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CLINICAL RESEARCH

Effects of Vildagliptin on Ventricular Function in Patients With Type 2 Diabetes Mellitus and Heart Failure

A Randomized Placebo-Controlled Trial

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ABSTRACT

OBJECTIVES This study sought to examine the safety of the dipeptidyl peptidase-4 inhibitor, vildagliptin, in patients with heart failure and reduced ejection fraction.

BACKGROUND Many patients with type 2 diabetes mellitus have heart failure and it is important to know about the safety of new treatments for diabetes in these individuals.

METHODS Patients 18 to 85 years of age with type 2 diabetes and heart failure (New York Heart Association functional class I to III and left ventricular ejection fraction [LVEF] <0.40) were randomized to 52 weeks treatment with vildagliptin 50 mg twice daily (50 mg once daily if treated with a sulfonylurea) or matching placebo. The primary endpoint was between-treatment change from baseline in echocardiographic LVEF using a noninferiority margin of −3.5%.

RESULTS A total of 254 patients were randomly assigned to vildagliptin (n = 128) or placebo (n = 126). Baseline LVEF was 30.6 ± 6.8% in the vildagliptin group and 29.6 ± 7.7% in the placebo group. The adjusted mean change in LVEF was 4.95 ± 1.25% in vildagliptin treated patients and 4.33 ± 1.23% in placebo treated patients, a difference of 0.62 (95% confidence interval [CI]: −2.21 to 3.44; p = 0.667). This difference met the predefined noninferiority margin of −3.5%. Left ventricular end-diastolic and end-systolic volumes increased more in the vildagliptin group by 17.1 ml (95% CI: 4.6 to 29.5 ml; p = 0.007) and 9.4 ml (95% CI: −0.49 to 19.4 ml; p = 0.062), respectively. Decrease in hemoglobin A_{1c} from baseline to 16 weeks, the main secondary endpoint, was greater in the vildagliptin group: −0.62% (95% CI: −0.93 to −0.30%; p < 0.001; −6.8 mmol/mol; 95% CI: −10.2 to −3.3 mmol/mol).

CONCLUSIONS Compared with placebo, vildagliptin had no major effect on LVEF but did lead to an increase in left ventricular volumes, the cause and clinical significance of which is unknown. More evidence is needed regarding the safety of dipeptidyl peptidase-4 inhibitors in patients with heart failure and left ventricular systolic dysfunction. (Effect of Vildagliptin on Left Ventricular Function in Patients With Type 2 Diabetes and Congestive Heart Failure; NCT00894868) (J Am Coll Cardiol HF 2018;6:8-17) © 2018 by the American College of Cardiology Foundation.

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Type 2 diabetes is common in patients with heart failure, with reported prevalences of between 25% and 40% in trials and registries (1–5). Heart failure patients with diabetes have worse symptoms, greater functional limitation, and higher rates of hospitalization and death than heart failure patients without diabetes (1–5). The safety of established treatments for diabetes in patients with heart failure is uncertain. Sulfonylureas and insulin can cause hypoglycemia and it has been thought that metformin may increase the risk of lactic acidosis, although this has never been demonstrated (6,7). Thiazolidinediones increase the risk of patients with diabetes developing heart failure (8,9). Thiazolidinediones also increase the risk of worsening of heart failure in patients with that condition (10,11).

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Consequently, it is important that the safety of new treatments for diabetes is studied in patients with heart failure. One group of new treatments is the dipeptidyl peptidase (DPP)-4 inhibitors, which block the degradation of endogenous glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP), which stimulate insulin secretion in a glucose-dependent manner, suppress glucagon release, and slow gastric emptying (12–14). Three recent large, randomized controlled trials have reported conflicting evidence about the risk of heart failure with different agents in this class (15–17). None, however, characterized patients with heart failure at baseline or those developing heart failure during follow-up. Furthermore, none of the studies examined the effect of a DPP-4 inhibitor on left ventricular function. Here we report a study of the effects of the DPP-4 inhibitor vildagliptin in patients with heart failure and reduced ejection fraction (HFrEF) (18,19).

METHODS

The VIVIDD (Vildagliptin in Ventricular Dysfunction Diabetes) trial was a prospective, randomized, double-blind, parallel-group trial comparing vildagliptin with placebo, added to standard therapy for 52 weeks in patients with type 2 diabetes and HFrEF. An ethics committee approved the trial at each site, and patients provided written informed consent. Patient safety was reviewed by an independent committee throughout the trial and cardiovascular, hepatic, and cutaneous (including suspected angioedema) adverse events were adjudicated by independent and masked committees. All echocardiographic analyzes were carried out by blinded assessors in a core laboratory (Perceptive Informatics Inc., Billerica, Massachusetts). The study results were analyzed by Novartis and confirmed by (J.L.) an independent statistician at the University of Glasgow.

ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

DPP = dipeptidyl peptidase

GLP = glucagon-like peptide

HFrEF = heart failure and reduced ejection fraction

NYHA = New York Heart Association

PARTICIPANTS. Briefly, men and women between 18 and 85 years of age with type 2 diabetes (hemoglobin A_{1c}: 6.5% to 10.0% [48.0 to 86.0 mmol/mol]), body mass index ranging from 22 to 42 kg/m^2, heart failure with a reduced ejection fraction (<40%), and in New York Heart Association (NYHA) functional class I to III were eligible. The key exclusion criteria were NYHA functional class IV, a fasting plasma glucose concentration of ≥15 mmol/l, receiving thiazolidinedione or incretin therapy, a recent cardiovascular event or procedure, creatinine clearance of <30 ml/min, and liver disease or elevated transaminases or bilirubin.

RANDOMIZATION AND MASKING. Eligible patients were randomly assigned in a 1:1 ratio according to a central randomization scheme, stratified by NYHA functional class, to 1 of 2 treatment groups: vildagliptin, 50 mg twice daily (50 mg once daily if concomitant treatment with a sulfonylurea) or placebo. Randomization was conducted using an interactive voice response system. Vildagliptin and placebo were identical in packaging, labelling, appearance, and schedule of administration.

PROCEDURES. From May 4, 2009 (Figure 1), subjects who met the inclusion/exclusion criteria (including echocardiographic criteria) at the screening visit entered a 2- to 4-week run-in period during which the individuals continued their usual diet, exercise regimen, and drug therapy for diabetes (if taking drug therapy). Patients completing this period returned for baseline assessment including measurement of B-type natriuretic peptide (BNP) and were then randomized to vildagliptin or placebo as described above. Patients were examined every 4 weeks up to week 24 and every 8 weeks thereafter

Novartis. Dr. Bolli is a consultant to and has been paid for giving lectures for Sanofi-Aventis and Menarini. Dr. Ponikowski is a consultant for Novartis and Boehringer Ingelheim. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Dr. Krum is deceased.

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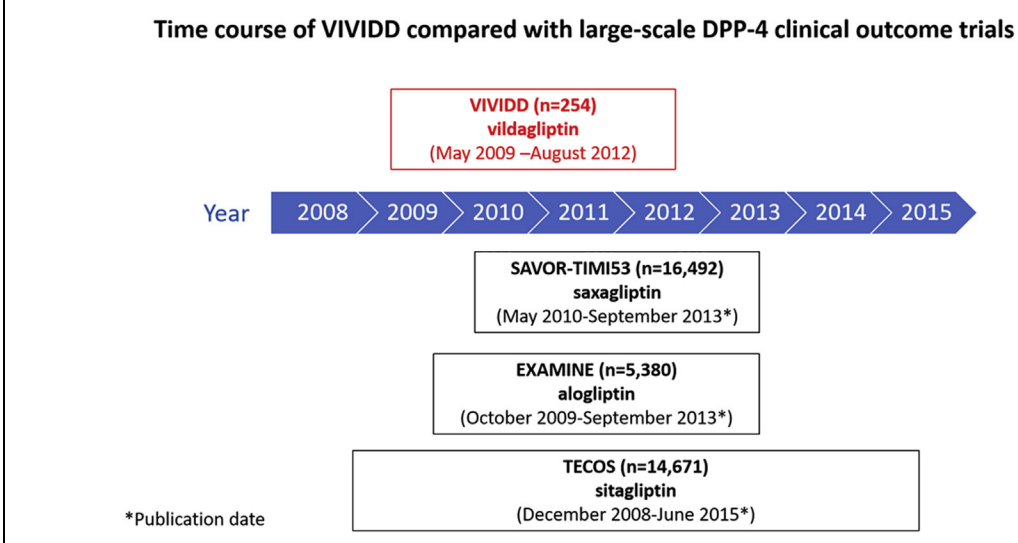
FIGURE 1 Study Timeline



DPP = dipeptidyl peptidase; EXAMINE = Examination of Cardiovascular Outcomes With Alogliptin vs Standard of Care; SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus-Thrombolysis In Myocardial Infarction 53; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; VIVIDD = Vildagliptin in Ventricular Dysfunction Diabetes trial.

(diabetes "rescue" therapy could be used from week 16 onward). Repeat BNP measurements and echocardiography were performed at 24 and 52 weeks. Patients who permanently stopped treatment before 52 weeks were asked to return for a final assessment, including an echocardiogram and BNP measurement. Factors of NYHA functional class, dyspnea, and edema were evaluated at baseline and at each of the follow-up visits, as was blood chemistry (including hemoglobin A_{1c}) and hematological measurements.

