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Effects of Dapagliflozin on Epicardial Fat in Subjects with Type 2 Diabetes

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Protocol Title

EFFECTS OF DAPAGLIFLOZIN ON EPICARDIAL FAT IN SUBJECTS WITH TYPE 2 DIABETES

INVESTIGATOR-INITIATED STUDY

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SUMMARY

A number of evidences indicate that subjects with excess visceral fat accumulation are at higher risk for cardio-metabolic diseases and diabetes. With this in mind, I have focused my attention to an emerging visceral fat depot, the epicardial adipose tissue (EAT), and developed a methodology through which EAT can be visualized and measured using standard two-dimensional echocardiography. This approach has several advantages, including its low cost, easy accessibility and good reproducibility. Clinical assessment of EAT is rapidly growing as diagnostic tool for cardio-metabolic risk stratification. Echocardiographic EAT is an inexpensive, reproducible and direct measure of visceral fat. In fact, EAT strongly reflects the intra-abdominal accumulation of visceral fat as measured by magnetic resonance imaging (MRI), and does so better than waist circumference.EAT correlates with insulin resistance, fasting glucose, metabolic syndrome, coronary artery disease, sub-clinical atherosclerosis and Left Ventricular Mass (LVM), an independent cardiovascular risk factor.

An interest clinical application of the EAT is its potential use as therapeutic target during weight lost interventions or pharmaceutical treatments directly or indirectly targeting the adipose tissue. EAT significantly decreased in studies that included adipose tissue modulation and changes, such as TZD or statins. Its reduction was earlier and more significant than changes in BMI and waist circumference during weight loss.

Dapagliflozin is a new and emerging anti-diabetes medication. Dapagliflozin is a selective sodium-glucose cotransporter 2 (SGLT2) inhibitor, reduces hyperglycemia in patients with type 2 diabetes mellitus (T2DM) by increasing urinary glucose excretion, and weight loss is a consistent associated finding. Because dapagliflozin increases urinary glucose excretion, weight loss could result from reduced body fat secondary to caloric loss or from fluid loss secondary to osmotic diuresis or from a combination of both factors. Nevertheless, whether Dapagliflozin may cause a reduction in visceral fat is unknown. Also whether Dapagliflozin can reduce EAT, visceral fat of the heart, and improve cardiac performance, is unexplored.

Hence, in this study we would like to test the hypotheses that Dapagliflozin (a) causes a rapid and significant reduction of EAT, as marker of visceral fat, in type 2 diabetic patients, (b) Dapagliflozin-induced EAT reduction is associated with a significant reduction of LVM. These hypotheses would be tested in an interventional, double-blind, parallel group, placebo controlled study in 100 overweight or obese type 2 diabetes subjects.

This proposal therefore contains a number of novel concepts and an innovative methodology with immediate and important clinical application.

Key words: visceral fat; epicardial fat; Dapagliflozin; type 2 diabetes

Background

Visceral Fat and Cardiovascular Risk

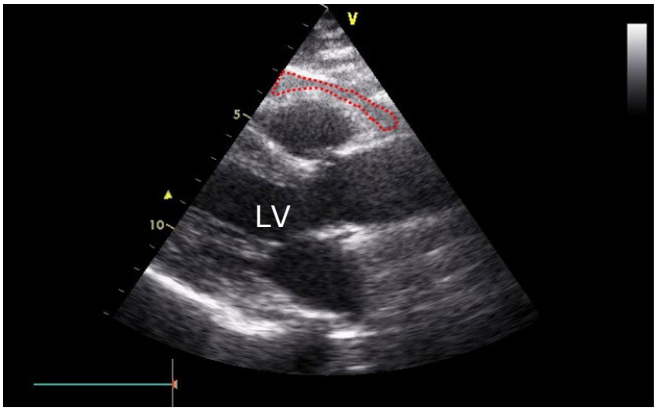
Different body fat distribution has been clearly associated with different cardiovascular risk. A number of evidences indicate that subjects with excess visceral fat accumulation are at higher risk for cardio-metabolic diseases and diabetes. Traditionally, most of the attention has been focused to the intra-abdominal visceral fat accumulation and waist circumference has been largely used as surrogate marker of visceral adiposity. However, waist circumference may provide incomplete information or be subject to operator variability. Imaging studies, as well as MRI or computed tomography are certainly more accurate estimates of body visceral fat content, but more costly and invasive. With this in mind, I have focused my attention to an emerging visceral fat depot, the epicardial fat, and developed a methodology through which epicardial fat can be visualized and measured using standard two-dimensional echocardiography with several advantages, including its low cost, easy accessibility and good reproducibility

<u>Epicardial Fat</u>

Epicardial adipose tissue (EAT) is a peculiar visceral fat depot (1-8). It has anatomical and functional contiguity to the myocardium and coronary arteries. Under physiological conditions epicardial adipose tissue displays biochemical, mechanical and thermogenic cardio-protective properties. Under pathological circumstances, EAT could locally affect the heart and the coronary arteries through vasocrine or paracrine secretion of pro-inflammatory cytokines. What could influence this equilibrium between harmful or protective effects is still unclear.

