

# BMJ Open A protocol for a randomised, double-blind, placebo-controlled study of the effect of Liraglutide on left Ventricular function in chronic heart failure patients with and without type 2 diabetes (The LIVE Study)

Anders Jorsal,<sup>1,2</sup> Henrik Wiggers,<sup>1,2</sup> Pernille Holmager,<sup>3</sup> Brian Nilsson,<sup>4</sup> Roni Nielsen,<sup>1,2</sup> Trine Welløv Boesgaard,<sup>5</sup> Anja Kumme,<sup>6</sup> Jacob Eifer Møller,<sup>6</sup> Lars Videbæk,<sup>6</sup> Caroline Kistorp,<sup>3</sup> Ida Gustafsson,<sup>7</sup> Lise Tarnow,<sup>5,8,9</sup> Allan Flyvbjerg<sup>8,10</sup>

**To cite:** Jorsal A, Wiggers H, Holmager P, *et al.* A protocol for a randomised, double-blind, placebo-controlled study of the effect of Liraglutide on left Ventricular function in chronic heart failure patients with and without type 2 diabetes (The LIVE Study). *BMJ Open* 2014;**4**:e004885. doi:10.1136/bmjopen-2014-004885

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2014-004885>).

Received 20 January 2014  
Revised 24 April 2014  
Accepted 30 April 2014



CrossMark

For numbered affiliations see end of article.

#### Correspondence to

Dr Anders Jorsal;  
[anders.jorsal@ki.au.dk](mailto:anders.jorsal@ki.au.dk)

#### ABSTRACT

**Introduction:** Heart failure is one of the most common cardiovascular complications of diabetes and the most disabling and deadly complication too. Many antidiabetic agents have been associated with increased morbidity and mortality in a subset of patients with chronic heart failure (CHF); thus, new treatment modalities are warranted. Interestingly, a beneficial effect of the incretin hormone, GLP-1, on cardiac function has been suggested in patients with diabetes and patients without diabetes. Liraglutide (Victoza) is a GLP-1 analogue developed for the treatment of type 2 diabetes (T2D); however, its impact on cardiac function has not previously been investigated in patients with CHF. This prompted us to investigate whether liraglutide treatment for 24 weeks improves left ventricular ejection fraction (LVEF) in patients with CHF with and without T2D compared with placebo treatment.

**Methods and analysis:** An investigator-initiated, multicentre, randomised, double-blind, parallel, placebo-controlled intervention trial. In total, 240 patients with CHF (with and without T2D) with LVEF $\leq$ 45% will be randomised to either subcutaneous injection of liraglutide 1.8 mg or matching placebo once daily for 24 weeks. The effect of liraglutide on left ventricular function will be evaluated by advanced echocardiography, including three-dimensional contrast echocardiography.

**Ethics and dissemination:** The study will be performed and monitored according to the Good Clinical Practice-International Conference on Harmonisation (GCP-ICH) regulations and conducted according to the principles of the Helsinki Declaration. The Danish Medicines Agency, the local Research Ethics Committee and the Danish Data Protection Agency have approved the study.

**Trial registration number:** ClinicalTrials.gov Identifier: NCT01472640.

#### Strengths and limitations of this study

- Large multicentre, double-blinded, randomised, placebo-controlled study.
- Using advanced three-dimensional contrast echocardiography.
- The LIVE-study will provide no data on long-term treatment.

#### INTRODUCTION

Therapy with ACE inhibitors,  $\beta$ -blockers and spironolactone reduces mortality in patients with chronic heart failure (CHF) and modestly improves left ventricular ejection fraction (LVEF).<sup>1–4</sup> However, long-term survival remains markedly decreased in patients with CHF, especially in patients with diabetes.<sup>5–6</sup> In addition, achievement of glycaemic control in patients with type 2 diabetes (T2D) and CHF is complicated. Many antidiabetic agents have been associated with increased morbidity and mortality in a subset of patients with CHF and reduced LVEF.<sup>7–8</sup> Consequently, there is a need for new, safe treatment modalities of hyperglycaemia in CHF and for treatment options that can improve CHF symptoms and survival in patients with and without T2D.

