Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial

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Summary

Background **The EXAMINE trial showed non-inferiority of the DPP-4 inhibitor alogliptin to placebo on major adverse cardiac event (MACE) rates in patients with type 2 diabetes and recent acute coronary syndromes. Concerns about excessive rates of in-hospital heart failure in another DPP-4 inhibitor trial have been reported. We therefore assessed hospital admission for heart failure in the EXAMINE trial.**

Methods **Patients with type 2 diabetes and an acute coronary syndrome event in the previous 15–90 days were randomly assigned alogliptin or placebo plus standard treatment for diabetes and cardiovascular disease prevention. The prespecified exploratory extended MACE endpoint was all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, urgent revascularisation due to unstable angina, and hospital admission for heart failure. The post-hoc analyses were of cardiovascular death and hospital admission for heart failure, assessed by history of heart failure and brain natriuretic peptide (BNP) concentration at baseline. We also assessed changes in N-terminal pro-BNP (NT-pro-BNP) from baseline to 6 months. This study is registered with ClinicalTrials.gov, number NCT00968708.**

Findings **5380 patients were assigned to alogliptin (n=2701) or placebo (n=2679) and followed up for a median of 533 days (IQR 280–751). The exploratory extended MACE endpoint was seen in 433 (16·0%) patients assigned to alogliptin and in 441 (16·5%) assigned to placebo (hazard ratio [HR] 0·98, 95% CI 0·86–1·12). Hospital admission for heart failure was the first event in 85 (3·1%) patients taking alogliptin compared with 79 (2·9%) taking placebo (HR 1·07, 95% CI 0·79–1·46). Alogliptin had no effect on composite events of cardiovascular death and hospital admission for heart failure in the post hoc analysis (HR 1·00, 95% CI 0·82–1·21) and results did not differ by baseline BNP concentration. NT-pro-BNP concentrations decreased significantly and similarly in the two groups.**

Interpretation **In patients with type 2 diabetes and recent acute coronary syndromes, alogliptin did not increase the risk of heart failure outcomes.**

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Introduction

Congestive heart failure is increasing in incidence due to reduced mortality from myocardial infarction and the ageing of the population worldwide. Type 2 diabetes mellitus increases the likelihood of developing heart failure[1]—almost half of patients develop heart failure[2,3]—and adversely affects the outcomes of patients with established heart failure.[4–6] The effects of treatment for type 2 diabetes on heart failure outcomes, however, has not been adequately addressed in trials, but potential cardiovascular harm has been suggested with several glucose-lowering medications.[7]

Two randomised controlled trials focusing on major cardiovascular outcomes in patients with type 2 diabetes assessed treatment with DPP-4 inhibitors. In the SAVOR TIMI 53 trial,[8,9] which enrolled 16 492 patients with type 2 diabetes and a history or risk of cardiovascular events, saxagliptin had no effect on the composite outcome of cardiovascular death, myocardial infarction, or ischaemic stroke. However, the rate of hospital admission for heart failure was higher with saxagliptin than with placebo (3·5% *vs* 2·8%, hazard ratio [HR] 1·27, 95% CI 1·07–1·51, p=0·007). In the EXAMINE trial,[10] which enrolled 5380 patients with type 2 diabetes and a recent acute coronary syndrome event, alogliptin was non-inferior to placebo in lowering the risk of the composite primary endpoint of cardiovascular death, myocardial infarction, or stroke (11·3% *vs* 11·8%, HR 0·96, upper boundary of the one-sided 95% CI 1·16). As part of EXAMINE, we investigated heart failure outcomes in patients with a history or high risk of cardiovascular disease in a prespecified exploratory analysis and in post-hoc analyses. We also assessed changes in N-terminal pro-BNP (NT-pro-BNP) from baseline to 6 months.

Methods

Study design

Details of the EXAMINE study design are published elsewhere.[10] The study was a multicentre, randomised, double-blind trial, into which patients were enrolled from 898 centres in 49 countries between October, 2009, and March, 2013. The EXAMINE trial was overseen by a

steering committee, data safety monitoring committee, and cardiovascular endpoints committee. The data safety monitoring committee was independent and had ongoing access to the unmasked data to advise the funder and steering committee. The cardiovascular endpoints committee, which was also independent and based at Cleveland Clinic, Cleveland, OH, USA, adjudicated all deaths and serious cardiovascular events, including heart failure, prospectively and without knowledge of treatment group. Statistical analyses were done independently by Pharmaceutical Product Development Inc, Wilmington, DE, a contract research organisation, in collaboration with investigators at the academic centres and the funder. Members of the steering committee vouched for the accuracy and completeness of the reported data. The appropriate national and institutional regulatory authorities and ethics committees approved the study design and all participants provided written informed consent.

Study patients

Patients were eligible for enrolment if they had a diagnosis of type 2 diabetes, were receiving antidiabetic therapy (with the exception of a DPP-4 inhibitor or GLP-1 analogue), and had had an acute coronary syndrome event within 15–90 days before randomisation. Further criteria for type 2 diabetes included a glycated haemoglobin A_{1c} (HbA_{1c}) concentration of 47·5–96·7 mmol/mol (6·5–11·0%) at baseline, or, if the antidiabetic regimen included insulin, 53·0–96·7 mmol/mol (7·0–11·0%). Major exclusion criteria included a diagnosis of type 1 diabetes, unstable cardiac disorders, such as New York Heart Association class IV heart failure, refractory angina, uncontrolled arrhythmia, critical valvular heart disease, severe uncontrolled hypertension, and dialysis within 14 days of screening. History of heart failure at baseline (before or after the index acute coronary syndrome event) was recorded by the physician investigator. Baseline concentration of brain natriuretic peptide (BNP), which was used as a cardiovascular prognostic biomarker, was assessed with ELISA on the ARCHITECT analyser (Abbott Laboratories, Abbott Park, IL, USA) in venous blood samples taken the day before randomisation.[11] In a biomarker substudy, we measured NT-pro-BNP, which is a biomarker for heart failure that is likely to be less affected by DPP-4 inhibitors than BNP, in all patients at baseline and at 6 months after randomisation. Concentrations in serum were measured with ELISA on the Cobas 6000 analyser (Roche Diagnostics, Indianapolis, IN, USA).