Clinical Measurement of EAT

Epicardial fat thickness can be visualized and measured with two-dimensional guided M-mode echocardiography using commercially available equipments, as I first proposed and validated (9-10). Standard parasternal long- and short-axis views permit the most accurate measurement of epicardial fat thickness. Epicardial fat is generally identified as the echo-free space between the outer wall of the myocardium and the visceral layer of pericardium



(*Echocardiographic image on the left: epicardial fat thickness is the space within the dotted red line*) and its thickness is measured perpendicularly on the free wall of the right ventricle at end-systole in three cardiac cycles. Epicardial fat thickness AT range varies from a minimum of 1 mm to a maximum measured value of almost 25 mm. The wide range of epicardial fat thickness likely reflects the substantial variation in abdominal visceral fat distribution. The majority of population-based clinical studies have reported excellent inter-observer and intra-observer agreement. Intuitively this procedure has several advantages, including its low cost, easy accessibility and good reproducibility.

Echocardiographic EAT as Marker of Visceral Fat

Echocardiographic epicardial fat is a marker of visceral fat. In fact, EAT strongly reflects the intra-abdominal visceral fat as measured by MRI and better than waist circumference does (9-11). In a multiple regression analysis that included waist circumference and epicardial fat thickness showed, intra-abdominal visceral fat was better and independently predicted by the epicardial fat that epicardial adipose tissue thickness (r^2= 0.44, $p<0.01$). Bland test confirmed the good agreement between the two methods. Other studies confirmed this finding in different populations. EAT is therefore an independent predictor of visceral adiposity and weakly reflects the obesity degree as measured by BMI. Subjects with higher waist circumference clearly show higher epicardial fat thickness, as previously reported. Ectopic fat deposition may occur within the organs and affect the function. EAT is associated with proton magnetic resonance spectroscopy (^{1}H-MRS) intra-myocardial fat *(12).* Hence, EAT can be considered primarily a simple and objective marker of visceral adiposity.

Echocardiographic epicardial fat predicts Cardiovascular Risk

An escalating number of evidences indicate that EAT measurement may play a role in the stratification and prediction of the cardio-metabolic risk (13-35). Several clinical studies showed that epicardial fat thickness is also related to traditional and novel cardiovascular risk factors. Epicardial fat thickness is significantly higher in subjects with metabolic syndrome than in those without. When cardio-metabolic parameters are considered separately, epicardial fat is independently associated with inflammatory markers and liver enzymes. EAT has been associated with the presence and severity of CAD in a large number of studies.

Epicardial Fat and LVM

Abnormal LV mass (LVM) and LV hypertrophy (LVH) are commonly observed in patients with diabetes and obesity. LVM and LVH can be calculated with standard echocardiography as well as the epicardial fat thickness. LVH is a well-established cardiovascular risk factor that can lead to heart failure. Our group showed that high echocardiographic EAT has been associated with increased LVM and abnormal geometry (17-19). Our echocardiographic findings are in agreement with autopsy studies. Mechanical and bio-molecular mechanisms have been evoked to explain these correlations. Increased epicardial fat by adding to the mass of the ventricles may increase the work of pumping. Increased LVM in obese diabetic subjects could be also due to a direct effect of excess epicardial fat. Remarkably, we also showed that decrease in EAT was independently associated with a decreae in LVM after 6 months of diet in obese subjects (36)

Epicardial fat thickness and Diabetes

Epicardial fat thickness and fasting plasma glucose (FPG) were measured in non-diabetic Caucasian subjects who underwent routine transthoracic echocardiogram (37). Study subjects were designated as having normal fasting glucose (NFG) with FPG < 100 mg/dl; and IFG with FPG (100 and < 126 mg/dl).Epicardial fat thickness was significantly higher in IFG than NFG subjects (8

± 3 vs 6 ± 2 mm; 7.1 ± 4 vs 5.8 ± 3 mm, $p < 0.001$ for both and respectively in men and women. Epicardial fat thickness was significantly correlated with FPG ($r = 0.60$, $p < 0.001$),.

Epicardial fat thickness is also inversely associated with insulin sensitivity, as assessed by euglycemic hyperinsulinemic clamp and directly related to clinical markers of insulin resistance in diabetics and non diabetic subjects (38).

Echocardiographic Epicardial Fat as Therapeutic Target

Weight loss target

An interesting clinical application of the EAT is its potential use as therapeutic target during weight lost interventions or pharmaceutical treatments directly or indirectly targeting the adipose tissue (36, 39-43). Improved local vascularization, weight loss and targeted pharmaceutical interventions might allow the epicardial fat to resume its physiological role. Epicardial fat reduced after very low calorie diet, bariatric surgery-induced weight loss and moderate aerobic exercise. Of great interest, the weight loss intervention study showed that the decrease in epicardial fat during weight loss was quicker and higher than decrease in common indices of body fatness. Interestingly, we reported that EAT significantly (12.3±1 vs 8.3±1 p<0.001) decrease after a 6 months very low calorie diet in morbidly obese subjects. We observed that changes in epicardial fat thickness were significantly higher than changes in BMI and waist circumference, -32% vs -23% vs -19%. Epicardial fat changes were also associated with improved cardiac performance and morphology in formerly severely obese subjects.

Pharmacological target

Given its rapid metabolism and its simple objective measurability, epicardial fat can serve as target for pharmaceutical agents commonly used in type 2 diabetes. The effect on the epicardial fat mass and function by medications which are known to modulate the adipose tissue, such as statins and thiazolidinediones, has been evaluated (44-47). Interestingly, epicardial fat thickness reduced in diabetic subjects treated with atorvastatin in comparison to those who received simvastatin and ezetimibe]. Consistently, atorvastatin therapy induced a reduction of computed tomography-measured epicardial fat in hyperlipidemic post-menopausal women, as very recently reported. The effect of atorvastatin on epicardial fat was independent of lipid lowering or coronary artery disease progression. In this context, it certainly notable that epicardial fat overexpression of lipoprotein receptors such as low-density lipoprotein receptor-related protein 1 and very low-density lipoprotein receptor has been recently suggested to play a role in changes of lipid metabolism commonly associated with type 2 diabetes mellitus. Thiazolidinediones were also targeted to the epicardial fat. Notably, epicardial fat inflammatory secretome improved with pioglitazone treatment. In fact, treatment with pioglitazone in type 2 diabetic patients was associated with reductions in expression of interleukin-1β and other proinflammatory genes in epicardial fat. Interestingly, a recent study reveals that peroxisome proliferator–activated receptor-γ (PPAR-γ) agonist can induce a rapid browning of the epicardial fat in experimental models.