Glucagon-like peptide 1 (GLP-1) is a natural hormone secreted from the small intestine in response to food intake as part of the incretin system.<sup>9</sup> It stimulates insulin production and inhibits glucagon excretion from the pancreas and thereby reduces blood glucose.<sup>9</sup> Numerous preclinical studies

in rodents have also investigated the cardiovascular mechanisms of GLP-1 receptor stimulation.<sup>10–11</sup> Observed responses include increased cardiac glucose uptake, reduced free fatty acid metabolism and triglyceride accumulation, enhanced nitric oxide (NO) production, increased vasorelaxation/afterload reduction and augmented cardiac contractility.<sup>10–11</sup> However, the exact cellular localisation of the GLP-1 receptor is poorly understood; yet, recent data suggest that receptors in the heart are localised in the sino-atrial node.<sup>12–13</sup> The localisation of GLP-1 receptor expression to atrial, but not to ventricular cardiomyocytes raises questions regarding the direct cardioprotective actions of GLP-1 receptor agonists. Nevertheless, experimental studies suggest that GLP-1 may improve a failing heart's function. For example, in a hypertensive and heart failure-prone rat, GLP-1 improved survival and preserved left ventricular function.<sup>14</sup> Furthermore, the GLP-1 analogue, liraglutide, decreased left ventricular structural remodelling and improved cardiac output in mice after occlusion of the left anterior descending coronary artery.<sup>15</sup> Similar results have been shown for the GLP-1 analogue, exenatide.<sup>16</sup> Taken together, available data support a beneficial role of native GLP-1 and GLP-analogues in preclinical models of heart failure.

### Clinical perspective

The effects of GLP-1 receptor agonists on vasodilation, blood pressure and triglyceride concentration have been reproduced in humans with native GLP-1 and different GLP-1 receptor agonists.<sup>10</sup> A recent clinical study has shown reduced infarct size in patients with ST-segment elevation myocardial infarction (STEMI) following treatment with a GLP-1 analogue.<sup>17</sup> However, data on GLP-1 treatment and its effects on systolic left ventricle function in patients with CHF are sparse. Only four small studies have investigated the impact of GLP-1 treatment in patients with CHF.<sup>18–21</sup> Importantly, the used concentrations of GLP-1 were different, and the studies measured improvements at different intervals of time. Moreover, only one short-term study was double-blinded and randomised.<sup>21</sup> With this in mind, a recent meta-analysis showed an improvement in LVEF of 4.4% compared with placebo.<sup>22</sup> There was no significant change in the N-terminal of brain natriuretic peptide (NT-proBNP) or heart rate.<sup>22</sup> In contrast, the dipeptidyl peptidase-4 (DPP-4) inhibitor vildagliptin did not improve LVEF in patients with T2D and CHF.<sup>23</sup> EXAMINE and SAVOR-TIMI 53 which tested the DPP-4 inhibitors, alogliptin and saxagliptin, did not increase or decrease the rate of ischaemic events although the rate of hospitalisation for heart failure was slightly increased in SAVOR-TIMI 53.<sup>24–25</sup> However, only a minority of patients had a heart failure diagnosis and echocardiography was not mandatory to enter the study. Moreover, DPP-4 inhibitors and GLP analogues are different compounds and GLP-1 analogues are more potent in reducing the blood glucose and have interesting

cardiovascular effects on blood pressure and triglyceride concentration.<sup>26–27</sup> Taken together, the GLP-1 analogue liraglutide may improve LVEF in patients with CHF with and without T2D. Nevertheless, the impact of liraglutide on the cardiac function of patients with CHF has not previously been investigated.

### Hypothesis

Liraglutide treatment for 24 weeks improves LVEF in patients with CHF with and without T2D compared with placebo treatment.

### Objectives

The objective of the present protocol is to evaluate the effect of liraglutide on left ventricular systolic function compared with placebo in patients with CHF with and without T2D. The primary outcome parameter is the change in LVEF as determined by three-dimensional (3D) contrast echocardiography from randomisation to final follow-up. Secondary outcome measures include advanced echocardiographic assessment of left ventricular systolic and diastolic function, functional capacity measured by a 6-minute walk test (6MWT), plasma NT-proBNP levels, blood pressure and quality of life estimated by the Minnesota Living with Heart Failure questionnaire (MLHF). The study will also give rise to important data on heart rate and weight loss, eg Holter monitors with subsequent analyses of heart rate variability and DXA scan with measurement of total body composition and fat content will be performed in substudies.

