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Title: Effects of vildagliptin on ventricular function in patients with type 2 diabetes mellitus and heart failure: a randomized placebo-controlled trial

Brief title: Vildagliptin in Heart Failure.

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On behalf of the Vildagliptin in Ventricular Dysfunction Diabetes trial (VIVIDD) Committees and investigators

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ABSTRACT

Objectives: To study 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 aged 18 to 85 years 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 non-inferiority margin of -3.5%.

Findings: 254 patients were randomly assigned to vildagliptin (n=128) or placebo (n=126). Baseline LVEF was 30.6 (SD 6.8)% in the vildagliptin group and 29.6 (7.7)% in the placebo group. The adjusted mean change in LVEF was 4.95 (SE 1.25)% in vildagliptin treated patients and 4.33 (1.23)% in placebo treated patients – a difference of 0.62 (95% CI -2.21, 3.44); p=0.667. This difference met the predefined non-inferiority margin of -3.5%. Left ventricular end-diastolic and end-systolic volumes increased more in the vildagliptin group: by 17.1 (4.6, 29.5) ml; p=0.007 and 9.4 (-0.49, 19.4) ml; p=0.062, respectively. Decrease in haemoglobin A1c from baseline to 16 weeks, the main secondary endpoint, was greater in the vildagliptin group: -0.62 (-0.93, -0.30); p<0.001.
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.

Key words: Diabetes, Heart Failure.

Trial registration: ClinicalTrials.gov NCT00894868
INTRODUCTION

Type 2 diabetes is common in patients with heart failure with reported prevalences of between 25 and 40 per cent in trials and registries.\textsuperscript{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.\textsuperscript{1-5} The safety of established treatments for diabetes in patients with heart failure is uncertain. While there are no known concerns about sulfonylureas and insulin, it has been thought that metformin might increase the risk of lactic acidosis although this has never been demonstrated.\textsuperscript{6,7} Thiazolidinediones increase the risk of patients with diabetes developing heart failure.\textsuperscript{8,9} Thiazolidinediones also increase the risk of worsening of heart failure in patients with that condition.\textsuperscript{10,11}

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

The Vildagliptin in Ventricular Dysfunction Diabetes trial (VIVIDD) was a prospective, randomized, double-blind, parallel-group trial comparing vildagliptin and placebo, added to standard therapy, for 52 weeks in patients with type 2 diabetes and heart failure with a reduced ejection fraction. 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 analyses were carried out by blinded assessors in a core laboratory (Perceptive Informatics Inc., a subsidiary of Parexel International - see below). The study results were analysed by Novartis and confirmed by an independent statistician at the University of Glasgow (J.L.).

Participants

In brief, men and women aged between 18 and 85 years with type 2 diabetes (hemoglobin A1c 6.5% - 10.0%), body mass index 22 – 42 kg/m², 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 of ≥15 mmol/l, thiazolidinedione or incretin therapy, a recent cardiovascular event or procedure, creatinine clearance <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 class, to one of two 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 04 May 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 reviewed every 4 weeks up to week 24 and every 8 weeks thereafter (diabetes “rescue” therapy could be used from week 16 onwards). Repeat BNP measurements and echocardiography were performed at 24 and 52 weeks. Patients permanently stopping treatment before 52 weeks were asked to return for a final assessment, including an echocardiogram and BNP measurement. NYHA class, dyspnea and edema were evaluated at baseline and at each of the follow-up visits, as was blood chemistry (including hemoglobin A1c) 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 (BNP)**

BNP was measured using a triage Beckman Coulter Immunoassay (Covance Central Laboratory services).
Study objectives

This was a safety study. The primary objective was to show that vildagliptin was at least non-inferior 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 remodelling 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 one follow-up echocardiogram recorded 22 weeks or more after randomization. The key secondary endpoint was change in hemoglobin A1c 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 class and breathlessness and edema at each study visit and adjudication of suspected worsening heart failure symptoms (see Appendix 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 one-sided significance level of 0.025 to declare non-inferiority of vildagliptin, compared with placebo, for the effect of treatment of LVEF, using a margin of -3.5% and an expected difference between the two treatments of 0%. The choice of the non-inferiority margin was based on clinical importance and prior use. The calculation was performed using nQuery Advisor® version 5.0 and based on a LVEF standard deviation (SD) of 7% (derived from prior trials). We calculated that a
total of 172 patients with at least one LVEF measurement after randomization were required. The sample-size was inflated to 246 patients to allow for approximately 30% of patients not having a LVEF measurement after randomization. An analysis of co-variance model (ANCOVA) was fitted including terms for treatment, baseline LVEF, NYHA 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 two treatment groups, and the two-sided 95% confidence interval (CI), were obtained from this model.