Dapagliflozin

Dapagliflozin is a new and emerging anti-diabetes medication. Dapagliflozin is a selective sodium-glucose cotransporter 2 (SGLT2) inhibitor, reduces hyperglycemia in patients with type 2 diabetes mellitus (T2DM) by increasing urinary glucose excretion, and weight loss is a consistent associated finding. Because dapagliflozin increases urinary glucose excretion, weight loss could result from reduced body fat secondary to caloric loss or from fluid loss secondary to osmotic diuresis or from a combination of both factors. Two clinical trials reported significant weight loss in type 2 diabetic patients who received Dapagliflozin. Dapagliflozin patients had significantly greater weight loss than placebo patients over 102 weeks ($p < 0.05$). Dapagliflozin 10 mg/d or placebo was added to open-label metformin for 24 wk. Dapagliflozin reduced total body weight, predominantly by reducing fat mass (FM) , VAT and subcutaneous (SAT) in T2DM inadequately controlled with metformin (50-51). Dapagliflozin produced greater mean reductions from baseline in VAT and SAT compared with placebo at 24 wk. Patients treated with Dapagliflozin exhibited a significant mean decrease from baseline body weight compared with a significant weight gain in patients administered glimepiride (–3.1 lb [–1.4 kg] vs +2.9 lb [+1.3 kg], respectively)

RATIONALE OF THE STUDY

Patients treated with Dapagliflozin exhibited a significant decrease in body weight. Whether Dapagliflozin may cause a reduction in visceral fat is unknown. Although the mechanisms are still unclear, preclinical evidence suggests that SGLT2 inhibitors may modulate the adipose tissue and exert favorable cardiovascular effects. Nevertheless, whether Dapagliflozin-related improved cardio-metabolic profile can be attributed to a direct effect to EAT, visceral fat of the heart, is unknown and unexplored.

SIGNIFICANCE AND INNOVATION

Increased visceral fat is an established risk factor for a poor cardiometabolic profile. Type 2 diabetes is frequently accompanied with excessive visceral fat accumulation. Dapagliflozin has shown to improve glucose control and induce weight loss in subjects with type 2 diabetes. Whether the weight loss effect of Dapagliflozin is characterized by a rapid reduction in visceral fat is unknown, but it would be great clinical relevance. Recently it has been suggested that Dapagliflozin can cause weight loss and improve cardio-metabolic profile beyond the glycemic control. Whether this effect can be also explained by a reduced visceral fat is unexplored. Whether Dapagliflozin can reduce the risk of LVH and ultimately heart failure is unknown. Achieving this knowledge may be of great importance in the management of overweight/obese type 2 diabetic subjects at higher cardiovascular risk. Given the poor accurateness and sensitivity of the traditional anthropometric markers of intra-abdominal fat, such as BMI and waist circumference, there is a great scientific effort in finding reliable and easy markers of the visceral, organ-specific adiposity. We already showed that EAT, as measured with echocardiography, precisely reflects visceral adiposity and rapidly changes during medical interventions targeting the fat. If our hypothesis is true, EAT can serve as simple and non invasive marker of visceral fat loss during therapy with Dapagliflozin. This proposal therefore contains a novel concept and an innovative methodology with immediate and important clinical application

HYPOTHESIS OF THE STUDY

In this study we would like to test the hypothesis that Dapagliflozin may improve cardio-metabolic profile through a direct effect on an easily-accessible organ-specific visceral fat.

STUDY HYPOTHESES

1. We hypothesize that Dapagliflozin can induce a significant and rapid decrease in EAT, as marker of visceral adiposity. Given the rapid metabolism of EAT and its capacity to significantly decrease with agents targeting the fat, as previously reported, we hypothesize that EAT can be significantly changed during treatment with Dapagliflozin.
2. We previously showed that EAT significantly and independently correlate with LVM. We also showed that EAT reduction was independently associated with reduction in LVM. Given these findings, we hypothesize that Dapagliflozin can reduce LVM through an effect on EAT.

SPECIFIC AIMS

a) Dapagliflozin causes a rapid and significant reduction of EAT in type 2 diabetic patients
b) Dapagliflozin-induced EAT reduction would be associated with a significant reduction of LV mass, independent cardiovascular risk factor.

ENDPOINTS:

Primary Endpoint: EAT (Epicardial fat thickness) will be measured with echocardiography according to the method described and validated by Iacobellis et al.Full description of the measurement is reported in the section "Methodology"

Secondary Endpoint: LVM (left Ventricular Mass) will be measured with echocardiography according to the standard formula, fully described in the section "Methodology"

SPECIFIC OBJECTIVES

Primary Objective:

a) Does treatment with Dapagliflozin cause a significant decrease in EAT in subjects with type 2 diabetes?

Secondary Objective:

b) Does treatment with Dapagliflozin cause a significant decrease in LVM, through the reduction of EAT, in subjects with type 2 diabetes?

