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ORIGINAL ARTICLE

Effects of Dipeptidyl Peptidase-4 Inhibitor Linagliptin on Left Ventricular Dysfunction in Patients with Type 2 Diabetes and Concentric Left Ventricular Geometry (the DYDA 2™ Trial). Rationale, Design, and Baseline Characteristics of the Study Population

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Abstract

Purpose A multicentre, randomized, double-blind, placebo-controlled, parallel-group study aimed to define the potential positive effect of dipeptidyl peptidase-4 inhibition on left ventricular systolic function (LVSF) beyond glycemic control in type 2 diabetes mellitus (T2DM) (DYDA 2™ trial).

Methods Individuals with fairly controlled T2DM and asymptomatic impaired LVSF were randomized in a 1:1 ratio to receive for 48 weeks either linagliptin 5 mg daily or placebo, in addition to their stable diabetes therapy. Eligibility criteria were age ≥ 40 years, history of T2DM with a duration of at least 6 months, HbA1c ≤ 8.0% (≤ 64 mmol/mol), no history or clinical signs/symptoms of cardiac disease, evidence at baseline echocardiography of concentric LV geometry (relative wall thickness ≥ 0.42), and impaired LVSF defined as midwall fractional shortening (MFS) ≤ 15%. The primary end-point was the modification from baseline to 48 weeks of MFS. As an exploratory analysis, significant changes in LV global longitudinal strain and global circumferential strain, measured by speckle tracking echocardiography, were also considered. Secondary objectives were changes in diastolic and/or in systolic longitudinal function as measured by tissue Doppler.

Results A total of 188 patients were enrolled. They were predominantly males, mildly obese, with typical insulin-resistance comorbidities such as hypertension and dyslipidemia. Mean relative wall thickness was 0.51 ± 0.09 and mean MFS 13.3% ± 2.5.

Conclusions DYDA 2 is the first randomized, double-blind, placebo-controlled trial to explore the effect of a dipeptidyl peptidase-4 inhibitor on LVSF in T2DM patients in primary prevention regardless of glycemic control. The main characteristics of the enrolled population are reported.

Trial registration ClinicalTrial.gov Identifier: NCT02851745.

Keywords Dipeptidyl peptidase-4 inhibition · Linagliptin · Type 2 diabetes · Glycemic control · Concentric geometry · Left ventricular dysfunction

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Introduction

Heart failure (HF) is a common and serious condition in patients with type 2 diabetes mellitus (T2DM), as well as the leading cause of hospital admission [1]. Patients with T2DM are 2.5 times more likely to develop HF than the general population [2], and this is not necessarily related to ischemic heart disease or other concomitant risk factors.

Beyond those with overt cardiac disease, a remarkable proportion of patients with T2DM have asymptomatic left ventricular (LV) systolic dysfunction (LVSD) [3–7] even though

conventional echocardiographic indexes reflecting systolic function at the chamber level (LV ejection fraction (LVEF)) are still normal [8]. This condition of subclinical LVSD can be revealed by the assessment of midwall fractional shortening (MFS), a parameter independent of LV geometry, which identifies early systolic impairment of wall mechanics [8] and therefore an estimate of LV systolic function different from LVEF. It has been shown that impaired MFS is an early and reliable indicator of the transition phase between normal cardiac function and clinically manifest HF [9]. Such early impairment in LVSF is strongly associated with concentric LV geometry [3–5]. A significant, positive association between impaired MFS and risk of CV mortality was observed several years ago in non-diabetic patients with hypertension [10], in patients with chronic HF and preserved LVEF [11], and, more recently, in people with T2DM [12]. Furthermore, in T2DM patients with no history of cardiovascular disease, a high rate of cardiovascular events was also associated with impaired global longitudinal strain, an index of LVSF derived by the analysis of speckle tracking echocardiography. This index, in patients with T2DM, provided incremental prognostic value to the traditional risk factors evaluated [13]. No randomized clinical trial has been carried out in patients with T2DM or even in hypertensive patients with chronic HF to assess the effect of glucose-lowering medications on LVSF or clinical outcomes.

