# Microvascular Assessment of Ranolazine in Non-Obstructive Atherosclerosis (MARINA)

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# I. Objectives

The goal of this proposal is to evaluate the effects of Ranolazine compared to Placebo on anginal symptoms, exercise tolerance, and coronary microvascular function in patients with mild to moderate non-obstructive atherosclerosis.

# II. Scientific Rationale, Background and Significance

While it is well known that cardiovascular disease is the most common cause of morbidity and mortality in the developed nations and is rapidly becoming so in the developing countries, what is less recognized is that both epicardial and microvascular disease contribute to these devastating sequelae. In fact, coronary microvascular disease likely precedes the development of epicardial disease and represents the "base of the iceberg" of cardiovascular disease. Yet, much of the diagnostic and therapeutic focus has been limited to epicardial disease, neglecting the contribution of dysfunctional microvasculature towards ischemic symptoms and adverse outcomes.[1-6] Coronary microvascular disease results from a combination of structural and functional abnormalities, so it is important to have reliable diagnostic tools that do not rely solely on imaging. Although there has been substantial interest in the development of non-invasive functional assessments, the gold-standard for testing continues to involve invasive hemodynamic measurements such as coronary flow reserve (CFR) and hyperemic microcirculatory resistance (HMR).[1]

Ranolazine is a relatively new U.S Food and Drug Administration-approved anti-anginal agent.[7-10] The anti-anginal mechanism of Ranolazine has not been fully elucidated yet but the leading hypothesis is that Ranolazine inhibits the late inward sodium channels, a factor in ion homeostasis and myocardial contractility.[11-13] Ranolazine appears to positively impact on the subjective assessment of angina as measured by the Seattle Angina Questionnaire (SAQ) in patients with coronary microvascular disease;[14,15] however, there are no publications on the effect of Ranolazine on CFR or HMR.

# III. Our Research Group

Our research specializes in assessing structural and functional aspects of the coronary vasculature with a focus on studying the effects of pharmacological interventions on coronary epicardial and microvascular function as well as wall shear stress using computational fluid

dynamic models created in collaboration with researchers at the Georgia Institute of Technology and the Department of Mathematics and Computer Science at Emory University.

## IV. Hypotheses

1. Ranolazine therapy, as compared to placebo, improves weekly angina frequency and nitroglycerin consumption in patients who have non-obstructive atherosclerosis, have persistent stable angina, and are already on disease-modifying medical therapy (DMT).
2. Ranolazine therapy, as compared to placebo, improves peak $VO_2$ in patients who have non-obstructive atherosclerosis, have persistent stable angina, and are already on DMT.
3. Ranolazine therapy, as compared to placebo, improves microvascular function, resulting in increased CFR and decreased HMR.

## V. Specific Aims

Primary Aims:

In patients with stable angina already on DMT and angiographically normal or near normal coronary arteries, Ranolazine 1000 mg twice daily, as compared to placebo, after 12 weeks, improves patients' weekly angina frequency and nitroglycerin consumption (SAQ angina frequency dimension).

Secondary Aims:

In patients with stable angina already on DMT and angiographically normal or near normal coronary arteries, Ranolazine 1000 mg twice daily, as compared to placebo, after 12 weeks:

1. Improves patients' SAQ subscores regarding physical limitation, angina stability, treatment satisfaction, and disease perception.
2. Improves patients' peak $VO_2$, exercise duration, and time to angina, as evaluated by cardiopulmonary exercise testing (CPET).
3. Increases CFR as measured by velocity Doppler wires
4. Decreases HMR as measured by pressure and velocity Doppler wires

# VI. Study Design

## A. Description

Patients with persistent stable angina and on DMT (ASA, statin) will be recruited from multiple centers throughout Atlanta, GA. They will undergo baseline evaluation of their angina using SAQ, CPET, and cardiac catheterization with coronary microvascular function assessment with combined pressure and flow wire system (ComboMap® Pressure and Flow System, Volcano Therapeutics, Inc.).

Subsequently, patients will be randomized to treatment with DMT plus Ranolazine twice daily versus DMT plus Placebo twice daily for 12 weeks. Initially, patients will be on Ranolazine/placebo 500 mg twice daily, and the dose will be increased one week later as tolerated to Ranolazine/placebo 1,000 mg twice daily. Ranolazine has been FDA approved and is prescribed in the same dosages that this study uses. Therefore, it is noteworthy to mention that we are not studying a new drug in this study, but rather investigating whether this drug has new implications. Enrolled patients will be treated with Ranolazine/placebo 1,000 mg twice daily for 12±3 weeks.

