Metformin in Heart Failure (Met-HeFT)

Barry Fine MD PhD, March 3rd 2020
Protocol Version 10
Main Study: IRB AAAR5389 (CUIMC)
PET Sub-study: IRB AAAR9360 (CUIMC)
HAZMAT (JRSC): APH-AAAZ6251
NCT 03331861

Summary of Protocol Changes from v.9

-We are modifying any hospitalization within the past 3 months as an exclusion criteria to any heart failure hospitalization within the past 3 months.

-We are adding a stationary bicycle as a mode for performing a cardiopulmonary exercise test for patients who cannot or do not want to exercise on a treadmill.

Summary of Protocol Changes from v.8

-Liver Function Tests were reclassified as a screening test from a baseline test since abnormal liver function is an exclusion criteria and not an outcome.

-Listing venous lactate as a baseline laboratory value to reflect Table 1 procedural timeline more accurately

-Specific statement that any laboratory value obtained for clinical purposes within three months of screening can be used for screening

-Removal of Dr. Reshad Garan from the DSMB and replacement with Dr. Susan Restaino

Summary of Protocol Changes from v.7

-Microbiome elements were removed from the protocol

Summary of Protocol Changes from v.6

- The PET radiotracers oxygen, palmitate and acetate are not available.
- The PET protocol is changed to just FDG and NH3, both of which are FDA approved.
- Change in effective radiation dose due to change in radiotracers
- We are pre-specifying a plan to pursue IRB/RDRC/JRSC approval for palmitate, acetate and oxygen when available from research radio-pharmacy to be started during active enrollment of the Met-HeFT trial.

Purpose:

This study evaluated the efficacy of metformin on myocardial function in non-diabetic patients with systolic heart failure. Fifty patients will be randomized to either metformin or placebo for 6 months in addition to regular therapy.

Hypothesis

The primary hypothesis is that metformin will improve myocardial performance in patients with

stable systolic heart failure without diabetes.

Endpoints

Primary endpoint: change in VE/VCO2 over 6 months of treatment.
Secondary endpoints:
a) heart failure decompensation (unscheduled office IV diuretic therapy, ED visit for decompensated heart failure or hospital admission for decompensated heart failure)
b) Minnesota Health Living with Heart Failure Questionnaire Score
c) LVEF,
d) GLS and GLSR
e) BNP
f) body weight
g) changes in dyspnea assessment score (VAS and 7-Likert scale),
h) peak VO2

Background

Diabetes and heart failure often overlap within the same patients(1). In one study, up to 44% of patients admitted for decompensated heart failure were found to be diabetic(2). Diabetes within heart failure patients has been associated with increased risk of death(3). The relationship between diabetes has been classically attributed to increased coronary artery disease and ischemic cardiomyopathy however there is also evidence that heart failure itself promotes insulin resistance(4, 5).

Metformin hydrochloride (also known as Glucophage) is a biguanide that is a direct activator of 5'- adenosine monophosphate activated protein kinase (AMPK) which is a regulator of cellular lipid and glucose metabolism especially in times of energetic stress (6). It is one of the most widely used drugs in diabetes as an oral agent, with an estimated 60 million prescriptions filled in 2012 in the United States(7). Clinically, it improves glucose uptake in peripheral muscle, decreases hepatic gluconeogensis and improves insulin sensitivity(8). Interestingly, metformin has also been reported to have cardio-protective effects and favorable improvement in left ventricular function(9). In preclinical studies in non-diabetic animal models, metformin has been shown to significantly ameliorate myocardial damage from infarction as well as improved myocardial performance in heart failure, effects that were independent of glycemic control (10-13). In one of the landmark trials of metformin in diabetes, the UKPDS study, metformin was associated with a 36% reduction in all-cause mortality, a 39% reduction in myocardial infarction and a 30% reduction in macrovascular end points(14).

