ORIGINAL RESEARCH

Early and Chronic Dipeptidyl-Peptidase-IV Inhibition and Cardiovascular Events in Patients With Type 2 Diabetes Mellitus After an Acute Coronary Syndrome: A Landmark Analysis of the EXAMINE Trial

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***Background*—**Antihyperglycemic therapies may increase the risk of cardiovascular events including hospitalization for heart failure. There is a paucity of data evaluating the cardiovascular safety of antihyperglycemic therapies in the high-risk period following an acute coronary syndrome (ACS).

***Methods and Results*—**The EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) trial randomized 5380 patients who were 15 to 90 days post ACS to the dipeptidyl dipeptidase-IV (DPP-IV) inhibitor alogliptin versus placebo; mean follow-up was 18 months. Using a landmark analysis, we assessed the (1) burden of cardiovascular events from randomization to 6 months (early period) and from 6 months to the end of follow-up (late period) and (2) the risk of cardiovascular events associated with early (up to 6 months) and chronic (6 months to end of follow-up) DPP-IV inhibition with alogliptin. Patients with early versus late events had similar baseline demographic profiles. Overall, 42.1% of the composite of cardiovascular death/myocardial infarction/stroke and 47.5% of hospitalization for heart failure occurred in the early period. Early DPP-IV inhibition did not increase the risk of early cardiovascular death/myocardial infarction/stroke (hazard ratio 0.96, 95% confidence interval, 0.76–1.21) or hospitalization for heart failure (1.23, 95% confidence interval, 0.84–1.82). Similarly, chronic DPP-IV inhibition did not increase the risk of late cardiovascular death/myocardial infarction/stroke (hazard ratio 1.03, 95% confidence interval, 0.89–1.26) or hospitalization for heart failure (hazard ratio 1.02, 95% confidence interval, 0.85–1.22).

***Conclusions*—**Early after an ACS, patients with type 2 diabetes mellitus experience a significant burden of HF events and recurrent ACS. DPP-IV inhibition with alogliptin appears to be safe even in the high-risk period following an ACS. **(*J Am Heart Assoc.* 2018;7:e007649. DOI: 10.1161/JAHA.117.007649.)**

Key Words: acute coronary syndrome • alogliptin • dipeptidyl dipeptidase-4 inhibitor • diabetes mellitus • medical therapy • medication

Diabetes mellitus is an established cardiovascular risk factor and independently increases the risk of acute coronary syndromes (ACS)[1,2] and heart failure (HF).[1,3–6] The first 6 months following an ACS represent a high-risk period for heart failure hospitalization (HHF) and recurrent ACS, especially among patients with type 2 diabetes mellitus (T2DM).[7–9] There are concerns about safety regarding the initiation of antihyperglycemic medications and the risk of cardiovascular events including ACS and HF events.[10] Early dipeptidyl dipeptidase-IV (DPP-IV) inhibition with saxagliptin,

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Accompanying Tables S1 through S12 are available at //jaha.ahajournals.org/content/7/11/e007649/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- There has been little evaluation of the safety of early and chronic dipeptidyl dipeptidase-4 inhibition among stable patients who have type 2 diabetes mellitus and who recently experienced an acute coronary syndrome (ACS).
- Using data from the EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin Versus Standard of Care) trial, we demonstrate that in the early period following an ACS (within 6 months), patients with type 2 diabetes mellitus experience a large burden of clinical events such as heart failure and recurrent ACS.
- However, even in this high-risk early period, dipeptidyl dipeptidase-IV inhibition with alogliptin appears to be safe.

What Are the Clinical Implications?

- The overall safety of initiating antihyperglycemic therapies among patients with type 2 diabetes mellitus shortly after an ACS has not been well established.
- To date, the EXAMINE trial is one of the only cardiovascular outcomes trials to randomize patients shortly after an ACS.
- The post-ACS period reflects a natural time period when antihyperglycemic therapies can be optimized. Given the large burden of cardiovascular events in the early period following an ACS, further studies are needed to ensure the safety of antihyperglycemic therapies that are initiated during this time period.

compared with placebo, increased the risk of HHF within 6 months of drug initiation; although this population was at a high risk of ACS, patients with recent myocardial infarctions (MI) were excluded.[11] Guidelines have recommended optimizing comorbidities such as diabetes mellitus shortly after cardiovascular events[12]; however, there is a paucity of data evaluating the safety of initiating antihyperglycemic therapies in this high-risk post-ACS period. Furthermore, despite the risk of a recurrent cardiovascular event even in the late periods following ACS,[7] there is little evidence of the safety of antihyperglycemic therapies in this time frame; evaluating for safety signals associated with the use of antihyperglycemic medications during this time period remains warranted. In order to address these significant knowledge gaps, we evaluated data from the EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin Versus Standard of Care) trial,[13,14] which enrolled a population of stable patients with T2DM within 15 to 90 days of an ACS. Using a landmark analysis, we evaluated the (1) burden of vascular and HF events in the early (within 6 months) and late periods (after 6 months) following the index ACS and (2) the risk of cardiovascular events, including HF, associated with early (within 6 months) and chronic (after 6 months) DPP-IV inhibition with alogliptin.

Methods

Details of the design and results of the EXAMINE trial have been previously reported.[13,14] In brief, the EXAMINE trial was a double-blind, placebo-controlled, noninferiority trial that randomized 5380 patients with T2DM and an ACS within 15 to 90 days before enrollment to either alogliptin or placebo. Patients with T2DM were eligible if they had a hemoglobin A1c between 6.5% and 11% (if on insulin, a hemoglobin A1c of 7% and 11% was required), and were receiving treatment for diabetes mellitus with drugs other than a glucagon-like peptide-1 receptor agonist or DPP-IV inhibitor. Exclusion criteria included type 1 DM, end-stage renal disease on dialysis, New York Heart Association class IV HF, refractory angina, uncontrolled arrhythmias, significant valvular heart disease, or severe uncontrolled hypertension. The median follow-up time was 18 months. All patients randomized in the trial provided informed consent. The Institutional Review Board or Ethics Committee for each participating institution reviewed and approved the trial. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

End Points

We evaluated (1) time to first event of the primary EXAMINE trial end point (composite of cardiovascular death or MI or stroke); and (2) the prespecified exploratory major adverse cardiac event (MACE) composite end point of the EXAMINE trial (death or MI or stroke or revascularization for unstable angina or HHF). We also evaluated the following HF outcomes: (1) cardiovascular death or HHF; (2) HHF; and (3) an exploratory post hoc outcome of cardiovascular death or HHF or outpatient initiation of loop diuretics.[15]

