

Rationale and Design of the Vasospastic Angina Treatment by Endothelin Receptor Antagonism (VERA) Trial

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Abstract

Background Pharmacological treatment of patients diagnosed with vasospastic angina (VSA) or microvascular angina (MVA) is challenging and often patients remain symptomatic. Endothelin (ET)-1 plays an important role in the regulation of the vascular tone and stimulation of ET-1 receptors can induce a potent and long-lasting vasoconstriction. Macitentan is a potent, inhibitor of the ET_A receptor.

Purpose This prospective, randomized, double-blind, placebo-controlled, sequential cross-over proof-of-concept trial is designed to investigate macitentan as a potential novel treatment for patients with VSA due to epicardial spasm or MVA due to microvascular spasm, together defined as coronary artery spasm (CAS).

Methods and Results A total of 30 patients with CAS will receive treatment with either 10 mg of macitentan daily for 4 weeks followed by placebo for 4 weeks, or vice versa, in random order. The primary outcome is the reduction in angina, calculated as (1) the frequency of angina attacks * severity (on a VAS scale 1-10); and (2) the duration (in minutes) * severity (on a Visual Analogue Scale (VAS) pain scale 1-10) during medication use (macitentan or placebo) up to 2 weeks after discontinuation of the study medication. The primary analysis will assess the within-subject differences in the burden of anginal symptoms following treatment with macitentan versus placebo.

Conclusions The VERA trial will be the first to evaluate the efficacy of the ET_A receptor antagonist, macitentan, in the treatment of VSA due to epicardial spasm and MVA due to microvascular spasm.

Trial Registration trialregister.nl, Identifier: NL7546. Registration date: 20 February 2019.

Introduction

A considerable proportion of patients with typical anginal complaints and/or myocardial ischemia have no or only mildly obstructive coronary artery disease (ANOCA) as diagnosed by coronary angiography (CAG) [1]. Considered a working diagnosis, there is a broad differential diagnosis that may cause angina symptoms or even myocardial ischemia (MINOCA). A frequently overlooked diagnosis for ANOCA/MINOCA are vasomotor disorders, because routine diagnostic tests often show no abnormalities, are focussed on fixed obstructive disease and specific diagnostic tests are not routinely performed. Coronary vasomotor dysfunction can be identified using comprehensive protocols for invasive coronary vasomotor function testing, typically using acetylcholine (ACh) provocation testing to document vasospasm and combined coronary pressure and flow measurements to assess microvascular hemodynamics. Two endotypes of vasomotor disorders are defined as mechanisms of ANOCA/MINOCA, namely epicardial vasospastic angina (VSA) and microvascular angina (MVA) [2,3]. VSA is characterized by spontaneous episodes of angina, usually at rest, due to reversible constriction (vasospasm) of a coronary artery at the epicardial domain. Episodes of VSA occur most often between night and early morning, are usually short in duration, have a prompt reaction to short acting nitrates, and are associated with electrocardiographic changes during an attack. MVA is the clinical manifestation of

myocardial ischaemia caused by coronary microvascular dysfunction (CMD). CMD can be defined as a mismatch of myocardial blood supply and oxygen consumption due to a dysregulation of the coronary microvasculature. CMD is characterized by a diminished flow augmentation in response to a pharmacological vasodilator or reduced coronary flow reserve (CFR, CFR <2,5 is abnormal). In CMD, 2 distinct processes contribute to a low CFR: i) an increased baseline flow due to reduced microvascular resistance at rest (functional CMD); and ii) a reduced hyperaemic flow due to high minimal microvascular resistance (structural CMD) [4]. MVA patients often present with exercise-induced retrosternal, oppressive chest discomfort, pain, and/or dyspnoea. Symptoms can be triggered by exercise but, in contrast to typical angina, often develop after the exercise has ceased [5]. In addition, patients may experience episodes of chest pain at rest, atypical in character and variable in duration. Table 1 outlines the diagnostic criteria as proposed by the Coronary Vasomotor Disorders International Study (COVADIS) working group for VSA and MVA [6,7].