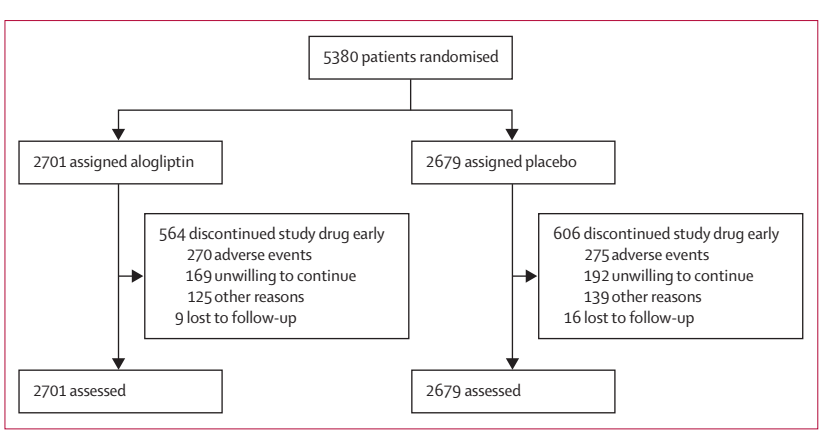

Figure 1: **Trial profile**

Study treatment and procedures

Due to renal clearance, alogliptin and matching placebo doses were modified according to kidney function at baseline and after randomisation, on the basis of estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease study group formula: patients with eGFR 60 mL/min per 1·73 m² or higher received 25 mg daily; those with eGFR lower than 60 but at least 30 mL/min per 1·73 m² received 12·5 mg daily; and those with eGFR lower than 30 mL/min per 1·73 m² received 6·25 mg daily. Throughout the study, patients were required to receive standard treatment for type 2 diabetes and cardiovascular risk factors, according to regional guidelines.

Endpoints

The primary composite major adverse cardiac events (MACE) endpoint was cardiovascular death, non-fatal acute myocardial infarction, and non-fatal stroke. Cardiovascular death was defined as death from cardiac and cerebrovascular causes and any death without another known cause. The secondary MACE composite endpoint was cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and urgent revascularisation due to unstable angina. We investigated a prespecified exploratory extended MACE composite endpoint that combined the first occurrence of all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, urgent revascularisation due to unstable angina, and hospital admission for heart failure. The latter component of hospital admission for heart failure was defined as an inpatient admission or an emergency department visit of more than 12 h with clinical manifestations of heart failure, including new or worsening dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, peripheral oedema, bibasilar rales on pulmonary examination, jugular venous distention, new third heart sound, radiographic evidence of heart failure, and parenteral diuretic, inotropic, or vasodilator therapy, ultrafiltration or dialysis, or mechanical or surgical intervention (including heart transplant). We also explored the following two post-hoc composite endpoints: all-cause death and hospital admission for heart failure, and cardiovascular death and hospital admission for heart failure.

Post-hoc subgroup analyses were done according to history of heart failure at baseline, including history of chronic heart failure before the index acute coronary syndrome event or heart failure that developed during or

after the index acute coronary syndrome event but before randomisation, and according to quartile of baseline BNP concentration.

Statistical analyses

All analyses were done by intention to treat. Baseline characteristics were summarised as frequencies for