Initially metformin was contraindicated in heart failure due to concern for lactic acidosis, which had been primarily observed in phenformin, a related biguanide (15). However multiple retrospective nonrandomized studies have shown that metformin is safe and associated with lower morbidity and mortality in diabetic patients with heart failure when compared to other diabetic agents(16, 17). Propensity score matched analysis demonstrated lower rates of death

in ambulatory heart failure patients compared to placebo(18). Furthermore, a meta-analysis of over 34,000 patients in nine cohort studies showed that in terms of overall safely, no increased risk was detected in metformin patients compared to other diabetic agents and, as before, a lower rate of morbidity and mortality was detected among those patients taking metformin(19). A prospective randomized control trial on metformin in heart failure patients with diabetes had to be abandoned because the trialists were unable to find enough patients who met their eligibility criteria due to common use of metformin in the diabetic heart failure population(20). No increased risk of lactic acidosis has been detected clinically and the FDA removed its warning on the use of metformin in stable CHF in 2006.

In the GIPS-III trial, metformin was studied in non-diabetic patients after ST elevation myocardial infarction(21). In this prospective trial of 380 patients with ST elevation MI, metformin was studied for four months at a dose of 500mg twice a day. There was no change in the primary endpoint of left ventricular ejection fraction as measured by CMR, though both groups displayed near normal ejection fractions after four months (53.1% for the metformin group and 54.8% for the placebo group). Though the dose and effect size may have been underpowered for this trial, it did demonstrate outstanding safety profile in cardiovascular patients. There was no reported hypoglycemia or lactic acidosis. Similar safety had been previously seen in pre-diabetic patients, in which a prospective trial of over 3000 patients, randomized to either physical activity, metformin or both, also showed no incidences of hypoglycemia(22).

There have been 11 observational studies published on metformin and heart failure outcomes. In multiple cohorts, metformin use has been associated with decreased mortality, decreased cardiovascular mortality and decreased readmissions(19, 23). In a small randomized pilot of 58 insulin resistant patients with heart failure, metformin use was associated with a decrease in the VE/VCO2 slope by 4.5

Study Design:

Prospective, single-center, double-blind, randomized placebo controlled trial of 6 months duration, conducted in a tertiary hospital. Patients will be recruited from the General Cardiology Clinics and Center for Advanced Cardiac Care at New York Presbyterian-Columbia Medical Center. This is an extremely busy outpatient heart failure program in which over 2,500 patients are seen yearly. We propose to enroll n=50 patients.

Study Participants: 50 male and female patients will be recruited.
Inclusion Criteria:

- Age >18yrs old
- Patients with chronic heart failure (defined as >6 months duration) uptitrated to recommended or maximally tolerated dose of ACE-I/ARB (unless contraindicated) and beta-blocker (unless contraindicated). If indicated, an aldosterone receptor antagonist should be given (unless

contraindicated). An ICD and/or CRT should be implanted, if indicated. Patients with a CRT device should be treated for > 3 months.

- Reduced ejection fraction defined as LVEF ≤ **35%**
- NYHA-class II or III with stable symptoms for at least the past 3 months
- Renal Function by eGFR ≥ 45 ml/min (MDRD equation) in accordance with FDA guidance on metformin use in CKD(24)
- Non-insulin resistant defined as a fasting insulin resistance index, or HOMA-IR of <2.7.
- Non-diabetic defined as a HgbA1c <6.0

Exclusion Criteria

- Any oral or injectable hypoglycemic therapy (e.g. insulin, sulfonylureas)
- Known allergy to metformin or major side effects to metformin treatment
- Concomitant use of a carbonic anhydrase inhibitor (such as acetazolamide or topirafmate)
- Heart Failure Hospitalizations in the past 3 months (primary diagnosis on admission is heart failure)
- Acute myocardial infarction, unstable angina or revascularization with prior 3 months at the time of randomization
- Planned coronary revascularization, heart surgery, CRT implantation or other intervention during the study period that would potentially affect the function of the heart
- Significant, uncorrected primary cardiac valve disease, specifically severely stenotic or regurgitant mitral or aortic valves
- Cardiac arrest or life threatening ventricular arrhythmias within the last 3 months (unless treated with an ICD)
- Atrial fibrillation with poorly controlled ventricular rate at rest (> 110 beats/min)
- Hypertrophic or restrictive cardiomyopathy, infiltrative or storage myocardial disease, active myocarditis, or pericardial disease.
- Planned major surgery within the study period
- Female patients who are pregnant, nursing, or of childbearing potential while not practicing effective chemical contraceptive methods (i.e. oral, implanted, injectable, or transdermal contraceptive hormones; intrauterine device)
- Current abuse of alcohol or drugs
- Life-expectancy of less than 1 year due to co-existing morbid illness
- Liver disease with ALT or AST >3 times upper normal limit (it is possible to repeat this measurement once within a month)
- Advanced lung disease such as COPD
- Significant comorbidity or issue that makes the patient unsuitable for participation as judged by the investigator

