


# Rivaroxaban with Aspirin Versus Aspirin for Peripheral Arterial Disease and Intermittent Claudication. Rationale and Design of the COMPASS CLAUDICATION Trial

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## Abstract

**Background:** The COMPASS trial demonstrated that in patients with peripheral arterial disease, the combination of rivaroxaban and aspirin compared with aspirin reduces the risk of major adverse limb events, but it is not known whether this combination can also improve symptoms in patients with intermittent claudication. The primary objective of this study is to evaluate the effect of the combination on claudication distance.

**Study design:** Eighty-eight patients with intermittent claudication will be randomized to receive rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily or aspirin 100 mg once daily for 24 weeks. The primary outcome is the change in claudication distance from the baseline to 24 weeks, measured by 6 min walking test and treadmill test. The primary safety outcome is the incidence of major bleeding and clinically relevant non-major bleeding according to the International Society on Thrombosis and Hemostasis criteria.

**Summary:** The COMPASS CLAUDICATION trial will provide high-quality evidence regarding the effect of the combination of rivaroxaban and aspirin on claudication distance in patients with peripheral arterial disease.

## Keywords

intermittent claudication, peripheral arterial disease, anticoagulation, direct oral anticoagulants, rivaroxaban

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## Introduction

Peripheral arterial disease (PAD) is now the preferred term for partial or complete obstruction of peripheral arteries and one of the most common manifestations of atherosclerosis, affecting 27 million individuals in Europe and North America and 15 million in Latin America.<sup>1</sup> Although most patients with PAD are asymptomatic, a significant number of patients (around 5%) develop limb claudication and pain,<sup>2</sup> and 1% develop critical limb ischemia (CLI).<sup>3</sup>

It has long been recognized that insufficient blood supply to the legs could cause pain and dysfunction in the same way that coronary heart disease could lead to angina. This type of pain is known as intermittent claudication (IC) and is characterized as leg pain associated with walking and relieved by rest. IC is generally indicative of exercise-induced ischemic pain, especially in the calf, caused by PAD.<sup>3</sup> IC, a classic symptom of PAD, is the main barrier for physical activity practice, leading to reduced levels of physical activity, impairments in cardiovascular health, poor physical fitness, and decreased quality of life, which are proportional to the degree of walking impairment.<sup>4</sup>

The relative efficacy of treatments available for patients with IC, such as supervised exercise, medical therapy, and revascularization (either by surgical bypass or endovascular interventions), is not well established and has inconsistent results.<sup>5</sup> The Pivotal COMPASS study<sup>6</sup> showed that in patients with PAD, the vascular dose of rivaroxaban (2.5 mg orally twice daily) plus aspirin compared with aspirin alone reduced both major adverse cardiovascular events (MACE) and major adverse member events (MALE), including a 70% reduction in the risk of amputations. However, the effects of the combination of rivaroxaban and aspirin on IC have not been evaluated.<sup>7</sup>

The benefits of the combination of rivaroxaban and aspirin compared with aspirin alone in preventing MALE in patients with PAD are believed to be due to the prevention of recurrent thromboembolism, which can cause distal thrombotic luminal occlusion, especially in infrapopliteal arteries.<sup>8</sup> We hypothesized that by preventing distal thromboembolism, the vascular dose of rivaroxaban would also improve IC symptoms in symptomatic patients with PAD. This study aims to evaluate the effect of the vascular dose of rivaroxaban (2.5 mg twice daily) in combination with aspirin 100 mg once daily versus aspirin alone on claudication distance in patients with PAD.

## Methods

### Study Design

In this prospective, randomized, double-blind, active-controlled study, patients with documented PAD and symptomatic IC of the lower-extremities arteries from 5 selected sites in Brazil will be enrolled after signing informed consent. All data will be recorded with a pre-established clinical recording file (CRF) to demographics, risk factors (smoke, sedentary life), and clinical aspects of the patient's comorbidities. Previous treatment with physical exercises

will be allowed, and patients will be encouraged to keep their last physical activities.