ECHOCARDIOGRAPHY. Each echocardiogram was analyzed by a minimum of 2 qualified echocardiographers blinded to treatment assignment and according to a pre-specified protocol. The Simpson biplane method of discs was used to calculate LVEF (20).

B-TYPE NATRIURETIC PEPTIDE. B-type natriuretic peptide was measured using a triage Beckman Coulter immunoassay (Covance Central Laboratory, Princeton, New Jersey).

STUDY OBJECTIVES. This was a safety study. The primary objective was to show that vildagliptin was at least noninferior to placebo with respect to change in LVEF from baseline to end of study. Recognizing that not all patients would complete the planned maximum of 52 weeks of treatment and that an effect of drugs on left ventricular remodeling may be apparent within 6 months, the original protocol was altered during the trial (but before any results were known) to define the primary analysis of LVEF to include any patient who had at least 1 follow-up echocardiogram recorded 22 weeks or more after randomization. The key secondary endpoint consisted of a change in hemoglobin A_{1c} from baseline to 16 weeks (with censoring for use of rescue therapy before that time point).

SAFETY ASSESSMENTS. In addition to conventional adverse event reporting, specific safety assessments were made including assessment of NYHA functional class and breathlessness and edema at each study visit and adjudication of suspected worsening heart failure symptoms (Online Table 1), and possible cardiovascular, liver, and cutaneous events, as well as deaths, by the adjudication committees described above.

STATISTICAL ANALYSIS. The study sample size was calculated based upon 90% power and a 1-sided significance level of 0.025 to declare noninferiority of vildagliptin compared with placebo for the effect of treatment of LVEF, using a margin of −3.5% and an expected difference between the 2 treatments of 0%. The choice of the noninferiority margin was based on clinical importance and prior use (10). The calculation was performed using nQuery Advisor version 5.0 (Statsols, Cork, Ireland) and based on a LVEF ±7% (derived from prior trials). We calculated that a total of 172 patients with at least 1 LVEF measurement after randomization were required. The sample size

was inflated to 246 patients to allow for approximately 30% of patients not having an LVEF measurement after randomization. An analysis of covariance model (ANCOVA) was fitted, including terms for treatment, baseline LVEF, NYHA functional class, and region. The least-square mean (LSM, "adjusted mean") change from baseline in LVEF was calculated for each treatment group and the difference in LSM between the 2 treatment groups and the 2-sided 95% confidence interval (CI) were obtained from this model.

An ANCOVA model fitted with terms for treatment, baseline hemoglobin A_{1c}, and region was used to analyze LSM change in hemoglobin A_{1c}. Other exploratory variables were analyzed in a similar way with appropriate transformations if the normality assumption was questionable. The statistical software used was SAS version 9.2 (Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS AND TREATMENT. A total of 254 patients were randomized at 67 sites in 15 countries. Their mean age was 63 years of age, and 77% were male. Other key demographic characteristics, medical history, and treatment at baseline are shown in Table 1. The first patient visit was May 4, 2009, and the last patient visit was August 13, 2012. Overall, patients had a mean duration of diabetes of 9.3 years (median: 6.8 years), and the mean hemoglobin A_{1c} at baseline was 7.8% (62.0 mmol/mol); 34% of patients were treated with metformin, and the same proportion with insulin, either as monotherapy or in combination with other glucose-lowering agents. The median duration of heart failure was 3.3 years, mean left ventricular ejection fraction was 30%, median BNP was 231 pg/ml, and most patients were in NYHA functional class II (53%) or III (37%); 48% of patients had a history of hospital admission for heart failure. More than 90% of patients were treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; 78% with a beta-blocker; and 42% with a mineralocorticoid receptor antagonist. Baseline characteristics between treatment groups were well balanced, except that more patients in the vildagliptin treatment group had a history of smoking, prior hospitalization for heart failure, or chronic obstructive pulmonary disease.

FOLLOW-UP AND ADHERENCE. Overall, 101 patients (79%) assigned to vildagliptin and 100 patients (79%) assigned to placebo completed the 52-week follow-up as planned (Figure 2). There were 11 deaths (8.6%) in the vildagliptin group and 4 deaths (3.2%) in the

