STUDY PROTOCOL

Phase 3 Randomized Controlled Trial Evaluating the Effect of Laparoscopic Roux-en-Y Gastric Bypass (LRYGB) on Hypertension Medication Reduction, Blood Pressure Levels and Others Cardiovascular Risk Factors.

GATEWAY (GAstric bypass surgery to TrEat patients With steAdy hYpertension)

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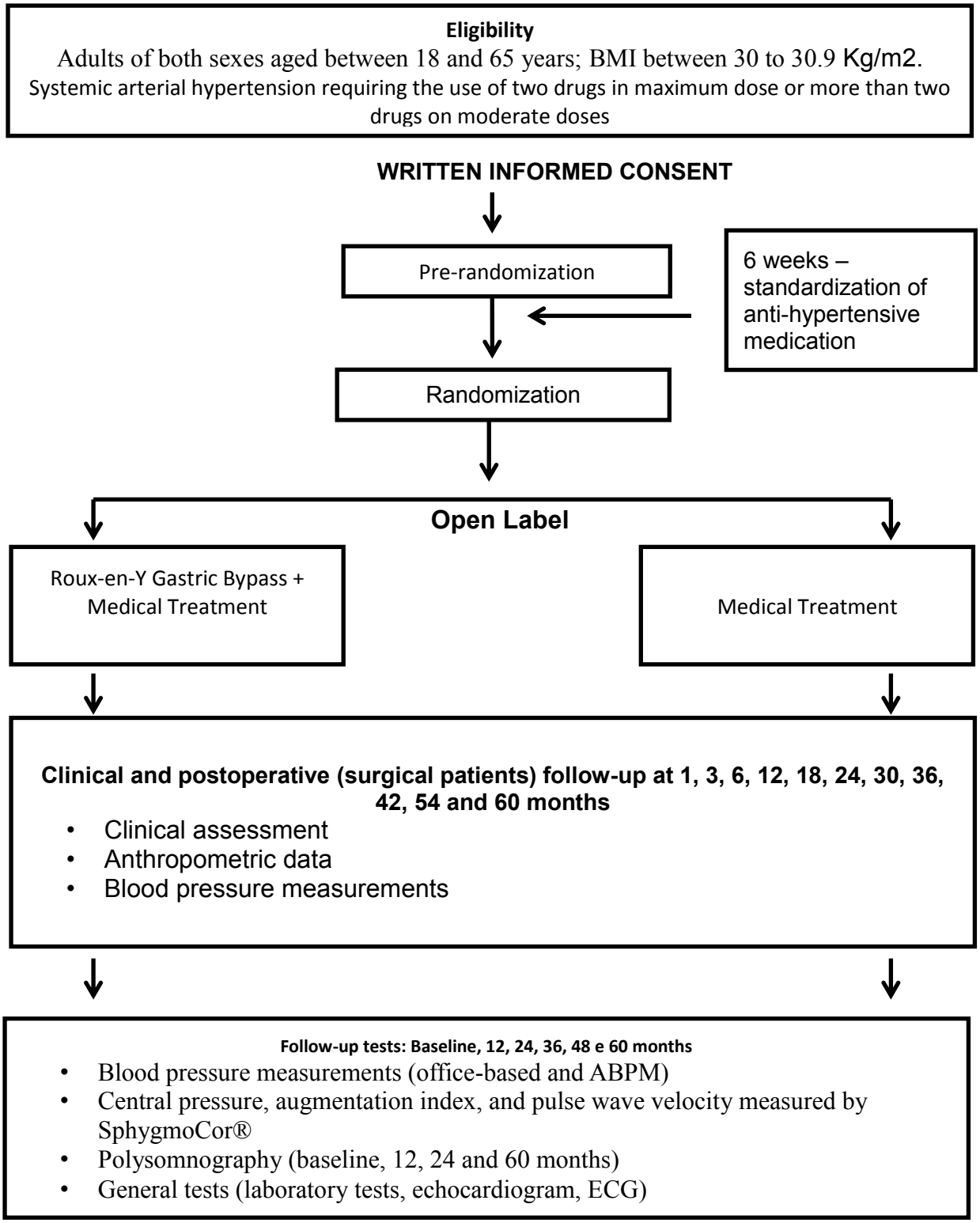
SUMMARY

TITLE	Phase 3 Randomized Controlled Trial Evaluating the Effect of Laparoscopic Roux-en-Y Gastric Bypass (LRYGB) on hypertension Medication Reduction, Blood Pressure Levels and Others Cardiovascular Risk Factors.
PRIMARY OBJECTIVE	To assess the efficacy of Roux-en-Y gastric bypass plus medical treatment compared to medical treatment alone in reducing at least 30%of the total number of antihypertensive drugs, while maintaining controlled blood pressure (SBP<140 and DBP <90mmHg) at 12 months.
SECONDARY OBJECTIVES	To assess the efficacy of Roux-en-Y gastric bypass plus medical treatment compared to medical treatment alone, in obese hypertensive patients, on the following outcomes at 12 months: • Number of antihypertensive drugs • Systolic blood pressure. • Diastolic blood pressure. • Body weight and BMI. • Waist circumference. • Fasting glucose levels, HbA1c and insulin resistance • LDL-cholesterol levels. • HDL-cholesterol levels. • Triglyceride levels. • Uric acid levels. • High-sensitivity C-reactive protein levels. • Echocardiographic parameters • Estimated risk for cardiovascular disease (Framingham Risk Score). • Adverse events. • Systolic and diastolic blood pressure measured by ABPM • Central pressure, augmentation index, and pulse wave velocity measured by SphygmoCor®. • Sleep quality as assessed by polysomnography. To assess the efficacy of Roux-en-Y gastric bypass plus medical treatment compared to medical treatment alone on all primary and secondary outcomes between 24 and 60 months of follow-up.
STUDY DESIGN	This is a randomized, single-center, phase III clinical trial, planned to be performed with concealed allocation of participants and intention-to-treat analyses, comparing gastric bypass plus medical therapy with medical therapy alone in patients with obesity and hypertension.
RATIONALE	Evidence from randomized clinical trials shows that patients undergoing bariatric surgery are able to reduce the number of drugs for the treatment of several cardiovascular risks factors after 12 months of surgery. However, a detailed analysis shows that this reduction was observed only in drugs for the treatment of type 2 diabetes mellitus. Additionally, results of meta-analyses of studies, mostly observational, evaluating the effect of bariatric surgery on parameters other than weight loss suggest that bariatric surgery may reduce blood pressure. Thus, these findings should be confirmed by a study whose primary objective is to evaluate the effect of bariatric surgery on blood pressure levels in hypertensive patients.

