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A randomized, open-label, active comparator trial assessing the effects of 26 weeks of liraglutide or sitagliptin on cardiovascular function in young obese adults with type 2 diabetes

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Abstract

Aim: To compare the effects of a glucagon-like peptide-1 receptor agonist and a dipeptidyl peptidase-4 inhibitor on magnetic resonance imaging-derived measures of cardiovascular function.

Materials and methods: In a prospective, randomized, open-label, blinded endpoint trial liraglutide (1.8 mg) and sitagliptin (100 mg) were compared in asymptomatic, non-insulin treated young (aged 18-50 years) adults with obesity and type 2 diabetes. The primary outcome was difference in circumferential peak early diastolic strain rate change (PEDSR), a biomarker of cardiac diastolic dysfunction 26 weeks after randomization. Secondary outcomes included other indices of cardiac structure and function, HbA1c and body weight.

Results: Seventy-six participants were randomized (54% female, mean ± SD age 44 ± 6 years, diabetes duration 4.4 years, body mass index 35.3 ± 6.1 kg m^{-2}), of whom 65% had ≥1 cardiovascular risk factor. Sixty-one participants had primary outcome data available. There were no statistically significant between-group differences (intention-to-treat; mean [95% confidence interval]) in PEDSR change (–0.01 [–0.07, +0.06] s^{-1}), left ventricular ejection fraction (–1.98 [–4.90, +0.94]%), left ventricular mass (+1.14 [–5.23, +7.50] g) or aortic distensibility (–0.35 [–0.98, +0.28] $mmHg^{-1} \times 10^{-3}$) after 26 weeks. Reductions in HbA1c (–4.57 [–9.10, –0.37] mmol mol^{-1}) and body weight (–3.88 [–5.74, –2.01] kg) were greater with liraglutide.

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Conclusion: There were no differences in cardiovascular structure or function after short-term use of liraglutide and sitagliptin in younger adults with obesity and type 2 diabetes. Longer studies in patients with more severe cardiac dysfunction may be necessary before definitive conclusions can be made about putative pleiotropic properties of incretin-based therapies.

KEYWORDS

cardiac magnetic resonance, diastolic dysfunction, liraglutide, obesity, peak early diastolic strain rate, randomized controlled trial, sitagliptin, type 2 diabetes, young adults

1 | INTRODUCTION

Heart failure is a leading cause of death and disability in people with diabetes.[1] Drugs commonly used to control glucose appear to have differing effects on this important patient-centred outcome. Sodium-glucose co-transporter-2 (SGLT-2) inhibitors reduce all-cause mortality and heart failure hospitalization through mechanisms believed to be independent of their capacity to lower blood glucose.[2] The impact (if any) of pharmacotherapy directly or indirectly activating the glucagon-like peptide-1 (GLP-1) receptor is less certain.[3] In 2013, concern was raised after the dipeptidyl peptidase-4 (DPP-4) inhibitor saxagliptin was associated with increased hospitalization for congestive cardiac failure in a secondary endpoint analysis of the Savor-Timi 53 trial.[4] This finding generated the hypothesis that incretin-based treatments exert disparate actions on cardiac function. More recently, a number of studies have explored the actions of both GLP-1 receptor agonists and DPP-4 inhibitors on mostly echocardiographic estimates of cardiac function in patients with type 2 diabetes and co-existent heart failure.[5-10] Depending on the population studied, these have reported little or no effect on left ventricular ejection fraction (LVEF) and are consistent with the generally neutral findings of heart failure hospitalization endpoint analyses of more recent major cardiovascular outcome trials.[11-19]

To our knowledge there has been only one randomized study exploring the effects of incretins on diabetes-related measures of cardiac dysfunction using cardiac magnetic resonance (CMR) imaging and none directly comparing a GLP-1 receptor agonist and DPP-4 inhibitor. CMR imaging is the gold standard non-invasive technique for the assessment of cardiac structure and function.[20]

We therefore aimed to compare the GLP-1 receptor agonist liraglutide with the DPP-4 inhibitor sitagliptin using change in CMR imaging-derived subclinical diastolic dysfunction as the primary outcome measure in younger asymptomatic adults with type 2 diabetes who have a significant lifetime risk of developing heart failure.[21]