Dipeptidyl Peptidase-4 Inhibition in Patients with Type 2 Diabetes. Clinical Evidence and Potential Pleiotropic Effects

DPP-4 inhibitors (gliptins) are oral incretin-based glucose-lowering agents with proven efficacy and safety in the management of T2DM. In addition, preclinical data and mechanistic studies suggest a possible additional non-glycemic beneficial action both on blood vessels and heart, via both GLP-1-dependent and GLP-1-independent effects [14, 15]. In patients with T2DM, in addition to glucose control, DPP-4 inhibitors improve control of other CV risk factors such as arterial pressure and postprandial (and even fasting) lipemia. DPP-4 inhibitors also reduce inflammatory markers and oxidative stress, improve endothelial function, and decrease platelet aggregation [16]. However, so far, results of cardiovascular outcomes trials with DPP4 inhibitors, compared with placebo or other active glucose-lowering agents [17–19], failed to demonstrate a superiority of these compounds in preventing CV disease. Unexpectedly, in 2013, an unexplained increase of hospitalization for HF of patients treated with the DDP-4 inhibitor saxagliptin in the SAVOR TIMI 53 trial raised some questions on the safety of this compound [18]. Subsequent analysis of randomized clinical trials did not confirm this finding. In contrast, observational analyses on real-world clinical practice suggest that DPP4 inhibitors therapy might be associated with reduction of risk of HF [20]. These conflicting data support the need of an in-depth mechanistic investigations in this field.

Specific Characteristics of DPP-4 Inhibitor Linagliptin

Linagliptin is an oral, once-daily DPP-4 inhibitor that prevents the inactivation of incretin hormones GLP-1 and glucose-dependent insulinotropic peptide, which stimulate glucose-dependent secretion of insulin. In large clinical trials conducted in patients with T2DM, linagliptin alone or in combination with other oral antidiabetic drugs has shown clinically meaningful efficacy with low risk of hypoglycemia and no weight gain [21, 22]. Recently, the **Carmelina Trial** [19] reported no increased CV and/or renal events with linagliptin compared to placebo in patients at high CV risk. In this study, also the risk for HF hospitalization was not modified. Furthermore, it was demonstrated that linagliptin reduces blood pressure and improves intracellular calcium mishandling and cardiomyocyte ultrastructure, which collectively result in improvements in diastolic LV function. Linagliptin also reduces infarct size after myocardial ischemia/reperfusion in rats [23]. The aim of the DYDA2 trial was to explore the unknown effect of linagliptin on LVSF in patients with T2DM.

Methods

Study Design and Setting

DYDA 2 was designed as a multicentre, randomized, double blind, parallel group comparison of an DPP-4 inhibitor, linagliptin 5 mg od, versus placebo in patients with T2DM and concentric LV geometry (defined as two times increased LV posterior wall-thickness/end-diastolic diameter ratio, named LV relative wall thickness, independently of the presence of LV hypertrophy) associated with LVSD at the midwall level documented at baseline echocardiograms. Inclusion and exclusion criteria are reported in Table 1 which shows the cut-off values for the recognition of concentric LV geometry and LVSD conditions. In brief, the aim of the study was to enroll stable compensated T2DM patients with no history of heart disease and normal LVEF.

Patients were centrally randomized with a web-based randomization system in a 1:1 ratio to receive either linagliptin 5 mg or placebo. Linagliptin and corresponding placebo were supplied to the investigator in tablet formulation of 5 mg for oral use and taken once daily with or without a meal at any time of the day.

During the double-blind study treatment period, the management of glycemia was left to the Investigator's judgment according to clinical guidelines, with the exclusion of other DPP-4 inhibitors or GLP-1 receptor agonists.