METHODOLOGICAL QUALITY	Central web-based randomization with allocation concealment. Intention-to-treat analysis
INCLUSION CRITERIA	• Adults aged between 18 and 65 years. • Patients with hypertension using at least 2 antihypertensive drugs at full doses or more than two drugs in moderate doses. • Grade 1 and 2 obesity: BMI between 30.0 to 39.9Kg/m2.
EXCLUSION CRITERIA	• Patients with blood pressure levels ≥ 180/120 mmHg; • Cerebrovascular disease (stroke) in the past 6 months. • Cardiac disease (myocardial infarction, angina, coronary revascularization, heart failure) that occurred or were diagnosed in the past 6 months. • Underlying psychiatric diseases: schizophrenia, bipolar disorder, severe depression, psychosis • Kidney disease: diabetic nephropathy, creatinine clearance < 30 ml/min. • Individuals with secondary hypertension, except due to sleep apnea. • Advanced peripheral artery disease • Patients with atrophic gastritis • Type 1 diabetes; latent autoimmune diabetes of adults; type 2 diabetes mellitus with HbA1c >7.0% • Alcoholism or use of illicit drugs • Current tobacco smoking habit • Previous abdominal surgery (except for MacBurney, Pfannenstiel, and video laparoscopic cholecystectomy) • Severe hepatic disease • Pregnant women or women at childbearing age not using effective contraceptive methods; • Neoplasm occurring in the past 5 years • Use of immunosuppressant drugs, chemotherapy or radiotherapy • Inability to understand or to adhere to study procedures
SAMPLE SIZE	A total of 100 patients will be included.
FOLLOW-UP	Short term: 12 months Long term: 24, 36, 48 and 60 months
TREATMENT REGIMENS	Intervention group: Laparoscopic Roux-en-Y gastric bypass combined with medical treatment. Control group: medical treatment alone.
COORDINATING CENTER	Research Institute HCor Abílio Soares St, n° 250 – Paraíso – S.Paulo – SP – CEP 04005-000 – BRAZIL
SPONSOR	Ethicon Inc. represented in Brazil by Johnson & Johnson do Brasil Ind. e Com. de Prod. para Saúde Ltda – Grant #IIS2012 100238

STUDY FLOW CHART



1. INTRODUCTION

1.1 Burden of cardiovascular diseases in Brazil and worldwide

Cardiovascular diseases (CVD), especially acute myocardial infarction (AMI) and stroke, are the main cause of mortality and disability in Brazil and Worldwide,[1,2,3] and the accelerated increase of the prevalence of these disease in developing countries is currently one of the most relevant public health issues. In 2020, it is projected that CVD will still be the leading cause of mortality and disability and that disability-adjusted life years (AVAIs) attributable to CVD will increase to nearly 140 to 160 million, with developing countries accounting for the highest incidence.

Considering that the genesis of CVD is multifactorial, some of the most important factors in this process are systemic arterial hypertension and overweight.

The association between hypertension with atherosclerotic disease is well established in the medical literature. Two systematic reviews of observational studies (involving more than 1.5 million individuals) provide enough evidence to confirm these findings.[4,5] This may be clearly inferred in the graph below which plots the risk of events on a logarithmic scale on the Y-axis and the risk factor (expressed by blood pressure values) on a continuous arithmetic scale on the X-axis as shown in Figure 1.[4] Therefore, consistent evidence supports the idea that there is a log-linear association between blood pressure and the risk of CVD.

