The Brazilian Cardioprotective Nutritional Program to reduce events and risk factors in secondary prevention for cardiovascular disease: study protocol (The BALANCE Program Trial)

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Abstract This article reports the rationale for the Brazilian Cardioprotective Nutritional Program (BALANCE Program) Trial. This pragmatic, multicenter, nationwide, randomized, concealed, controlled trial was designed to investigate the effects of the BALANCE Program in reducing cardiovascular events. The BALANCE Program consists of a prescribed diet guided by nutritional content recommendations from Brazilian national guidelines using a unique nutritional education strategy, which includes suggestions of affordable foods. In addition, the Program focuses on intensive follow-up through one-on-one visits, group sessions, and phone calls. In this trial, participants 45 years or older with any evidence of established cardiovascular disease will be randomized to the BALANCE or control groups. Those in the BALANCE group will receive the afore mentioned program interventions, while controls will be given generic advice on how to follow a low-fat, low-energy, low-sodium, and low-cholesterol diet, with a view to achieving Brazilian nutritional guideline recommendations. The primary outcome is a composite of death (any cause), cardiac arrest, acute myocardial infarction, stroke, myocardial revascularization, amputation for peripheral arterial disease, or hospitalization for unstable angina. A total of 2468 patients will be enrolled in 34 sites and followed up for up to 48 months. If the BALANCE Program is found to decrease cardiovascular events and reduce risk factors, this may represent an advance in the care of patients with cardiovascular disease. (Am Heart J 2016;171:73-81.e2.)

Cardiovascular disease (CVD) is the leading cause of death worldwide and in developing countries.[1] In Brazil, despite a recent decline, cardiovascular mortality rates remain higher than in the majority of other South American, North American, and European countries.[2]

Randomized studies show that the Mediterranean diet is beneficial for patients with established CVD or at risk of CVD development.[3,4] Indeed, the nutritional composition of the Mediterranean diet is one of the main references for dietary guidelines for treatment and prevention of CVD in Brazil and elsewhere.[5–11] However, in many countries, including Brazil, most of the Mediterranean diet foods are not widely available, may be expensive, or are not part of local eating habits. Hence, prescription of a Mediterranean diet intervention for CVD to Brazilian populations may be infeasible and lead to low adherence.[12–14] With a focus on the needs of the mostly low-income Brazilian population, a dietary and nutritional program that provides for these particularities has been developed.

The Brazilian Cardioprotective Nutritional Program (BALANCE Program) takes into account access to food and understanding of the nutrition prescription, which have already been tested in a pilot study. The results showed that the standardized Program diet seems to be feasible and effective, promoting reductions in blood pressure, fasting glucose concentration, weight, and body mass index (BMI) in patients with established CVD.[15]