An ANCOVA model fitted with terms for treatment, baseline haemoglobin A1c and region was used to analyse LSM change in hemoglobin A1c. Other exploratory variables were analysed in a similar way with appropriate transformations if the normality assumption was questionable. The statistical software used was SAS® (Version 9.2).
RESULTS

Baseline characteristics and treatment

A total of 254 patients were randomized at 67 sites in 15 countries. Their mean age was 63 years and 77% were male. Other key demographic characteristics, medical history and treatment at baseline are shown in Table 1. The first patient visit was 04 May 2009 and the last patient visit was 13 August 2012. Overall, patients had a mean duration of diabetes of 9.3 years (median 6.8 years) and the mean hemoglobin A1c at baseline was 7.8% per cent; 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 with exception of more patients in the vildagliptin treatment group having 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 placebo group. Other reasons for not completing follow-up were adverse events (5 vildagliptin versus 4 placebo), withdrawal of consent (3 versus 10), protocol violation (3 versus 2), loss-to-follow-up (2 versus 2), unsatisfactory therapeutic effect (2 versus 1) and administrative problems (1 versus 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**

LVEF was matched between treatment groups at baseline (Table 2). The intention to treat analysis is shown in Figure 2. 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 30.5 ± SE 0.67%) and 90 assigned to placebo (29.8 ± SE 0.78%). The adjusted mean change in LVEF was 4.95 (± SE 1.25)% in the vildagliptin group and 4.33 (± SE 1.23)% in the placebo group; a difference of 0.62 (95% confidence interval -2.21, 3.44; p=0.667). This difference met the predefined non-inferiority criterion of -3.5% at p=0.025. Analysis of the patients (88 vildagliptin, 89 placebo) with a 48 week follow-up measurement of LVEF gave almost identical findings (see sensitivity analyses Appendix Table A2).

**Other echocardiographic findings**

Changes in left ventricular volumes are shown in Table 2 and Figure 3. Left ventricular end-diastolic volume increased 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 Appendix Table A3). There was a significant increase in stroke volume but no change in left ventricular wall thickness or mass.

**Secondary endpoint: change in hemoglobin A1c**

The adjusted mean change from baseline to rescue-censored week 16 haemoglobin A1c was -0.45 (± SE0.12)% in the vildagliptin group and 0.17 (±SE 0.12)% in the placebo group, with an adjusted mean difference (vildagliptin – placebo) of -0.62 (95% CI -0.03, -0.30)%; p<0.001. The difference at week 52 was -0.36 (95% CI -0.71, -0.02)%; p=0.040.
Change in B-type natriuretic peptide

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, 0.93) in the vildagliptin group (n=75) and 0.86 (0.67, 1.12) in the placebo group (n=81). The ratio of ratios (vildagliptin/placebo) was 0.84 (0.62, 1.14), p=0.252.

Other measures 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 class distribution between the two 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 hospitalisation 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 [Appendix Table A4]. 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 hospital for a cardiovascular cause. In addition to heart failure (see above), these included acute coronary syndrome (6.3% versus 0.8%) and a cardiac arrhythmia (3.9% versus 1.6%).
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 (5 to cardiorespiratory arrest or sudden death and 2 to myocardial ischaemia 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 two treatment groups (4.7% with vildagliptin versus 5.6% with placebo). Two hepatic adverse events were confirmed on adjudication, both in the vildagliptin group. One was a case of cirrhosis and the other jaundice secondary to hepatocellular carcinoma, but neither was considered as 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 evaluate the effect of vildagliptin 50 mg twice daily, compared with placebo, added to conventional treatment for diabetes, on LVEF in patients with HF-REF. The study met the pre-specified objective of showing non-inferiority i.e. 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. Firstly, we showed that left ventricular volumes increased with vildagliptin treatment and secondly there were more deaths in the vildagliptin group compared with 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 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\(^\text{21,22}\) 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 deaths was 7 versus 4 (with none in the vildagliptin group attributed to
worsening heart failure). 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 Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial, the DPP-4 inhibitor studied led to a significant increase in risk of hospitalization for heart failure (289 versus 228 patients; P=0.007). Treatment with a different DPP-4 inhibitor in the Examination of Cardiovascular Outcomes With Alogliptin vs Standard of Care (EXAMINE) trial also led to a higher rate of hospitalization for heart failure although the difference from placebo was not statistically significant (106 versus 89 patients; P=0.22). Conversely, there was no suggestion of an increased risk of heart failure hospitalization (228 versus 229 patients; P=0.95) in the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS). It should be noted that the above mentioned trials were not conducted specifically in patients with heart failure and 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). VIVIDD was quite different in testing the effects of a DPP-4 inhibitor in patients with established heart failure and documented reduced left ventricular ejection fraction. While heart failure-related hospitalizations did not occur more frequently with vildagliptin (13 vs. 10 events, 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 (-0.32, 3.30; p=0.10), fulfilling non-inferiority according to the same criterion used in the present trial. Rosiglitazone did not increase left ventricular volumes (although did raise BNP). Despite this, it is clear that glitazones increase the risk of developing heart failure and the risk of worsening in patients
with heart failure. Consequently, while 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 three large trials including patients largely free of heart failure at baseline, lixisenatide, liraglutide and semaglutide had a neutral effect on heart failure outcomes. However, in two small studies in patients with established HF-REF there was the suggestion (but not definitive evidence) that treatment with liraglutide might lead to worse outcomes compared with placebo. In animal studies of myocardial infarction, DDP-4 inhibitors (including vildagliptin) have shown either a neutral or favorable effect on left ventricular remodeling.