- Participation in another study involving long-term medical intervention (participation in device studies is allowed)

Randomization: After obtaining informed consent, subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomized. Patients will be randomly assigned in a 1:1 ratio to metformin (1000mg twice a day) or placebo treatment groups. The randomization code will be generated by the Columbia University Irving Institution Biostatistics Epidemiology and Research Design Resource (BERD) and held by the Columbia University Medical Center (CUMC) research pharmacy in opaque envelopes prior to the initiation of patient recruitment to ensure allocation concealment. The study drug will be dispensed by the research pharmacy based on randomization assignment. Principal investigator/Co-investigators are responsible to assess the eligibility criteria. Patients and physicians will be blinded to the intervention allocation. Randomization will be performed in block permutations designed by BERD in order to balance the issue of maintaining similarity between treatment groups while simultaneously not employing block sizes which are so small that it is possible to guess some allocations, thus reducing blinding in the trial. A separate randomization table will be generated for those subjects who agree to the PET sub-study (IRB AAR9360). The goal of having two tables is to maintain balanced enrollment between those that do and do not agree to participate in the PET sub-study.

Study Intervention and Procedures

Patients will be randomized to either metformin or placebo. Metformin dose will begin with 500mg twice a day for the first two weeks and then increase to 1000mg twice a day for the remainder of the trial. In order to minimize GI side effects, the medication will be taken with a meal. The intervention will last 180 days. Prior to randomization all potential study subjects will be evaluated with complete medical history and brief physical examination, complete review of home medications, measurement of vital signs and body weight with calibrated scale, serum collection for basic metabolic panel, hemoglobin A1c and liver function test. All patients will also undergo cardiopulmonary exercise testing and transthoracic echocardiography. Patients who meet all the inclusion criteria will be required to complete the informed consent form. Patients will have 2 office visits in total, one at day 1 (baseline) and one on day 180 (final). On day 30, participants will have a blood work for basic metabolic panel, venous lactate and fasting plasma glucose for adverse event assessment (safety). On the final visit, patients will undergo repeat echo, labs and cardiopulmonary exercise testing. The timing of all procedures in this study is outlined in the table 1. Procedural timeline and further details of the relevant procedures are as follows:

Medical history and physical exam: Subjects will be asked to provide information about their basic demographics: age, gender, and race as well as previous and current health and medications. The subject will have his or her height, weight, blood pressure both supine and standing, heart rate, respiratory rate and body temperature recorded. A HF-focused physical examination will be performed and recorded. A Minnesota Living with Heart Failure Questionnaire will be completed.

Blood tests:

Blood be drawn via venipuncture. The following will be prospectively measured for every patient at the indicated time points.

- Screening: fasting insulin and glucose level, basic metabolic, liver function test and HgbA1c
- Baseline: , BNP, venous lactate
- Safety: basic metabolic panel, venous lactate and fasting glucose
- Final: basic metabolic panel, BNP

Plasma and serum (up to 50ml) will be stored for current and future analysis of biomarkers including but not limited to biomarkers of inflammation, endotoxemia/bacteremia, neurohormonal, immune and endothelial activation, angiogenesis, collagen turnover and congestion will be measured using established techniques. White blood cells may be isolated form collected blood, to assess patterns of inflammation and immune activation using established techniques. Additionally, novel biomarkers such as circulating microRNAs, non-coding RNAs may be utilized for biomarker analysis.

Dyspnea assessment: to be performed visual analogue scale (VAS) and seven-level Likert scale scores.

Echocardiogram: At baseline and final visit. The echocardiogram will be conducted according to the ASE Guidelines. M-Mode and two-dimensional (B-mode) imaging will be obtained from parasternal, apical and subcostal windows. LV dimensions will be measured at end systole and diastole from parasternal windows. EF will be calculated by Simpson's Biplane method. Right ventricular function will be assessed by tricuspid annular plane systolic excursion and right ventricular free wall excursion velocity on tissue doppler. Mitral valve inflow and tissue dopplers will be recorded to assess diastolic function. Speckle tracking echocardiography will be utilized to obtain global longitudinal strain and strain rate of all LV segments in four and two chamber views.