2 | METHODS

2.1 | Trial design and oversight

The effects of Liraglutide in Young adults with type 2 DIAbetes (LYDIA) study was a 26-week, single-centre, prospective, randomized, open-label, blinded endpoint active comparator trial. The rationale and detailed design of the study have been reported previously (Clinical trials.gov registration NCT02043054, EudraCT 2012-002422-78).[22] LYDIA was specifically designed to assess the relative effects of two drugs targeting the incretin pathway on a CMR imaging-derived biomarker of diastolic function, circumferential peak early diastolic strain rate (PEDSR). In a pilot trial conducted at the University of Leicester, excellent test-retest reproducibility for PEDSR was obtained and this measurement was significantly decreased in a cross-sectional comparison of younger adults with type 2 diabetes and healthy lean controls.[23] Consenting, eligible participants with type 2 diabetes were randomized 1:1 following baseline measurements to either liraglutide (Victoza), titrated to a maximum dose of 1.8 mg and self-administered via a once-daily subcutaneous injection, or to an active comparator agent, sitagliptin (Januvia) 100 mg, given as a once-daily oral tablet. The primary outcome was change in PEDSR from baseline to 26 weeks. The study was approved by the West Midlands NHS Research Ethics Committee and the Medicine and Healthcare products Regulatory Agency, conducted in accordance with good clinical practice guidelines and sponsored by the University of Leicester. This was a single-centre study, managed by a UK Clinical Research Collaboration-accredited clinical trials unit. The funder (NovoNordisk) had no role in operational aspects, recruitment, data analysis or interpretation.

2.2 | Study population

Eligible participants aged 18-50 years (upper limit revised to 60 years of age in 2017) were recruited from primary and secondary care diabetes clinics. Inclusion criteria were obesity (body mass index [BMI] ≥30 kg m^{-2} or ≥27 kg m^{-2} if of South Asian ethnicity) and type 2 diabetes treated with oral glucose-lowering agents (metformin and/or any sulphonylurea). Patients prescribed insulin, SGLT-2 inhibitor, GLP-1 receptor agonist or DPP-4 inhibitor therapies were excluded.

2.3 | Interventions

Randomization was concealed via an independent online assignment system after consent and baseline assessments. Liraglutide was administered via manufacturer-supplied and labelled 3 mL prefilled

pens (Victoza 6 mg mL^{-1}) at a starting dose of 0.6 mg daily. Weekly 0.6 mg incremental dose escalation then followed as per protocol and at the investigator's discretion. Sitagliptin 100 mg daily was obtained from the manufacturer and both drugs were dispensed by the hospital clinical trial pharmacy. There was no titration protocol for the active comparator. Glycaemic control was managed in accordance with national clinical practice guidance.[24] The dose of preprescribed sulphonylurea treatment was halved if either baseline HbA1c was less than 58 mmol mol^{-1} (7.0%) or any episodes of severe hypoglycaemia were reported during the trial. 'Rescue therapy', defined as the addition of non-incretin-based medication, was considered if fasting plasma glucose exceeded 11.0 mmol L^{-1} at visit 4 (12 weeks into the study).

2.4 | Measurements

2.4.1 | CMR image acquisition

CMR imaging was performed using a 1.5 T scanner (Siemens Avanto or Aera, Erlangen, Germany) with retrospective electrocardiographic gating and an 18-channel phased-array cardiac receiver coil. The protocol has been outlined previously.[25] In brief, after localizers, steady-state free precession cine images were acquired in four-, three- and two-chamber views. Perfusion images were then acquired after vasodilatory stress with adenosine (140 μg kg^{-1} min^{-1}, infused intravenously for 3-5 minutes). At peak stress, a gadolinium-based contrast agent (gadopentetate dimeglumine, Magnevist, Bayer HealthCare LLC, Germany) was injected (0.04 mmol kg^{-1}), followed by a 20 mL bolus of normal saline, at a rate of 5 mL s^{-1}, and perfusion images were acquired using a saturation recovery gradient echo pulse sequence for three slices (base, mid and apex). Rest perfusion images were acquired ~ 10 minutes after stress with a further 0.04 mmol kg^{-1} contrast. In between rest and stress imaging, a stack of short-axis slices was obtained using cine images to obtain coverage of the entire left ventricle. Following stress imaging, a cine image of the ascending aorta at pulmonary artery bifurcation with simultaneous blood pressure measurement was obtained to calculate aortic distensibility (AD).

2.4.2 | CMR image analysis

All CMR images were analysed offline blinded to all patient details including treatment allocation and study timing. Cardiac chamber volumes, function and strain were assessed by a single experienced observer (GSG) using cmr42 version 5 (Circle Cardiovascular Imaging, Calgary, Alberta, Canada).[25] Quantitative myocardial perfusion analysis was performed using signal versus time curves from the myocardium and blood pool, converted to contrast agent concentration curves assuming a linear signal response to contrast agent as previously described.[26] Myocardial blood flow (MBF) values were estimated using Fermi-constrained deconvolution. The precontrast baseline signal, end of first-pass time point, and the bolus arrival time delay between the blood pool and myocardial curves were calculated using previously described automated methods.

2.4.3 | Anthropometric and laboratory biochemistry

HbA1c was measured via high-performance liquid chromatography using standardized procedures within the pathology laboratories of University Hospitals of Leicester NHS Trust. Serum lipids and creatinine-derived estimated glomerular filtration rate were estimated using standard enzymatic techniques (ADVIA System, Bayer, NY). All analyses were undertaken by individuals blinded to the experimental condition.