Inevitably, the present study has limitations. While 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 completing the study as per protocol without major protocol deviations had at least one follow-up echocardiogram 22 or more weeks after randomization, although the number of patients with at least 2 analysable echocardiograms was more than needed according to our power calculations.

In conclusion, although the present study showed that vildagliptin was non-inferior 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.

**Clinical 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 heart failure and reduced ejection fraction (HFrEF). This is despite evidence that at least one 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 left ventricular ejection fraction (LVEF) over 52 weeks. Although vildagliptin, compared with placebo, met the prespecified non-inferiority margin for safety, vildagliptin led to an unexpected an 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 possibly vulnerable group.
REFERENCES


3. Dauriz M, Targher G, Laroche C, et al; ESC-HFA Heart Failure Long-Term Registry. Association Between Diabetes and 1-Year Adverse Clinical Outcomes in a Multinational Cohort of Ambulatory Patients With Chronic Heart Failure: Results From the ESC-HFA Heart Failure Long-Term Registry. Diabetes Care 2017; 40: 671-678.


TABLE LEGEND

Table 1  Baseline characteristics of patients and treatment

Table 2  Baseline echocardiographic measurements

Table 3  Non-fatal cardiovascular events and deaths

FIGURE LEGEND

Figure 1  Study timeline

Figure 2  Flow chart of participants

Figure 3  Change from baseline in left ventricular ejection fraction (primary endpoint) and other echocardiographic measures
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<td>Diuretic (loop)</td>
<td>71.1</td>
<td>70.7</td>
</tr>
<tr>
<td>ICD</td>
<td>9.4</td>
<td>7.9</td>
</tr>
<tr>
<td>CRT</td>
<td>10.2</td>
<td>11.9</td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>24.2</td>
<td>24.6</td>
</tr>
<tr>
<td>Any</td>
<td>35.2</td>
<td>33.3</td>
</tr>
<tr>
<td></td>
<td>Vildagliptin n=128</td>
<td>Placebo n=126</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------</td>
<td>---------------</td>
</tr>
<tr>
<td><strong>Treatment, % (continued)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral anti-diabetes therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>46.9</td>
<td>53.2</td>
</tr>
<tr>
<td>Metformin</td>
<td>36.7</td>
<td>32.5</td>
</tr>
<tr>
<td>AGI</td>
<td>0.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Glinide</td>
<td>1.6</td>
<td>0</td>
</tr>
<tr>
<td>Any oral therapy</td>
<td>63.3</td>
<td>68.3</td>
</tr>
<tr>
<td>Diet only</td>
<td>12.5</td>
<td>7.1</td>
</tr>
</tbody>
</table>

All values are mean unless indicated.

BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; ACE = angiotensin converting enzyme; bpm = beats per minute; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; MRA = mineralocorticoid receptor antagonist; PCI = percutaneous coronary intervention; ICD = implantable cardioverter defibrillator; NYHA = New York Heart Association; CRT = cardiac resynchronisation therapy; LVEF = left ventricular ejection fraction; AGI = alpha-glucosidase inhibitor; * = median
Table 2: Baseline echocardiographic measurements

<table>
<thead>
<tr>
<th></th>
<th>Vildagliptin (n=128*)</th>
<th>Placebo (n=126*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVIDD, cm (SD)</td>
<td>5.9 (0.91)</td>
<td>5.9 (0.93)</td>
</tr>
<tr>
<td>LVISD, cm (SD)</td>
<td>5.2 (0.93)</td>
<td>5.2 (0.91)</td>
</tr>
<tr>
<td>LVEDV*, ml (SD)</td>
<td>179 (59)</td>
<td>168 (66)</td>
</tr>
<tr>
<td>LVESV*, ml (SD)</td>
<td>125 (44)</td>
<td>120 (56)</td>
</tr>
<tr>
<td>LVSV, ml (SD)</td>
<td>54.3 (21.0)</td>
<td>48.1 (18.3)</td>
</tr>
<tr>
<td>LVEF, % (SD)</td>
<td>30.6 (6.8)</td>
<td>29.6 (7.7)</td>
</tr>
<tr>
<td>LV-SWT, cm (SD)</td>
<td>1.0 (0.24)</td>
<td>1.0 (0.25)</td>
</tr>
<tr>
<td>LV-PWT, cm (SD)</td>
<td>1.0 (0.20)</td>
<td>1.0 (0.21)</td>
</tr>
<tr>
<td>LVMi, g/m² (SD)</td>
<td>134 (39)</td>
<td>130 (41)</td>
</tr>
</tbody>
</table>

* not all measurements were obtained in every patient

*LVEDVi 92 ml/m²  LVESVi 65 ml/m²

LVIDD = left ventricular internal diastolic dimension; LVISD = left ventricular internal systolic dimension; LVEDV = left ventricular end diastolic volume; LVESV = left ventricular end systolic volume; LVEF = left ventricular ejection fraction; LVSV = left ventricular stroke volume; LV-SWT = left ventricular septal wall thickness; LV-PWT = left ventricular posterior wall thickness; LVMi = left ventricular mass index; LVEDVi = left ventricular end diastolic volume index; LVESVi = left ventricular end systolic volume index
Table 3: Non-fatal cardiovascular events and deaths.