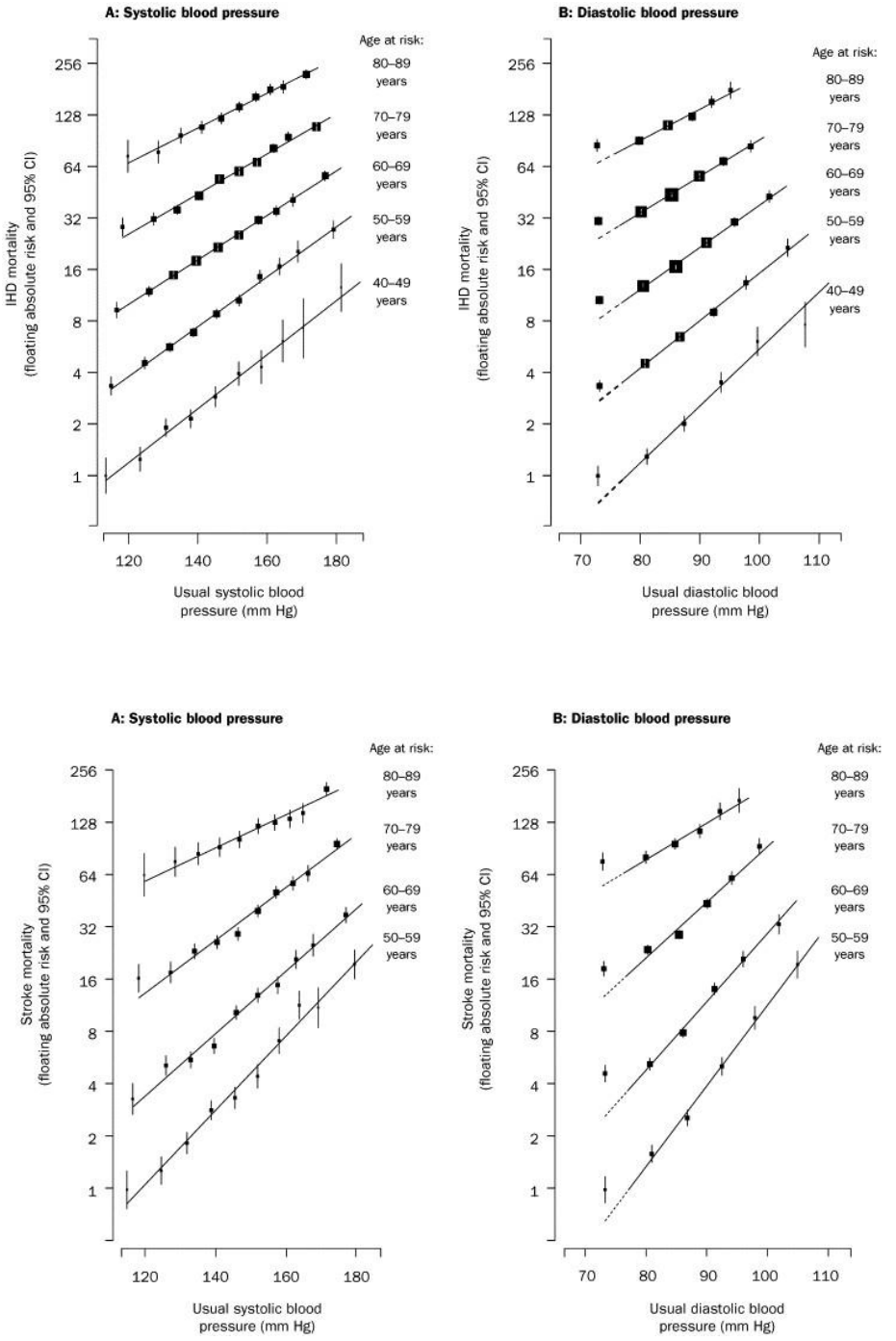


Fig. 1 - Association between pressure levels and coronary artery disease (A) and stroke (B) in a systematic review by the Prospective Studies Collaboration.[4]

In addition to its independent association with CVD, hypertension is a highly prevalent condition. In this sense, a series of cross-sectional studies showed that the prevalence of hypertension in Brazil (in adult participants) is nearly 25%.(3)

Equally important is the impact of obesity on cardiovascular risk. Obesity is currently considered a global epidemic. In the United States, one out of three individuals is obese. In Brazil, 49% of the adult population is overweight (BMI > 25kg/m2) and 14.8% is obese (BMI > 30kg/m2), according to the 2008-2009 Brazilian Household Budget survey conducted by the Brazilian Institute of Geography and Statistics (IBGE) (Table1). Increased obesity rates promote increased rates of several diseases, particularly those linked to metabolic syndrome, such as high blood pressure, type 2 diabetes, and dyslipidemias.

If, on one hand, the incidence of obesity is rapidly increasing, on the other hand, the therapeutic possibilities have become increasingly limited. Recently, the Brazilian National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária, ANVISA) decided to remove from the market most anti-obesity medications. The only medication currently available is sibutramine, which has a very limited indication, especially for patients with high blood pressure and CVD.

Adherence to diet and physical activity is challenging in the middle and long terms. Therefore, therapeutic outcomes are poor, especially for grade II and III obesity, promoting a total weight loss of nearly 10%, which is far from ideal for these grades of obesity.

Table 1.Prevalence of weight deficit, overweight and obesity in a population of individuals aged 20 years or more, based on criteria of the World Health Organization- OMS, by sex, according to age groups - Brazil – 2008-2009 period

Age Groups	Prevalence of weight deficit, overweight and obesity in a population of individuals aged 20 years or more, by sex (%)		
	Total	Men	Women
	weight deficit		
Total	2.7	1.8	3.6
20-24 years old	5.7	3.3	8.3
25-29 years old	3.2	2.1	4.3
30-34 years old	2.4	1.2	3.5
35-44 years old	1.4	0.9	1.9
45-54 years old	1.8	1.3	2.2
55-64 years old	2.1	2.0	2.2
65-74 years old	3.2	2.5	3.8
75 years old or more	4.4	3.1	5.4
	overweight		
Total	49.0	50.1	48.0
20-24 years old	27.3	30.2	24.2
25-29 years old	38.2	42.5	33.9
30-34 years old	47.3	52.7	42.2
35-44 years old	52.8	55.8	50.0
45-54 years old	58.3	58.7	58.0
55-64 years old	60.7	58.0	63.0
65-74 years old	56.2	52.2	59.5
75 years old or more	48.6	43.9	51.9
	obesity		
Total	14.8	12.5	16.9
20-24 years old	5.6	5.1	6.1
25-29 years old	9.7	9.3	10.0
30-34 years old	13.1	12.9	13.3
35-44 years old	15.6	13.6	17.4
45-54 years old	19.3	16.8	21.5
55-64 years old	21.3	15.9	26.0
65-74 years old	17.9	12.4	22.4
75 years old or more	15.8	11.9	18.6

1.2 Bariatric surgery

Considering the few therapeutic alternatives and the poor treatment outcomes, bariatric surgery is the best alternative for the treatment of patients with grade II obesity associated with comorbidities such as high blood pressure, diabetes, dyslipidemia, sleep apnea and with grade III obesity regardless of the presence of these comorbidities.

According to the Resolution No. 1,942/2010 of the Brazilian Federal Board of Medicine (Conselho Federal de Medicina, CFM), four bariatric surgery techniques are approved in Brazil:

- Adjustable gastric band;
- Sleeve gastrectomy;
- Roux-en-Y gastric bypass;
- Malabsorptive surgeries: Scopinaro and duodenal switch.

All of these techniques are currently performed by video laparoscopy, due to better post-operative outcomes and to lower incidence of complications. Of these techniques, the most widely used in Brazil and worldwide is Roux-en-Y gastric bypass.

Despite the benefits of surgery in the treatment of obesity and its comorbidities, this procedure is not exempt from risks. The Longitudinal Assessment of Bariatric Surgery (LABS) Consortium, which followed 2,975 participants undergoing Roux-en-Y gastric bypass for 30 days after surgery, reported 6 deaths among 2,975 participants, i.e., mortality rate of 0.2%. Other complications observed in this study included deep vein thrombosis with possible pulmonary embolism. Twelve of the 2,975 (0.4%) participants developed either of these symptoms. The most frequently reported event in this study was the need for abdominal reoperation. Reasons for reoperation were not describe in this study, but the most common are fistulas, hemorrhage, and intestinal obstruction. Percutaneous drainage was required in 13 of the 2,975 participants (0.4%), and reoperation was required in 94 of the participants (3.2%). In this study, 13 participants of the 2,975 (0.4%) remained hospitalized for more than 30 day.[11]

In addition to postoperative complications, patients undergoing Roux-en-Y gastric bypass may experience some nutritional deficiencies, especially of vitamin B12, iron (particularly in women of childbearing age), and calcium. Routine prophylaxes include multivitamin supplementation associated with parenteral complex B supplementation and specific supplementation regimens established according to clinical follow-up. Protein deficiency is extremely rare in this technique.

