Efficacy of Medical Therapy in Women and Men with Angina and Myocardial Bridging

Study Protocol and Statistical Analysis Plan

NCT04130438

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CLINICAL PROTOCOL SYNOPSIS

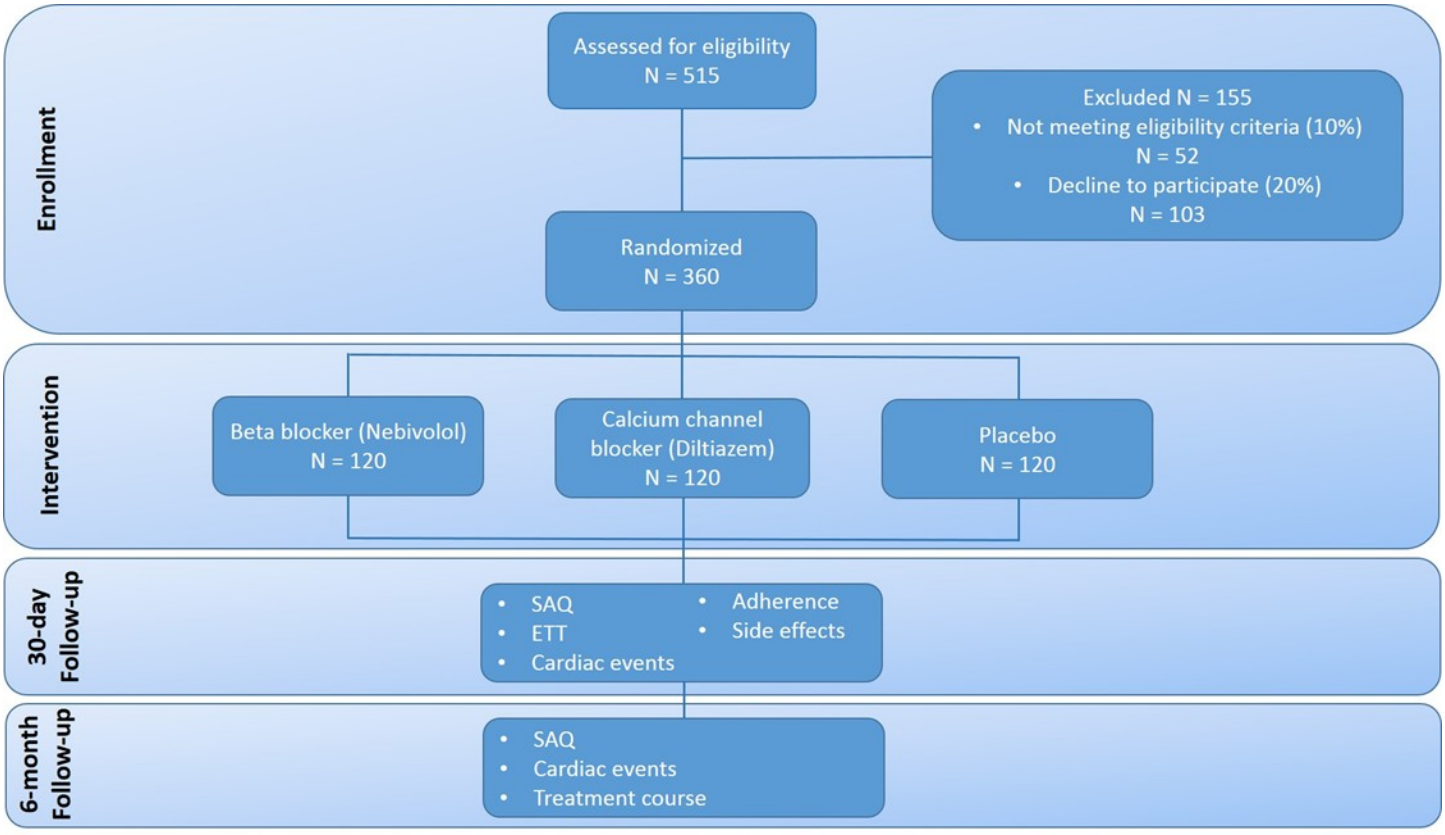
- **Protocol Title:** Efficacy of Medical Therapy in Women and Men with Angina and Myocardial Bridging

- **Focus of Study:** To determine the efficacy of medical therapy in patients with angina and a myocardial bridge (MB).