On follow-up, patients will again be evaluated with SAQ, CPET, and angiography with coronary physiology assessment. Subjective angina improvement, exercise capacity, and microvascular function will be compared to baseline measurements in both arms. While Ranolazine has previously been shown to improve both angina and exercise capacity,[8,9] there are no published randomized controlled trials with regards to the effects of Ranolazine on CFR or HMR. As the gold-standard for evaluation of coronary microvascular disease continues to involve these invasive hemodynamic measurements, a follow-up cardiac catheterization is necessary to assess the changes in CFR and HMR, objective evidence in the evaluation of coronary microvascular disease in patients.

## B. Inclusion criteria

1) History of typical angina or effort-induced anginal symptoms and are currently experiencing angina at least once per week;
2) Abnormal stress ECG, exercise stress imaging, or pharmacological stress imaging;
3) Non-obstructive coronary artery disease as defined by lesion stenosis ≤ 50% in any artery (left main, LAD, circumflex, diagonals, marginals, RCA, PDA, and posterior lateral) as visualized by

diagnostic angiography

**C. Exclusion criteria:**

1) Inability to provide informed consent;
2) Active Myocardial Infarction (STEMI or NSTEMI);
3) History of CABG;
4) Diagnosis of other specific cardiac disease such as severe valvular heart disease, cardiomyopathy, or variant angina;
5) Left Ventricular Ejection Fraction (LVEF) < 30%;
6) Known renal insufficiency (CrCl < 30 mL/min) or on dialysis;
7) Contraindications to the use of Ranolazine, including patients on CYP3A4 inducers/potent inhibitors, and patients with liver cirrhosis.

*Note:*

The following scenarios are not exclusions but do warrant monitoring or dose modifications:

1) Limit dose of Ranolazine to 500mg BID in patients who are currently on diltiazem or verapamil
2) Limit concurrent simvastatin to a maximum dose of 20 mg/day
3) Limit concurrent metformin to a maximum dose of 1,700 mg/day
4) Monitor for QT interval on ECG in patients with history of QT interval prolongation (familial, congenital, or acquired) or who are concurrently on QT interval-prolonging medications
5) Monitor renal function in patients with Cr < 60 mL/min.

**D. Study Protocol:**

<u>Baseline CPET (Visit 1a):</u>

-Consent form for study participation will be signed in person or by mail. Consent form may be mailed to the patient to be signed if patient's commute to Emory is limited (e.g. patients who live far from Emory campus).

-Stop all β-blockers and calcium channel blockers ≥48 hours prior to CPET

-Stop long-acting nitrates ≥24 hours prior to CPET

-Schedule appointments for follow-up CPET and angiography

-SAQ

-CPET within 1 week of angiography, ideally the day before angiography

Baseline angiography (Visit 1b):

-Coronary angiography with physiology and reactivity testing within 1 week of CPET, ideally the day after CPET

-Stop all β-blockers and calcium channel blockers ≥48 hours prior to catheterization

-Stop long-acting nitrates ≥24 hours prior to catheterization

-Laboratory measurements if not already obtained within the past 2 weeks (CBC, BMP, troponin, Hgb A1c, fasting lipid panel)

*Once CPET and cardiac catheterization are performed, patients will then be randomized to either Ranolazine or Placebo in addition to current medical therapy*

4 weeks follow-up:

-ECG

-SAQ

12-week follow-up CPET (Visit 2a):

-Stop all β-blockers and calcium channel blockers ≥48 hours prior to CPET

-Stop long-acting nitrates ≥24 hours prior to CPET

-SAQ

-CPET within 1 week of angiography, ideally day before angiography

12-week follow-up angiography (Visit 2b, scheduled separately from CPET):

-Coronary angiography with pressure and flow measurements within 1 week of CPET, ideally the day after CPET

-Stop all β-blockers and calcium channel blockers ≥48 hours prior to catheterization

-Stop long-acting nitrates ≥24 hours prior to catheterization

-Laboratory measurements (CBC, BMP, troponin, fasting lipid panel)