Statistical Analysis

The time period from randomization up to 6 months is defined as the "early period" and from 6 months to the end of follow-up is defined as the "late period." The 6-month time point reflects a natural time frame for assessment of outcomes. It has been used as a time point for various risk prediction models such as Global Registry of Acute Coronary Events Score (GRACE), and would enable comparisons with other DPP-IV inhibitor trial landmark analyses. Baseline characteristics between patients with early and late cardiovascular events were summarized using median (25th, 75th percentiles) for continuous variables and frequencies/percentages for categorical variables. The "late group" reflects patients who have experienced both early and late events. A landmark analysis was conducted at the 6-month time period, and patients who died in the early phase were excluded at the 6-month time period. The overall median

Table 1. Baseline Characteristics of Patients With Early Versus Late Events

Characteristics	Early End Point Patients (N=283)	Late End Point Patients (N=389)	No End Point Patients (N=4759)
Demographics			
Age (y)			
Mean±SD (N)	63.8±9.6 (283)	64.0±9.8 (389)	60.5±9.9 (4759)
Median (Q1, Q3)	64.0 (58.0, 70.0)	64.0 (57.0, 71.0)	60.0 (54.0, 68.0)
Range (min, max)	(39.0, 89.0)	(39.0, 89.0)	(26.0, 91.0)
Male	60.4% (171/283)	64.0% (249/389)	68.5% (3259/4759)
Race			
American Indian or Alaska Native	2.5% (7/283)	2.6% (10/389)	2.0% (94/4759)
Asian	16.3% (46/283)	17.2% (67/389)	20.6% (982/4759)
Black or African American	5.7% (16/283)	7.2% (28/389)	3.7% (174/4759)
Native Hawaiian or Other Pacific Islander	0.0% (0/283)	0.0% (0/389)	0.2% (11/4759)
White	74.6% (211/283)	72.2% (281/389)	72.7% (3458/4759)
Multiracial	1.1% (3/283)	0.8% (3/389)	0.8% (40/4759)
Ethnicity			
Hispanic or Latino	30.4% (86/283)	21.9% (85/389)	28.9% (1377/4759)
Not Hispanic or Latino	69.6% (197/283)	78.1% (304/389)	71.1% (3382/4759)
Current smoker	13.1% (37/283)	11.6% (45/389)	13.9% (660/4759)
NYHA Class			
I	15.7% (17/108)	19.4% (31/160)	22.9% (286/1251)
II	58.3% (63/108)	55.6% (89/160)	58.0% (725/1251)
III	24.1% (26/108)	22.5% (36/160)	18.1% (226/1251)
IV	1.9% (2/108)	2.5% (4/160)	1.1% (14/1251)
BMI, kg/m^2			
Mean±SD (N)	29.5±6.1 (283)	30.1±6.3 (389)	29.4±5.5 (4758)
Median (Q1, Q3)	28.5 (25.4, 32.8)	29.3 (25.4, 33.6)	28.7 (25.6, 32.5)
Range (min, max)	(15.6, 51.0)	(15.6, 56.8)	(15.7, 68.3)
Systolic BP, mm Hg			
Mean±SD (N)	132.8±18.6 (283)	132.7±17.2 (389)	128.5±16.4 (4759)
Median (Q1, Q3)	130.0 (120.0, 143.0)	132.0 (120.0, 143.0)	130.0 (120.0, 140.0)
Range (min, max)	(82.0, 188.0)	(86.0, 190.0)	(80.0, 202.0)
Diastolic BP, mm Hg			
Mean±SD (N)	75.1±10.4 (283)	76.0±11.0 (389)	76.5±9.5 (4759)
Median (Q1, Q3)	76.0 (69.0, 80.0)	78.0 (70.0, 83.0)	78.0 (70.0, 82.0)
Range (min, max)	(50.0, 107.0)	(45.0, 114.0)	(40.0, 122.0)
Medical history			
Hypertension	92.6% (262/283)	92.5% (360/389)	81.9% (3897/4759)
Myocardial infarction	91.9% (260/283)	94.6% (368/389)	87.4% (4157/4759)
Coronary bypass surgery	20.8% (59/283)	18.8% (73/389)	12.0% (573/4759)
Peripheral artery disease	20.5% (58/283)	15.9% (62/389)	8.6% (410/4759)
Congestive heart failure	38.2% (108/283)	41.1% (160/389)	26.3% (1252/4759)

Continued

Table 1. Continued

Characteristics	Early End Point Patients (N=283)	Late End Point Patients (N=389)	No End Point Patients (N=4759)
Labs			
eGFR, mL/min per 1.73 m^2			
Mean±SD (N)	60.8±23.1 (283)	63.1±22.4 (389)	72.1±21.0 (4759)
Median (Q1, Q3)	60.2 (45.1, 74.8)	63.1 (48.1, 77.0)	72.4 (58.1, 86.1)
Range (min, max)	(5.0, 143.0)	(11.0, 137.9)	(4.2, 186.1)
Glycosylated hemoglobin (%)			
Mean±SD (N)	8.0±1.0 (283)	8.1±1.1 (389)	8.0±1.1 (4758)
Median (Q1, Q3)	7.9 (7.2, 8.6)	8.0 (7.3, 8.7)	7.9 (7.2, 8.7)
Range (min, max)	(5.7, 11.3)	(5.7, 12.8)	(4.9, 12.7)
HDL cholesterol, mg/dL			
Mean±SD (N)	43.7±11.7 (283)	43.6±11.9 (389)	43.1±10.4 (4758)
Median (Q1, Q3)	43.0 (36.0, 51.0)	41.0 (36.0, 50.0)	42.0 (36.0, 49.0)
Range (min, max)	(22.0, 97.0)	(18.0, 115.0)	(11.0, 106.0)
Triglycerides, mg/dL			
Mean±SD (N)	174.8±99.6 (283)	165.2±91.9 (389)	164.3±105.4 (4759)
Median (Q1, Q3)	154.0 (109.0, 211.0)	144.0 (106.0, 196.0)	140.0 (103.0, 194.0)
Range (min, max)	(49.0, 767.0)	(43.0, 729.0)	(34.0, 1631.0)
Hemoglobin, g/dL			
Mean±SD (N)	12.7±1.7 (283)	13.1±1.7 (389)	13.5±1.5 (4748)
Median (Q1, Q3)	12.7 (11.6, 13.8)	13.2 (11.9, 14.3)	13.6 (12.6, 14.6)
Range (min, max)	(7.6, 16.9)	(8.1, 17.5)	(7.2, 19.7)
Baseline medications			
Diabetic agents	98.2% (278/283)	99.5% (387/389)	99.0% (4710/4759)
Sulfonylureas	42.0% (119/283)	47.3% (184/389)	46.6% (2219/4759)
Metformin	55.8% (158/283)	56.3% (219/389)	67.5% (3212/4759)
Insulin	40.6% (115/283)	37.5% (146/389)	28.8% (1369/4759)
Thiazolidinediones	1.4% (4/283)	3.1% (12/389)	2.4% (116/4759)
Pioglitazone	1.4% (4/283)	2.8% (11/389)	2.2% (107/4759)
Rosiglitazone	0.0% (0/283)	0.3% (1/389)	0.2% (9/4759)
Antiplatelet agents	96.1% (272/283)	95.9% (373/389)	97.4% (4637/4759)
ASA	90.1% (255/283)	90.5% (352/389)	90.8% (4322/4759)
Thieno	80.6% (228/283)	81.0% (315/389)	80.3% (3823/4759)
Cholesterol-lowering agents	89.4% (253/283)	91.0% (354/389)	92.1% (4381/4759)
Statin	88.3% (250/283)	89.5% (348/389)	90.6% (4314/4759)
Fibrate	5.3% (15/283)	8.7% (34/389)	4.9% (233/4759)
Niacin	1.1% (3/283)	1.5% (6/389)	0.9% (42/4759)
Ezetimibe	2.5% (7/283)	3.3% (13/389)	2.1% (102/4759)
β-Blockers	82.7% (234/283)	80.5% (313/389)	82.2% (3911/4759)
Renin-angiotensin system-blocking agents	80.9% (229/283)	85.1% (331/389)	81.7% (3890/4759)
ACEI	58.0% (164/283)	64.3% (250/389)	61.8% (2939/4759)
ARB	24.4% (69/283)	22.9% (89/389)	21.9% (1043/4759)