Table 1 Inclusion criteria and exclusion criteria

Inclusion criteria	Exclusion criteria
•Men and women aged equal to or more than 40 years at screening with history of T2DM lasting at least 6 months prior to the screening visit • HbA1c ≤ 8.0% (≤ 64 mmol/mol) at screening • Evidence of sinus rhythm at screening ECG evaluation • No clinical signs/symptoms of a cardiac disease and no evidence of coronary artery disease on the basis of clinical, electrocardiographic, and echocardiographic evaluation at screening • Evidence at baseline echocardiographic examination of (a) concentric left ventricular geometry defined as relative wall thickness ≥ 0.42[a] and (b) LV systolic dysfunction defined as Midwall fractional shortening (MFS) ≤ 15%	• Patients with a confirmed indication for an incretin treatment • Uncontrolled diabetes: HbA1c > 8.0% (> 64 mmol/mol) or fasting plasma glucose > 300 mg/dL measured at screening visit • Glitazones within the last 3 months • Permanent atrial fibrillation • Uncontrolled hypertension (defined as systolic blood pressure > 160 and/or diastolic blood pressure > 90) • Unstable dosage and changes in type of antihypertensive, lipid lowering, and antidiabetic drugs within 4 weeks before the screening visit • Severe chronic renal dysfunction (defined as estimated glomerular filtration rate < 30 ml/min/1.73 m^2) • Previous or current documented history of untreated (by using CPAP) obstructive sleep apnea syndrome • Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis • Previous or current documented history of malignant disease • Pregnancy and breast feeding • Documented alcohol and drug abuse • Anticipated poor compliance • Current participation in a clinical trial with other investigational products

[a] Relative wall thickness was calculated as two times the posterior wall thickness divided by the LV diastolic diameter

LV left ventricular, *MFS* midwall fractional shortening, *T2DM* type 2 diabetes mellitus

The enrollment period lasted altogether 28 months. Patients were enrolled by Centers in which subjects with T2DM are usually seen for diabetes management, including standard echocardiographic examination performed in referred echo-laboratories. The patients were followed up for 48 weeks from randomization. The follow-up was completed in April 2019.

At visit 1 (day − 7 to − 1) patients were assessed for eligibility. Complete transthoracic ColorDoppler echocardiographic examination and ECG were carried out to verify compliance with the inclusion/exclusion criteria. A blood sample was collected for local laboratory assessment of creatinine and HbA1c, if not available within prior 3 months.

If eligible, patients were randomized at visit 2 (day 0) into one of the two treatment groups (linagliptin 5 mg or placebo once daily) and blood samples collected for central analyses.

After randomization, patients were seen again after 2 weeks (visit 3) and at 3 months (visit 4, week 12). At visit 4, blood samples were collected again for central analyses.

Afterwards, a new control was scheduled at 24 weeks (visit 5) and a final visit at 48 weeks from randomization (visit 6), which included echocardiogram, ECG, and blood samples collected for central analyses.

ECG and transthoracic Doppler-echocardiography to define the primary and secondary endpoints were forwarded to the data management center for central reading. A post-treatment safety follow-up (clinical visit or phone contact) 30 days after the study treatment discontinuation was scheduled for patients still on study treatment at the time of final visit (visit 6).

The study protocol was approved by the Italian Competent Authority (AIFA-Italian Medicine Agency) and by the Institutional Review Board/Ethics Review Committee affiliated with each center. It was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided written informed consent before participation.

Efficacy and Safety Parameters Assessments

The primary objective of the study was to evaluate the effect of linagliptin 5 mg daily versus placebo on the circumferential component of LVSF measured by MFS. The primary efficacy variable was the modification of MFS calculated as changes from baseline to 48 weeks. In parallel to MFS evaluation, as an exploratory analysis, the study protocol also comprised an assessment of asymptomatic LVSF evaluated with the "Speckle-Tracking Echocardiography" (STE) technique, so-called global circumferential strain (GCS) and global longitudinal strain (GLS), which enables to measure such parameters with a method which is less dependent on LV load and end-systolic stress.

The main secondary objectives were the drug effects on diastolic LV function and the longitudinal component of LVSF, estimated by tissue-Doppler interrogation. The secondary efficacy variables were the following:

– Changes from baseline to 48 weeks in diastolic LV function: Transmitral peak *E* wave (pulse Doppler) and early

diastolic Tissue Doppler velocity of mitral annulus (E') were used to assess LV diastolic function together with other parameters (E/A ratio of transmitral flow, deceleration time of E, left atrial volume, pulmonary artery systolic pressure).

– Changes from baseline to 48 weeks in the longitudinal component of LVSF measured by tissue Doppler technique (peak systolic velocity of S' wave of mitral annulus); incidence of patients who had an improvement in $S' > 25\%$ from baseline. This value corresponded to a slightly higher value than the mean of $S' + 2$ SD of the mean found in our reference Italian healthy population analyzed in the participating center of Trento [24].

Safety assessments consisted of monitoring and recording the pre-defined safety and tolerability end-points, all serious adverse events, and the regular measurements of vital signs.