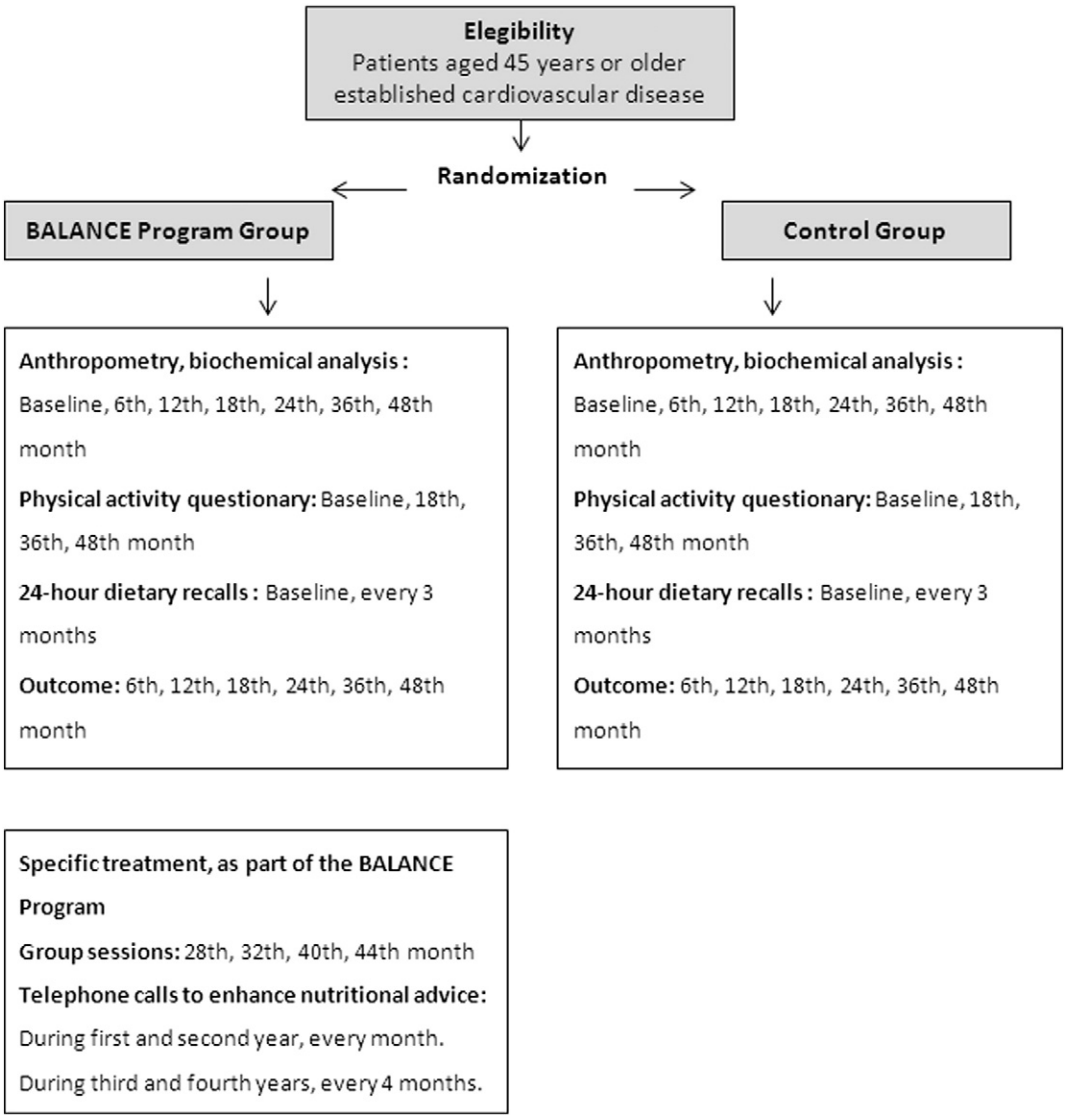
The BALANCE Program trial will investigate the effects of the Program on reducing cardiovascular events—such as cardiac arrest, acute myocardial infarction, stroke, myocardial revascularization, amputation for peripheral arterial disease, and hospitalization for unstable angina—or death in patients with established CVD. Moreover, it will evaluate the effects of the dietary program on reducing CV factors, such as BMI, waist circumference, blood pressure, total cholesterol, low-density lipoprotein, triglycerides, and fasting glucose.

Methods

Subjects

The BALANCE Program is a randomized, multicenter, national trial with allocation concealment and intention-

Figure 1



Study design flowchart.

to-treat analysis. We will include patients 45 years or older who have experienced one or more of the following indicators of established CVD in the preceding 10 years: (*a*) coronary disease (defined by previous myocardial infarction, stable or unstable angina, history of atherosclerotic stenosis ≥70% of the diameter of any coronary artery on conventional or computed tomographic (CT) coronary angiography, or history of angioplasty, stenting, or coronary artery bypass surgery); (*b*) previous stroke; (*c*) peripheral vascular disease (ankle/arm ratio <0.9 of systolic blood pressure in either leg at rest, angiography or Doppler demonstrating >70% stenosis in a cardiac artery, intermittent claudication, vascular surgery for atherosclerotic disease, amputation due to atherosclerotic disease, or aortic aneurysm).

The exclusion criteria will be: neurocognitive or psychiatric conditions that may hinder collection of reliable clinical data (defined at the trial investigator's discretion); life expectancy less than 6 months (eg, metastatic malignancy or other factor defined at the trial investigators' discretion); pregnancy or lactation; liver failure with a history of encephalopathy or anasarca; renal failure with indication for dialysis; congestive heart failure; previous organ transplantation; wheelchair use; or any restrictions to receiving an oral diet.

Figure 2

Food	Energy density ≤ 1.11 Kcal/g	Saturated fatty acid density ≤ 0.01 g/g	Cholesterol density ≤ 0.04 mg/g	Sodium density ≤ 2.01 mg/g	Group classification
Apple	0.56*	0.00*	0.00*	-	
Bread	**3.00***	0.01*	0.00*	**6.48***	
Cheese	**2.42***	**0.04***	**1.19***	**2.41***	

*Nutrient data according to Brazilian Food Composition Labels.

