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Effect of Once-Weekly Exenatide in Patients With Type 2 Diabetes With and Without Heart Failure and Heart Failure-Related Outcomes: Insights From the EXSCEL Trial

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Abstract

Background: Once-weekly exenatide (EQW) had a neutral effect on hospitalization for heart failure (hHF) in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL), with no differential treatment effect on major adverse cardiac events (MACE) by baseline heart failure (HF) status. EQW's effects on secondary endpoints based on hHF status have not been reported. The objective was to explore the effects of EQW on secondary endpoints in patients with and without baseline HF and test the effects of EQW on recurrent hHF events.

Methods: The prespecified analysis of the randomized controlled EXSCEL trial, which enrolled patients with type 2 diabetes with and without additional cardiovascular disease, analyzed EQW effects on all-cause death, each MACE component, first hHF and repeat hHF by baseline HF status (regardless of ejection fraction). A subgroup analysis of the population stratified by preserved or reduced baseline ejection fraction was performed.

Results: Of 14,752 EXSCEL participants, 2389 (16.2%) had HF at baseline. Compared with those without HF at baseline, patients with preexisting HF were older, more likely to be male and White, and with a higher burden of other cardiovascular diseases. Overall, those assigned to EQW had a lower incidence of all-cause death (HR 0.86, 95%CI 0.77–0.97) and the composite outcome of all-cause death or hHF (HR 0.89, 95%CI 0.80–0.99). When stratified by presence or absence of baseline HF, there was no observed reduction in all-cause death with EQW with baseline HF (HR 1.05, 95%CI 0.85–1.29), while the risk of mortality was reduced with EQW in the no-HF group

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(HR 0.79, 95%CI 0.68–0.92) with an interaction p-value of 0.031. Reduction in all-cause death or hHF seen with EQW in patients without baseline HF (HR 0.81, 95%CI 0.71–0.93) was not seen in patients with baseline HF (HR 1.07, 95%CI 0.89–1.29) (interaction p=0.015). First plus recurrent hHF was reduced in the exenatide group versus placebo (HR 0.82, 95%CI 0.68–0.99; p=0.038).

Conclusions: In EXSCEL, the use of EQW in patients with or without HF was well tolerated, but benefits of EQW on reduction in all-cause death and first hospitalization for HF were attenuated in patients with baseline HF.

Trial Registration: Clinicaltrials.gov

Keywords

GLP-1R agonist; exenatide; diabetes; heart failure; outcomes

Diabetes and heart failure (HF) are frequent comorbid conditions that can complicate disease management and worsen quality of life and clinical outcomes.[1–2] As mandated by the US Food and Drug Administration, new medications for the treatment of type 2 diabetes (T2D) are required to demonstrate cardiovascular (CV) safety. Yet, the focus to date for the primary study endpoints in most pivotal CV outcomes trials has been on CV death, myocardial infarction, and stroke, with relegation of HF effects to secondary endpoints.[3,4] Novel glucose-lowering agents such as the glucagon-like peptide-1 receptor agonists (GLP-1 RAs) albiglutide, dulaglutide, liraglutide, and semaglutide,[5–8] and the sodium-glucose cotransporter-2 inhibitors canagliflozin, dapagliflozin, empagliflozin and canagliflozin,[9–12] have demonstrated improved outcomes across a broad range of major adverse cardiac events (MACE) in trials that aimed for glycemic equipoise. However, no significant effect on MACE was seen with dipeptidyl peptidase-4 (DPP-4) inhibitors[13–16] or with the GLP-1 RA exenatide and lixisenatide.[17,18]

Concerns around the possibility of HF-specific effects of incretin drugs arose following the observation of a 27% significantly increased risk of hospitalization for HF (hHF) with saxagliptin in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 trial[13] and a non-significant 19% increase with aloglipitin in the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study.[14,19] The observed risk does not appear to have a class effect based on more recent data from the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) and the Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: (CARMELINA) showing a neutral impact with sitagliptin/linagliptin.[15,16]

Despite positive effects seen with GLP-1 RAs on blood glucose and decreases in body weight, blood pressure, and lipid levels[18,20,21] benefits specifically for patients with HF have not been seen to date. On the contrary, concerns have been raised regarding the effect of GLP-1 RAs on the heart given the observed heart rate elevation, and small HF-specific studies found an either a lack of CV[22] benefit or increased risk of cardiac adverse events[23].

In the recent Exenatide Study of Cardiovascular Event Lowering (EXSCEL), a large pragmatic clinical trial that included patients with T2D, with and without additional CV disease,[18,24,25] exenatide once-weekly (EQW) had a neutral effect on time to first hHF, without evidence of a differential treatment effect on the primary endpoint of MACE by baseline HF status. In a prespecified analysis, the aim was to further explore the effects of EQW on secondary endpoints in patients with and without baseline HF and test the effects of EQW on recurrent hHF events.

METHODS

Requests to access the data for this study from qualified researchers trained in human subject confidentiality protocols may be submitted at dcri.org/data-sharing.