	History of heart failure at baseline		No history of heart failure at baseline	
	Alogliptin (n=771)	Placebo (n=762)	Alogliptin (n=1930)	Placebo (n=1917)
Age (years)	63 (56–70)	62 (55–70)	60 (53–67)	60 (53–67)
Age ≥65 years	337 (43·7%)	305 (40·0%)	636 (33·0%)	629 (32·8%)
Male	467 (60·6%)	464 (60·9%)	1361 (70·5%)	1359 (70·9%)
Duration of diabetes (years)	7·9 (0·0–39·2)	6·8 (0·0–48·5)	6·8 (0·0–44·3)	7·3 (0·0–49·9)
Baseline HbA_{1c} concentration	8·12 (1·12)	8·15 (1·12)	7·99 (1·07)	7·99 (1·10)
Bodyweight (kg)	83·2 (70·0–95·8)	82·3 (70·3–95·0)	79·2 (68·0–93·0)	79·2 (68·0–92·0)
BMI (kg/m^2)	29·7 (26·1–33·5)	29·5 (25·8–33·5)	28·5 (25·3–32·2)	28·5 (25·4–32·3)
Ethnic origin*				
White	634 (82·2%)	604 (79·3%)	1332 (69·0%)	1339 (69·8%)
Black	39 (5·1%)	40 (5·2%)	62 (3·2%)	75 (3·9%)
Asian	83 (10·8%)	107 (14·0%)	464 (24·0%)	435 (22·7%)
Cardiovascular risk factors and history				
Current smoker	72 (9·3%)	105 (13·8%)	279 (14·5%)	278 (14·5%)
Hypertension	704 (91·3%)	694 (91·1%)	1525 (79·0%)	1546 (80·6%)
Myocardial infarction†	689 (89·4%)	691 (90·7%)	1700 (88·1%)	1654 (86·3%)
PCI†	389 (50·5%)	391 (51·3%)	1300 (67·4%)	1292 (67·4%)
CABG†	125 (16·2%)	124 (16·3%)	222 (11·5%)	217 (11·3%)
Stroke	29 (3·8%)	24 (3·1%)	46 (2·4%)	46 (2·4%)
Peripheral arterial disease	117 (15·2%)	124 (16·3%)	145 (7·5%)	128 (6·7%)
Renal function‡				
eGFR (mL/min per 1·73 m^2)	66·40 (51·52–80·39)	64·96 (50·50–82·04)	72·65 (59·94–86·08)	73·17 (59·80–86·96)
eGFR ≥60 mL/min per 1·73 m^2	482 (62·5%)	454 (59·6%)	1447 (75·0%)	1432 (74·7%)
eGFR <60 mL/min per 1·73 m^2	289 (37·5%)	308 (40·4%)	483 (25·0%)	485 (25·3%)
Index ACS event				
Myocardial infarction	536 (69·5%)	555 (72·8%)	1548 (80·2%)	1513 (78·9%)
Unstable angina	234 (30·4%)	203 (26·6%)	375 (19·4%)	402 (21·0%)
Time from index ACS event to randomisation (days)	47·0 (32·0–69·0)	48·0 (31·0–69·0)	42·0 (29·0–62·0)	44·0 (29·0–62·0)
NYHA CHF class				
I	174 (22·6%)	157 (20·6%)	NA	NA
II	424 (55·0%)	441 (57·9%)	NA	NA
III	148 (19·2%)	136 (17·8%)	NA	NA
IV	10 (1·3%)	10 (1·3%)	NA	NA
Baseline BNP concentration (pg/mL)	120 (45–287)	111 (43–284)	66 (27–145)	67 (27–139)
Baseline concomitant cardiovascular medications				
ACE inhibitor, ARB, or both	668 (86·6%)	651 (85·4%)	1533 (79·4%)	1559 (81·3%)
ACE inhibitor	525 (68·1%)	479 (62·9%)	1156 (59·9%)	1163 (60·7%)
ARB	166 (21·5%)	185 (24·3%)	408 (21·1%)	431 (22·5%)
β blockers	648 (84·0%)	629 (82·5%)	1560 (80·8%)	1574 (82·1%)
Diuretics				
All	466 (60·4%)	467 (61·3%)	539 (27·9%)	542 (28·3%)
Thiazide diuretics	138 (17·9%)	152 (19·9%)	249 (12·9%)	263 (13·7%)
Loop diuretics	254 (32·9%)	250 (32·8%)	228 (11·8%)	208 (10·9%)
MRAs	207 (26·8%)	179 (23·5%)	145 (7·5%)	149 (7·8%)

Data are median (IQR), number (%), or mean (SD). HbA_{1c}=glycated haemoglobin A_{1c}. BMI=body-mass index. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. eGFR=estimated glomerular filtration rate. ACS=acute coronary syndrome. NYHA=New York Heart Association. CHF=chronic heart failure. NA=not applicable. BNP=brain natriuretic peptide. ACE=angiotensin-converting-enzyme. ARB=angiotensin-receptor blockers. MRAs=mineralocorticoid-receptor antagoinists. *Self-reported. †Includes the index ACS event. ‡Calculated with the Modification of Diet in Renal Disease study group formula.

Table 1: **Baseline characteristics of patients by history of heart failure status**

	All patients		History of heart failure at baseline		No history of heart failure at baseline	
	Alogliptin (n=2701)	Placebo (n=2679)	Alogliptin (n=771)	Placebo (n=762)	Alogliptin (n=1930)	Placebo (n=1917)
Primary MACE endpoint						
Composite	305 (11·3%)	316 (11·8%)	123 (16·0%)	131 (17·2%)	182 (9·4%)	185 (9·7%)
Cardiovascular death	89 (3·3%)	111 (4·1%)	43 (5·6%)	59 (7·7%)	46 (2·4%)	52 (2·7%)
Non-fatal myocardial infarction	187 (6·9%)	173 (6·5%)	69 (8·9%)	66 (8·7%)	118 (6·1%)	107 (5·6%)
Non-fatal stroke	29 (1·1%)	32 (1·2%)	11 (1·4%)	6 (0·8%)	18 (0·9%)	26 (1·4%)
Hazard ratio (95% CI)	0·96 (≤1·16)†		0·94 (0·74–1·20)		0·97 (0·79–1·19)	
p value	0·315		0·622		0·772	
$p_{interaction}$ for treatment and history of heart failure	..	..	0·874	..	..	..
Secondary MACE endpoint						
Composite	344 (12·7%)	359 (13·4%)	127 (16·5%)	141 (18·5%)	217 (11·2%)	218 (11·4%)
Cardiovascular death	87 (3·2%)	111 (4·1%)	42 (5·4%)	59 (7·7%)	45 (2·3%)	52 (2·7%)
Non-fatal myocardial infarction	185 (6·8%)	169 (6·3%)	69 (8·9%)	65 (8·5%)	116 (6·0%)	104 (5·4%)
Non-fatal stroke	29 (1·1%)	32 (1·2%)	11 (1·4%)	6 (0·8%)	18 (0·9%)	26 (1·4%)
Urgent revascularisation due to unstable angina	43 (1·6%)	47 (1·8%)	5 (0·6%)	11 (1·4%)	38 (2·0%)	36 (1·9%)
Hazard ratio (95% CI)	0·95 (≤1·14)†		0·89 (0·70–1·14)		0·98 (0·81–1·18)	
p value	0·258		0·358		0·832	
$p_{interaction}$ for treatment and history of heart failure	..	..	0·581	..	..	..

MACE=major adverse cardiovascular endpoint. *Before or after index acute coronary syndrome event. †Upper bound of the one-sided 95% CI, α=0·01.