An example of food classification according to the Brazilian Cardioprotective Nutritional Program (color in print).

Randomization

The randomization list will be generated in blocks with stratification by site. Allocation concealment will be maintained by means of a Web-based, central, automated randomization system, available 24 hours a day, developed by the Research Institute at Hospital do Coração (IP-HCor).

Follow-up

Patients will be followed for no less than 36 months and no longer than 48 months. As the trial interventions do not generate harm, there will be no discontinuation or modification of allocated interventions for any participant (Figure 1). Any other treatments indicated or prescribed in parallel to the trial intervention will be allowed without restrictions, except for dietary interventions, as the BALANCE Program diet must be followed.

Control group

The Brazilian guidelines for the treatment of CVD[4–11] recommend a diet that provides 50% to 60% of energy from carbohydrate, 10% to 15% from protein, 25% to 35% from total fat, <7% from saturated fatty acids, <10% polyunsaturated fatty acids, <20% monounsaturated fatty acids, <1% trans fats, <200 mg/day cholesterol, 20 to 30 g/d fiber, and <2400 mg/d sodium. Control group participants will be encouraged to follow generic dietary advice prepared by dietitians and based on a low-fat, low-energy, low-sodium, low-cholesterol diet.[5–11] All will receive a folder containing lists of foods that should be preferred or avoided. In the control group, dietary prescriptions will be qualitative; hence, there will be no calculation of energy intake. Any caloric restriction will be accomplished by switching from foods with high energy density to others with lower energy density.

Participants in the control group will also attend one-on-one sessions with a registered dietitian or other healthcare professional (nurses, physicians, psychologists, and physical therapists) every 6 months for 4 years. The objective of these sessions is to collect anthropometric and dietary recall data, as well as information on lifestyle habits; in addition, professionals will distribute printed materials containing dietary guidance to participants.

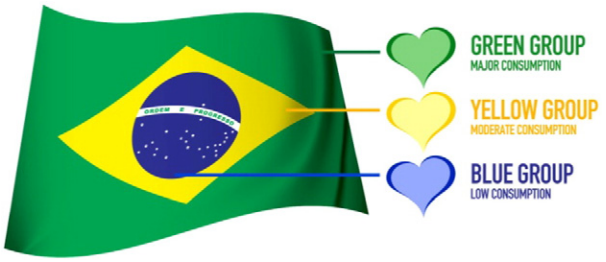
All professionals will receive uniform training in terms of data collection and reinforcement of dietary guidance provided in the printed material.

Experimental group: BALANCE program

The guidelines used to design the BALANCE Program nutritional prescription are essentially the same as those used for the control group, but the approach to implementation is substantially more elaborate and intensive. The BALANCE Program diet is designed to meet the nutritional recommendations proposed by the Brazilian Cardiovascular Guidelines,[4–11] which, in turn, are guided by the nutritional composition of diets such as the Mediterranean diet and the DASH diet. The proposal of is to ensure adequate nutrient intake with a locally appropriate diet, ie, one consisting of foods that are consumed in Brazil, not necessarily the foods consumed as part of the Mediterranean diet. The BALANCE Program is based on three concepts: (*a*) A dietary prescription guided by nutritional content recommendations from the Brazilian national guidelines; (*b*) A nutritional education program based on fun, playful strategies and suggestions of affordable foods; and (*c*) Intensive follow-up through one-on-one visits, group sessions, and phone calls.

To implement the guideline recommendations on nutritional advice and suggested menus, the first step

Figure 3



Graphical representation of the food groups in the Brazilian flag (color in print).

was to compile a list of cardioprotective foods, based on a set of qualitative criteria: (*a*) no added sugar; (*b*) low calorie content; (*c*) lack of nutrients that increase cardiovascular risk (cholesterol, saturated fat, and sodium); and d) presence of cardioprotective nutrients (antioxidants and dietary fiber). To compile this list of foods, we used the Nutriquanti software suite,[16] which prioritizes the Brazilian Food Composition Tables.[17–19] This qualitative selection generated a list consisting of nonfat yogurt and milk, fruits and vegetables, and beans cooked with garlic, onion, soybean oil (up to 1%) and refined salt (up to 0.5%). For didactic purposes, this food group was named the "green group". As a strategy to facilitate patient adherence to the BALANCE Program, we used semiotics to classify the food groups, which are represented by heart symbols of different colors.

