Study Title: Vericiguat in Patients with Metabolic Syndrome or Type 2 Diabetes Mellitus and Coronary Vascular Dysfunction

NCT Number: 05711719

Date: June 3, 2025

JHM IRB - eForm A – Protocol

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1. Abstract

Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

To this day, cardiovascular disease (CVD) continues to be the leading cause of death in the United States[1]. Although there has been a decrease in cardiovascular mortality, largely attributed to the identification and successful management of major risk factors such as hypertension and dyslipidemia, the rate of decline has recently slowed. The increasing prevalence of diabetes and of other, called "residual" risks that have not been adequately addressed, are two of the main reasons why several hundred thousand Americans continue to experience myocardial infarctions and the consequences of the infarction each year[1]. Important risk factors for these adverse events are diabetes and the metabolic syndrome, an incompletely addressed risk factor (RR 2.35, [95% CI 2.02-2.73])[1]. The components of MetS (abdominal obesity, high blood pressure, impaired fasting glucose, dyslipidemia) are associated with inflammation, which is thought to have significant adverse effects on the vascular endothelium[2,3]. Endothelial dysfunction is a driver of the development and progression of coronary atherosclerosis, initiating and propagating processes which ultimately result in coronary clinical events[4]. Endothelial dysfunction, therefore, is one of the "final common pathways" for the impact of multiple atherosclerotic risk factors. Our team has developed and implemented non-invasive MRI methods to evaluate coronary vascular function in healthy individuals and in those with cardiovascular risk factors and coronary disease by assessing changes in coronary vascular dimension and flow accompanying isometric handgrip exercise, an endothelial-dependent stressor.

Evaluating endothelial dysfunction by assessing coronary vascular function can thus not only index the adverse impact of multiple risk factors but also provide the opportunity to evaluate the benefit of an intervention which targets coronary vascular dysfunction. The synthesis and release of nitric oxide (NO) is an essential component of normal endothelial function. NO's downstream effects include not only vasodilation and a resultant increase in coronary flow, but also anti-proliferative, anti-coagulant, anti-adhesive, and anti-inflammatory effects[5]. Its beneficial vascular effects are mediated by stimulation of the soluble guanylyl cyclase (sGC) enzyme, which converts guanosine-5'-triphosphate (GTP) to the second messenger guanosine monophosphate (cGMP). cGMP activates GMP-dependent protein kinases (PKG) which in turn phosphorylate several proteins that have vasorelaxant and anti-atherosclerotic effects[6]. Reduced bioavailability of NO associated with endothelial dysfunction, therefore, leads to loss of its important downstream effects, and therefore may be one of the important mechanisms responsible for progression of atherosclerosis and its associated adverse clinical outcomes[7].

Hypothesis: Vericiguat improves coronary vascular endothelial function in patients with metabolic syndrome or type 2 diabetes mellitus and impaired coronary vascular function.

We will perform a placebo-controlled, randomized, double-blind study to test the hypothesis, that the administration of vericiguat, which increases soluble guanylate cyclase (sGC) activity despite low NO, improves coronary vascular function in patients with the metabolic syndrome or type 2 diabetes mellitus and coronary vascular dysfunction. We will be using MRI studies to evaluate coronary vascular function in response to study drug administration.

2. Objectives

(include all primary and secondary objectives)

Primary Objective:

1. To characterize the impact of vericiguat on global (micro- and macro- vascular function) coronary vascular function by comparing the responses prior to, and following, vericiguat administration, to isometric handgrip exercise, an endothelial-specific stressor in patients with the metabolic syndrome or type 2 diabetes mellitus and baseline coronary vascular dysfunction.

Secondary Objective:

1. To compare changes in resting, pre-isometric hand exercise (IHE), coronary blood flow before and following study drug administration within and between the vericiguat and placebo groups.

2. To compare coronary flow and cross-sectional area prior to the isometric handgrip exercise before, and following study drug administration within and between the vericiguat and placebo groups.

3. To obtain serum, plasma, and urine laboratory studies to characterize markers/mediators of inflammation and of the nitric oxide signaling pathway prior to and following up-titration of the study drug.

3. Background

(briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Coronary vascular function can be assessed by examining changes in coronary blood flow and dimension following initiation of a coronary endothelial-dependent stimulus. If function is normal, the stimulus results in a significant increase in coronary blood flow and dimension, but if abnormal, the result is only a small, or no, increase, or even a decrease. These changes were previously assessed via placement of a catheter within the studied artery[8]. Because that procedure is invasive, the associated risks did not justify most studies in individuals without known or suspected significant stenoses or in the serial studies required to assess the benefit of an intervention designed to improve coronary vascular function. The Hopkins investigator team for this proposed study, however, has extensive experience in using MRI methodology to non-invasively and safely study coronary vascular function in healthy individuals[9] and in those with pro-inflammatory states[10] and coronary disease[11] and to perform serial studies to assess the impact of interventions[12].