STUDY DESIGN

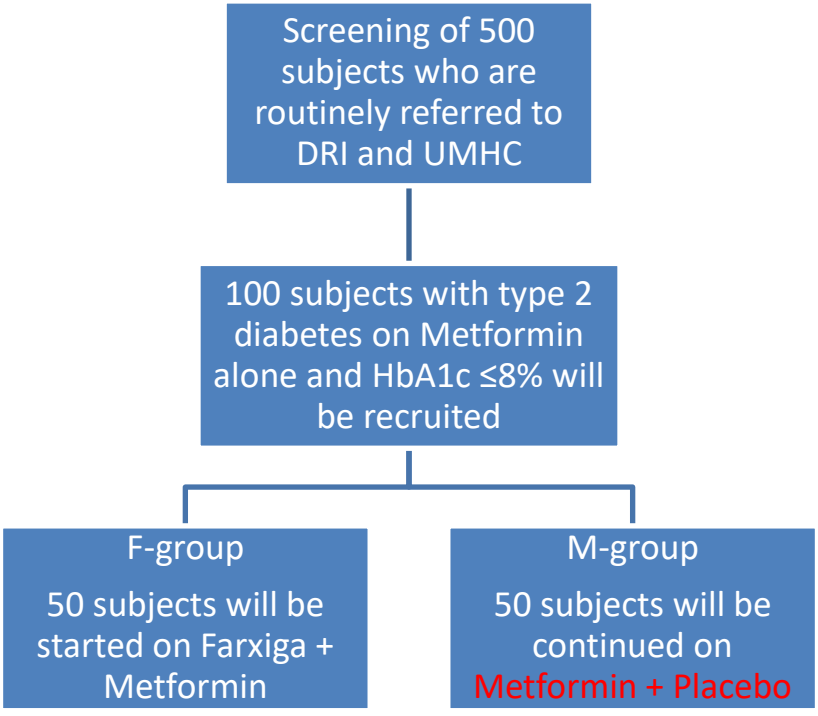
This will be an interventional, double-blind, parallel group, placebo controlled study in 100 overweight/obese type 2 diabetic subjects who are taking Metformin as monotherapy.

Individuals will be randomized in two groups of 50 patients, to receive additional Farxiga (Dapagliflozin) (F-group) or to remain on Metformin (M-group) plus placebo orally once daily.

- F-group: Dapagliflozin will be administered at the starting dose of 5 mg once daily, then if no safety issues will occur, it will be titrated up to 10mg once daily after 2 weeks. Metformin (from 500 mg twice daily to a maximum of 1000 mg twice daily) regimen will be continued to achieve fasting glucose between 80 and 140 mg/dl.

- M-group will be treated with Metformin plus placebo orally once daily for the duration of the study. Metformin (from 500 mg twice daily to a maximum of 1000 mg twice daily) regimen will be continued to achieve fasting glucose between 80 and 140 mg/dl.

  Both groups will receive lifestyle and diabetes education, as part of the standard care.



STUDY TIMETABLE

Participants will be scheduled for the first visit (visit 0) after an overnight fast. Patients will be randomly assigned to receive Farxiga 5 mg or placebo once daily. After 2 weeks patients will receive detailed instructions over the phone to titrate Farxiga or placebo up to 10 mg once daily. F- and M- group patients will undergo clinical examination, anthropometrics, transthoracic echocardiogram for EAT and LVM measurement and point of care (POCT) of fasting glucose and haemoglobinA1c (HbA1c) and estimated Glomerular Filtration Rate (eGFR) at each visit, baseline (visit t0), 3 (visit t3), and 6 months (visit t6)

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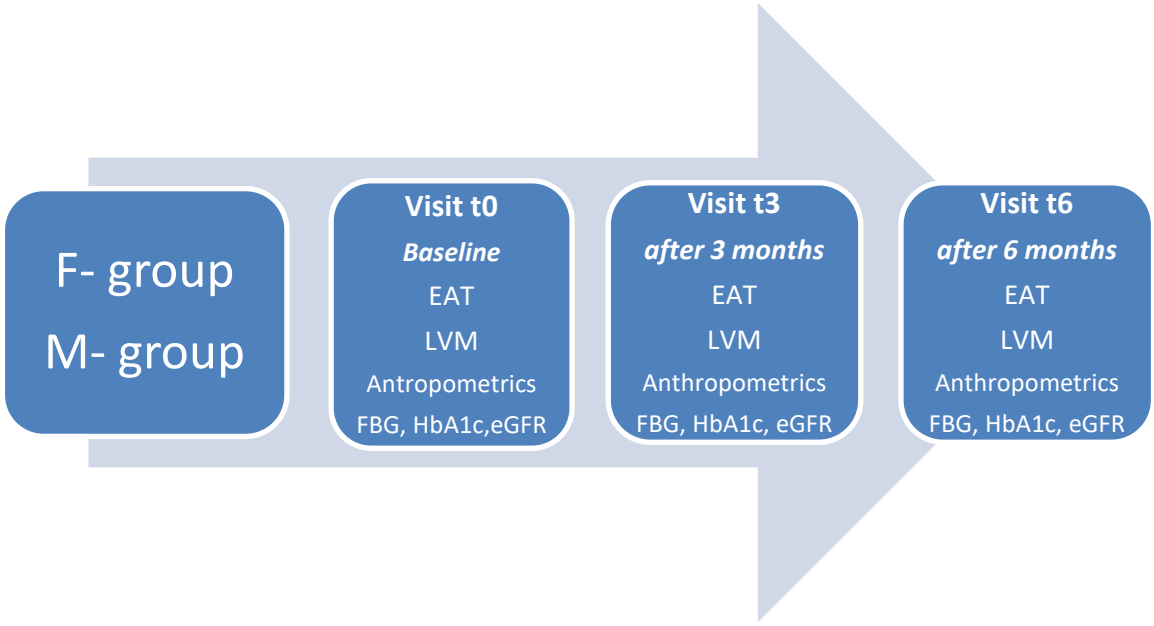

STUDY POPULATION

Number of subjects to be studied: One hundred overweight/obese type 2 diabetic subjects.