1.3 Effect of bariatric surgery on reducing drug prescription

Schauer et al.[12] conducted a randomized clinical trial that assessed the effect of two bariatric surgery techniques compared with intensive clinical treatment of obese patients with type 2 diabetes mellitus. In this study, the authors found that the two surgical techniques led to a statistically reduction in the number of antidiabetic drugs compared with clinical treatment after 12 months. Additionally, there has also been a significant reduction in the use of lipid-lowering medications, anticoagulant, and antihypertensive agents, especially angiotensin-converting enzyme inhibitors (ACE), angiotensin receptor blockers, and diuretics. There was no statistically significant reduction in the use of beta-blockers and calcium-channel blockers, because few patients used these drugs at baseline.

Reducing the number of prescribed medications is always a clinically relevant outcome, particularly when considering the issue of treatment adherence. This issue is even more relevant in the specific context of high blood pressure, due to the high prevalence of this condition (25% of the Brazilian population). However, nearly 50% of patients, regardless of clinical context, sex, age, or ethnicity, fail to adhere to prescribed drug regimen.[12-14] Several factors influence treatment adherence, the main factor is cost, especially that not covered in the household budget.[14]

In the context of CVD, several comorbidities are associated, and therapeutic complexity has also an important impact on patient adherence. Choudhry e col.[15] found that only 67% of patients adhered to the treatment prescribed. They received 11.4 prescriptions with mean prescription of 6.3 different medications in an intensive follow-up of 5 visits for only 3 months.

Finally, dosage regimen is another factor that may influence adherence. Claxton et al.[16] observed a 10% loss of adherence in drugs administered once a day compared with those administered twice a day.

In this sense, the impact of surgery on reducing drug prescription may be beneficial both for patient and for health systems, which often provide financial support to treatment.

1.4 Effect of bariatric surgery on cardiovascular risk

In a systematic review[17] including 52 studies involving 16,867 participants, the unweighted mean of relapse or resolution of hypertension was 68% in participants with high blood pressure, 75% in those with diabetes mellitus, and 71% in those with dyslipidemias. These improvements occurred over a short-term (3 months) following and persisted in the long-term (greater than 155 months) follow-up.

Moreover, pre and postoperative blood pressure measures, documented in 42% of the studies included, showed a reduction of mean systolic pressure from 139 to 124 mmHg and of mean diastolic pressure from 87 to 77 mmHg. The table 2 presents means for pre- and postoperative data for lipid profile, fasting glucose levels, glycated hemoglobin (reported in 42%, 27%, and 11.5% of studies, respectively), and other variables.

Table 2. Effects of bariatric surgery on cardiovascular risk

Variable	Baseline	Postoperative*
Fasting glucose levels (mg/dl)	126	92
HbA1c (%)	7.5	6.0
Systolic pressure	139	124
Diastolic pressure	87	77
Total cholesterol	205	169
LDL-cholesterol (mg/dL)	118	94
HDL-cholesterol (mg/dL)	49	52
Triglycerides	169	103
RCP (mg/dL)**	4.5	1.7
brachial artery (% of change)***	6%	16%

Adapted from systematic review by Heneghan et al.[17]
* after a 34-month follow-up
**based on 5 studies
***based on 3 studies

Overall mean weight loss, as assessed by percentage of excess weight loss, was 52% (ranging from 16% to 87%), including all types of surgical techniques. When stratified by surgical technique, the greatest losses were observed with Roux-en-Y gastric bypass and biliopancreatic diversion.

1.5 Effect of antihypertensive treatment

The benefit of pharmacological treatment with different agents in patients with hypertension has been established by a series of large randomized clinical trials and subsequent systematic reviews with meta-analysis of these trials.[18] The most recent and most cited reviews are those published by Psaty et al.[19], Stassen et al.[18] and Blood Pressure Lowering Trialists Collaboration[20] (the latter of which was recently updated). In these reviews, no differences were observed between treatments and clinical events or between “new drugs” and “Conventional drugs”, even for the outcomes stroke and heart failure.

Monotherapy is the standard initial treatment to reduce blood pressure in most patients with hypertension and changes to combined therapy (2 or more medications of different classes) when increased doses of antihypertensive fail to achieve the expected decrease in blood pressure.[21-24] The effect of medication(s) on reducing blood pressure was summarized in a meta-analysis with 42 factorial studies (10,968 participants).[25] This meta-analysis summarized the results of studies that randomly allocated subjects to receive only 1 medication of different classes, a combination of different medications, or placebo. Results showed that thiazide alone reduced means for systolic pressure in 7.3 mmHg when used alone and in 14.6 mmHg when combined with a medication of other class. The corresponding reductions were 9.3 mmHg and 18.9 mmHg for the use of beta-blocker; 6.8 mmHg and 13.9 mmHg for the use of ACEI; and 8.4 mmHg and 14.3 mmHg for the use of calcium-channel blockers. These estimates show the synergic effect of antihypertensive medications of different classes.

Conversely, most patients require combined treatment with two or more drugs as an initial treatment to achieve blood pressure control goals. A meta-analysis summarizing 354 clinical trials that compared combined drug regimens found that the combination of two or more medications is associated with better rates of therapeutic success and fewer side effects compared with high doses of only one medication[26] Such evidence justifies the frequent practice of using a combination of three or four drugs rather than administering the maximum dose of one drug to achieve adequate blood pressure control.

1.6 Rationale for Sphygmocor

Studies found that there is a higher correlation between central blood pressure and cardiovascular outcomes compared with peripheral blood pressure. In the Strong Heart Study,[27] central pulse pressure measured by the SphygmoCor was slightly more effective in predicting cardiovascular events than brachial pulse pressure in a population of American Indians, with a hazard ratio of 1.15 (95% confidence interval [95%CI] 1.07–1.24) versus 1.10 (95%CI 1.03–1.18).