Regulation of coronary blood flow occurs at the site of resistance vessels and allows for optimal matching between oxygen supply and demand. Normal vascular responses to endothelial-dependent stimuli are primarily mediated by nitric oxide (NO)[9]. Downstream effects of NO include vascular smooth muscle vasodilatation with a resultant increase in coronary dimension and flow. There are, as well, anti-proliferative, anti-coagulant, anti-adhesive, and anti-inflammatory effects of NO[5]. Reduced bioavailability of NO with resultant impaired downstream signaling is thought to be one of the central consequences of many established and residual risk factors and one responsible mechanism for the impact of these risk factors on progression of atherosclerosis and its associated adverse clinical outcomes[7]. NO is formed by a reaction catalyzed by endothelial nitric oxide synthase (eNOS), present in both endothelial and red blood cells[13], which uses L-arginine, NADPH, H^+, and O_2 substrates to form NO as well as citrulline, H_2O, and NADP. Its beneficial vascular effects are mediated by stimulation of soluble guanylyl cyclase (sGC), which converts guanosine-5'-triphosphate (GTP) to the second messenger guanosine monophosphate (cGMP). cGMP activates GMP-dependent protein kinases (PKG) which in turn phosphorylate several proteins that have vasorelaxant and anti-atherosclerotic effects[6].
Decreased eNOS activity or "uncoupling" of the eNOS reaction in the setting of established and residual risk factors associated with pro-inflammatory and oxidative stresses decreases NO bioavailability which not only results in loss of NO's beneficial effects but also may result in the formation of peroxynitrite, which generates free radicals[14].

Vericiguat stimulates sGC both independently of, and synergistically with, NO[15]. Vericiguat enhances the cGMP pathways by directly stimulating sGC through a binding site independent of NO, and it sensitizes sGC to any bioavailable NO by stabilizing NO binding to the sGC binding site[15]. Thus, the beneficial attributes of NO bioavailability may accrue despite the decreased bioavailability associated with the metabolic syndrome. Our study will test whether the coronary vascular response to isometric handgrip exercise (IHE), an endothelial-dependent stressor, improves from the study performed prior to and that performed following the administration of vericiguat. We will also test whether the response differs from the response in those randomized to placebo and whether the results on the follow-up exams differ between those randomized to vericiguat and those randomized to placebo.

If successful, a sGC mediated prevention strategy could be tested to learn whether improved coronary vascular function would improve outcomes in those with, and at risk for, the development and progression of coronary vascular disease (Figure 1).

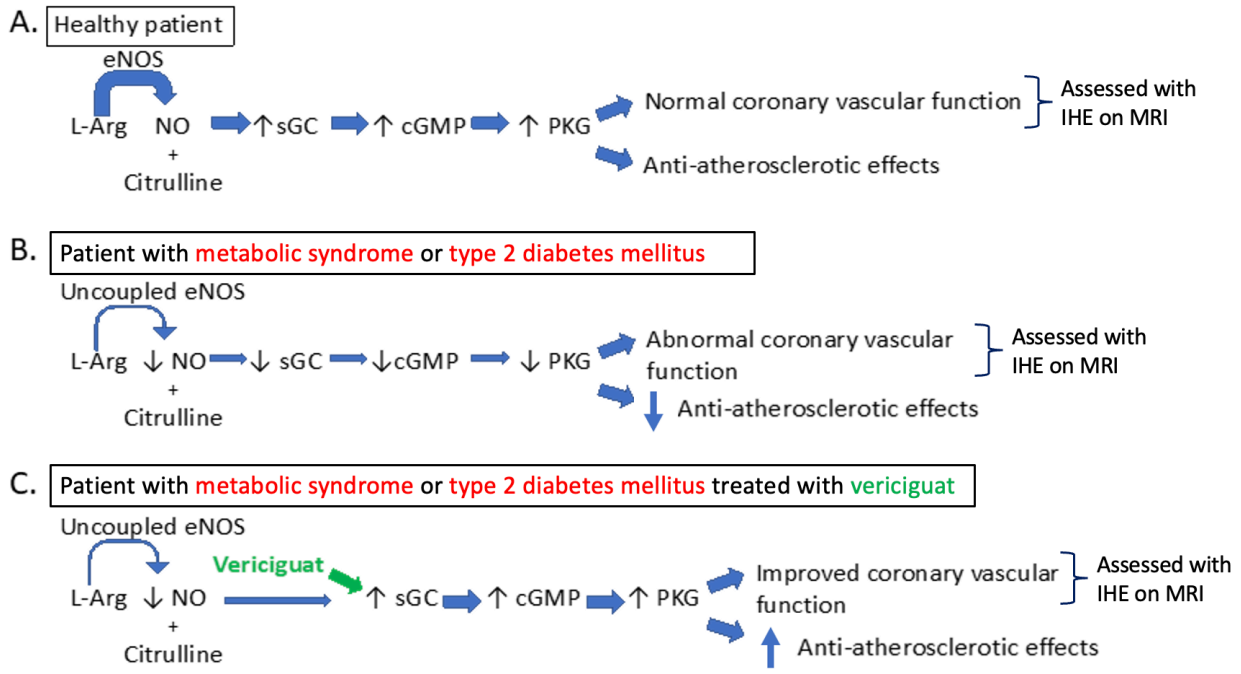

Figure 1: Hypothesis: Vericiguat improves coronary vascular endothelial function in patients with the metabolic syndrome or type 2 diabetes mellitus and impaired coronary vascular function. L-Arg= L-arginine, NO= nitric oxide, eNOS= endothelial nitric oxide synthase, sGC= soluble guanylyl cyclase, cGMP= cyclic guanosine monophosphate, PKG= cyclic GMP–dependent protein kinases

We have extensive experience using magnetic resonance imaging (MRI) to assess coronary endothelial-dependent vascular function non-invasively in healthy individuals and in those with coronary disease[11] and pro-inflammatory states[10] using isometric handgrip exercise, an endothelial NO pathway-specific stressor[9]

