Circulation

ORIGINAL RESEARCH ARTICLE

Linagliptin Effects on Heart Failure and Related Outcomes in Individuals With Type 2 Diabetes Mellitus at High Cardiovascular and Renal Risk in CARMELINA

Editorial, see p 362

Darren K. McGuire, MD, MHSc
John H. Alexander, MD, MHSc
Odd Erik Johansen, MD, PhD
Vlado Perkovic, MBBS, PhD
Julio Rosenstock, MD
Mark E. Cooper, MBBS, PhD
Christoph Wanner, MD
Steven E. Kahn, MB, ChB
Robert D. Toto, MD
Bernard Zinman, MD
David Baanstra, MSc, MBA
Egon Pfarr, MSc
Sven Schnaidt, MSc
Thomas Meinicke, MD
Jyothis T. George MD, PhD
Maximilian von Eynatten, MD
Nikolaus Marx, MD
On behalf of the CARMELINA Investigators

BACKGROUND: Individuals with type 2 diabetes mellitus are at increased risk for heart failure (HF), particularly those with coexisting atherosclerotic cardiovascular disease and/or kidney disease. Some but not all dipeptidyl peptidase-4 inhibitors have been associated with increased HF risk. We performed secondary analyses of HF and related outcomes with the dipeptidyl peptidase-4 inhibitor linagliptin versus placebo in CARMELINA (The Cardiovascular and Renal Microvascular Outcome Study With Linagliptin), a cardiovascular outcomes trial that enrolled participants with type 2 diabetes mellitus and atherosclerotic cardiovascular disease and/or kidney disease.

METHODS: Participants in 27 countries with type 2 diabetes mellitus and concomitant atherosclerotic cardiovascular disease and/or kidney disease were randomized 1:1 to receive once daily oral linagliptin 5 mg or placebo, on top of standard of care. All hospitalization for HF (hHF), cardiovascular outcomes, and deaths were prospectively captured and centrally adjudicated. In prespecified and post hoc analyses of HF and related events, Cox proportional hazards models adjusting for region and baseline history of HF were used. Recurrent hHF events were analyzed using a negative binomial model. In a subset of participants with left ventricular ejection fraction captured within the year before randomization, HF-related outcomes were assessed in subgroups stratified by left ventricular ejection fraction > or ≤50%.

RESULTS: CARMELINA enrolled 6979 participants (mean age, 65.9 years; estimated glomerular filtration rate, mL/min per 1.73m^2; hemoglobin A1c, 8.0%; 62.9% men; diabetes mellitus duration, 14.8 years), including 1873 (26.8%) with a history of HF at baseline. Median follow-up was 2.2 years. Linagliptin versus placebo did not affect the incidence of hHF (209/3494 [6.0%] versus 226/3485 [6.5%], respectively; hazard ratio [HR], 0.90; 95% CI, 0.74–1.08), the composite of cardiovascular death/hHF (HR, 0.94; 95% CI, 0.82–1.08), or risk for recurrent hHF events (326 versus 359 events, respectively; rate ratio, 0.94; 95% CI, 0.75–1.20). There was no heterogeneity of linagliptin effects on hHF by history of HF at baseline, baseline estimated glomerular filtration rate or urine albumin-creatinine ratio, or prerandomization left ventricular ejection fraction.

CONCLUSIONS: In a large, international cardiovascular outcome trial in participants with type 2 diabetes mellitus and concomitant atherosclerotic cardiovascular disease and/or kidney disease, linagliptin did not affect the risk of hHF or other selected HF-related outcomes, including among participants with and without a history of HF, across the spectrum of kidney disease, and independent of previous left ventricular ejection fraction.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01897532.

Key Words: cardiovascular disease ■ chronic kidney diseases ■ heart failure ■ type 2 diabetes mellitus

Sources of Funding, see page 360

https://www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- In patients with type 2 diabetes mellitus and concomitant atherosclerotic vascular disease and/or diabetic kidney disease, the antihyperglycemic medication linagliptin did not affect risk for heart failure hospitalization or other associated heart failure–related complications.
- These findings were consistent across a group of individual and composite outcomes, most of which we prespecified, across sensitivity analyses, and across numerous subgroup analyses, underscoring the robustness of the observations.

What Are the Clinical Implications?

- In a patient population at very high risk for heart failure and its complications, linagliptin can be used without increasing the risk for hospitalization for heart failure.
- Within the class of dipeptidyl peptidase-4 inhibitors used for the treatment of hyperglycemia in type 2 diabetes mellitus, with cautions and warnings about an increased risk for heart failure for some but not all members of the class, these data provide robust assurance that linagliptin does not increase heart failure risk.

Type 2 diabetes mellitus (T2DM) is commonly complicated by atherosclerotic cardiovascular disease (ASCVD) and/or chronic kidney disease,[1,2] and is also associated with an increased risk of hospitalization for heart failure (hHF) and heart failure (HF)–related outcomes.[3–5] The increased risk for hHF is particularly strong in people with coexisting chronic kidney disease,[6,7] or with pre-existing HF.[4,5] Since 2008, evaluation of the cardiovascular safety of new glucose-lowering medications for T2DM has been required by international regulatory agencies.[8,9] To date, results from 3 cardiovascular outcome trials (CVOTs) of dipeptidyl peptidase-4 (DPP-4) inhibitors have consistently demonstrated cardiovascular safety with regard to ASCVD outcomes, but none has demonstrated incremental cardiovascular efficacy.[10–12] Across these trials, there has been heterogeneity with regard to the effects of the 3 DPP-4 inhibitors on the risk of hHF, ranging from no effect with sitagliptin,[3] numeric imbalance that was not statistically significant with alogliptin,[13] and statistically significant increased risk with saxagliptin.[14] In a pooled analysis including data from the 3 pivotal CVOTs with saxagliptin, alogliptin, and sitagliptin, the overall hHF risk was not significantly different (hazard ratio [HR], 1.14; 95% CI, 0.97–1.34), but because of heterogeneity across the trials, a meta-analytic approach to this matter is of uncertain validity.[3]

CARMELINA (The Cardiovascular and Renal Microvascular Outcome Study With Linagliptin) was designed to evaluate the cardiovascular safety and kidney outcomes of linagliptin, a highly selective DPP-4 inhibitor with minimal renal excretion,[15] in people with T2DM at high cardiovascular and renal risk.[16] The overall trial results revealed safety but not incremental efficacy of linagliptin with respect to the primary composite outcome of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke as well as for all-cause mortality,[17] in line with observations from 3 other DPP-4 inhibitor CVOTs.[10–12] The primary analysis for CARMELINA revealed no difference in risk for hHF with linagliptin. Here, we comprehensively explore the impact of linagliptin on hHF and associated clinical outcomes using a statistical analysis plan specific to HF-related outcomes, with most analyses being prespecified, in the overall study population and in key participant subgroups. These analyses include assessments of recurrent hHF events in the overall cohort and of outcomes by baseline history of HF, chronic kidney disease categories, and the subset of participants with such information available, by left ventricular ejection fraction (LVEF).

METHODS

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.

Study Oversight

The oversight and conduct of CARMELINA has been described previously.[16] The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and was approved by local authorities. An independent ethics committee or institutional review board approved the clinical protocol for each participating center. All individuals provided written informed consent before entering the trial.

