Magnetic Resonance Assessment of Victoza Efficacy in the Regression of Cardiovascular Dysfunction In Type 2 Diabetes Mellitus

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Study 1:1) To test the hypothesis that Liraglutide improves cardiovascular function in DM2 patients and whether the improvement is associated with redistribution of ectopic fat stores. 2) To test the hypothesis that Liraglutide activates BAT in DM2...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Myocardial disorders
Study type	Interventional

Summary

ID

NL-OMON44757

Source
ToetsingOnline

Brief title
MAGNA VICTORIA

Condition

- Myocardial disorders
- Diabetic complications
- Vascular injuries

Synonym
1. Pre-clinical diabetic cardiomyopathy in type 2 diabetes mellitus; 2. Early cardiac dysfunction in type 2 diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: farmaceutische industrie,Novo Nordisk

Intervention

Keyword: Cardiovascular function, Diabetes mellitus type 2, Liraglutide, MRI

Outcome measures

Primary outcome

Study 1 and 2:

Heart function:

- Systolic function: stroke volume, ejection fraction, cardiac output, cardiac index, peak ejection rate

- Diastolic function: early peak filling rate (E), early deceleration peak (E dec peak), atrial peak filling rate (A), E/A ratio, peak mitral annulus longitudinal motion (Ea), MR estimate of LV filling pressure (E/Ea).

Secondary outcome

Study 1 and 2:

- Heart dimensions: End diastolic volume, end-systolic volume, LV mass, LV mass index, LVMI/EDVI, percentage scar tissue

- Aorta and carotid vessel wall imaging: total vessel wall area, average vessel wall thickness, minimum vessel wall thickness, maximum vessel wall thickness, vascular distensibility; carotid artery intima media thickness (IMT) by ultrasound.

- Body fat distribution: Adipose tissue distribution, visceral and subcutaneous fat volume at level of L4-L5 vertebra, total fat distribution including BAT,

epicardial fat volume, Magnetic Resonance Spectroscopy of the heart, liver and

kidney triglyceride content

- Glycemic control: HBA1C and fasting blood glucose level

Study description

Background summary

Study 1:
The most important cause of mortality amongst DM2 patients is cardiovascular disease. An early finding of cardiovascular disease in DM2 and obesity is diastolic dysfunction. Diastolic dysfunction is an independent predictor of mortality and has been shown to improve in patients on a low calorie diet. The improvement of diastolic function was associated with a reduction in triglyceride accumulation in the heart and liver. A relatively new widely prescribed therapeutic agent for DM2 patients is Liraglutide (Victoza®). Liraglutide is a Glucagon Like Peptide - 1 homologue that improves glucose homeostasis and reduces blood pressure and body weight. Next to the induction of weight loss, which is potentially beneficial for cardiac function, GLP-1 therapy might have a direct advantageous effect on the cardiovascular system. However, the effect of Liraglutide on cardiovascular function has not been investigated yet. We hypothesize that treatment of DM2 patients with Liraglutide is associated with improvement of cardiovascular function and a reduction of triglyceride accumulation in end-organs.

Study 2:
Among South Asians, there is an increased susceptibility to DM2 and a markedly enhanced risk of cardiovascular disease in comparison to the Western European population. The disadvantageous metabolic phenotype as seen in South Asians includes a relatively large total fat mass, with predominately visceral (VAT) relative to subcutaneous adipose tissue (SAT) and lower brown adipose tissue (BAT) volume and activity, accompanied by increased lipid levels (*thin fat phenotype*). Interestingly, the key elements in the mechanism of action of the GLP-1 analogue Liraglutide correspond to these differences in metabolic profile between South Asians and Western Europeans.

Considering the aforementioned metabolic differences, the effects of Liraglutide as found in DM2 patients of Western European descent cannot be extrapolated to the South Asian DM2 patients. There has already been evidence that the glucose lowering effects of Liraglutide are stronger among South Asians, as compared to Western-Europeans. Moreover, BMI values associated with increased risk of DM2 and cardiovascular disease are known to be lower for

South Asians as compared to Western Europeans. Up till now, the criteria for financial reimbursement of Liraglutide, as employed by the health insurance companies, have been based on BMI values applicable to the Western European population. However, regarding cardiovascular protection, Liraglutide-induced weight reduction may already be beneficial at lower BMI for South Asian DM2 patients. Also, considering the elevated cardiovascular event rate, there is an additional need to assess the cardioprotective potential of Liraglutide among South Asians.