- **Objectives:** The primary objective is to determine if beta blockers and/or calcium channel blockers will improve angina in patients with angina and an MB compared with placebo. The secondary objective is to identify predictors of efficacy of beta blockers and calcium channel blockers in treating patients with angina and an MB.

- **Study Design:** The design of the study is a randomized, double-blind, placebo-controlled phase II clinical trial.

- **Intervention to Be Tested:** The intervention to be tested is oral beta blocker (nebivolol 2.5 mg) vs. calcium channel blocker (diltiazem SR 120 mg) vs. placebo. Once enrolled, baseline data will be gathered and subjects will be randomly assigned to a treatment arm. Subjects will be instructed to take their assigned study drug once a day for 30 days. They will be given a diary in order to note any days missed and any side effects. If they stop taking their assigned study drug, they will be asked to note the last day the study drug was taken and the reason for stopping. They will also be asked to keep the bottle and any unused pills, which they will be instructed to bring back, along with the diary, at the 30-day follow-up visit. Adherence will be defined by the proportion of treatment intervention pills taken, as assessed by a pill count. At the 30-day follow-up visit, they will repeat data collection, as well as an optional exercise treadmill test (ETT). Following completion of the 30-day follow-up, subjects will be unblinded to their study drug and will continue with usual care under the direction of their primary physician. They will be contacted again at 6 months for final data collection. Following completion of the 6-month follow-up, their participation in the study will end.



- **Primary and Important Secondary Endpoints:** The primary endpoint is change in angina after treatment as assessed by the Seattle Angina Questionnaire (SAQ) at 30-day follow-up. The secondary endpoints are 1) change in exercise parameters at 30 days, 2) treatment adherence (pill counts) and self-reported side effects at 30 days, 3) occurrence of cardiac events at 30 days, 4) change in angina by SAQ at 6 months, 5) occurrence of cardiac events at 6 months, and 6) treatment course at 6 months, following the 30-day treatment period.

    - The SAQ is a self-report instrument with 19 items that yields five subscale scores: physical limitation, angina stability, angina frequency, treatment satisfaction, and disease perception. The range of scores for each of these subscales is 0 to 100, with higher scores indicating a higher quality of life. A difference of 10 is considered clinically meaningful.

    - Exercise parameters include duration of exercise, METs achieved, percentage of maximal predicted heart rate achieved, Duke Activity Status Index (DASI), symptoms (onset and duration), and EKG changes (ST-segment changes, arrhythmia, and heart rate recovery).

    - Cardiac events include myocardial infarction, sustained ventricular arrhythmia, cardiac arrest, cardiac death, and emergency room visits/hospitalizations for angina.

    - Treatment course includes 1) if they stayed on the study drug at the initial dose, 2) stayed on the study drug at a different dose, 3) switched to an alternate therapy, and/or 4) underwent further cardiac testing.

- **Schedule of Clinical and Laboratory Evaluations:** Potential subjects will be recruited from the physician investigators' (Tremmel, Schnittger, and Rogers) outpatient clinics. Informed consent will be sought, and if obtained, subjects will be screened for eligibility by reviewing the inclusion and exclusion criteria. If successfully enrolled in the trial, they will be scheduled for their baseline visit, which may occur on the same day as screening. Baseline data, including demographics, cardiac risk factors, current cardiac medications, results of prior cardiac testing, and prior cardiac events will be collected. The subject will also complete the SAQ and SF-12. Following data collection, the subject will be randomized to their assigned treatment arm. They will be given their study drug and instructed to take their study drug once a day for 30 days. They will also be given a diary and instructions for use. Their 30-day visit will be scheduled, along with an optional exercise treadmill test. The 30-day visit will need to occur while the subject is still on the study drug, so may occur anywhere within days 25 to 30. At 5 days and 2 days prior to their 30-day follow-up visit, subjects will be sent HIPAA-compliant reminders via the phone and electronic messaging about their upcoming visit, as well as the need to bring their pill bottles, unused study drug (if any), and diary. At the 30-day follow-up visit, subjects will repeat the SAQ and SF-12, and complete data collection about adherence (pill count), side effects, and subsequent cardiac events. They will also undergo an exercise treadmill test (ETT) if they agreed to one being ordered. Once all requirements for the 30-day follow-up visit are complete, the subject and their physician will be unblinded to their treatment assignment. They will then begin usual care as determined by their treating physician. Similar to the 30-day visit, at 5 days and 2 days prior to their 6--month follow-up visit, subjects will be sent HIPAA-compliant reminders via the phone and electronic messaging about their upcoming visit. At the 6-month follow-up visit, subjects will be asked to complete a final SAQ and SF-12, and data will be collected regarding any subsequent cardiac events, as well as their treatment course following unblinding. Once they have completed all requirements for their 6 month follow-up visit, their participation in the study will end. All variables to be collected are detailed in the *Data Management Plan*. The Schedule of Evaluations is presented in the Figure below.