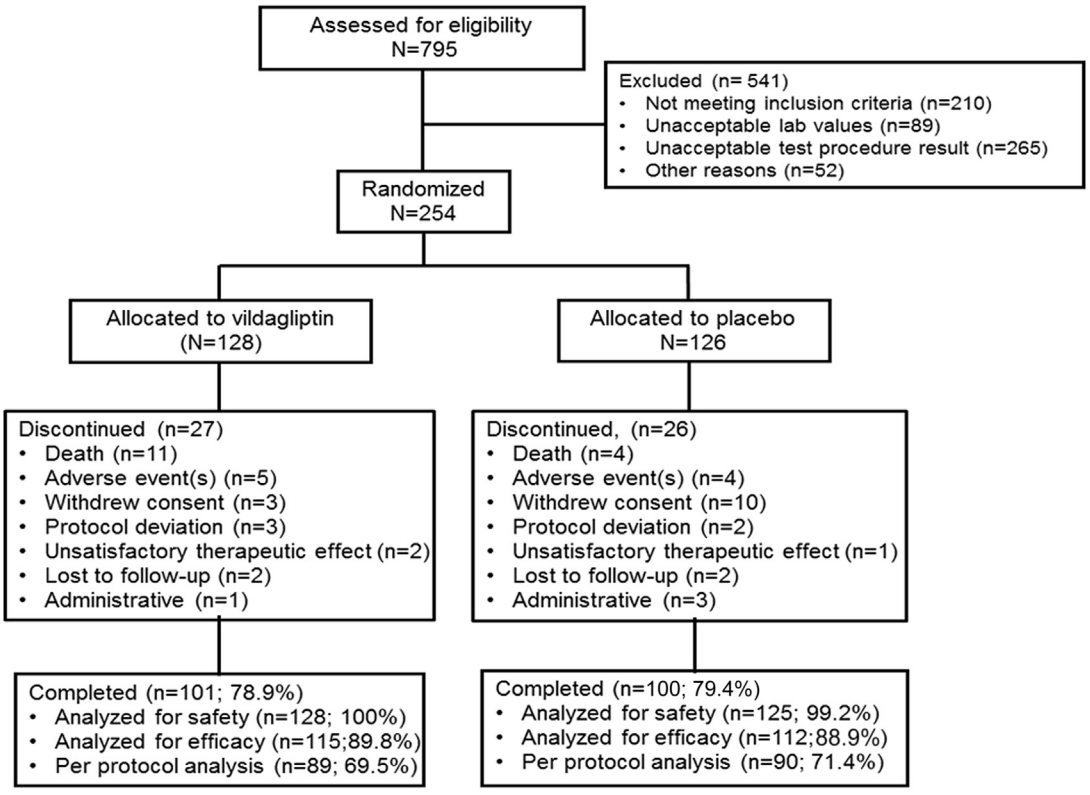
TABLE 1 Baseline Characteristics of Patients and Treatment

	Vildagliptin (n = 128)	Placebo (n = 126)
Age, yrs	62.9 ± 8.5	63.4 ± 10.2
Females,	29 (22.7)	30 (23.8)
BMI, kg/m^2	29.6 ± 4.6	29.3 ± 4.7
Obese,	54 (42.2)	50 (39.7)
Current smoker	21 (16.4)	9 (7.1)
Systolic blood pressure, mm Hg	130.4 ± 16.3	127.9 ± 15.3
Diastolic blood pressure, mm Hg	77.6 ± 8.9	77.2 ± 8.7
Heart rate, beats/min	73.1 ± 10.1	73.5 ± 9.3
History		
Myocardial infarction	82 (64.1)	80 (63.5)
Angina pectoris	55 (43.0)	48 (38.1)
CABG	30 (23.4)	30 (23.8)
PCI	24 (18.8)	22 (17.5)
Stroke	12 (9.4)	11 (8.7)
Atrial fibrillation	29 (22.7)	34 (27.0)
Hypertension	112 (87.5)	108 (85.7)
Prior hospitalization for HF	66 (51.6)	55 (43.7)
COPD	16 (12.5)	8 (6.3)
Diabetes status		
Duration of diabetes, yrs	9.5 ± 8.1	9.1 ± 7.8
Hemoglobin A_{1c}, %; mmol/mol	7.8 ± 0.95; 62.0 ± 10.4	7.8 ± 1.07; 62.0 ± 11.7
Heart failure status		
NYHA functional class		
I	13 (10.2)	12 (9.5)
II	68 (53.1)	66 (52.4)
III	47 (36.7)	48 (38.1)
LVEF, %	30.6 ± 6.8	29.6 ± 7.7
LVEF, ≤35%	91 (71.1)	96 (76.2)
BNP, pg/ml	244 (133–558)	217 (113–430)
Treatment, %		
ACE inhibitor	71.8	61.9
ARB	23.4	28.6
Beta-blocker	79.7	76.2
MRA	46.1	37.3
Digitalis glycoside	28.9	23.0
Diuretic (loop)	71.1	70.7
ICD	9.4	7.9
CRT	10.2	11.9
Insulin		
Monotherapy	24.2	24.6
Any	35.2	33.3
Oral anti-diabetes therapy		
Sulfonylurea	46.9	53.2
Metformin	36.7	32.5
AGI	0.8	3.2
Glinide	1.6	0
Any oral therapy	63.3	68.3
Diet only	12.5	7.1

Values are mean ± SD, n (%), median (interquartile range), or %.