Population

Between June 2010 and September 2015, EXSCEL enrolled 14,752 patients at 687 sites in 35 countries. The design, baseline characteristics, and primary results of EXSCEL (including the CONSORT flow diagram for the trial) have been published.[18,24,25] In brief, the trial studied the effects of EQW at a dose of 2 mg compared to placebo. The study included adults with T2D (defined as a glycated hemoglobin [A_{1c}] of 6.5 to 10.0%) with the goal to enroll approximately 70% of participants with prior CV events including previous coronary, cerebrovascular, or peripheral vascular events or stenosis. Key exclusion criteria were a history of type 1 diabetes, two or more episodes of severe hypoglycemia during the preceding 12 months, and an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2. Race was self-reported. Presence or absence of clinical HF was captured upon enrolment into the trial. HF status at baseline was prospectively recorded by the clinician-investigator based on all available clinical data including patients' signs/symptoms and objective measures such as echocardiography and biomarker data (e.g., natriuretic peptide levels). A blinded, independent clinical events classification committee adjudicated all the components of the primary composite outcome and secondary outcomes including hHF. The definitions for these events are outlined in the Supplementary Appendix of the primary results publication.[18] All patients provided informed consent. Ethics committees at each participating site approved the protocol. The trial was conducted by the Duke Clinical Research Institute and the University of Oxford Diabetes Trials Unit in collaboration with industry sponsorship.

Statistical Analysis

The study population was stratified by baseline HF status. Baseline characteristics were summarized by counts and percentages for categorical variables and by medians with interquartile ranges for continuous variables. The treatment effects of EQW on the secondary endpoints of all-cause death, the individual components of the primary composite endpoint (CV death, myocardial infarction, and stroke), and hHF were analyzed. In a pre-specified analysis, a potentially different effect of EQW in patients with and without baseline HF was evaluated. To do so, a Cox regression analysis stratified by prior CV event with treatment, history of HF, and their interaction in the model was performed.

The relationship of EQW on hHF was analyzed as time-to-first event and recurrent hHF. Time to first hHF was analyzed using a Cox model with additional adjustment for age, sex, ethnicity, race, region, diabetes duration, diabetes therapy at baseline (any oral agent, insulin, DPP-4 inhibitor, or biguanide), prior coronary artery disease, prior cerebrovascular disease, prior peripheral arterial disease, prior myocardial infarction, prior HF, qualifying A_{1c}, baseline eGFR (mL/min/1.73 m^2), body mass index, cigarette smoking status, hypertension, hyperlipidemia/dyslipidemia, baseline systolic blood pressure, baseline diastolic blood pressure, baseline heart rate, baseline use of angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta-blockers, and aldosterone antagonists. For the recurrent hHF analysis, the pre-specified Andersen-Gill method within the framework of Cox proportional hazard regression, stratified by prior CV event with treatment group and baseline of HF as explanatory variables was used. Briefly, Andersen-Gill method uses the traditional Cox regression model, except after having the first event, the patient is not removed from the analysis and remains “at risk” for the subsequent events. The method estimates the common treatment effect for preventing any occurrence of the hHF.

All analyses were performed on the intention-to-treat population. Analyses were conducted with the use of SAS software, version 9.4 (SAS Institute Inc.).

RESULTS

Preexisting Heart Failure – Baseline Characteristics and Outcomes

In EXSCEL, the 2389 (16.2%) patients with known HF were randomized to EQW (N=1161, 7.9%) or placebo (N=1228, 8.3%). Compared with those without HF at baseline, patients with preexisting HF were older, more likely to be male and White, and with a higher burden of other CV diseases such as coronary artery disease and cerebrovascular disease (Table 1, Supplemental Table 1). Patients with HF had a greater body mass index and lower eGFR, and >85% of these patients had New York Heart Association (NYHA) class I or II symptoms. Use of oral glucose-lowering drugs was less common for patients with HF versus those without HF, whereas use of insulin therapy was more common. The breakdown of CV-specific drugs by presence or absence of HF is presented in Supplemental Table 2. In patients with HF, left ventricular ejection fraction (LVEF) was preserved (>55%) in 22% (516/2389), borderline (40–55%) in 24% (574/2389) or reduced in 13% (303/2389). In 42% (996/2389) of patients with HF, LVEF was not documented.

Over a median follow-up period of 3.2 years (interquartile range 2.2–4.4), 353 (14.8%) patients died in the HF group and 738 (6.0%) in the non-HF group. HF-related hospitalizations were more commonly encountered amongst patients with a baseline of HF (N=177, 7.4%) than patients without HF (N=273, 2.2%).

The effects of EQW on clinical outcomes, stratified by presence or absence of HF, are presented in Figure 1. Overall, those assigned to EQW had a lower incidence of all-cause death (HR 0.86, 95% CI 0.77–0.97) and the composite outcome of all-cause death or hHF (HR 0.89, 95% CI 0.80–0.99) (Figure 2, Supplemental Table 3 for breakdown by mode of death). No statistically significant change was observed in CV death (HR 0.88, 95% CI 0.76–1.02) and the composite outcome of CV death or hHF (HR 0.92, 95% CI 0.81–1.04).