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

* Patients counted only once, even if multiple events. There were 4 non-cardiovascular deaths in the vildagliptin group: from hepatic neoplasm, lung neoplasm, septic shock, and surgery for intestinal obstruction due to peritoneal adhesions.
Figure 1: Study timeline

Time course of VIVIDD compared with large-scale DPP-4 clinical outcome trials

- **VIVIDD (n=254)**
  - vildagliptin
  - (May 2009 – August 2012)

- **SAVAR-TIMI53 (n=16,492)**
  - saxagliptin
  - (May 2010 – September 2013*)

- **EXAMINE (n=5,380)**
  - alogliptin
  - (October 2009 – September 2013*)

- **TECOS (n=14,671)**
  - sitagliptin
  - (December 2008 – June 2015*)

*Publication date
Figure 2: Flow chart of participants

Assessed for eligibility  
N=795

Excluded (n=541)  
- Not meeting inclusion criteria (n=210)  
- Unacceptable lab values (n=69)  
- Unacceptable test procedure result (n=265)  
- Other reasons (n=62)

Randomized  
N=254

Allocated to vildagliptin  
(N=128)

Discontinued (n=27)  
- Death (n=11)  
- Adverse event(s) (n=5)  
- Withdrew consent (n=3)  
- Protocol deviation (n=3)  
- Unsatisfactory therapeutic effect (n=2)  
- Lost to follow-up (n=2)  
- Administrative (n=1)

Completed (n=101; 78.9%)  
- Analyzed for safety (n=128; 100%)  
- Analyzed for efficacy (n=115; 89.9%)  
- Per protocol analysis (n=80; 60.5%)

Allocated to placebo  
(N=126)

Discontinued (n=26)  
- Death (n=4)  
- Adverse event(s) (n=4)  
- Withdrew consent (n=10)  
- Protocol deviation (n=2)  
- Unsatisfactory therapeutic effect (n=1)  
- Lost to follow-up (n=2)  
- Administrative (n=3)

Completed (n=101; 78.9%)  
- Analyzed for safety (n=125; 99.2%)  
- Analyzed for efficacy (n=112; 89.9%)  
- Per protocol analysis (n=90; 71.4%)
Figure 3. Change from baseline in left ventricular ejection fraction (primary endpoint) and other echocardiographic measures

A. Change in LVEF (%). Difference in adjusted mean change 0.62 (95% CI: -2.21, 3.44; P=0.667)*.

*Meets criteria for non-inferiority to comparator as the lower limit of the two sided 95% CI for the difference in mean change in LVEF is greater than -3.5%. Primary analysis is based on Per Protocol. B. Change in LVEDV (mL). Difference in adjusted mean change 17.06 (95% CI: 4.62, 29.51; P=0.007). Full analysis set. C. Change in LVESV. Difference in adjusted mean change 9.44 (95% CI: -0.49, 19.38; P=0.062). Full analysis set. D. Change in LVSV. Difference in adjusted mean change 9.00 (95% CI: 3.38, 14.62; P=0.002). Full analysis set.
Title: Effects of vildagliptin on ventricular function in patients with type 2 diabetes mellitus and heart failure: a randomized placebo-controlled trial

Brief title: Vildagliptin in Heart Failure.

Authors: John J. V. McMurray MD
Piotr Ponikowski MD
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Valentina Lukashevich MD
Plamen Kozlovski MD
Wolfgang Kothny MD
James D Lewsey PhD
Henry Krum MD

On behalf of the Vildagliptin in Ventricular Dysfunction Diabetes trial (VIVIDD) Committees and investigators

Affiliations: "BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland, UK; "Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland; "Department of Medicine, Perugia University Medical School, Perugia, Italy; "Novartis Pharmaceuticals Corporation, East Hanover, USA; "Novartis Pharma AG, Basel, Switzerland; "Institute of Health and Wellbeing, University of Glasgow, Glasgow, Scotland,
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**Word Count:**
4,500

**Disclosures:**
VL, PK, WK are employees of Novartis. All other authors or their institutions were paid for their role as A Steering Committee member for this trial.

**Funding:**
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ABSTRACT

Objectives: To study 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 aged 18 to 85 years 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 non-inferiority margin of -3.5%.

Findings: 254 patients were randomly assigned to vildagliptin (n=128) or placebo (n=126). Baseline LVEF was 30.6 (SD 6.8)% in the vildagliptin group and 29.6 (7.7)% in the placebo group. The adjusted mean change in LVEF was 4.95 (SE 1.25)% in vildagliptin treated patients and 4.33 (1.23)% in placebo treated patients – a difference of 0.62 (95% CI -2.21, 3.44); p=0.667. This difference met the predefined non-inferiority margin of -3.5%. Left ventricular end-diastolic and end-systolic volumes increased more in the vildagliptin group: by 17.1 (4.6, 29.5) ml; p=0.007 and 9.4 (-0.49, 19.4) ml; p=0.062, respectively. Decrease in haemoglobin A1c from baseline to 16 weeks, the main secondary endpoint, was greater in the vildagliptin group: -0.62 (-0.93, -0.30); p<0.001.
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.