ACE = angiotensin-converting enzyme; AGI = alpha-glucosidase inhibitor; ARB = angiotensin receptor blocker; beats/min = beats per minute; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; CABG = coronary artery bypass grafting; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

FIGURE 2 Flow Chart of Participants



placebo group. Other reasons for not completing follow-up were adverse events (5 vildagliptin vs. 4 placebo), withdrawal of consent (3 vs. 10), protocol violation (3 vs. 2), loss to follow-up (2 vs. 2), unsatisfactory therapeutic effect (2 vs. 1), and administrative problems (1 vs. 3). Overall, 16 patients (12.5%) assigned to vildagliptin and 22 patients (17.4%) assigned to placebo discontinued study drug early for reasons other than death.

PRIMARY ENDPOINT: CHANGE IN LVEF. The LVEF was matched between treatment groups at baseline (Table 2). The intention to treat analysis is shown in Figure 3. The pre-specified primary analysis (patients with a baseline and follow-up measurement of LVEF ≥22 weeks) included 89 patients assigned to vildagliptin (mean baseline LVEF of 30.5 ± 0.67%) and 90 assigned to placebo (29.8 ± 0.78%). The adjusted mean change in LVEF was 4.95 ± 1.25%) in the vildagliptin group and 4.33% (± SE 1.23%) in the placebo group; a difference of 0.62% (95% CI: −2.21 to 3.44; p = 0.667). This difference met the predefined noninferiority criterion of −3.5% at p value of 0.025. Examination of the patients (88 vildagliptin, 89 placebo) with a 48-week follow-up measurement of LVEF gave almost identical findings (for sensitivity analyses see Online Table 2).

OTHER ECHOCARDIOGRAPHIC FINDINGS. Changes in left ventricular volumes are shown in Table 2 and Figure 3. Left ventricular end-diastolic volume increased

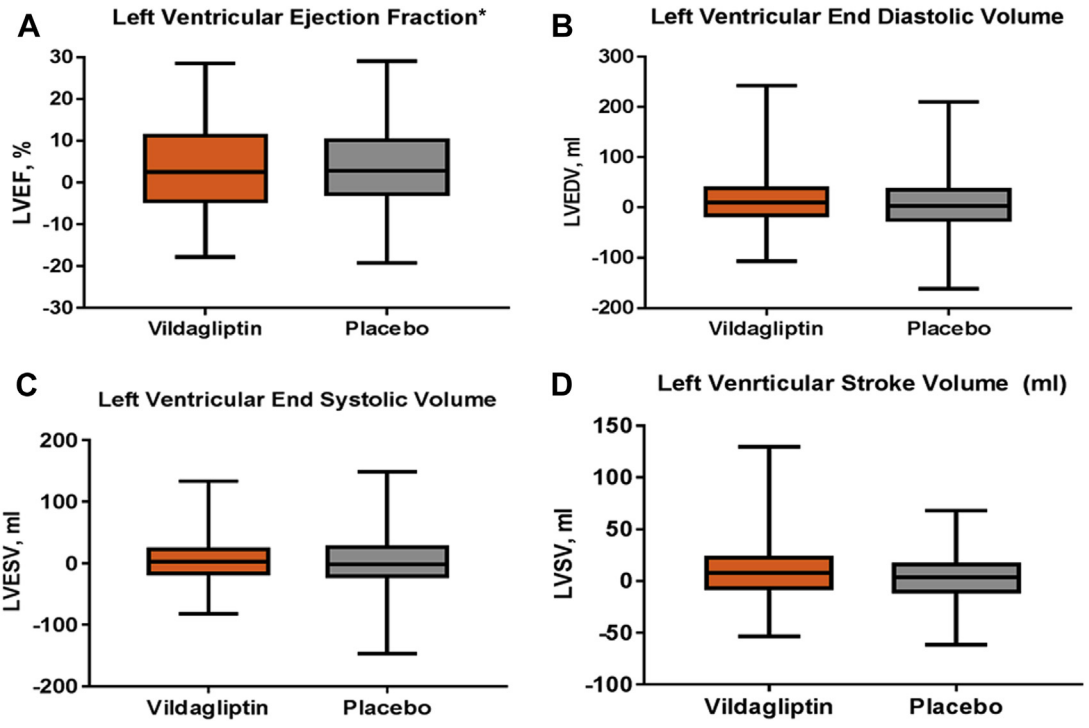
TABLE 2 Baseline Echocardiographic Measurements

	Vildagliptin (n = 128*)	Placebo (n = 126*)
LVIDD, cm†	5.9 ± 0.91	5.9 ± 0.93
LVISD, cm†	5.2 ± 0.93	5.2 ± 0.91
LVEDV, ml*	179 ± 59	168 ± 66
LVESV, ml*	125 ± 44	120 ± 56
LVSV, ml	54.3 ± 21.0	48.1 ± 18.3
LVEF, %	30.6 ± 6.8	29.6 ± 7.7
LV-SWT, cm	1.0 ± 0.24	1.0 ± 0.25
LV-PWT, cm	1.0 ± 0.20	1.0 ± 0.21
LVMi, g/m^2	134 ± 39	130 ± 41

Values are mean ± SD. *Not all measurements were obtained in every patient. †LVEDVi = 92 ml/m^2; LVESVi = 65 ml/m^2.