Study Design

The CARMELINA design has previously been described.[16] In brief, this was a randomized, double-blind, placebo-controlled clinical trial conducted at 605 centers in 27 countries, designed to continue until at least 611 participants had an adjudication-confirmed primary outcome event. Adults with T2DM, hemoglobin A1c 6.5% to 10.0%, at high cardiovascular risk were eligible for inclusion. High risk was defined as (1) prevalent ASCVD with micro- or macroalbuminuria, defined as urinary albumin:creatinine ratio >30 mg/g or equivalent; or (2) impaired kidney function (estimated glomerular filtration rate [eGFR] 45–75 mL/min per 1.73m^2 and urinary albumin:creatinine ratio >200 mg/g or equivalent; or eGFR 15–45 mL/min/1.73m^2 regardless of urinary albumin:creatinine ratio). Established ASCVD eligibility criteria included history of myocardial infarction, coronary artery disease, stroke, carotid artery disease, or peripheral artery disease. Participants with end-stage kidney disease, defined as

eGFR<15 mL/min/1.73m^2 or requiring maintenance dialysis, were excluded, as were those who, before providing informed consent at screening, had been treated ≥7 consecutive days with a glucagon-like protein 1 receptor agonist, other DPP-4 inhibitors, or sodium glucose cotransporter 2 inhibitors.

Study Procedures

Eligible individuals were randomized 1:1 to once-daily double-blind oral linagliptin 5 mg or matching placebo. After randomization, participants returned for study visits after 12 weeks and then every 24 weeks until study end. A final follow-up visit was scheduled 30 days after the end of treatment. In an attempt to maintain glycemic equipoise between the groups, investigators were encouraged throughout the trial to monitor and use additional medication for glycemic control (except DPP-4 inhibitors, glucagon-like protein 1 receptor agonists, and sodium glucose cotransporter 2 inhibitors) according to regional standards of care, independent of study treatment assignment that remained blinded. Treatment of other cardiovascular risk factors was encouraged in accordance with applicable guidelines and current standards of care. Participants who prematurely discontinued study medication were followed for ascertainment of cardiovascular and key secondary kidney outcome events, and attempts were made to collect vital status information on every randomized patient at study completion, in compliance with local laws and regulations.

Outcomes

Definitions of the major clinical outcomes in the CARMELINA trial have been published.[16] All cardiovascular outcome events, including hHF, were prospectively captured and centrally adjudicated by an independent Clinical Events Committee masked to treatment assignment. The primary outcome was defined as the time to first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (3-point major adverse cardiovascular event). Other HF-related outcomes prespecified in the statistical analysis plan included hHF, the composite outcomes of hHF or cardiovascular death and hHF or all-cause death, and investigator-reported HF. Post hoc analyses included first plus recurrent hHF, the composite of investigator-reported adverse event of HF and hHF, initiation of loop diuretics, and the composite of hHF and initiation of loop diuretics. Prespecified subgroup analyses were performed by baseline characteristics, including the presence/absence of a history of HF, by baseline eGFR, and urinary albumin:creatinine ratio status; and by pretrial LVEF. In addition to demographic, clinical, and laboratory defined subgroups, we predefined an analysis of hHF by LVEF at baseline for those participants with an LVEF assessment available within the year before enrollment.

Hospitalization for HF was defined in accord with contemporary regulatory guidance[18] as an event requiring inpatient admission or a ≥12-hour stay in the emergency department as a result of clinical manifestations of new or worsening HF. These included dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, rales, jugular venous distension, third heart sound or gallop rhythm, and/or radiological evidence of HF. An additional criterion was the need for added or increased therapy that included (1) initiation or up-titration of diuretics, inotropes, and/or vasodilator therapy or (2) initiation of mechanical or surgical therapy, such as mechanical circulatory support, heart transplantation, or ventricular pacing to improve cardiac function, and/or (3) use of ultrafiltration, hemofiltration, or dialysis directed at the treatment of HF. Investigator-reported HF events were identified based on adverse event reporting using the Medical Dictionary for Regulatory Activities (MedDRA) narrow standardized MedDRA query for "cardiac failure" (Table I in the online-only Data Supplement). Safety was assessed based on reported adverse events coded using MedDRA version 20.1.

Statistical Analysis

Time-to-event outcomes were analyzed using Cox proportional hazards regression models, with randomized treatment and geographical region as factors; hHF and hHF or cardiovascular death analyses additionally included a factor for baseline history of HF. Censoring was applied the day a participant was last known to be free of the specific outcome event. To account for potential competing risks, the main composite HF outcomes incorporated either cardiovascular or all-cause mortality as part of a composite outcome. Analyses of other, nonfatal HF-related outcomes were planned with the assumption of a neutral effect of linagliptin on overall mortality, and therefore did not account for the competing risk of death. All analyses were performed using the intention-to-treat principle, modified to exclude randomized participants who did not take at least 1 dose of study medication (treated set). In addition, for the key outcome of hHF, prespecified sensitivity analyses were also conducted for participants with a minimum treatment duration of 30 days (on-treatment set), and by censoring at day 0 (treated set + 0) and day 30 (treated set + 30) after the last dose of study drug taken, respectively. For analysis of first plus recurrent hHF events, the effect estimate (rate ratio) was derived from a negative binomial model.

Subgroups were prespecified, and a formal test of heterogeneity of the treatment effect among subgroups was performed for each group. A 2-sided $P<0.05$ was considered significant for all analyses with no adjustments made for multiple testing. Iteratively measured continuous parameters were analyzed using mixed-effect models for repeated measures, and overall safety assessments were conducted using descriptive statistics for adverse events. Analyses were conducted with SAS version 9.4 (SAS Institute; Cary, NC).

RESULTS

Baseline Characteristics and Effects of Treatment on Cardiovascular Risk Factors

The cohort comprised 6991 participants randomized between August 2013 and August 2016, of whom 6979 received at least 1 dose of study drug and are included in the present analyses. Vital status was available for 99.7% of participants at study completion (linagliptin, 99.8%; placebo, 99.6%).

Baseline clinical characteristics were balanced between treatment arms, with participants having longstanding diabetes mellitus and 26.8% having a history of HF at baseline (Table 1). Further, they had relatively

Table 1. Baseline Characteristics of Participants in CARMELINA With or Without a History of Heart Failure