Nutrient and energy density was evaluated[20] to assess the nutritional composition of foods in the green group. These foods were found to have an energy density of ≤1.11 kcal/g, a saturated fatty acid density of ≤0.01 g/g, a cholesterol density of ≤0.04 mg/g, and a sodium density of ≤2.01 mg/g. Hence, all foods with energy, sodium, saturated fat, and cholesterol density values equal to or less than these cutoff points will be assigned to the green group. Foods that have other density values of these nutrients will be classified into other groups. Foods containing 1 or 2 nutrient densities above the established cutoff points were assigned to a "yellow" group, whereas those containing three or four nutrient densities above the established cutoff points were categorized into the "blue" group. An example of this food classification typology is shown in Figure 2.

Unfortunately, some nutrients, such as trans fats and refined sugar, could not be included in the methodology, as Brazilian food composition labels do not provide information on the content of these nutrients; this limited our classification efforts and nutritional guidance. To address this limitation, another classification was created: the "red" group, which is composed of foods known to be sources of trans fats, refined sugar, artificial sweeteners, and preservatives—ie, ultra-processed foods.[21] Consumption of such foods is strongly discouraged within the BALANCE Program.

The second concept is the recreational strategy. On the basis of the aforementioned color groups, the dietary guide for patients was created using the Brazilian flag colors as a reference: the largest field on the flag is green, which ties into the concept that the foods in the green group should be heavily present in the diet. The second largest portion of the flag is yellow, which suggests that this food group should be somewhat less prevalent in the diet. Finally, blue is present only on a small part of the flag, which suggests that intake of foods from this group should be highly restricted (Figure 3). In allusion to the absence of red in the Brazilian flag, foods from the red group should not be consumed at all. The strategy of food classification into color groups in accordance with their unhealthy nutrient densities is also used by the Traffic Light Diet; foods are categorized as green, yellow, or red based on their nutrient density. Red foods are described as being higher in energy density than foods in the other groups, whereas green foods (most vegetables and fruits) are described as "very high" in nutrients and low in fat.[22]

Dietary prescription for weight loss (obese or overweight participants), the total energy content of the diet will be calculated using the formula 20 kcal/kg current body weight (eg, a patient weighing 70 kg will be prescribed a diet that provides 1750 kcal/d). For weight maintenance (participants with normal weight), the prescribed diet will follow an energy formula of 25 kcal/kg current body weight (eg, 2000 kcal/d for a patient weighing 100 kg). In addition to this formal caloric restriction, it is worth stressing that, within the BALANCE Program foods are classified according to their caloric and nutrient density. As the Program recommends greater intake of low-energy-density foods, participants will consequently reduce their caloric intake. To facilitate adherence to the BALANCE Program prescription, 1,400- to 2,400-calorie menus (at 200-kcal intervals) were designed, stipulating the amount of green, yellow, and blue food servings. A cookbook of regional Brazilian recipes was also devised and will be given to the participants as an educational tool.

The third concept is composed of intensive, dietitian-led follow-up. Participants will attend one-on-one sessions with a registered dietitian every 6 months for 2 years. Once monthly, participants will receive telephone calls to assess their understanding of the Program diet and to reinforce nutritional advice. During years 3 and 4 of the trial, participants will take part in two group sessions and one individual session per year, and will receive phone calls every 4 months.

Blinding

Due to the nature of the intervention, blinding of investigators and participants is not possible. However, the end point adjudication committee will be blinded.

Data collection

We will visit all sites to train local researchers. Visits will last 2 days and will cover a discussion of the trial protocol and standardization of data collection procedures. Data will be collected both from outpatients and from inpatients. Only the coordinating center will have access to the final trial dataset.

Height, weight, and waist circumference will be measured at baseline and at follow-up visits. Every follow-up visit, participants will be classified according to smoking status as current smokers, non-smokers, and former smokers and information about hypoglycemic, antihypertensive, hypolipidemic, and antithrombotic drugs usage will also be considered. Although no interventions related to physical activity are planned, participants' activity levels will be classified as sedentary, light, moderate, or intense. Physical activity and alcohol consumption will be recorded at baseline, 18th, 36th, and 48th month. For biochemical analyses (total cholesterol, high-density lipoprotein, glucose, and triglycerides), blood samples will be collected and handled according to routine hospital practice. All participants will be fasted for at least 12 hours before phlebotomy. At baseline, income data will be assessed according to the established Brazilian Economic Classification Criterion[23] and the average income of each stratum calculated. Level of education will be recorded as the highest degree attained. All data will be recorded in an electronic case report form (e-CRF). Food intake data will be obtained by 24-hour dietary recalls[24] and recorded in the Nutriquanti software suite.[16] A photo album containing images of standardized food portion sizes, prepared by our group, will be used to assist food intake assessment.