When stratified by presence or absence of baseline HF, there was no observed change in all-cause death with exenatide in the group with baseline HF (HR 1.05, 95% CI 0.85–1.29), while the risk of mortality was reduced with EQW in the no HF group (HR 0.79, 95% CI 0.68–0.92) with an interaction p value of 0.031. Similarly, the reduction in the composite outcome of all-cause death or hHF seen with EQW in patients without baseline HF (HR 0.81, 95% CI 0.71–0.93) was not seen in patients with baseline HF (HR 1.07, 95% CI 0.89–1.29) (interaction p=0.015). The treatment effect of EQW in CV death (HR 1.03, 95% CI 0.80–1.31) versus non-CV death (HR 1.11, 95% CI 0.74–1.64) in patients with prior HF showed no interaction (p=0.756). For the remaining clinical endpoints, there was no evidence of a differential effect of EQW on clinical endpoints in those with vs. without baseline HF (all interaction p>0.1).

An LVEF-based subgroup analysis (<40% vs. ≥40%) was performed in patients with baseline HF and documented LVEF, which represents 9.4% of the total trial population (Supplemental Table 4). The incidence of primary and secondary outcomes during study follow-up appeared not different between LVEF subgroups.

Hospitalization for Heart Failure During Follow-up

In EXSCEL, patients who experienced a first hHF event during study follow-up tended to be older than patients without HF episodes, regardless of the study intervention that they received (Table 2). Further, patients with hHF were more commonly male, with a higher burden of comorbid CV disease, such as known HF (more than twice the prevalence at baseline), coronary artery disease, and cerebrovascular disease. Further, hHF was more common among patients with a longer duration of diabetes, higher body mass index, and worse renal function, again irrespective of treatment assignment (Table 2).

In total, 219 patients experienced at least one hHF in the exenatide arm and 231 in the placebo arm. Time to first adjudicated hHF event was not different in both treatment arms (HR 0.95, 95% CI 0.79–1.14; p=0.55). Similar results were observed in a multivariable-adjusted Cox proportional hazards regression analysis (HR 0.92, 95% CI 0.76–1.12; p=0.42). Due to recurrent hHF among patients, the total number of first plus recurrent hHF was more than 50% higher than first hHF (exenatide, N=351 vs. placebo, N=362). However, the risk for first plus recurrent hHF was lower in the EQW group compared with placebo (HR 0.82, 95% CI 0.68–0.99; p=0.038) (Supplemental Table 5). There was no interaction when comparing the treatment effect of EQW vs placebo on first plus recurrent hHF by baseline HF status (p=0.53). Among patients who experienced a hHF, the subsequent risk for MACE was not different between patients treated with exenatide or placebo (Supplemental Table 6).

DISCUSSION

New glucose-lowering drugs such as GLP-1 RAs hold promise to change the landscape of CV disease management in T2D.[7–12] Patients with HF and T2D are at the highest risk for poor CV outcomes,[4,26] with only few medical therapies targeting the cardiometabolic pathology. Initial concerns of an increased hHF risk with some glucose-lowering agents used to treat T2D (including DPP-4 inhibitors) were extended to GLP-1 RAs use in patients with

HF. In previously published analyses, there was no evident benefit for GLP-1 RAs with respect to hHF. In the analysis of EXSCEL, the largest GLP-1 RA trial reported to date, the use of EQW among patients with and without baseline HF was associated with no difference in clinical outcomes across most endpoints. The 14% risk reduction seen with EQW on all-cause death in the full study cohort and the 21% risk reduction seen in the subset of patients without baseline HF was not observed in patients with baseline HF. Further, when compared with placebo, EQW was associated with no difference in risk for time to first hHF event but an 18% lower risk for recurrent hHF during study follow-up.

Mounting evidence supports the CV safety and efficacy of GLP-1 RAs. In regard to HF, safety concerns were raised following the observation of an increased hHF risk with DPP-4 inhibitors. The risk of hHF was significantly increased with saxagliptin in SAVOR-TIMI 53[13] and with a non-significant trend in the same direction with aloglipitin in EXAMINE.[14,19] With respect to GLP-1 RAs, two small studies raised awareness of potential HF-specific safety concerns. The Effect of LIraglutide on Left VEntricular Function in Chronic Heart Failure Patients With and Without Type 2 Diabetes (LIVE) trial tested the efficacy of liraglutide in patients with chronic stable systolic HF and found no improvement in LVEF, with a statistical increase in serious cardiac events (combination of arrhythmic, coronary, death and HF events).[23] Further, the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) study examined the effects of liraglutide in patients with systolic HF and recent hHF, thus deemed to have advanced HF.[22] The authors found no benefit in clinical outcomes, with a non-significant trend toward higher rate of recurrent hHF. Compared with EXSCEL, LIVE (N=241) and FIGHT (N=300) were small, with limited follow-up, restricted to patients with systolic HF and not powered for clinical outcomes. However, the observed signals from these trials paired with the repeated observation of an increased heart rate with all GLP-1 RAs have been linked to worse outcomes in patients with systolic or diastolic HF,[27] and demands close evaluation of the risk for HF-related events in patients with and without HF.