Planned number of subjects to be screened: Five hundred subjects will be screened among the outpatient population who routinely refer to Dr Iacobellis' University of Miami Diabetes Clinic at the Diabetes Research Institute (UMMG-DRI), out-patient clinics. Dr Iacobellis visits approximely 2000 diabetic patients per year.

Anticipated number of trial sites: UMMG-DRI out-patient diabetes clinics, University of Miami.

INCLUSION CRITERIA

- Type 2 diabetes, as defined by ADA criteria
- HbA1c < 8% measured at least 1 week prior to the study
- BMI ≥27 kg/m^2
- Pre-treatment with Metformin as monotherapy
- Age > 18 and < 65 years old
- Normal and stable hemodynamic status

EXCLUSION CRITERIA

- Known contra-indications to Farxiga, in accordance with risks and safety information included in the latest updated Prescribing Information
- Type 1 diabetes, as defined by American Diabetes Association (ADA) criteria
- Insulin dependent or treated type 2 diabetes
- Current use of other SGLT2 inhibitors, GLP- 1 analogs or DPP4 inhibitors
- Glomerular Filtration Rate (GFR) < 60 mL/min/1.73 m2
- Signs or symptoms of hypovolemia
- Patients with poor glycemic control (HbA1c ≥ 8%) will be excluded to maximize long-term patient retention without need
- History of diabetes ketoacidosis
- Patients with active bladder cancer or with a prior history of bladder cancer
- Acute or chronic infective, including genital mycotic infections
- Clinical signs or symptoms of New York Heart Association (NYHA) class III-IV heart failure
- Clinical or laboratory evidences of chronic active liver diseases
- Acute or chronic infective diseases
- Cancer or chemotherapy
- Current use of systemic corticosteroids or in the 3 months prior this study
- Known or suspected allergy to Dapagliflozin, excipients, or related products
- Pregnant, breast-feeding or the intention of becoming pregnant
- Females of childbearing potential who are not using adequate contraceptive methods

Withdrawal Criteria

Study subject may withdraw at will at any time.

Repeated eGFR <60 mL/min/1.73 m2 and hypoglycaemic (< 70 mg/dl) episodes will mandate discontinuation of the patient from the study.

VISIT PROCEDURES

Once patient eligibility and written consent are obtained, the participant is then scheduled for the baseline (t0) clinic visit through the University of Miami UChart (Epic) electronic system. The visits will be coordinated by the research coordinator. Each patient will undergo a baseline echocardiographic study for the measurement of EAT and LVM. Each patient will also have a full physical examination, body weight, height, waist and hip circumference measured, a point of care of fasting glucose and haemoglobinA1c (HbA1c). Echocardiographic study will be performed on site by Dr Iacobellis and by an experienced cardiac imaging technician who will be trained to measure echocardiographic EAT by Dr. Iacobellis. The same visit procedures will be repeated after 3 (t3) and 6 (t6) months.

DESCRIPTION OF STUDY SITE

UM Miller School of Medicine has been the site of several National Institutes of Health studies and many peer-reviewed, epidemiologic and health services research publication. The Division of EDM is fully equipped and trained to visit, follow up and manage patients with diabetes. UMMG-DRI is fully accredited and equipped to perform state-of- the-art diagnostic tests assisting in the diagnosis and management of diabetes. The Division is also equipped with a state-of-the-art echocardiographic unit, Siemens, Acuson, USA, for the measurement of the EAT. Dr Iacobellis pioneered the echocardiographic measurement of the epicardial fat and he is considered the leading expert in epicardial fat research

METHODOLOGY

Informed consent will be in place before any study related procedures will be conducted.

Echocardiographic Epicardial Fat Thickness Echocardiographic studies will be performed onsite by Dr Iacobellis and a technician trained in echocardiography. Standard parasternal and apical views will be obtained in the left lateral decubitus position. All echocardiograms will be recorded on DVDs and subsequently digitized will be analyzed offline for epicardial fat thickness quantification according to the method firstly described and validated by Iacobellis et al (9-10). Briefly, epicardial fat will be identified as the echo-free space between the outer wall of the myocardium and the visceral layer of pericardium. Epicardial fat thickness will be measured perpendicularly on the free wall of the right ventricle at end-systole in three cardiac cycles. Parasternal long- and short-axis views allow the most accurate measurement of epicardial adipose tissue on the right ventricle, with optimal cursor beam orientation in each view. Maximum epicardial fat thickness will be measured at the point on the free wall of the right ventricle along the midline of the ultrasound beam, perpendicular to the aortic annulus, used as anatomical landmark for this view. For the midventricular parasternal short-axis assessment, maximum epicardial fat thickness will be measured on the right ventricular free wall along the midline of the ultrasound beam, perpendicular to the interventricular septum at mid-chordal and tip of the papillary muscles level, as anatomic landmark. The average value of three cardiac cycles from each echocardiographic view will be considered.