Weight was measured to the nearest 0.1 kg using standard weighing scales. Height was measured to the nearest millimetre using a stadiometer. Blood pressure and heart rate were measured using standard operating procedures and equipment (sphygmomanometer and brachial inflation cuff HEM-7200 M3, Omron Healthcare, Kyoto, Japan).

2.4.4 | Cardiorespiratory fitness

Participants underwent a maximal incremental exercise test on a stationary electromagnetically braked cycle ergometer. Throughout the test, expired gases were sampled continuously and analysed using indirect calorimetry (Cortex 3B, Cortex Biophysik, Leipzig, Germany) to determine maximal oxygen consumption ($VO_{2\ max}$), the gold standard technique for assessment of cardiovascular fitness.

2.5 | Outcomes

The primary outcome was between-arm difference in circumferential PEDSR at 26 weeks. This measure declines with early diastolic dysfunction and typifies diabetic heart disease. It was chosen based on our previously published data in young people with type 2 diabetes.[27,28] Secondary outcomes were other CMR imaging-derived measures of left ventricular strain (longitudinal PEDSR, global longitudinal/circumferential strain [LVGLS/LVGCS]), geometry (left ventricular end diastolic mass index [LVMI], end-systolic and end-diastolic volume indices [LVESVI and LVEDVI, respectively]) and function (LVEF), together with measures of vascular structural integrity, AD, MBF and myocardial perfusion reserve (MPR). Secondary cardiometabolic outcomes included HbA1c, plasma lipids (total, LDL- and HDL-cholesterol and triglycerides), standard plasma liver and renal function, brachial blood pressure and pulse rate, $VO_{2\ max}$ and anthropometrics (body weight, BMI).

2.6 | Statistical analysis and power calculation

This study was designed to assess whether liraglutide was superior to sitagliptin at producing an increase in PEDSR of more than 0.2 s^{-1}

after 26 weeks of treatment. A difference of 0.2 s^{-1} is equivalent to the difference between patients with diabetes and non-diabetic obese controls observed previously,[27,28] and is therefore likely to be clinically meaningful. To detect this treatment difference of 0.2 s^{-1}, 72 participants (36 per group) were required to complete the trial (80% power, two-sided alpha = 0.05), assuming a standard deviation of 0.3 s^{-1} in circumferential PEDSR.[27,28] Baseline characteristics were compared by group. Generalized linear models were used to generate treatment effects for the primary and secondary outcomes adjusted for baseline values along with age, gender, baseline HbA1c and baseline weight, with results presented as mean between group differences (liraglutide minus sitagliptin) with 95% confidence intervals. The primary analysis was conducted on a complete case basis using intention-to-treat principles. An additional sensitivity analysis was conducted for the primary outcome where missing data were replaced with multiple imputations across 20 datasets. Missing data were imputed using the auto imputations command in SPSS conditional on the following variables: age, gender, blood pressure and BMI. All statistical tests were two-sided and P <0.05 was considered statistically significant. Data were analysed using SPSS version 26.

3 | RESULTS

3.1 | Participants and interventions

Between 2 January 2014 (first person first visit) and 13 September 2018 (last person last visit), 230 people with type 2 diabetes who met the initial age criteria were screened for eligibility. A total of