Table 2: **Risk of composite primary and secondary endpoints and components by history of heart failure at baseline***

	Alogliptin (n=2701)	Placebo (n=2679)	Hazard ratio (95% CI)	p value
Composite	433 (16·0%)	441 (16·5%)	0·98 (0·86–1·12)	0·728
All-cause mortality	106 (3·9%)	131 (4·9%)	0·80 (0·62–1·03)	0·081
Non-fatal myocardial infarction	171 (6·3%)	155 (5·8%)	1·10 (0·88–1·37)	0·393
Non-fatal stroke	28 (1·0%)	29 (1·1%)	0·97 (0·58–1·62)	0·898
Urgent revascularisation due to unstable angina	43 (1·6%)	47 (1·8%)	0·90 (0·60–1·37)	0·632
Hospital admission for heart failure	85 (3·1%)	79 (2·9%)	1·07 (0·79–1·46)	0·657

Table 3: **Risk of composite prespecified exploratory endpoint and first occurrence of components**

categorical variables and descriptive statistics for continuous variables. Time to the first occurrence of an endpoint component was analysed with Cox's proportional hazards model. For the component analysis of the post-hoc composite endpoint of cardiovascular death and hospital admission for heart failure, all cardiovascular deaths were included without censoring by hospital admission. Recurrent admissions for heart failure were analysed with the conditional model of Prentice and colleagues.[12] This model included treatment as the single factor and was stratified by geographic region and renal function at baseline. Changes from baseline in HbA_{1c} and NT-pro-BNP concentrations were assessed with an ANCOVA model with terms for treatment, geographic region, and renal function at baseline, and the corresponding baseline HbA_{1c} and NT-pro-BNP values as covariates. Incidence of hypoglycaemia was analysed by logistic regression with terms for treatment, geographic region, and screening renal function, and baseline HbA_{1c} concentration as a covariate. All statistical analyses were assessed at a two-sided significance level of 5% and all CI were reported as two-sided values with a confidence level of 95%. No adjustments were made to the nominal p values for multiple testing. All statistical analyses were done with SAS (version 9.2). This study is registered with ClinicalTrials.gov, number NCT00968708.

Role of funding source

The funder of the study supervised enrolment of patients and study conduct at the clinical sites and collaborated with the authors in data interpretation and writing of the report, but had no role in study design, data collection, and data analysis. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

5380 patients were enrolled, of whom 2701 received alogliptin and 2679 received placebo (figure 1). Approximately 60% of the patients with heart failure at baseline had a history of heart failure before the index acute coronary syndrome event. Patients with history of heart failure at baseline were older, more frequently women, and had higher baseline BNP concentrations and lower eGFR values, than patients with no history of heart failure (table 1). Otherwise, baseline characteristics were similar. Additionally, within each

	All patients		History of heart failure at baseline		No history of heart failure at baseline	
	Alogliptin (n=2701)	Placebo (n=2679)	Alogliptin (n=771)	Placebo (n=762)	Alogliptin (n=1930)	Placebo (n=1917)
Cardiovascular death and hospital admission for heart failure	201 (7·4)	201 (7·5)	107 (13·9)	120 (15·7)	94 (4·9)	81 (4·2)
Hazard ratio (95% CI)	1·00 (0·82–1·21)		0·90 (0·70–1·17)		1·14 (0·85–1·54)	
p value	0·976		0·446		0·337	
$p_{interaction}$ for treatment and history of heart failure	..	..	0·221	..	..	..
Cardiovascular death*	112 (4·1)	130 (4·9)	55 (7·1)	69 (9·1)	57 (3·0)	61 (3·2)
Hazard ratio (95% CI)	0·85 (0·66–1·10)		0·77 (0·54–1·09)		0·92 (0·64–1·32)	
p value	0·212		0·141		0·643	
$p_{interaction}$ for treatment and history of heart failure	..	..	0·508	..	..	..
Hospital admission for heart failure	106 (3·9)	89 (3·3)	63 (8·2)	65 (8·5)	43 (2·2)	24 (1·3)
Hazard ratio (95% CI)	1·19 (0·90–1·58)		1·00 (0·71–1·42)		1·76 (1·07–2·90)	
p value	0·220		0·996		0·026	
$p_{interaction}$ for treatment and history of heart failure	..	..	0·068	..	..	..

*Analysis includes all cardiovascular deaths, including those that followed heart failure that were not counted in the analysis of the composite endpoint.

Table 4: **Risk of events assessed in the post-hoc analysis, by history of heart failure**

heart failure subgroup, baseline characteristics did not differ by treatment assignment (table 1). The median follow up time was 533 days (IQR 280–751).

At baseline, more than 80% of patients were taking angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers and β blockers (table 1). More patients with history of heart failure at baseline were taking diuretics at baseline than those without a history of heart failure. Initiation of loop diuretic therapy after randomisation was similar in the alogliptin and placebo groups, including by history of heart failure at baseline (appendix).

Results for the primary and secondary composite MACE endpoints were similar in the alogliptin and placebo groups, for all patients and by history of heart failure, with no significant interactions seen between endpoints and history of heart failure (table 2). The risk of cardiovascular events was substantially higher in patients with a history of heart failure at baseline than in those with no history of heart failure (table 2).

The risks of the exploratory extended composite MACE endpoint and for its separate components, was similar in the alogliptin and placebo groups (table 3). The risk of hospital admission for heart failure occurring as the first event also did not differ significantly between treatment groups (table 3).