Clinical diagnosis will be performed by a trained member of each team, with standard clinical evaluations, including imaging when indicated. Patients will be considered eligible if they have symptomatic PAD, have signed the informed consent form (ICF), and presents a resting ankle-brachial index (ABI) < 0.85 in at least one member, absolute claudication distance (ACD) < 500 meters, age > 18 years, no history of lower-limbs arterial bypass surgery or angioplasties in the last year, walking ability limited by the symptom of claudication, and the ability to complete a treadmill test. Patients with noncompressible vessel disease will not be included in this trial. The detailed inclusion and exclusion criteria are listed in Table 1.

## Randomization and Intervention

### Randomization

Participants will be randomly assigned to one of two treatment groups based on a computer-generated randomization schedule prepared before the study. In group 1, patients will receive rivaroxaban 2.5 mg BID plus aspirin 100 mg (acetylsalicylic acid) daily. In group 2, patients will receive 100 mg daily active aspirin, initiated (or continued) at randomization. Patients will be randomized electronically using dedicated CRF (RedCap version 11.0.3) in a ratio of 1:1. Randomization will be balanced using randomly swapped blocks. This is an open-label study.

The randomization list will be generated using validated software (RedCap) and blocks of variable sizes. To include the patient in the trial, investigators will have to access this trial website and complete a simple medical record form.

### Intervention

Patients will be submitted to an initial screening evaluation during their first visit and then undergo a single 6-min walking test (6MWT) followed by a treadmill test on a subsequent day. They are then randomized to either rivaroxaban vascular dose (2.5 mg bid plus aspirin) or placebo (rivaroxaban 2.5 mg bid) plus active aspirin on top of best medical management for IC treatment PAD patients. The 6MWT and the treadmill walking test will be repeated 12 and 24 weeks after randomization for primary efficacy endpoint evaluation.

A modified version of the Modified Walking Impairment Questionnaire (WIQ) will be administered at baseline before 6MWT and treadmill testing on the same day and at each visit (12 and 24 months).

### Ankle-brachial index (ABI)

Two experienced evaluators will measure ankle and brachial systolic blood pressure simultaneously, as described and validated previously. Brachial systolic blood pressure will be measured by auscultation, and ankle (posterior tibial or dorsalis pedis) systolic blood pressure was assessed using a portable unidirectional

**Table 1.** Inclusion and exclusion criteria.**Inclusion criteria**

Patients with symptomatic PAD who signed the informed consent form (ICF) with:

- (a) Ankle-brachial index (ABI) < 0.85 in at least one member, and
- (b) ACD < 500 meters
- (c) age > 18 years
- (d) No history of lower-limbs arterial bypass surgery or angioplasties in the last year
- (e) walking ability limited by the symptom of claudication and
- (f) ability to complete a treadmill test

**Exclusion criteria**

- (a) high risk of bleeding  
Evidence of a recent history of bleeding in the last three months, hemorrhagic diathesis in the last three months, changes in coagulation tests (INR > 1.5 or aPTT > 2), pulmonary bronchiectasis, active cancer, active gastroduodenal ulcer, use of dual antiplatelet therapy.
- (b) Recent hemorrhagic stroke (1 month) or any history of previous hemorrhagic or lacunar stroke, if detected by occasional prior tomography, which is not part of the study protocol.
- (c) severe heart failure (NYHA class III and IV)
- (d) advanced stable kidney disease (estimated creatinine clearance < 15 ml per minute), defined as eGFR < 15 mL/min by 1.73 m<sup>2</sup> calculated by the abbreviated formula Diet Modification in Kidney Disease (MDRD).
- (e) Continuous use of pentoxifylline or cilostazol
- (f) Cardiac conditions that may lead to heart failure, such as unstable angina, arrhythmias, acute myocardial infarction in the last three months
- (g) Non-cardiovascular conditions are considered by the researcher as associated with a poor prognosis.
  - (a) Active cancer with a life expectancy of fewer than six months
  - (b) Collagen limiting diseases
  - (c) Previous or scheduled surgeries that prevent functional evaluation
  - (d) Orthopedic diseases that hinder functional evaluation
- (h) Pregnancy. Women with the potential to bear children should be under contraceptive strategies and take a negative pregnancy test to be enrolled.
- (i) Patients with COVID in the contagious phase (PCR +)