LVEDV = left ventricular end diastolic volume; LVEDVi = left ventricular end diastolic volume index; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; LVESVi = left ventricular end systolic volume index; LVIDD = left ventricular internal diastolic dimension; LVISD = left ventricular internal systolic dimension; LVMi = left ventricular mass index; LV-PWT = left ventricular posterior wall thickness; LVSV = left ventricular stroke volume; LV-SWT = left ventricular septal wall thickness.

FIGURE 3 Change From Baseline in LVEF (Primary Endpoint) and Other Echocardiographic Measurements



(A) Change in LVEF (%). Differences in adjusted mean change 0.62 (95% CI: −2.21 to 3.44; p = 0.667)*. *Meets criteria for noninferiority to comparator as the lower limit of the 2-sided 95% CI for the differences in mean change in LVEF is >−3.5%. Primary analysis is based on per protocol. **(B)** Change in LVEDV (ml). Differences in adjusted mean change 17.06 (95% CI: 4.62 to 29.51; p = 0.007). Full analysis set. **(C)** Change in LVESV. Differences in adjusted mean change 9.44 (95% CI: −0.49 to 19.38; p = 0.062). Full analysis set. **(D)** Change in the LVSV. Difference in adjusted mean change 9.00 (95% CI: 3.38 to 14.62; p = 0.002). Full analysis set. CI = confidence interval; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; LVSV = left ventricular stroke volume.

significantly with vildagliptin compared with placebo, and there was a trend in the same direction for end-systolic volume which was of borderline statistical significance (6- and 12-month volumes are shown in Online Table 3). There was a significant increase in stroke volume but no change in left ventricular wall thickness or mass.

SECONDARY ENDPOINT: CHANGE IN HEMOGLOBIN A_{1c}. The adjusted mean change from baseline to rescue-censored week 16 hemoglobin A_{1c} was −0.45 ± 0.12% (−4.9 ± 1.3 mmol/mol) in the vildagliptin group and 0.17 ± 0.12% (1.9 ± 1.3 mmol/mol) in the placebo group, with an adjusted mean difference (vildagliptin − placebo) of −0.62% (95% CI: −0.93 to −0.30%; p < 0.001; −6.8 mmol/mol; 95% CI: −10.2 to −3.3 mmol/mol). The difference at week 52 was −0.36% (95% CI: −0.71 to −0.02%; p = 0.040; −3.9 mmol/mol; 95% CI: −7.8 to −0.2 mmol/mol).

CHANGE IN BNP. Baseline geometric mean BNP values for those with an end of study measurement were 227 pg/ml in patients assigned to vildagliptin and 214 pg/ml in those assigned to placebo. A reduction in geometric mean BNP values from baseline was observed in both treatment groups: ratio of 52 weeks/baseline: 0.72 (95% CI: 0.56 to 0.93) in the vildagliptin

TABLE 3 Nonfatal Cardiovascular Events and Deaths

	Vildagliptin (n = 128)	Placebo (n = 126)	Rate Difference, % (95% CI)
Any fatal or nonfatal cardiovascular event*	35 (27.3)	31 (24.6)	2.7 (−9.5 to 15.0)
Death from cardiovascular causes	7 (5.5)	4 (3.2)	2.3 (−10.3 to 14.6)
Worsening heart failure	23 (18.0)	22 (17.5)	0.5 (−11.9 to 12.7)
Acute coronary syndrome	7 (5.5)	3 (2.4)	3.1 (−9.5 to 15.4)
Cardiac arrhythmia	9 (7.0)	4 (3.2)	3.9 (−8.7 to 16.1)
Stroke	1 (0.8)	4 (3.2)	−2.4 (−14.9 to 10.1)
Death from any cause	11 (8.6)	4 (3.2)	5.4 (−7.2 to 17.6)

Values are n (%). *Patients were counted only once, even if there were multiple events. There were 4 noncardiovascular deaths in the vildagliptin group, resulting from hepatic neoplasm, lung neoplasm, septic shock, and surgery for intestinal obstruction due to peritoneal adhesions.

group (n = 75) and 0.86 (95% CI: 0.67 to 1.12) in the placebo group (n = 81). The ratio of ratios (vildagliptin/placebo) was 0.84 (95% CI: 0.62 to 1.14; p = 0.252).