Key words: Diabetes, Heart Failure.

Trial registration: ClinicalTrials.gov NCT00894868
INTRODUCTION

Type 2 diabetes is common in patients with heart failure with reported prevalences of between 25 and 40 per cent in trials and registries.\textsuperscript{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.\textsuperscript{1-5} The safety of established treatments for diabetes in patients with heart failure is uncertain. While there are no known concerns about sulfonylureas and insulin, it has been thought that metformin might increase the risk of lactic acidosis although this has never been demonstrated.\textsuperscript{6,7} Thiazolidinediones increase the risk of patients with diabetes developing heart failure.\textsuperscript{8,9} Thiazolidinediones also increase the risk of worsening of heart failure in patients with that condition.\textsuperscript{10,11}

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

The Vildagliptin in Ventricular Dysfunction Diabetes trial (VIVIDD) was a prospective, randomized, double-blind, parallel-group trial comparing vildagliptin and placebo, added to standard therapy, for 52 weeks in patients with type 2 diabetes and heart failure with a reduced ejection fraction. 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 analyses were carried out by blinded assessors in a core laboratory (Perceptive Informatics Inc., a subsidiary of Parexel International - see below). The study results were analysed by Novartis and confirmed by an independent statistician at the University of Glasgow (J.L.).

Participants

In brief, men and women aged between 18 and 85 years with type 2 diabetes (hemoglobin A1c 6.5% - 10.0%), body mass index 22 – 42 kg/m², heart failure with a reduced ejection fraction (< 40%) and inNew York Heart Association (NYHA) functional class I to III were eligible. The key exclusion criteria were NYHA functional class IV, a fasting plasma glucose of ≥15 mmol/l, thiazolidinedione or incretin therapy, a recent cardiovascular event or procedure, creatinine clearance <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 class, to one of two 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 04 May 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 reviewed every 4 weeks up to week 24 and every 8 weeks thereafter (diabetes “rescue” therapy could be used from week 16 onwards). Repeat BNP measurements and echocardiography were performed at 24 and 52 weeks. Patients permanently stopping treatment before 52 weeks were asked to return for a final assessment, including an echocardiogram and BNP measurement. NYHA class, dyspnea and edema were evaluated at baseline and at each of the follow-up visits, as was blood chemistry (including hemoglobin A1c) 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.\textsuperscript{20}

**B-type natriuretic peptide (BNP)**

BNP was measured using a triage Beckman Coulter Immunoassay (Covance Central Laboratory services).
**Study objectives**

This was a safety study. The primary objective was to show that vildagliptin was at least non-inferior 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 remodelling 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 one follow-up echocardiogram recorded 22 weeks or more after randomization. The key secondary endpoint was change in hemoglobin A1c 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 class and breathlessness and edema at each study visit and adjudication of suspected worsening heart failure symptoms (see Appendix 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 one-sided significance level of 0.025 to declare non-inferiority of vildagliptin, compared with placebo, for the effect of treatment of LVEF, using a margin of -3.5% and an expected difference between the two treatments of 0%. The choice of the non-inferiority margin was based on clinical importance and prior use.\(^\text{10}\) The calculation was performed using nQuery Advisor\(^\text{®}\) version 5.0 and based on a LVEF standard deviation (SD) of 7% (derived from prior trials). We calculated that a
total of 172 patients with at least one LVEF measurement after randomization were required. The sample-size was inflated to 246 patients to allow for approximately 30% of patients not having a LVEF measurement after randomization. An analysis of co-variance model (ANCOVA) was fitted including terms for treatment, baseline LVEF, NYHA 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 two treatment groups, and the two-sided 95% confidence interval (CI), were obtained from this model.

An ANCOVA model fitted with terms for treatment, baseline haemoglobin A1c and region was used to analyse LSM change in hemoglobin A1c. Other exploratory variables were analysed in a similar way with appropriate transformations if the normality assumption was questionable. The statistical software used was SAS® (Version 9.2).
RESULTS

Baseline characteristics and treatment

A total of 254 patients were randomized at 67 sites in 15 countries. Their mean age was 63 years and 77% were male. Other key demographic characteristics, medical history and treatment at baseline are shown in Table 1. The first patient visit was 04 May 2009 and the last patient visit was 13 August 2012. Overall, patients had a mean duration of diabetes of 9.3 years (median 6.8 years) and the mean hemoglobin A1c at baseline was 7.8% per cent; 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 with exception of more patients in the vildagliptin treatment group having 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 placebo group. Other reasons for not completing follow-up were adverse events (5 vildagliptin versus 4 placebo), withdrawal of consent (3 versus 10), protocol violation (3 versus 2), loss-to-follow-up (2 versus 2), unsatisfactory therapeutic effect (2 versus 1) and administrative problems (1 versus 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**

LVEF was matched between treatment groups at baseline (Table 2). The intention to treat analysis is shown in Figure 2. 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 30.5 ± SE 0.67%) and 90 assigned to placebo (29.8 ± SE 0.78%). The adjusted mean change in LVEF was 4.95 (± SE 1.25)% in the vildagliptin group and 4.33 (± SE 1.23)% in the placebo group; a difference of 0.62 (95% confidence interval -2.21, 3.44; p=0.667). This difference met the predefined non-inferiority criterion of -3.5% at p=0.025. Analysis of the patients (88 vildagliptin, 89 placebo) with a 48 week follow-up measurement of LVEF gave almost identical findings (see sensitivity analyses Appendix Table A2).