Data are conflicting with regard to the clinical relevance of augmentation index. Some studies observed that augmentation index was correlated with coronary artery disease and cardiovascular events,[28,29] while other studies did not find this association[30]. The use of augmentation index may be limited by the fact that it can only be measured in patients with normal ventricular function and controlled heart rate. Changes in pattern or duration of ventricular ejection reduce augmentation index regardless of arterial stiffness.[31]

The Conduit Artery Function Evaluation (CAFE) showed that there was a greater reduction on systolic pressure measured by SphygmoCor with the amlodipine regimen compared with the atenolol regimen (mean 4.3 mmHg; 95%CI 3.3–5.4 vs. mean 3.0; 95%CI 2.1–3.9 mmHg; $P < 0.0001$), although the reduction in peripheral blood pressure was similar in both regimens.[32]

The effect of bariatric surgery on central pulse wave has not been investigated yet. Weight loss induced by bariatric surgery is expected to reduce peripheral vascular resistance, which may result in reduced central systolic pressure and augmentation index. In order to analyze these variables, we will measure central pulse wave using SphygmoCor at baseline 12, 24, 36, 48 and 60 months after randomization.

1.7 Study rationale

In view of CVD burden and the difficulty in controlling risk factors, bariatric surgery appears to have promising effects. Although some randomized controlled trials investigated the effect of this surgery on the remission or improvement of type 2 diabetes mellitus, no randomized controlled trial was

originally designed to assess the effect of bariatric surgery on high blood pressure.

2. OBJECTIVES OF THE STUDY

2.1 Primary objective

To assess the efficacy of Roux-en-Y gastric bypass plus medical treatment compared to medical treatment alone in reducing at least 30%of the total number of antihypertensive drugs, while maintaining controlled blood pressure (SBP<140 and DBP <90mmHg) at 12 months.

2.2 Secondary objectives

To assess the efficacy of Roux-en-Y gastric bypass plus medical treatment compared to medical treatment alone, in obese hypertensive patients, on the following outcomes at 12 months:

- Number of antihypertensive drugs
- Systolic blood pressure.
- Diastolic blood pressure.
- Body weight and BMI.
- Waist circumference.
- Fasting glucose levels, HbA1c and insulin resistance
- LDL-cholesterol levels.
- HDL-cholesterol levels.
- Triglyceride levels.
- Uric acid levels.
- High-sensitivity C-reactive protein levels.
- Heart anatomy as evaluated by echocardiogram examination.
- Estimated risk for cardiovascular disease (Framingham Risk Score).
- Adverse events.
- Systolic and diastolic blood pressure measured by ABPM
- Central pressure, augmentation index, and pulse wave velocity measured by SphygmoCor®.
- Sleep quality as assessed by polysomnography.

To assess the efficacy of Roux-en-Y gastric bypass plus medical treatment compared to medical treatment alone on all primary and secondary outcomes between 24 and 60 months of follow-up.

3. STUDY METHODS

3.1 Study design

Phase 3, single-center, randomized clinical trial, with allocation concealment, blinded outcome evaluators, and intention-to-treat analysis to evaluate the efficacy of video laparoscopic Roux-en-Y Gastric Bypass in the reduction of antihypertensive drugs prescription, systemic arterial blood pressure and other risk factors for cardiovascular events when compared to clinical treatment.

3.2 Randomization

Participants who fulfill all eligibility criteria and provide written informed consent will be allocated to either Roux-en-Y gastric bypass or medical treatment, in a 1:1 randomization ratio basis. The randomization list will be generated electronically using appropriate software, and it will be performed in blocks containing 10 patients to guarantee equal group sizes. Allocation concealment will be ensured using a web-based central, automated randomization system made available 24 hours a day by the System of Clinical Studies of HCor (Sistema de Estudos Clínicos do IEP HCor) Each investigator or study team will have access to the system through a specific username and password.

3.3 Blinding procedure

Because the study involves a surgical procedure, investigators and patients cannot be blinded in terms of treatment allocated to patients.

3.4 Video laparoscopic Roux-en-Y Gastric Bypass Description

Patients will be admitted to the *Hospital do Coração (HCor)* at least 12 hours before surgery. On the day before surgery, patients should follow a liquid diet and start fasting 10 hours before surgery. Current medications will be maintained, except otherwise recommended by attending physician.

Patients will be assessed in a pre-anesthetic visit after admission and will receive relevant medication according to this evaluation.

Patients will undergo general anesthesia and be placed in the horizontal dorsal recumbence with the right arm held close to the body.
Deep vein thrombosis will be prevented with high compression elastic stockings and lower limb pneumatic compression. Cefazolin 2 g at the induction stage of anesthesia and 8h thereafter is used as a prophylactic antibiotic.

Description of procedure (Fig. 3):

- Antisepsis with alcoholic chlorhexidine;
- Placement of surgical drapes;
- Performing pneumoperitoneum using a Veress needle, intra-abdominal pressure of 15 mm Hg;
- Performing five punctures – two measuring 12 mm and three measuring 5 mm.

Intestinal time:

- Identification of the angle of Treitz
- Measurement of the biliopancreatic limb – 100 cm;
- Sectioning using a white load stapler (Echelon flex 45);
- Measurement of the alimentary limb – 150 cm;
- Latero-lateral jejuno-jejununal anastomosis between the biliopancreatic limb and the alimentary limb at the point 150cm with a white load stapler (Echelon flex 45);
- Closing of stump with manual suture - Ethibond 2.0 suture;
- Closure of the mesenteric gap with Ethibond 2.0 suture;
- Measurement of common channel;
- Sectioning of the omentum near the border of the transverse colon.

Gastric time:

- Creation of a 20-30mL gastric pouch using a blue load stapler (Echelon flex 45);
- First staple line between the first and second vessels of the lesser curvature;
- Second and/or third staple lines near the angle de His.

- Gastro-jejunal anastomosis (alimentary limb) using Echelon flex 45 stapler at 3-cm stapler ruler
- Insertion of nasogastric tube through anastomosis;
- Closure of stapler opening with manual suture – Ethibond 2.0 suture;
- Assessment of anastomosis integrity using the air test.
- In case of leakage - correction with manual suture;
- Closure of Petersen's space;
- Review of abdominal cavity;
- Removal of trocars by direct view;
- Closure by planes;
- Dressing.

