

A Fixed-Dose Triple-Combination Therapy for the Initial Steps of Hypertension Treatment: Protocol for the NEXT Randomized Clinical Trial

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Introduction

Complications from arterial hypertension account for an estimated 18 deaths per minute worldwide,¹ establishing it as the second leading risk factor for global mortality.² Between 1990 and 2019, the number of adults with arterial hypertension doubled from 650 million to 1.3 billion. Of these, only 54% are diagnosed, 42% are treated, and a mere 21% of those treated achieve adequate blood pressure (BP) control.¹

Although effective BP control often requires the use of multiple drugs, monotherapy remains a predominant initial approach to arterial hypertension management globally, which limits the timely achievement of therapeutic goals.³ This is significant because even modest reductions in systolic BP of 5 mmHg are associated with an approximate 10% reduction in the risk of major cardiovascular events, irrespective of pre-existing cardiovascular disease.⁴

In this context, numerous studies and international guidelines recommend initiating treatment with low-dose combination therapy, preferably in a fixed-dose, single-pill formulation, to improve patient adherence and achieve more effective BP control.⁵⁻⁸ Beyond improved efficacy, fixed-dose combinations reduce the need for frequent dose titrations

and are associated with a lower incidence of cardiovascular events compared to monotherapy.⁹⁻¹³

Recent strategies have explored the use of triple fixed-dose combinations at low or moderate doses. These have demonstrated superior BP control, fewer adverse effects, and better performance compared to the conventional up-titration of dual therapy, along with good tolerability and clinical superiority over traditional stepped-care approaches.¹³⁻¹⁶ This approach challenges the paradigm of clinical inertia by providing a more potent initial intensification strategy.¹⁷⁻¹⁹

The assessment of cardiovascular risk can be enhanced by utilizing advanced vascular biomarkers. These include pulse wave velocity (PWV), the gold-standard non-invasive method for assessing arterial stiffness and an independent predictor of cardiovascular mortality, and flow-mediated dilation (FMD), the gold-standard method for evaluating endothelial function, which also has established prognostic value.^{20,21}

Given this scenario, this randomized clinical trial was designed to compare the impact of a triple versus a dual fixed-dose combination on peripheral and central BP, arterial stiffness, and endothelial function. The central hypothesis is that the triple-therapy strategy will provide greater efficacy and vascular protection in patients requiring an intensification of their antihypertensive regimen.

Keywords

Hypertension; Cardiology; Randomized Controlled Trial; Cardiovascular Diseases

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Objectives

Primary objective

To evaluate whether a fixed-dose triple therapy at low to moderate doses is superior to a fixed-dose dual therapy at moderate to high doses in reducing peripheral and central BP and improving arterial stiffness, as measured by PWV, and endothelial function, assessed by FMD, over a 90-day treatment period.

Secondary objectives

- To compare the efficacy of triple therapy versus dual therapy in controlling peripheral BP.
- To compare the efficacy of triple therapy versus dual therapy in controlling central BP.
- To determine the effect of triple therapy compared to dual therapy in reducing arterial stiffness, assessed by PWV.
- To determine whether triple therapy, compared to dual therapy, improves endothelial function, as measured by FMD, in a predefined subgroup of participants enrolled at a designated center.

Safety secondary objectives

- To evaluate changes in renal function, assessed by estimated glomerular filtration rate (eGFR), calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
- To assess changes in serum potassium levels.
- To evaluate the incidence of adverse events and serious adverse events.
- To assess treatment discontinuation due to adverse events.

Methods

Study type and setting

This is a national, multicenter, prospective, randomized, open-label, blinded-endpoint (PROBE), phase IV clinical trial with a parallel-group design involving two active treatment arms (triple versus dual therapy). The trial is registered in the Brazilian Clinical Trials Registry (ReBEC RBR-5p9w6vz; UTN U1111-1318-0831) and follows the SPIRIT recommendations.

It will be conducted across six Brazilian academic referral centers, coordinated by the Hypertension Unit of the Federal University of Goiás, and will enroll participants with arterial hypertension. Individual study duration is approximately 101 days, including an 11-day screening and a 90 ± 4 -day treatment period. The study aims to compare the efficacy of two antihypertensive strategies in reducing peripheral and central BP, as well as in improving markers of arterial stiffness and endothelial function.