Our MRI technique can detect meaningful changes in coronary vascular function in people with impaired baseline coronary vascular function following an intervention and we will use this methodology in the proposed study to assess the impact of stimulating sGC with vericiguat on coronary vascular function in patients with impaired baseline function.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Participants who meet enrollment criteria will be asked to provide consent. Women of reproductive capacity will undergo a urine pregnancy test and those who are pregnant will be excluded from further participation. Men over 40 years of age and women over 50 years of age with no clinical coronary angiographic study within the prior 36 months demonstrating no significant coronary disease in at least one major coronary artery will undergo a research CT scan to measure coronary calcium score. If the score is ≤10 in at least one major coronary artery, they, and those who meet the other eligibility criteria will undergo assessment of coronary vascular function using MRI methodology. Those with normal function will not undergo any additional study

procedures. Those with abnormal global (micro- and macro- vascular function) coronary vascular function will undergo an echocardiographic study to assess systolic and diastolic function and baseline laboratory studies. They will then be randomized to vericiguat or placebo in a 2:1 ratio. Following randomization, the participants will undergo a study drug titration phase as follows: Initial 2.5 mg/day for two weeks, then 5 mg/day for two weeks, and then 10 mg/day for two weeks. Blood pressure and clinical symptoms will be assessed following each two-week period to determine whether the up titration should be performed, as guided by evaluation of blood pressure and clinical symptoms[21]. Identical appearing placebo tablets will also be titrated so as to maintain double-blinding of the investigators and participants. Next, study participants will continue the maximally tolerated maintenance dose for an additional 6 weeks. The study concludes with a final assessment of global (micro- and macro- vascular function) coronary vascular function with the same MRI protocol and follow-up laboratory studies and an echocardiogram. (Figure 2)

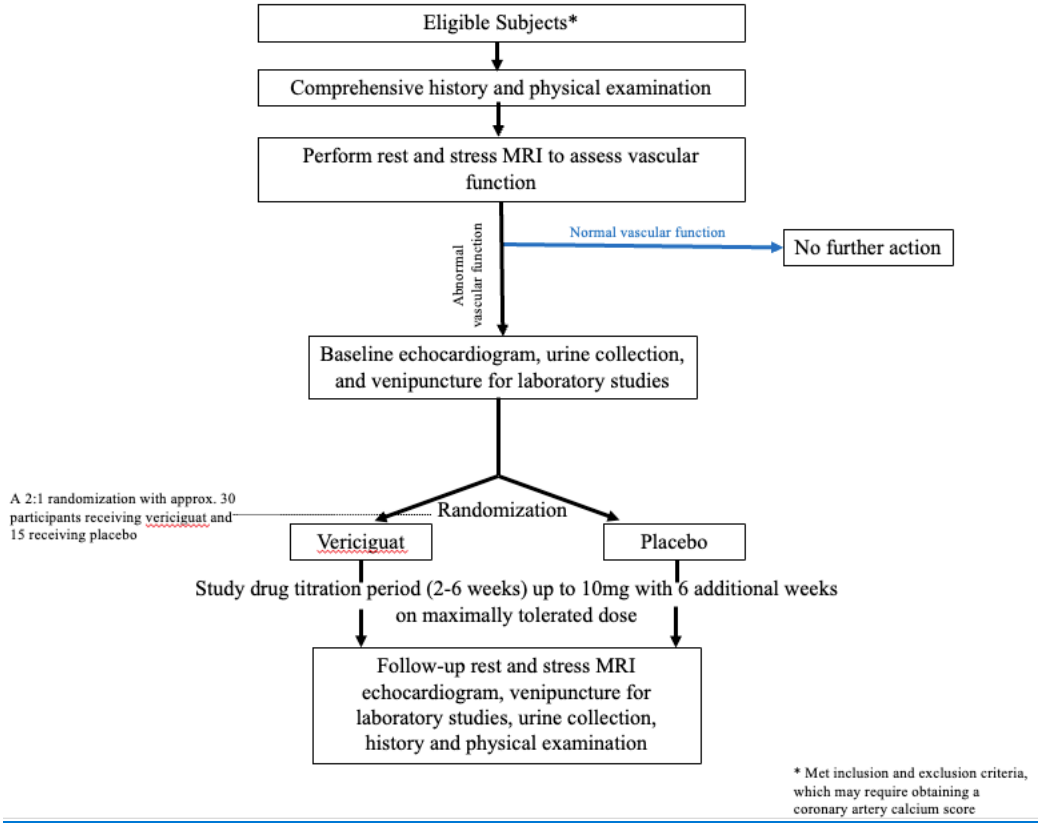

Figure 2: Study overview: Vericiguat in Patients with Metabolic Syndrome or type 2 diabetes mellitus and Coronary Vascular Dysfunction.

Study type: Interventional-treatment

Trial design: Randomized

Number of Enrolled Participants: 45 total participants, 30 in the vericiguat and 15 in the placebo group.

Coronary Artery Calcium (CAC) Score

For men >40 and women >50 years of age who have not had coronary angiography (including CT angiography) within the prior 36 months, a CAC score will be determined. A computed tomography (CT) scan will be performed without contrast agents with 10 to 15 minutes of total room time at about 1 to 2.5 mSv of radiation[22].