Continued

Table 1. Continued

Characteristics	Early End Point Patients (N=283)	Late End Point Patients (N=389)	No End Point Patients (N=4759)
Diuretics	51.9% (147/283)	53.2% (207/389)	35.6% (1694/4759)
Thiazide	15.5% (44/283)	18.5% (72/389)	14.8% (706/4759)
Loop	31.8% (90/283)	32.6% (127/389)	15.6% (744/4759)
Nitrates	43.5% (123/283)	41.6% (162/389)	31.5% (1497/4759)
Calcium channel blockers	30.4% (86/283)	29.6% (115/389)	21.4% (1019/4759)

Patients in the late event column include 50 patients who also experienced early events. ASA indicates acetylsalicylic acid; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; eGFR estimated glomerular filtration rate; HDL, high-density lipoprotein; NYHA, New York Heart Association.

follow-up in our analysis was 640 days and after the 180-day landmark it was 460 days. The median follow-up was the same in both treatment groups. The first clinical event in the early and late period was reported; in the late period, patients who experienced an early event were not excluded from subsequent analyses. The risk of events associated with early (randomization up to 6 months) versus chronic (6 months to end of follow-up) DPP-IV inhibition with alogliptin (versus placebo) was assessed using Cox proportional hazard models. A sensitivity analysis looking at on-treatment analysis was also conducted. We also conducted a multivariable adjustment for clinically important variables including age, sex, index event type, history of HF, estimated glomerular filtration rate, and prior hypertension when assessing the risk of cardiovascular outcomes associated with randomization to alogliptin versus placebo. All statistical calculations were conducted using SAS 9.4 (SAS Institute, Inc, Cary, NC).

Results

Baseline Characteristics

Patients with early versus late events had similar median ages (64.0 years versus 64.0 years), distribution of race, New York Heart Association functional class, body mass index (median 28.5 kg/m^2 versus 29.3 kg/m^2), and cardiovascular comorbidities. Furthermore, there was similar use of antiplatelet agents and statins (Table 1). Patients with early events were slightly less likely to be male (60.4% versus 64.0%), slightly less likely to have a baseline history of MI (91.9% versus 94.6%), slightly more likely to be on insulin (40.6% versus 37.5%), and less likely to be on renin–angiotensin system blocking agents (80.9% versus 85.1%). In comparison, patients with early and late events were older than patients without clinical events and had a greater burden of cardiovascular comorbidities (Table 1). In total, 50 patients experienced early and late events.

Distribution of Early and Late Cardiovascular Events

Overall, 5.3% (283/5380) of the total population experienced cardiovascular death/MI/stroke in the early phase compared with 8.1% (389/4791) with the late phase (Table 2). In total, 42% of cardiovascular death/MI/stroke occurred in the early phase. For cardiovascular death, 1.8% (97/5380) of the population had an event in the early phase versus 3.0% (145/4791) in the late phase. In total, 40.1% of cardiovascular

Table 2. Distribution of Early Versus Late Cardiovascular Events

	Early Events Total Population (N=5380)	Late Events Total Population* (N=4791)	% Events in the Early Period
Composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke	5.3% (283/5380)	8.1% (389/4791)	42.1% (283/672)
Nonfatal MI	3.2% (170/5380)	4.8% (232/4791)	42.2% (170/402)
Nonfatal stroke	0.4% (23/5380)	1.0% (46/4791)	33.3% (23/69)
Cardiovascular death	1.8% (97/5380)	3.0% (145/4791)	40.1% (97/242)
All-cause mortality	2.2% (120/5380)	4.3% (206/4791)	36.8% (120/326)
Sudden cardiac death	0.9% (50/5380)	1.7% (82/4791)	37.8% (50/132)

MI indicates myocardial infarction.
*Patients with follow-up time <180 days are excluded for late events analysis.

Table 3. Distribution of Early Versus Late HF Events

	Early Events Total Population (N=5380)	Late Events Total Population* (N=4791)	% Events in the Early Period
Composite of all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, urgent revascularization because of unstable angina, and hospital admission for HF	7.8% (420/5380)	11.6% (556/4791)	43.0% (420/976)
Cardiovascular death or HF hospitalization	3.6% (191/5380)	5.1% (245/4791)	43.8% (191/436)
HF hospitalization	1.9% (103/5380)	2.4% (114/4791)	47.5% (103/217)
Cardiovascular death or HF hospitalization or initiation of loop diuretics	7.1% (384/5380)	10.1% (482/4791)	44.3% (384/866)

HF indicates heart failure; MI, myocardial infarction.
*Patients with follow-up time <180 days are excluded for late-events analysis.

deaths occurred in the early phase. For sudden cardiac death, 0.9% (50/5380) of the population had an event in the early period versus 1.7% (82/4791) in the late period. Overall, 37.9% of all sudden deaths occurred in the early period (Table 2).

Distribution of Early and Late HF Events

In the early period, 7.8% (420/5380) experienced the composite of all-cause mortality/nonfatal MI/nonfatal stroke/urgent revascularization because of unstable angina/HHF compared with 11.6% (556/4791) in the late period; overall, 43.0% of events occurred in the early period (Table 3). For cardiovascular death/HHF 3.6% (191/5380) of the population experienced an event in the early period compared with 5.1% (245/4791) in the late period; overall, 43.8% of events occurred in the early period. HHF occurred in 1.9% (103/5380) in the early period versus 2.4% (114/4791) in the late period; in total, 47.5% of HHF events occurred in the early period (Table 3).