Characteristic	Participants With HF at Baseline		Participants Without HF at Baseline		Total CARMELINA Population
	Linagliptin	Placebo	Linagliptin	Placebo	
N (%)	952 (100)	921 (100)	2542 (100)	2564 (100)	6979 (100)
Age, y	66.5 (8.64)	65.8 (8.95)	65.9 (9.2)	65.6 (9.2)	65.9 (9.10)
Male, n (%)	561 (58.9)	581 (63.1)	1587 (62.4)	1661 (64.8)	4390 (62.9)
Race, n (%)					
White	845 (88.8)	813 (88.3)	1982 (78.0)	1956 (76.3)	5596 (80.2)
Asian	38 (4.0)	26 (2.8)	269 (10.6)	307 (12.0)	640 (9.2)
Black/African American	43 (4.5)	57 (6.2)	151 (5.9)	160 (6.2)	411 (5.9)
Other*	26 (2.7)	25 (2.7)	140 (5.5)	141 (5.5)	332 (4.8)
Region, n (%)					
Europe (including South Africa)	589 (61.9)	572 (62.1)	884 (34.8)	889 (34.7)	2934 (42.0)
Latin America	187 (19.6)	192 (20.8)	969 (38.1)	962 (37.5)	2310 (33.1)
North America	142 (14.9)	136 (14.8)	451 (17.7)	451 (17.6)	1180 (16.9)
Asia	34 (3.6)	21 (2.3)	238 (9.4)	262 (10.2)	555 (8.0)
Smoking status, n (%)					
Never smoker	553 (58.1)	539 (58.5)	1344 (52.9)	1317 (51.4)	3753 (53.8)
Ex-smoker	310 (32.6)	300 (32.6)	921 (36.2)	976 (38.1)	2507 (35.9)
Current smoker	88 (9.2)	81 (8.8)	274 (10.8)	269 (10.5)	712 (10.2)
Missing	1 (0.1)	1 (0.1)	3 (0.1)	2 (0.1)	7 (0.1)
History of heart failure, n (%)	952 (100)	921 (100)	0 (0)	0 (0)	1873 (26.8)
Ischemic heart disease, n (%)	745 (78.3)	760 (82.5)	1284 (50.5)	1292 (50.4)	4081 (58.5)
History of hypertension, n (%)	884 (92.9)	855 (92.8)	2287 (90.0)	2323 (90.6)	6349 (91.0)
Atrial fibrillation, n (%)	171 (18.0)	171 (18.6)	148 (5.8)	183 (7.1)	673 (9.6)
eGFR (MDRD), mL/min/1.73 m^2	55.8 (24.3)	55.1 (24.7)	54.2 (25.4)	54.3 (25.0)	54.6 (25.0)
eGFR (MDRD), n (%)					
≥60 mL/min/1.73 m^2	367 (38.6)	367 (39.8)	927 (36.5)	970 (37.8)	2631 (37.7)
≥45 to <60 mL/min/1.73 m^2	208 (21.8)	166 (18.0)	482 (19.0)	492 (19.2)	1348 (19.3)
≥30 to <45 mL/min/1.73 m^2	263 (27.6)	249 (27.0)	731 (28.8)	695 (27.1)	1938 (27.8)
<30 mL/min/1.73 m^2	114 (12.0)	139 (15.1)	402 (15.8)	407 (15.9)	1062 (15.2)
UACR, mg/g, median (25th–75th percentile)	139 (36–589)	158 (46–727)	173 (47–753)	163 (43–758)	162 (44–728)
UACR, n (%)†					
<30 mg/g	215 (22.6)	184 (20.0)	481 (18.9)	512 (20.0)	1392 (19.9)
30–300 mg/g	397 (41.7)	389 (42.2)	1066 (41.9)	1042 (40.6)	2894 (41.5)
>300 mg/g	340 (35.7)	348 (37.8)	993 (39.1)	1009 (39.4)	2690 (38.5)
BMI, kg/m^2	31.9 (5.3)	31.9 (5.3)	31.0 (5.3)	31.1 (5.4)	31.3 (5.3)
HbA1c, %	7.93 (1.00)	8.03 (1.02)	7.94 (1.00)	7.94 (1.00)	7.95 (1.01)
Fasting plasma glucose, mg/dL	151.9 (43.0)	154.8 (46.3)	150.9 (47.0)	149.9 (45.8)	151.2 (46.0)
Diabetes mellitus duration, y	14.2 (9.5)	13.8 (9.2)	15.3 (9.7)	14.8 (9.2)	14.8 (9.5)
Systolic blood pressure, mm Hg	138.8 (17.1)	138.9 (18.0)	141.0 (17.9)	141.2 (18.0)	140.5 (17.9)
Diastolic blood pressure, mm Hg	77.3 (10.2)	78.4 (10.7)	77.9 (10.6)	77.7 (10.3)	77.8 (10.5)
Heart rate, bpm, mean (SD)	70.2 (11.9)	70.6 (12.6)	69.7 (12.3)	69.4 (12.2)	69.8 (12.2)
Glucose-lowering therapy, n (%)					
Metformin	521 (54.7)	492 (53.4)	1360 (53.5)	1435 (56.0)	3808 (54.6)
Sulfonylurea	320 (33.6)	321 (34.9)	782 (30.8)	819 (31.9)	2224 (32.1)
Insulin	535 (56.2)	511 (55.5)	1521 (59.8)	1484 (57.9)	4051 (58.0)

(*Continued*)

Table 1. Continued

Characteristic	Participants With HF at Baseline		Participants Without HF at Baseline		Total CARMELINA Population
	Linagliptin	Placebo	Linagliptin	Placebo	
Antihypertensives, n (%)					
ACE inhibitors or ARBs	782 (82.1)	761 (82.6)	2078 (81.7)	2037 (79.4)	5658 (81.1)
β-Blockers	718 (75.4)	684 (74.3)	1362 (53.6)	1389 (54.2)	4153 (59.5)
Diuretics	621 (65.2)	636 (69.1)	1271 (50.0)	1300 (50.7)	3828 (54.9)
Calcium antagonists	343 (36.0)	334 (36.3)	1090 (42.9)	1112 (43.4)	2879 (41.3)
ASA, n (%)	646 (67.9)	644 (69.9)	1520 (59.8)	1534 (59.8)	4344 (62.2)
Statins, n (%)	685 (72.0)	686 (74.5)	1810 (71.2)	1837 (71.6)	5018 (71.9)

Data are mean (SD) unless otherwise specified. ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; ASA, acetylsalisylic acid; BMI, body mass index; bpm, beats per minute; CARMELINA, The Cardiovascular and Renal Microvascular Outcome Study With Linagliptin trial; eGFR, estimated glomerular filtration rate; HbA1c, glycohemoglobin A1c; HF, heart failure; MDRD, Modification of Diet in Renal Disease study equation; and UACR, urinary albumin-to-creatinine ratio.

*American Indian/Alaska Native or Native Hawaiian/other Pacific Islander.

†UACR: Data missing for 3 (0.0%) participants: 2 (0.1%) linagliptin and 1 (0.0%) placebo.

well-controlled blood pressure, lipids, and glycemic control (Table 1). Participants with previous HF more frequently had cardiac comorbidities (atrial fibrillation, ischemic heart disease) and more prevalent use of cardiovascular medications (β-blockers, diuretics, aspirin). Median (first quartile – third quartile) treatment duration and observation time were 1.9 (1.2–2.5) and 2.2 (1.6–3.0) years, respectively, with no differences between the groups.

Those randomized to linagliptin had lower hemoglobin A1c throughout the trial observation period (overall mean [95% CI] difference linagliptin versus placebo, –0.36% [95% CI, –0.42 to –0.29] based on least square means), with no statistically significant differences between groups in change from baseline in blood pressure (systolic/diastolic blood pressure, –0.67 [–1.55 to 0.20]/–0.38 [–0.87 to 0.12] mm Hg), low-density lipoprotein cholesterol (–0.03 [–2.27 to 2.21] mg/dL), high-density lipoprotein cholesterol (0.25 [–0.84 to 0.33] mg/dL), or weight (–0.15 [–0.43 to 0.12] kg). Also, the introduction of additional cardiovascular therapies was comparable across arms, and the overall safety profile of linagliptin was consistent with previous clinical data.