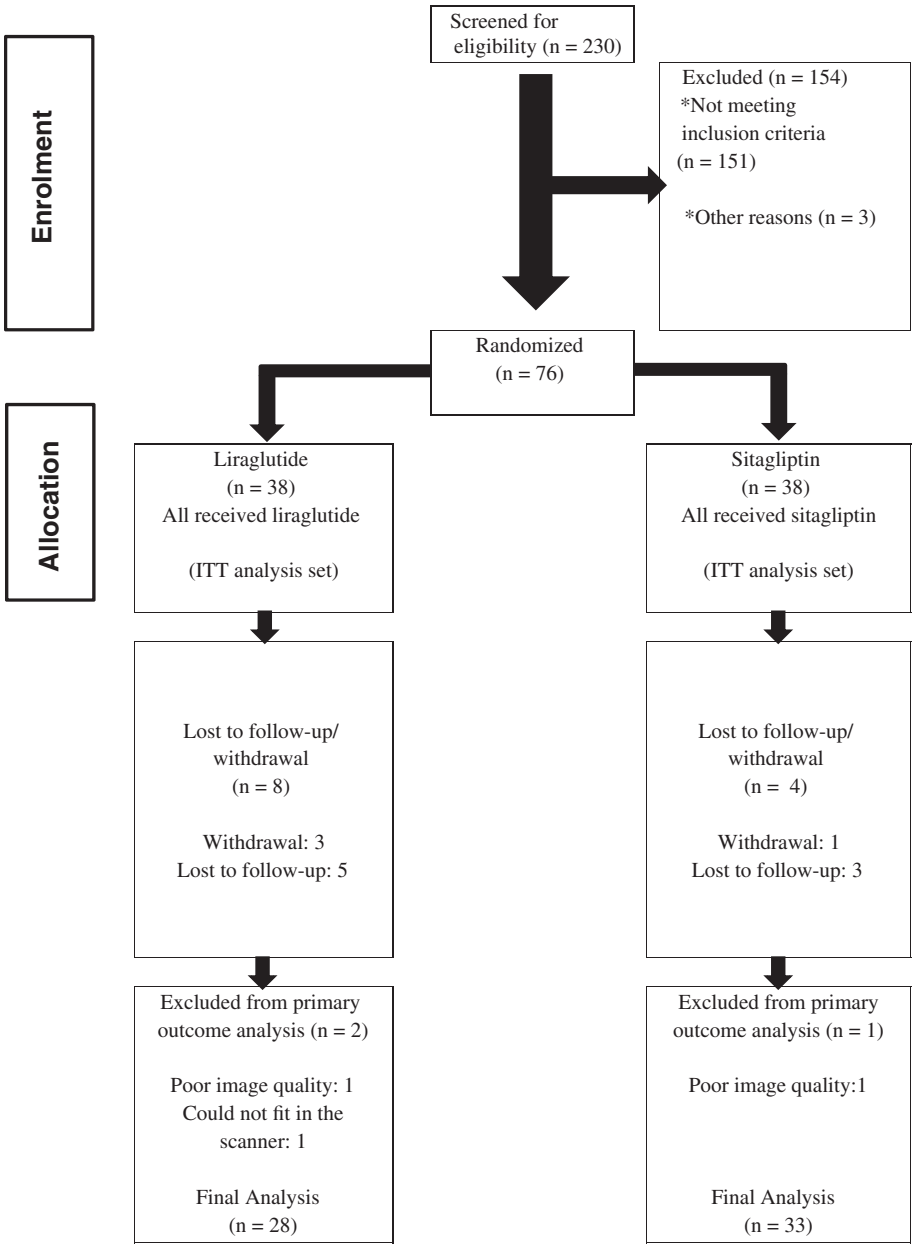

FIGURE 1 LYDIA study consort flow diagram. ITT, intention-to-treat

76 people were enrolled and randomly assigned to either liraglutide or sitagliptin. All participants received at least one dose of study medication. A total of 64 participants completed the study, for whom primary outcome data were available for 61 CMR imaging scans. The flow of participants through the trial is shown in Figure 1.

Characteristics of the study groups were balanced at baseline (Table 1). The mean age (± SD) of the combined population was 44 (± 6) years. A total of 54% were female and the mean duration of diabetes was 4.4 years. There was no significant difference in baseline characteristics between participants completing (n = 64) and not completing the study (n = 12) (data not shown).

3.2 | Effects on cardiac structure and function

Both groups showed a reduction in diastolic function (circumferential PEDSR) from baseline of −0.06 (−0.10, −0.01) and −0.05 (−0.10,

TABLE 1 Baseline characteristics

	Liraglutide		Sitagliptin	
	n		n	
Age (years)	38	43.4 (7.0)	38	44.8 (5.9)
Female, n (%)	38	18 (47.4)	38	23 (60.5)
Duration of diabetes (years)	38	4.5 (4.5)	38	4.4 (4.4)
Current smoker, n (%)	38	11 (29.0)	38	8 (21.1)
Weight (kg)	38	100.8 (18.8)	38	100.7 (21.1)
Body mass index (kg m^{-2})	38	35.7 (7.0)	38	34.9 (5.3)
Systolic blood pressure (mmHg)	38	129 (11.9)	38	128 (15.6)
Diastolic blood pressure (mmHg)	38	86 (9.0)	38	85 (9.8)
Heart rate (min^{-1})	38	81.0 (11.1)	38	76.5 (11.9)
HbA1c (%)	38	7.5 (0.8)	38	7.6 (0.8)
HbA1c (mmol mol^{-1})	38	58.4 (9.3)	38	59.1 (9.1)
Total cholesterol (mmol L^{-1})	38	4.7 (1.2)	38	4.6 (0.9)
LDL-C (mmol L^{-1})	36	2.3 (0.8)	36	2.4 (0.6)
HDL-C (mmol L^{-1})	38	1.1 (0.2)	37	1.2 (0.3)
Triglycerides (mmol L^{-1})	38	2.6 (1.5)	38	2.4 (1.7)
Alanine transaminase (IU L^{-1})	38	39.6 (21.8)	38	33.1 (14.7)
eGFR (mL min^{-1})	38	87.6 (4.6)	38	89.1 (3.3)
VO_{2max} (mL kg^{-1} min^{-1})	32	23.7 (6.1)	30	23.5 (5.0)
CMR imaging measures				
PEDSR (s^{-1}) circumferential	34	1.1 (0.3)	35	1.0 (0.3)
PEDSR (s^{-1}) longitudinal	34	0.9 (0.2)	35	0.9 (0.2)
LVGCS (%)	34	−19.0 (3.3)	35	−19.4 (2.8)
LVGLS (%)	34	−15.8 (2.8)	35	−16.4 (2.3)
LVEDVI (mL m^{-2})	34	69.9 (15.0)	35	70.8 (13.9)
LVEF (%)	34	64.5 (10.4)	35	65.6 (6.2)
LVM (g)	34	120.6 (28.7)	35	118.0 (27.8)
LVMI (g m^{-2})	34	55.3 (10.3)	35	54.5 (8.7)
LV peak filling rate (mL s^{-1})	34	555.9 (109.4)	34	547.7 (108.0)
LVM/V (g mL^{-1})	34	0.80 (0.13)	35	0.79 (0.14)
Max. LA vol. (mL)	32	68.3 (21.0)	35	73.7 (20.1)
Global stress MBF (mL min^{-1} g^{-1})	30	3.7 (1.2)	34	3.6 (0.9)
Global rest MBF (mL min g^{-1})	30	1.4 (0.5)	33	1.4 (0.5)
MPR	30	3.0 (1.2)	33	2.9 (1.0)
Mean AD ($mmHg^{-1} \times 10^{-3}$)	32	4.1 (1.3)	26	4.2 (1.9)

