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Colchicine for Left Ventricular Infarct Size Reduction in Acute Myocardial Infarction: A Phase II, Multicenter, Randomized, Double-Blinded, Placebo-Controlled Study Protocol – The COVERT-MI Study

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Keywords

Colchicine · Left ventricular remodeling · ST-segment elevation myocardial infarction · Acute myocardial infarction · Magnetic resonance imaging · Inflammation

Abstract

Inflammatory processes have been identified as key mediators of ischemia-reperfusion injury in ST-segment elevation myocardial infarction (STEMI). They add damage to the myo-

cardium and are associated with clinical adverse events (heart failure and cardiovascular death) and poor myocardial recovery. Colchicine is a well-known alkaloid with potent anti-inflammatory properties. In a proof-of-concept phase II trial, colchicine has been associated with a significant 50% reduction of infarct size (assessed by creatine kinase levels) in comparison to placebo in acute STEMI patients referred for primary percutaneous coronary interven-

Trial registration: ClinicalTrials.gov identifier: NCT03156816.

tion (PPCI). The Colchicine in STEMI Patients Study (COVERT-MI) is an ongoing confirmative prospective, multicenter, randomized, double-blind trial testing whether a short course oral treatment with colchicine versus placebo decreases myocardial injury in patients presenting with STEMI referred for PPCI. Adult patients, with a first STEMI episode and an initial TIMI flow ≤ 1 , referred for PPCI, will be randomized ($n = 194$) in a 1:1 ratio to receive an oral bolus of colchicine of 2 mg followed by 0.5 mg b.i.d. treatment during 5 days or matching placebo. The primary endpoint will be the reduction in infarct size as assessed by cardiac magnetic resonance at 5 ± 2 days between both groups. The main secondary endpoints will be tested between groups in hierarchical order with left ventricular ejection fraction at 5 days, microvascular obstruction presence at 5 days, and absolute adverse left ventricular remodeling between 5 days and 3 months. This academic study is being financed by a grant from the French Ministry of Health (PHRCN-16-0357). Results from this study will contribute to a better understanding of the complex pathophysiology underlying myocardial injury after STEMI. The present study describes the rationale, design, and methods of the trial.

Introduction

Acute myocardial infarction (AMI) is a frequent and disabling disease, with nearly 45 new cases per 100,000 inhabitants each year in Europe [1, 2]. Heart failure is a common outcome of AMI with a mortality rate of up to 50% at 5 years [3]. Studies have demonstrated that infarct size is a major determinant of prognosis after AMI [4–6]. Interventions aimed at reducing infarct size may, therefore, be of major clinical interest to improve AMI patients' prognosis.

Reestablishing the patency of the culprit occluded coronary artery is the first-line treatment of AMI. A large number of reports show that efficient reperfusion improves the long-term outcome [7]. On the other hand, experimental and clinical reports indicate that reperfusion also induces deleterious effects, including myocardial stunning, ventricular arrhythmias, and no-reflow [8, 9]. The final infarct size results from the combination of injuries occurring during the ischemic phase, but also during the phases following reperfusion [8, 9]. Several postconditioning interventions targeting the initial phase of reperfusion injury showed positive results in experimental and small clinical trials but failed for clinical translation in large phase III multicenter studies [10, 11].

There is, therefore, a need to explore new targets to pursue efficient infarct size reduction in ST-segment elevation myocardial infarction (STEMI) patients.

Study Rationale

In a pilot study performed in 151 acute STEMI patients treated with primary percutaneous coronary intervention (PPCI), Deffereos et al. [12] showed a 50% reduction of infarct size estimated by the area under the curve of the creatine kinase-MB release with a short-course treatment of colchicine (starting with a loading dose of 2 mg and continuing with 0.5 mg twice daily, for 5 days) in comparison to placebo [12]. This reduction of infarct size could induce a subsequent reduction of adverse left ventricular (LV) remodeling, which is particularly relevant as LV remodeling is part of the healing process of myocardium after MI. It is defined as the end-diastolic volume increase in the first months after MI [13]. Adverse LV remodeling is increased by inflammation and ultimately leads to heart failure. We therefore implemented a randomized controlled trial (COVERT-MI Study) to investigate whether colchicine with its anti-inflammatory properties significantly reduces the myocardial injury caused by acute post-MI inflammation, thereby limiting adverse LV remodeling, together with a significant reduction of microvascular obstruction in comparison to placebo in acute STEMI patients referred for PPCI.