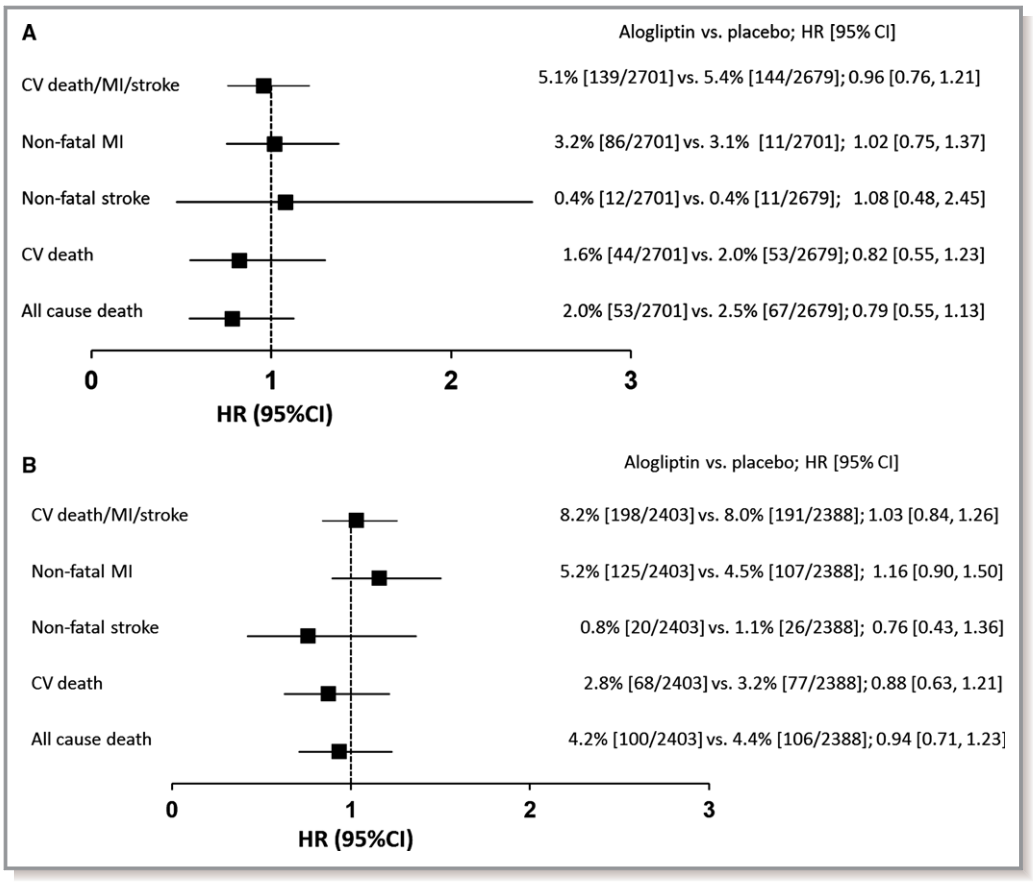

Figure 1. A, Risk of cardiovascular events associated with early DPP-IV inhibition with alogliptin. B, Risk of cardiovascular events associated with late DPP-IV inhibition. CI indicates confidence interval; CV, cardiovascular; DPP-IV, dipeptidyl dipeptidase-IV; HR, hazard ratio; MI, myocardial infarction.

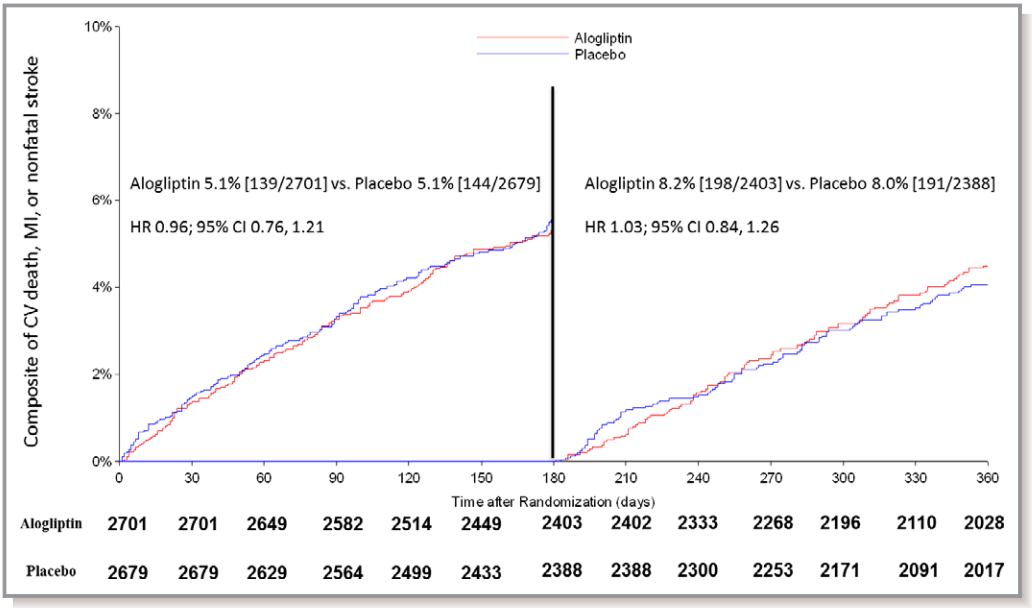

Figure 2. Kaplan–Meier curves for landmark analysis of cardiovascular events. CV indicates cardiovascular; HR, hazard ratio; MI, myocardial infarction.

Impact of Early and Chronic DPP-IV Inhibition on Risk of Events

Early DPP-IV inhibition with alogliptin, compared with placebo, did not increase the risk of the composite of cardiovascular death/MI/stroke (hazard ratio [HR] 0.96, 95% confidence interval [CI], 0.76–1.21). Similarly, the risk of cardiovascular death/MI/stroke was not increased with chronic DPP-IV inhibition (HR 1.03, 95% CI, 0.84–1.26). The risk of cardiovascular death was numerically but nonsignificantly reduced with early (HR 0.82, 95% CI, 0.55–1.23) and late (HR 0.88, 95% CI, 0.63–1.21) DPP-IV inhibition. The risk of other events including nonfatal MI, nonfatal stroke, and all-cause mortality were not increased in the early or late periods (Figures 1 and 2, Tables S1 and S2).