Reliability of echocardiographic measurement of EAT

Reliability of echocardiographic measurement of EAT will be assessed by the intra-class correlation coefficient. Inter- and intra-observer reproducibility will be evaluated by the intra-class correlation coefficient in all subjects. Echocardiograms will be read by Dr Iacobellis and an experienced cardiac imaging technician who will be blinded to the patients' study group. Previously published studies have shown that intra- and inter-observer reproducibility of epicardial fat measurement was excellent. Intra-class correlation coefficients varied from 0.90 to 0.98 and from 0.93 to 0.98, respectively indicating good reproducibility and reliability. Both readers will be blinded to the subjects' clinical data. Although its advantages overcome the disadvantages, echocardiography measurement may have some limitations. Echocardiographic EAT is a linear measurement at a single location and therefore may not reflect the variability of fat thickness or total epicardial fat volume

Echocardiographic LVM and LVH measurement

LV mass will be estimated by using the anatomically validated formula of Devereux, and then adjusted as LV mass/body surface area (BSA) and LV mass/height$^{2.7}$ ($h^{2.7}$). Left ventricular hypertrophy (LVH) will be defined as LV mass/BSA >134 g/m^2 for men and >110 g/m^2 for women and as LV mass/$h^{2.7}$ >51 g/m$^{2.7}$ in both sexes. Relative wall thickness (RWT) will be calculated as 2 posterior wall (PW)/LV end – diastolic – diameter. Four LV geometric patterns (normal, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy) will be determined using values of RWT and LV mass as follows: normal (no LVH and RWT < 0.44), concentric remodeling (no LVH and RWT > 0.44), concentric hypertrophy (LVH and RWT > 0.44), and eccentric hypertrophy (LVH and RWT < 0.44).

Physical Examination

All anthropometric measures will be obtained by the study nurse. Height (in cm) and weight (in kg) will be measured, and BMI will be automatically calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Waist circumference (in cm) will be measured as the minimum circumference between the lower rib margin and the iliac crest. Hip circumference (in cm) will be measured as the widest diameter over the greater trochanters). Blood pressure will be measured in the seated position, using an automated cuff and digital readout, and entered by the study nurse into the electronic database.

Blood Measurements

Fasting point of care tests will be obtained from all individuals according to the study design timetable. Blood parameters will be measured according to standard and previously described procedures.

Follow up of glucose profile Study patients will be advised to monitor their capillary glucose twice daily, fasting in the morning and post-prandially. Glucose profile will be tracked weekly by the research coordinator using myUhealth, a new and convenient UM online method of communication with the sponsor investigator, or by telephone. Research coordinator will inform the sponsor investigator on patients' glucose readings.

COMPLIANCE AND RETENTION STRATEGY We estimate that the majority of the participants who will be considered eligible will complete the study. Attrition can be estimated as lower than 10%. In the event that participants are lost to follow-up, the research coordinator will contact with the study participant by telephone. The research coordinator will be trained in effective telephone technique to maximize recruitment success.

STATISTICAL CONSIDERATIONS:

Iacobellis' group previously showed and published that epicardial fat thickness decreased from 12.3 ± 1.8 to 8.3 ±1 mm $P < 0.001$ after the 6-month very low calorie diet, accounting for a 32% reduction from the baseline. Average weight loss after the 6-month VLCD in those morbidly obese subjects was approximately 20 kg. It has been reported that Dapagliflozin can cause an approximately 1.5 kg decrease of body weight.

We expect that Dapagliflozin will cause a significant decrease in EAT, but much smaller when compared to weight loss interventions such as a VLCD. EAT decrease has been shown to vary (between -12% and -32%) after different interventions. EAT reduction is anticipated to be between -15% and -25% after 3 months of treatment with Dapagliflozin. A hypothesis of at least 15% reduction in EAT is based on: a) the previously reported weight-loss caused by Dapagliflozin, b) previously-reported responsiveness (decrease) of EAT to pharmacological agents targeting the fat. A reduction of 15%, an absolute difference of 1.2 mm from baseline, will be considered not only statistically, but clinically significant of visceral fat reduction. It is worthwhile to note that a reduction of 0.4 and 1.4 mm in EAT after atorvastatin and bariatric surgery, respectively, was previously considered statistically and clinically significant. However, it is possible to expect a larger difference after 6 months of treatment

Given the reference value and the expected difference in EAT, the statistical power of the study (two-sided, $\alpha=0.05$) was calculated.

Outcome	**Reference value±SD**	**Expected Difference**	**Detectable difference with 80% power α=0.05**	**Detectable difference with >99% power α=0.05**
EAT (mm)	8±3	-15-or -25%	-15% (absolute difference = 1.2)	-25% (absolute difference = 2)

A convenience sample of 50 individuals for each group will therefore provide the statistical power (80%) to detect an expected difference of -15% in the EAT before and after treatment with Dapagliflozin. Baseline SD of 3 is expected to lower to approximately 2 for the expected change. The expected change of SD will assure significant statistical power of the comparative test.

Study Hypothesis 1 Dapagliflozin causes a significant and rapid decrease in EAT. Comparative statistical analysis between F and M-group will be performed to tests this hypothesis**.** Continuous variables will be considered as age-adjusted and sex-adjusted means with their standard deviations (SDs). Two-tailed $p < 0.05$ indicates statistical significance. ANOVA model with adjustment for baseline will be used to calculate the changes (Δ) in EAT between baseline, 3 and 6 months in both F and M-group.