Recruitment

For this study, the inclusion and exclusion criteria will be widely disseminated among cardiologists at the participating institutions. Additionally, a thorough review of electronic patient databases will be conducted to identify potential candidates. Eligible participants will be contacted by telephone to schedule the initial visit at the research center.

The study will include three main visits: a screening/selection visit (V –1), a randomization visit (V0), and a final visit (V1). The study workflow is described in Figure 1.

During the screening visit, a researcher will explain the study objectives and procedures to potential participants. Individuals meeting the eligibility criteria and agreeing to participate will provide written informed consent by signing

the informed consent form. The consent process will include a detailed explanation of the study's objectives, potential risks and benefits, and the participant's right to withdraw from the study at any time without penalty.

Following consent, a blood sample will be collected to assess renal function (creatinine and potassium) and pregnancy status (beta-human chorionic gonadotropin [β -hCG] in women of childbearing potential). Renal function will be evaluated by eGFR using the CKD-EPI equation.^{22,23} The research team will conduct a comprehensive eligibility assessment to confirm compliance with all inclusion and exclusion criteria. Additionally, contact information, including the participant's or a caregiver's telephone number, will be recorded to facilitate communication and follow-up throughout the study period.

Inclusion criteria for this study are as follows: (1) adults aged 18 years or older; (2) diagnosis of arterial hypertension currently managed with a low-dose dual drug combination, presenting with office systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg.

Exclusion criteria are: (1) presence of any clinical or laboratory condition that, in the investigator's judgment, poses a risk to study participation or indicates uncontrolled chronic disease (e.g., diabetes mellitus with HbA1c $> 9\%$); (2) history of alcohol or illicit drug use disorder within the preceding 2 years; (3) women of childbearing potential not using reliable contraception or who are pregnant, breastfeeding, or planning pregnancy during the study period; (4) known allergy or hypersensitivity to any study drug (olmesartan, hydrochlorothiazide, or amlodipine); (5) chronic kidney disease with a persistent eGFR < 30 mL/min/1.73 m², calculated using the CKD-EPI equation; (6) participation in another interventional clinical trial within the past 12 months, unless the investigator determines potential direct benefit to the patient.

Sample size

The sample size was calculated based on the mean and standard deviation of systolic BP reduction reported by Oparil et al.²³ Considering an effect size of 0.7 and a systolic BP difference of 9 mmHg, the G*Power software ($\alpha = 0.05$; power = 95%) indicated the need for 54 participants per group (1:1 randomization). For a mean difference of 5 mmHg and an effect size of 0.4, the same criteria ($\alpha = 0.05$; power = 95%; 1:1 randomization) resulted in 151 participants per group.

The study population will consist of participants with arterial hypertension, recruited from academic referral centers. The sample size was set at 336 individuals, considering a 10% margin for potential dropouts. Thus, the final sample should consist of approximately 300 participants, equally distributed into two groups of 150 subjects each.

Randomization

After confirming all inclusion and exclusion criteria, peripheral and central BP measurements will be performed. Participants will then be randomized in a 1:1 ratio to one of the two treatment arms using a secure, web-based platform (Randomizer.org). Patients enrolled through the Hypertension Unit will undergo assessment of endothelial function by FMD.