The risk of events assessed in the post-hoc composite endpoint of cardiovascular death and hospital admission for heart failure was similar for alogliptin and placebo, in the whole cohort and by history of heart failure at baseline (table 4, figure 2), despite a higher event rate in patients with a history of heart failure. Furthermore, we found no significant difference in the component events between alogliptin and placebo in the whole cohort (table 4). For patients with a history of heart failure at baseline, risk of cardiovascular death and hospital admission for heart failure was similar in the two treatment groups. In those without a history of heart failure at baseline, the risk of cardiovascular death was similar in the two treatment groups, but that of hospital admission for heart failure was higher in the alogliptin group. We found no interaction between treatment and history of heart failure (table 4). The risk of recurrent hospital admission for heart failure was similar for the alogliptin and placebo groups (HR 1·05, 95% CI 0·82–1·34, p=0·707). Post-hoc analysis of all-cause death and hospital admission for heart failure yielded results consistent with those for cardiovascular death and hospital admission for heart failure (history of heart failure before randomisation HR 0·91, 95% CI 0·71–1·16, p=0·445; no history of heart failure before randomisation 1·07, 0·82–1·39, p=0·641).

See Online for appendix

Risk of cardiovascular death and hospital admission for heart failure increased proportionally with increasing quartile of baseline BNP concentration, and rates were similar for alogliptin and for placebo in all quartiles (figure 3). The rate of cardiovascular death was similar in the alogliptin and placebo groups in the first to third quartiles of BNP concentration, but was significantly higher in the placebo group in the highest quartile (figure 3). No significant differences were seen between treatments for hospital admission for heart failure in any quartile of BNP concentration (figure 3).

Concentrations of NT-pro-BNP decreased significantly from baseline to 6 months in the alogliptin group (median value at baseline 423 pg/mL [IQR 156–1103] *vs* 220 pg/mL [89–551] at 6 months, p<0·001). Similar changes were observed in the placebo group (399 pg/mL [149–982] *vs* 213 pg/mL [88–564], p<0·001) The difference in change between treatment groups was not

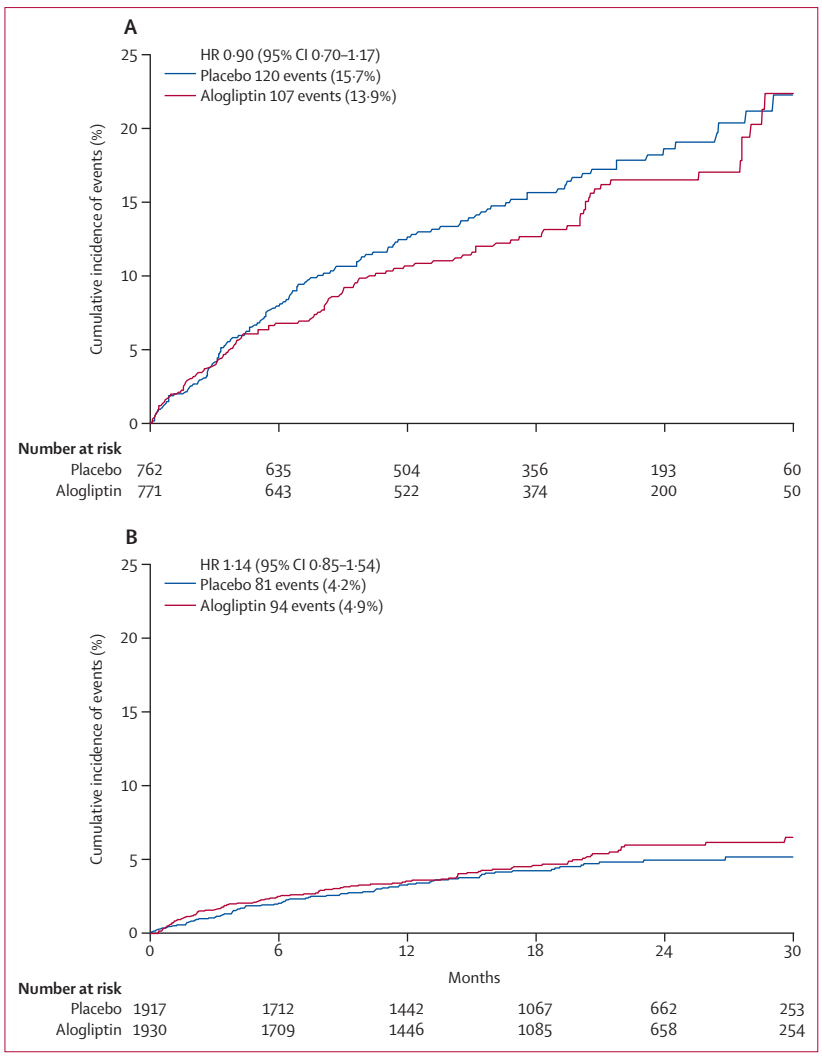

Figure 2: **Kaplan-Meier curves of the post-hoc composite endpoint**
(A) Patients with a history of heart failure at baseline at risk of cardiovascular death and hospital admission for heart failure. (B) Patients without a history of heart failure at baseline at risk of cardiovascular death and hospital admission for heart failure. HR=hazard ratio.

significant (p=0·077). In patients with a history of heart failure at baseline, NT-pro-BNP concentrations were higher than in those without. Concentrations decreased significantly from baseline to 6 months in the alogliptin (699 pg/mL [210–1712] *vs* 389 pg/mL [146–1022], p<0·001) and placebo groups (630 pg/mL [230–1648] *vs* 374 pg/mL [142–987], p<0·001), with no significant difference between treatment groups (p=0·831).

HbA_{1c} concentrations were, overall, significantly lower in the alogliptin group than in the placebo group at the end of the trial (least squares mean difference –0·36%, p<0·001). Changes from baseline to study end did not differ significantly between treatments within history of heart failure subgroups (appendix). Additionally, the incidence of hypoglycaemia was similar in patients with and without history of heart failure at baseline (appendix).