Regarding HF events, the risk of death/MI/stroke/revascularization for unstable angina/HHF was not increased with early (HR 0.96, 95% CI, 0.79–1.16) or chronic DPP-IV inhibition (HR 1.64, 95% CI, 0.88–1.23) with alogliptin (Figures 3 and 4, Tables S3 and S4). Similarly, the risk of cardiovascular death/HHF was not increased with early (HR 1.01, 95% CI, 0.76–1.34) or chronic DPP-IV inhibition (HR 1.01, 95% CI, 0.79–1.30). The risk of HHF was numerically, but nonsignificantly increased with early DPP-IV inhibition (HR 1.23, 95% CI, 0.84–1.82) and was similar in the late period (HR 1.1, 95% CI, 0.76–1.59; Figure 5). Using the sensitive HF end point of cardiovascular death/HHF/initiation of loop diuretics, early DPP-IV inhibition did not increase the risk events (HR 1.01, 95% CI, 0.83–1.24); similar findings were seen with late DPP-IV inhibition (HR 1.02, 95% CI, 0.85–1.22) (Figure 3). The on-treatment analysis demonstrated similar results (Tables S5 through S8). After multivariable adjustment, our results remained unchanged (Tables S9 through S12).

Discussion

There are limited data assessing the safety of early and chronic DPP-IV inhibition in patients with T2DM following an ACS. Using data from the EXAMINE trial, we have identified the following major findings: (1) Patients experience a significant burden of cardiovascular events including recurrent ACS and HF events in the early period following an ACS, and (2) early and chronic DPP-IV inhibition with alogliptin does not significantly increase the risk of cardiovascular events, including HF. Given the paucity of evidence regarding the initiation of antihyperglycemic therapies in the post ACS setting, our findings have significant clinical implications; early and chronic DPP-IV inhibition with alogliptin appears to be safe in patients following an ACS.

The finding of a high risk of death and vascular events in the early period post ACS has been described in other populations.[8,16,17] In 9492 patients undergoing percutaneous coronary intervention for an ACS, among those with diabetes mellitus (n=1927, 20.3%), 60% of all deaths in 1 year occurred within 30 days post ACS; similarly, 67% of all recurrent MIs in 1 year occurred within the first 30 days.[18] Our analysis expands on these findings by demonstrating that a substantial number of HHFs occur early post ACS. Furthermore, using a sensitive HF outcome that includes initiation of loop diuretics, our results suggest that a significant number of outpatients may be developing worsening HF in the early post ACS period

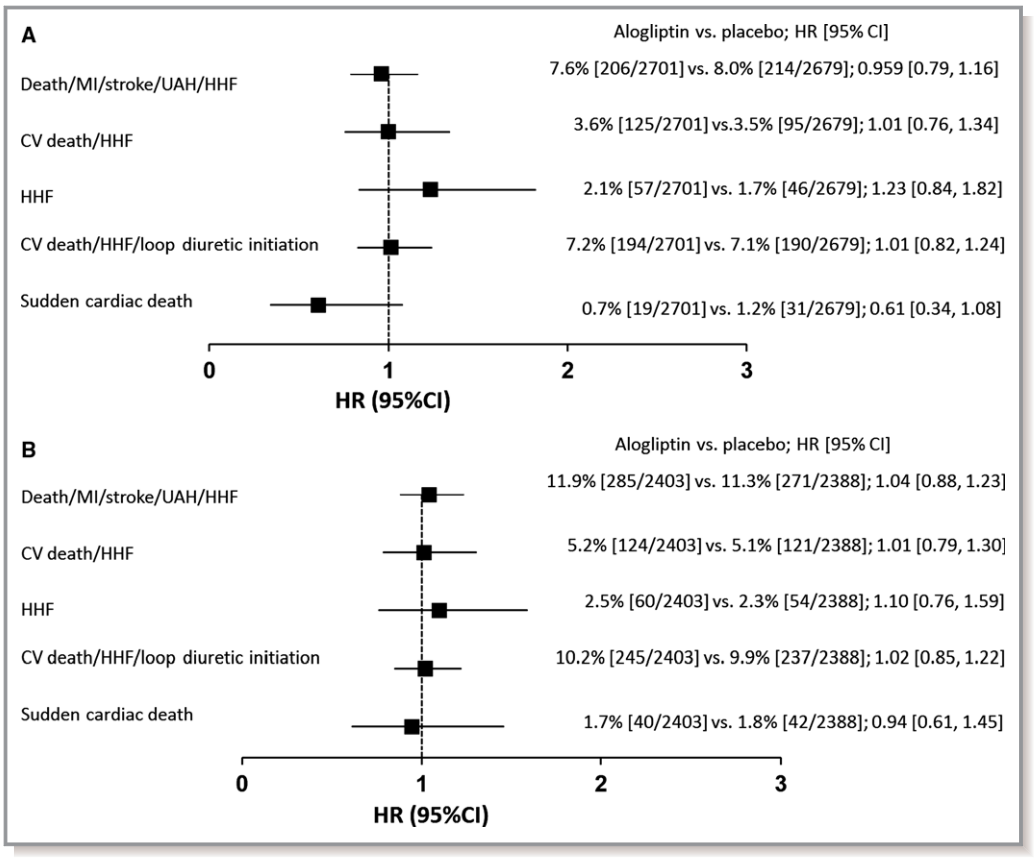

Figure 3. A, Risk of HF heart failure events associated with early DPP-IV inhibition with alogliptin. B, Risk of HF events associated with late DPP-IV inhibition with alogliptin. CI indicates confidence interval; CV, cardiovascular; DPP-IV, dipeptidyl-dipeptidase-IV; HF, heart failure; HHF, hospitalization for heart failure; HR, hazard ratio; MI, myocardial infarction; UAH, unstable angina hospitalization.

as reflected by intensification of medical therapy. Further studies evaluating strategies to identify and treat patients with T2DM who may develop incident and worsening HF early post ACS are warranted.