The following clinical combined outcome measures were considered a safety end-point: cardiovascular death, non-fatal-MI, non-fatal stroke, hospitalization for HF, hospitalization for coronary revascularization procedure, acute pancreatitis, any type of cancer. A Clinical Event Committee was in charge of a central adjudication of these events.

As regards severe hypoglycemia, it was defined as an event requiring assistance of another person to actively administer carbohydrates, glucagons, or other resuscitative actions. All serious adverse events (SAEs) and all adverse events suspected to be related to the study treatment were collected in the study.

Strengths and Reproducibility of MFS

The echocardiographic methodology applied in the DYDA2 investigation, and in particular the use of midwall shortening in place of ejection fraction as parameter of LVSF, deserves some attention. When LV geometry changes towards a concentric fashion, the shortening of myocardial fibers is reduced at the midwall level mainly due to fiber de-arrangement, intramyocardial fibrosis, and/or micro-vascular ischemia, while it can be amplified at the level of the endocardium. This amplification is closely and directly related to wall thickness. It is a compensatory phenomenon (amplification of shortening across the myocardium) named "cross-fiber shortening" [8] and is much effective at the endocardium than at midwall, because it is limited to the effect of external myocardial layers and long-axis shortening [25–28]. Thus, increased wall thickness can augment at the endocardial level the shortening of myocardial fibers, allowing preservation of LVEF (which is an index of global LV chamber function) despite depressed midwall shortening [25–28]. In clinical practice, about one sixth of asymptomatic hypertensive patients and one third of asymptomatic T2DM patients exhibit LVSD at the midwall level, though their endocardial shortening measured as LVEF is normal [3]. These pathophysiological phenomena are at the basis of a better prediction of cardiovascular adverse events in T2DM patients based on LV wall mechanics measures (i.e., midwall shortening) than of LV chamber function measures (i.e., LVEF) [12]. They also are the rationale of the echocardiographic assessment of LVSF by midwall shortening in the DYDA2 trial.

Echocardiographic reproducibility of MFS was tested by using the recordings of 50 patients with T2DM part of the study cohort and randomly selected. Data were all analyzed by an expert cardiologist skilled in echocardiography twice per each patient. The mean difference between two measurements was ± 0.3%. The standard deviation of this difference was ± 4%. Bland-Altman plot shows that the intra-observed variability was statistically acceptable. Indeed, in none of these 50 subjects, the deviation of values of MFS measured twice at two different times in the same patient exceeded the 2 standard deviations of the mean of MFS between the two measures (Fig. 1). Inter-observer variability for MFS was tested by comparing these measures with those acquired by a second sonographer: The mean difference between two measurements was 0.55%. The standard deviation of this difference was ± 4%.

Sample Size and Data Analysis

The study was designed to test the hypothesis that treatment of patients with T2DM and concentric LV geometry and LVSD with the dipeptidyl-peptidase-4 inhibitor, linagliptin, may determine an improvement on the LVSF measured by MFS.

A sample size of 93 patients in each treatment group was estimated (using the PS Power and Sample Size Calculations software version 3.0) to provide a 95% power at the 0.01 level of statistical significance to detect an improvement in MFS of 10%, assuming a mean MFS of 13.6% at baseline, a standard

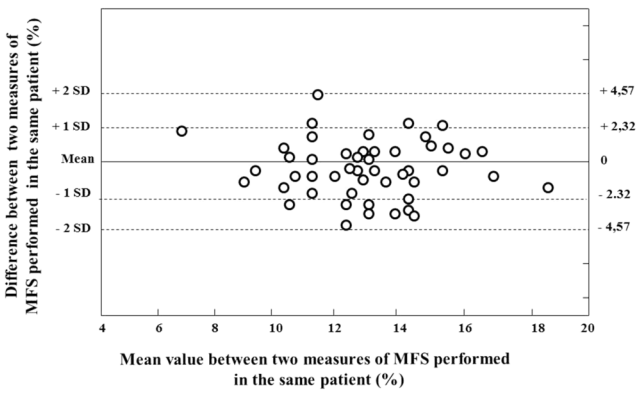

Fig. 1 Bland-Altman plot showing the deviation of values of midwall fractional shortening (MFS) measured twice in the same patient with T2DM at two different times from the mean value of MFS between the two measures. This test of reproducibility of MFS was performed using the (CD) recordings of 50 patients with T2DM part of the study cohort and randomly selected. MFS midwall fractional shortening