Abbreviations: AD, aortic distensibility; CMR, cardiac magnetic resonance imaging measures; eGFR, estimated glomerular filtration rate; LV, left ventricular; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVGCS, left ventricular global circumferential strain; LVGLS, left ventricular global longitudinal strain; LVM, left ventricular mass; LVMI, left ventricular mass index; LVM/V, left ventricular mass/volume ratio; max. LA vol., maximum left atrial volume; MBF, myocardial blood flow; MPR, myocardial perfusion reserve; PEDSR, peak early diastolic strain rate; VO_{2max}, maximal oxygen consumption.

−0.01) s^{-1} for liraglutide and sitagliptin, respectively (Table 2). However, there was no difference in change between groups (intervention effect = −0.01 [−0.07, 0.06] s^{-1}). Similarly, there were no between-group differences in other CMR imaging-derived measures of cardiovascular structure and function between baseline and 26 weeks. Multiple imputations for missing data did not change the interpretation (Table 2).

3.3 | Effects on cardiometabolic measures

After 26 weeks of treatment there was an intervention effect in favour of liraglutide for a reduction in HbA1c of −4.57 (−9.10, −0.37) mmol mol^{-1} (−0.42 [−0.83, −0.01%]). There was also greater body weight reduction in the liraglutide arm (mean body weight and BMI difference −3.88 [−5.74, −2.01] kg [P <0.001], −1.32 [−2.03, −0.62] kg m^{-2} [P <0.001], respectively) and a significant reduction in the liver function test for alanine transaminase with liraglutide (−11.27 [−20.17, −2.37] IU^{-1}). There were no between-group differences in brachial blood pressure (mmHg), heart rate (min^{-1}) or cardiorespiratory fitness ($VO_{2\ max}$) (mL kg^{-1} min^{-1}) (Table 3).

3.4 | Safety

Safety data are summarized in Table S1, with a full list of non-serious adverse events (split by medication) presented in Table S2. Six participants withdrew because of side effects attributable to the study medication. These were predominantly gastrointestinal in origin, notably nausea, vomiting and diarrhoea. There were four serious adverse events reported in the sitagliptin arm, all deemed unrelated to the medication, and none in the liraglutide arm of the study. There were no reported severe hypoglycaemic episodes and no participants required glucose-lowering rescue therapy during the trial. There were eight reported episodes of minor hypoglycaemia, comprised of six individuals (two in liraglutide vs. four in sitagliptin).

4 | DISCUSSION

The LYDIA study shows that short-term use of the GLP-1 receptor agonist liraglutide did not affect PEDSR compared with the DPP-4 inhibitor sitagliptin, with both groups showing a small decrease over time. There were no significant between-group differences in any CMR imaging-measured markers of structure and function.

TABLE 2 Summary of primary and secondary cardiac magnetic resonance (CMR) imaging outcomes