To date, there is limited evidence of the cardiovascular and HF safety of antihyperglycemic therapies that are initiated after an ACS.[19,20] The ELIXA (The Evaluation of Lixisenatide in Acute Coronary Syndrome) trial, evaluating the glucagon-like peptide-1 receptor agonist lixisenatide, is the only other antihyperglycemic drug trial that randomized patients post ACS, although this study enrolled patients within 180 days post ACS.[21] There is significant need to assess the safety of antihyperglycemic therapies in patients shortly after an acute cardiovascular event. This time period reflects an important period where patients are in closer contact with healthcare providers, and guidelines have recommended that optimization of comorbidities such as diabetes mellitus should occur in this time period.[12] However, initiation of certain antihyperglycemic therapies during this time period may be associated with increased risk of harm. Among patients with HF and reduced ejection fraction who were recently hospitalized for HF (within 2 weeks), randomization to the glucagon-like peptide-1 receptor agonist liraglutide versus matching placebo was associated with a trend towards worsening HF outcomes in patients with diabetes mellitus (death/HHF risk with liraglutide versus placebo; HR 1.52; 95% CI, 0.97–2.46, P=0.07).[22]

The EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial was a cardiovascular safety trial of the SGLT-2 inhibitor empagliflozin.[23] The trial randomized 7020 patients with T2DM and established cardiovascular disease to receive empagliflozin 10 mg, 25 mg, or placebo. Empagliflozin reduced the primary MACE end point compared with placebo (10.5% versus 12.1%; HR 0.86, 95% CI, 0.74–0.99). Furthermore, empagliflozin reduced the risk of HF admissions compared with placebo (4.1% versus 2.7%; HR 0.65, 95% CI, 0.50–0.85). The CANVAS (Canagliflozin Cardiovascular Assessment Study) program integrated 2 clinical trials with a total of 10 142 patients with T2DM and high cardiovascular risk.[24] Patients were randomized to canagliflozin or placebo and the trial demonstrated a significant reduction in the risk of cardiovascular death, nonfatal MI, or nonfatal stroke (26.9 versus 31.5 per 1000 patient-years; HR 0.86, 95% CI, 0.75–0.97).

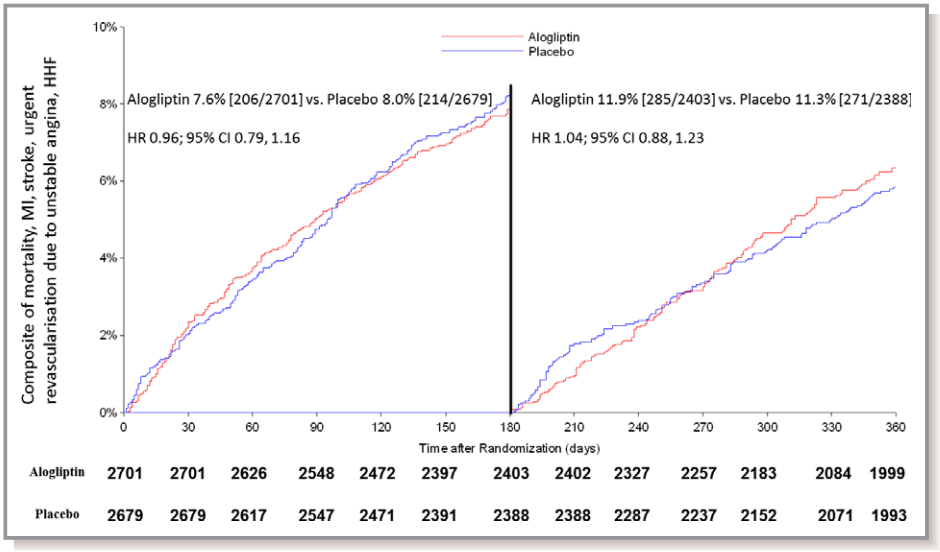

Figure 4. Kaplan–Meier curves for landmark analysis of cardiovascular events including HF. CI indicates confidence interval; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Randomization to canagliflozin was associated with a reduced risk of HHF (5.5 versus 8.7 per 1000 patient-years; HR 0.67, 95% CI, 0.52–0.87). The ability of SGLT-2 inhibitors to optimize volume status through glycosuria and also inhibit sodium–hydrogen exchanger in the kidneys and the heart may result in a cascade of responses including increased natriuresis, decreased myocardial fibrosis, and increased cardiac contractility. However, none of these studies have established the safety and efficacy of SGLT-2 inhibition in the early or late periods following an acute MI.

Our results suggest that early and chronic DPP-IV inhibition with alogliptin is not associated with an increased risk of cardiovascular events. These results align with the overall HF results of the EXAMINE trial.[25] Concerns regarding the risk of HF development with DPP-IV inhibitors have resulted in a US Food and Drug Administration warning against alogliptin- and saxagliptin-containing medications.[26] Sitagliptin was not associated with an increased risk of HHF.[27,28] The SAVOR-TIMI-53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus) trial randomized

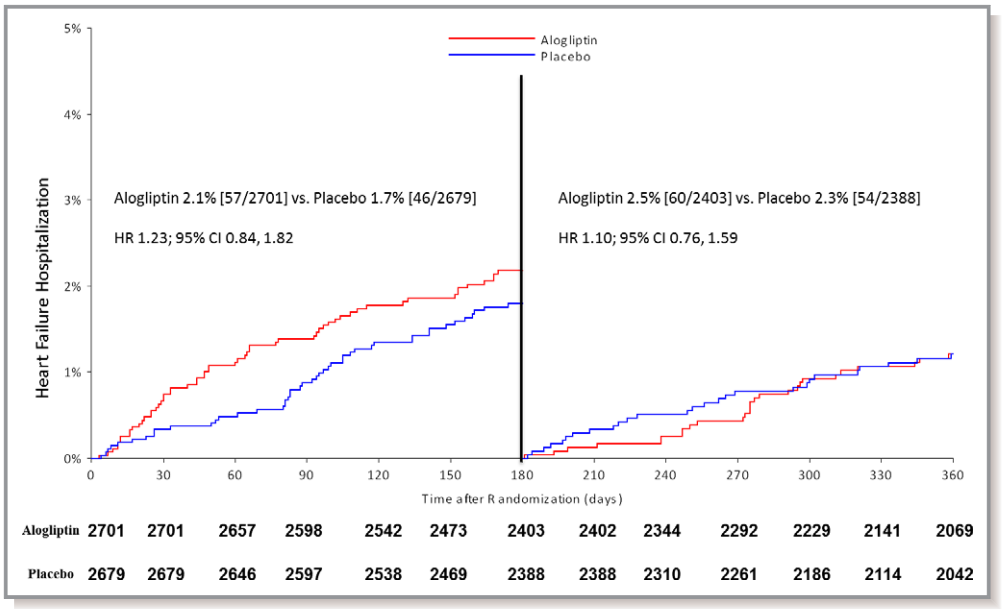

Figure 5. Kaplan–Meier curve for landmark analysis of HF hospitalization. CI indicates confidence interval; HF, heart failure; HR, hazard ratio.