Besides lifestyle management and control of traditional risk factors for cardiovascular disease, treatment of patients with vasomotor disorders often remains empiric and should be adapted to the underlying pathophysiological mechanism as much as possible. In patients with evidence of either VSA or MVA following coronary vasomotor function testing, calcium channel blockers (CCB) should be considered as first-line therapy as it provides vasodilation of the coronary arteries. If VSA or functional CMD patients remain symptomatic, long-acting nitrates or nicorandil can be added besides nitroglycerin s.l. on demand. If MVA patients remain symptomatic, beta-blockers are indicated, in particular in structural CMD preferably nebivolol as it exhibits a nitric oxide (NO)-releasing effect. In addition, renin-angiotensin system (RAS) inhibitors may be beneficial because of their protective effect on endothelial function [3]. Despite these pharmacological agents, a substantial amount of patients remain symptomatic.

Macitentan

Endothelin-1 (ET-1) is a small peptide predominantly released by vascular endothelial cells. Through its paracrine action ET-1 plays an important physiological and pathophysiological role, especially in the regulation of vascular tone [8]. ET-1 induces an extremely potent and long-lasting vasoconstriction. Moreover, ET-1 affects the production of other local mediators of the vascular tone, including NO, prostacyclin, and platelet-activating factor [9]. Other effects of ET-1 include pro-inflammatory actions, mitogenic and proliferative effects, stimulation of free radical formation and platelet activation [10]. Importantly, ET-1 receptors have two subtypes, ET_A and ET_B. Activation of the ET_A receptor in smooth muscle cells results in vasoconstriction, whereas, stimulation of the ET_B receptor that are present in endothelial and vascular smooth muscle cells have both vasoconstrictive and dilatory effects [11]. It is becoming increasingly clear that an imbalance between ET-1 and NO plays an important role in endothelial dysfunction and increased levels of ET-1 have been linked to coronary vasospasm [11–13]. In addition, ET-1 levels are associated with impaired coronary vasodilatory response [14].

In vitro, the novel endothelin receptor antagonist (ERA) macitentan, is 100x more selective for the ET_A-receptor than the ET_B-receptor. Macitentan shows high affinity and long-term occupancy of the ET-

receptors in smooth muscle cells of the arteries. This prevents endothelin-mediated activation of second messenger systems that leads to vasoconstriction and proliferation of the smooth muscle cells. The safety and efficacy of macitentan has not been evaluated in patients with VSA or MVA, but has been documented in patients with idiopathic pulmonary fibrosis in a prospective, randomised, double-blind, multicentre, parallel-group, placebo-controlled phase II trial (NCT00903331) [15]. A total of 178 patients with idiopathic pulmonary fibrosis of <3 years duration and a histological pattern of usual interstitial pneumonia on surgical lung biopsy were randomised (2:1). Long-term exposure to macitentan was well tolerated with a similar, low incidence of elevated hepatic aminotransferases in each treatment group. In the SERAPHIN study, the efficacy of macitentan was assessed in symptomatic pulmonary arterial hypertension patients [16]. A total of 250 patients were randomly assigned to placebo, 250 to the 3 mg macitentan dose, and 242 to the 10 mg macitentan dose. Adverse events more frequently associated with macitentan than with placebo were headache, nasopharyngitis, and anaemia. The percentage of patients who discontinued the study drug owing to adverse events was similar (placebo: 12.4%; 3 mg macitentan: 13.6%, 10 mg macitentan: 10.7%). The incidence of elevated hepatic aminotransferases (>3 times the upper limit of the normal) were similar across the 3 treatment groups (4.5%, 3.6% and 3.4%, respectively after a follow-up of 36 months).

Methods

Trial design

The primary objective of the VERA trial (trialregister.nl, Identifier: NL7546) is to assess whether the ET_A receptor antagonist macitentan at a dose of 10 mg once daily will reduce the frequency and severity of anginal complaints in patients diagnosed with VSA due to epicardial spasm or MVA due to microvascular spasm (i.e. functional CMD), together defined as coronary artery spasm (CAS).

This proof-of-concept study with a prospective, randomized, double-blind, placebo-controlled, sequential cross-over design will include multiple centers in the Netherlands (Amsterdam University Medical Centers, Radboud University Medical Center, HeartLife Clinics). A total of 30 symptomatic participants with CAS despite background anti-anginal therapy (at least treatment with CCB and/or long-acting nitrates, angiotensin converting enzyme inhibitors or angiotensin receptor antagonists) will be included. Participants will be randomized to double-blind treatment with either 10 mg of macitentan once daily for 4 weeks, and subsequently placebo for 4 weeks, or vice versa. In between treatment with macitentan or placebo, there is a 2-week wash-out period. (Fig. 1.)