Outcomes

The primary composite outcome will be the occurrence of any of the following cardiovascular events: cardiac arrest, acute myocardial infarction, stroke, myocardial revascularization, amputation for peripheral arterial disease, hospitalization for unstable angina, cardiovascular death, or death from any cause (Appendix 1).

The secondary outcomes are as follows: BMI, waist circumference, blood pressure, total cholesterol, low-density lipoprotein, fasting glucose, cardiac arrest, acute myocardial infarction, stroke, myocardial revascularization, amputation for peripheral arterial disease, hospitalization for unstable angina, or isolated cardiovascular death. Primary and secondary outcomes will be evaluated at month 48.

Adjudication

The Clinical End points Committee (CEC) will be responsible for adjudication of primary composite outcome components. All suspected events will be entered into the CEC tracking database and independently reviewed by two CEC physicians. If the two adjudicators agree, event adjudication will be considered complete. If there is disagreement, the final decision will be made by a third, independent adjudicator (Appendix 2).

During visits that include outcome data collection, outcome information will be flagged in the eCRF and prompt the coordinating center to contact the lead investigator at the participating center to provide guidance on the relevant procedures. In the investigator manual and during in-person training and monitoring visits, we highlight the importance of gathering supporting documentation for each outcome event/end point and its potential relations. The participating center is required to contact the participant's family or physician to obtain these documents. If difficulties are encountered during this process, assistance from the coordinating center will be available. Once supporting documents have been forwarded to the coordinating center, there will be an administrative review of each of the end points to check that all necessary documents are available. The coordinator center will print out the necessary documents from the eCRF, include additional supporting information in a completed CEC package, and send it to the CEC.

Clinical data management system and quality control

Data quality will be guaranteed by automated data entry checks, monthly contact with investigators, on-site monitoring visits, and central statistical monitoring. General feedback will be provided at investigators' meetings and through periodic newsletters. Throughout the study, monitoring visits will be proposed for sites which exhibit increased difficulty recruiting patients or have data quality control issues.

Sample size

For a type I error rate of 5%, a statistical power of 80%, a 20% incidence rate of the primary outcome in the control group, and a relative risk reduction of 30% in the intervention group[4,25–27] at least 2,468 individuals will have to be randomized. Regular web conferences and trial meetings will be conducted to encourage investigators to achieve adequate participant enrollment.

Statistical analysis plan

All analyses will follow the intention-to-treat principle. Baseline patient characteristics will be compared between the two groups using Fisher's exact test, Student's *t*-test, or Wilcoxon rank sum as appropriate. Cox regression analysis will be used to address the primary composite outcome and its components considering random effects by sites (frailty models). There will be no adjustment for baseline characteristics in the primary analysis. Cardiovascular risk factors and dietary nutrients, defined as continuous variables, will be analyzed over time by repeated-measures analysis of variance using a

mixed model or generalized estimating equations. The proper covariance structure will be selected to ensure the lowest Akaike information criterion after adjusting models with alternative covariance structures.[28–30] Cox regression analysis considering random effects by sites (frailty models) adjusted by sex, age, income, and educational status, BMI, CV risk factor status, baseline CVD, medication, physical activity, alcohol consumption, will be conducted as sensitivity analysis. Pre-specified subgroup analyses will be conducted according to sex, age, BMI, CV risk factor status, and baseline CVD. There is no interim analysis planned. The significance level will be set at 5% for two-tailed hypotheses tests. All statistical analyses will be performed in the R software environment (V.3.1.0, R Core Team, 2014).

Ethical aspects

Each study site will submit the trial protocol to its human research ethics committee (institutional review board-equivalent), and the study will only start after approval. Written informed consent will be obtained from each participant by a trained investigator at each site. This trial protocol is in compliance with Brazilian and international ethical standards, and is registered at ClinicalTrials.gov with identifier NCT01620398. Trial results will be communicated to participants, healthcare professionals, and the general public through publications. For ethical propose, according to Brazilian rules, control group will receive nutritional counselling post trial if the intervention group demonstrate clear benefits.