patients with T2DM at high cardiovascular risk to saxagliptin or placebo. There was no increase in the risk of the primary end point of cardiovascular death/MI/stroke (HR 1.00, 95% CI, 0.89–1.12, *P*=0.99). The risk of cardiovascular death was similar between randomization arms (HR 1.03, 95% CI, 0.87–1.22, *P*=0.72). However, an increased risk of HHF was seen with saxagliptin (HR 1.27, 95% CI, 1.07–1.51, *P*=0.007).[11,29] Based on landmark analysis beginning at 6 and 12 months, the risk of HHF for patients randomized to saxagliptin was similar to placebo (6-month HR 1.11; 95% CI, 0.91–1.36; *P*=0.31; 12-month HR 1.09; 95% CI, 0.85–1.39; *P*=0.51), suggesting that the primary increase in HF risk occurred within the first 6 months of initiating saxagliptin. In comparison, our analysis demonstrated a numerical but nonsignificant decrease in the risk of cardiovascular death in patients with early or late DPP-IV inhibition with alogliptin. This was associated with a numeric but nonsignificant increase in HHF risk with early DPP-IV inhibition with alogliptin. The risk of HHF was similar between alogliptin and placebo after the 6-month landmark. Prior analysis of the EXAMINE trial demonstrated that the number of days from index ACS event to randomization was not associated with increased risk of adverse HF outcomes.[30] No increased risk of HF events was seen with early or late DPP-IV inhibition when examining the sensitive HF outcome that included initiation of loop diuretics. Regarding secondary cardioprotective therapies, in this study the use of ezetimibe was low; however, the results of IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)[31] were not available until after the EXAMINE trial was released. The absence of information from the IMPROVE-IT trial may have contributed to the low use of ezetimibe overall.

Limitations

Our study is post hoc and is subject to the inherent limitations of this type of analysis. Furthermore, this study may be limited by the reduction in statistical power to detect differences in events induced by a landmark analysis; however, there was a consistent absence of harm across a spectrum of end points. The increased number of events introduced by sensitive HF end point also enables greater confidence in the results of the landmark analysis. In addition, the 6 months following an ACS likely represents the highest risk period following an ACS, and focusing on the safety of DPP-IV inhibition during this time period is clinically important. The introduction of the landmark analysis at 6 months may cause imbalances in the treatment arms for the analysis of late events, and patients who had events in the early period were not excluded from analysis in the late period. However, after multivariable adjustment our results remained unchanged while several potential time points for the landmark analysis could have been considered, such as 30 days; 6 months was used as it would enable some comparison with other studies.[27] The EXAMINE trial enrolled stable patients 15 to 90 days after the index ACS, and does not necessarily represent a population of patients immediately post ACS; however, of the completed antihyperglycemic drug trials, the EXAMINE trial enrolled one of the highest numbers of cardiovascular risk patients.

Conclusion

Among a contemporary cohort of patients with T2DM, a large burden of vascular and HF events occur in the 6-month period following an ACS. Studies to identify patients at high risk of developing early or late cardiovascular events are required. Early and chronic DPP-IV inhibition with alogliptin was not associated with an increased risk of cardiovascular events including HF. Future trials evaluating the risks of cardiovascular outcome after initiating antihyperglycemic therapies in patients after recent vascular and HF events are needed.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Distribution of early cardiovascular events.

Event	Total Population (N = 5380)	Alogliptin (N = 2701)	Placebo (N = 2679)	HR [95% CI]
Early				
Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	5.3% (283/5380)	5.1% (139/2701)	5.4% (144/2679)	0.958 [0.759, 1.210]
Non-fatal MI	3.2% (170/5380)	3.2% (86/2701)	3.1% (84/2679)	1.017 [0.753, 1.374]
Non-fatal stroke	0.4% (23/5380)	0.4% (12/2701)	0.4% (11/2679)	1.081 [0.477, 2.450]
CV death	1.8% (97/5380)	1.6% (44/2701)	2.0% (53/2679)	0.824 [0.552, 1.229]
All cause mortality	2.2% (120/5380)	2.0% (53/2701)	2.5% (67/2679)	0.785 [0.547, 1.125]

Table S2. Distribution of late cardiovascular events.

Event	Total Population* (N = 4791)	Alogliptin* (N = 2403)	Placebo* (N = 2388)	HR [95% CI]
Late				
Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	8.1% (389/4791)	8.2% (198/2403)	8.0% (191/2388)	1.029 [0.843, 1.255]
Non-fatal MI	4.8% (232/4791)	5.2% (125/2403)	4.5% (107/2388)	1.158 [0.895, 1.499]
Non-fatal stroke	1.0% (46/4791)	0.8% (20/2403)	1.1% (26/2388)	0.761 [0.425, 1.362]
CV death	3.0% (145/4791)	2.8% (68/2403)	3.2% (77/2388)	0.875 [0.631, 1.212]
All cause mortality	4.3% (206/4791)	4.2% (100/2403)	4.4% (106/2388)	0.935 [0.711, 1.228]

Table S3. Distribution of early heart failure events.

Event	Total Population (N = 5380)	Alogliptin (N = 2701)	Placebo (N = 2679)	HR [95% CI]
Early				
Composite of all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, urgent revascularisation due to unstable angina, and hospital admission for heart failure	7.8% (420/5380)	7.6% (206/2701)	8.0% (214/2679)	0.959 [0.792, 1.161]
CV death or heart failure hospitalization	3.6% (191/5380)	3.6% (96/2701)	3.5% (95/2679)	1.007 [0.758, 1.337]
Heart failure hospitalization	1.9% (103/5380)	2.1% (57/2701)	1.7% (46/2679)	1.234 [0.837, 1.820]

Table S4. Distribution of late heart failure events.

Event	Total Population* (N = 4791)	Alogliptin* (N = 2403)	Placebo* (N = 2388)	HR [95% CI]
Late				
Composite of all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, urgent revascularisation due to unstable angina, and hospital admission for heart failure	11.6% (556/4791)	11.9% (285/2403)	11.3% (271/2388)	1.042 [0.883, 1.231]
CV death or heart failure hospitalization	5.1% (245/4791)	5.2% (124/2403)	5.1% (121/2388)	1.012 [0.788, 1.301]
Heart failure hospitalization	2.4% (114/4791)	2.5% (60/2403)	2.3% (54/2388)	1.097 [0.760, 1.585]

Table S5. On-treatment analysis of early cardiovascular events.

Event	Total Population (N = 4210)	Alogliptin (N = 2137)	Placebo (N = 2073)	HR [95% CI]
Early				
Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	2.8% (119/4210)	2.8% (59/2137)	2.9% (60/2073)	0.953 [0.665, 1.365]
Non-fatal MI	2.5% (107/4210)	2.6% (55/2137)	2.5% (52/2073)	1.027 [0.703, 1.500]
Non-fatal stroke	0.3% (13/4210)	0.2% (5/2137)	0.4% (8/2073)	0.605 [0.198, 1.849]
CV death	0.0% (0/4210)	0.0% (0/2137)	0.0% (0/2073)	1.000 [1.000, 1.000]
All cause mortality	0.0% (0/4210)	0.0% (0/2137)	0.0% (0/2073)	1.000 [1.000, 1.000]

Table S6. On-treatment analysis of late cardiovascular events.