deviation of 2.0% and a dropout rate of 15%. This assumption was based on the analysis of the DYDA Registry [3, 4] and also on the clinical outcomes data derived from the "Verona Diabetes Study" [12]. This experience demonstrated that patients with impaired MFS had a considerably worse prognosis at long-term than counterparts with normal MFS at baseline echocardiographic evaluation. In the DYDA2 contest, an improvement of 10% of MFS (from baseline 13.6% to final 14.96%) would correspond to the achievement of mean MFS values very close to a mean absolute MFS value of 15%, which represents the prognostic cut-off value of MFS defined by the literature [12]. According to the above estimation, 186 patients had to be randomized in the trial.

The primary analysis population were on all randomized patients with baseline and 48 weeks ECHO available. On analyses based on this population, the echocardiographic measures detected at the entry visit will be compared with the echocardiographic measures detected at study end (48 weeks). The treatment effect on the echocardiographic measurements (both for primary and secondary efficacy endpoints) were tested by one-way ANOVA on the intra-subjects difference between basal and end of treatment response using treatment group as factor and basal response as covariate. Patients were analyzed according to treatment received at randomization.

The analysis was also performed on the per-protocol population that was on all patients who received, at least 40 weeks of study medication and who were still on treatment at the final echocardiographic evaluation.

The safety analysis were performed on all patients that received at least one dose of study medication and had at least one post-baseline safety assessment. Patients were analyzed according to treatment received.

Results

DYDA 2 enrollment was initiated on July 23, 2015 and terminated on April 26, 2018. A total of 14 centres recruited patients in the trial. The follow-up was completed in April 2019.

The main clinical, laboratory, and ECG characteristics of the enrolled population are reported in Table 2. On the whole, they reflect those of the average T2DM seen in general practices and diabetes units in Italy: rather old patients, predominantly males, and mildly obese, with typical insulin-resistance co-morbidities such as hypertension and dyslipidemia. The effort to search for compensated, asymptomatic patients, with no history of CV disease, may be responsible for the short mean duration of the disease. Renal function is characterized by a borderline mild renal failure which bears no clinical implication. The mean value of HbA1c level confirms that the objective to enroll compensated patients, in order to rule out the possible interfering effects of hyperglycemia, was achieved. Hypertension was properly controlled.

Table 2 Main clinical, laboratory, and ECG characteristics of the DYDA 2 population

Variables	Total study population ($n = 188$)
Clinical	
Age (years), mean ± SD	69 ± 9
≥ 75 years, *n* (%)	46 (24.5)
Female gender, *n* (%)	83 (44.2)
Body mass index (kg/m^2), mean ± SD	30.0 ± 5.1
Obesity (BMI ≥ 30 kg/m^2), *n* (%)	80 (42.6)
Current smoker, *n* (%)	24 (12.8)
History of hypertension, *n* (%)	154 (81.9)
Dyslipidemia, *n* (%)	139 (73.9)
Treated dyslipidemia, *n* (%)	131 (69.7)
Family history of coronary artery disease, *n* (%)	42 (22.3)
Peripheral vascular disease, *n* (%)	31 (16.5)
Duration of diabetes (years), median [IQR]	7 [4–12]
Systolic blood pressure (mmHg), mean ± SD	136 ± 15
Diastolic bloood pressure (mmHg), mean ± SD	77 ± 8
Heart rate (beats/min), mean ± SD	71 ± 9
Laboratory (local laboratory assessment)	
HbA1c (%), mean ± SD	6.7 ± 0.8
HbA1c (mmol/mol), mean ± SD	48.7 ± 8.9
Creatinine (mg/dl), mean ± SD	0.9 ± 0.2
eGFR (ml/min/1.73 m^2), mean ± SD	81.7 ± 22.4
eGFR < 60 ml/min/1.73 m^2, *n* (%) *available for 185 pts*	31 (16.8)
Electrocardiographic measures	
LV hypertrophy (Cornell voltage), *n* (%) *available for 187 pts*	12 (6.4)
QRS duration (V3) (ms), median [IQR]	90 [90–100]
Typical strain, *n* (%)	5 (2.7)

BMI body mass index, *LV* left ventricular, *IQR* interquartile range, *SD* standard deviation

As regards drug therapies (Table 3), in line with the existing guidelines, metformin was the most used medication, whereas a small proportion of subjects was on sulfanylurea and glinides whose negative effects on myocardium are still debated. Noteworthy, 13% of patients were on insulin.