Cardiopulmonary Exercise Test (CPET): At baseline and final visit. The CPET is to be performed on a either a treadmill with a Medgraphics Ultima metabolic cart or a Corival CPET Ergometer (stationary bicycle) in the Cardiopulmonary Exercise Lab. All testing is to be done in the Cardiopulmonary Exercise Lab in Milstein, a clinical cardiopulmonary exercise testing laboratory. There will be a physician present at all tests, and the appropriate emergency equipment and trained personnel are available should difficulties arise during the exercise test. The CPET will be conducted per ATS and AHA guidelines (25, 26). For a treadmill test: Participants will exercise on a treadmill at an increasing rate of 0.1MPH per minute and 1% grade per minute starting at a speed of 1.0 MPH at 0% grade. For a bicycle test: The participants will performa 15 watt ramp protocol and instructed to pedal to a rate of 50-60 rpm. The protocol begins at zero watts and will increase in resistance by either 15 watts/minute (for female patients) or 20 watts/minute (for male patients) Heart rate, BP and perceived exertion score (RPE, reported on a scale from 0-10.0) will be recorded in one-minute intervals. Oxygen consumption (VO2) (ml/min), Carbon Dioxide production (VCO2) (ml/min), and minute Ventilation (VE) (L/min) will be measured on a

breath by breath basis. Peak VO2, VE/VCO2 and respiratory exchange ratio (RER) will be computed.

Biobank: Serum samples will be stored in a biobank repository in the CCTI Biobank Core Facility. The purpose of this biobank is to characterize serum biomarkers of patients with heart failure who have been exposed to metformin versus placebo. The registry will include previously gathered clinical information in electronic medical records. This data includes demographics, clinical comorbidities, hemodynamics, echocardiographic indices of structure and function, hospitalizations, medication use and laboratory data. All specimens/data will be distributed at the discretion of the principal investigator. The purpose of this dissemination will be for experimental collaboration. We will review to make sure collaborators have an existing approved IRB before we distribute. The proper MTA will be executed prior to delivery of samples. All samples will be coded so the recipient will not have any direct patient identifiers linked to these samples.

Clinical Data Collection: This study will collect all data obtained during routine clinical care of all patients who participate in this study. Retrospective data will be collected. All patients will be followed prospectively until death. Trained research staff will extract data from electronic medical records. We will acquire longitudinal clinical information, including complications, hospitalizations, medication use, laboratory values, echocardiographic data, hemodynamic data, as well as mortality.

Table 1: Procedural Timeline

Day Number	0	30	180	210
Type of Visit	Screening/Baseline	Safety	Final Visit	Safety Follow
Informed Consent	X			
Medical History	X			
Vital Signs	X			
MLHFQ	X		X	
Physical Exam	X		X	
Adverse Event		X	X	X
Pregnancy Test	X		X	
Basic Metabolic Panel	X	X		
Fasting Plasma Glucose	X	X	X	
Fasting Insulin Level	X			
Hepatic Function Panel	X			
BNP	X		X	
Hemoglobin A1c	X		X	

Venous Lactate	X	X	X	
VAS and Likert Scale	X		X	
Echocardiogram	X		X	
Venous Reactivity	X		X	
CPET	X		X	
Study Med Allocation	X			
Biomarker Blood Samples	X		X	
PET Substudy				
13N-Ammonia	X		X	
18F-FDG	X		X	

Primary Endpoint Rationale: The primary endpoint is a change in the slope of the ventilation versus carbon dioxide production (VE/VCO2). Peak VO2 has been considered in heart failure literature as a strong predictor for HF outcomes and was the original variable studied in that population. However, a confounder with metformin is that in normal patients without heart failure, metformin treatment has been shown to slightly decrease VO2(27). The mechanism behind this is possible direct inhibition of complex I of the mitochondrial electron transport system(28). The slope of the relationship between minute ventilation and CO2 production (VE/VCO2) has been also thoroughly studied in systolic heart failure as a marker of ventilator efficiency and overall prognosis(29). As demonstrated in over 20 papers (summarized in reference 29) and in the AHA guidelines (26), the VE/VCO2 slope more powerfully predicts mortality, hospitalization or both than peak VO2. This has been shown to be a sensitive index of cardiorespiratory fitness in patients taking metformin with insulin resistance and heart failure and is not confounded by any inhibitory interactions between metformin and the variable (30). Thus we have excluded peak VO2 as a primary endpoint and will instead use VE/VCO2 as the primary endpoint for power analysis.