Participant Selection

A potential candidate will be identified at the outpatient clinic and have had invasive coronary vasomotor function testing to diagnose VSA due to epicardial vasospasm or MVA due to microvascular spasm as per the COVADIS guidelines (Table 1). For MVA patients, only those with evidence of microvascular spasm defined as *coronary microvascular spasm, defined as reproduction of symptoms*,

ischemic ECG shifts but no epicardial spasm during ACh testing (Table 1. MVA criteria: 4b) will be included. The diagnostic classification of VSA and MVA are endorsed by the European Society of Cardiology practice guidelines of 2019 [17]. Other inclusion criteria are: (1) age ≥ 18 and < 75 years old; (2) absence of significant obstructive coronary artery disease (defined as stenosis $> 50\%$ in an epicardial coronary artery) documented by invasive coronary angiography; (3) persistent anginal complaints with a frequency of at least 3 times per week despite anti-anginal treatment; (4) anginal complaints for at least 3 months despite optimal anti-anginal treatment, which is at the discretion of the treating cardiologist; (5) able to comply with the study procedures; (6) able to provide written informed consent. The exclusion criteria are listed in Table 2. MVA patients who meet the MVA criteria 4a, b or d (see Table 1) will be excluded as they are diagnosed with structural CMD.

Endpoints

The primary endpoint of the VERA trial is to determine whether the macitentan reduces the burden of anginal symptoms in patients with CAS, calculated as:

1. The frequency of angina attacks * severity (on a VAS scale 1-10) during medication use (macitentan or placebo) up to 2 weeks after discontinuation of the study medication.
2. The duration (in minutes) * severity (on a Visual Analogue Scale (VAS) pain scale 1-10) during medication use (macitentan or placebo) up to 2 weeks after discontinuation of the study medication.

The VAS score is widely used to measure pain intensity and has been found to be valid, reliable and appropriate for use in clinical practice, using black lines and a numeric scale [18].

The pre-specified secondary *efficacy* endpoints include (1) incidence and severity of angina complaints as obtained on a weekly basis by the Seattle Angina Questionnaire (SAQ) during medication use (macitentan or placebo) up to 2 weeks after discontinuation of the study medication, and (2) patients reported outcomes measures (PROMS) via an angina diary. The SAQ is a valid and reliable, disease-specific 19-item self-administered questionnaire that quantifies the physical limitation caused by angina, the frequency of angina, treatment satisfaction, and subjective perception of quality of life [19]. The SAQ is sensitive to subtle clinical change, as seen among outpatients treated with pharmacotherapy as well as in patients with VSA and MVA [20,21]. SAQ scores are independently associated with hospitalization and mortality [22–24]. In the angina diary patients are asked to report on a daily basis the frequency, duration, and severity (on a VAS scale 1-10) of angina episodes, as well as under which circumstances the complaints developed, and use of sublingual nitroglycerin tablets or sprays.

The pre-specified secondary *safety* outcomes include (1) detrimental changes in physical, laboratory or ECG parameters during medication use (macitentan or placebo) up to 2 weeks after discontinuation of the study medication, and (2) the occurrence of adverse events (i.e. hospitalization for anginal symptoms and/or myocardial infarction) during the study period. All possible side effects associated with macitentan will be recorded during the study period.

Randomization

Randomization will occur during visit 2, but only if they have experienced anginal complaints during the run-in period of 4 weeks on background anti-anginal therapy. Randomization will be performed using a computerized randomization tool. Eligible and consenting patients will be randomized with equal probability to the two groups reflecting the sequential order of macitentan or placebo in Phase 1 and Phase 2, respectively: Group 1 = macitentan in Phase 1 then placebo in Phase 2; Group 2 = placebo in Phase 1 then macitentan in Phase 2.

Study Visit and Follow-up

The study visits are shown in Fig. 1. After obtaining informed consent, during visit 1, we check the inclusion and exclusion criteria and collect baseline information (including pharmacological therapy, clinical examination and laboratory measurements). Visit 2 takes place after 4 weeks of background anti-anginal therapy (at least treatment with CCB and/or long-acting nitrates, angiotensin converting enzyme inhibitors or angiotensin receptor antagonists). Symptomatic participants, despite background anti-anginal therapy, will be randomized to double-blinded treatment with either 10 mg of macitentan once daily for 4 weeks. Visit 3 takes place after 8 weeks: after 4 weeks of study medication (macitentan or placebo); visit 4 takes place after 10 weeks: after 2 weeks wash-out, cross-over of treatment allocation; visit 5 takes place at 14 weeks: after 4 weeks study medication (macitentan or placebo); and visit 6 takes place at 16 weeks: after 2 weeks wash-out, end of the study. At visit 3, 4, 5 and 6 the patient's well-being and the occurrence of adverse events (including hospitalization) are assessed. At visit 3 and 5 a blood sample is drawn and analyzed to check haemoglobin, haematocrit, erythrocytes, leucocyte, thrombocytes, sodium, potassium, high-sensitive troponin T, creatinine, urea, ALAT, ASAT, gamma-GT and AF, bilirubin, and NT-proBNP.