	Mean change from baseline (95% CI)					
	n	Liraglutide	n	Sitagliptin	Intervention effect (liraglutide minus sitagliptin)	*P*-value
Primary outcome						
PEDSR complete case ITT Circ. (s^{-1})	28	−0.06 (−0.10, −0.01)	33	−0.05 (−0.10, −0.01)	−0.01 (−0.07, 0.06)	0.874
PEDSR IMP Circ. (s^{-1})	31	−0.07 (−0.12, −0.02)	33	−0.06 (−0.10, −0.01)	−0.01 (−0.08, 0.05)	0.707
Secondary outcomes						
PEDSR ITT long. (s^{-1})	28	−0.08 (−0.13, −0.03)	33	−0.04 (−0.08, −0.01)	−0.04 (−0.11, 0.03)	0.254
LVGCS (%)	28	0.66 (0.15, 1.17)	33	0.27 (−0.20, 0.73)	0.39 (−0.30, 1.09)	0.274
LVGLS (%)	28	0.33 (−0.35, 1.01)	33	0.43 (−0.19, 1.05)	−0.09 (−1.05, 0.85)	0.841
LVEDVI (mL m^{-2})	28	−0.23 (−2.90, 2.44)	33	−1.50 (−3.93, 0.92)	1.27 (−2.40, 4.94)	0.497
LVEF (%)	28	−0.60 (−2.72, 1.53)	33	1.39 (−0.52, 3.30)	−1.98 (−4.90, 0.94)	0.183
LVM (g)	28	0.72 (−3.94, 5.37)	33	−0.43 (−4.59, 3.75)	1.14 (−5.23, 7.50)	0.726
LVMI (g m^{-2})	28	1.27 (−0.88, 3.42)	33	−0.26 (−2.22, 1.69)	1.54 (−1.41, 4.49)	0.308
LV peak filling rate (mL s^{-1})	28	10.9 (−18.0, 39.7)	32	−18.7 (−44.9, 7.5)	29.6(−10.2, 69.3)	0.145
LVM/V (g mL^{-1})	28	0.03 (−0.11, 0.07)	32	0.01 (−0.03, 0.05)	0.02 (−0.04, 0.07)	0.510
Max. LA vol. (mL)	28	−3.82 (−8.88, 1.23)	32	−0.81 (−5.49, 3.85)	−3.01 (−10.10, 4.09)	0.406
Global stress MBF (mL min^{-1} g^{-1})	25	−0.21 (−0.49, 0.06)	30	−0.15 (−0.40, 0.97)	−0.06 (−0.44, 0.32)	0.748
Global rest MBF (mL min^{-1} g^{-1})	25	−0.14 (−0.26, −0.02)	30	−0.21 (−0.32, −0.10)	0.07 (−0.09, 0.23)	0.412
MPR	25	−0.09 (−0.46, 0.28)	30	0.19 (−0.15, 0.53)	−0.28 (−0.79, 0.24)	0.291
Mean AD ($mmHg^{-1} \times 10^{-3}$)	24	−0.05 (−0.48, 0.38)	24	0.30 (−0.13, 0.73)	−0.35 (−0.98, 0.28)	0.275

Abbreviations: AD, aortic distensibility; CMR, cardiac magnetic resonance imaging measures; LV, left ventricular; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVGCS, left ventricular global circumferential strain; LVGLS, left ventricular global longitudinal strain; LVMI, left ventricular mass index; LVM/V, left ventricular mass/volume ratio; max. LA vol., maximum left atrial volume; MBF, myocardial blood flow; MPR, myocardial perfusion reserve; PEDSR complete case ITT Circ., peak early diastolic circumferential strain rate complete case intention-to-treat analysis (primary outcome, primary analysis); PEDSR IMP Circ., peak early diastolic circumferential strain rate multiple imputation analysis (primary outcome, sensitivity analysis); PEDSR Long., peak early diastolic longitudinal strain rate intention-to-treat analysis.

TABLE 3 Summary of secondary cardiometabolic outcomes

	Mean change from baseline (95% CI)					
	Liraglutide		Sitagliptin			
	n		n		Intervention effect (liraglutide minus sitagliptin)	*P*-value
HbA1c (%)	31	−0.89 (−1.18, −0.60)	33	−0.48 (−0.76, −0.18)	−0.42 (−0.83, −0.01)	**0.048**
HbA1c (mmol mol^{-1})	31	−9.90 (−13.12, −6.67)	33	−5.32 (−8.46, −2.19)	−4.57 (−9.10, −0.37)	
Weight (kg)	31	−4.51 (−5.84, −3.19)	33	−0.63 (−1.92, 0.66)	−3.88 (−5.74, −2.01)	**<0.001**
BMI (kg m^{-2})	31	−1.60 (−2.10, −1.10)	33	−0.28 (−0.77, 0.20)	−1.32 (−2.03, −0.62)	**<0.001**
Systolic BP (mmHg)	31	−8.90 (−12.02, −5.78)	33	−8.73 (−11.77, −5.69)	−0.17 (−4.56, 4.22)	0.939
Diastolic BP (mmHg)	31	−5.15 (−7.61, −2.70)	33	−3.88 (−6.27, −1.50)	−1.49 (−5.07, 2.09)	0.473
Heart rate (min^{-1})	31	13.49 (9.57, 17.41)	33	7.96 (4.15, 11.78)	5.53 (−0.06, 11.12)	0.052
Total cholesterol (mmol L^{-1})	31	0.11 (−0.11, 0.34)	33	−0.23 (−0.45, −0.01)	0.35 (0.02, 0.67)	**0.036**
LDL-C (mmol L^{-1})	28	0.21 (0.02, 0.40)	31	−0.09 (−0.27, 0.09)	0.29 (0.03, 0.57)	**0.028**
HDL-C (mmol L^{-1})	30	0.03 (−0.02, 0.08)	32	0.01 (−0.04, 0.07)	0.02 (−0.06, 0.10)	0.620
Triglycerides (mmol L^{-1})	31	−0.32 (−0.57, −0.06)	33	−0.35 (−0.60, −0.10)	0.04 (−0.32, 0.39)	0.833
Alanine transaminase (IU L^{-1})	31	−4.92 (−11.22, 1.37)	33	6.35 (−0.23, 12.46)	−11.27 (−20.17, −2.37)	**0.013**
eGFR (mL min^{-1})	31	−0.58 (−2.47, 1.31)	33	−3.02 (−4.85, −1.18)	2.43 (−0.29, 5.16)	0.080
VO_{2max} (mL kg^{-1} min^{-1})	22	0.46 (−0.40, 1.33)	24	−0.47 (−1.30, 0.35)	0.94 (−0.29, 2.17)	0.135