Trial status

The BALANCE Program trial includes 34 sites in Brazil. Enrollment began in March 2013. As of March 2015, a total of 2,537 patients had been included in the study. Treatment and follow-up of all participants are planned to continue until December 2017.

Financial disclosure

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Discussion

The Mediterranean diet has a remarkable effect on cardiovascular prevention and rehabilitation,[3,4] and forms the groundwork of all major global and national nutritional recommendations for the prevention and treatment of CVD.[5–11] Although the nutritional composition of a diet designed for prevention and treatment of CVD is clear, the optimal form of prescribing such diets is not yet established, and there are no data on how such recommendations could be achieved using foods affordable for the Brazilian population. Another important factor that must be taken into account is adherence to recommendations. It is estimated that, in developed countries, only 50% of patients with chronic diseases adhere to treatment recommendations.[31] In Brazil, dietary compliance is roughly 40%.[32] Within this context, the BALANCE Program was developed with the objective of being a nutritional education tool that is accessible to the population and incorporates guideline recommendations for CVD management, with a view to improving patient understanding of the dietary prescription and enhancing compliance.

It is important to highlight that this is a comprehensive nutritional program, not simply a diet. The BALANCE Program consists of nutritional guidance designed to be fun and accessible, intensive contact with nutritionists through one-on-one visits and group sessions, and telephone calls to reinforce guidance; these three strategies are meant to enhance adherence.

It has been postulated that the Mediterranean diet could not be feasible in Brazil because of the high cost of its components in the country. Conversely, with the BALANCE Program strategy, cost should not be a barrier to adherence to a healthy diet.[12] The proposal of this trial is to ensure adequate nutrient intake by means of a locally appropriate diet, ie, one consisting of foods that are consumed in Brazil. The key point of the Program is to achieve a balance among foods in the diet so as to ensure correct proportions of all nutrients recommended for dietary management of cardiovascular disease. Furthermore, the educational strategy of allocating foods into groups based on the colors that appear on the national flag and associating the recommended intake frequency of each food group with the space each corresponding color occupies on the flag should facilitate understanding and, therefore, enhance compliance. The efficacy of this method was tested in a pilot study. To wit: in the pilot study of this trial, 120 patients with established heart disease receiving secondary prevention, 45 years or older, were randomized across three groups and followed for 3 months. The objective of the pilot study was to evaluate the effect of the BALANCE Program on reducing CV risk factors. Outcome data were collected once monthly. One arm received the BALANCE Program intervention, including weekly participant contact with investigators to address any questions about the prescribed diet. The second arm received qualitative guidance on following a low-calorie, low-fat, and low-sodium diet, with meetings between investigator and participant as frequently as in the BALANCE Program (ie, weekly participant contact with investigators to address any questions about the prescribed diet). Finally, participants allocated to the third arm received the same guidance as those in the second arm, but meetings between investigator and participant took place once monthly. The BALANCE Program appeared to be effective in reducing weight, BMI, blood pressure, and fasting

glucose levels in patients with previous CVD.[16] The good results of our pilot study prompted this nationwide multicenter study to test its effectiveness in reducing major cardiovascular events. For the nationwide study, some adjustments were required. The objective was no longer assessment of the effects of the BALANCE Program on CV risk factors, but assessment of its effect on CV events and mortality. Only two arms were retained: the BALANCE Program group and a control group receiving qualitative guidance on following a low-calorie, low-fat, and low-sodium diet with relatively infrequent contact between investigators and participants, which was felt to better mimic the reality of care in the Brazilian public health system. Furthermore, the intervention materials had to be adjusted, because the pilot study was performed in a sample of patients living in the city of São Paulo, which has specific dietary patterns that differ from those of the North, South, and Northeast regions of the country.

In short, the Brazilian Cardioprotective Nutritional Program is a proposed novel intervention with the potential for low cost and high feasibility for use in Brazil. If effective, it could be used to support the development of specific national programs to reduce the incidence of new CV events.

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Appendix 1. Clinical end points

Death

Death will be classified as Cardiovascular, Non-cardiovascular, or Unknown. The cause of death will be determined by the principal condition that caused the death, not the immediate cause of death. All deaths will be assumed to be cardiovascular in nature unless a non-cardiovascular cause can be clearly demonstrated, with the exception of death without any additional information, which will be classified as *Unknown*.