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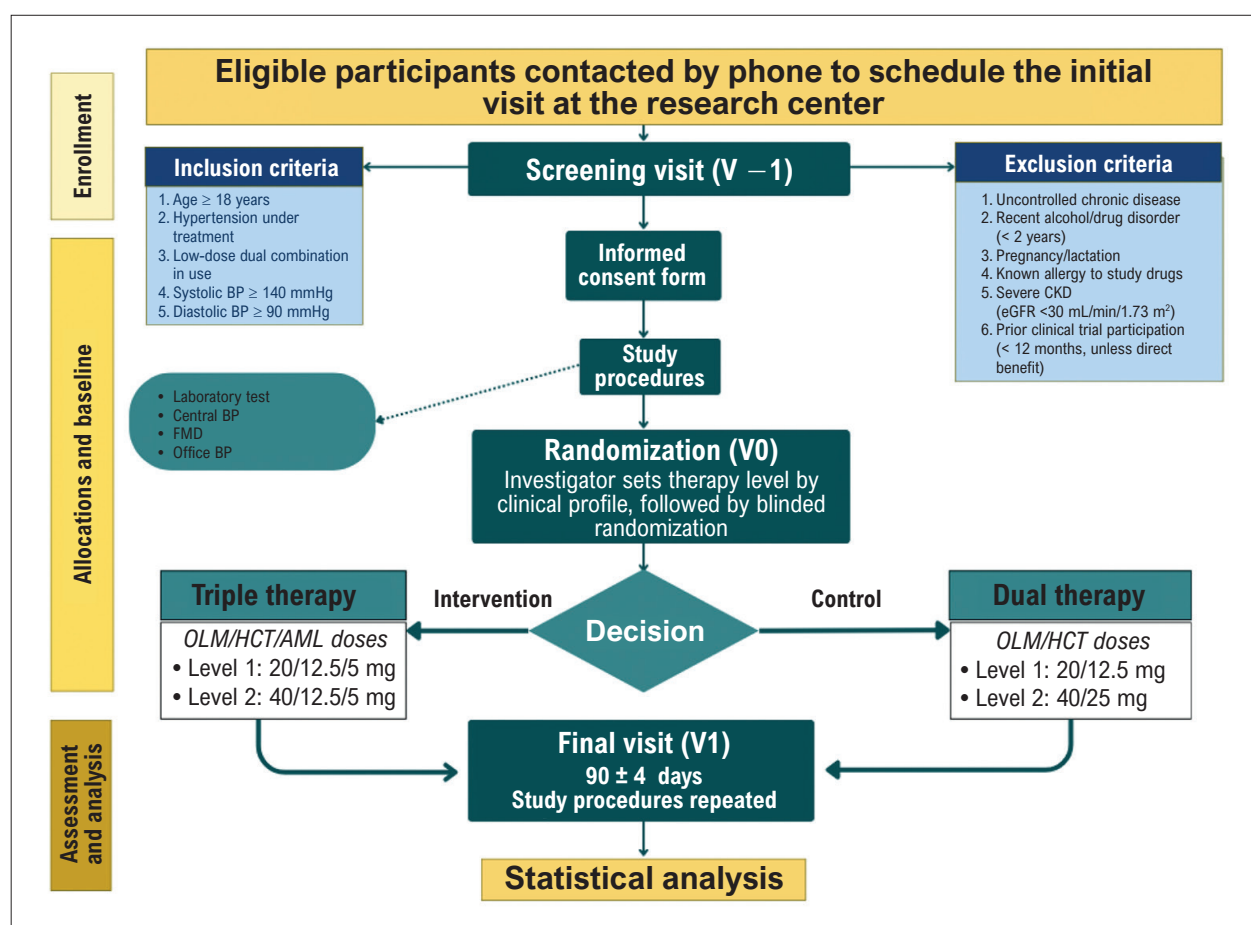


Figure 1 – NEXT flow diagram. AML: amlodipine; BP: blood pressure; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; FMD: flow-mediated dilation; HCT: hydrochlorothiazide; OLM: olmesartan.

Treatment will be maintained for 90 $\pm$ 4 days. Between visits V0 and V1, participants will be instructed to immediately report any suspected adverse events to the study team. All reported events will be recorded by the investigator in the medical record and coded according to Medical Dictionary for Regulatory Activities (MedDRA) terminology.

No washout will be implemented. Participants are hypertensive patients with uncontrolled BP despite ongoing dual therapy; therefore, temporary discontinuation of antihypertensive treatment could expose them to unnecessary clinical risk. The study was designed as a pragmatic comparison of treatment intensification strategies, reflecting real-world practice. Baseline assessments will be performed under stable therapy prior to randomization.

Blinding

At the initial medical evaluation, the investigator will determine the appropriate therapeutic level (level 1 or level 2) for dose intensification based on predefined clinical criteria, including baseline BP values and prior antihypertensive therapy, in order to ensure patient safety and reflect routine clinical practice. This information will be provided to an unblinded member of the research team, who will perform

the randomization and dispense the study medication. The investigator responsible for outcome assessments will remain blinded to the treatment allocation.

Interventions

Experimental intervention

Intervention group (triple therapy): Participants will receive a fixed-dose combination of olmesartan/hydrochlorothiazide/amlodipine at a dose of 20/12.5/5 mg (level 1) or 40/12.5/5 mg (level 2), administered once daily for 90 $\pm$ 4 days.

Control intervention

Control group (dual therapy): Participants will receive a fixed-dose combination of olmesartan/hydrochlorothiazide at a dose of 20/12.5 mg (level 1) or 40/25 mg (level 2), administered once daily for 90 $\pm$ 4 days.