Doppler ultrasound unit. Resting ABI will be calculated for each leg using the higher ankle systolic blood pressure from the two arteries, divided by the higher brachial systolic blood pressure from the arms. The leg with the lowest ABI value will be used to define the ABI of each patient.<sup>9</sup>

**Six-Minutes Walking Test**

To analyze the walking capacity, each patient will undergo a 6MWT supervised by a trained kinesiologist. Two cones will be placed 30 meters apart in a marked corridor as previously described.<sup>10</sup> Patients will be instructed to walk as many laps around the cones as possible and inform when the claudication symptom occurred. The kinesiologist will record the initial claudication distance (ICD) and total walking distance (TWD) to evaluate the walking capacity. Furthermore, distance walked under claudication symptoms will be calculated by the delta between TWD and ICD ( $\Delta TWD - ICD$ ). In PAD patients, 6MWT presents high reliability with the intraclass correlation coefficient ranging between 0.94 and 1.00 and the coefficient of variation ranging between 0.4 and 1.6%. During the test, the walking velocity will be calculated by dividing TWD by six minutes (test duration).

**Treadmill Walking Test**

To analyze the walking capacity, each patient from the subset will undergo a treadmill walking test supervised by a trained

kinesiologist. The treadmill walk will occur using a constant workload protocol. This means that the treadmill speed will be constant at 3.2 km/h, with a 12% grade or incline. The intermittent claudication distance (ICD) and ACD are calculated using a standardized treadmill test given the day-to-day variation in claudicant.<sup>11</sup> It includes two baseline measures and 12 and 24 weeks at the end of the treatment study.

**Modified Walking Impairment Questionnaire (WIQ)**

A modified version of the WIQ will be administered at baseline before treadmill testing on the same day and at each visit after that. The WIQ is a validated tool used to assess walking ability, specifically walking distance, speed, and stair climbing, in patients with PAD and IC. This questionnaire will be administered at 12- and 24-weeks post-randomization to all individuals enrolled in the trial.

**Primary Objectives / Outcomes**

Evaluate if the vascular dose of rivaroxaban (rivaroxaban 2.5 mg twice daily + aspirin 100 mg once daily) is superior to active aspirin 100 mg once daily in patients with PAD and IC in functional walking tests. This is an exploratory study, hypothesis-generating of the possible superiority of the vascular dose of rivaroxaban compared to aspirin in improving the distance of IC of the lower limbs.

## Primary Efficacy Outcomes

1. Improvement of the initial claudication distance (ICD) and the total walking distance (TWD) in meters to evaluate walking capacity. The distance walked under claudication (DWUC, which is the delta between TWD and ICD [TWD - ICD]) and walking velocity speed (WV) in the functional test – 6-min walk test (6MWT).
2. The absolute claudication distance (ACD) while walking on a treadmill. ACD is defined as the total distance traveled on a treadmill until it stops due to IC pain.
3. Modified Walking Impairment Questionnaire (WIQ): A modified version of WIQ will be administered at baseline before the treadmill test on the same day and each visit after that. WIQ is a validated tool used to assess walking ability, specifically walking distance, speed, and stair climbing, in patients with PAD and IC.

## Secondary Efficacy Endpoints / Outcomes

Exploratory efficacy assessment: major adverse cardiovascular events - MACE, and major adverse events of the limbs - MALE)

Cardiovascular events will be captured as Adverse Events of special interest.

## Safety Objectives / Outcomes

For this purpose, exploratory outcomes (major bleeding + clinically non-relevant bleeding) will be used, according to the International Society on Thrombosis and Hemostasis (ISTH) bleeding criteria.<sup>12</sup>

Severe bleeding according to the modified ISTH is defined as:

- (a) fatal bleeding and
- (b) symptomatic bleeding in a vital area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial or intramuscular region with compartment syndrome, or bleeding at the surgical site that requires further surgery, and
- (c) bleeding leading to hospitalization.