Cardiovascular deaths include but are not limited to atherosclerotic coronary heart disease (acute myocardial infarction, sudden cardiac death, non-sudden death with gradually worsening cardiac symptoms, unwitnessed death without a clear alternative cause, procedural death related to cardiac surgery or coronary angiography), atherosclerotic vascular disease (cerebrovascular disease including stroke and hemorrhage; aortic, mesenteric, renal vascular, or peripheral arterial disease; procedural deaths related to a non-coronary vascular procedure), and other cardiovascular (pulmonary embolism, endocarditis, congestive heart failure, valvular heart disease, arrhythmia). Examples of non-cardiovascular deaths include those with an infectious, malignant, pulmonary, gastrointestinal, accidental, or renal primary cause, as well as suicide. Cardiovascular deaths will be further categorized into sudden, non-sudden, and unwitnessed.

Myocardial infarction

All MI events will be classified into three general categories. The Clinical Endpoints Committee (CEC) will adjudicate events using the following definition as a guide:

Peri-PCI Myocardial Infarction

Peri-PCI MI is defined by any of the following criteria. Symptoms of cardiac ischemia are not required.

1. If baseline cardiac biomarkers (baseline and 1–2 hour sample) are normal: Elevated CK-MB ≥3 × URL or troponin ≥5 × URL (if CK-MB not available) within 48 hours of PCI.
2. If baseline cardiac biomarkers are elevated and decreasing prior to the suspected MI: Elevated CK-MB ≥3 × ULN or troponin ≥5 × URL (if CK-MB not available) **AND** A ≥20% increase in the cardiac biomarker compared with the nadir pre-procedure value (baseline or 2-hour sample)
3. If baseline cardiac biomarkers are elevated and increasing prior to the suspected MI or are unknown: New ischemic symptoms for at least 20 minutes **AND** Further elevation in post-procedural levels of CK-MB and/or troponin, with levels rising to at least ≥3 × ULN (CK-MB) or ≥5 × URL (troponin, if CK-MB not available) **AND** at least one of the following: A site-reported angiographic procedural complication during PCI **OR** New ischemic changes on a procedural or post-procedural 12-lead ECG tracing
4. Evidence of acute MI on autopsy (if not index MI).

Spontaneous MI (>48 hours after PCI)

A spontaneous MI will be defined as a rise and/or fall in cardiac biomarkers (CK-MB or troponin) with at least one value above the URL and at least one of the following: Clinical presentation consistent with ischemia; ECG evidence of acute myocardial ischemia; Development of new pathological Q waves; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Evidence of acute myocardial infarction on autopsy will be used as a stand-alone criterion for MI. If biomarkers are elevated from a prior infarction, then diagnosis of a spontaneous MI will require:

- Evidence that cardiac biomarker values were decreasing prior to the suspected MI **AND** a ≥20% increase (>URL) in CK-MB (≥3 × ULN) or troponin (≥5 × ULN) between a measurement obtained at the time of initial presentation and an additional sample **AND** at least one of the following:
- Clinical presentation consistent with ischemia;
- ECG evidence of acute myocardial ischemia;
- New pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

In this setting, autopsy evidence of new acute myocardial infarction will be used as a stand-alone criterion for MI.

Peri-Coronary Artery Bypass Graft MI

Peri-coronary artery bypass graft (CABG) MI will be defined by the following criteria: Biomarker elevations within 72 hours of CABG with CK-MB >5 × URL or troponin >10 × URL (if CK-MB is not available) **AND** no evidence that cardiac biomarkers were elevated prior to the procedure, **OR** evidence that cardiac biomarker values were decreasing prior to the procedure **AND** ≥50% increase in cardiac biomarker values **AND** one of the following: new pathological Q waves persisting for 30 days, new persistent non-rate-related LBBB, angiographically documented new graft or native coronary artery occlusion, other complications in the operating room resulting in loss of myocardium, imaging evidence of new loss of viable myocardium, **OR** evidence of acute MI on autopsy.

Stroke

Stroke is defined as an acute focal neurological deficit of sudden onset:

(*a*) that is not reversible within 24 hrs or results in death (in <24 hours) and is not due to an identifiable non-vascular cause (eg, brain tumor, trauma) **OR** (*b*) that resolves in <24 hours and is accompanied by clear evidence of a new stroke on neuroimaging.