## METHODS AND ANALYSIS

### Research design

The LIVE study is an investigator-initiated, Danish multi-centre, randomised, double-blinded, parallel, placebo-controlled intervention trial, protocol V.5, June 2011. In total, 240 patients with CHF, New York Heart Association (NYHA) class I–III and LVEF ≤ 45% will be randomised to either subcutaneous injection of liraglutide or matching placebo for 24 weeks. Two strata of patients will be randomised: (1) patients with T2D and (2) patients without T2D.

Simple randomisation will occur consecutively in both groups according to a computer-generated randomisation list in a 1:1 randomisation ratio. Treatment allocation is web based and can be unblinded in case of medical emergencies if deemed necessary by the investigator. Unblinding can be made individually so that treatment blinding of other patients in the group remains unaffected.

### Study population

All patients who meet the main inclusion and exclusion criteria will be invited for screening. Eligible and amenable patients who still meet the inclusion criteria after screening will be enrolled. The main inclusion and exclusion criteria are listed in [table 1](#). The initial

**Table 1** Overview of inclusion and exclusion criteria in the LIVE-study

Inclusion criteria	
General	Patients with diabetes
<ul style="list-style-type: none"> <li>▶ Age 30–85 (both inclusive)</li> <li>▶ CHF and LVEF<math>\leq</math>45% (NYHA-class I, II or III)</li> <li>▶ Stable and optimal pharmacological treatment of heart failure according to ESC guidelines and implantation of bi-ventricular pacemaker (if indicated) at minimum three months before randomisation</li> <li>▶ Able to understand the written patient information and to give informed consent</li> </ul>	<ul style="list-style-type: none"> <li>▶ T2D (WHO criteria), diagnosed at least 3 months before screening</li> <li>▶ Stable dose of antidiabetic treatment for 30 days before randomisation</li> <li>▶ Patients must be without antidiabetic treatment or treated with oral antidiabetic drugs and/or insulin, except fast-acting insulin</li> </ul>
Exclusion criteria	
General	Cardiovascular
<ul style="list-style-type: none"> <li>▶ Known or suspected hypersensitivity to trial product or related products</li> <li>▶ Alcohol/drug abuse</li> <li>▶ Pregnant or nursing women</li> <li>▶ Fertile women not using chemical (tablet/pill, depot injection of progesterone, subdermal gestagen implantation, hormonal vaginal ring or transdermal hormonal patch) or mechanical (spirals) contraceptives</li> <li>▶ Cancer unless in complete remission for <math>\geq</math>5 years</li> <li>▶ Liver disease with elevated plasma alanine aminotransferase of more than three times the upper limit of normal</li> <li>▶ Inflammatory bowel disease</li> <li>▶ Acute or chronic pancreatitis</li> <li>▶ Compromised kidney function (eGFR <math>&lt;</math>30 mL/min), dialysis or kidney transplantation</li> <li>▶ History of thyroidea adenoma or carcinoma</li> <li>▶ Severely elevated blood pressure (systolic <math>&gt;</math>180 mm Hg and/or diastolic <math>&gt;</math>105 mm Hg)</li> <li>▶ Other concomitant disease or treatment that according to the investigator's assessment makes the patient unsuitable for study participation</li> <li>▶ Participation in any other clinical intervention trial</li> </ul>	<ul style="list-style-type: none"> <li>▶ CHF (NYHA class IV)</li> <li>▶ Hospitalisation due to uncompensated heart disease within 30 days prior to randomisation</li> <li>▶ Myocardial infarction within the past 3 months before screening</li> <li>▶ Coronary revascularisation within the past 3 months before screening</li> <li>▶ Atrial fibrillation with ventricular frequency <math>&gt;</math>100/min in rest</li> <li>▶ ECG suggestive of malignant ventricular arrhythmia</li> <li>▶ Prolonged QT-interval (<math>&gt;</math>500 ms), unless caused by bundle branch block</li> <li>▶ Uncorrected valvular heart disease</li> <li>▶ Current myocardial or pericardial infection</li> <li>▶ Obstructive hypertrophic cardiomyopathy</li> <li>▶ Planned coronary revascularisation</li> <li>▶ Poor image quality on echocardiography</li> </ul>
	Diabetes
	<ul style="list-style-type: none"> <li>▶ Type 1 diabetes</li> <li>▶ HbA1c <math>&gt;</math>10% measured at screening</li> <li>▶ Use of GLP-1 receptor agonists (exenatide, liraglutide or other) or glitazones, pramlintide or any DPP-4 inhibitor within 30 days prior to randomisation</li> <li>▶ Diabetic gastroparesis</li> </ul>