Clinically relevant non-major bleeding according to the modified ISTH is defined as:

Any sign or symptom of bleeding (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found only by imaging) that does not fit the criteria for ISTH definition of severe bleeding but meets at least one of the following criteria:

- (a) requiring medical intervention by a health professional
- (b) leading to hospitalization or increased level of care
- (c) requesting a presentational assessment (ie, not just a telephone or electronic evaluation)

## COVID Management

COVID positive (detected by PCR) patients will not be included. If developing COVID during the protocol, patients will undergo routine follow-up in the study (design and analysis are intention-to-treat) if asymptomatic. If symptomatic, patients are called for an extra visit and excluded if considered compromised to perform functional tests by the principal investigator. Given the study's exploratory nature and the small sample, we will complete the inclusion until reaching the proposed sample (88 patients), even if a significant number of patients develop symptomatic COVID.

Figure 1 depicts the Compass Claudication study design in detail.

## Statistical Analysis

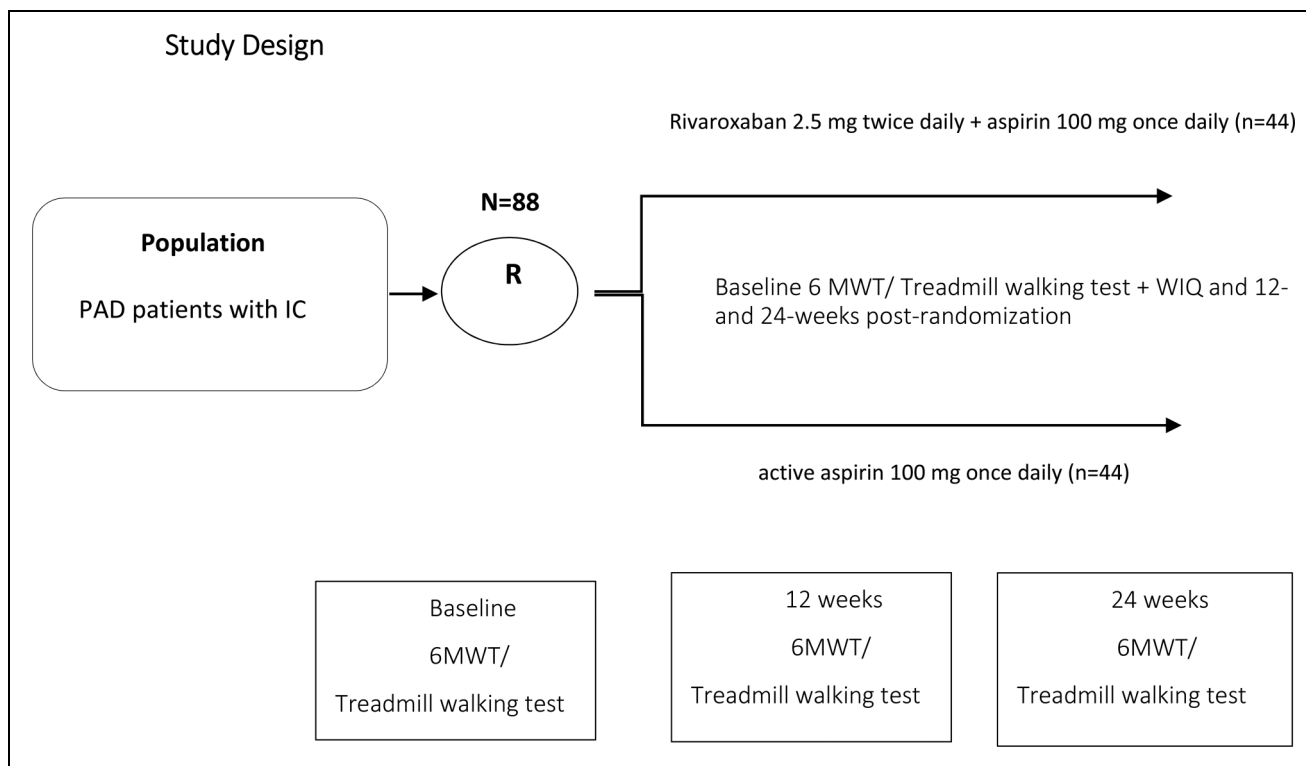
The original sample size estimate was calculated for the primary efficacy outcome of the change in the TWD log at baseline until week 24. Grouped SD estimates were based on a previous clinical study using a Gardner-grade treadmill protocol in a similar patient population. The drug effect study is unknown, but extrapolations of statin effects on HF were improved TWD averages by 63% (81.15 s) in the 80 mg atorvastatin treatment group compared to 38% (39.8 s,  $P=0.025$ ) in the placebo group.<sup>13</sup> Based on these studies, we expect standard deviations of around 12% in the outcomes studied. Forty patients per arm would provide 80% of power with an  $\alpha=0.05$ , based on a test of 2 samples of equal variance  $t$ , to detect a difference in treatment in the change in the TWD log on day 168 (week 24) 40%. To account for a dropout rate of 10%, the inclusion of 44 patients per arm was planned ( $n=88$  total).