Discussion

The EXAMINE trial showed that treatment with the DPP-4 inhibitor alogliptin had similar outcomes for heart failure to placebo in patients with type 2 diabetes and a recent acute coronary syndrome event (panel). Subgroup analyses by history of heart failure at baseline showed that alogliptin did not lead to more new hospital admissions for heart failure or worse outcomes for existing heart failure outcomes in patients with the comorbidity of heart failure. Previously, we had reported that the rate of MACE was similar in patients receiving alogliptin and placebo.[10] Hence, our findings in this report that alogliptin neither increased cardiovascular morbidity or mortality nor worsened heart failure outcomes are reassuring for patients with type 2 diabetes and increased cardiovascular risk, including those with recent acute coronary syndrome events and a history of heart failure. While these analyses are limited by their post-hoc nature, their interpretation is strengthened by the relatively large sample size, high event rates, and prespecified, prospectively adjudicated outcomes.

Epidemiological studies show that type 2 diabetes nearly doubles the likelihood of developing heart failure.[1] Additionally, the hazard of incident heart failure is increased by 66% in people with type 2 diabetes and is affected by poor metabolic control.[13] In a systematic review and meta-analysis in patients with type 2 diabetes, the overall adjusted risk ratio for heart failure was 1·15 [95% CI 1·10–1·21] for each percentage point increase of HbA_{1c}.[14] Therefore, improved glycaemic control over time could be speculated to prevent new hospital admissions for heart failure in patients with type 2 diabetes, although this finding was not noted in the EXAMINE trial. However, due to its intermediate median duration of treatment of 18 months, the results of EXAMINE do not rule out the possibility of longer-term benefits or risks of alogliptin with respect to cardiovascular endpoints, including heart failure.

The safety and efficacy of type 2 diabetes therapies in patients with heart failure have not been thoroughly addressed in prospective clinical trials.[15] Metformin is widely used in patients with heart failure relatively safely, provided they do not have severe renal or hepatic impairment,[16–19] but there are few data on heart failure outcomes. Thiazolidinediones might cause sodium and water retention leading to increased risk of worsening heart failure and hospital admission, while the risk of cardiovascular death has not been increased with this class of type 2 diabetes therapy.[20–22] For the DPP-4 inhibitors, the results from EXAMINE show that alogliptin has not induced increases in heart failure in a group of patients at high risk of cardiovascular events with type 2 diabetes across a wide spectrum of renal function.

In EXAMINE, adjudicated hospital admission for heart failure as a component in a prespecified exploratory composite endpoint that also included all-cause mortality, non-fatal myocardial infarction, non-fatal

stroke, and urgent revascularisation due to unstable angina was not significantly different between alogliptin and placebo. A more specific composite endpoint to assess heart failure risk, cardiovascular death, and hospital admission for heart failure, also did not show a difference in risk between alogliptin and placebo. Even in the subgroup of patients at the highest risk of death and hospital admission for heart failure—those with a history of heart failure—the composite endpoint of cardiovascular death and hospital admission for heart failure was not increased with alogliptin. Interestingly, the alogliptin profile for the composite outcome in this high-risk subgroup was characterised by non-significant trends of reduced cardiovascular death and increased hospital admission for heart failure suggesting the possibility of a survivor bias. In the lower-risk subgroup of patients without a history of heart failure at baseline, there was also no increased risk of the composite endpoint of cardiovascular death and hospital admission for heart failure for alogliptin versus placebo, although there was a small absolute increase in hospital admission for heart failure for alogliptin versus placebo (0·9%). However, in this same group of patients, cardiovascular-death rates were nominally lower in those taking alogliptin and diuretic use was not increased compared with placebo. Hence, on the basis of this evidence, the finding of a higher rate of hospital admission for heart failure with alogliptin in patients without a history of heart failure at baseline could be due to chance. The results of the conventional heart failure composite endpoint, which avoids confounding by mortality, shows that alogliptin does not increase the risk of heart failure outcomes.

Preclinical and clinical studies have investigated the cardiovascular effects of DPP-4 inhibitors or GLP-1 analogues in heart failure experimental models or heart failure patients[23–25] and shown improvements in cardiac function and protection against the development of adverse remodelling, suggesting that incretin-based therapy could have potential as a novel therapeutic strategy in heart failure patients with type 2 diabetes. In addition, circulating DPP-4 activity has been shown to correlate with poor cardiovascular outcomes in human and experimental heart failure, and long-term DPP-4 inhibition has mitigated the development and progression of heart failure in rats.[26] Taken together, current experimental knowledge raises the possibility of using DPP-4 as a diagnostic surrogate or a therapeutic target for chronic heart failure. Few randomised controlled trials have reported heart failure outcomes data on either DPP-4 inhibitors or GLP-1 analogues. Compared with other cardiovascular safety studies of antihyperglycaemic therapies,[8,27,28] our population included patients at substantially higher cardiovascular risk. In patients with left ventricular ischaemic systolic dysfunction, infused GLP-1 improved cardiac function in patients with diabetes,[29] but not in patients without type 2 diabetes.[30]