HF-Related Outcomes

Results of analyses of HF-related outcomes by randomized treatment groups are presented in Table 2 and Figure 1. In total, 435 participants (6.2%) had at least 1 hHF event, and the rate of first hHF events did not differ between the groups, with 209 (6.0%) events occurring in the linagliptin group (2.8 per 100 patient-years), and 226 (6.5%) in the placebo group (3.0 per 100 patient-years), yielding a HR of 0.90 (95% CI, 0.74–1.08). There was also no difference for linagliptin versus pla-

Table 2. Heart Failure–Related Outcomes for Linagliptin Versus Placebo in CARMELINA

Outcome	Linagliptin (N=3494)		Placebo (N=3485)		HR (95% CI)	*P* Value
	n (%)	Rate per 100 Patient-Years	n (%)	Rate per 100 Patient-Years		
Hospitalization for HF (hHF); ITT analysis (n=6979)	209 (6.0)	2.77	226 (6.5)	3.04	0.90 (0.74, 1.08)	0.26
Effects on additional HF outcomes						
hHF or CV death	406 (11.6)	5.37	422 (12.1)	5.66	0.94 (0.82, 1.08)	0.39
hHF or all-cause death	499 (14.3)	6.59	518 (14.9)	6.94	0.95 (0.84, 1.07)	0.40
Investigator-reported HF adverse event	243 (7.0)	3.68	271 (7.8)	4.24	0.87 (0.73, 1.03)	0.10
hHF or reported HF adverse event	305 (8.7)	4.09	326 (9.4)	4.44	0.92 (0.79, 1.08)	0.31
First + recurrent events of hHF	326*	N/A	359*	N/A	0.94 (0.75, 1.20)†	0.63
Initiation of loop diuretics (n=4991)‡	318/2530 (12.6)	6.09	324/2461 (13.2)	6.48	0.94 (0.81, 1.10)	0.47
Initiation of loop diuretic or hHF (n=4991)‡	330/2530 (13.0)	6.33	333/2461 (13.5)	6.68	0.95 (0.82, 1.11)	0.53

Analyses were prespecified with the exception of the following, which were post hoc: hHF or reported HF adverse event, first and recurrent events of hHF, initiation of loop diuretics, and initiation of loop diuretic or hHF. CARMELINA indicates The Cardiovascular and Renal Microvascular Outcome Study With Linagliptin trial; CV, cardiovascular; ITT, intention-to-treat; HF, heart failure; hHF, hospitalization for heart failure; HR, heart rate; and N/A, not applicable.

*n refers to total number of hospitalization for heart failure episodes relative to the treated set and not individual participants.

†Effect estimate (rate ratio) derived by a negative binomial model.

‡Number of patients not treated with diuretics at baseline.

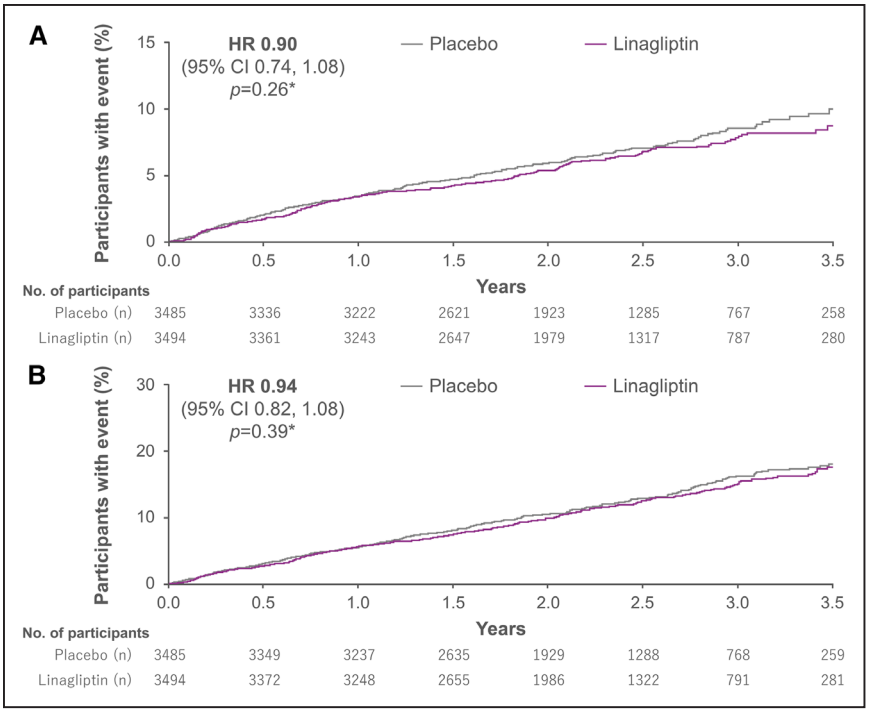

Figure 1. Kaplan–Meier plots according to treatment with linagliptin vs placebo. First occurrence of (**A**) adjudication-confirmed hospitalization for heart failure and (**B**) adjudication-confirmed hospitalization for heart failure or cardiovascular death. *Two-sided *P* value. HR indicates hazard ratio.

cebo for the composite outcomes of hHF or death (406 versus 422 events; HR, 0.94; 95% CI, 0.82–1.08), hHF or all-cause mortality (499 versus 518 events; HR, 0.95; 95% CI, 0.84–1.07), investigator-reported HF events (276 versus 305 events; HR, 0.89; 95% CI, 0.76–1.05), or the combination of time to first event of investigator-reported events or adjudicated hHF (305 versus 326 events; HR, 0.92; 95% CI, 0.79–1.08; Figure I in the online-only Data Supplement). In recurrent event analysis, the cumulative number of hHF events (first + recurrent) was not different between the linagliptin and placebo groups (326 versus 359 events; rate ratio, 0.94; 95% CI, 0.75–1.20), and in total 60 (1.7%) participants in the linagliptin group and 78 (2.2%) in the placebo group had ≥2 hHF events. New introduction of loop diuretics was not different between linagliptin and placebo (318/2530 versus 324/2461 participants; HR, 0.94; 95% CI, 0.81–1.10), with no difference in the composite outcome of new initiation of loop diuretics or hHF (330/2530 versus 333/2461 participants; HR, 0.95; 95% CI, 0.82–1.11). Prespecified and post hoc–defined sensitivity analyses of hHF yielded consistent results with the primary analysis (Figure 2).

The incidence of hHF varied substantially across subgroups defined by baseline characteristics (Table II in the online-only Data Supplement). However, among the subset of participants with or without a history of HF at baseline, there were no significant differences observed between the treatment groups in hHF (Figure 3A and 3B; $P_{interaction}$=0.81). Also, no heterogeneity was observed for the effects of the randomized treatment assignment by baseline HF history for cardiovascular death (Figure 3C and 3D; $P_{interaction}$=0.97) or the primary outcome 3-point major adverse cardiovascular event ($P_{interaction}$=0.96).