MRI methods for Coronary Vasoreactivity:
MR will be performed on a 3 T CMR scanner (Achieva, Philips Healthcare, Best, NL) in the morning after an overnight fast. For endothelial function imaging, alternating anatomical and velocity-encoded images will be collected at baseline and during approximately 6 min of continuous isometric handgrip exercise (IHE). The exercise is performed using a handgrip dynamometer at 30% of each participant's maximum force, which is determined prior to the MRI study, as previously reported[9,23]. Images will be taken perpendicular to a proximal or mid-straight segment of the coronary artery and/or coronary sinus best identified on survey scans[11]. Cross-sectional anatomical (bright blood sequence) and phase contrast velocity encoded spiral CMR will be obtained using single breath-hold cine sequences with reproducibility of the techniques published previously[9,23]. The MRI will be used to measure cross-sectional area (CSA), coronary flow velocity (CFV), and to calculate coronary blood flow (CBF) changes in response to the IHE. If technical problems prevent adequate interrogation of the coronary response, the participant will be asked to undergo a second screening MRI study. Coronary MRI will be repeated following the study drug administration period with an identical protocol with special attention taken to interrogate the same coronary segments as those studied at baseline, using anatomic landmarks of coronary ostia and branch vessels- as we have done in the past[9] and to replicate the identical MRI IHE protocol.

MRI analysis:
Images will be analyzed blinded to study-drug assignment and clinical information for CEF (e.g., change in cross-sectional area (CSA), coronary flow velocity (CFV), and calculated coronary blood flow (CBF), as previously validated and described[9,23]. Coronary CSA will be quantified using a semi-automated software tool (Cine version 3.15.17, General Electric, Milwaukee, WI, USA) as previously reported[11]. For CBV and CBF measurements, phase-contrast images will be analyzed using semi-automated commercial software (FLOW Version 3.0, Medis, NL); the coronary blood-flow (CBF, in ml/minute) is derived from diastolic coronary flow velocity (CFV, in cm/sec) as previously described[9,11]. Only native coronary segments will be analyzed. Our prior studies using this methodology demonstrated low intra- and inter-observer variability with good reproducibility over eight weeks[9].

Echocardiography
Participants may also be asked to undergo echocardiographic studies to evaluate cardiac function. Systolic function will be assessed by measuring the ejection fraction (EF), calculated as stroke volume divided by the end-diastolic volume. Diastolic function will be assessed by looking at the annular e' velocity, the septal and lateral e' velocities, the average E/e' ratio, the LA volume index and the peak TR velocity[24]. We will obtain images before and after a 90 second passive leg raise as well to assess hemodynamic variations [25]. Strain and strain rate measurements will be obtained

using myocardial speckle tracking to evaluate regional myocardial contractile function[26].

b. *If your study involves data/biospecimens from participants enrolled under other research studies with a written consent or under a waiver of consent, please list the IRB application numbers for those studies. Please note: Certificate of Confidentiality (CoC) protections applied to the data in source studies funded by NIH or CDC will extend to this new study if the funding was active in 2016. If this situation applies, Section 36, question 6 in the application will need to be answered "Yes" and "Hopkins Faculty" should be selected in question 7. No other documents are required.*

Not applicable

c. Study duration and number of study visits required of research participants.
Study Duration: 24 months
Number of study visits per participant: 4 to 8, depending on whether the MRI and echo will be performed on the same day and how many titration steps are performed.

d. Blinding, including justification for blinding or not blinding the trial, if applicable.
This study will be double-blinded to minimize bias and maximize the validity of the results. All study personnel and the participants will be blinded to study drug assignment to avoid bias in data collection and analysis. The Hopkins Investigational Pharmacy will have access to study drug assignment if there is a clinical need for the subjects' treating physicians to be aware of assignment.

e. Justification of why participants will not receive routine care or will have current therapy stopped.
Participants will continue to receive routine care and will not have any current therapy stopped.

f. Justification for inclusion of a placebo or non-treatment group.
This study is intended to develop an intervention and does not require participants to forgo treatment they would otherwise receive. Vericiguat is not considered a treatment for this patient population so the placebo group is not considered a "non-treatment" group.

g. *Definition of treatment failure or participant removal criteria.*
There is no defined treatment failure.
Participation in this study is on a volunteer basis. As such, individuals may decline continued participation. If new data appear indicating risks not presently foreseen associated with administration of the study drug or any of the study procedures, the study may be terminated and participants removed.

h. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.
The study drug is not considered a treatment and thus will no longer receive the drug when the study ends or if participation ends prematurely.

i. If biological materials are involved, please describe all the experimental procedures and analyses in which they will be used.

The experimental procedure is venipuncture. Analyses for routine chemistry and hematology studies as well as markers/mediators of inflammation and the nitric oxide signaling pathway will be performed.