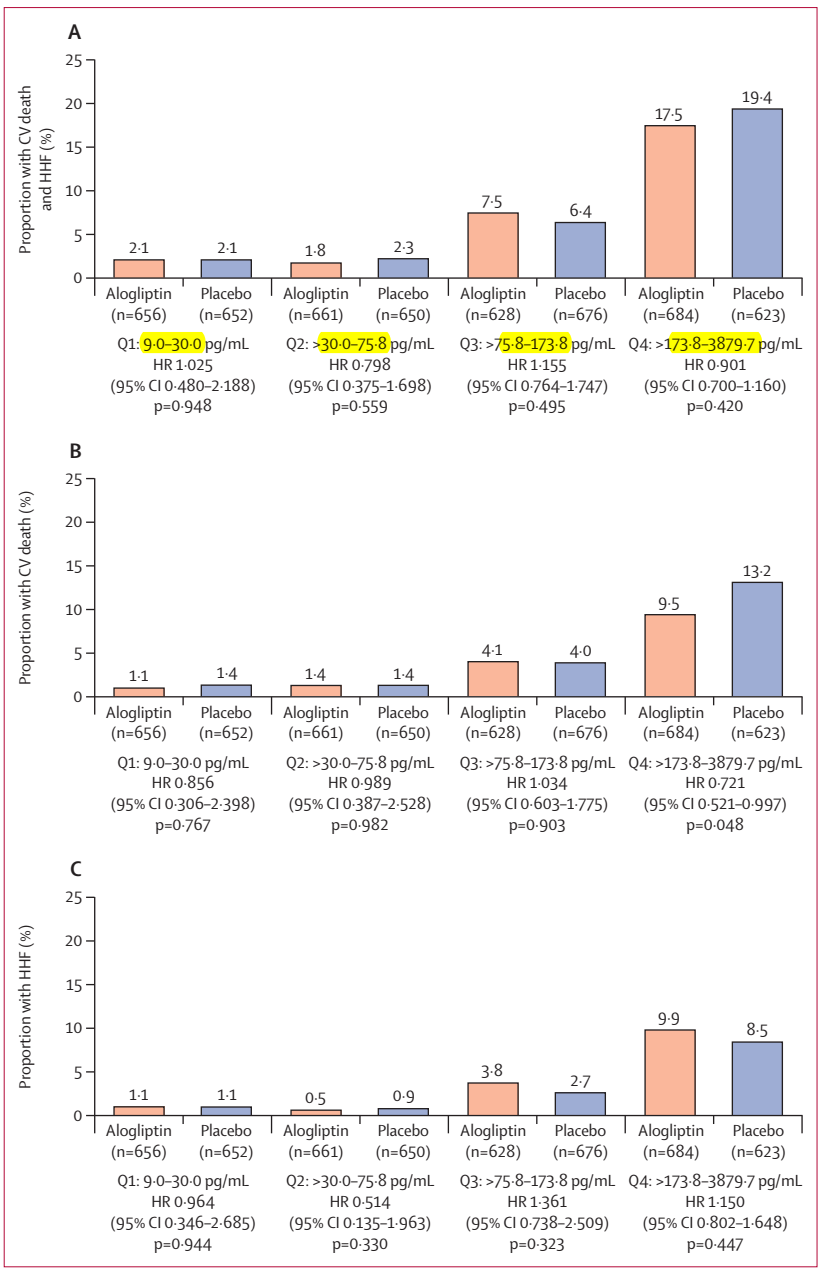

Figure 3: **Rates of the composite post-hoc endpoint and separate components by quartile of brain natriuretic peptide concentration at baseline**
CV=cardiovascular. HHF=hospital admission for heart failure. HR=hazard ratio. Q=quartile.

Hence, other exploratory studies are in progress.[15,23] The results of a randomised placebo-controlled mechanistic study entitled Vildagliptin in Ventricular Dysfunction Diabetes trial (VIVIDD)[31] tested the effects of the DPP-4 inhibitor vildagliptin added to standard glucose-lowering treatment and standard heart failure therapy in 254 patients with both type 2 diabetes and heart failure and systolic dysfunction. The primary endpoint was the change in left ventricular ejection fraction over 52 weeks, to demonstrate non-inferiority compared with placebo.

Panel: **Research in context**

Systematic review

In December, 2008, the US Food and Drug Administration advised that to establish the safety of a new therapy to treat type 2 diabetes, pharmaceutical manufacturers should show that it will not result in an unacceptable increase in cardiovascular risk. We searched PubMed for supporting studies with the search terms "cardiovascular safety of diabetes therapies". Major trials of cardiovascular outcomes in patients with type 2 diabetes treated with dipeptidyl dipeptidase-4 inhibitors were started as a direct result of the Food and Drug Administration guidance. The SAVOR TIMI 53 trial,[8,9] enrolled patients with type 2 diabetes and a history or risk of cardiovascular events. The EXAMINE trial,[10] enrolled patients with type 2 diabetes and a recent acute coronary syndrome event. Both trials assessed non-inferiority for risk of major adverse cardiovascular events (MACE). In SAVOR TIMI 53, the rates of hospital admission for heart failure were significantly higher with saxagliptin than with placebo, particularly in patients with the highest concentrations of brain natriuretic peptide at study baseline. Because the risk of developing heart failure is notably increased in patients with type 2 diabetes and because diabetes adversely affects the outcomes of patients with established heart failure, antihyperglycaemic treatment strategies in patients with heart failure are an important area for investigation.

Interpretation

We assessed data for a prespecified endpoint and did a post-hoc analysis of heart failure outcomes for alogliptin in the EXAMINE trial. We found that risk of cardiovascular outcomes, including hospital admission for heart failure, was not increased with alogliptin compared with placebo. This finding was not affected by a history of heart failure, raised NT-pro brain natriuretic peptide concentration, or both at baseline. Additionally, patients treated with alogliptin and placebo had similar reductions in NT-pro brain natriuretic peptide concentrations after 6 months of treatment, and use of diuretics was similar in the two groups. Thus, volume expansion due to alogliptin was unlikely in high-risk patients with type 2 diabetes and recent acute coronary syndromes.