RAAS inhibitors, especially ACE inhibitors, were the most used classes to treat hypertension and possibly to prevent microalbuminuria evolution. The use of beta-blockers, diuretics, and other classes of medication were in line with other real-life surveys on treatment of hypertension in T2DM [29]. A remarkable 60% of patients were on statins.

Table 4 reports the echocardiographic characteristic of the enrolled population. As expected by protocol, all patients had a concentric LV geometry, the mean value of relative wall thickness was particularly high, more than half of the

Table 3 Pharmacological therapy

Variables	Total study population ($n = 188$)
Pharmacological treatment for diabetes	
Sulfanylurea, *n* (%)	23 (12.2)
Metformin, *n* (%)	158 (84.0)
Repaglinide, *n* (%)	15 (8.0)
Acarbose, *n* (%)	3 (1.6)
Insulin, *n* (%)	25 (13.3)
Pharmacological treatment for hypertension and cardiovascular risk factors	
Loop or thiazide diuretics, *n* (%)	74 (39.4)
ACE inhibitors, *n* (%)	78 (41.5)
Angiotensin T1-receptors blockers, *n* (%)	61 (32.5)
Beta blockers, *n* (%)	52 (27.7)
Aldosterone blockers, *n* (%)	5 (2.7)
Calcium antagonists, *n* (%)	52 (27.7)
Doxazosin or alpha1 blockers, *n* (%)	16 (8.5)
Other anti-hypertensive agents, *n* (%)	16 (8.5)
Statins, *n* (%)	113 (60.1)
Antiplatelet agents, *n* (%)	102 (54.3)

ACE angiotensin-converting enzyme

Table 4 Echocardiographic characteristics of the study patients

Variables	Total study population ($n = 187$)
Left ventricular geometry	
End-diastolic diameter (cm/m^2), mean ± SD	2.5 ± 0.3
End-sistolic diameter (cm/m^2), mean ± SD	1.6 ± 0.3
End-diastolic volume (ml/m^2), mean ± SD	45.8 ± 11.5
End-sistolic volume (ml/m^2), mean ± SD	15.8 ± 5.4
Relative wall thickness, mean ± SD	0.51 ± 0.09
LV mass index (g/m$^{2.7}$), mean ± SD	54.9 ± 14.5
LV hypertrophy, n. (%)	105 (56.2)
LV systolic function	
Stroke volume (ml), mean ± SD	75.5 ± 21.6
Cardiac index (l/min/m^2), mean ± SD	2.8 ± 0.9
Ejection fraction (%), mean ± SD	65.5 ± 8.1
Midwall fractional shortening (%), mean ± SD	13.3 ± 2.5
Circumferential end-systolic stress (dynes/cm^2), mean ± SD	121.2 ± 40.8
Global longitudinal strain (%), mean ± SD	−15.6 ± 3.87
Global circumferential strain (%), mean ± SD	−21.2 ± 6.09
LV diastolic function	
Peak *E* velocity (cm/s), mean ± SD	68.8 ± 18.5
Peak *A* velocity (cm/s), mean ± SD	87.0 ± 19.2
E/*A* ratio, mean ± SD	0.8 ± 0.3
Deceleration time *E* wave (msec), mean ± SD	255.9 ± 64.4
Peak *E*′ velocity, mean ± SD	8.8 ± 2.3
E/*E*′ ratio, mean ± SD	8.2 ± 2.8
Left atrium	
Maximal volume (ml/m^2), mean ± SD	23.1 ± 10.1

LV left ventricular, *SD* standard deviation

population (56%) showed a pattern of LV concentric hypertrophy. LVEF and cardiac index were normal in all patients. Mean MFS was 13.3% corresponding to a value slightly lower than that predicted according to the analysis of the DYDA Registry (13.6%). Regarding the multiparametric analysis of the diastolic LV function, it is of interest to underline the normality of the mean value of *E*/*A* ratio of the trans-mitral flow pattern, the mean value of *E*/*E*′ ratio close to the cut-off of normality and the normal value of left atrial maximal volume found in most of patients.