5. Inclusion/Exclusion Criteria

Inclusion Criteria:

- Age range 35-85 years
- Presence of type 2 diabetes mellitus or of the metabolic syndrome defined by the NCEP ATP III definition, with at least three of the following five criteria:
  - waist circumference > 40 inches (men) or > 35 inches (women)
  - blood pressure > 130/85 mmHg
  - fasting triglyceride (TG) level > 150 mg/dL
  - fasting high-density lipoprotein (HDL) cholesterol level < 40 mg/dL in men or < 50 mg/dL in women
  - fasting blood glucose > 100 mg/dL or HbA1c ≥5.7%
- Either one of the following:
  - Men ≤ 40 or women ≤ 50 years of age with no history or symptoms of ischemic heart disease, or
  - Men >40 or women >50 years of age with either one of the following:
    - a coronary angiography (including CT angiography) within the past 36 months showing no significant coronary artery disease in at least one major coronary artery, defined as >50% stenosis of the left main coronary artery and/or >70% stenosis of another major coronary vessel, or
    - a coronary artery calcium score obtained within the prior 36 months or if no prior calcium scan, one performed as a research study following consent with a score ≤10 in at least one major coronary artery.
- IHE-induced %-change in coronary flow < or equal to 13%

Exclusion Criteria:

- Systolic blood pressure <110 mm Hg
- Current or anticipated use of long-acting nitrates, a sGC stimulator, or phosphodiesterase type 5 (PDE5) inhibitors
- Hematocrit <30%
- Unable to understand the risks, benefits, and alternatives of participation so as to provide informed consent
- Women who are pregnant.
- Women who are breastfeeding
- Women with reproductive capacity not using an acceptable form of contraception
- History of claustrophobia
- Inability to lie flat and still for 45 minutes

- Presence of non-MR-compatible objects or devices, such as intra-orbital debris, intra-auricular implants, intra-cranial clips, an implanted defibrillator or a pacemaker
- History as a machinist, welder, metal worker or a similar activity that poses the risk of metal exposure to the eyes

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

As detailed above, we propose using vericiguat to "bypass" the requirement for nitric oxide synthesis in an attempt to improve endothelial function and hence coronary vascular function in individuals with preexisting dysfunction[27]. If successful, a sGC-directed prevention strategy may improve coronary vascular function and decrease cardiovascular risk. The dose and titration described to reach the dose is that used for patients with heart failure and approved by the FDA to treat those patients[28].

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Vericiguat is approved for reducing the risk of cardiovascular death and heart failure hospitalization following hospitalization or need for outpatient intravenous diuretics in adults with symptomatic chronic heart failure and ejection fraction less than 45%. The dose and route of administration are the same as that administered for this FDA approved indication. The dose is not changed from that used for the marketed drug.

c. *Justification and safety information if non-FDA approved drugs without an IND will be administered.*

We will be using an FDA approved drug.

7. Study Statistics

a. Primary outcome variable.

In a paired analysis, we hypothesize that there is a significant change in coronary flow and dimension with isometric handgrip exercise (IHE) in the group randomized to vericiguat from that measured at baseline, prior to the initiation of vericiguat, to that measured following vericiguat administration and up-titration. We will be using either a paired student t-test or a Wilcoxon test to examine this hypothesis.

In unpaired analyses, we hypothesize that the change in the vericiguat group from baseline to post-up titration with be greater than the change in the placebo group. We will be using either an unpaired student t-test or a Mann-Whitney test to examine this hypothesis

b. Secondary outcome variables.

We will conduct bivariate analyses to compare markers/mediators of inflammation and that of the nitric oxide pathway.

Other exploratory outcome variable that we are interested in include age, sex, and race. We will be using parametric and non-parametric tests for continuous variables and chi-square or Fisher's exact tests for categorical variables.

c. Statistical plan including sample size justification and interim data analysis.

All sample size calculations are based on 80% power and 5% alpha error for two-sided tests. We have prior studies with small sample sizes to inform our baseline expectations[12]. For our primary analysis, our minimum expected difference in change in coronary flow with IHE in the vericiguat group with our planned sample size of n=30 in the vericiguat group, allowing for 10% loss to follow-up at 8 weeks (n=27 remaining), with 80% power and an alpha of 0.05 is 7.8% ± 13.6%. The detectable effect size at 90% power is 9.1% ± 13.6%. (Figure 3).