Sample Size Determination and Statistical Analysis

The VERA trial is a crossover trial design in which each patient will serve as his/her own control thus controlling for confounding variables (e.g., age and sex) requiring a lower sample size than parallel-group trials to meet the same criteria in terms of type I and type II error risks. As this is a proof-of-concept study no formal sample size calculation is performed. In this study, we aim to include 30 patients.

Analyses will be done by intention-to-treat and on-treatment principle. Descriptive data are summarized as numbers with percentages for categorical variables, as mean with standard deviation for continuous variables with normal distribution and as median with (interquartile) range for continuous data with skewed distribution. Potential imbalances in protocol violation, lost-to-follow-up are evaluated with a Student independent T test, or a Chi-Square test if appropriate. The level of significance to be used for tests will be 0.05.

Study administration and Management

The trial is registered as trialregister.nl, Identifier: NL7546. The VERA trial is approved by the Dutch Medical Ethics Committee of the Amsterdam University Medical Centers (Reference 2018_213). The VERA trial is an investigator-initiated clinical trial. Actelion Pharmaceuticals Nederland B.V. has provided the investigational medicinal product. Actelion Pharmaceuticals reviewed and approved the protocol. The company did not have any role in the conduct of the trial, analysis of the data, or publication of the results.

An independent Data Safety Monitoring Board (DSMB) including two independent medical experts (one interventional cardiologist and one general cardiologist) and a statistician is established to assure the safety of participants in this trial. The DSMB will review the trial for safety and overall trial conduct. At the end of the trial, the DSMB may adjudicate final outcome based on clinical information.

Since the trial is a crossover proof-of-concept trial, and is not designed to assess between-group differences in clinical endpoints, a Clinical Event Committee is not required. The trial management team is solely responsible for the design and conduct of this trial, all study analyses, the drafting and editing of the manuscript and its final content. Monitoring of the trial will be performed by an independent Clinical Research Unit with Clinical Research Associates.

The study is currently ongoing and recruited 17 patients. Patient mean (SD) age is 55.5 (8.5) years, 82% are female, and 8 have VSA whereas 9 have MVA due to microvascular spasm. Due to SARS-COVID19 inclusion of participants was temporarily halted between February 2020 and August 2020.

Discussion

The VERA trial aims to assess whether the ET_A receptor antagonist macitentan reduces the frequency and severity of anginal complaints in patients diagnosed with VSA or MVA due to epicardial or microvascular spasm, respectively.

In recent years, there have been significant advances in the understanding of the pathophysiology VSA and MVA. However, the development of effective treatment has lagged behind. Current guidelines recommend traditional antianginal drugs, i.e. CCB and nitrates, as first-line treatments for patients with coronary artery vasospasm whilst disregarding the endotype of spasm [17, 25]. Despite guidelines recommendation, evidence for pharmacological treatments is limited to small study populations which are often not well characterised. Thus, therapeutic management remains mostly empirical with a “trial-and-error” approach. This often leads to polypharmacy in patients and repeated clinic visits due to chronic, refractory symptoms. Noteworthy, VSA and MVA are not a prognostically benign condition, as recent studies have reported increased rates of major adverse cardiovascular events [26–28]. Therefore, novel pharmacotherapeutic options are urgently required for these patients with an unmet clinical need.

The beneficial effect of an ET-1 receptor antagonist (ERA) in the treatment VSA was evaluated in two case reports using bosentan [29, 30]. Bosentan is an ERA with affinity for both the ET_A - and ET_B -receptor. Treating VSA or MVA due to epicardial or microvascular spasm is conceptually even more interesting with