Discussion

The characteristics of DYDA 2 population correspond to the typology of T2DM patients required for this protocol, namely subjects well compensated, with prognostically relevant asymptomatic echo abnormalities [12] and least interference due to metabolic instability. The study should be considered as a proof-of-concept intervention to explore the potential treatment effect of linagliptin on the LVSF. Conclusive evidence on the impact of linagliptin to alter the natural course of LV geometry and function leading to HF in T2DM, however, can only emerge from larger, long-term, and adequately powered randomized studies.

Four years ago, at the time DYDA 2 was conceived and designed, very little was known on the effects of incretin-based therapies on the heart, and DPP4 I and GLP1-RA were considered as different only in terms of anti-hyperglycemic potency. Nowadays, it is known that DPP-4 inhibitors differ from GLP1-RA in that they are effective in preventing microvascular complication (specifically eye and kidney), but they are neutral in terms of prevention of coronary events [30]. Cardiovascular outcome trials with saxagliptin, alogliptin [17–19], and sitagliptin demonstrated safety and non-inferiority in terms of CV prevention, but failed to highlight any further advantage.

In the recently published trial **Carmelina** [19], linagliptin showed a CV and renal safety in compromised patients at high risk of cardiac and/or renal complications. However, no evidence of superiority of linagliptin versus usual care was observed in terms of CV, total mortality, and coronary cerebrovascular events. Recently, the results the VIVIDD (Vildagliptin in Ventricular Dysfuncion Diabetes) trial were published [31]. The authors found that, compared to placebo, 1 year of treatment with Vildagliptin had no effect on LVEF but led to an

increase of left ventricular volume of unknown significance. The objective, the design, and the size of the study may resemble those of the DYDA 2 study, but several key differences must be considered. First, in VIVIDD, patients, as regards LVSF, were far more compromised than in DYDA2. Second, the ECHO measures adopted in DYDA2 explore more precocious and accurate aspects of LV. Furthermore, the pharmacokinetic and dynamic of Vildagliptin are largely different from those of linagliptin. In VIVIDD, HbA1c reduction was a secondary endpoint, making it impossible to rule out some possible interference of the metabolic control.

DYDA 2 trial holds its strength in answering the question whether linagliptin may exert any effect on LV contractility, regardless of the mechanism, GLP-1 receptor stimulation, or DPP-4 inhibition. In fact, animal studies reported that the sole DPP-4 inhibition decreases elevated myocardial fatty acid uptake and oxidation in the heart. These observations support the possibility of a role of DPP-4 inhibition per se on several heart functions.

In the last 3 years, SGLT-2 inhibitors have emerged as a class with definite favorable evidence on HF hospitalization and mortality. Nevertheless, the current evolution towards combo formulation, DPP4 and SGLT-2 inhibitors in the same tablet, can make the information provided by DYDA2 of utmost relevance. From this point of view, even a neutral impact of linagliptin on the myocardium would be a valuable piece of information.

Conclusions

In conclusion, a body of experimental evidence has shown that DPP-4 inhibition may improve the progressive course of HF due to these agents' antifibrotic, anti-oxidative, and anti-inflammatory properties. However, a reliable evidence defining the LV effects of DPP-4 inhibition is not yet available. Utilizing the DPP-4 inhibitor linagliptin, DYDA2 represents a randomized clinical trial, adequately designed and powered, to provide, through detailed echocardiographic parameters, robust and reliable data on the impact on LV functions.

Authors' Contributions CBG, GC, APM literature search, study design, data collection and interpretation, writing; DL data collection, analysis and interpretation; EN, FO literature search, data collection; CM, RL data management, reading and interpretation. No other persons have made substantial contributions to this manuscript. All authors approved the final version.

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Compliance with Ethical Standards

Conflict of Interest CBG has nothing to disclose with respect to the present manuscript. In 2018, he received fees from Boehringer Ingelheim, Italy, for data interpretation of other trials. GC, EN, RL, and CM have nothing to disclose. DL is employee of Heart Care Foundation, which conducted the study with an unrestricted grant by Boehringer Ingelheim, Italy. APM nothing to disclose with respect to the present manuscript. Personal fees for participation in study committees sponsored by Bayer, Fresenius, and Novartis.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any study with animals performed by any of the authors.

Appendix

Steering Committee

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