Study Objectives

The objective of the study is to assess the safety and efficacy of colchicine, which is administered at the time of reperfusion and pursued for 5 days to reduce infarct size in patients treated for STEMI. Comparative efficacy between colchicine and placebo-treated patients will be assessed on infarct size using late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) imaging.

In the first version of the protocol, the primary outcome was the absolute adverse LV remodeling as defined by the percent increase in LVEDV measured by cine-CMR between the acute phase and 3-month follow-up between both groups. Because of a rate of missing CMR studies at 3 months in the ongoing recruitment (~20% of missing CMR studies at follow-up vs. an expected rate of 14% of lost to follow-up), and under the assumption of data missing at random, the primary outcome was revised. Thus, the final primary outcome of this trial is the

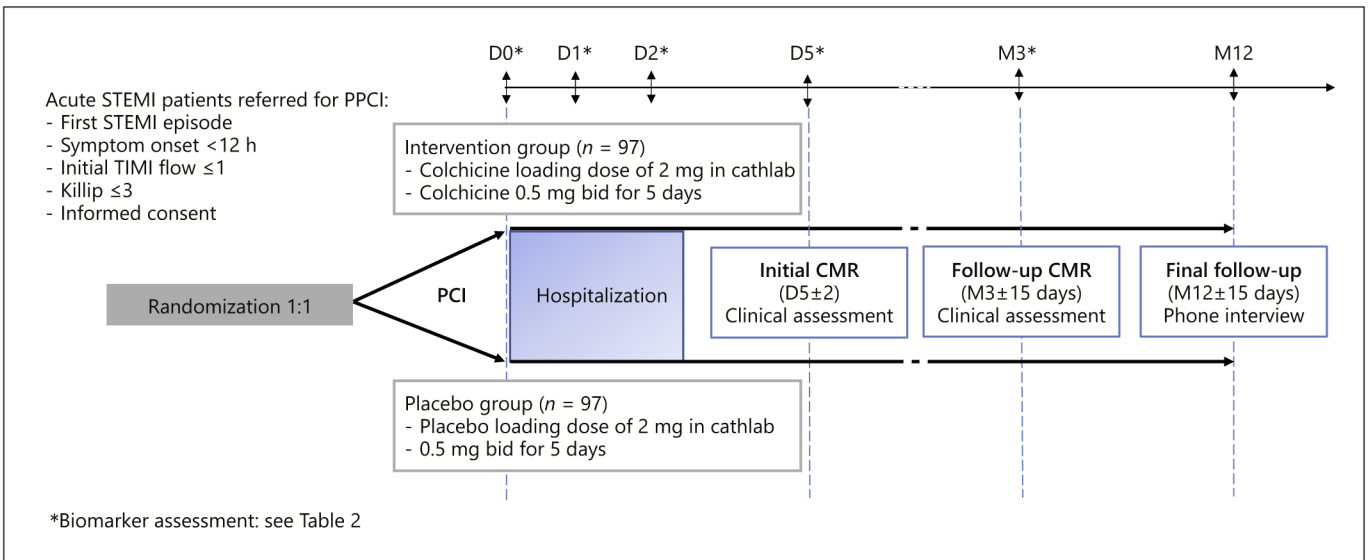


Fig. 1. Study diagram. PPCI, primary percutaneous coronary intervention; PCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; CMR, cardiac magnetic resonance.

infarct size (in % of LV mass) as assessed by LGE-CMR at 5 days of follow-up in both groups.

Taking advantage of the protocol revision for the primary outcome, the main secondary outcomes will be considered in hierarchical order to increase evidence-based conclusions according to the following order:

1. left ventricular ejection fraction (LVEF) at 5 days by CMR;
2. microvascular obstruction at 5 days by CMR;
3. absolute adverse LV remodeling between 5 days and 3 months by CMR;
4. relative LV remodeling between 5 days and 3 months (%);
5. infarct size at 3 months;
6. LVEF at 3 months;
7. LV end-diastolic volume at 3 months;
8. LV end-systolic volume at 3 months; and
9. LV thrombus frequency at the acute phase or during follow-up.