CHF, chronic heart failure; DPP-4, dipeptidyl peptidase-4 inhibitor; eGFR, estimated-glomerular filtration rate; ESC, European Society of Cardiology; GLP-1, glucagon-like peptide 1; HbA1c, glycated haemoglobin; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; T2D, type 2 diabetes.

screening is followed by a 24-week treatment period. An outline of the trial visits and examinations is shown in [table 2](#).

### Trial visits and examinations

#### Visit 0—screening/start of run in period

When the informed consent has been obtained, general information about demography, medical history and concomitant medication will be gathered. Blood sampling will be performed, in addition to a full physical examination including stethoscopy, assessment of oedema, ECG and comprehensive echocardiography. All female participants of childbearing potential will be tested for pregnancy and assurance of adequate use of anticonceptives throughout the study period will be obtained. Once all data related to the screening visit have been obtained, the investigator will review the data to ensure that the participant is eligible to continue in

the study. If the participant is not eligible, the participant will be a screening failure. This will be registered, including the reason for screen failure. Recruitment will be followed in real time in the electronic case record form (eCRF) and new sites will be initiated as necessary.

#### Visit 1–4—randomisation, clinical controls and last visit

During the intervention, all participants will attend four planned visits: randomisation (week 0), two clinical controls (weeks 3 and 12) and end-of-study/intervention (week 24) ([table 2](#)). Echocardiography will be performed in the morning at randomisation and at end-of-study, and all patients are fasting, which includes that no antidiabetic therapy is allowed, until all blood samples have been taken; however, all patients are advised to take their usual heart failure medication before both visits. Patients are also advised to take the study medication before the end-of-study visit. The

**Table 2** Flowchart of study visits

	Visit 0 Screening	Visit 1 Randomi- sation	Phone contacts	Visit 2 Clinical control	Visit 3 End of first period	Visit 4 End of second period
<b>Time (weeks)</b>	-1- -4	0	—	3±2	12±2	24±2
<b>General</b>						
Assessment of inclusion and exclusion criteria	X	X				
Demography	X					
Medical history	X					
<b>Endpoints</b>						
Echocardiography	X	X				X
Six-minute walk test		X				X
Blood pressure	X	X		X	X	X
Minnesota Living with Heart Failure questionnaire		X				X
<b>Clinical assessment</b>						
Physical assessment	X	X		X	X	X
ECG	X	X				X
<b>Biosamples</b>						
Biobank/biomarkers		X				X
U-albumin/creatinine		X				X
<b>Safety</b>						
Adverse events		X	X	X	X	X
Blood tests	X	X			X	X
<b>Study medication</b>						
Study drug dose titration			X			
Concomitant medication	X	X	X	X	X	X

investigator/designee will contact the participant by phone between the randomisation and the clinical control in week 3 to monitor the study drug dose escalation and to investigate the participant's tolerance to the drug/placebo. At all visits full physical examination will be performed, adverse events will be assessed and safety blood tests will be carried out. In addition, echocardiography and 6MWT will be performed, the MLHF questionnaire filled by participants and biosamples collected for a biobank during randomisation and at the patient's last visit. If a patient withdraws prematurely, the last visit will be performed as soon as possible.

#### Study medication/intervention

**Name:** Victoza—Liraglutide or matching placebo, which are visually identical.

**Pharmaceutical form:** Solution for subcutaneous injection in pre-filled pen.

**Pharmaceutical dosage:** Liraglutide or placebo will be introduced at a dose of 0.6 mg/day, which will gradually be increased to 1.2 mg/day after 1 week and thereafter to 1.8 mg/day. A dose increase can be postponed based on the participant's tolerance to the trial product. Furthermore, the trial drug dose can be reduced at any time during the trial if required. Injection can be carried out at any time during the day; it is, however, recommended that the time of injection is consistent from day to day.