Nominally significant statistical heterogeneity of linagliptin effects on hHF was observed in some subgroups (Table II in the online-only Data Supplement): by region (Figure II in the online-only Data Supplement), by insulin use at baseline (Figure III in the online-only Data Supplement), and by baseline blood pressure. Event rates for hHF were 2.7-fold higher in participants in the placebo

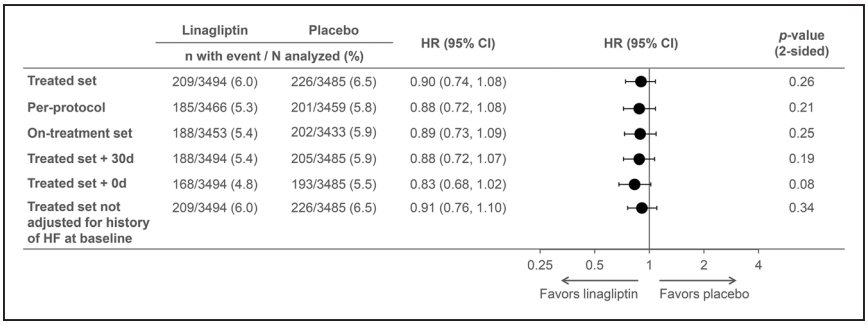

Figure 2. Sensitivity analyses for hospitalization for heart failure by prespecified and post hoc–defined analysis sets. All analyses were prespecified except the per-protocol analysis set, which was post hoc. HF indicates heart failure; and HR, hazard ratio.

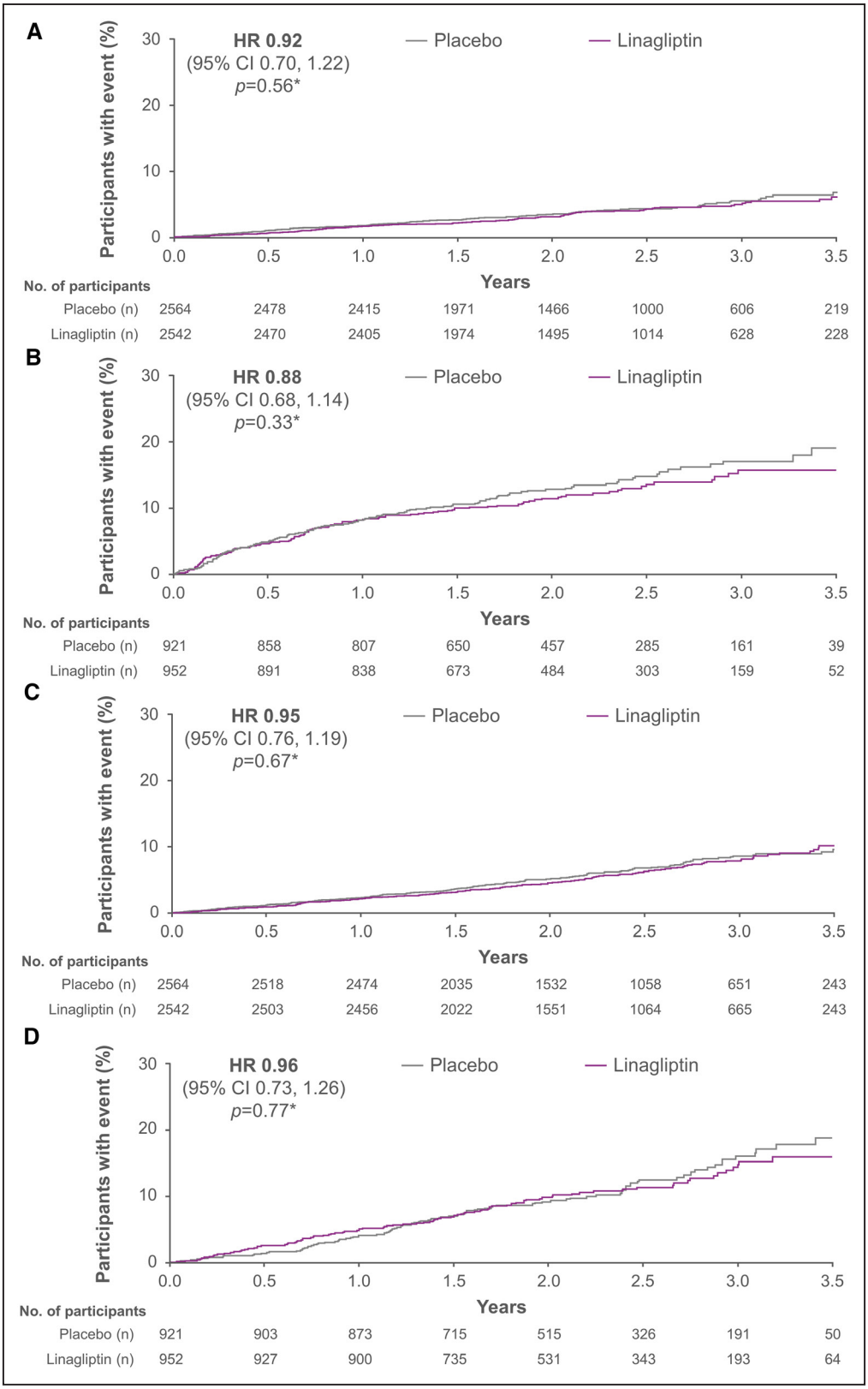

Figure 3. Kaplan-Meier plots for hospitalization for heart failure (hHF) and cardiovascular death by treatment groups in participants with and without a history of heart failure (HF) at baseline.

A, hHF in participants with no history of HF at baseline. **B**, hHF in participants with a history of HF at baseline. **C**, Cardiovascular death in participants with no history of HF at baseline. **D**, Cardiovascular death in participants with a history of HF at baseline. *Two-sided *P* value. HR indicates hazard ratio.

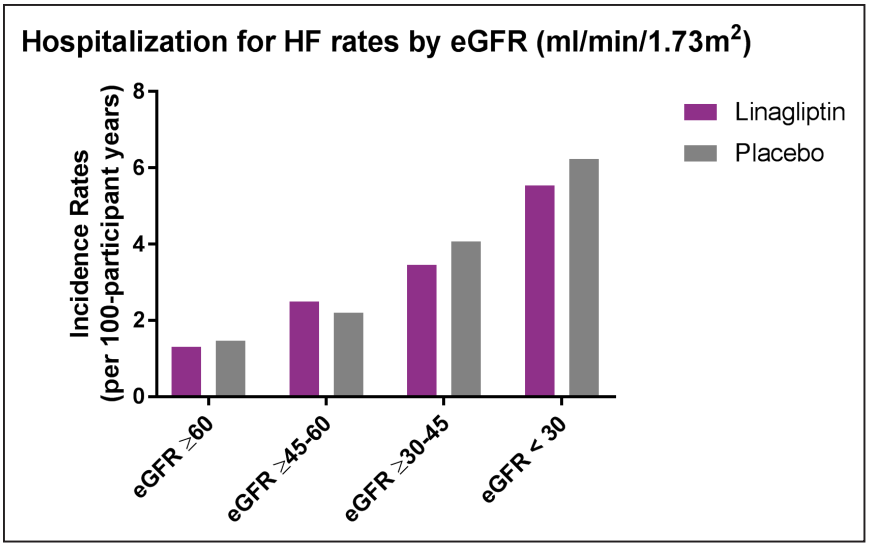

Figure 4. Histogram with incidence rates for hospitalization for heart failure by treatment groups by categories of estimated glomerular filtration rate at baseline.
eGFR indicates estimated glomerular filtration rate; and HF, heart failure.

groups with prevalent kidney disease (defined as baseline eGFR <60 mL/min/1.73m^2 and macroalbuminuria: 3.7 per 100 patient-years versus 1.4 in those without) at baseline, and 4.2-fold higher in participants with low eGFR (eGFR <30 mL/min/1.73m^2: 6.2 per 100 patient-years versus 1.5 with eGFR ≥60 mL/min/1.73m^2; Figure 4). However, no heterogeneity of effect by treatment arm was noted ($P_{interaction}$=0.39 and 0.88).