### E. Study Chart

| | Baseline | 4 weeks | 12 weeks |
|---|---|---|---|
| Informed consent | X | | |
| Medical history | X | | |
| CPET | X | | X |
| Cardiac Catheterization with Reactivity Testing | X | | X |
| SAQ (full) | X | X | X |
| Current Medications | X | X | X |
| Study Medication Adjustment (if needed) | | X | |

## VIII. Methodology

### A. Cardiopulmonary Exercise Testing (CPET)

In order to standardize exercise stress testing, CPET will be performed under the guidance of the MET-TEST CPET network in Atlanta, led by Dr. Sundeep Chaudhry. The MET-TEST was created in 2003 and is a high-precision stress test with detailed physiological assessment, allowing accurate and reproducible measurements of peak $VO_2$. Individuals may demonstrate an abnormal CPET response before they develop symptoms or present with cardiac events,[16,17] and abnormal CPET results are strong predictors of future adverse outcomes.[18] Having performed over 65,000 tests and participated in studies since its inception, the MET-TEST CPET network will help ensure the quality of the collected data. Peak $VO_2$, exercise duration, and time to angina will be obtained at baseline and at follow-up, thus determining changes in peak $VO_2$, exercise duration, and time to angina (secondary endpoints).

### B. Angiography with Coronary Physiology and Reactivity Testing

After routine coronary biplane angiography, the microvascular function of each coronary artery will be assessed using intravenous infusion of adenosine at 140 micrograms/kg/minute for 3 minutes to achieve maximal hyperemia. Continuous recordings of aortic pressure and electrocardiogram are done during baseline and during drug infusion periods. A 0.014-inch

combined pressure and Doppler flow velocity monitoring guidewire (ComboWire® XT Pressure and Flow Wire, Volcano Therapeutics, Inc.) is advanced into the target vessel chosen to make Doppler and hemodynamic recordings. It is important to note that adenosine is the drug of choice to induce hyperemia and that its role in coronary physiology assessment differs from its role in pharmacological stress testing.

CFR is defined as the ratio of average peak velocity (APV) at maximal hyperemia to baseline. HMR is defined as the ratio of hyperemic distal pressure to APV.[19] CFR and HMR will be calculated at baseline and 12-week post-Ranolazine therapy, thus determining change in CFR and HMR value (secondary endpoints).

Coronary endothelial function will also be evaluated by measurement of coronary blood flow during infusion of intracoronary acetylcholine. Coronary blood flow (CBF) is defined as diameter $(D)^2$ x APV / 8. Percent change in CBF (%ΔCBF) is calculated by $(CBF_{ACh} - CBF_{baseline}) / CBF_{baseline}$ x 100%, where a >50% increase in CBF in response to acetylcholine is considered normal.[20] The effect of Ranolazine vs. placebo on endothelial function between baseline and follow-up will also be assessed (secondary endpoint).

## C. Patient Population

A minimum of 50 patients will be enrolled into this double-blind study and randomized in a 1:1 ratio to receive Ranolazine twice daily versus placebo twice daily while on DMT. Patients will be called one week after randomization for study medication dose adjustment, with the goal of Ranolazine/placebo 1,000 mg twice daily during the study period as tolerated. We expect to conduct 12-week follow-up evaluation on a total of at least 40 patients accounting for 20% drop out rate due to the invasive nature.

## D. Endpoints

Primary Endpoint: Change in weekly angina frequency and nitroglycerin consumption (SAQ angina frequency dimension) after 12 weeks therapy with Ranolazine compared with placebo.

Secondary Endpoints:

1. Change in SAQ score (composite and individual dimensions) after 12 weeks therapy with Ranolazine compared with placebo.

2. Change in peak $VO_2$, time to angina, and exercise duration as measured by CPET after 12 weeks therapy with Ranolazine compared with placebo.
3. Change in CFR after 12 weeks therapy with Ranolazine compared with placebo.
4. Change in HMR after 12 weeks therapy with Ranolazine compared with placebo.
5. Change in %ΔCBF after 12 weeks therapy with Ranolazine compared with placebo.