Abbreviations: BP, brachial blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; $VO_{2\ max}$, maximal oxygen consumption.
Note: Data adjusted for baseline value along with age, baseline HbA1c and baseline weight. Mean (SD). *P* in bold indicates statistical significance.

Importantly, LYDIA specifically targeted asymptomatic younger adults with obesity and type 2 diabetes because this group has a significant lifetime risk of cardiovascular complications and in many cases evidence of subclinical but probable reversible cardiac dysfunction.[27,28] Any observed benefit from early intervention in this group is therefore likely to be extremely relevant to clinical practice as these agents are already licenced for use in the glucose-lowering management of adults with type 2 diabetes.

In this rapidly evolving field, a number of large clinical trials have reported their findings since the LYDIA study was first designed. Some of these have advanced our understanding of the cardiovascular effects of these and other glucose-lowering therapies and help place our findings in context. Increased hospitalization for heart failure with the DPP-4 inhibitor saxagliptin in the Savor-Timi 53 trial and a non-statistically significant increase in the same outcome in the EXAMINE study of alogliptin provided the original rationale for a potentially sizeable active comparator differential with liraglutide in LYDIA.[4,11] Subsequent publication of the TECOS (sitagliptin), CARMELINA (linagliptin), ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN-6 (semaglutide), EXSEL (exenatide), HARMONY (albigltuide) and REWIND (dulaglutide) trials indicates that incretin medications probably have no overall effect on heart failure outcomes in older (50-60-year-old) people with type 2 diabetes at high risk of cardiovascular events.[12-19] The secondary findings of these large cardiovascular outcome trials are in part supported by recently reported echocardiographic data by Margulies et al and Jorsal et al.[8,9] Importantly, these randomized, placebo-controlled studies have shown that liraglutide seemingly has no beneficial effect on LVEF, rehospitalization for heart failure or death in patients with previously documented cardiac disease. Similar results were observed in a smaller 12-week study of the GLP-1 receptor agonist albiglutide in patients with New York Heart Association class III heart failure[29] but contradict the only reported CMR imaging study.[20] In that study liraglutide was associated with improved diastolic function, but this was measured using mitral valve-filling characteristics, which are more prone to alteration with changes in filling pressure, unlike PEDSR.[20] A very small reduction in left ventricular (LV) mass was also shown and this may be primarily because of the use of placebo as a comparator, rather than our active control with sitagliptin. We await with interest the results of other CMR imaging studies, including the saxagliptin on cardiac structure and function study (SCARF, NCT 02481479), which aims to examine the effects of this drug in patients without LV dysfunction and will provide additional information about potential DPP-4 class effects.

Our results are in line with meta-analyses of trial and observational data showing either little effect on or even a signal for deterioration in heart failure outcomes in patients with type 2 diabetes treated with incretin-based therapies.[30-35] In this respect our findings are timely in adding scarce CMR imaging data to the available evidence assessing the short-term effects of GLP-1 receptor agonists and DPP-4 inhibitors on indices of cardiac function. This work also adds to our understanding of the significant improvements seen in mortality and cardiovascular disease outcomes in recent outcome trials of certain GLP-1 receptor agonists.