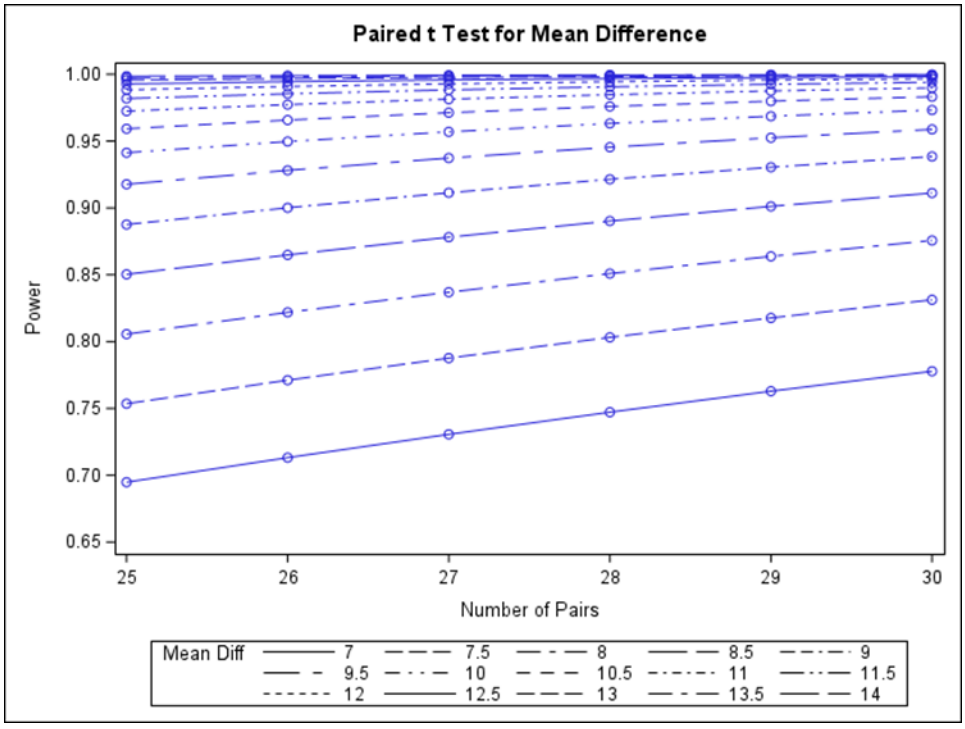

Figure 3: Power and sample size calculated for estimated difference in change in coronary flow with IHE from baseline to 8 weeks in the vericiguat group

The study investigators will be responsible for analyzing the study data to assess the completeness of data collection, to assess any adverse events, and to identify any findings which may have clinical relevance. This will be performed while maintaining the blind. A Data Safety and Monitoring Committee will review and, if necessary unblind, the data when the outcomes of the first third (n=15) of the anticipated enrolled participants are available and at the end of the study. This committee may request to review/audit the data at any time.

The data will be maintained in a REDCap database.

The data will be unblinded following the completion of the protocol, and medical/scientific review has been completed, protocol violators have been identified and data has been declared complete, although the Hopkins Institutional Review Board and Data Safety and Monitoring Committee may request prior unblinding.

The routine safety laboratory studies will be analyzed within 48 hours of collection. The MRI data will be analyzed within two months of each study

d. Early stopping rules.

The study will be stopped early on the recommendation of the Data Safety and Monitoring Committee or if there is any new published information regarding the safety of the study drug or the study procedures.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Study Drug:

Vericiguat is available in an oral tablet formulation. These tablets may be crushed and mixed with water immediately before administration for patients with swallowing difficulties. There is a risk of developing hypotension as a result of receiving this medication. In the clinical trial for heart failure with reduced ejection fraction [28], patients who had concurrent or anticipated use of long-acting nitrates (e.g, isosorbide mononitrate, isosorbide dinitrate, transdermal nitroglycerin) were excluded. In the same trial, anemia developed in more patients in the vericiguat group than placebo (7.6% vs 5.6%), however, anemia was common at randomization and although vericiguat modestly lowered hemoglobin by 16 weeks, this effect did not further progress[29].

Serum Samples:

Obtaining samples may cause slight discomfort when the needle is inserted into the arm vein. The potential side effects of taking blood samples may include dizziness, soreness and/or bruising of the skin for several days. In very rare circumstances, bleeding or infection can develop at the needle puncture site. However, the procedure is performed by trained personnel using sterile and standard medical practices.

Cardiac MRI:

The risks of this study are the same as the risks of a patient receiving a clinical cardiac MRI exam.

All MRI equipment used in this study is the same as the equipment that is used for standard clinical care. There are no studies showing any health hazard associated with magnetic field exposure (Yamaguchi 2011 and Schenck 2000) itself.

Ferromagnetic objects may experience forces near the MRI scanner and elongated metallic implants may lead to unintended heating around the implant during MRI scanning. The potential for injury related to such objects is well described (Schenck 2000) and patients with such risks are excluded from participating in this study.

Echocardiography

A transthoracic echocardiogram uses ultrasound technology that is based on transducing harmless sound waves. It is noninvasive and does not use radiation.

Coronary artery calcium score:
CAC scoring is obtained using 1-2.5 mSv (depending on participant size) of ionizing radiation. By comparison, the average American is exposed to about 3 mSv of radiation from natural sources per year[30].

b. Steps taken to minimize the risks.

To protect against and minimize the potential risks of vericiguat, study participants will undergo a careful history as well as physical examinations at baseline and during the titration and follow-up visits to identify any potential or new health conditions which might increase the risk of taking the study drug. . Concurrent or anticipated use of long-acting nitrates, sGC stimulators or PDE5 inhibitors, which might potentiate any hypotensive effects is an exclusion criterion for participation in the study. Those with a hematocrit of <30% will also be excluded. The study drug will be titrated every two weeks to a maximum dose of 10 mg with close monitoring of the systolic blood pressure. In the clinical trial for HFrEF[28], the main reason for not up-titrating to target per protocol was a SBP in the 90-100 mmHg range. Dose decreases were rarely required for SBP <90 mmHg, and the 10 mg dose was considered safe and well tolerated. The study drug will not be further up-titrated if the systolic blood pressure is< 110 mmHg. If the systolic pressure is <100 mmHg, the dose will be decreased. Trained personnel will perform the blood collection procedure and will make every effort to minimize any associated risks or discomfort.

The MRI scanning will be performed using the same MRI Device Safety Protocol used for the device MRI study (Protocol NA_00051707).

c. Plan for reporting unanticipated problems or study deviations.

All clinically significant unanticipated problems and study deviations will be reported to the DSMC and the IRB according to The Johns Hopkins Medicine Institutional Review Board published guidelines. The anticipated three-member DSMC will include at least one cardiologist familiar with the management of patients with coronary disease, and a statistician. The DSMC will have access to study drug assignment if requested and will make recommendations to Dr. Leucker regarding any safety concerns and recommendations regarding continuation of the study

d. Legal risks such as the risks that would be associated with breach of confidentiality.