Clinical Events: Subjects will be followed for 180 days following their enrollment and the following ADHF-events will be recorded every three months during office visits or by telephone contact: (i) Unscheduled intravenous diuretic therapy in-office; (ii) Emergency room visit for ADHF; (iii) Hospital admission for ADHF.

Data Management: Study data will be collected and recorded by study personnel under the supervision of the principal investigator. All subjects enrolled in the study will be given a unique identifier, which will be used for all further evaluations. Any information obtained during this study and identified with the patient will remain confidential. All the data will be stored on a mainframe network computer, which can only be retrieved by members of the research team through personalized logon codes. At least quarterly, data analyses regarding accuracy of data entry will be performed by a biostatistical consultant and potential errors will be reported to the principal investigator and study personnel for correction.

Safety Monitoring: A data monitoring committee of three members (Dr. Susan Restaino, Dr.

Matthew Lewis and Dr. Veli Topkara) will be established to evaluate safety, with a pre-specified stopping rule for harm but not for efficacy. Renal function, fasting glucose and venous lactate will be assessed at baseline, safety lab (day 30) and final visit (day 90). Safety will be assessed by tracking all adverse events on a weekly basis and serious adverse events within 24 hours of discovery. Serious adverse events for this trial will include death, life threatening illness, disability, congenital abnormality, any hospitalization, hypoglycemia (serum glucose <60g/dL), and new lactic acidosis (lactate >2.0mmol/L) with specific responses to these events as detailed in the Protection of Human Subjects section.

Statistical Approach

The primary outcome in this study will be change in VE/VCO2 slope. The VO2 change outcomes will be assessed for normality using standard visual assessments (Q-Q plots and histograms) and statistical tests (Kolmogorov-Smirnov). If VE/VCO2 slope change demonstrates evidence for non-normality, we will natural log transform values for our primary analyses. Prior to testing for differences, we will compare important clinical, laboratory and demographic characteristics between groups (treatment vs. control) to ensure that randomization achieved between groups balance on these important covariates. For variables that are unbalanced by treatment group (determined via statistically significant difference $p<0.05$), we will include these variables in multivariable models of the primary endpoint as described below. Linear regression models will be used to regress mean weight change on treatment group using intention-to-treat principles. If preliminary descriptive analyses indicate a need for multivariable models (see above), the relevant adjustments will be made to our regression models. Analysis of secondary outcomes will be conducted using contingency tables and Fisher's exact chi-square tests; for these outcomes, we will also utilize a modified Poisson regression model with robust error variance to assess the relative risk (separate regressions for each outcome). This modified Poisson model has been described previously and allows for multivariable models to be constructed should they be deemed necessary. Once a patient is randomized, they will be included in final analyses according to intention-to-treat principles regardless of whether they complete the study protocol. If patients are lost-to-follow up and final outcome assessments cannot be made we will use the "last observation carried forward" approach to assign a final outcome value. Additional sensitivity analyses will be performed by assigning final outcome values assuming patients in the treatment group had 10% lower mean weight loss and patients in the control group had 10% greater mean weight loss. This is very conservative approach that will inform the potential for differential outcomes according to follow-up status to explain our observed findings. However, we expect very little loss-to-follow up as these patients receive regular care at our center and are likely to return to the hospital regardless of continued study participation.

Power for VE/VCO2: We base the sample size calculation on data from Wong et al (31). We estimate the average effect size of metformin on the slope of VE/VCO2 to be -5 with a starting average slope of 32 and a variance of 6. In order to achieve 83% power with an alpha of 0.05, we will enroll 25 patients in each arm.