It has been postulated that liraglutide may mediate anti-inflammatory and or anti-atherosclerotic effects, which probably take some time to become clinically apparent. In this situation changes occurring over months and possibly reflecting comparatively rapid structural or haemodynamic changes would be improbable with this pharmacological action. Interestingly, in the LYDIA study there were no between-group differences in high sensitivity CRP and other pro-inflammatory biomarkers after 26 weeks (data not shown), although it should be recognized that the study was not powered to detect changes in those measures. We also assessed changes in myocardial perfusion, which would have improved if there was a significant effect of these treatments on atherosclerosis, which is of particular interest because GLP-1 receptor agonists have been associated with a reduction in both myocardial infarction and stroke.[18,19] No significant changes were observed in perfusion but a longer duration of follow-up may be required, in particular because the reduction of atherosclerotic events with GLP-1 receptor agonist therapy appears slow compared with the rapid reductions in atherosclerotic episodes and heart failure hospitalizations with SGLT-2 inhibitors.[35-40]

Future placebo-controlled studies of longer duration, incorporating additional measures of inflammation and possibly also including members of the SGLT-2 inhibitor family may provide additional useful insights. Following on from the EMPA-REG (empagliflozin), CANVAS, CANVAS-R, CREDENCE (canagliflozin) and DECLARE-TIMI 58 (dapagliflozin) trials, there is now considerable interest in the therapeutic potential of SGLT-2 inhibition in heart failure.[35-40] The EMPA-Heart study has shown a small (2.6 g m^{-2}) but significant reduction in LV mass with empagliflozin.[40] The current study failed to show a benefit in LV mass reduction in either arm, despite marked reductions in blood pressure and a 4.5 kg reduction in weight with liraglutide.

Absence of a control arm in LYDIA prevents firm conclusions being drawn about the individual effects of these agents on PEDSR. However, in the absence of a beneficial effect over sitagliptin, it is important to consider the secondary glucose- and weight-lowering efficacy of GLP-1 receptor agonist-based treatments in this unique population. Diabetes management as judged by HbA1c and body weight were improved compared with DPP-4 inhibition and both treatments were well tolerated with no severe hypoglycaemic episodes when added to preprescribed oral therapies. These results emphasize the importance of adopting an individualized approach to diabetes care when considering type 2 diabetes treatments and suggest that early use of weight-sparing or weight-lowering agents in younger obese patients is an effective option.

This trial does have some important limitations. First, the choice of an open-label comparator rather than blinded placebo or three-arm design makes it difficult to estimate individual drug effects compared with a 'control' comprising no additional treatment. However, the primary endpoint was robustly blinded not only to therapy but also to whether the scan was baseline or follow-up. No positive effect of liraglutide on PEDSR or strain was observed compared with sitagliptin and it can be confidently stated that short-term treatment does not improve or dramatically worsen diastolic cardiac function in one medication compared with the other. Although a small worsening in PEDSR was observed in both intervention groups over time, this effect was unlikely to be clinically meaningful and the study design does not allow conclusions to be drawn as to whether this was because of the study drugs, natural worsening of PEDSR over time, or a measurement artefact. Second, the study was not designed to achieve glycaemic equipoise and hence it is not possible to directly distinguish between glucose-lowering or pleiotropic actions on CMR imaging outcomes. Third, higher than anticipated attrition and dropout inevitably affected the certainty (power) of detecting a true difference in our primary outcome (PEDSR). However, multiple imputations for missing data did not materially change the results. Fourth, we saw increases in heart rate and larger reductions in blood pressure than expected, which may have been overestimated by not including ambulatory monitoring. Increased chronotropic activity after GLP-1 receptor agonist use in LYDIA may have had an effect on CMR imaging measurement acquisition. Also, we did not specifically screen for diabetes-related microangiopathic complications such as cardiac autonomic neuropathy as the duration of diabetes was comparatively short. We did exclude participants with evidence of severe coronary artery disease or alternative cardiovascular structural abnormalities after baseline CMR imaging. Finally, a treatment exposure time of 26 weeks may not have been sufficient to detect CMR imaging changes occurring over a longer duration, while the study population may not be representative of most people with type 2 diabetes or those with more advanced cardiac dysfunction.

Comprehensive assessment and detailed phenotyping enabled us to precisely match treatment groups, examine a range of secondary outcomes and explore potential novel interactions for future research. These data come at an important time in the evolution of incretin-based treatments and add new information about the treatment of type 2 diabetes. Further CMR imaging studies are needed to explore the longer term effects of these therapies on cardiac function in people with type 2 diabetes and should be compared with or in combination with an SGLT-2 inhibitor.

In conclusion, among young patients with obesity and type 2 diabetes, the use of liraglutide resulted in greater weight loss and glucose control than sitagliptin but did not lead to improvements in subclinical cardiac dysfunction.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare with respect to this study.

AUTHOR CONTRIBUTIONS

MJD, TY, DRW and GPM conceived the idea and designed the study. ZZH, EMB, JS, FZ and DRW managed the trial, recruited the patients and wrote the manuscript. DJS and GSG performed the MRIs and analysed scans. JB performed the quantitative myocardial perfusion analyses. LJG performed the power calculations and the statistical analyses. MW and HLW performed biochemical analyses. All authors contributed equally to and are responsible for the final paper. MJD is the principal investigator and custodian of the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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