Study Hypothesis 2

Dapagliflozin reduces LVM through an effect on EAT. Based on our previous data (36) we know that LVM reduction is independently related to epicardial fat reduction. We hypothesize that LVM will reduce in the F-group and better than in the M-group. ANOVA test with 95% CI will be used to calculate the changes (Δ) in study parameters between baseline, 3 and 6 months in both F and M-group. Relations between Δepicardial fat, ΔBMI, Δwaist circumference and ΔLVM will be calculated using simple linear regression analysis. Variables with a $p<0.1$ value on univariate analysis will be entered in different multivariate analysis models to assess the independent determinants of ΔLVM, as dependent variables. Echocardiographic epicardial fat will be compared to BMI, waist circumference and to waist-hip ratio as independent predictor of ΔLVM. The optimum sensitivity and specificity of threshold values of EAT to predict reduction in LVM will be examined by receiver operating characteristics (ROC) analysis by plotting sensitivity vs. 100 – specificity.

DATA HANDLING AND RECORD KEEPING:

Data Collection: Each of the dedicated clinic exam rooms at the UMMG-DRI provides direct access to the clinical research study electronic data capture (EDC) eVelos system provided by the Clinical Research Informatics and Data Management Unit of the Center for Health Informatics and Bioinformatics at UM. The sponsor investigator and research coordinator will collect and manage the data.

ETHICS:

Informed Consent

Eligible and willing participant will be contacted by the research coordinator and consented. Previous to the signing of the informed consent, extensive oral and written information will be given to the subjects, including information about risks associated with Dapagliflozin treatment (in accordance with the updated Prescribing Information) before initiating any study related activity.

Confidentiality of data The sponsor investigator will explain that participant confidentiality will be maintained, data will only be identified by a number and that their consent forms with identification number will be kept locked in a filing cabinet.

Protections against Risk

The risks to patients are extremely minimal in this study. There is a theoretical small increased risk of hypoglycaemic events in the Dapagliflozin + metformin group. There are no other foreseen risks to participants involved in the study. Patients will be required to remove their shirts for echocardiographic evaluation and may feel embarrassed. In addition, the patient may worry that their participation might be disclosed in a weight loss program. Patients will be informed of the echocardiography procedure prior to consenting. There may be some embarrassment from having their waist and hips measured three times throughout the course of a year. Participants

would undergo blood test regardless their participation in the study. The researcher assistant will be advised of any required sensitivity towards participating members

Other Ethical considerations

The study has been submitted to the University of Miami local institutional review board (IRB). Final approval is pending, but highly anticipated. The study will be conducted in accordance with the Declaration of Helsinki. The study will be conducted in accordance with the ICH GCP guidelines. The sponsor-investigator will comply with all applicable regulatory and legal requirements, ICH GCP guidelines and the Declaration of Helsinki in obtaining and documenting the informed consent.

STUDY SCHEDULE:

Planned recruitment period: 1 year

Expected milestones:

- start of study: 01/01/2015
- first patient first visit 01/01/2015
- last patient last visit 12/01/2016
- Planned completion of integrated final study report 01/1/2017

STUDY DRUGS AND MATERIALS:

Study medication

FARXIGA (Dapagliflozin) is SGLT2 inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Study Medication supply

Farxiga will be supplied to each study subjects by Astra Zeneca

Labelling of Study Medication

No IND is required. Study medication will be in accordance to current labelling.

Storage and Drug Accountability of Study Medication

The sponsor-investigator will ensure the availability of proper storage conditions and record and evaluate the temperature.

Randomization

This will be an open randomized study. The method of allocation generation will be a computerized random-number generator. The sequence will be generated by the process of restricted randomization. This has greater potential benefit in small trials, as in the present study.

CONCOMITANT ILLNESSES AND MEDICATIONS:

Details of all concomitant illnesses and medication will be recorded at the first visit. Any changes in concomitant medication will be recorded at each visit. If the change influences the subject's eligibility to continue in the trial, the Sponsor will be informed. The information collected for each concomitant medication includes, at a minimum, start date, stop date or continuing, and indication. For each concomitant illness, date of onset, date of resolution or continuing, at a minimum, will be recorded.

SAFETY

Adverse Event (AE):

An AE is any undesirable medical event occurring to a subject in a clinical trial, whether or not related to the trial product(s). This includes events reported from the first trial related activity after the subject has signed the informed consent and until post treatment follow-up period as defined in the protocol. The following should not be recorded as AEs, if recorded as medical history/concomitant illness on the CRF at screening:

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent
- Pre-existing conditions found as a result of screening procedures

Adverse events:

In the case of an AE, the sponsor-investigator will comply with all local legal, regulatory, and IRB requirements. The sponsor-investigator will be responsible for reporting of all adverse events including serious adverse events (SAE), suspected unexpected serious adverse reactions (SUSARs), serious adverse drug reactions (SADRs) to the competent authority and independent ethics committee/institutional review boards based upon federal regulations and local/IRB policies. The sponsor-investigator will report to Astra-Zeneca all SAEs, SUSARs, and SADRs at the same time such events are reported to regulatory authorities or within 15 days from the sponsor-investigator becoming aware of such adverse events, whichever comes first.

The sponsor-investigator will use the approved Updated Prescribing Information for Farxiga

The sponsor-investigator will collect the following information at minimum for each of these events:

1. Study name
2. Patient identification
3. Event (preferably a diagnosis)
4. Drug
5. Reporter identification

Clinical Laboratory Adverse Event:

A clinical laboratory AE is any clinical laboratory abnormality regarded as clinically significant i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity, which requires active management, (i.e. change of dose, discontinuation of trial product, more frequent follow-up or diagnostic investigation).