Among the patients enrolled in EXSCEL, 16.2% (N=2,387) had a baseline of HF at enrollment, which is greater than the number of HF patients in any of the three other major GLP-1 RA trials (Harmony Outcomes[8] [N=1922, 20%]; Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [LEADER][6] [N=1305, 14%]; and Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes [SUSTAIN-6][7] [N=777, 23.6%]). EXSCEL patients with HF at baseline were older, had more comorbid CV conditions, and were at greater risk for adverse clinical outcomes during follow-up when compared to patients without HF. The beneficial effects of EQW on all-cause death seen in the overall cohort were not observed in the HF subgroup. Similarly, LEADER[6] found a reduced effect of liraglutide on the primary outcome (first occurrence of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) in patients with baseline HF, which reached statistical significance for heterogeneity for between-group differences (liraglutide vs. placebo). The interaction analysis in SUSTAIN-6 indicated a trend toward attenuation of the semaglutide effect in patients with baseline HF.[7] However, the recently presented Harmony Outcomes[8] indicated no such attenuation of GLP-1 RA effect in patients with baseline HF, if at all, the risk of patients with baseline HF was trending lower with albiglutide versus placebo (HR 0.70, 95%

CI 0.54–0.90 vs. HR 0.82, 95% CI 0.69–0.98; p=0.278). Despite some evidence for an attenuated effect, the lack of therapeutic effect of EQW or the class of GLP-1 RAs in patients with pre-existing HF remains speculative at this time and requires dedicated HF-specific clinical trials. The overall modest length of exposure to the study drug, particularly in EXSCEL, and modest medication adherence could have contributed to a weakened effect on patients with HF, who were at the highest risk of adverse clinical outcomes. Specifically, patients with preexisting HF had more advanced CV and non-CV comorbidities which were unlikely to be fully accounted for by statistical adjustment. Given the minimal evidence of heterogeneity, it also needs to be considered that the finding of attenuated exenatide effect on all-cause mortality in patients with HF could have been the result of chance. Finally, the exploratory analysis of LVEF subgroups restricted to a small subpopulation of the EXSCEL-HF trial did not appear to support differential outcomes in patients with HF and reduced or preserved LVEF.

Preclinical and clinical work supports the CV protective properties of GLP-1 RAs. In animal models, GLP-1 RAs were found to slow the development of HF.[28] In humans, there is evidence of cardiometabolic protection given sustained reduction in HbA_{1c}, blood pressure, weight loss,[29] and improved LVEF.[30] Additional cardioprotective properties of GLP-1 RAs might derive from the anti-inflammatory effects seen in small human studies.[31, 32] Ischemic HF events could be more favorably affected by GLP-1 RAs, given evidence of limited infarct size in preclinical and clinical myocardial infarction studies.[33–35] This hypothesis needs to be further explored in future studies, since HF etiology and serial LVEF measurements were not performed in EXSCEL.

Since HF is characterized by repeated hospitalizations, the analysis of all events is more likely to give a complete picture of treatment effect than the evaluation of the time to first event alone.[36] In the whole patient cohort, the non-significant trend toward fewer HF events in the EQW group strengthened further with the increased power in the prespecified first plus recurrent hHF analyses. Here EQW was associated with a significant reduction in the burden of HF rehospitalizations.

Limitations

Despite the size of EXSCEL and the formal adjudication of clinical outcome events, the study has several limitations. First, although this analysis was prespecified, it can be subject to unmeasured bias and no adjustments were made for multiple testing. However, given that the study populations were randomly assigned to study treatment, the HF and no-HF study groups were balanced between the treatment arms upon entry into the study. Second, baseline HF status was clinically defined by the treatment team and was not formally adjudicated. Functional assessment was limited to NYHA status and assessment of LVEF was missing in about 42% of the cases, so serial evaluation was not performed. Although the present findings are hypothesis-generating, the analysis offers the largest HF-specific analysis of patients treated with a GLP-1 RA.

Conclusion

In EXSCEL, the use of EQW in patients with or without HF was well tolerated, but benefits of EQW on reduction in all-cause death and first hospitalization for HF were attenuated in patients with baseline HF. EQW did not increase the risk for hHF, but on the contrary, EQW use was associated with a lower risk of recurrent hHF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CARMELINA	Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk
CV	cardiovascular
DPP-4	dipeptidyl peptidase-4
eGFR	estimated glomerular filtration rate
EQW	Once-weekly exenatide
EXAMINE	Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care
EXSCEL	Exenatide Study of Cardiovascular Event Lowering
FIGHT	Functional Impact of GLP-1 for Heart Failure Treatment
GLP-1 RA	glucagon-like peptide-1 receptor agonists

HF	heart failure
hHF	hospitalization for heart failure
LIVE	The Effect of LIraglutide on Left VEntricular Function in Chronic Heart Failure Patients With and Without Type 2 Dia
LVEF	left ventricular ejection fraction
MACE	major adverse cardiac events
NYHA	New York Heart Association
T2D	type 2 diabetes
TECOS	Trial Evaluating Cardiovascular Outcomes with Sitagliptin
SAVOR TIMI	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction 53 trial

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Clinical Perspective:

What is new?