The incidence of major adverse cardiovascular events at discharge (all-cause death, nonfatal myocardial infarction, stroke, or heart failure events) at 3 months and 1-year follow-up, quality of life measured at 12 months, and markers of inflammation during the acute phase are considered as exploratory secondary outcomes. Besides efficacy, the trial addresses the issue of safety by the evaluation of the incidence of treatment discontinuations during the study and the incidence of intestinal symp-

toms and major adverse cardiovascular events declared by investigational centers as being potentially related to investigative drug/placebo.

Study Design

COVERT-MI is a prospective, multicenter, randomized, double-blind, parallel-group trial, performed in patients presenting with STEMI referred for PPCI. The trial is conducted in 10 tertiary referral hospitals. An overview of enrollment, interventions, and follow-up of participants in the COVERT-MI trial is shown in Figure 1.

The trial is supported by a grant from the French Ministry of Health (Programme Hospitalier de Recherche Clinique National 2016) and the study sponsor is the Hospices Civils de Lyon. The study was registered in ClinicalTrials.gov (NCT03156816).

Regulation

The trial is conducted following the principles of the Declaration of Helsinki 1964 as revised in 2013 and the International Conference of Harmonisation Guidelines for Good Clinical Practice (ICH GCP E6 guidelines). Under French laws, the trial was authorized by the French national drug agency (Agence Nationale de la Sécurité du Médicament, ANSM) on December 22, 2017. The study was also approved by the Institutional Review Board (Co-

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

Age >18 and <80 years

First AMI defined as: new ST-segment elevation ≥ 0.2 mV in 2 contiguous leads or new onset of left bundle branch block

Presentation within 12 h of chest pain onset

Occlusion of the culprit artery with TIMI flow 0–1 before PCI

Clinical decision to treat with PCI

Signed informed consent to participate in the trial before any study-related procedure or oral consent with subsequent signed informed consent (patient should sign the informed consent form as soon as possible)

Exclusion criteria

Cardiogenic shock

Chronic treatment with colchicine

Any obvious contraindication to magnetic resonance imaging (claustrophobia, pacemaker, defibrillator, history of hypersensitivity to gadoteric acid or gadolinium contrast agents or meglumine)

Severe liver or known renal dysfunction¹

Treatment by macrolides or pristinamycin

Lactose intolerance

Swallowing disorders

No health insurance coverage

Patients with any legal protection measure

Patients loss of consciousness or confused

Female currently pregnant or women of childbearing age not using contraception²PCI, percutaneous coronary intervention. ¹ Known glomerular filtration rate ≤ 30 mL/min. ² Oral diagnosis.

mité de Protection des Personnes CCP Sud-Est IV) on January 16, 2018. The trial has been registered under www.clinicaltrials.gov (NCT03156816 and EudraCT No. 2017-004090-13) before the enrolment of the first patient in the study. All trial organization information, with committees and CoreLabs, is reported in the Appendix-www.karger.com/doi/10.1159/000512772, as well as the subsequent dissemination strategy.

Patient Population

All patients admitted to the participating centers are screened against eligibility criteria. The study population

includes patients >18 and <80 years of age with a first-time AMI. Patient inclusion and exclusion criteria are listed in Table 1.

Informed Consent

At the patient's arrival in the catheterization laboratory, the study investigator will check for all the exclusion and inclusion criteria and decide if the patient can be included. Informed consent must be obtained before inclusion. If the written consent cannot be obtained, an oral consent can be obtained in the presence of an impartial witness, independent of the study investigator. In case of preliminary oral informed consent only, written informed consent is obtained within 24 h of admission. After patient information and acceptance, randomization will be performed at the time of PCI.

Randomization

After consent, eligible patients are randomly assigned to received colchicine or matching placebo. The randomization with a ratio of 1:1 is stratified by center and by culprit coronary artery (to ensure equivalent rates of left anterior descending vs. non-left anterior descending culprit artery MIs in both groups). This randomization, performed centrally by Internet using the ClinSight™ software (Ennov Clinical Software, Paris, France), after secure login into the internet case-report form of the study, will give the treatment number allocated to the patient.