Subjects preoperatively diagnosed with cholelithiasis will undergo cholecystectomy after gastric bypass:

- Dissection of cystic duct and artery
- Placement of LT-300 clips on cystic duct and artery;
- Sectioning of duct and artery;
- Electro cautery with cholecystectomy;
- Review of hemostasis;
- Removal of gallbladder by 12-mm puncture.

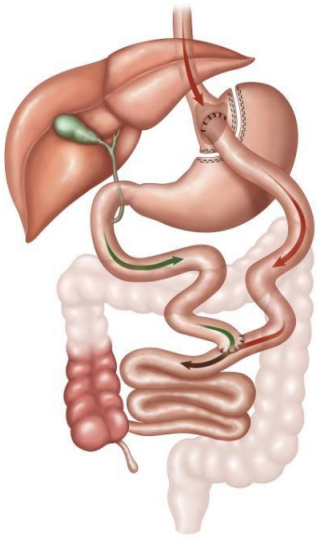


Fig.2: Laparoscopic Roux-en-Y Gastric Bypass

Immediate postoperative period:

- Total fasting;
- Maintenance fluid;
- Analgesia with 500mg dipyrone every 6 hours and nalbuphine if required;
- Gastric protector with 40mg pantoprazole every 12 hours;
- Antiemetics: bromopride 1ampoule every 8 hours and ondasentron 8 mg every 6 hours;
- Maintenance of compression stockings and pneumatic compressor;
- Walking allowed with aid;
- Antihypertensive medication: Sublingual 25mg Captopril if DBP>110mmHg

First postoperative period:

- Start of liquid diet;
- Discontinuation of fluid maintenance therapy if food acceptance is good;
- Maintenance of analgesia, gastric protector, and antiemetics;
- Walking allowed;
- Reintroduction of antihypertensive medication according to blood pressure outcomes.

Second postoperative

- Hospital discharge if food acceptance is good and there are no systemic changes.

3.5 Antihypertensive Treatment

Medical treatment will be standardized for all patients based on office BP levels. Patients will be preferably treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers and a calcium-channel blocker, except if these are contraindicated or if the patient has already controlled BP levels with their current regimen. If the above-mentioned association is already in use and the patient maintained systolic blood pressure (SBP) higher than 130mmHg or diastolic blood pressure (DBP) higher than 80mmHg, the combination with a thiazide diuretic will be preferred. If a diuretic is contraindicated or if other medications are deemed necessary, spironolactone

or clonidine will be used. Medications will be discontinued or reduced if patients presented with SBP lower than 130mmHg or DBP lower than 80mmHg associated with symptoms of orthostatic hypotension.[33] In patients who achieve SBP lower than 110mmHg or DBP lower than 70mmHg, dose reduction of antihypertensive medications will eventually be attempted even in the absence of symptoms; reduced doses were maintained if SBP and DPB levels sustained below 140mmHg and 90mmHg. For patients submitted to bariatric surgery, the necessity of reintroducing antihypertensive medication will be initially checked on a daily basis in the immediate post-operative period, in the first visit one week after the procedure, as well as in the remaining follow-up visits according to the visit schedule. Patients will be treated for other associated co-morbidities according to national and international guidelines.[34,36-38] Adherence to treatment will be based on patient self-report after hospital discharge.

3.6 Measurements of blood pressure and heart rate

The participants invited to attend screening visits will have a confirmed diagnosis of arterial hypertension requiring the use of at least 2 antihypertensive drugs at their full doses and will have their blood pressure measured according to the following tests described below.

3.6.1 Ambulatory blood pressure monitoring (ABPM)

Participants will have an Ambulatory Blood Pressure Monitoring test (ABPM) scheduled according to V Brazilian Guidelines for Ambulatory Blood Pressure Monitoring (ABPM)[(39)] on the day preceding the Initial visit, and after 12, 24, 36, 48 and 60 months

3.6.2 Office blood pressure measurements

On every follow-up visit, study participants will have their blood pressure measured in the doctor's office according to the protocol described below. Systolic (Korotkoff sound I; appearance of the first sound) and diastolic (Korotkoff sound V; disappearance of sounds) blood pressures will be measured using a standard mercury sphygmomanometer or a properly calibrated aneroid sphygmomanometer with the cuff size adjusted to the

circumference of the arm, and patients should avoid consuming tobacco, alcohol, or caffeinated drink for at least 2 hours before examination. The same observer, using the same equipment, will take all measures and on the arm at the same level after patients remained sitting for 5 minutes with their arms positioned at the heart level. Measurements will be taken in triplicate and heart rate will be assessed at a 2-minute interval between two measurements.

3.6.3. Central pressure and associated measures (SphygmoCor®)

Central pressure and arterial stiffness will be assessed by SphygmoCor® (AtCor Medical). This device consists of a tonometer (pressure sensor) placed on the wrist directly above the radial artery, where the operator detects the strongest signal on pulse taking. A computer program accompanying the device allows for the calculation of central pressure and measures to assess arterial stiffness, such as pulse wave velocity and augmentation index. Patients should avoid consuming caffeine for at least 3 hours and alcohol for 10 hours before measurements. Measures should be taken preferably in the supine position.

Tests with SphygmoCor® will be conducted at the Instituto Dante Pazzanese de Cardiologia.

3.6.4 Polysomnography

Patients will be referred for polysomnography at the Instituto do Coração (Instituto do Coração, School of Medicine, Universidade de São Paulo, FMUSP). This method will be used after randomization (baseline) visits after 12, 24, 36, 48 and 60

3.7 Anthropometric measures

During clinical visits, a previously trained professional will measure weight, height, and waist circumference.

Weight will be measured using a mechanical platform or digital scale with an accuracy of 100 g. Measures should be obtained twice and the mean of the two measurements will be considered the actual weight of the participant. If the difference between measures is greater than 1 cm, the procedure will have to be repeated until reaching an acceptable difference.

Height will be measured using a stadiometer with an accuracy of 0.5 cm. Measures should be obtained twice and the mean of the two measurements will be considered the actual height of the participant If the difference between measures is greater than 1 cm, the procedure must be repeated until reaching an acceptable difference.

Weight and height will be used to calculate the derived variable body mass index (BMI). BMI is calculated dividing current weight in kg by squared height in meters.