Stroke will be sub-classified into one of the following 4 groups:

- *Non-Hemorrhagic Cerebral Infarction*—stroke without focal collections of intracerebral blood on brain imaging. This category will be further classified into suspected embolic vs other.

- *Non-Hemorrhagic Infarction with Hemorrhagic Conversion*—cerebral infarction with blood felt to represent hemorrhagic conversion and not a primary hemorrhage. Hemorrhagic conversion usually occurs on the cortical surface. Hemorrhagic conversion deeper in the brain requires evidence of non-hemorrhagic infarction in the same vascular territory. Microhemorrhages evident on MRI, whether in the cortex or deep brain structures, are not considered to be consistent with a hemorrhagic conversion end point.
- *Primary Hemorrhagic*
- *Intracerebral Hemorrhage*—Stroke with focal collections of intracerebral blood seen on brain imaging (CT or MRI) or postmortem examination, not likely to represent hemorrhagic conversion. Primary hemorrhages cause hematomas which are usually easily discriminated by their subcortical location and rounded or elliptical shape. Microhemorrhages incidentally discovered on brain imaging in the absence of associated symptoms will not be considered to be a primary intracranial hemorrhage end point.
- *Subarachnoid Hemorrhage*—High-density fluid collection in the subarachnoid space on brain imaging or blood in the subarachnoid space on autopsy
- *Uncertain*—Any stroke without brain imaging (CT or MRI) or autopsy documentation of type, or if tests are inconclusive

Subdural hematoma will not be classified as a stroke but rather as a bleeding event (intracranial hemorrhage). Intracerebral microhemorrhages will be classified in a separate category for analysis. Microhemorrhages are defined as rounded foci <10 mm in diameter that appear hypointense and that are distinct from other causes of signal loss on gradient-echo MRI sequences (eg, vascular flow voids, leptomeningeal hemosiderosis, or non-hemorrhagic subcortical mineralization).

Transient ischemic attack is defined by:

a. acute focal neurological deficit lasting <24 hours and not due to an identifiable non-vascular cause (eg, brain tumor, trauma), AND
b. absence of new infarct on brain imaging (*if obtained*).

Hospitalization for unstable angina

Hospitalization for at least 24 hours due to ischemic symptoms lasting more than 5 minutes at rest and at least one of the following:

- ST depression >1 mm, T-wave inversion on at least 2 leads in the absence of troponin (T or I) or CK-MB.
- Occurrence of unplanned percutaneous coronary intervention (PCI) or CABG.

Coronary revascularization

Occurrence of percutaneous coronary intervention (PCI) with or without stenting. Occurrence of on- or off-pump CABG.

Amputation

Amputation due to nontraumatic cause. Includes amputations due to acute arterial insufficiency, chronic arterial insufficiency, venous insufficiency, diabetic foot, osteomyelitis, and gangrene.

Reversed cardiac arrest

Cardiac arrest from any cause that is successfully reversed.

Supplementary Appendix 2. Adjudication process

To ensure adequate reporting of all clinical events, all investigators in all trial sites will receive training on how to identify a primary outcome. Refresher training (online or in person) will be provided every 6 months to all sites, at which time we will discuss the importance of correct outcome identification. Although most participating investigators are dietitians, they will receive support from clinicians and study coordinators when screening potential outcome events for reporting and gathering of documentation to be sent to the CEC.

The CEC is responsible for adjudicating the components of the composite primary outcome. All suspected events will be entered into the CEC tracking database. There will be an administrative review of each of the end points to check that all necessary documents are available. IP-HCor staff will print out the necessary documents from the eCRF and include additional supporting information in a complete CEC package.

IP-HCor staff will forward two copies of each end point package to two independent physician reviewers. The physician reviewers will independently review the cases assigned to them, document and provide supporting information for each event's adjudication directly in the end point package. If the two adjudicators agree, event adjudication is considered complete. If there is a discrepancy between the reviewers, or at the discretion of one of the reviewers, the case will be forwarded for analysis by at least one additional reviewer to establish a final adjudication. The final adjudication result will be entered into the database by the CEC coordinator. A copy of all signed adjudication forms is filed in each respective CEC folder and will be stored at the CEC.

All adjudications are documented, within the event review package, with respect to the supporting end point criteria that were met. For any case that sets precedent, the CEC Chair will document the details of the adjudication and the case will be recorded in a log which will serve as a guide for reviewers, to ensure consistency with respect to application of end point definitions.