In the care of DM2, ethnicity-specific guidelines have already been implemented. For example, in primary care, ethnicity-specific cut-off values for age have been defined, at which DM2 screening is considered to be indicated. This study may support further development of personalized care, addressing ethnicity-specific complications risks.

With the increasing therapeutic options to target DM2, this study evaluates the cardiovascular effects of Liraglutide in South Asian patients specifically at risk for cardiovascular DM2-related complications.

Study objective

Study 1:
1) To test the hypothesis that Liraglutide improves cardiovascular function in DM2 patients and whether the improvement is associated with redistribution of ectopic fat stores. 2) To test the hypothesis that Liraglutide activates BAT in DM2 patients. 23) To investigate the metabolic and cardiovascular effects related to DM2.

Study 2:
1) To test the hypothesis that Liraglutide results in more improvement of cardiovascular function in DM2 patients of South Asian descent compared to Western European and whether the improvement is associated with a higher redistribution of ectopic fat stores. 2) To test the hypothesis that Liraglutide activates BAT in DM2 patients of South Asian descent, in higher degree as compared to DM2 patients of Western European descent. 3) To investigate the metabolic and cardiovascular effects related to DM2 among South Asians.

Study design

Study 1 and 2:
A 26 weeks double blind, placebo controlled, randomized clinical trial, extended by an observational study at baseline including healthy controls.

Intervention

Study 1 and 2:
The intervention group of 25 patients injects Liraglutide (Victoza®) once daily subcutaneously, the control group of 25 patients injects Liraglutide-Placebo subcutaneously once daily.
The thirty healthy controls are compared with the fifty DM2 patients at baseline and receive no intervention.

Study burden and risks

Study 1 and 2:

Risks:
Patients eligible for study inclusion have an indication for additive glucose lowering therapy, amongst which is the study medication. The risk of the use of study medication is therefore considered to be acceptable. However, Liraglutide is not recommended for use by current clinical guidelines because of a lack of studies on the efficacy on clinical endpoints as morbidity and mortality. Liraglutide is commonly expected to be favorable on these parameters by physicians proven by the large amount of prescriptions; the associated weight loss is a very important aspect of the popularity of the drug. Therefore, clinical experience with Liraglutide has grown in the years since introduction in 2010. Liraglutide is well tolerated with the most important clinical side effect being mild and usually transient nausea. Furthermore hypoglycemic episodes can occur, most often seen during co-treatment with SU-derivatives. Patients will be instructed how to recognize a hypoglycemic episode and how to act when hypoglycemia is proven or suspected. Apart from study medication, patients will be treated according to current clinical guidelines. This implies that patients in the control group will be treated exactly according to clinical guidelines, apart from the study procedures. The risk of the study procedures is limited: there is a minimal risk of anaphylactic reaction (< 1:100.000 cases) upon administration of the MRI contrast medium.

Burden:
The burden of the study protocol consists of a total time expenditure of thirteen hours in 26 weeks, a standard physical examination at screening, to study days and five doctor's visits for history taking, measurement of weight, pulse and blood pressure and interpretation of laboratory examinations to guide treatment and study medication dosage. In total eight blood samples will be taken with a volume of 300 ml. Furthermore patients are instructed to perform fasting blood glucose monitoring once a week. The study medication consists of a subcutaneous injection once daily which is well tolerated in general. Two MRI scans will be performed with a maximal scan duration of four hours. The MRI scan has the risk of the determination of an incidental finding. Three/four times indirect calorimetry will be performed with a total duration of two hours. Last, patients are asked not to actively change their diet and level of physical activity during the study period.