While the effect of vildagliptin on left ventricular ejection fraction was non-inferior to that of placebo and the drug reduced HbA_{1c} concentrations compared with placebo, it also increased left ventricular end-diastolic and end-systolic volume. BNP concentrations decreased equally with vildagliptin and placebo. The authors hypothesised that such combination of findings might be explained by an increase in left ventricular compliance. In EXAMINE, we assessed the changes in NT-pro-BNP serum concentrations in all patients who had available data at baseline and at 6 months after randomisation. Although it has been reported that BNP is a substrate to DPP-4, there is no evidence that this might be also the case for NT-pro-BNP.[32] Of note, NT-pro-BNP levels decreased significantly in all patients as well as in patients with history of heart failure, and to a similar extent in patients randomised to alogliptin or placebo. That NT-pro-BNP, a powerful marker of filling pressures, was not increased by alogliptin suggests that this therapy does not seem to have an adverse effect on filling pressures, consistently with the lack of increased heart failure outcomes.

The EXAMINE and SAVOR TIMI 53 trials[8–10] represent the first placebo-controlled cardiovascular safety trials of antidiabetic drugs in patients with increased cardiovascular risk according to the 2008 FDA guidance.[33] Neither trial showed an increase in the primary endpoint of MACE, either in patients with a recent acute coronary syndrome event (EXAMINE)[10] or in patients who had a history of or were at risk of cardiovascular events.[8,9] In SAVOR TIMI 53, more patients in the saxagliptin group than in the placebo group were admitted to hospital for heart failure (3·5% *vs* 2·8%, according to 2-year Kaplan-Meier estimates; HR 1·27, 95% CI 1·07–1·51, p=0·007). The explanation for the discrepant results between SAVOR TIMI 53 and EXAMINE is unclear, but SAVOR TIMI 53 analyses of the composite endpoint of all-cause death and hospital admission for heart failureand of changes in NT-proBNP could be informative. The cardiovascular risk of the study population was clearly higher in EXAMINE, as all patients were enrolled shortly after an acute coronary syndrome event, and, indeed, the annualised cardiovascular event rate was around twice that in SAVOR TIMI 53. In subsets of patients at highest cardiovascular risk, either because of prevalent heart failure (tables 2, 4) or with the highest baseline BNP concentrations (figure 2), heart failure outcomes for alogliptin were consistently similar to those for placebo. By contrast, the increase in absolute risk of hospital admission for heart failure with saxagliptin in SAVOR TIMI 53 was highest among patients with raised baseline concentrations of natriuretic peptides and established cardiovascular disease.[9]

Meta-analyses[34,35] have suggested small but significant increases in heart failure outcomes in patients with type 2 diabetes treated with DPP-4 inhibitors. However, the results of these meta-analyses should be interpreted with caution, since they are substantially affected by the results from SAVOR TIMI 53, which contributed almost 70% of the hospital admissions for heart failure events. As reported here, the hospital admission for heart failure results from the two largest trials with the greatest treatment exposure (EXAMINE and SAVOR TIMI 53) differ. The issue as to whether the effect of DPP-4 inhibition on hospital admission for heart failure is a class effect might become more clear when the results of other continuing placebo-controlled large trials, such as the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS),[36] become available.

Intrinsic pharmacological differences, including differences in pharmacokinetics between the agents are unlikely to explain the differential effect on heart failure outcomes.[37] The association between mortality and HbA_{1c} in patients with type 2 diabetes and heart failure seems to be U shaped, with the lowest risk of death being in patients with intermediate glucose control (HbA_{1c} values of 54·1–61·7 mmol/mol [7·1–7·8%]) and with risk being increased in those with extremely high or low HbA_{1c} concentrations.[38,39] The effects of DPP-4 inhibition on glycaemic control was similar in the EXAMINE and SAVOR TIMI 53 trials. Thus, it is unlikely that glycaemic control could explain the differential effects on heart failure outcomes. Furthermore, whether different rates

of hypoglycaemic events could play a role in the differential findings is only speculative, since the definition of hypoglycaemic events was not consistent in the two trials.[8,10]

In conclusion, in patients with type 2 diabetes and recent acute coronary syndrome events, the EXAMINE trial showed that alogliptin does not increase the risk of heart failure outcomes, including cardiovascular death and hospital admission for heart failure. Additionally, reductions in NT-pro-BNP concentrations with alogliptin therapy and use of diuretics (both thiazide and loop) were similar to that seen with placebo at 6 months.

Contributors

FZ, CPC, WCC, ATP, PRF, CRM, SK, HL, and WBW designed the study and FZ, CPC, WCC. ATP, PRF, CRM, and WBW oversaw the execution and completion of the study. CW and HL did the statistical analysis. FZ, CPC, WCC, GLB, VM, ATP, PRF, CRM, SK, CW, and WBW were involved in data analysis and interpretation. FZ, GLB, VM, PRF, SK, HL, and WBW contributed to the writing of the report, and CPC, WCC, PRF, CRM, and WBW to the editing of drafts.

Declaration of interests

FZ has received personal fees from Air Liquide, Bayer, Biotronik, Boston Scientific, Janssen, Novartis, Pfizer, Resmed, Servier, St Jude, and Takeda, and non-financial support from Cardiorenal Diagnostics and CVCT. CPC has received grants from Accumetrics, Arisaph, AstraZeneca, Boehringer Ingelheim, CSL Behring, Essentialis, GlaxoSmithKline, Janssen, Merck, Regeneron, Sanofi, and Takeda. WCC has received personal fees from Janssen, Lilly, Merck, National Heart, Lung, and Blood Institute, and Takeda. GLB has received grants from Medtronic, Reypsa, and Takeda, and other support from Bayer, CVRx, Eli Lilly/Boeringher Ingelheim, GlaxoSmithKline, Janssen, Medtronic, and Novartis. VM has received support via institutional research funding from Takeda. ATP, CW, and HL are employees of Takeda Development Center Americas. PRF and SK are employees of Takeda Pharmaceuticals International. CRM is an employee of Cytel software and consulting services. WBW has recevied personal fees from Ardea Biosciences, AstraZeneca, Forest Research Institute, Roche, Takeda, and Teva, and is a member of cardiovascular endpoint committees for other compounds.

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