At baseline, LVEF was captured for 945 (13.5%) participants within a year before randomization (458 in the linagliptin and 487 in the placebo group). The mode of ejection fraction (EF) assessment varied (Table III in the online-only Data Supplement), but echocardiography was by far the most commonly used method (90.2%). The average prerandomization EF was 53.6% in the linagliptin group and 54.5% in the placebo group, with 31.9% and 29.2%, respectively, having EF ≤50% (mean±SD LVEF, respectively, 39.1±8.4% and 39.2±7.6%), and only 11.6% and 11.7% having EF ≤40% (mean±SD LVEF, respectively, 29.7±6.4% and 31.7±6.1%). In total, 118 hHF events occurred in participants with EF assessment before randomization. Among these with ≥1 hHF event, the average prerandomization EF was 46.1±13.8% versus 47.7±12.8% in the linagliptin versus placebo group, respectively, whereas the corresponding average prerandomization LVEF in those without a hHF event were 54.7±11.8% and 55.2±12.0%, respectively. There was no heterogeneity of linagliptin effect on risk by prerandomization LVEF categorized by EF <50% or ≥50% for hHF ($P_{interaction}$=0.14), for the composite outcome of hHF or cardiovascular death ($P_{interaction}$=0.16), or for 3-point major adverse cardiovascular event ($P_{interaction}$=0.31; Figure 5).

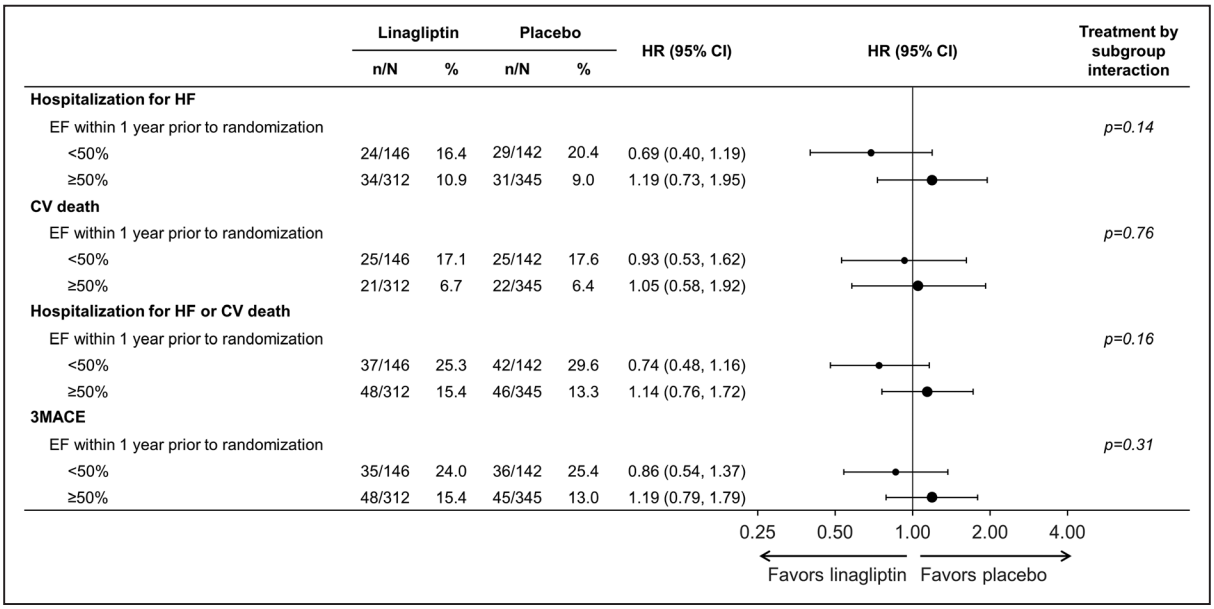

Figure 5. Hospitalization for heart failure (HF), 3-point major adverse cardiovascular event (3MACE), and cardiovascular (CV) death by treatment group stratified by prerandomization left ventricular ejection fraction (EF) <50% and ≥50%.
HR indicates hazard ratio.

DISCUSSION

In individuals with T2DM and prevalent ASCVD or kidney disease participating in CARMELINA, linagliptin compared with placebo did not affect the risk for hHF or for the composite outcomes of hHF or cardiovascular death or hHF or all-cause death outcomes. There was also no difference between the randomized groups in the risk of hHF in subgroups of participants with or without a history of HF at baseline.

The assessment of hHF in CARMELINA was underpinned by prospectively defined analyses for HF-related outcomes and ascertainment of a large number of prospectively collected and centrally adjudicated hHF episodes with a total of 435 first hHF and 685 total (first or recurrent) events of hHF. Overall, linagliptin had no effect on the risk for hHF in CARMELINA, in line with observations from the CVOT of sitagliptin,[3,12] but contrasting importantly with the significantly increased hHF risks with saxagliptin.[10,14]

The present results amplify the probability of heterogeneity across the DPP-4 inhibitor class with regard to effects on the risk for HF outcomes, with linagliptin and sitagliptin having no effects, saxagliptin increasing risk, and ongoing uncertainty with regard to the effects of alogliptin on HF risk. Mechanistic explanations for the apparent heterogeneity seen with respect to HF of DPP-4 inhibitors are unknown, but these agents have clear differences in their molecular structures that may account for diverse off-target effects. Several hypotheses and observations in this regard from preclinical studies have been published.[19–22] Differences in the trial populations and underlying degree of hHF risk are unlikely to explain these discordant effects. In this context, the hHF risk in CARMELINA was, by virtue of the planned recruitment of a higher risk population, far greater than the 3 previous reported DPP-4 inhibitor CVOTs. In the control group of CARMELINA, the annualized hHF incidence was 3%, with observations of 2.7 to 4.2 higher event rates in those with prevalent kidney disease, or reduced eGFR, which contrasted with 1% to 2% in the previous trials.[3,13,14] The finding that the incidence of hHF did not differ between the linagliptin and control groups despite participants in CARMELINA being at very high risk underscores the HF safety of linagliptin in a population with ASCVD or kidney disease and provides reassurance regarding the safety of linagliptin for this outcome. Similarly, trial duration is also not likely to account for different observations between trials, as the median follow-up in CARMELINA is quite similar to that in the CVOTs of saxagliptin and alogliptin, yet shorter than that for sitagliptin.[10–12] It is important to note that although HF outcomes were not part of the primary cardiovascular analysis plan of any of the CVOTs of DPP-4 inhibitors, all of the DPP-4 inhibitor CVOTs completed to date prospectively collected and centrally adjudicated hHF events, using nearly identical criteria for hHF event definitions across the trials, in accord with the guidance of the 2014 American College of Cardiology/American Heart Association Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials publication.[18] Finally, given that no adverse effects on hHF have been observed with sitagliptin and linagliptin, and that the numeric imbalance observed with alogliptin did not achieve statistical difference, it remains possible that the observed increased risk with saxagliptin is a spurious finding. However, given the temporal association of hHF soon after starting saxagliptin in the SAVOR TIMI 53 trial (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus [SAVOR] - Thrombolysis in Myocardial Infarction [TIMI] 53) and the robustness of analyses underpinned by blinded central adjudication and ascertainment of 517 hHF events for analysis, this is not a likely explanation.[14]

Acknowledging the statistical limitations of interpreting a large number of secondary/subgroup analyses, we did observe statistical heterogeneity of the effect of linagliptin on hHF by region, by baseline insulin use, and, not consistently, by baseline blood pressure. Each of these observations of interaction is hypothesis-generating in light of the neutral overall effect of linagliptin on this outcome, the most interesting of which is the interaction with insulin use given the known associations of insulin with HF related to sodium and fluid retention.[23,24] However, because of the large number of subgroup analyses conducted, we cannot exclude that these interactions may be spurious.