**Accountability:** Log of supplied and returned study medication is kept on patient and site levels.

**Side effects:** Common side effects (1–10%): Nausea, vomiting, diarrhoea, obstipation and headache.

**Shipping and packing:** All trial products will be delivered, packed and labelled by Novo Nordisk A/S.

#### Concomitant medication

Before enrolment it is confirmed that patients are on optimal medical therapy for heart failure and if appropriate that cardiac resynchronisation therapy has been established. Investigators will be encouraged to manage participants' diabetes and cardiovascular risk according to the current best available evidence. Participants with diabetes will all be subject to the same standard operating procedure and may continue receiving the oral hypoglycaemic agents and/or insulin that they were prescribed before enrolment. Insulin and sulphonylurea (SU) will initially be reduced by 30% to avoid hypoglycaemia, and a fixed algorithm using measurements of self-monitored blood glucose will subsequently guide management. If hypoglycaemia requires reduction of medication, the investigators will reduce or otherwise modify the dosing of non-investigational drugs before reducing the dose of the trial product. In case of hypotension, diuretics might be reduced, but anticongestive medication will not be changed. The study medication can, if required, be

titrated down. Anticongestive medication includes ACE inhibitors, angiotensin receptor blockers,  $\beta$ -blockers and aldosterone blockers.

### Echocardiography

3D and two-dimensional (2D) echocardiography will be performed according to international recommendations on a General Electric VIVID 9, BT12 ultrasound system. Screening visit will confirm an acceptable apical acoustic window. The following echocardiographic measurements will be performed: LVEF, left ventricular end diastolic and end systolic volumes and diameters, left ventricular mass and left atrial volume. From pulsed wave Doppler, mitral inflow curves E-wave, A-wave and E-decT will be recorded. Tissue Doppler imaging (TDI) will be obtained in the apical 4-chamber, 2-chamber and apical long-axis for evaluation of peak systolic ( $s'$ ), early diastolic ( $e'$ ) and late diastolic ( $a'$ ) velocities. Averaging myocardial velocities in the septal, lateral, inferior, posterior and mitral annular positions will be used to assess the longitudinal tissue velocity of the LV. Myocardial global strain will be assessed using 2D speckle tracking. Diastolic function will be assessed according to the European Association of Echocardiography (EAE) and the American Association of Echocardiography (ASE) recommendations.<sup>28</sup> The degree of diastolic dysfunction will be graded accordingly and the number of patients with improvement and worsening  $\geq 1$  grade will be reported. It is relevant to address the potential confounding effect of heart rate on diastolic function and systolic function; thus, post hoc regression and multiple linear regression analysis will be performed to clarify this issue.

All 2D and Doppler measurements will be measured and averaged over three consecutive cardiac cycles in end-expiration. In case of atrial fibrillation, five consecutive heart cycles will be analysed. Unless there is a clear LV endocardial border detection at end-systole and end-diastole, LV opacification will be enhanced using a commercially available ultrasound contrast agent (SonoVue).

The primary endpoint—LVEF—will be measured by 3D-echocardiography with contrast.<sup>29</sup> In case of low 3D-echocardiographic image quality, 2D echocardiography with or without contrast can be chosen; however, the same modality will be used to analyse the baseline and the follow-up recordings. Importantly, the recordings will be exchanged between centres, thus no investigators will analyse the recordings from patients they have investigated and all personnel will be blinded to treatment allocation. Furthermore, the investigators analysing echocardiographies are all experienced, and a standard operating procedure for the analysis of echocardiography has been followed to minimise the intraobserver and interobserver variability. The variability is acceptable and expected to be published in a subsequent paper.

### Biochemistry

Routine laboratory analysis will be made locally at the study sites. Frozen serum samples will be analysed at the two core-laboratories at the Department of Endocrinology and Internal Medicine, Aarhus University Hospital, and the Department of Endocrinology and Internal Medicine, Herlev University Hospital, Copenhagen.