selective ET_A-receptor blockers that leave the ET_B-receptor and its downstream denominator NO relatively unopposed. In a small randomized double-blind, study by Reriani, et al., the effect of a selective ET_A-receptor antagonist, atrastentan (10 mg o.d.), versus placebo on the coronary endothelial function in patients with early atherosclerosis was evaluated [31]. Forty-seven patients with coronary microvascular endothelial dysfunction were randomized. Microvascular endothelial dysfunction was defined as $\leq 50\%$ increase in coronary blood flow (CBF) in response to the maximal dose of ACh compared with baseline CBF. After 6 months treatment, coronary microvascular endothelial function improved significantly compared to baseline in the atrastentan group as versus the placebo group (Δ CBF: 39.67 % (23.23, 68.21) vs. -2.22 % (- 27.37, 15.28), $P < 0.001$). Unfortunately, following neutral results from phase III trials relating to the primary indications of atrastentan (hormone-refractory prostate cancer) its production was discontinued, thereby stopping any further investigation of its potential application in MVA. Macitentan is widely available and its safety has been documented in numerous clinical trials. In the VERA trial we will assess whether the ET_A receptor antagonist macitentan is beneficial in the treatment of CAS. For this trial we have chosen to only include patients diagnosed with VSA or MVA due to microvascular spasm (functional CMD) only as we do not expect that the vasodilatory capacity of macitentan will have a beneficial effect in structural CMD as there is a fixed reduced microcirculatory conductance.

Current European Society of Cardiology (ESC), American College of Cardiology Foundation/American Heart Association (ACC/AHA), and Japanese Circulation Society (JCS) guidelines emphasise that testing of coronary vasomotor function should be applied in routine practice in patients with suspected VSA or MVA [17, 25, 32, 33]. Although many reports are available that evaluate medical treatment in VSA and MVA patients, most studies include patients with suspected coronary vasomotor dysfunction without having performed invasive function testing, thereby disregarding the endotype of vasomotor disorder. The importance of coronary vasomotor function testing is to distinguish between vasodilation and vasoconstriction abnormalities of the epicardial and microvascular domains as these require a different diagnostic and therapeutic approach. Coronary vasomotor disorders that result in vasoconstriction are assessed with endothelial-dependent vasodilators and can occur either at the epicardial and/or microvascular level. MVA may be due to microvascular vasoconstriction and/or impaired conductance that is assessed using either endothelial-dependent or endothelial-independent testing respectively. Finally, a considerable proportion of patients have co-existing VSA and MVA. Without knowing the endotype of coronary vasomotor disorder in symptomatic patients, it can be difficult to establish optimal treatment. In our trial we aim to include only patients that underwent coronary vasomotor function testing and diagnosed with CAS. We have chosen to include VSA and MVA due to microvascular spasm patients as the ET-1 pathway might be involved both endotypes.

There are potential limitations due to the study design. The protocol involves a relative short duration of treatment (4 weeks) that may not reveal all unexpected adverse reaction to be expected during long-term use. Theoretically, the washout period could increase the possibility of unblinding by giving the participants additional insights into the effects of the trial medication. Since our trial was designed as a proof-of-concept, future clinical trials are needed to assess the outcomes in a real-world setting.

In summary, medicinal treatment of coronary artery spasm is challenging as patients often remain symptomatic and remain at risk for adverse cardiac events. The results of the VERA study will assess whether the selective ET_A receptor antagonist macitentan reduces the frequency and severity of anginal complaints in patients diagnosed with vasospastic angina due to epicardial spasm or microvascular angina due to microvascular spasm.

Declarations

Funding The VERA trial is an investigator-initiated clinical trial. This study was financially sponsored by Janssen-Cilag B.V.. Actelion Pharmaceuticals Nederland B.V. has provided the investigational medicinal product.

Conflicts of interest/competing interests Outside of the submitted work the authors disclose the following: P.D. has received consultancy fees from Philips and Abbott and research grants from Philips and Abbott. J.P. has received consultancy fees from Philips. The remaining authors have nothing to disclose.

Availability of data and material There is currently no plan to make individual participant data publicly available for this trial.

Code availability Not applicable.

Author contributions Rutger Feenstra: Conceptualization, Methodology, Investigation, Project administration, Data curation, Writing-Original draft preparation. Matthijs Boekholdt: Conceptualization, Methodology, Funding acquisition, Writing-review & editing. Yolande Appelman: Investigation, Writing-review & editing. Peter Damman: Investigation, Writing-review & editing. Marianne Wittekoek: Investigation, Writing-review & editing. Robbert de Winter: Writing-review & editing. Tim van de Hoef: Investigation, Writing-review & editing. Jan Piek: Investigation, Writing-review & editing. Marcel Beijck: Conceptualization, Methodology, Funding acquisition, Investigation, Project administration, Data curation, Writing-Original draft preparation, Supervision.