Positron Emission Tomography (PET) Sub-study (IRB AAAR 9360)

The goal of this sub-study is to enroll patients to undergo cardiac PET imaging before and after treatment with either metformin or placebo. In this pilot sub-study, we will recruit patients at the time of their enrollment into Met-HeFT to undergo serial PET scans with metabolic tracers. We will specifically use FDA approved radiotracers for this study including 18F-Fluorodeoxyglucose (18F-FDG) to track myocardial glucose consumption and 13N-ammonia (13N-NH3) to track perfusion. With these combination of radiotracers, we will be able to quantitatively measure myocardial metabolism and its reliance on different pathways that may be influenced by metformin.

Consecutive patients in Met-HeFT will be recruited at the time they are enrolled in the trial to be included in the sub-study. The decision to enroll in this sub-study will have no effect on their enrollment in Met-HeFT. After enrollment, patients will undergo a PET scan using two radiotracers: F18-FDG and 13N-ammonia. Scans will occur prior to initiation of the study drug and at the 6 month end of study mark. Patient randomization will be maintained and both the study participants, coordinators and investigators will be blinded to patient assignment.

Inclusion/Exclusion Criteria: Any patient enrolled and meeting all inclusion criteria for Met-HeFT will be eligible to elect for inclusion into this sub-study.

Pregnancy Test: Women of childbearing potential will provide a urine specimen to determine if they are pregnant. Pregnant women will be excluded from the study. The source of the urine specimen will be from Columbia and/or NYPH Subjects/Patients or repositories managed by Columbia. The specimen will be labeled with direct identifiers.

Imaging Procedures: Each patient will undergo two cardiac PET/CTAC scans using a Siemens mCT scanner: at the beginning of the study and at the end of the trial (6 months). During the PET/CTAC scan each patient will receive 2 subsequent radiotracers intravenously; dose parameters will be consistent with the principles of ALARA. Scanning time (when patients are being imaged under the camera) will be 30-75 minutes. Subjects will be asked not to eat anything after midnight before the scan. Subjects may take their prescribed medications before and after the imaging study. For the PET-CTAC scans patients will receive about 19.34 mSv effective dose of radiation (9.65 mSV per scan visit). In comparison the background radiation a person is exposed to is 3.1 mSv.

Dosage of each radiotracer will be determined by weight, according to the following parameters:

- 13N-NH3 [10 mCi standard; 15-20mCi for obese persons]
- 18F-FDG - 0.143mCi/kg [5-15 mCi range, 10mCi expected]

Participant will have an IV inserted prior to going under the camera. The order of tracers is as follows:

- Inject with 13N-Ammonia, 10cc saline flush, Acquisition: 10-15 min
- Inject with 18F-FDG, 10cc saline flush, Acquisition: 20 min or 60 min

Total time under scanner: 30 min or 75 min

Imaging parameters:
CT attenuation correction scan:
Collimation: 16 x 1.2 mm
Tube Voltage: 120 kVp
Tube Current: 25 mAs
Rotation: 0.5 sec
Pitch 1.5
Slice Thickness: 3 mm
Slice Interval: 3 mm
SFOV for transmission: 500 mm
Reconstruction diameter: 300 mm
Reconstruction kernel: B19f
Reconstruction window: Abdomen

Emission scan:
Acquisition: List Mode
Recons: AC Static
Reconstruction Algorithm: Iterative
Iterations: 3
Image Size: 128
Subsets: 24
Zoom: 2
Filter: Butterworth
FWHM: 10
Match CT Slice Location: Off
Trigger/Gates: N/A
Scatter Correction: On
Delay: N/A sec
Data Management

Specific study risks

Study Drug: Metformin is a biguanide oral anti-hyperglycemic agent which generic formulation is available. It is not standard of care in heart failure patients without diabetes and thus patients in this study will have never been exposed to metformin prior to this study.

The main known adverse reaction to metformin is lactic acidosis. Metformin associated lactic acidosis (MALA) is exceedingly rare and is manifested as nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence. The incidence of MALA is exceedingly rare approximately 0.03 to 0.06 per 1000 patient years (32). In post marketing data analysis, there have been 47 documented MALA events in 1 million users. Metformin-associated lactic acidosis is characterized by elevated blood lactate concentrations (>5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate:pyruvate ratio. According to FDA insert, metformin associated lactic acidosis primarily occurs in patients with renal impairment. Thus to minimize the risk of adverse, we have added a safety time point to measure renal function during the course of the study. We will follow guidelines from the FDA which limit initiation of Metformin to patients with GFR's over 45 ml/min*1.73m^2 (23). If the GFR drops to between 30 and 45 ml/min*1.73m^2, despite the fact that the FDA allows continuation of metformin until a GFR of 30 ml/min*1.73m^2 we will dose reduce to 1 gram total per day of study drug as per American Diabetes Association Guidelines(33).