Justification:
Above mentioned risks and burden are acceptable in our opinion given the fact that the knowledge provided by the study can be of benefit for the study participants themselves. We think that the treatment of DM2 patients can be optimized with the insight in the cardiovascular effects of Liraglutide since cardiovascular disease is the most important contributor to mortality in this group of patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Study 1
- Informed consent
- Age > 18 years and < 70 years

- BMI > 25 kg/m2
- DM2 treated with metformin, metformin + SU derivative, metformin + SU derivative + insulin, or metformin + insulin for at least 3 months in the maximum tolerable dosage
- HbA1c >=7% and <= 10.0 %
- EGFR > 60 ml/min
- Normal sitting blood pressure < 150/85 mm Hg and stable for at least one month
Study 2
- Ethnicity: South Asian descent (i.e. Hindustani Surinamese), based on self-identified ethnicity and self-reported origin of the mother, the father and the mother*s ancestors. Both parents and the mother*s ancestors should be South Asian for inclusion.
- Informed consent
- Age > 18 years and < 75 years
- BMI > 23 kg/m2
- DM2 treated with metformin and/or SU derivative and/or insulin for at least 3 months in stable dosage
- HbA1c >= 6.5% and <= 11.0 %
- EGFR > 30 ml/min;Study 1 healthy controls
- No Hindustani Surinamese descent
Study 2 healthy controls
- Hindustani Surinamese descent (based on self-identified ethnicity and self-reported origin of the mother, the father and the mother*s and father's ancestors. Both parents and the mother*s and father's ancestors should be South Asian for inclusion)

Exclusion criteria

Study 1 and study 2:
- Use of thiazolidinediones (TZD), GLP-1 analogues, DPP-IV inhibitors, fibrates, prednisone, cytostatic or antiretroviral therapy within 6 months prior to the study
- Hereditary lipoprotein disease
- Psychiatric disorders and / or use of antipsychotic or antidepressant drugs at present or in the past
- Hepatic disease (AST/ALT > 2 times reference values)
- Endocrine disease other than diabetes mellitus type 2
- Any significant chronic disease (e.g. inflammatory bowel disease)
- Any significant abnormal laboratory results found during the medical screening procedure
- Gastrointestinal surgery (e.g. gastric bypass)
- Pregnant woman or a woman who is breast-feeding
- Female of child-bearing potential intending to become pregnant or is not using adequate contraceptive methods while sexually active
- Allergy to intravenous contrast
- Known or suspected hypersensitivity to trial products or related products
- Chronic pancreatitis or previous acute pancreatitis
- Personal history or family history of medullary thyroid carcinoma or personal history of multiple endocrine neoplasia type 2
- Claustrophobia

- Metal implants or other contraindications for MRI
- Recent participation in other research projects within the last 3 months or participation in 2 or more projects in one year;Study 1:
- History or presence of cardiovascular disease;Study 2:
- Uncontrolled treated or untreated hypertension (systolic blood pressue > 180 mmHg and/or diastolic blood pressure > 110 mmHg)
- Acute coronary or cerebrovascular event within 30 days prior to study
- Congestive heart failure NYHA III-IV;Exclusion criteria healthy controls study 1 and study 2:
- Known acute or chronic disease based on history (which is of influence on primary or secondary outcome measures, at the discretion of the investigator) and physical examination and standard laboratory tests (blood counts, fasting blood glucose, lipids, eGFR, liver enzymes, and electrocardiogram)
- Chronic use of any drug (which is of influence on primary or secondary outcome measures, at the discretion of the investigator), and impaired glucose tolerance (as excluded by a 75-g oral glucose tolerance test)
- Pregnant woman or a woman who is breast-feeding
- Female of child-bearing potential intending to become pregnant or is not using adequate contraceptive methods while sexually active
- Allergy to intravenous contrast
- Claustrophobia
- Metal implants or other contraindications for MRI

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-11-2013
Enrollment:	160

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Victoza
Generic name:	Liraglutide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	25-01-2013
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	19-04-2013
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	17-02-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Not approved Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	07-05-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	22-07-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	24-07-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	28-04-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	02-07-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	15-07-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	12-11-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	24-11-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	25-02-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	09-03-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	09-08-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	24-08-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	23-10-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	01-12-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-001623-12-NL
ClinicalTrials.gov	NCT01761318;NCT02660047
CCMO	NL42089.058.13