**Other echocardiographic findings**

Changes in left ventricular volumes are shown in Table 2 and Figure 3. Left ventricular end-diastolic volume increased 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 Appendix Table A3). There was a significant increase in stroke volume but no change in left ventricular wall thickness or mass.

**Secondary endpoint: change in hemoglobin A1c**

The adjusted mean change from baseline to rescue-censored week 16 haemoglobin A1c was -0.45 (± SE0.12)% in the vildagliptin group and 0.17 (±SE 0.12)% in the placebo group, with an adjusted mean difference (vildagliptin – placebo) of -0.62 (95% CI -0.03, -0.30)%; p<0.001. The difference at week 52 was -0.36 (95% CI -0.71, -0.02)%; p=0.040.
Change in B-type natriuretic peptide

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, 0.93) in the vildagliptin group (n=75) and 0.86 (0.67, 1.12) in the placebo group (n=81). The ratio of ratios (vildagliptin/placebo) was 0.84 (0.62, 1.14), p=0.252.

Other measures 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 class distribution between the two 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 hospitalisation 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 [Appendix Table A4]. 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 hospital for a cardiovascular cause. In addition to heart failure (see above), these included acute coronary syndrome (6.3% versus 0.8%) and a cardiac arrhythmia (3.9% versus 1.6%).
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 (5 to cardiorespiratory arrest or sudden death and 2 to myocardial ischaemia 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 two treatment groups (4.7% with vildagliptin versus 5.6% with placebo). Two hepatic adverse events were confirmed on adjudication, both in the vildagliptin group. One was a case of cirrhosis and the other jaundice secondary to hepatocellular carcinoma, but neither was considered as 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 evaluate the effect of vildagliptin 50 mg twice daily, compared with placebo, added to conventional treatment for diabetes, on LVEF in patients with HF-REF. The study met the pre-specified objective of showing non-inferiority i.e. 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. Firstly, we showed that left ventricular volumes increased with vildagliptin treatment and secondly there were more deaths in the vildagliptin group compared with 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 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\textsuperscript{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 deaths was 7 versus 4 (with none in the vildagliptin group attributed to
worsening heart failure). 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 Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial, the DPP-4 inhibitor studied led to a significant increase in risk of hospitalization for heart failure (289 versus 228 patients; \( P=0.007 \)).\(^{12,16}\) Treatment with a different DPP-4 inhibitor in the Examination of Cardiovascular Outcomes With Alogliptin vs Standard of Care (EXAMINE) trial also led to a higher rate of hospitalization for heart failure although the difference from placebo was not statistically significant (106 versus 89 patients; \( P=0.22 \)).\(^{13,17}\) Conversely, there was no suggestion of an increased risk of heart failure hospitalization (228 versus 229 patients; \( P=0.95 \)) in the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS).\(^{14,15}\) It should be noted that the above mentioned trials were not conducted specifically in patients with heart failure and 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).\(^{15,17}\) VIVIDD was quite different in testing the effects of a DPP-4 inhibitor in patients with established heart failure and documented reduced left ventricular ejection fraction. While heart failure-related hospitalizations did not occur more frequently with vildagliptin (13 vs. 10 events, \( p=0.55 \)) 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 (-0.32, 3.30; \( p=0.10 \)), fulfilling non-inferiority according to the same criterion used in the present trial.\(^{11}\) Rosiglitazone did not increase left ventricular volumes (although 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. Consequently, while 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 three large trials including patients largely free of heart failure at baseline, lixisenatide, liraglutide and semaglutide had a neutral effect on heart failure outcomes. However, in two small studies in patients with established HF-REF there was the suggestion (but not definitive evidence) that treatment with liraglutide might lead to worse outcomes compared with placebo. In animal studies of myocardial infarction, DDP-4 inhibitors (including vildagliptin) have shown either a neutral or favorable effect on left ventricular remodeling.

Inevitably, the present study has limitations. While 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 completing the study as per protocol without major protocol deviations had at least one follow-up echocardiogram 22 or more weeks after randomization, although the number of patients with at least 2 analysable echocardiograms was more than needed according to our power calculations.

In conclusion, although the present study showed that vildagliptin was non-inferior 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.