Outcomes and measurements

The primary outcomes of the study are the changes in systolic and diastolic BP, both peripheral and central, from

baseline (V0) to day 90 (V1), and the change in arterial stiffness assessed by PWV using an Arteriograph AOP device.

The secondary outcomes include the proportion of participants achieving BP control, the change in endothelial function assessed by FMD using an UNEX EF 38G ultrasound system in a predefined subgroup.

As a safety outcome, renal function will be monitored through eGFR, calculated using the CKD-EPI equation based on serum creatinine, to evaluate the safety of the proposed interventions.

Blood pressure, vascular function, and laboratory assessments

During the screening visit, after signing the informed consent form, peripheral blood samples will be collected for the measurement of creatinine, potassium, and β -hCG (in women of childbearing potential). These tests will provide baseline information on renal function and exclude pregnancy prior to randomization, ensuring participant safety before initiation of treatment. The study assessment schedule is summarized in Table 1.

Central blood pressure measurement

Central BP will be assessed at two time points, randomization (V0) and the final visit (V1), using an Arteriograph AOP device, a validated non-invasive system capable of simultaneously measuring central and peripheral BP, PWV, augmentation index, central pulse pressure, and amplified pulse pressure. These parameters provide comprehensive information on arterial resistance and compliance, allowing the evaluation of both hemodynamic and vascular effects of the study interventions over time.

Flow-mediated dilation

Endothelial function will be evaluated by measuring FMD of the brachial artery in a predefined subgroup of participants. FMD will be assessed in a predefined subgroup of participants enrolled at the coordinating center, where certified equipment and trained personnel are available for standardized analysis. The subgroup is defined solely based on logistical feasibility, as only one center has the necessary infrastructure to perform this examination.

This technique is safe, non-invasive, and reproducible, and it reflects the functional status of the vascular endothelium.²⁴ Values below 10% are associated with an increased risk of cardiovascular events.²⁵ The examination will be performed at visits V0 and V1 following a standardized procedure: a cuff will be inflated on the forearm to 50 mmHg above systolic BP and maintained for 5 minutes. Upon rapid deflation, brachial artery dilation will be recorded using dynamic ultrasound with continuous monitoring for up to 180 seconds. The entire process will be automated using the UNEX EF 38G device, recognized as the gold standard for this methodology, and conducted in accordance with the International Brachial Artery Reactivity Task Force recommendations.²⁶

Office blood pressure measurement

Office BP will be measured at all study visits according to national and international guideline recommendations. Measurements will be taken by trained members of the research team using a validated semi-automatic oscillometric device (Omron HEM-7113). Three consecutive readings will occur after a 5-minute rest in a quiet environment, with the participant seated, legs uncrossed, and back supported. The mean of the last two readings will be used for analysis, ensuring greater accuracy and reproducibility across assessments.

Statistical analysis

Data will be recorded in the electronic case report form via the REDCap platform and exported for analysis using Stata version 14. Variables related to the effectiveness and safety of the interventions will be evaluated. Qualitative variables will be described as absolute and relative frequencies, while quantitative variables will be expressed as means and standard deviations or medians and interquartile ranges, depending on the distribution as assessed by the Kolmogorov–Smirnov test. Comparisons of baseline characteristics between groups will be performed using the chi-square test for qualitative variables and the Student's t-test or Mann–Whitney U test for quantitative variables, as appropriate.

The primary analysis will be conducted on the intention-to-treat population, defined as all randomized participants analyzed in the group to which they were assigned,

Table 1 – Study assessment schedule

Visit	Timing	Key assessments
V – 1 (Screening)	Within 11 days before baseline	Eligibility check, consent, creatinine, potassium, β -hCG (women)
V0 (Randomization)	Day 0	Baseline office BP, central BP, PWV, FMD (subgroup); randomization; dispensing medication
V1 (Final visit)	Day 90 $\pm$ 4	Repeat all baseline measures; return of unused tablets for adherence check

All data are entered into the REDCap electronic case-report form (eCRF). BP: blood pressure; FMD: flow-mediated dilation; PWV: pulse wave velocity; β -hCG: beta-human chorionic gonadotropin.

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regardless of adherence or protocol deviations. The primary outcomes (change in BP and PWV) will be compared between groups using an analysis of covariance (ANCOVA) model, with the baseline value of the respective outcome included as a covariate. A significance level of $p < 0.05$ will be adopted for all analyses. A per-protocol analysis will also be performed as a sensitivity analysis.