### Statistics

#### Sample size

The primary outcome parameter is the change in LVEF from visit 1 to week 24. A total of 240 patients will be randomised to allow for approximately 20% of the randomised patients with major protocol deviations or withdrawal. With 90% power and with a two-sided significance level of 0.05, the sample size analysis estimated the study to detect a difference of 2.5% in LVEF in absolute values. The power analysis was based on a SD of 6% in  $\delta$  EF (absolute units).<sup>30</sup> An absolute difference of 2.5% change from baseline between the two treatment groups was based on clinical relevance as determined from the studies of the impact of ACE inhibitors and  $\beta$ -blockers on LVEF.<sup>2, 3</sup> The primary analysis will be based on the intention-to-treat principle. A per protocol analysis will also be performed.

#### Data management and analysis

Data are collected in real time in a custom-made web-based eCRF hosted by an external data management unit at the Aarhus University. In compliance with GCP, a study manual on the collection of endpoints and procedures has been developed and quality assurance of relevant instruments has been collected in the sponsors' trial master file.

Data on other adverse events assessed by the investigator as clinically significant, including abnormal laboratory values, will be collected and recorded on standardised forms at each contact. These data will be reported to the relevant authorities in accordance with current legislation and ICH-GCP guidelines. An unblinded data monitoring committee, consisting of independent cardiologists and endocrinologists, will be established to evaluate events during study conduct.

Data will primarily be analysed according to the intention-to-treat principle. Sites are encouraged to obtain a final measure of the primary endpoint as soon as possible in patients terminating study medication prematurely. Last observation-carried forward methods will be applied to handle missing data on the primary endpoint. Data will be analysed as the difference from baseline to follow-up. Normally distributed variables will be presented as mean  $\pm$ SD, whereas non-normally distributed variables will be presented as median (range). Comparisons between groups will be performed by an unpaired Student's *t*-test or analysis of variance (ANOVA) when data are normally distributed. Mann-Whitney U test or Kruskal-Wallis one-way analysis will be used for non-normally distributed data. Subgroup analyses will be made with respect to

presence of diabetes, presence of insulin resistance, cause of heart failure (ischaemic/non-ischaemic), body mass index, NYHA-class, LVEF above/below mean and atrial fibrillation. Linear regression will be used to study the correlation between outcome parameters and baseline patient characteristics. Categorical variables will be presented as number and percentage;  $\chi^2$ -test will be used to compare groups of categorical variables. p Values <0.05 will be considered statistically significant. All calculations will be performed using a commercially available program (SPSS for Windows and Mac, V.21.0).

## Outcome measures

### Primary objective

To investigate the effect of liraglutide uptitrated to a maximum of 1.8 mg once daily compared with placebo for 24 weeks on the difference in LVEF from baseline to follow-up in patients with CHF with and without T2D.

### Secondary objectives

To investigate the effect of liraglutide compared with placebo in terms of:

- ▶ Systolic function measured by TDI:
  - I. Summed systolic peak velocities (s') in the atrioventricular-plane
  - II. Global longitudinal strain
- ▶ End-systolic volume (ESV) and end-diastolic volume (EDV)
- ▶ Grade of diastolic function
- ▶ Functional capacity measured by a 6MWT
- ▶ Plasma NT-proBNP levels
- ▶ Blood pressure
- ▶ Quality of life evaluated by the MLHF questionnaire
- ▶ Hospitalisation for CHF<sup>i</sup>
- ▶ Mortality (will be confirmed by the Central Personal Register)

## ETHICS AND DISSEMINATION

The study will be performed in accordance with the Helsinki Declaration, EU directive on good clinical practice (GCP) and ICH-GCP guidelines after approval by the Regional Scientific Ethical Committee, the Danish Medicines Agency and the Data Monitoring Board. The study is registered on <http://www.clinicaltrials.gov> and monitored by the GCP units in Aarhus, Copenhagen and Odense. An audit was performed by the University GCP Unit in 2013.

The investigator will ensure that amenable patients are adequately informed about the study background and design, in spoken words and in writing. Before signing

<sup>i</sup>CHF will be adjudicated in the case of an unplanned presentation for worsening heart failure requiring an overnight stay in which the patient receives treatment with parenteral therapy including diuretics, inotropic or vasodilator agents. In the absence of documentation of these therapies, description of significant diuresis will be considered as criteria for heart failure therapy.