Clinical 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 heart failure and reduced ejection fraction (HFrEF). This is despite evidence that at least one 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 left ventricular ejection fraction (LVEF) over 52 weeks. Although vildagliptin, compared with placebo, met the prespecified non-inferiority margin for safety, vildagliptin led to an unexpected an 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 possibly vulnerable group.
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3. Dauriz M, Targher G, Laroche C, et al; ESC-HFA Heart Failure Long-Term Registry.. Association Between Diabetes and 1-Year Adverse Clinical Outcomes in a Multinational Cohort of Ambulatory Patients With Chronic Heart Failure: Results From the ESC-HFA Heart Failure Long-Term Registry. Diabetes Care 2017; 40: 671-678.


27. Margulies KB, Hernandez AF, Redfield MM, et al; NHLBI Heart Failure Clinical Research Network.. Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. JAM. 2016; 316: 500-8.


TABLE LEGEND

Table 1  Baseline characteristics of patients and treatment

Table 2  Baseline echocardiographic measurements

Table 3  Non-fatal cardiovascular events and deaths

FIGURE LEGEND

Figure 1  Study timeline

Figure 2  Flow chart of participants

Figure 3  Change from baseline in left ventricular ejection fraction (primary endpoint) and other echocardiographic measures
Table 1: Baseline characteristics of patients and treatment

<table>
<thead>
<tr>
<th></th>
<th>Vildagliptin n=128</th>
<th>Placebo n=126</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>62.9 (8.5)</td>
<td>63.4 (9.3)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>29 (22.7)</td>
<td>30 (23.8)</td>
</tr>
<tr>
<td>BMI, kg/m² (SD)</td>
<td>29.6 (4.6)</td>
<td>29.3 (4.7)</td>
</tr>
<tr>
<td>Obese, (%)</td>
<td>54 (42.2)</td>
<td>50 (39.7)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>21(16.4)</td>
<td>9 (7.1)</td>
</tr>
<tr>
<td>Systolic BP, mmHg (SD)</td>
<td>130.4 (16.3)</td>
<td>127.9 (15.3)</td>
</tr>
<tr>
<td>Diastolic BP, mmHg (SD)</td>
<td>77.6 (8.9)</td>
<td>77.2 (8.7)</td>
</tr>
<tr>
<td>Heart rate, bpm (SD)</td>
<td>73.1 (10.1)</td>
<td>73.5 (9.3)</td>
</tr>
<tr>
<td><strong>History, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>80 (62.5)</td>
<td>79 (62.7)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>55 (43.0)</td>
<td>49 (38.9)</td>
</tr>
<tr>
<td>CABG</td>
<td>30 (23.4)</td>
<td>30 (23.8)</td>
</tr>
<tr>
<td>PCI</td>
<td>24 (18.8)</td>
<td>22 (17.5)</td>
</tr>
<tr>
<td>Stroke</td>
<td>12 (9.4)</td>
<td>11 (8.7)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>29 (22.7)</td>
<td>34 (27.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>112 (87.5)</td>
<td>108 (85.7)</td>
</tr>
<tr>
<td>Prior hospitalization for HF</td>
<td>66 (51.6)</td>
<td>55 (43.7)</td>
</tr>
<tr>
<td>COPD</td>
<td>16 (12.5)</td>
<td>8 (6.3)</td>
</tr>
<tr>
<td><strong>Diabetes status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of diabetes, years (SD)</td>
<td>9.5 (8.1)</td>
<td>9.1 (7.8)</td>
</tr>
<tr>
<td>Hemoglobin A1c, % (SD)</td>
<td>7.8 (0.95)</td>
<td>7.8 (1.07)</td>
</tr>
<tr>
<td></td>
<td>Vildagliptin n=128</td>
<td>Placebo n=126</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------</td>
<td>--------------</td>
</tr>
<tr>
<td><strong>Heart failure status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>13 (10.2)</td>
<td>12 (9.5)</td>
</tr>
<tr>
<td>II</td>
<td>68 (53.1)</td>
<td>66 (52.4)</td>
</tr>
<tr>
<td>III</td>
<td>47 (36.7)</td>
<td>48 (38.1)</td>
</tr>
<tr>
<td>LVEF, % (SD)</td>
<td>30.6 (6.8)</td>
<td>29.6 (7.7)</td>
</tr>
<tr>
<td>LVEF ≤ 35 %, n (%)</td>
<td>91 (71.1)</td>
<td>96 (74.2)</td>
</tr>
<tr>
<td>BNP pg/ml (IQR)*</td>
<td>244 (133, 558)</td>
<td>217 (113, 430)</td>
</tr>
<tr>
<td><strong>Treatment, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>71.8</td>
<td>61.9</td>
</tr>
<tr>
<td>ARB</td>
<td>23.4</td>
<td>28.6</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>79.7</td>
<td>76.2</td>
</tr>
<tr>
<td>MRA</td>
<td>46.1</td>
<td>37.3</td>
</tr>
<tr>
<td>Digitalis glycoside</td>
<td>28.9</td>
<td>23.0</td>
</tr>
<tr>
<td>Diuretic (loop)</td>
<td>71.1</td>
<td>70.7</td>
</tr>
<tr>
<td>ICD</td>
<td>9.4</td>
<td>7.9</td>
</tr>
<tr>
<td>CRT</td>
<td>10.2</td>
<td>11.9</td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>24.2</td>
<td>24.6</td>
</tr>
<tr>
<td>Any</td>
<td>35.2</td>
<td>33.3</td>
</tr>
<tr>
<td>Treatment, % (continued)</td>
<td>Vildagliptin n=128</td>
<td>Placebo n=126</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Oral anti-diabetes therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>46.9</td>
<td>53.2</td>
</tr>
<tr>
<td>Metformin</td>
<td>36.7</td>
<td>32.5</td>
</tr>
<tr>
<td>AGI</td>
<td>0.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Glinide</td>
<td>1.6</td>
<td>0</td>
</tr>
<tr>
<td>Any oral therapy</td>
<td>63.3</td>
<td>68.3</td>
</tr>
<tr>
<td>Diet only</td>
<td>12.5</td>
<td>7.1</td>
</tr>
</tbody>
</table>