Study drug treatment will be discontinued in the following situations: 1) when subject withdraw consent, 2) in case of pregnancy, 3) when subjects develop severe renal dysfunction (defined as estimated GFR <30 ml/min*1.73 m^2), or 4) when subjects develop a condition which, in the investigator's judgment, precludes further therapy (please see Data Safety Monitoring Plan). Temporary discontinuation of the drug will occur if the patient is to undergo a procedure that include iodinated contrast agent that could affect renal function. Discontinuation will have no consequence on regular patient care. There will be no dose modifications of the study medication as there is none indicated by the FDA.

Blood Draw: Phlebotomy is a commonly used medical procedure for screening and follow-up of disease. Efforts to decrease the risks associated with blood draws include using highly experienced staff, applying external pressure to the site of the blood draw for a specified time following the draw, and the use of aseptic technique throughout the procedures. The amount of blood phlebotomized for analysis (20 mL) is not anticipated to be associated with significant risk.

Cardiopulmonary exercise test: These tests can be associated with dizziness, chest pain, shortness of breath, and fatigue. These symptoms are judged as likely to occur in at least some participants. In rare cases arrhythmia, syncope, or even death have been reported although we expect minimal chance of these more significant events. All six-minute walk testing and cardiopulmonary exercise testing will be performed in the presence of healthcare staff trained to respond to emergencies and certified in Advanced Cardiac Life Support procedures.

Data and Safety Monitoring Plan

1. Informed consent, Personal Identification

Upon recognition of eligible subjects by the primary cardiologist/heart failure specialist and patients' willingness for participation, the study team will be notified and review the patients' willingness as documented. The investigator will review all the inclusion and exclusion criteria as outlined in the proposal. The principal investigator will obtain an appropriately signed and witnessed informed consent and HIPAA authorization form. All participants in this study, including co-investigators and research staff have been certified in Good Clinical Practices. All subjects will be assigned a unique identification (ID) number by the study. This ID number will be used on all clinical measurement forms, questionnaires, databases, and computer data entry screens. This number will be linked to subjects only in individual charts maintained in secure storage areas. Blood and urine specimens will be labeled with an institution-specific record number and sent to the Center for Advanced Laboratory Medicine (CALM) at Columbia University Medical Center for processing; results will be tracked through password-protected, access-controlled electronic medical record systems. The laboratory results will be entered by study personnel into a password protected study database containing only the study ID number as an identifier. The identification of subjects will not be included in any description or publication of the results. The protocol will be approved by the Institutional Review Board (IRB). A Data and Safety Monitoring Board (DSMB) composed of three independent cardiologists (Dr. Veli Topkara, Dr. Matthew Lewis and Dr. Susan Restaino) will be established and all adverse events will be promptly reported and updates will be sent to the institutional IRB. The Data Safety Monitoring Board will meet prior to the start of the trial and agree on safety measures outlined in this protocol. This will include defining it deliberative process, criteria for un-blinding or unmasking, criteria for triggering an unscheduled review and voting procedures. They will also meet both with the PI and in subsequent closed sessions to review any adverse events that occur throughout the protocol. The DSMB will meet at least one time every six months to review any events. The PI will notify the DSMB and the IRB of any serious adverse events within 24 hours of their occurrence. The DSMB will not monitor this trial for any efficacy boundary given its small nature.

We plan to collect and store biological samples for later batch analysis. These samples will be stored in the Columbia University, Dr. Colombo Biorepository Lab. Subjects will be fully informed regarding the storage and potential future use of their samples during the consent process for the study.