Study Interventions

The investigational medicinal product is colchicine®. For the study, the experimental product and its placebo will be provided in 0.5 mg capsule, in specific conditioning for patient treatment box: 16 single-capsules per patient (4 capsules for the loading dose, 10 capsules for the treatment during D1–D5 [0.5 mg b.i.d.], and 2 additional capsules for a safety margin).

Colchicine 0.5 mg and placebo capsules are provided in the same appearance (color, size, and packaging) by the sponsor. Production, blinded labeling, packaging, and delivering of the study drugs in every participating center of the trial will be performed by a provider following the European Union's Good Manufacturing Practice.

The study drugs and placebo are prepared, blinded and packaged by the Pharmacy of the Edouard Herriot Hospital (Groupement Hospitalier Centre, Hospices Civils Lyon, France) according to good preparation practices from the tablets of a commercial specialty of colchicine (from specialty Colchicine Opocalcium® 1 mg; Laboratory MAYOLY SPINDLER, France).

Table 2. COVERT-MI biology schedule

Patient localization	Cath lab	Intensive care unit					Outpatient follow-up visit	
		H0 (before PCI)	H4	H24	H48	before discharge	D5	3 months
General biomarkers: Serum Cr, blood glucose, electrolytes, hematology, hemoglobin, and blood coagulation tests	X		X	X				X
Hepatic panel: Serum total bilirubin, γ -glutamyltransferase, alkaline phosphatase, amino transferase, and alanine amino transferase	X							
Inflammation biomarkers: C-reactive protein and fibrinogen	X		X	X				X
Myocardial biomarkers: total creatine kinase	X	X	X	X				
Hypersensitive troponin T	X							
N-terminal prohormone of brain natriuretic peptide				X				X
Lipid panel: total cholesterol, triglyceride, and low- and high-density lipoprotein cholesterol						X		
Hemoglobin A1c						X		
Centralized biomarkers (blood biobank)*	X	X	X	X			X	X

PCI, percutaneous coronary intervention. * Optional only for centers participating in the biomarker substudy.

After randomization, each patient receives the attributed box of colchicine or matching placebo, the closer as possible to PCI: subjects are given 4 pills (2 mg) as loading dose. Qualified site personnel of the cath lab will ensure that the number on the medication blister given to the subject is the same as the randomization number issued by the eCRF.

This loading dose will be taken by the subject if possible before PCI; if not possible the loading dose will be administered immediately after the PCI. The coronary angiography data will be stored, anonymized, and sent to the coordinating center for central reading. The myocardial area at risk will be assessed centrally using the angiographic APPROACH score [14]. Except for the tested product administration, patients will receive all standard care following international guidelines [2].

Assessments during initial follow-up are made at inclusion, and on H24, H48, and hospital discharge (Fig. 1). Patients will remain in the hospital as long as medically indicated.

At 5 ± 2 days of follow-up, patients will undergo an initial CMR study for primary endpoint assessment. A clinical visit is scheduled at 3 months (± 15 days) with a CMR follow-up study endpoint evaluation.

Blood samples for routine biomarker assessment will be drawn during each clinical visit at baseline, 24, 48, $5 \pm$

2 days, and 3 months of follow-up. Additional optional serum samples will be collected in centers for biobanking purposes enabling future exploratory studies. All biomarkers that will be tested are reported in Table 2.

Finally, a 1-year phone call will be performed by a trained research coordinator to collect cardiovascular adverse events and quality of life. The investigation schedule is shown in Figure 1.

Cardiac Magnetic Resonance

CMR is the gold standard noninvasive imaging method to assess LV volumes and mass as well as myocardial edema, infarct size, and microvascular obstruction with high levels of reproducibility [15]. All CMR studies will be performed on 1.5 or 3-T scanners (multivendor Siemens, Phillips, General Electric) at 5 ± 2 days and 3 months ± 15 days following admission. All sequences are performed using vectocardiogram monitoring and 12-element phased-array cardiac receiver coils. After localization, rest LV function is assessed with retrospective electrocardiogram-gated steady-state free precession pulse cine sequences in long- and short-axis views in the true heart axis. The short-axis scans will cover the whole left ventricle.

Native T1 mapping, T2-mapping, and T2-star mapping in 3 (basal, mid-ventricular and apical) short-axis

slices will be performed in centers with the corresponding sequences to assess myocardial edema and myocardial hemorrhage. These sequences are optional.