**Table 3** Overview of randomisation and patient characteristics at baseline (20th April 2014)

Baseline characteristics	
Inclusion and randomisation	
Screened	317
Randomised	177
Characteristics (%)	
Ischaemic heart disease	65
Diabetes	35
NYHA classes (%)	
1	38
2	46
3	16
0	0
Smoking (%)	
Currently	20
Previous	52
Never	28
Treatment (%)	
ACE inhibitor	64
ARB	30
Aspirin	63
$\beta$ -Blocker	90
Statin	81
Safety	
Adverse events	224
Serious adverse events	23

ARB, angiotensin 2 receptor blocker.

the consent form, the patient will be given sufficient time to reconsider. Should the patient need further time, a follow-up meeting will be scheduled. Patients are informed that they can withdraw their informed consent to participate in the study at any time and that this will not have any consequences on their future treatment. No study-related examinations will be conducted until the informed consent form has been signed.

Data on adverse events and serious adverse events are recorded in the eCRF in compliance with GCP.

## Dissemination

Positive/negative study results will be published in an international scientific journal and made publically available at <http://www.clinicaltrials.gov>. AJ will draft the first manuscript and be the first author thereof. Novo Nordisk A/S was allowed to comment on the protocol, but will neither be involved in recruitment or patient investigations nor in analysis, interpretation of data and writing of the report. However, Novo Nordisk A/S will be given 4 weeks to comment on the manuscript before submission is made. Data from substudies will not be submitted for publication until the primary publication, the LIVE study, has been accepted for publication.

Table 3 shows an overview of randomisation and baseline characterisation as per 20 April 2014. The numbers of adverse and serious adverse events are somewhat below the expected and we expect to stop enrolment in October 2014 and expect to publish data in 2015.

### Author affiliations

<sup>1</sup>Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark

<sup>2</sup>Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark

<sup>3</sup>Department of Endocrinology and Internal Medicine, Herlev University Hospital, Copenhagen, Denmark

<sup>4</sup>Department of Cardiology, Herlev University Hospital, Copenhagen, Denmark

<sup>5</sup>Steno Diabetes Center, Gentofte, Denmark

<sup>6</sup>Department of Cardiology, Odense University Hospital, Odense, Denmark

<sup>7</sup>Department of Cardiology, Hvidovre University Hospital, Copenhagen, Denmark

<sup>8</sup>Faculty of Health, Aarhus University, Aarhus, Denmark

<sup>9</sup>Nordsjaellands University Hospital, Hilleroed, Denmark

<sup>10</sup>Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark

**Contributors** AF, AJ, CK, HW, IG, TWB and LT conceived the study and participated in its design and coordination. AJ, PH, RN, HW, CK, IG, BN and TWB are responsible for inclusion and examination of patients in Aarhus and Copenhagen. LV, JEM and AK from Odense University Hospital began recruitment in November 2013. The sponsor has assigned the task of study coordination to professor LT, who oversees the progress of the study together with AJ and TWB, who also provide written and verbal guidance on recruitment and retention strategies. All relevant permissions were obtained in cooperation with the Clinical Research Unit, Steno Diabetes Center.

**Funding** The investigators received an unrestricted grant from Novo Nordisk A/S to enable them to conduct the trial. The study is investigator-initiated and design, data collection and analyses will be undertaken by the investigators.

**Competing interests** AJ, LT and TWB hold shares in Novo Nordisk A/S. TWB is employed at the Steno Diabetes Centre, a public hospital owned by Novo Nordisk A/S.