Once the data are acquired, they will be assigned a code for each subject with identification secured and accessible only to the principal and other investigators, and the research coordinators. Patient clinical information such as copies of clinical studies and imaging reports will be filed in a locked filing cabinet with access under control of Dr. Leucker, the other investigators, and study coordinators. Patient information summarized and/or converted into electronic form (tables, images, etc.) will be identified by the assigned code. We will abide by the Johns Hopkins Institutional policy that all identifiers in images and data acquired under IRB-approved research protocols must be removed if they leave the institution, for example in presentations.

e. Financial risks to the participants.

All study related costs will be paid from research sources, as stated in the consent form

9. Benefits

a. Description of the probable benefits for the participant and for society.

There will be no direct benefit to individuals who participate in this study. Participants in clinical trials may benefit from receiving closer follow-up and improved access to physicians when compared to those not participating in such studies. If the results regarding the safety and efficacy outcomes demonstrate a favorable effect of vericiguat, then their participation in this study would expect to benefit future patients with the metabolic syndrome or type 2 diabetes mellitus and endothelial dysfunction.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Each study participant will receive $100 for each visit during which an MRI will be performed and $60 for other visits. In addition, participants will be reimbursed for transportation and parking expenses and given a $10 meal voucher following procedures requiring prior fasting.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There is no cost to the participants related to the study procedures or drug.

12. Transfer of Materials

Transfer of biospecimens from Johns Hopkins to another organization for research purposes and receipt of biospecimens from an outside organization for your research must adhere to JHU policies for material transfer (https://ventures.jhu.edu/faculty-inventors/forms-policies/) and biospecimen transfer (https://hpo.johnshopkins.edu/enterprise/policies/176/39187/policy_39187.pdf?_=0.622324232879).

***Please complete this section if your research involves transfer or receipt of biospecimens**.*

*a. Will you **receive** biospecimens from an external entity for this research? [Yes/No].*
If "Yes", please confirm you will secure an MTA/research agreement from the appropriate office (JHTV/ORA) prior to transfer.
See: https://ventures.jhu.edu/technology-transfer/material-transfer-agreements/ .

No

*b. Will you **transfer** biospecimens to an external entity as part of this research? [Yes/No]*
If "Yes", please address each of the following:

No

1) *Describe the nature of the research collaboration with the external entity and the rationale for the transfer. (Include an explanation of your intellectual contribution to the design of the research study, resulting data and sharing, and participation in the planned publications.)*

2) *Please confirm you will secure an MTA through the appropriate office (JHTV or ORA) prior to transfer.*
(See: https://ventures.jhu.edu/technology-transfer/material-transfer-agreements/.)

3) *If the biospecimens you intend to transfer were obtained through clinical or research procedures at Johns Hopkins and "Other" is selected in Item 4, Section 23, please submit the following items in that Section:*

   a. *A pdf version of a completed JHTV Online "Material Transfer Agreement Request Form for Outbound Material" https://ventures.jhu.edu/technology-transfer/material-transfer-agreements/* ***OR*** *a copy of the COEUS PD (Proposal Development Summary).*
   b. *A completed Biospecimen Transfer Information Sheet https://www.hopkinsmedicine.org/institutional_review_board/forms/.*
   c. *A signed and dated "De-identified Human Subject Certification" https://www.hopkinsmedicine.org/institutional_review_board/forms/*
   d. *Approval documents from recipient site, if applicable.*
   e. *Copies of the consent forms associated with the IRB protocols under which the biospecimens were collected, with language appropriate to this transfer highlighted.*
   f. *The name of the specialist you are working with in ORA to complete a contract/MTA.*

Please see the following website for more information about transferring human biospecimens to outside entities: https://www.hopkinsmedicine.org/institutional_review_board/news/announcement_transfer_human_biospecimens_outside_entities.html/ .

References:

1. Heart Disease and Stroke Statistics—2022 Update: A Report From the American Heart Association. https://www.ahajournals.org/doi/epub/10.1161/CIR.0000000000001052 doi:10.1161/CIR.0000000000001052.

2. Tziomalos, K., Athyros, V. G., Karagiannis, A. & Mikhailidis, D. P. Endothelial dysfunction in metabolic syndrome: Prevalence, pathogenesis and management. *Nutr. Metab. Cardiovasc. Dis.* **20**, 140–146 (2010).
3. Grundy, S. M., Brewer, H. B., Cleeman, J. I., Smith, S. C. & Lenfant, C. Definition of Metabolic Syndrome. *Circulation* **109**, 433–438 (2004).
4. Davignon, J. & Ganz, P. Role of Endothelial Dysfunction in Atherosclerosis. *Circulation* **109**, III–27 (2004).
5. Jones, S. P. & Bolli, R. The ubiquitous role of nitric oxide in cardioprotection. *J. Mol. Cell. Cardiol.* **40**, 16–23 (2006).
6. Tsai, E. J. & Kass, D. A. Cyclic GMP signaling in cardiovascular pathophysiology and therapeutics. *Pharmacol. Ther.* **122**, 216–238 (2009).
7. Lundberg, J. O., Gladwin, M. T. & Weitzberg, E. Strategies to increase nitric oxide signalling in cardiovascular disease. *Nat. Rev. Drug Discov.* **14**, 623–641 (2015).
8. Ong, P. *et al.* Clinical Usefulness, Angiographic Characteristics, and Safety Evaluation of Intracoronary Acetylcholine Provocation Testing Among 921 Consecutive White Patients With Unobstructed Coronary Arteries. *Circulation* **129**, 1723–1730 (2014).
9. Hays, A. G. *et al.* Coronary vasomotor responses to isometric handgrip exercise are primarily mediated by nitric oxide: a noninvasive MRI test of coronary endothelial function. *Am. J. Physiol.-Heart Circ. Physiol.* **308**, H1343–H1350 (2015).
10. Leucker, T. M. *et al.* Coronary Endothelial Dysfunction Is Associated With Elevated Serum PCSK9 Levels in People With HIV Independent of Low-Density Lipoprotein Cholesterol. *J. Am. Heart Assoc.* **7**, e009996 (2018).