Serious Adverse Event (SAE):

A serious AE is an experience that at any dose results in any of the following:

- Death
- A life-threatening* experience
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening*, or require hospitalisation may be considered an SAE when, based upon appropriate medical judgement, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

*The term life-threatening in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

Serious Adverse Drug Reaction (SADR):

An adverse drug reaction (ADR) is an adverse event for which a causal relationship (Possible/Probable relation) between the study drug and the occurrence of the event is suspected. The ADR should be classified as **serious** if it meets one or more of the seriousness criteria.

Medical Events of Special Interest (MESI): A MESI is (1) a medication error (e.g. wrong drug administration or wrong route of administration) or (2) a suspected transmission of an infectious agent via the product

Non-Serious Adverse Event:

A non-serious AE is any AE which does not fulfil the definition of an SAE.

Severity Assessment Definitions:

- Mild: Transient symptoms, no interference with the subject's daily activities
- Moderate: Marked symptoms, moderate interference with the subject's daily activities
- Severe: Considerable interference with the subject's daily activities, unacceptable

Relationship to study medication Assessment Definitions:

- Probable: Good reasons and sufficient documentation to assume a causal relationship
- Possible: A causal relationship is conceivable and cannot be dismissed
- Unlikely: The event is most likely related to an etiology other than the trial product

Outcome Categories and Definitions:

- Recovered: Fully recovered or by medical or surgical treatment the condition has returned to the level observed at the first trial related activity after the subject signed the informed consent
- Recovering: The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the trial
- Recovered with sequelae: As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed). Any AE recovered with sequelae should be rated as an SAE
- Not recovered
- Fatal
- Unknown

Collection, Recording and Reporting of Adverse Events

All events meeting the definition of an adverse event will be collected and reported from the first trial related activity after the subject has signed the informed consent and until the end of the post-treatment follow-up period as stated in the protocol.

Follow-up of Adverse Events

During and following a subject's participation in a clinical trial, the sponsor-investigator and institution will provide adequate medical care to the study subject for any study-related adverse events, including clinically significant laboratory values related to the study. This medical care for study subjects will be provided regardless of their insurance status.

All adverse events classified as serious or severe or possibly/probably related to the trial product will be followed until the subject has recovered and all queries have been resolved. For cases of chronic conditions follow-up until the outcome category is "recovered" is not required, as these cases can be closed with an outcome of "recovering" or "not recovered". All other adverse events will be followed until the outcome of the event is "recovering" (for chronic conditions), or "recovered" or until the end of the post-treatment follow-up stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved.

Pregnancy

Study subjects will be instructed to notify the sponsor-investigator immediately if they become pregnant. The sponsor-investigator will report to Astra Zeneca any pregnancy occurring during the trial period. Reporting of pregnancy by sponsor-investigator will occur within the same timelines described above for reporting of Adverse Events. Pregnancy complications will be recorded as adverse event(s). If the infant has a congenital anomaly/birth defect this must be reported and followed up as a serious adverse event.

Precautions/Over-dosage

Precautions and procedures will be observed in the event of overdose of Dapagliflozin provided during the study.

REPORTING OF SERIOUS ADVERSE EVENTS

Investigators and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AZ. A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

When reporting to AstraZeneca, a cover page should accompany the MedWatch/AdEERs form indicating the following:

- Investigator Sponsored Study (ISS)

- The investigator IND number assigned by the FDA

- The investigator's name and address

- The trial name/title and AstraZeneca ISS reference number

Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.
Send SAE report and accompanying cover page by way of fax to AstraZeneca's designated fax line: 1-866-984-7229

Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events.
In the case of blinded trials, AstraZeneca will request that the Sponsor either provide a copy of the randomization code/ code break information or unblind those SAEs which require expedited reporting. All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

LIABILITY AND SUBJECT INSURANCE:

The sponsor-investigator should state that during and following a subject's participation in trial, the sponsor-investigator and his/her institution will provide adequate medical care to the study subject for any study-related adverse events, including clinically significant laboratory values related to the study. This medical care for study subjects will be provided regardless of their insurance status.

The sponsor-investigator will be responsible for the conduct of the study and agrees to defend, indemnify, and hold harmless Astra-Zeneca, any of its parent companies, affiliates, or subsidiaries, and their respective officers, directors, employees, agents, representatives, distributors, salespersons, customers, licensees, and end-users from and against any claim, suit, demand, loss, damage, expense or liability imposed by any third party arising from or related to: (a) any breach of sponsor-investigator's obligations; or (b) sponsor-investigator's negligent or grossly negligent use or willful misuse of the study drug, the results, or services derived there from. This indemnification shall not apply in the event and to the extent that a court of competent jurisdiction or a duly appointed arbiter determines that such losses or liability arose as a result of Astra-Zeneca gross negligence, intentional misconduct, or material breach of its responsibilities.

PUBLICATION PLAN:

Data generated from the study will be published in highly ranked peer reviewed scientific journals and presented at national and international meetings. Astra-Zeneca will have any manuscripts for publication for review with a right to comment.

The sponsor-investigator will register the study with a publicly assessable database such as clinicaltrials.gov.

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Most Frequently Used Acronyms

Presented is a list of acronyms that are frequently used through this proposal.

Acronym	Definition
BMI	Body Mass index
EAT	Epicardial Fat Thickness
EDM	Division of Endocrinology, Diabetes and Metabolism
LVM	Left Ventricular Mass
MRI	Magnetic Resonance Imaging
UM	University of Miami
UMH	University of Miami Hospitals
UMHC	University of Miami Hospital and Clinics