Waist circumference will be measured using a non-stretch tape measure made of resistant material and accurate to 0.1 cm. Waist circumference will be measured at the midpoint between the last rib and the iliac crest in the midaxillary line. Measures should be obtained twice and the mean of the two measurements will be considered the actual waist circumference of the participant. If the difference between measures is greater than 1 cm, the procedure will have to be repeated until reaching an acceptable difference. Additionally, body composition (body fat percentage vs. lean mass percentage) will be measured by bioimpedance.[40]

3.8 Food intake data and Nutritional advice

Dietary intake will be assessed using a 24-hour diet recall. This instrument investigates the type of food, preparations, portions, home measures, amounts, and times when meals are consumed 24 h before the visit. A photo book showing standard home measures will be used to assist the collection of the 24-hour diet recall. Nutritional composition in terms of energy and nutrients will be analyzed using a computerized system (Nutriquanti System).

Patients from both groups will receive nutritional advice that is based on national statements for hypertension and obesity.[34] A visit to a dietitian from the investigation team will follow each medical visit at the hospital to reinforce the nutritional recommendations previously indicated. Nutritional advices in the clinical group will be mainly directed at weight reduction and blood pressure control.[34-36] Aiming at progressive weight loss over time, the total daily energy consumption calculated as 20 kcal/kg of ideal body weight per day will be

stimulated among the patients. Similarly, for the improvement of blood pressure control, the ingestion of food with high sodium concentration, such as snacks, sausages and fast food, will be discouraged and the reduction of salt used for cooking at home or added to the already prepared food will be encouraged. Consuming fruits and vegetables will be stimulated also to increase potassium intake.

3.9 Laboratory tests

This protocol includes the following laboratory tests:

LABORATORY TESTS	
Tests undertaken by the 2 study groups during visits	• Fasting glucose levels • HbA1c • Insulin • High-sensitivity c-reactive protein • Complete blood count • Lipid profile • Hepatic enzymes (AST, ALT) • Uric acid • 24-h urinary sodium and potassium • 24-h urinary creatinine • Creatinine • Potassium • Urine analysis • Echocardiogram, Electrocardiogram, SphygmoCor® • ABPM • Polisomnography
Tests undertaken only by the intervention group (bariatric surgery)	• Iron, Ferritin • Vitamin B12 • Total proteins and fractions • PTH • Parasitological stool test • Coagulogram

LABORATORY TESTS	
	• Full abdominal ultrasound • Upper abdomen ultrasound • Pelvic ultrasound • Upper digestive endoscopy with *H.pilory* search

3.10 Psychological assessment and follow-up

A psychological assessment will be performed at the baseline visit. This assessment will include scales to evaluate binge eating disorder, symptoms of anxiety and depression, and quality of life. Throughout the study, participants of both groups will receive psychological follow-up consisting of individual visits for participants of the surgical group and multidisciplinary group meetings for participants of the clinical group.

3.11 Outcomes of interest

3.11.1 Primary outcome

Reduction on the total antihypertensive medications of at least 30% while maintaining controlled BP levels (SBP<140 and DBP <90mmHg) at 12 months.

3.11.2 Secondary outcomes

Reduction on the total antihypertensive medications of at least 30% while maintaining controlled BP levels (SBP<140 and DBP <90mmHg) at 24, 36, 48 and 60 months.

The following secondary outcomes (absolute change from baseline) will be assessed at 12, 24, 36, 48 and 60 months:

- Systemic blood pressure measured by ambulatory blood pressure monitoring (ABPM)
- Central pressure, augmentation index, and pulse wave velocity measured by SphygmoCor®
- Systolic blood pressure (measured at office visits)
- Diastolic blood pressure (measured at office visits)
- Body weight and BMI.

- Waist circumference.
- Fasting glucose levels, HbA1c and insulin resistance
- LDL-cholesterol levels.
- HDL-cholesterol levels.
- Triglyceride levels.
- Uric acid levels.
- High-sensitivity C-reactive protein levels.
- Estimated risk for cardiovascular disease (Framingham Risk Score).
- Echocardiographic parameters
- Sleep quality by polisomnography.
- Adverse events.

3.12 Patients' identification

Participants will be selected to participate in the study at HCor and may be referred from hypertension outpatient clinics of the Heart Institute (HC-FMUSP), from Instituto Dante Pazzanese de Cardiologia, from doctor's offices, or at patient's own initiative after being informed about the study through advertisement in print or digital media. Patients must have a previous diagnosis of hypertension and be taking maximum doses of at least two antihypertensive drugs or moderate doses of more than two antihypertensive drugs. Patients will be assessed by the study with regard to other eligibility criteria. Patients who met inclusion criteria in this outpatient phase will be invited to participate in the study and will be randomized to one of the treatment strategies.

3.13 Visits scheme

All visits will be scheduled according the date of inclusion of the patient in the study, with a time window of more or less 3 days.
Follow-up visits are described in the sections below.

3.13.1 Screening visit

Participants will be fully informed about study methods and all the procedures they will be subjected to during the observation period, as well as

the risks implicated in each procedure. Participants will be assessed for inclusion and exclusion criteria and for current hypertensive medication. When the candidate agrees to participate, and is in accordance with the eligibility criteria, he or she will be asked to sign the informed consent form. Then, antihypertensive treatment is adjusted as explained in session 3.5.

3.13.2 Randomization visit

This visit will be scheduled approximately 6 weeks after the screening visit. In this visit, a thorough medical history will be obtained and eligibility criteria confirmed. Participants meeting eligibility criteria will be randomized to undergo video laparoscopic Roux-en-Y gastric bypass or to receive medical treatment.

After randomization, patients will receive an identification number code, which will be used in all documents from study subjects, including clinical records, mail, and any other elements requiring identification.

Blood samples will be collected for baseline laboratory analysis (section 3.9).

Subjects allocated to the intervention group (video laparoscopic Roux-en-Y gastric bypass) will undergo additional preoperative examinations to identify possible contraindications to surgery and assess adverse events associated with surgery. The following tests will be performed: full abdominal ultrasound, upper gastrointestinal endoscopy with search for *H. pylori*, coagulogram, and parasitological stool test. On this occasion, patients allocated to the surgical group will start multivitamin supplementation, which should be maintained up to the day before surgery.