LGE will be evaluated in short-axis orientation covering the whole ventricle 10 min after contrast injection of gadolinium-DOTA (0.2 mmol/kg body weight; Dotarem; Guerbet, France) using 3D-gradient spoiled inversion recovery TurboFLASH sequence covering the left ventricle in short-axis. Additional 2-chamber and 4-chamber long-axis phase-sensitive inversion recovery sequences were also performed for better spatial assessment of LGE-enhanced areas. This will also allow the diagnosis of LV thrombus. Postprocessing of all imaging data will be performed in a centralized CoreLab (Appendix).

Statistical Considerations

First, the trial was calibrated on a mean relative increase in LV end-diastolic volume of $15 \pm 10\%$ and a decrease of this evolution of 30% under colchicine; thus, 84 patients were planned to be recruited.

Assuming a decrease of the infarct size at 5-day follow-up from 34 to 24 g (30%) with a standard deviation of 22 g corresponds to an effect size of 0.455. A sample size of 83 in each group will have 80% power to detect a probability of 0.374 that observation in group 1 is smaller than an observation in group 2 using a Wilcoxon (Mann-Whitney) rank-sum test with a 0.050 two-sided significance level. With a drop-out rate of 15% (CMR study not performed or suboptimal quality of CMR data, lost to follow-up at the 3-month CMR study, patient death, and withdrawal), the total number to be included in the study is 194 (97 patients in each study group). To reach an 80% power to show improvement of LVEF at 5-day follow-up from 44 to 48.4% using a similar test as for the primary outcome, 58 patients per arm are required. Thus, the enrolment of 97 patients per arm ensures a 95% power for the LVEF improvement based on the a priori assumptions.

Statistical Analysis

The trial will end once 194 patients have been enrolled and have completed the 1-year phone call follow-up visit. A detailed statistical analysis plan will be drawn up by the statistical team (Hospices Civils Lyon) before the trial database is locked. A first statistical analysis will be performed on the primary and secondary endpoints once all patients will have undergone the 3-month CMR follow-

up study. Before performing any statistical tests or fitting statistical models, an exploratory analysis of the baseline variables will be completed. The number and pattern of missing data for baseline variables and outcomes will be established by forming appropriate tables, and likely causes of any missing values will be investigated. An independent statistician will perform the data analysis before breaking the randomization code. The final version of the Statistical Analysis Plan will be validated prior to breaking the randomization code. The primary analyses will be carried out on an intention-to-treat basis. Per protocol analysis will be secondary performed. A probability value of <0.05 will be considered to indicate the statistical significance, and 95% confidence intervals will be calculated. To address the issue of multiple testing, a hierarchical test sequence is planned. The secondary composite efficacy endpoints will be tested individually, in the order in which they are listed above, until the first nonsignificant difference would be found between the 2 treatment arms. Other treatment comparisons will be examined in an exploratory manner. No multiplicity adjustment will be made to the confidence intervals for association measures.

Discussion

After AMI, an important inflammatory response takes place starting in the minutes following reperfusion and peaking at 24 h after reperfusion [16]. Inflammatory cells such as neutrophils, followed by monocytes and macrophages, infiltrate rapidly the injured myocardium. These inflammatory cells triggered by myocardial damage also secrete a variety of pro-inflammatory cytokines at the initial stage [17, 18]. These pro-inflammatory cytokines and extracellular matrix metalloproteinases (MMPs) cause additional damage to the myocardium and promote deleterious LV remodeling [19]. The inflammatory processes have been identified as key mediators of ischemia-reperfusion injury in STEMI [20]. They are associated with poor myocardial recovery, adverse remodeling, and clinical adverse events (heart failure and cardiovascular death) [19, 21].

Currently, all the different anti-inflammatory approaches to reduce reperfusion injury have been disappointing [22]. Altogether, the search for finding new targets to reduce myocardial infarct size remains an open field with many trials performed without success in the field of immediate reperfusion injury. Different strategies are still under evaluation, but for now the promises ob-

tained in experimental models of ischemia reperfusion have failed to translate in properly powered clinical trials [23, 24]. In this quest to reduce infarct size in the era of PPCI, very few trials have aimed at reducing the inflammatory cascade in the following hours of myocardial reperfusion.