Data management

Study data will be securely recorded in REDCap and accessible only to authorized investigators. Participants will be identified by coded IDs, ensuring confidentiality. Records will be stored for ≥ 5 years after trial completion.

Patient and public involvement

Participants or the public were not involved in designing, conducting, or reporting this trial.

Ethics and dissemination

The clinical trial will be conducted in accordance with the ethical principles of the Declaration of Helsinki, the guidelines of the ICH Good Clinical Practice Manual, and current Brazilian legislation, including Brazilian National Health Council (CNS) Resolution No. 466/12. The protocol was approved by the Research Ethics Committee of the Clinical Hospital of the Federal University of Goiás (CAAE: 80032924.8.0000.5078) on July 11, 2024.

All participants will sign the informed consent form prior to undergoing any study-related procedures. Potential risks, such as discomfort from venipuncture and BP measurements, will be minimized through the application of standardized techniques performed by properly trained professionals. The research team will be available full-time to provide continuous monitoring and appropriate management of any adverse events that may occur during the study.

Participants' information will be coded to ensure confidentiality, and the data will be securely stored for a minimum period of 5 years, after which it will be properly discarded. There will be no cost to participants for any procedures performed within the scope of the study.

Monitoring and safety procedures

Participants will be instructed to report any adverse events throughout the 90 ± 4 -day treatment. All events will be recorded and coded using MedDRA terminology. The research team will provide continuous clinical monitoring and appropriate management of adverse events.

Discontinuation criteria

1. Participants may discontinue the study treatment or be withdrawn from the trial under the following circumstances:
2. Serious adverse events: Occurrence of any serious adverse event related to the study medication or that, in the investigator's judgment, compromises participant safety.

3. Clinically relevant symptoms or clinical conditions considered by the investigator to be related to the study intervention include recurrent episodes of symptomatic hypotension requiring medical evaluation, therapeutic intervention, or adjustment of the study medication outside the protocol specifications, as well as uncontrolled hypertension defined as persistent systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg despite confirmed adherence to the study medication, requiring additional therapeutic intervention.
4. Participant withdrawal: Withdrawal of informed consent at any time, without need for justification.
5. Investigator decision: If, in the investigator's clinical judgment, continued participation is not in the best interest of the participant.
6. Protocol non-adherence: Significant non-compliance with study procedures that may affect data integrity or participant safety.

Participants who discontinue treatment will be encouraged to complete outcome assessments whenever possible to preserve intention-to-treat analysis.

Protocol validation

The early use of fixed-dose combinations of three antihypertensive agents for treatment intensification may provide more effective control of both peripheral and central BP compared to escalating dual-therapy doses. This strategy has the potential to improve key hemodynamic parameters, such as arterial compliance, which may indicate additional cardiovascular benefits beyond BP reduction alone. The overall rationale, intervention strategy, participating centers, and primary outcomes evaluated in the NEXT trial are summarized in Figure 2.

If the hypothesis of the superiority of triple therapy is confirmed, the results could underscore the need to revise current therapeutic approaches for the management of hypertension in patients requiring treatment intensification. This evidence may support changes in treatment guidelines, promoting more effective interventions with a measurable impact on cardiovascular morbidity and mortality.

Study strengths and limitations

Strengths

- This is a national, multicenter, prospective, randomized, open-label, blinded-endpoint (PROBE), phase IV clinical trial, providing high external validity while ensuring blinded outcome assessment.
- The study evaluates both peripheral and central BP and includes arterial stiffness and endothelial function, which are advanced vascular biomarkers with proven prognostic value.
- The design follows intention-to-treat analysis principles, strengthening the robustness and clinical applicability of results.