Event	Total Population* (N = 3848)	Alogliptin* (N = 1952)	Placebo* (N = 1896)	HR [95% CI]
Late				
Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	4.3% (167/3848)	4.6% (89/1952)	4.1% (78/1896)	1.112 [0.820, 1.507]
Non-fatal MI	3.7% (144/3848)	3.9% (77/1952)	3.5% (67/1896)	1.118 [0.806, 1.551]
Non-fatal stroke	0.5% (21/3848)	0.5% (10/1952)	0.6% (11/1896)	0.885 [0.376, 2.083]
CV death	0.2% (6/3848)	0.2% (3/1952)	0.2% (3/1896)	0.964 [0.194, 4.774]
All cause mortality	0.2% (6/3848)	0.2% (3/1952)	0.2% (3/1896)	0.964 [0.194, 4.774]

Table S7. On-treatment analysis of early heart failure events.

Event	Total Population (N = 4210)	Alogliptin (N = 2137)	Placebo (N = 2073)	HR [95% CI]
Early				
Composite of all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, urgent revascularisation due to unstable angina, and hospital admission for heart failure	4.7% (199/4210)	4.6% (99/2137)	4.8% (100/2073)	0.962 [0.728, 1.270]
CV death or heart failure hospitalization	1.3% (55/4210)	1.4% (30/2137)	1.2% (25/2073)	1.166 [0.686, 1.983]
Heart failure hospitalization	1.3% (55/4210)	1.4% (30/2137)	1.2% (25/2073)	1.166 [0.686, 1.983]
CV death or heart failure hospitalization or initiation of loop diuretics	4.6% (192/4210)	4.9% (104/2137)	4.2% (88/2073)	1.147 [0.863, 1.523]
Sudden Cardiac Death	0.0% (0/4210)	0.0% (0/2137)	0.0% (0/2073)	1.000 [1.000, 1.000]

* Patients with follow-up time less than 180 days are excluded for late events analysis.

Table S8. On-treatment analysis of late heart failure events.

Event	Total Population* (N = 3848)	Alogliptin* (N = 1952)	Placebo* (N = 1896)	HR [95% CI]
Late				
Composite of all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, urgent revascularisation due to unstable angina, and hospital admission for heart failure	6.4% (247/3848)	6.6% (128/1952)	6.3% (119/1896)	1.046 [0.815, 1.343]
CV death or heart failure hospitalization	1.6% (62/3848)	1.7% (34/1952)	1.5% (28/1896)	1.179 [0.715, 1.944]
Heart failure hospitalization	1.5% (56/3848)	1.6% (31/1952)	1.3% (25/1896)	1.204 [0.711, 2.038]
CV death or heart failure hospitalization or initiation of loop diuretics	6.2% (240/3848)	6.5% (126/1952)	6.0% (114/1896)	1.069 [0.830, 1.377]
Sudden Cardiac Death	0.1% (2/3848)	0.1% (1/1952)	0.1% (1/1896)	0.981 [0.061, 15.683]

* Patients with follow-up time less than 180 days are excluded for late events analysis.

Table S9. Distribution of Early Cardiovascular Events.

Event	Total Population (N = 5380)	Alogliptin (N = 2701)	Placebo (N = 2679)	HR [95% CI]
Early				
Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	5.3% (283/5380)	5.1% (139/2701)	5.4% (144/2679)	0.968 [0.767, 1.222]
Non-fatal MI	3.2% (170/5380)	3.2% (86/2701)	3.1% (84/2679)	1.026 [0.759, 1.386]
Non-fatal stroke	0.4% (23/5380)	0.4% (12/2701)	0.4% (11/2679)	1.090 [0.481, 2.471]
CV death	1.8% (97/5380)	1.6% (44/2701)	2.0% (53/2679)	0.824 [0.552, 1.229]
All cause mortality	2.2% (120/5380)	2.0% (53/2701)	2.5% (67/2679)	0.786 [0.548, 1.128]

Table S10. Distribution of Late Cardiovascular Events.

Event	Total Population* (N = 4791)	Alogliptin* (N = 2403)	Placebo* (N = 2388)	HR [95% CI]
Late				
Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	8.1% (389/4791)	8.2% (198/2403)	8.0% (191/2388)	1.032 [0.846, 1.259]
Non-fatal MI	4.8% (232/4791)	5.2% (125/2403)	4.5% (107/2388)	1.166 [0.901, 1.510]
Non-fatal stroke	1.0% (46/4791)	0.8% (20/2403)	1.1% (26/2388)	0.767 [0.428, 1.374]
CV death	3.0% (145/4791)	2.8% (68/2403)	3.2% (77/2388)	0.875 [0.632, 1.213]
All cause mortality	4.3% (206/4791)	4.2% (100/2403)	4.4% (106/2388)	0.931 [0.708, 1.223]

Table S11. Distribution of Early Heart Failure Events.

Event	Total Population (N = 5380)	Alogliptin (N = 2701)	Placebo (N = 2679)	HR [95% CI]
Early				
Composite of all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, urgent revascularisation due to unstable angina, and hospital admission for heart failure	7.8% (420/5380)	7.6% (206/2701)	8.0% (214/2679)	0.971 [0.802, 1.176]
CV death or heart failure hospitalization	3.6% (191/5380)	3.6% (96/2701)	3.5% (95/2679)	1.025 [0.771, 1.362]
Heart failure hospitalization	1.9% (103/5380)	2.1% (57/2701)	1.7% (46/2679)	1.281 [0.866, 1.894]
CV death or heart failure hospitalization or initiation of loop diuretics	7.1% (384/5380)	7.2% (194/2701)	7.1% (190/2679)	1.026 [0.839, 1.253]
Sudden Cardiac Death	0.9% (50/5380)	0.7% (19/2701)	1.2% (31/2679)	0.610 [0.345, 1.080]

Table S12. Distribution of Late Heart Failure Events.

Event	Total Population* (N = 4791)	Alogliptin* (N = 2403)	Placebo* (N = 2388)	HR [95% CI]
Late				
Composite of all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, urgent revascularisation due to unstable angina, and hospital admission for heart failure	11.6% (556/4791)	11.9% (285/2403)	11.3% (271/2388)	1.043 [0.883, 1.232]
CV death or heart failure hospitalization	5.1% (245/4791)	5.2% (124/2403)	5.1% (121/2388)	1.015 [0.790, 1.304]
Heart failure hospitalization	2.4% (114/4791)	2.5% (60/2403)	2.3% (54/2388)	1.104 [0.764, 1.595]
CV death or heart failure hospitalization or initiation of loop diuretics	10.1% (482/4791)	10.2% (245/2403)	9.9% (237/2388)	1.020 [0.853, 1.220]
Sudden Cardiac Death	1.7% (82/4791)	1.7% (40/2403)	1.8% (42/2388)	0.937 [0.608, 1.446]