11. Hays, A. G. *et al.* Noninvasive Visualization of Coronary Artery Endothelial Function in Healthy Subjects and in Patients With Coronary Artery Disease. *J. Am. Coll. Cardiol.* **56**, 1657–1665 (2010).

12. Leucker, T. M. *et al.* Evolocumab, a PCSK9-Monoclonal Antibody, Rapidly Reverses Coronary Artery Endothelial Dysfunction in People Living With HIV and People With Dyslipidemia. *J. Am. Heart Assoc.* **9**, e016263 (2020).

13. Leo, F. *et al.* Red Blood Cell and Endothelial eNOS Independently Regulate Circulating Nitric Oxide Metabolites and Blood Pressure. *Circulation* **144**, 870–889 (2021).

14. Karbach, S., Wenzel, P., Waisman, A., Munzel, T. & Daiber, A. eNOS Uncoupling in Cardiovascular Diseases - the Role of Oxidative Stress and Inflammation. *Curr. Pharm. Des.* **20**, 3579–3594.

15. Stasch, J.-P., Pacher, P. & Evgenov, O. V. Soluble Guanylate Cyclase as an Emerging Therapeutic Target in Cardiopulmonary Disease. *Circulation* **123**, 2263–2273 (2011).

16. Al-Daghri, N. M. *et al.* Whole Serum 3D LC-nESI-FTMS Quantitative Proteomics Reveals Sexual Dimorphism in the Milieu Intérieur of Overweight and Obese Adults. *J. Proteome Res.* **13**, 5094–5105 (2014).

17. Garbis, S. D. *et al.* A Novel Multidimensional Protein Identification Technology Approach Combining Protein Size Exclusion Prefractionation, Peptide Zwitterion−Ion Hydrophilic Interaction Chromatography, and Nano-Ultraperformance RP Chromatography/nESI-MS2 for the in-Depth Analysis of the Serum Proteome and Phosphoproteome: Application to Clinical Sera Derived from Humans with Benign Prostate Hyperplasia. *Anal. Chem.* **83**, 708–718 (2011).

18. Williams, S. A. *et al.* Plasma protein patterns as comprehensive indicators of health. *Nat. Med.* **25**, 1851–1857 (2019).

19. Leopold, J. A. & Loscalzo, J. The Emerging Role of Precision Medicine in Cardiovascular Disease. *Circ. Res.* **122**, 1302–1315 (2018).

20. Adhikari, S. *et al.* A high-stringency blueprint of the human proteome. *Nat. Commun.* **11**, 5301 (2020).

21. Armstrong, P. W. *et al.* A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy and Safety of the Oral Soluble Guanylate Cyclase Stimulator: The VICTORIA Trial. *JACC Heart Fail.* **6**, 96–104 (2018).

22. Greenland, P., Blaha, M. J., Budoff, M. J., Erbel, R. & Watson, K. E. Coronary Calcium Score and Cardiovascular Risk. *J. Am. Coll. Cardiol.* **72**, 434–447 (2018).

23. Hays, A. G. *et al.* Local coronary wall eccentricity and endothelial function are closely related in patients with atherosclerotic coronary artery disease. *J. Cardiovasc. Magn. Reson.* **19**, 51 (2017).

24. Nagueh, S. F. *et al.* Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J. Am. Soc. Echocardiogr.* **29**, 277–314 (2016).

25. Gadela, N. V., Muniz, J. & Chen, K. Passive leg raise induced variation in hemodynamic parameters in patients with diastolic dysfunction. *J. Am. Coll. Cardiol.* **77**, 1332–1332 (2021).

26. Dandel, M., Lehmkuhl, H., Knosalla, C., Suramelashvili, N. & Hetzer, R. Strain and Strain Rate Imaging by Echocardiography – Basic Concepts and Clinical Applicability. *Curr. Cardiol. Rev.* **5**, 133–148 (2009).

27. Farah, C., Michel, L. Y. M. & Balligand, J.-L. Nitric oxide signalling in cardiovascular health and disease. *Nat. Rev. Cardiol.* **15**, 292–316 (2018).

28. Armstrong, P. W. *et al.* Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *N. Engl. J. Med.* **382**, 1883–1893 (2020).

29. Ezekowitz, J. A. *et al.* Hemoglobin and Clinical Outcomes in the Vericiguat Global Study in Patients With Heart Failure and Reduced Ejection Fraction (VICTORIA). *Circulation* **144**, 1489–1499 (2021).

30. Understanding Radiation Risk from Imaging Tests. https://www.cancer.org/treatment/understanding-your-diagnosis/tests/understanding-radiation-risk-from-imaging-tests.html.