Study Visit	Screening	Day 0 (Baseline)	5 days and 2 days prior to follow-up visit	30-day visit (Between Day 25-30)	6-month visit
Informed Consent Form (ICF)	X				
Inclusion/Exclusion Criteria reviewed	X				
Subject scheduled for initial visit-Day 0 (Baseline)	X				
Demographics		X			
Cardiac risk factors		X			
Review of medications		X			
Results of prior cardiac testing (including exercise parameters of exercise stress echo, and CCTA)		X			
Medical history, including prior cardiac events		X			
Seattle angina questionnaire (SAQ) and SF-12		X		X	X
Randomization		X			
Instructions for study drug and diary		X			
Schedule 30-day and 6-month visits		X			
Reminders via phone and e-mail about diary, pill bottles, and 30-day/6-month follow-up visit			X		
Exercise treadmill test (if applicable)				X	
Subsequent cardiac events				X	X
Pill count for adherence				X	
Side effects				X	
Unblinding				X	
Treatment course					X
Study completion					X

- **Study Population:** The sample size is 360 subjects. Based on our previous experience, we expect 60% will be men and 40% will be women. They are expected to range in age from 18 years to 80 years. Given our catchment area, the majority of subjects will come from within a 120 mile radius of the San Francisco Bay area. Based on our local demographics, the vast majority (70%) will be white (18% of which are Hispanic), and approximately 11% will be Asian, with the remainder being Native Indian, Pacific Islander, or black. All patients will have stable angina in the absence of obstructive CAD and an MB, but will otherwise be relatively healthy.

- **Statistical Design and Power:** We will enroll 120 subjects in each treatment arm for a total of 360 subjects. The sample size per treatment arm was calculated through a simulation study, using ANCOVA models. We found we need 120 subjects per treatment arm (360 total) to find a clinically meaningful and statistically significant effect in the primary outcome (>10 change in SAQ), assuming

moderate variation (standard deviation=4) with at least 0.80 power. To determine the primary endpoint, we will evaluate changes (post- minus pre-treatment) in each of the five SAQ subscales with an ANCOVA that includes pre-treatment SAQ subscale scores and treatment as explanatory variables. We will compare the treatment effect of beta blocker and calcium channel blocker to each other and to the control (placebo) for each of the five subscales. This analysis plan adheres to the intent--to--treat principle; all randomized subjects will be included in the analysis and analyzed according to their original treatment assignment. If a subject stops treatment prior to the 30--day follow--up, we will only use the subject's baseline measurements in the primary analysis, but will complete a sensitivity analysis that evaluates the endpoint in the presence of these measurements by accounting for the number of days on the assigned treatment. Subjects will be instructed to take their study drug once a day for 30 days. Adherence will be assessed by pill count. With regard to intervention discontinuation, subjects may withdraw voluntarily from participation in the study at any time and for any reason. If given permission, we will continue to follow subjects even if the study intervention is discontinued. If any subject discontinues because of an adverse event or serious adverse event, safety data will continue to be collected.

- **Group Assignment:** We will use stratified randomization. Specifically, subjects will be randomly assigned to a treatment arm: beta blocker (nebivolol), calcium channel blocker (diltiazem), or placebo (1:1:1), stratified on sex to ensure a balance of women and men in each arm.

- **Subject Participation Duration:** 6 months.

- **Study Duration:** Estimated time from when the study opens to enrollment to completion of data collection is 51 months. Estimated time from when the study opens to enrollment to final data analyses is 54 months.