Colchicine is a well-known major alkaloid from *Colchicum autumnale* with potent anti-inflammatory properties [25]. It accumulates in white blood cells and decreases their motility, mobilization (especially chemotaxis), and adhesion to the endothelium, thereby reducing the proinflammatory cytokine release in the injured myocardium. Experimental data indicate that targeting postinfarct inflammation by the use of a short course treatment of colchicine can reduce infarct size [26]. This finding was also shown in a pilot clinical study by Deftereos et al. [12] with a 50% reduction in infarct size as assessed by the area under the curve of creatine kinase-myocardial brain fraction.

More recently, in the multicenter international COLCOT trial, long-term colchicine given at a dose of 0.5 mg daily, within a month following MI in patients, led to a significantly lower risk of ischemic cardiovascular events than placebo. In this study, the treatment by colchicine also showed very good levels of safety compared to placebo [27]. However, the primary pathophysiology target in this study was not the inflammatory response following reperfusion-injury within the myocardium, but rather the chronic inflammation associated with atherosclerosis. A recent sub-analysis of the COLCOT trial suggested that the early administration of colchicine within 3 days of STEMI onset was associated with the greatest benefit [28]. The benefit of low-dose colchicine on adverse outcomes in patients with chronic atherosclerosis has been confirmed even more recently in the LoDoCo-2 trial, with excellent safety [29]. The cost-effectiveness of this therapy has also been demonstrated [30].

Clinical Implications

The protocol describes a confirmative randomized controlled trial designed to evaluate the efficacy of colchicine on infarct size (in % of LV mass) and secondly on the LV ejection fraction at 5 days after myocardial infarction. The conduct of the COVERT-MI trial is in broad agreement with the international guidelines. COVERT-MI trial has sufficient power to detect a significant decrease in infarct size, which is known to ultimately lead to heart failure.

The results of this phase II trial will not provide a definitive answer on whether targeting the inflammatory

Table 3. Current baseline characteristics of included patients (inclusions until the May 31, 2020)

Baseline characteristic	Acute STEMI patients ($n = 168$)
Age, mean \pm SD, years	60.0 \pm 10.6
Male sex	134 (79.8)
BMI, mean \pm SD, kg/m ²	27.1 \pm 4.9
Killip class at admission	
I	144 (85.7)
II	14 (8.3)
\geq III	0 (0)
Undetermined	10 (6.0)
Medical history	
Current smoker	70 (41.7)
Hypertension	54 (32.1)
Diabetes mellitus	24 (14.3)
Dyslipidemia	53 (31.5)
Previous ischemic heart disease	5 (3.0)
With CABG	0 (0)
With PCI	5 (100)
Previous heart failure	1 (0.6)

Values indicate n (%) unless otherwise indicated. SD, standard deviation; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

process after myocardial infarction is useful to improve myocardial function in STEMI patients, but are expected to provide essential data for the understanding of colchicine effects and for the design of phase III trials with hard clinical endpoints.

Trial Status

Recruitment started in July 2018 and is expected to be completed in August 2020. The baseline characteristics of all patients included until the May 31, 2020, are reported in Table 3. The final results of the day 5 and 3 months clinical primary endpoints are expected end of Q1 2021, and results of the 1-year follow-up are expected end of Q3 2021.

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Statement of Ethics

Ethics approval, competent authority, and registration. The protocol was approved (#17/084) by the Institutional Review Board *Comité de Protection des Personnes CCP SUD-EST IV*, France, on January 2018 and approved (170715A-21) by French competent authority ANSM on December 2017. The trial has been registered under www.clinicaltrials.gov: NCT03156816 and EudraCT No. 2017-004090-13.

Conflict of Interest Statement

The authors declare that they have no conflict of interest related to the present work.

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Author Contributions

N.M., D.M.B., and N.E.J. drafted the first version of the manuscript. N.M., P.C., and M.O. conceived and designed the trial and requested funding from the Ministry of Health. N.E.J., C.D., M.O., T.B., and C.D.B. provided significant input to the study design. D.B., F.R., F.P., C.P., C.B., O.D., T.B., D.A., G.R., O.D., G.S., F.R., D.B., M.E., and F.I. contributed to patient inclusion and data collection, and revised the initial version of this manuscript. All authors approved the final manuscript.

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DSMB, data safety and monitoring board; CMR, cardiac magnetic resonance.

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