Europe and Africa (as compared to United States/Canada)	0.86 [0.63-1.16]	0.31
Asia, Pacific Islands (as compared to United States/Canada)	0.62 [0.44-0.88]	0.01
Myocardial Infarction*	119.72 [72.49- 197.72]	<0.001
PCI*	138.79 [85.69- 224.80]	<0.001
CABG*	80.58 [41.52- 156.39]	<0.001

* Prior to randomization and before the index ACS