All values are mean unless indicated.

BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; ACE = angiotensin converting enzyme; bpm = beats per minute; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; MRA = mineralocorticoid receptor antagonist; PCI = percutaneous coronary intervention; ICD = implantable cardioverter defibrillator; NYHA = New York Heart Association; CRT = cardiac resynchronisation therapy; LVEF = left ventricular ejection fraction; AGI = alpha-glucosidase inhibitor; * = median
Table 2: Baseline echocardiographic measurements

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

* not all measurements were obtained in every patient

\(^{+}\) LVEDVi 92 ml/m\(^2\) LVESVi 65 ml/m\(^2\)

LVIDD = left ventricular internal diastolic dimension; LVISD = left ventricular internal systolic dimension; LVEDV = left ventricular end diastolic volume; LVESV = left ventricular end systolic volume; LVEF = left ventricular ejection fraction; LVSV = left ventricular stroke volume; LV-SWT = left ventricular septal wall thickness; LV-PWT = left ventricular posterior wall thickness; LVMi = left ventricular mass index; LVEDVi = left ventricular end diastolic volume index; LVESVi = left ventricular end systolic volume index
Table 3: Non-fatal cardiovascular events and deaths.

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

* Patients counted only once, even if multiple events. There were 4 non-cardiovascular deaths in the vildagliptin group: from hepatic neoplasm, lung neoplasm, septic shock, and surgery for intestinal obstruction due to peritoneal adhesions.
Figure 1: Study timeline

Time course of VIVIDD compared with large-scale DPP-4 clinical outcome trials

VIVIDD (n=254)
vidagliptin
(May 2009 – August 2012)

Year

SAVOR-TIMI53 (n=16,492)
saxagliptin
(May 2010-September 2013*)

EXAMINE (n=5,380)
salogliptin
(October 2009-September 2013*)

TECOS (n=14,671)
sitagliptin
(December 2008-June 2015*)

*Publication date
Figure 2: Flow chart of participants

- Assessed for eligibility: N=795
  - Excluded (n=541)
    - Not meeting inclusion criteria (n=210)
    - Unacceptable lab values (n=89)
    - Unacceptable test procedure result (n=265)
    - Other reasons (n=82)
  - Randomized: N=254
    - Allocated to vildagliptin (N=128)
      - Discontinued (n=27)
        - Death (n=11)
        - Adverse event(s) (n=5)
        - Withdrew consent (n=3)
        - Protocol deviation (n=3)
        - Unsatisfactory therapeutic effect (n=2)
        - Lost to follow-up (n=2)
        - Administrative (n=1)
      - Completed (n=101; 78.9%)
        - Analyzed for safety (n=128; 100%)
        - Analyzed for efficacy (n=115; 89.8%)
        - Per protocol analysis (n=80; 60.5%)
    - Allocated to placebo (N=126)
      - Discontinued, (n=26)
        - Death (n=4)
        - Adverse event(s) (n=4)
        - Withdrew consent (n=10)
        - Protocol deviation (n=2)
        - Unsatisfactory therapeutic effect (n=1)
        - Lost to follow-up (n=2)
        - Administrative (n=3)
      - Completed (n=101; 78.9%)
        - Analyzed for safety (n=125; 99.2%)
        - Analyzed for efficacy (n=112; 89.9%)
        - Per protocol analysis (n=90; 71.4%)
Figure 3. Change from baseline in left ventricular ejection fraction (primary endpoint) and other echocardiographic measures

A. Change in LVEF (%). Difference in adjusted mean change 0.62 (95% CI: -2.21, 3.44; P=0.667)*.

*Meets criteria for non-inferiority to comparator as the lower limit of the two sided 95% CI for the difference in mean change in LVEF is greater than -3.5%. Primary analysis is based on Per Protocol. B. Change in LVEDV (mL). Difference in adjusted mean change 17.06 (95% CI: 4.62, 29.51; P=0.007). Full analysis set. C. Change in LVESV. Difference in adjusted mean change 9.44 (95% CI: -0.49, 19.38; P=0.062). Full analysis set. D. Change in LVSV. Difference in adjusted mean change 9.00 (95% CI: 3.38, 14.62; P=0.002). Full analysis set.