Limitations

We studied individuals with established ASCVD or kidney disease, and the present observations may not apply to those without such criteria. However, demonstration of safety in the highest-risk cohorts typically translates to lower-risk groups; of note, no increased HF risk was observed with linagliptin across all ranges of kidney function with or without prevalent ASCVD. Nominally significant statistical heterogeneity of linagliptin effects on hHF was observed in some subgroups, but in the context of analyzing 33 prespecified subgroups and in the absence of correction for multiplicity, it is not possible to conclude whether these represent true heterogeneity or spurious findings. Pretrial LVEF data were only available in a minority of participants. For those with HF events, cardiac imaging was not systematically captured, and no biobank of blood was collected to assess natriuretic peptides.

CONCLUSIONS

In conclusion, the results of CARMELINA demonstrate that linagliptin did not affect the risk for hHF or related HF outcomes, overall or across selected subgroups of interest. In the context of the primary findings on 3-point major adverse cardiovascular events demonstrating

noninferiority of the effects of linagliptin versus placebo on top of standard of care, these data provide further support that linagliptin may be safely used, without concerns for increasing HF risk, in a high-risk population of individuals with T2DM with concomitant atherosclerotic cardiovascular disease and/or kidney disease.

ARTICLE INFORMATION

Received October 10, 2018; accepted October 15, 2018.

Guest Editor for this article was Frans Van de Werf, MD, PhD.

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.118.038352.

Correspondence

Darren K. McGuire, MD, MHSc, Division of Cardiology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75235–8830. Email darren.mcguire@utsouthwestern.edu

Affiliations

University of Texas Southwestern Medical Center, Dallas (D.K.M., R.D.T.). Duke Clinical Research Institute, Duke Health, Durham, NC (J.H.A.). Boehringer Ingelheim Norway, Asker (O.E.J.). The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, Australia (V.P.). Dallas Diabetes Research Center at Medical City, TX (J.R.). Department of Diabetes, Central Clinical School, Monash University, Melbourne, Australia (M.E.C.). Department of Medicine, Division of Nephrology, Würzburg University Clinic, Germany (C.W.). Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, Veterans' Administration Puget Sound Health Care System and University of Washington, Seattle (S.E.K.). Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, and Division of Endocrinology, University of Toronto, Canada (B.Z.). Boehringer Ingelheim, Alkmaar, The Netherlands (D.B.). Boehringer Ingelheim Pharma GmbH & Co. Ingelheim, Germany (E.P., S.S.). Boehringer Ingelheim International, Ingelheim, Germany (J.T.G., M.v.E.). Boehringer Ingelheim International GmbH, Biberach, Germany (T.M.). Department of Internal Medicine I, University Hospital Aachen, Rheinisch-Westfälische Technische Hochschule Aachen University, Germany (N.M.).

Acknowledgments

We thank the participants, without whom this study and these analyses would not have been possible. The corresponding author drafted the manuscript, and all coauthors reviewed the data and revised the manuscript. The authors were fully responsible for all content and have approved the final version. Support for preparation of Kaplan Meier plots and Forest Plots was provided by Matt Smith, PhD CMPP, and Giles Brooke, PhD CMPP, from Envision Scientific Solutions for graphical support, supported financially by Boehringer Ingelheim.

Sources of Funding

This work was supported by the Boehringer Ingelheim and Eli Lilly and Co Diabetes Alliance. Boehringer Ingelheim was involved in the design and conduct of the study; collection, analysis, and interpretation of data; and preparation of this manuscript. Dr Marx received grant support from the German Research Foundation: SFB TRR 219 (projects M-03 and M-05).

Disclosures

Dr McGuire has received personal fees from Boehringer Ingelheim, Janssen Research and Development LLC, Sanofi-Aventis Group, Genentech Inc, Merck Sharp and Dohme, Daiichi Sankyo Inc, Lilly USA, Novo Nordisk, GlaxoSmithKline, Bristol-Myers Squibb, AstraZeneca, Lexicon, Eisai Janssen, Boehringer Ingelheim, Merck, Pfizer, Metavant, and Applied Therapeutics. Dr Alexander has received personal fees from Abbvie, Bristol-Myers Squibb, CSL Behring, Jansen Pharmaceutics, Novo Nordisk, Pfizer, Portola, and Teikoku and institutional research support from Boehringer Ingelheim, Bristol-Myers Squibb, Cryolife, CSL Behring, Tenax Therapeutics, and VoluMetrix. Dr Erik Johansen is employed by Boehringer Ingelheim. Dr Perkovic has received research support from the Australian National Health and Medical Research Council (Project and Program Grant), has severed on steering committees for trials supported by AbbVie, Boehringer Ingelheim, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Novartis, Novo Nordisk, Pfizer, Retrophin, and Tricida, and has served on advisory boards or spoken at scientific meetings for AbbVie, Astellas Pharma, AstraZeneca, Bayer, Baxter, Bristol-Myers Squibb, Boehringer Ingelheim, Durect Corp, Eli Lilly and Co, Gilead Sciences, GlaxoSmithKline, Janssen, Merck & Co, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Roche, Sanofi, Servier, and Vitae; Dr Perkovic has a policy of having honoraria paid to his employer. Dr Rosenstock has served on scientific advisory boards and received honoraria or consulting fees from Eli Lilly, Sanofi, Novo Nordisk, Janssen, AstraZeneca, Boehringer Ingelheim, and Intarcia; he has also received grants/research support from Merck, Pfizer, Sanofi, Novo Nordisk, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Genentech, Janssen, Lexicon, Boehringer Ingelheim, and Intarcia. Dr Cooper has received fees for advisory services to Boehringer Ingelheim. Dr Wanner has received fees for advisory services to Boehringer Ingelheim. Dr Kahn has received personal fees from Boehringer Ingelheim, Elcelyx, Eli Lilly, Intarcia, Janssen, Merck, Neurimmune, and Novo Nordisk. Dr Toto is a consultant to Amgen, Boehringer Ingelheim, ZS Pharma, Relypsa, Novo Nordisk, Reata, and AstraZeneca and receives grant support from the National Institutes of Health. Dr Zinman has received grant support from Boehringer Ingelheim, AstraZeneca, and Novo Nordisk and consulting fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi Aventis. D. Baanstra, E. Pfarr, S. Schnaidt, and Drs Meinicke, George, and von Eynatten are employed by Boehringer Ingelheim. Dr Marx has given lectures for Amgen, Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca, Lilly, and Novo Nordisk, has received unrestricted research grants from Boehringer Ingelheim, and has served as an advisor for Amgen, Bayer, Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca, and Novo Nordisk. In addition, Dr Marx has served in trial leadership for Boehringer Ingelheim and Novo Nordisk; Dr Marx declines all personal compensation from pharmaceutical or medical device companies.