OTHER MEASUREMENTS OF HEART FAILURE STATUS. Changes in dyspnea and edema from baseline over the course of the study were small and did not differ between treatment groups. There was no difference in change in NYHA functional class distribution between the 2 treatment groups, and the proportion of patients with an increase in heart failure medication during the study was 26.6% in the vildagliptin group and 24% in the placebo group (p = 0.640). Specifically, the proportion of patients taking loop diuretics at baseline was 64.8% and 65.9% of patients in the vildagliptin and the placebo groups, respectively, and increased during the study to 71.1% and 72.2%, respectively. Worsening heart failure (including hospitalization for heart failure) was confirmed by the endpoint committee in 23 patients (18.0%) in the vildagliptin group and 22 patients (17.6%) in the placebo group; the number of episodes of worsening was 39 versus 33, respectively (Online Table 4). Hospital admissions for heart failure were reported in 13 patients (10.2%) in the vildagliptin group and 10 patients (8.0%) in the placebo group (p = 0.552).

OTHER ADJUDICATED CARDIOVASCULAR EVENTS, HEPATIC EVENTS, AND DEATHS. Overall, 19 vildagliptin-treated patients (14.8%) and 14 placebo patients (11.2%) were admitted to the hospital for a cardiovascular cause (Table 3). In addition to heart failure (see above), these causes included acute coronary syndrome (6.3% vs. 0.8%, respectively) and a cardiac arrhythmia (3.9% vs. 1.6%, respectively).

Atrial fibrillation was detected on analysis of electrocardiograms in 6 vildagliptin-treated and 0 placebo-treated patients. Of the 11 deaths in the vildagliptin group, 7 were attributed to cardiovascular causes (Table 3) (5 to cardiorespiratory arrest or sudden death and 2 to myocardial ischemia or infarction), 2 to cancer, 1 to infection, and 1 to intestinal obstruction. All 4 deaths in the placebo group were attributed to cardiovascular causes.

OTHER ADVERSE EVENTS. Reports of hypoglycemia were similar in the 2 treatment groups (4.7% with vildagliptin vs. 5.6% with placebo). Two hepatic adverse events were confirmed on adjudication, both in the vildagliptin group. One event was a case of cirrhosis and the other jaundice secondary to hepatocellular carcinoma, but neither was considered drug-related. No predefined significant elevations in transaminases or bilirubin occurred in either treatment group. One patient in the vildagliptin group died from hepatic cancer. No cases of pancreatitis were reported. There were no cases of angioedema confirmed by the adjudication committee.

OTHER FINDINGS. There were no significant differences between treatment groups for change from baseline to end of study in weight, heart rate, blood pressure, estimated glomerular filtration rate, or urinary albumin-to-creatinine ratio.

DISCUSSION

The primary goal of this safety study was to compare the effect of vildagliptin, 50 mg twice daily, with that of placebo, added to conventional treatment for diabetes, on LVEF in patients with HFrEF. The study met the pre-specified objective of showing noninferiority, that is, it showed that vildagliptin, compared with placebo, did not cause a major reduction in LVEF. Indeed, mean LVEF increased slightly from baseline in each treatment group. Two other findings, however, were unexpected and merit comment. First, we showed that left ventricular volumes increased with vildagliptin treatment, and second, there were more deaths in the vildagliptin group than in the placebo group.

The increase in left ventricular volumes is hard to explain and could reflect baseline imbalances (see Results) or the play of chance. Baseline end-diastolic volume was higher in the vildagliptin group, as was BNP concentration and the percentage of patients with prior hospitalization for HF, suggesting that the patients in this group might have also been more susceptible to adverse left ventricular remodeling. However, if vildagliptin induced adverse left ventricular remodeling, a decline in LVEF and a rise in BNP would have been expected. Instead, we observed a slightly greater increase in LVEF and a trend to a greater reduction in BNP in the vildagliptin group, although neither trend was significant. Similarly, adverse remodeling might also have been reflected in evidence of worsening heart failure, which was not seen.

On the other hand, the potentially harmful consequences of left ventricular enlargement, if real, cannot be ignored. Increase in left ventricular volume is associated with worse clinical outcomes, including mortality, in heart failure (21,22). This draws attention to the second surprising observation in the present study, which was of a higher mortality rate in the vildagliptin group. However, the total number of deaths was small and the imbalance in deaths attributable to a cardiovascular-cause death was 7 versus 4 (with none in the vildagliptin group

attributed to worsening heart failure), respectively. We believe, therefore, this imbalance most likely reflects the play of chance.