- In EXSCEL, the largest GLP-1 RA trial reported to date, the use of EQW among patients with and without baseline HF was associated with no difference in clinical outcomes across most endpoints.
- The 14% risk reduction seen with EQW on all-cause death in the full study cohort and the 11% risk reduction seen in the subset of patients without baseline HF was not observed in patients with baseline HF.
- Compared with placebo, EQW was associated with no difference in risk for time to first HF hospitalization event but 18% lower risk for first plus recurrent HF hospitalization during study follow-up.

What are the clinical implications?

- In EXSCEL, in the overall analysis the use of EQW was well tolerated with no difference in first HF hospitalization, but benefits of EQW on reduction in all-cause death and first hospitalization for HF were attenuated in patients with baseline HF.
- EQW use was associated with a lower risk of first plus recurrent HF hospitalizations.

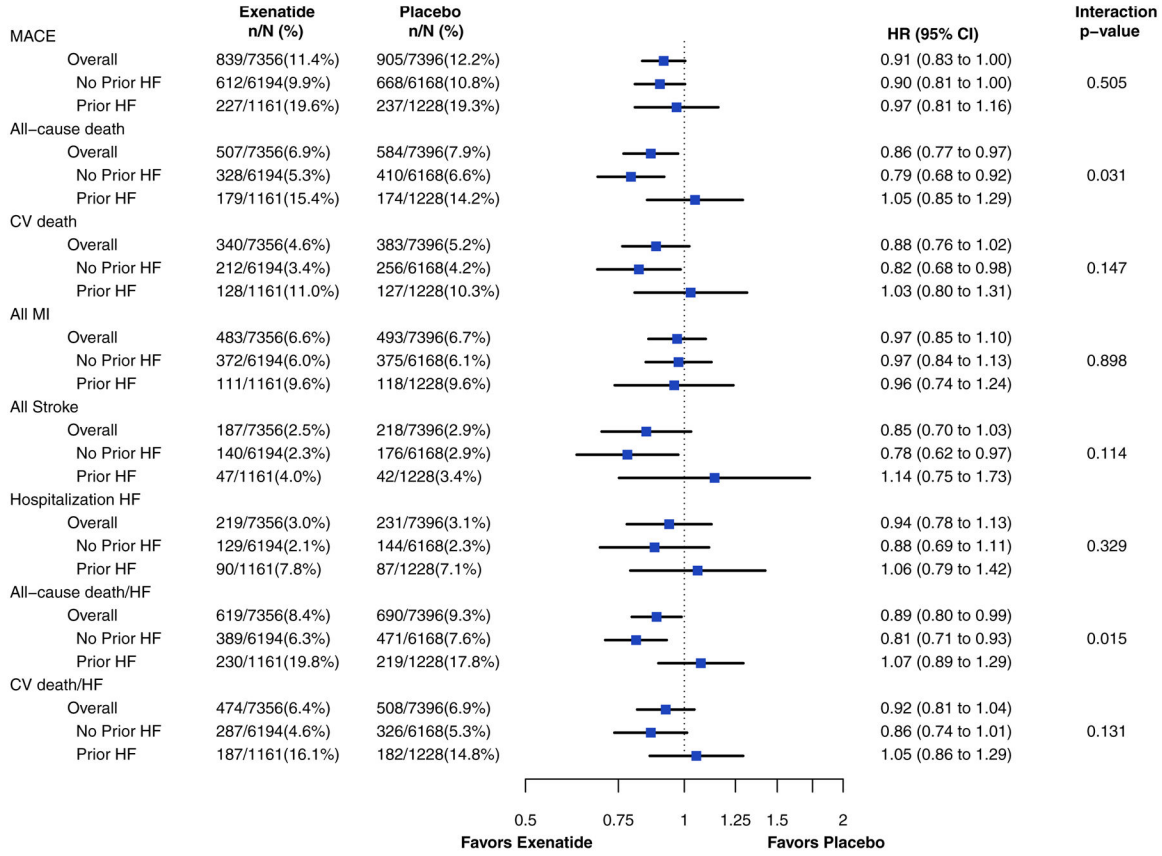

Figure 1.

Forest plot for clinical outcomes stratified by treatment group and baseline of heart failure. Abbreviations: MACE, major adverse cardiac event; CV, cardiovascular; HF, heart failure; MI, myocardial infarction.