**Ethics approval** The Danish Medicines Agency, the local Research Ethics Committee and the Danish Data Protection Agency have approved the study.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** No unpublished data are available other than for the steering committee.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/3.0/>

### REFERENCES

- Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med* 1987;316:1429–35.
- Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med* 1991;325:293–302.
- Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001–7.
- Pitt B, Zannad F, Remme WJ, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341:709–17.
- Haffner SM, Lehto S, Ronnema T, *et al.* Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339:229–34.
- Gustafsson I, Brendorp B, Seibaek M, *et al.* Influence of diabetes and diabetes-gender interaction on the risk of death in patients hospitalized with congestive heart failure. *J Am Coll Cardiol* 2004;43:771–7.
- Eurich DT, McAlister FA, Blackburn DF, *et al.* Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review. *BMJ* 2007;335:497.
- Gitt AK, Halle M, Hanefeld M, *et al.* Should antidiabetic treatment of type 2 diabetes in patients with heart failure differ from that in patients without? *Eur J Heart Fail* 2012;14:1389–400.
- Drucker DJ. The biology of incretin hormones. *Cell Metab* 2006;3:153–65.
- Ussher JR, Drucker DJ. Cardiovascular biology of the incretin system. *Endocr Rev* 2012;33:187–215.
- Seino Y, Yabe D. Glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1: incretin actions beyond the pancreas. *J Diabetes Invest* 2013;4:108–30.
- Kim M, Platt MJ, Shibasaki T, *et al.* GLP-1 receptor activation and Epac2 link atrial natriuretic peptide secretion to control of blood pressure. *Nat Med* 2013;19:567–75.
- Pyke C, Heller RS, Kirk RK, *et al.* GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology* 2014;155:1280–90.
- Poornima I, Brown SB, Bhashyam S, *et al.* Chronic glucagon-like peptide-1 infusion sustains left ventricular systolic function and prolongs survival in the spontaneously hypertensive, heart failure-prone rat. *Circ Heart Fail* 2008;1:153–60.
- Noyan-Ashraf MH, Momen MA, Ban K, *et al.* GLP-1R agonist liraglutide activates cytoprotective pathways and improves outcomes after experimental myocardial infarction in mice. *Diabetes* 2009;58:975–83.
- Liu Q, Anderson C, Broyde A, *et al.* Glucagon-like peptide-1 and the exenatide analogue AC3174 improve cardiac function, cardiac remodeling, and survival in rats with chronic heart failure. *Cardiovasc Diabetol* 2010;9:76.
- Lonborg J, Kelbaek H, Vejstrup N, *et al.* Exenatide reduces final infarct size in patients with ST-segment-elevation myocardial infarction and short-duration of ischemia. *Circ Cardiovasc Interv* 2012;5:288–95.
- Thrainsdottir I, Malmberg K, Olsson A, *et al.* Initial experience with GLP-1 treatment on metabolic control and myocardial function in patients with type 2 diabetes mellitus and heart failure. *Diab Vasc Dis Res* 2004;1:40–3.
- Nikolaidis LA, Mankad S, Sokos GG, *et al.* Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. *Circulation* 2004;109:962–5.
- Sokos GG, Nikolaidis LA, Mankad S, *et al.* Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. *J Card Fail* 2006;12:694–9.
- Halbirk M, Norrelund H, Moller N, *et al.* Cardiovascular and metabolic effects of 48-h glucagon-like peptide-1 infusion in compensated chronic patients with heart failure. *Am J Physiol Heart Circ Physiol* 2010;298:H1096–102.
- Munaf M, Pellicori P, Allgar V, *et al.* A meta-analysis of the therapeutic effects of glucagon-like peptide-1 agonist in heart failure. *Int J Pept* 2012;2012:249827.
- O'Riordan M. Vildagliptin in HF patients with diabetes meets echo end point, but questions remain. 2013. <http://www.medscape.com/viewarticle/804836>
- White WB, Cannon CP, Heller SR, *et al.* Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013;369:1327–35.
- Scirica BM, Bhatt DL, Braunwald E, *et al.* Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369:1317–26.
- Pratley RE, Nauck M, Bailey T, *et al.* Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet* 2010;375:1447–56.
- VilSBoll T, Christensen M, Junker AE, *et al.* Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2012;344:d7771.
- Nagueh SF, Appleton CP, Gillebert TC, *et al.* Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;22:107–33.
- Jenkins C, Moir S, Chan J, *et al.* Left ventricular volume measurement with echocardiography: a comparison of left ventricular opacification, three-dimensional echocardiography, or both with magnetic resonance imaging. *Eur Heart J* 2009;30:98–106.
- Thorstensen A, Dalen H, Amundsen BH, *et al.* Reproducibility in echocardiographic assessment of the left ventricular global and regional function, the HUNT study. *Eur J Echocardiogr* 2010;11:149–56.