However, it is not certain that all DPP-4 inhibitors are safe in patients with heart failure. In the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus-Thrombolysis In Myocardial Infarction 53) trial, the DPP-4 inhibitor studied led to a significant increase in risk of hospitalization for heart failure (289 vs. 228 patients, respectively; $p = 0.007$) (12,16). Treatment with a different DPP-4 inhibitor in the EXAMINE (Examination of Cardiovascular Outcomes With Alogliptin vs Standard of Care) trial also led to a higher rate of hospitalization for heart failure, although the difference from placebo was not statistically significant (106 vs. 89 patients, respectively; $p = 0.22$) (13,17). Conversely, there was no suggestion of an increased risk of heart failure hospitalization (228 vs. 229 patients, respectively; $p = 0.95$) in the TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin) study (14,15). It should be noted that the above-mentioned trials were not conducted specifically in patients with heart failure and that the minority of patients with heart failure at baseline in those trials were not phenotyped according to left ventricular function (and nor were those hospitalized during follow-up) (15,17). The VIVIDD trial was quite different in testing the effects of a DPP-4 inhibitor in patients with established heart failure and documented reduced LVEF. While heart failure-related hospitalizations did not occur more frequently with vildagliptin (13 vs. 10 events, respectively; $p = 0.55$) in the present study, our trial was small and was not powered to detect differences in clinical outcomes. Consequently, we could have missed a safety signal in VIVIDD. Indeed, in a trial very similar to the present one in terms of design and size assessing the thiazolidinedione rosiglitazone in patients with systolic heart failure, the difference between rosiglitazone and placebo in change in LVEF from baseline was 1.49 (95% CI: −0.32 to 3.30; $p = 0.10$), fulfilling noninferiority according to the same criterion used in the present trial (11). Rosiglitazone did not increase left ventricular volumes (although it did raise BNP) (11). Despite this, it is clear that glitazones increase the risk of developing heart failure and the risk of worsening in patients with heart failure (8,9). Consequently, although all of the concerning findings in the various DPP-4 inhibitor trials described above may be due to chance and unrelated, the possibility exists that these drugs could have adverse effects on myocardial structure and function. In relation to this, it is also worth examining the GLP-1 receptor agonist trials which used agents sharing a similar (but not identical) mechanism of action to that of the DPP-4 inhibitors. In 3 large trials including patients largely free of heart failure at baseline, lixisenatide, liraglutide, and semaglutide had a neutral effect on heart failure outcomes (23–25). However, in two small studies in patients with established HFrEF, there was the suggestion (but not definitive evidence) that treatment with liraglutide might have led to worse outcomes than placebo (26,27). In animal studies of myocardial infarction, DDP-4 inhibitors (including vildagliptin) have shown either a neutral or favorable effect on left ventricular remodeling (28–30).

STUDY LIMITATIONS. Inevitably, the present study has limitations. Although sufficiently powered to evaluate the primary endpoint, it was still a relatively small trial and was not powered to robustly assess clinical outcomes. There was a small difference in baseline left ventricular volumes that could have influenced subsequent changes in these measurements. The rate of discontinuation was relatively high (**Figure 2**), and only 70% of patients who completed the study according to protocol without major protocol deviations had at least 1 follow-up echocardiogram 22 or more weeks after randomization, although the number of patients with at least 2 analyzable echocardiograms was more than needed according to our power calculations.

CONCLUSIONS

Although the present study showed that vildagliptin was noninferior to placebo with respect to change in LVEF, it did show that use of this DPP-4 inhibitor was associated with an increase in left ventricular volumes. However, there was no increase in BNP or any other indication of worsening heart failure status. Whether the increase in ventricular volumes indicates some unexplained action of vildagliptin on left ventricular remodeling or a chance finding is unknown, as are its clinical implications. More evidence is needed regarding the safety of DPP-4 inhibitors in patients with established heart failure and left ventricular systolic dysfunction.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: While it is now accepted that the cardiovascular safety of new glucose-lowering treatments for type 2 diabetes must be demonstrated before marketing, there is no specific requirement to show safety in patients with HFrEF. This is despite evidence that at least 1 class of hypoglycemic drugs, the thiazolidinediones, can lead to the worsening of heart failure. We studied the safety of the dipeptidyl peptidase-4 inhibitor, vildagliptin, in patients with type 2 diabetes and HFrEF by measuring change in LVEF over 52 weeks. Although vildagliptin, compared with placebo, met the prespecified noninferiority margin for safety, vildagliptin led to an unexpected and unexplained increase in left ventricular volumes.

TRANSLATIONAL OUTLOOK: While the clinical significance of our findings is unknown, there are other data with an agent in the same class, saxagliptin, showing an increase in risk of incident heart failure hospitalization. While both sets of results may reflect the play of chance, they do, along with the earlier thiazolidinedione findings, highlight the need to examine the safety of new glucose-lowering treatments specifically in patients with diabetes and HFrEF who are a particularly high risk and vulnerable group.

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KEY WORDS diabetes, heart failure

APPENDIX For supplemental tables, please see the online version of this paper.