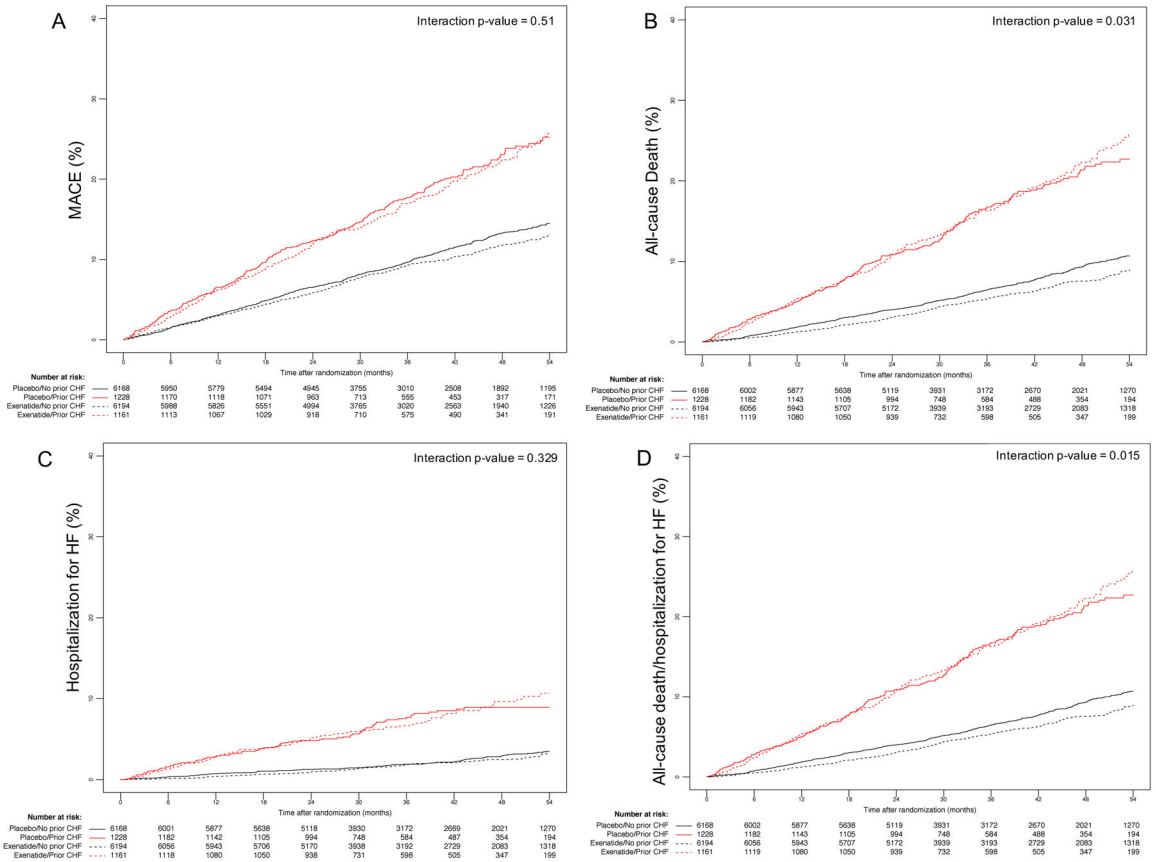

Figure 2.

Kaplan-Meier event curves for (A) MACE, (B) all-cause death, (C) time to first HF hospitalization and (D) all-cause death and time to first HF hospitalization.

Abbreviations: MACE, major adverse cardiac event; HF, heart failure.

Table 1.

Baseline characteristics of patients with and without heart failure

	History of Heart Failure		
	Yes N=2389	**No N=12,362**	**P-value**
Age at randomization (years) *			<0.001
Median (Q1, Q3)	64.0 (58.0, 69.0)	62.0 (55.0, 68.0)	
Sex			0.007
Male	1540 / 2389 (64.5%)	7609 / 12362 (61.6%)	
Race			<0.001
White	2120 / 2389 (88.7%)	9055 / 12357 (73.3%)	
Black	83 / 2389 (3.5%)	795 / 12357 (6.4%)	
Asian	79 / 2389 (3.3%)	1373 / 12357 (11.1%)	
Indian (American) or Alaska Native	5 / 2389 (0.2%)	68 / 12357 (0.6%)	
Native Hawaiian or Other Pacific Islander	4 / 2389 (0.2%)	31 / 12357 (0.3%)	
Hispanic	98 / 2389 (4.1%)	1035 / 12357 (8.4%)	
Region			<0.001
Europe	1666 / 2389 (69.7%)	5122 / 12362 (41.4%)	
North America	403 / 2389 (16.9%)	3305 / 12362 (26.7%)	
Latin America	243 / 2389 (10.2%)	2483 / 12362 (20.1%)	
Asia Pacific	77 / 2389 (3.2%)	1452 / 12362 (11.7%)	
Prior CV event at randomization			<0.001
Yes	2067 / 2389 (86.5%)	8714 / 12362 (70.5%)	
No	322 / 2389 (13.5%)	3648 / 12362 (29.5%)	
Coronary artery disease	1733 / 2389 (72.5%)	6060 / 12362 (49.0%)	<0.001
Cerebrovascular disease	500 / 2389 (20.9%)	2009 / 12360 (16.3%)	<0.001
Peripheral arterial disease	425 / 2389 (17.8%)	2375 / 12361 (19.2%)	0.104
Prior MI	1258 / 2389 (52.7%)	3420 / 12362 (27.7%)	<0.001
NYHA class			
I	738 / 2387 (30.9%)	-	
II	1333 / 2387 (55.8%)	-	
III	303 / 2387 (12.7%)	-	