REFERENCES

1. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson AM, Miftaraj M, McGuire DK, Sattar N, Rosengren A, Gudbjörnsdottir S. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med*. 2017;376:1407–1418. doi: 10.1056/NEJMoa1608664
2. Wen CP, Chang CH, Tsai MK, Lee JH, Lu PJ, Tsai SP, Wen C, Chen CH, Kao CW, Tsao CK, Wu X. Diabetes with early kidney involvement may shorten life expectancy by 16 years. *Kidney Int*. 2017;92:388–396. doi: 10.1016/j.kint.2017.01.030
3. McGuire DK, Van de Werf F, Armstrong PW, Standl E, Koglin J, Green JB, Bethel MA, Cornel JH, Lopes RD, Halvorsen S, Ambrosio G, Buse JB, Josse RG, Lachin JM, Pencina MJ, Garg J, Lokhnygina Y, Holman RR, Peterson ED and Trial Evaluating Cardiovascular Outcomes With Sitagliptin Study G. Association between sitagliptin use and heart failure hospitalization and related outcomes in type 2 diabetes mellitus: secondary analysis of a randomized clinical trial. *JAMA Cardiol*. 2016;1:126–35.
4. Ofstad AP, Atar D, Gullestad L, Langslet G, Johansen OE. The heart failure burden of type 2 diabetes mellitus: a review of pathophysiology and interventions. *Heart Fail Rev*. 2018;23:303–323. doi: 10.1007/s10741-018-9685-0
5. McMurray JJ, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. *Lancet Diabetes Endocrinol*. 2014;2:843–851. doi: 10.1016/S2213-8587(14)70031-2
6. Wang Y, Katzmarzyk PT, Horswell R, Zhao W, Johnson J, Hu G. Comparison of the heart failure risk stratification performance of the CKD-EPI equation and the MDRD equation for estimated glomerular filtration rate in patients with type 2 diabetes. *Diabet Med*. 2016;33:609–620. doi: 10.1111/dme.12859
7. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Hallé JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S; HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA*. 2001;286:421–426. doi: 10.1001/jama.286.4.421
8. US Department of Health and Human Services Food and Drug Administration. Guidance for Industry. Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. 2008. www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf. Accessed October 16, 2018.
9. European Medicines Agency Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf. Accessed October 16, 2018.

10. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369:1317–1326. doi: 10.1056/NEJMoa1307684
11. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369:1327–1335. doi: 10.1056/NEJMoa1305889
12. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR and Group TS. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;373:232–242. doi: 10.1056/NEJMoa1501352
13. Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Lam H, White WB; EXAMINE Investigators. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet*. 2015;385:2067–2076. doi: 10.1016/S0140-6736(14)62225-X
14. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, Udell JA, Mosenzon O, Im K, Umez-Eronini AA, Pollack PS, Hirshberg B, Frederich R, Lewis BS, McGuire DK, Davidson J, Steg PG, Bhatt DL; SAVOR-TIMI 53 Steering Committee and Investigators. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. *Circulation*. 2014;130:1579–1588. doi: 10.1161/CIRCULATIONAHA.114.010389
15. Schnapp G, Klein T, Hoevels Y, Bakker RA, Nar H. Comparative analysis of binding kinetics and thermodynamics of dipeptidyl peptidase-4 inhibitors and their relationship to structure. *J Med Chem*. 2016;59:7466–7477. doi: 10.1021/acs.jmedchem.6b00475
16. Rosenstock J, Perkovic V, Alexander JH, Cooper ME, Marx N, Pencina MJ, Toto RD, Wanner C, Zinman B, Baanstra D, Pfarr E, Mattheus M, Broedl UC, Woerle HJ, George JT, von Eynatten M, McGuire DK; CARMELINA® investigators. Rationale, design, and baseline characteristics of the CArdiovascular safety and Renal Microvascular outcomE study with LINAgliptin (CARMELINA®): a randomized, double-blind, placebo-controlled clinical trial in patients with type 2 diabetes and high cardio-renal risk. *Cardiovasc Diabetol*. 2018;17:39. doi: 10.1186/s12933-018-0682-3
17. Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, Alexander JH, Pencina M, Toto RD, Wanner C, Zinman B, Woerle HJ, Baanstra D, Pfarr E, Schnaidt SY, Meinicke T, George JT, von Eynatten M, McGuire DK, for the CARMELINA® investigators. Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults with Type 2 Diabetes and High Cardiovascular and Renal Risk. The CARMELINA Randomized Clinical Trial. *JAMA*. 2018; In press. doi: 10.1001/jama.2018.18269
18. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, Fonarow GC, Jacobs JP, Jaff MR, Lichtman JH, Limacher MC, Mahaffey KW, Mehran R, Nissen SE, Smith EE, Targum SL; American College of Cardiology; American Heart Association. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *Circulation*. 2015;132:302–361. doi: 10.1161/CIR.0000000000000156
19. Koyani CN, Kolesnik E, Wölkart G, Shrestha N, Scheruebel S, Trummer C, Zorn-Pauly K, Hammer A, Lang P, Reicher H, Maechler H, Groschner K, Mayer B, Rainer PP, Sourij H, Sattler W, Malle E, Pelzmann B, von Lewinski D. Dipeptidyl peptidase-4 independent cardiac dysfunction links saxagliptin to heart failure. *Biochem Pharmacol*. 2017;145:64–80. doi: 10.1016/j.bcp.2017.08.021
20. Batchu SN, Thieme K, Zadeh FH, Alghamdi TA, Yerra VG, Hadden MJ, Majumder S, Kabir MG, Bowskill BB, Ladha D, Gramolini AO, Connelly KA and Advani A. The dipeptidyl peptidase-4 substrate CXCL12 has opposing cardiac effects in young mice and aged diabetic mice mediated by Ca(2+) flux and phosphoinositide 3-kinase gamma. *Diabetes*. 2018. doi: 10.2337/db18-0410 [Epub ahead of print]
21. Mulvihill EE, Varin EM, Ussher JR, Campbell JE, Bang KW, Abdullah T, Baggio LL, Drucker DJ. Inhibition of dipeptidyl peptidase-4 impairs ventricular function and promotes cardiac fibrosis in high fat-fed diabetic mice. *Diabetes*. 2016;65:742–754. doi: 10.2337/db15-1224
22. Drucker DJ. The cardiovascular biology of glucagon-like peptide-1. *Cell Metab*. 2016;24:15–30. doi: 10.1016/j.cmet.2016.06.009
23. Cosmi F, Shen L, Magnoli M, Abraham WT, Anand IS, Cleland JG, Cohn JN, Cosmi D, De Berardis G, Dickstein K, Franzosi MG, Gullestad L, Jhund PS, Kjekshus J, Køber L, Lepore V, Lucisano G, Maggioni AP, Masson S, McMurray JJV, Nicolucci A, Petrarolo V, Robusto F, Staszewsky L, Tavazzi L, Teli R, Tognoni G, Wikstrand J, Latini R. Treatment with insulin is associated with worse outcome in patients with chronic heart failure and diabetes. *Eur J Heart Fail*. 2018;20:888–895. doi: 10.1002/ejhf.1146
24. Wang Q, Liu Y, Fu Q, Xu B, Zhang Y, Kim S, Tan R, Barbagallo F, West T, Anderson E, Wei W, Abel ED and Xiang YK. Inhibiting insulin-mediated beta2-adrenergic receptor activation prevents diabetes-associated cardiac dysfunction. *Circulation*. 2017;135:73–88. doi: 10.1161/CIRCULATIONAHA.116.022281