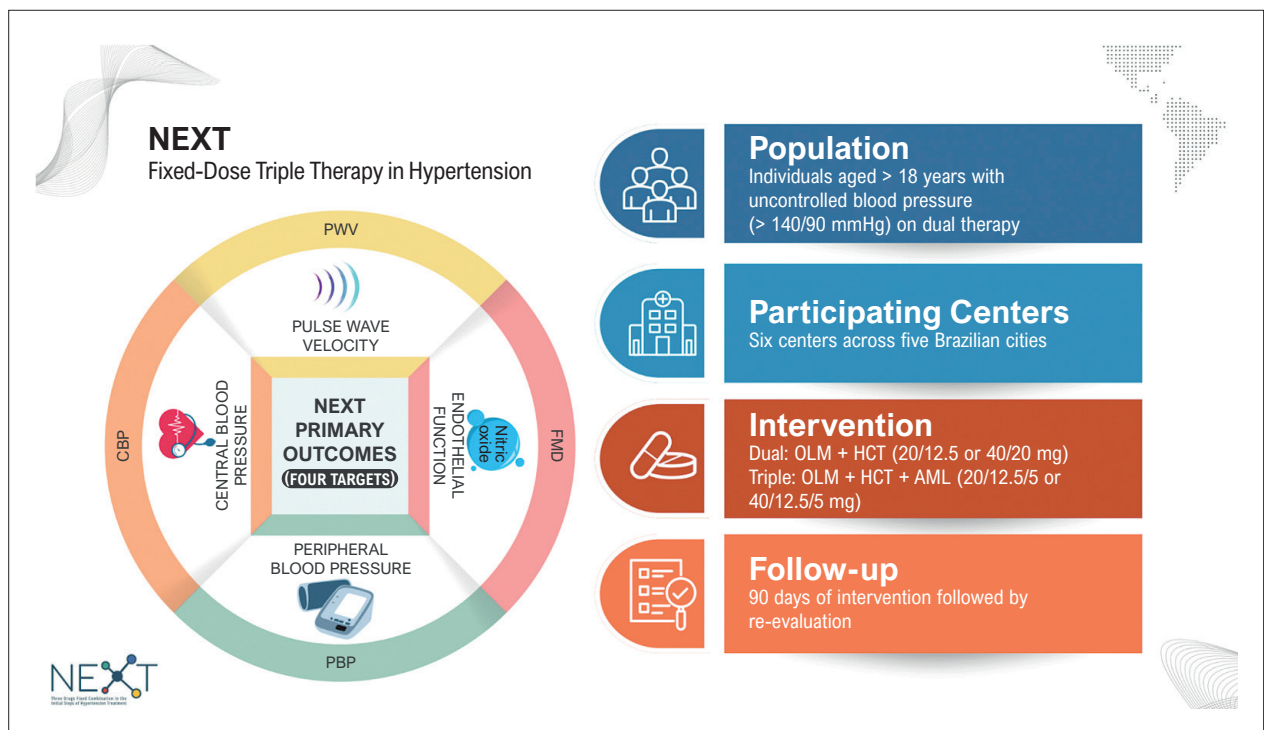


Figure 2 – A Fixed-Dose Triple-Combination Therapy for the Initial Steps of Hypertension Treatment: Protocol for the NEXT Randomized Clinical Trial. AML: amlodipine; HCT: hydrochlorothiazide; OLM: olmesartan.

- The protocol explores an early fixed-dose triple-combination strategy, potentially shifting the paradigm of hypertension treatment intensification and supporting future guideline updates.
- The trial uses standardized, validated equipment (ArteriS AOP and UNEX EF 38G) across all sites to ensure methodological consistency and reproducibility.

Limitations

- The short follow-up period (90 days) may not capture long-term cardiovascular outcomes.
- FMD will be measured only in a predefined subgroup, which may limit the generalizability of endothelial function findings.
- The study population consists of patients under specialist care, which may reduce extrapolation to primary care settings.

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Author Contributions

Conception and design of the research: Sousa ALL, Vitorino PVO, Souza WKS. Acquisition of data:

Orlow R, Sousa CC, Inuzuka S, Feitosa A, Brandão A, Gomes MM, Guimarães Neto VS, Bezerra R, Santos MC, Cestario EES, Barbosa ECD, Souza WKS. Analysis and interpretation of the data: Orlow R, Sousa ALL. Statistical analysis: Sousa ALL. Obtaining financing: Souza WKS. Writing of the manuscript: Orlow R. Critical revision of the manuscript for intellectual content: Orlow R, Sousa CC, Inuzuka S, Feitosa A, Brandão A, Gomes MM, Guimarães Neto VS, Bezerra R, Santos MC, Cestario EES, Barbosa ECD, Sousa ALL, Souza WKS.

Potential Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. This study received partial financial and material support from Daiichi Sankyo Brasil Farmacêutica Ltda. The sponsor had no influence on the study design, data analysis, interpretation of results, or decision to publish the manuscript.

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Study Association

This article is part of the thesis of Doctoral submitted by Rogerio Orlow de Oliveira, from Universidade Federal de Goiás.

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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Universidade Federal de Goiás under the protocol number 80032924.8.0000.5078. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

All datasets supporting the results of this study are available upon request from the corresponding author.

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