2. List of specific tests that will be done to monitor patient safety

The following tests will be performed to ensure patients' safety:

a) Serum chemistry (creatinine) and venous lactate on day 0, 30 and 180
b) Vital Signs on day 30 and 180
c) Physical Exam on day 180
d) Adverse Event check at 30 days after endpoint of the trial (after last known dose of either placebo or study drug)

3. What adverse events/toxicities are expected?

Three safety outcomes have been designated:

a) Worsening renal function: Decline in eGFR to <45ml/min*1.73m^2, day 30
b) Venous Lactate: Rise in venous lactate level to ≥2.0mmol/L on day 30

c) Hypoglycemia defined as a fasting glucose <60mg/dL on day 30

4. What are the serious adverse events?
Serious adverse events have been designated:

a) Death
b) Life threatening illness
c) Congenital Abnormality
d) Hospitalization
e) Venous Lactate: Rise in serum lactate ≥2mmol/L, at any point
f) Hypoglycemia: Fasting glucose <60mg/dL, at any point

GFR falling below 45ml/min is defined as a safety event because it requires dose adjustment however it is not defined as a serious adverse event.

Specific responses to anticipated possible adverse events are detailed below:

Table 2: Serious Adverse Events

Adverse Event	Action
Death	Discontinuation of study drug. DSMB will unblind the allocation and determine if the death was related to the study drug.
Life threatening illness	Discontinuation of study drug if it is either 1) unsafe to continue for medical reasons by either the treating physicians, the PI of the study, or the DSMB, or 2) if it deemed by the DSMB to related to the study drug. The DSMB will unblind the allocation and determine if the illness is related to the study drug.
Congenital Abnormality	Pregnancy is an exclusion criteria for this study and patients will be advised not to become pregnant during this study. However, if we detect a pregnancy that occurs during the study (there is a pregnancy test at the end of study), we will stop the study for that patient. We will mandate that we follow the patient until after birth to determine if there is a congenital abnormality. If we detect this event, the DSMB will be required to unblind the allocation (if the trial is ongoing) and determine if the congenital abnormality is related to the study drug.
Hospitalization	Discontinuation of study drug if it is either 1) unsafe to continue for medical reasons by either the treating physicians, the PI of the study, or the DSMB, or 2) if it deemed by the DSMB to related to the study drug. The DSMB will unblind the allocation and determine if the hospitalization is related to the study drug.
Venous Lactate rises to >2mmol/L	Discontinue study drug, de-identification of study medication. Repeat lactate daily until normalizes. Contact primary cardiologist. Consider inpatient hospitalization.
Fasting Serum Glucose <60mg/dL	Discontinue current regimen. Administer patient oral glucose. Repeat value until normalizes. Referral to primary physician/cardiologist. Referral to ED if for referral or assessment if symptomatic and non-responsive to glucose tabs.

Renal Impairment for already enrolled patients

Glomerular Filtration Rate	Action
GFR≥45ml/min/1.73m^2	No action
GFR 30 - 44ml/min/1.73m^2	Reduce total dosage to 500mg twice a day. Schedule follow up basic metabolic panel in 3 months if GFR measurement occurs >3 months from scheduled end of trial. If follow up GFR is greater than 45 ml/min/1.73m^2, then patient can revert dosage to 2 grams per day. If GFR is less than 30 ml/min/1.73m2, study drug and patient enrollment will be terminated.
GFR <30ml/min/1.73m^2	Stop Drug and patient enrollment in trial

5. Reporting of adverse events/adverse drug reactions

Adverse events (AEs) will be reported to the IRB and the DSMB. Adverse events will be reported on a weekly basis to the DSMB and serious adverse events will be reported to the IRB and DSMB within 24 hours of being detected.

6. Who will review AEs and other safety data?

Adverse events will be reviewed on a weekly basis by three independent cardiologists (Drs. Veli Topkara, Matthew Lewis and Susan Restaino). Serious adverse events will be reported to the Columbia IRB per institutional guidelines within 24 hours.

7. Who is monitoring the study?

The principal investigator/co-Investigators will collect and manage the data for the entire study. The DSMB will monitor the safety of the study.

8. DSMB Meetings:

The DSMB will meet at 6 month scheduled intervals. They can also meet, at their discretion, in response to any SAE that is reported. At a meeting, the DSMB can request unblinding of the trial and for a statistical analysis of safety events without the PI present. In response to the analysis, they can recommend: continuation of the study without modification, continuation of the study with suggestion, continuation of the study with mandatory changes, suspension of enrollment and termination of study. All recommendations will be part of a DSMB report and will be submitted to the IRB after every meeting.

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