The primary analysis will be based on a test of 2 samples of equal variance  $t$  of the null hypothesis that the difference between the treatment groups in the change of baseline to day 168 (week 24) in the TWD log was the same in both groups. Natural TWD logarithm transformations will be used due to the known distorted distribution of TWDs. Data transformed into log table scans will be transformed into geometric media for presenting data in units of seconds. The percentage variation of the baseline geometric mean for week 24 will be presented for each group with a 95% confidence interval (CI).

Secondary endpoints, including WQF, will be analyzed with mixed models. This strategy allows the inclusion of all data obtained over the 24 weeks of testing and testing the overall treatment interaction by time. Random subject effects and a self-correlation term will be included in the model.

For the secondary analysis (MACE and MALE and bleeding), Kaplan-Meier curves will be constructed to assess whether rivaroxaban 2.5 mg BID plus aspirin compared to aspirin only will change the time to a combined efficacy and safety outcome as judged by the Clinical Events Committee.

The study results will be analyzed with version 9.1 of the SAS (SAS Institute Inc, Cary, NC). Efficacy analyses will be performed in the intention to treat population, defined as subjects who completed at least 6 MWT post-baseline test.



**Figure 1.** Compass Claudication trial study design.

Safety data are reported for all individuals who received at least one dose of study medication (intent to treat). Categorical variables will be summarized using frequency and percentage by group, and baseline values were compared using  $X^2$  tests or fisher’s exact test when appropriate. The continuous variables will be summarized by the total number, mean, and SD; baseline values will be compared using t-tests. All statistical tests will be two sides with an alpha level of 0.05.

Currently (December 2021), 49 patients have been enrolled. The total enrollment (88 patients) is expected for February 2022. The trial is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT 04853719).

**Discussion**

Despite the robust evidence from the COMPASS trial demonstrating the efficacy of the combination of rivaroxaban and aspirin compared with aspirin in reducing MACE and MALE in patients with PAD, it is not known whether the combination can improve walking distance in patients with IC.

Pentoxifylline and cilostazol are currently the only FDA-approved therapies to improve walking performance in patients with PAD and are widely used despite their limited efficacy. Cilostazol is generally preferred because it improves walking distance (by around 60 meters) but also has adverse effects, including an increased risk of bleeding. There is currently insufficient data on whether cilostazol reduces major CV or limb events or improves the quality of life.<sup>13</sup>

The widespread use of cilostazol in patients with PAD and IC has an important impact on patient care. In patients already taking cilostazol, clinicians are reluctant to consider the further use of rivaroxaban, both because of the additional cost (cilostazol is expensive) and the further increase in the risk of bleeding. If rivaroxaban is shown to improve walking distance in patients with IC, it is expected to rapidly replace cilostazol in patients with IC because of its proven cardiovascular benefits.

A possible limitation of the COMPASS CLAUDICATION trial is that it is powered to detect a 40% improvement in walking distance with the combination compared with aspirin alone. Power to detect a smaller but still clinically worthwhile improvement would be desirable but requires a larger study.

**Conclusion**

The COMPASS CLAUDICATION trial results will provide high-quality evidence for the efficacy of the combination of the vascular dose of rivaroxaban in PAD patients with limiting IC.

**Declaration of Conflicting Interests**

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### Ethical Approval

Ethical approval to report this case was obtained from Comitê de Ética Hospital Leforte (#40190420.0.1001.5485).

### Informed Consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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### Trial Registration

This trial is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT04853719).

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