	History of Heart Failure		
	Yes N=2389	**No N=12,362**	**P-value**
IV	13 / 2387 (0.5%)	-	
Most recent assessment of left ventricular function (ejection fraction)			
Normal (>55%)	516 / 2389 (21.6%)	2409 / 12362 (19.5%)	
Mild Dysfunction (40–55%)	574 / 2389 (24.0%)	924 / 12362 (7.5%)	
Moderate Dysfunction (25–39%)	247 / 2389 (10.3%)	141 / 12362 (1.1%)	
Severe Dysfunction (<25%)	56 / 2389 (2.3%)	25 / 12362 (0.2%)	
Unknown	996 / 2389 (41.7%)	8863 / 12362 (71.7%)	
Duration of type 2 diabetes (years)			0.051
Median (Q1, Q3)	12.0 (7.0, 18.0)	12.0 (7.0, 18.0)	
Antihyperglycemic agents therapy			
None	25 / 2389 (1.0%)	203 / 12362 (1.6%)	0.031
Oral agents use	1904 / 2389 (79.7%)	10587 / 12362 (85.6%)	<0.001
Insulin use	1222 / 2389 (51.2%)	5613 / 12362 (45.4%)	<0.001
DPP-4 inhibitor therapy	280 / 2389 (11.7%)	1923 / 12362 (15.6%)	<0.001
Biguanides	1681 / 2389 (70.4%)	9614 / 12362 (77.8%)	<0.001
SGLT-2 inhibitors[≠]	4/1334 (0.3%)	73/7205 (1.0%)	0.011
A_{1c} (%)			<0.001
Median (Q1, Q3)	8.1 (7.4, 9.0)	8.0 (7.3, 8.8)	
Body mass index (kg/m^2)			<0.001
Median (Q1, Q3)	32.9 (29.3, 37.4)	31.6 (28.1, 35.9)	
eGFR (mL/min/1.73 m^2) [**]			<0.001
Median (Q1, Q3)	70.4 (56.6, 88.2)	77.2 (62.4, 92.9)	

Total cohort of 14,752. One patient's history of heart failure status was missing.

[*] Age = ((date of randomization - date of birth) + 1) / 365.25 rounded down to the nearest whole year.

[≠] Information regarding SGLT-2 inhibitor use and 'other antihyperglycemic agent' use was added to the electronic case report form on May 9, 2013.

[**] MDRD formula was used to calculate the eGFR. Site-reported values are presented in the table.

A_{1C}, glycated hemoglobin; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; NYHA, New York Heart Association; Q1, Q3, interquartile range; SGLT-2, sodium-glucose co-transporter 2.

Table 2.

Baseline characteristics by incidence of first heart failure event requiring hospitalization and treatment