Ethics approval The VERA trial was approved by by the Dutch Medical Ethics Committee of the Amsterdam University Medical Centers (Reference 2018_213).

Consent to participate Informed consent will be obtained from all individual participants before study entry.

Consent for publication Not applicable.

Declarations of interest: none

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Tables

Due to technical limitations, table 1-2 is only available as a download in the Supplemental Files section.

Figures

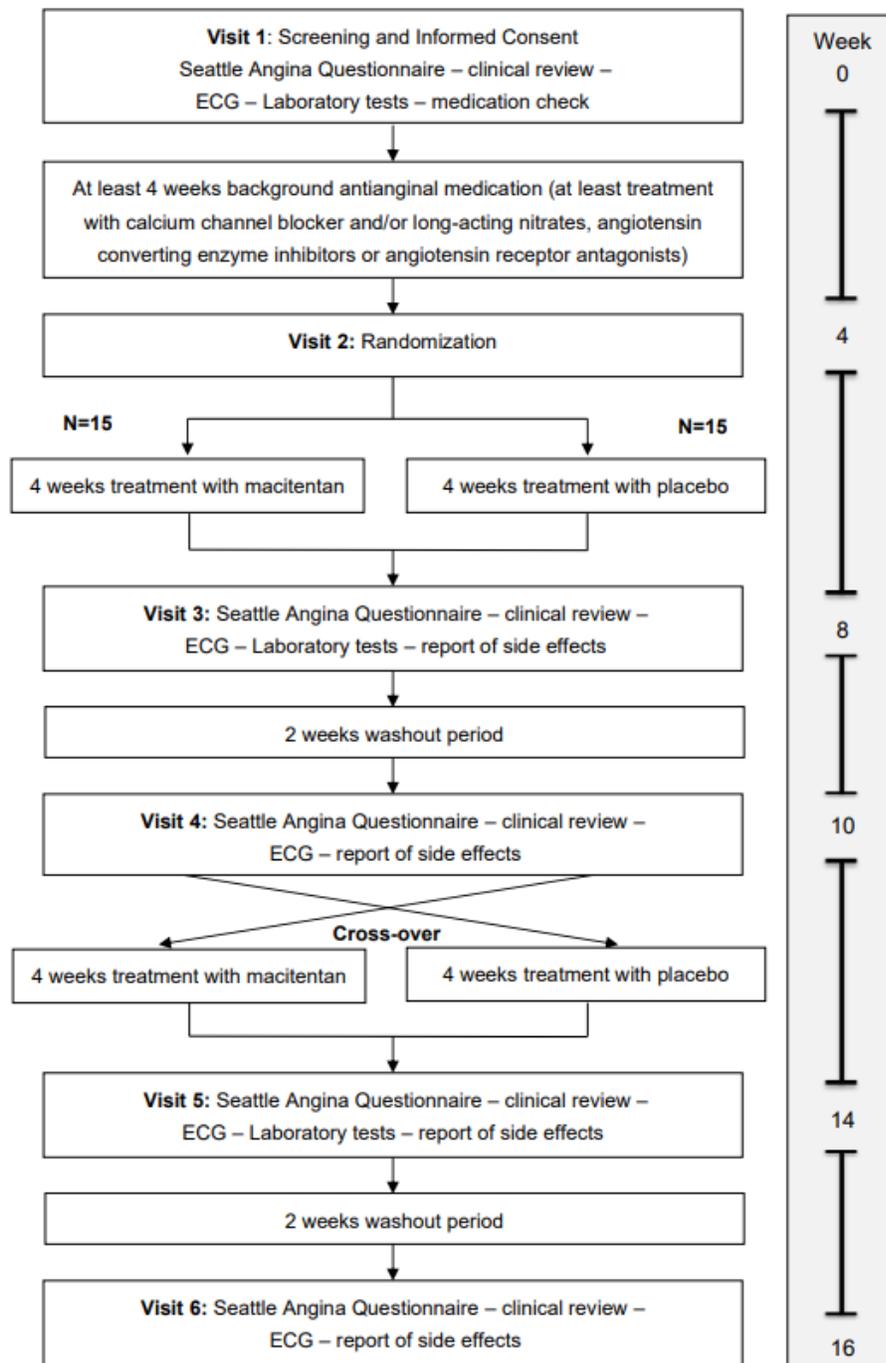


Figure 1

Schematic study design: flow diagram.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.xls
- Table2.xls