## E. Statistical Methods

The power calculations for this study are informed by other published studies on Ranolazine. In the CARISA trial (3-group parallel arms, n=823), Chaitman et al. reported mean weekly angina frequency decreased from 4.5 attacks per week to 3.3 ± 0.3 for Placebo and 2.1 ± 0.2 for Ranolazine 1,000mg (P<0.001). In the ERICA trial (n=565), Stone et al. reported mean weekly angina frequency decreased from 5.7 to 3.3 attacks per week for Placebo and from 5.6 to 2.9 attacks per week for Ranolazine 1,000mg (P=0.028). Sample size calculations for these two trials suggest a minimum of 36 patients for 99% 2-sided confidence interval, 95% power, and 1:1 ratio. In a more recent study evaluating the impact of Ranolazine in 20 women with angina and non-obstructive CAD, Mehta et al. showed that, compared to Placebo, Ranolazine improved angina stability (p=0.008), physical functioning (p=0.046) and quality of life (p=0.021) as measured on the SAQ.[14] Taken together, we believe that 50 patients should provide adequate power to detect changes in the SAQ.

For an invasive evaluation of patients with coronary microvascular disease (secondary endpoint), there are no trials regarding the effects of Ranolazine on measurements such as CFR or HMR, so this study will generate data to determine the need for future larger studies and/or future sample size calculations. The closest published study found in the literature was by Mehta et al., in which the investigators measured myocardial perfusion reserve index (MPRI) scores by cardiac magnetic resonance (CMR), which is not the gold standard invasively measured indices as performed in this trial. MPRI can be a surrogate for invasive coronary hemodynamic measurements but is not as well validated. Patients in this study had MPRI scores of 2.4 ± 0.4 while on Ranolazine, compared with 2.1 ± 0.4 while on Placebo.[14] Using these results, we estimate that the study, with a power of 80%, 1:1 ratio, and two-sided confidence interval of 85%, will require a sample size of 38 patients. Assuming 20-25% drop-out due to the invasive nature of the study, we anticipate enrolling 50 patients.

For biostatistical data analysis, continuous variables will be reported as mean and standard

deviation (1 SD), and a t-test or U-test will be employed depending on whether or not the variables are normally distributed and the standards of deviations are the same. Analysis of variables at the level of patient, treatment arm, and lesion will be performed using multilevel regression models. Chi-square test or Fisher's exact test will be used, as appropriate, to compare categorical variables. All statistical analyses will be carried out using the Statistical Package for Social Sciences (SPSS) software (SPSS, Inc., Chicago, IL) or Statistical Analysis System (SAS) software (SAS Institute Inc., Cary, NC). A two-sided p-value of $<0.05$ will be considered statistically significant.

## F. Data Management

All documents and subsequent versions related to this study will be identifiable, traceable and appropriately stored to provide a complete history of the clinical study. The principal investigator is responsible for the accuracy, legibility, and security of all clinical study data, documents, and subject records at the investigator's participating medical site. Designated study staff (principal investigator, co-investigators, clinical coordinators, and other appropriately trained personnel) is responsible for entering the data and access to the database will be limited to these persons.

All data and information concerning subjects collected during the course of this study will be kept strictly confidential according to applicable laws and regulations. The informed consent form shall be signed and dated by the principal investigator or his authorized designee(s). This form and all other source documents will be maintained by the research team throughout the clinical study in subject specific folders in a locked filing cabinet. All coronary angiography and physiology data will be recorded on compatible compact discs (CD-ROM or DVD) and stored in a locked filing cabinet. Electronic information will be kept on password-protected computers and secured access network drives. All records and reports prepared in connection with this study will be maintained in a secure location for a minimum period of 15 years post approval or longer as may be otherwise required by law.

All public reporting of the results of the study will eliminate identifiable references to the subjects. The results of this clinical study will be submitted for publication following study completion and data analysis. Study data published in medical journals and/or presented at scientific conferences will not allow the identification of study subjects.

## G. Monitoring and Reporting

Processes to ensure site record keeping, data entry, and reporting are well-defined to ensure timely access to clinical trial data and supporting documentation. Investigators are required to keep records on all relevant observations, including records concerning adverse effects, whether anticipated or unanticipated. All adverse events will be captured on an adverse event case report form, tracked from time of study enrollment until completion of follow-up, and promptly reported to the IRB and Gilead Sciences. The investigator will also notify the IRB regarding new and significant safety information and any event that requires expedited reporting as serious, unexpected, and related to the clinical study drug. The principal investigator, IRB or a regulatory authority may suspend or prematurely terminate participation in this clinical study if suspicion of an unacceptable risk to subjects arises during the study. The study shall be terminated if an unacceptable risk is confirmed.

## H. Duration of study and Follow Up

It is estimated that it will take 1 year to enroll patients and collect baseline data and 4 months for follow-up data collection.

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