	Heart Failure Event Requiring Hospitalization		No Heart Failure Events	
	Exenatide N=219	**Placebo N=231**	**Exenatide N=7137**	**Placebo N=7165**
Age at randomization (years) *				
Median (Q1, Q3)	66.0 (9.3)	65.4 (8.3)	61.7 (9.4)	61.8 (9.4)
Sex				
Male	155 / 219 (70.8%)	164 / 231 (71.0%)	4407 / 7137 (61.7%)	4423 / 7165 (61.7%)
Ethnicity				
White	190 / 219 (86.8%)	193 / 231 (83.5%)	5364 / 7135 (75.2%)	5428 / 7162 (75.8%)
Black	15 / 219 (6.8%)	20 / 231 (8.7%)	427 / 7135 (6.0%)	416 / 7162 (5.8%)
Asian	4 / 219 (1.8%)	6 / 231 (2.6%)	721 / 7135 (10.1%)	721 / 7162 (10.1%)
Indian (American) or Alaska Native	0 / 219 (0.0%)	2 / 231 (0.9%)	38 / 7135 (0.5%)	33 / 7162 (0.5%)
Native Hawaiian or Other Pacific Islander	0 / 219 (0.0%)	0 / 231 (0.0%)	18 / 7135 (0.3%)	17 / 7162 (0.2%)
Hispanic	10 / 219 (4.6%)	10 / 231 (4.3%)	567 / 7135 (7.9%)	547 / 7162 (7.6%)
Region				
Europe	84 / 219 (38.4%)	99 / 231 (42.9%)	3305 / 7137 (46.3%)	3300 / 7165 (46.1%)
North America	112 / 219 (51.1%)	111 / 231 (48.1%)	1722 / 7137 (24.1%)	1763 / 7165 (24.6%)
Latin America	12 / 219 (5.5%)	12 / 231 (5.2%)	1352 / 7137 (18.9%)	1351 / 7165 (18.9%)
Asia Pacific	11 / 219 (5.0%)	9 / 231 (3.9%)	758 / 7137 (10.6%)	751 / 7165 (10.5%)
Coronary artery disease	172 / 219 (78.5%)	169 / 231 (73.2%)	3726 / 7137 (52.2%)	3727 / 7165 (52.0%)
Cerebrovascular disease	52 / 219 (23.7%)	52 / 231 (22.5%)	1181 / 7135 (16.6%)	1224 / 7165 (17.1%)
Peripheral arterial disease	41 / 219 (18.7%)	61 / 231 (26.4%)	1359 / 7136 (19.0%)	1339 / 7165 (18.7%)
Prior MI	112 / 219 (51.1%)	110 / 231 (47.6%)	2236 / 7137 (31.3%)	2221 / 7165 (31.0%)
NYHA class				
I	21 / 89 (23.6%)	21 / 87 (24.1%)	344 / 1071 (32.1%)	352 / 1140 (30.9%)
II	42 / 89 (47.2%)	53 / 87 (60.9%)	586 / 1071 (54.7%)	652 / 1140 (57.2%)
III	24 / 89 (27.0%)	10 / 87 (11.5%)	138 / 1071 (12.9%)	131 / 1140 (11.5%)
IV	2 / 89 (2.2%)	3 / 87 (3.4%)	3 / 1071 (0.3%)	5 / 1140 (0.4%)
Most recent assessment of left ventricular function (ejection fraction)				
Normal (>55%)	37 / 219 (16.9%)	51 / 231 (22.1%)	1410 / 7137 (19.8%)	1427 / 7165 (19.9%)

	Heart Failure Event Requiring Hospitalization		No Heart Failure Events	
	Exenatide N=219	**Placebo N=231**	**Exenatide N=7137**	**Placebo N=7165**
Mild Dysfunction (40–55%)	37 / 219 (16.9%)	48 / 231 (20.8%)	706 / 7137 (9.9%)	707 / 7165 (9.9%)
Moderate Dysfunction (25–39%)	34 / 219 (15.5%)	18 / 231 (7.8%)	176 / 7137 (2.5%)	160 / 7165 (2.2%)
Severe Dysfunction (<25%)	15 / 219 (6.8%)	9 / 231 (3.9%)	27 / 7137 (0.4%)	30 / 7165 (0.4%)
Unknown	96 / 219 (43.8%)	105 / 231 (45.5%)	4818 / 7137 (67.5%)	4841 / 7165 (67.6%)
Duration of type 2 diabetes (years)				
Median (Q1, Q3)	14.0 (8.0, 21.0)	15.0 (9.0, 22.0)	12.0 (7.0, 17.0)	12.0 (7.0, 18.0)
Antihyperglycemic therapy				
None	3 / 219 (1.4%)	4 / 231 (1.7%)	104 / 7137 (1.5%)	117 / 7165 (1.6%)
Oral agents use	148 / 219 (67.6%)	165 / 231 (71.4%)	6065 / 7137 (85.0%)	6113 / 7165 (85.3%)
Insulin use	140 / 219 (63.9%)	152 / 231 (65.8%)	3257 / 7137 (45.6%)	3287 / 7165 (45.9%)
DPP-4 inhibitor therapy	27 / 219 (12.3%)	24 / 231 (10.4%)	1091 / 7137 (15.3%)	1061 / 7165 (14.8%)
Biguanides	125 / 219 (57.1%)	138 / 231 (59.7%)	5493 / 7137 (77.0%)	5539 / 7165 (77.3%)
Insulin use, alone or in combination	140 / 219 (63.9%)	152 / 231 (65.8%)	3257 / 7137 (45.6%)	3287 / 7165 (45.9%)
A_{1c} (%)				
Median (Q1, Q3)	62.8 (57.4, 73.8)	65.0 (56.6, 73.8)	63.9 (56.3, 73.8)	63.9 (56.3, 73.8)
Body mass index (kg/m^2)				
Median (Q1, Q3)	34.6 (30.7, 39.4)	35.2 (31.0, 40.9)	31.8 (28.1, 36.1)	31.6 (28.2, 36.0)
eGFR group (mL/min/1.73 m^2)**				
eGFR ≥60	122 / 216 (56.5%)	142 / 231 (61.5%)	5647 / 7118 (79.3%)	5603 / 7140 (78.5%)
eGFR <60	94 / 216 (43.5%)	89 / 231 (38.5%)	1471 / 7118 (20.7%)	1537 / 7140 (21.5%)

*Age = ((date of randomization - date of birth) + 1) / 365.25 rounded down to the nearest whole year.

**MDRD formula was used to calculate the eGFR. Site reported values are presented in the table.

A_{1C}, glycated hemoglobin; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; NYHA, New York Heart Association.