Office-based blood pressure will be measured. All the following exams are schedule close to the randomization visit: central pressure, pulse wave velocity, and augmentation index as measured by SphygmoCor®; ABPM; echocardiogram; electrocardiogram; bioimpedance; and polysomnography.

3.13.3 - Baseline visit

The baseline visit will be scheduled as soon as all the exams are ready. After this visit, patients of the gastric bypass group will undergo surgery. On this occasion, coagulation parameters should be normal.

If cholelithiasis is identified on abdominal ultrasound, cholecystectomy will be simultaneously performed; H. Pylori positive patients will be treated with a triple regimen for 10 days – amoxicillin 2 g/day, clarithromycin 1 g/day, and pantoprazole 80 mg/day; subjects diagnosed with intestinal parasitosis will receive specific treatment.

If test results contraindicate surgery, the patient will be excluded from the study and regarded as a randomization failure.

A psychologist will see the participants of both groups. In the surgical group, psychological visits will focus on evaluating whether the patient is psychologically prepared to cope with changes resulting from surgery. In the clinical group, the focus will be on evaluating patient motivation to adhere to intervention.

The participants of both groups will also be seen by a dietitian to assess baseline anthropometric measures, body composition by bioimpedance, a 24-hour diet recall, and to receive nutritional counselling on weight control and salt intake.

3.13.4 Follow-up visit 1 (week 1 after surgery)

This will be a clinical visit involving the following procedures:

- Measurement of office-based systemic blood pressure and heart rate.
- Report if any adverse events, whether related or not with the study treatment.
- Dietitians visit to collect anthropometric measures and provide nutritional counselling (guidance on the use of protein supplements).
- Patients will provide information on treatment adherence.
- Multivitamin supplementation will be restarted.

3.13.5 Follow-up visit 2 (week 4 after baseline visit)

This will be a clinical visit involving the following procedures:

- Measurement of office-based systemic blood pressure and heart rate.
- Report if any adverse events, whether related or not with the study treatment.
- Dietitians visit to collect anthropometric measures and provide nutritional counselling (check on the use of protein supplements for postsurgical patients).
- Patients will provide information on treatment adherence.
- A psychologist will see patients in the surgical group, whereas those randomized to the clinical group were invited to group meetings.

3.13.6 Follow-up visit 3 (month 3 after baseline visit)

This will be a clinical visit involving the following procedures:

- Measurement of office-based systemic blood pressure and heart rate.
- Dietitians visit to collect anthropometric measures and provide nutritional counselling.
- Report if any adverse events, whether related or not with the study treatment.
- Patients will provide information on treatment adherence.
- A psychologist will see patients in the surgical group, whereas those randomized to the clinical group were invited to group meetings.
- Subjects in the surgical group will undergo ultrasound of liver and biliary structures for those who have not had their gallbladder removed. Participants with positive results for biliary calculus will undergo elective cholecystectomy.

3.13.7 Follow-up visit 4 (month 6 after baseline visit)

This will be a clinical visit involving the following procedures:

- Measurement of office-based systemic blood pressure and heart rate.
- Report if any adverse events, whether related or not with the study treatment.
- Dietitian visit to collect anthropometric measures, provide nutritional counselling, and obtain a 24-hour diet recall.

- Patients will provide information on treatment adherence.
- A psychologist will see patients in the surgical group, whereas those in the clinical group will be invited to group meetings.

3.13.8 Follow-up visit 5 (month 12 after baseline visit)

Before the scheduled visit, patients will undergo ABPM, Echocardiogram, Electrocardiogram, polysomnography, SphygmoCor®.

This will be a clinical visit involving the following procedures:

- Measurement of office-based systemic blood pressure and heart rate.
- Dietitian visit to collect anthropometric measures, provide nutritional counselling, and obtain a 24-hour diet recall.
- Patients will provide information on treatment adherence
- Blood samples will be collected for laboratory analysis (section 3.9).
- A psychologist will see patients in the surgical group, whereas those randomized to the clinical group will be invited to group meetings.

3.13.9 Follow-up visit 6 (month 18 after baseline visit)

This will be a clinical visit involving the following procedures:

- Measurement of office-based systemic blood pressure and heart rate
- Dietitians visit to collect anthropometric measures, provide nutritional counselling, and obtain a 24-hour diet recall
- Collection of data on any adverse event, whether related or not with study treatments
- Patients will provide information on treatment adherence

3.13.10 Follow-up visit 7 (month 24 after baseline visit)

Before the scheduled visit, subjects will undergo ABPM, Echocardiogram, Electrocardiogram, polysomnography, SphygmoCor®.

This will be a clinical visit involving the following procedures:

- Measurement of office-based systemic blood pressure and heart rate
- Dietitians visit to collect anthropometric measures, provide nutritional counselling, obtain a 24-hour diet recall, and measure body composition by

bioimpedance.

- Report if any adverse events, whether related or not with the study treatment.
- Blood samples will be collected for laboratory analysis (section 3.9).
- Collection of information on treatment adherence
- Participants in the surgical group will be seen by a psychologist, whereas those in the will be invited to group meetings.

3.13.11 Follow-up visits – 30, 42 and 54 months after baseline visit:

These visits will include the same procedures conducted in the 18-months follow-up visit.

3.13.12 Follow-up visits – 36, 48 and 60 months after baseline visit:

These visits will include the same procedures conducted in the 24-months follow-up visit. Polysomnography will be done only at 60 months.

3.14 Adverse event report

The investigator will check for the occurrence of adverse events at all study visits. In case of an adverse event, complete and detailed information related to this event should be obtained and recorded on medical and clinical records with great detail, including treatment information.

The following data should be provided when reporting an adverse event:

- Start and end date;
- Duration of the event in days;
- Intensity of the event (mild, moderate, or severe);
- Frequency of the event (unique, intermittent, or continuous);
- Severity;
- Nature of severity (fatal, life-threatening, permanent disability, need of hospitalization, congenital anomaly, or significant risk);
- Relationship between the events and study medication/procedure;
- Action taken;
- Event outcome (recovered, not recovered, with sequelae, or fatal).

If the event is fatal, it will be necessary to record date of death, cause of death, and whether autopsy was performed.

3.14.1 Serious adverse event reporting

The investigator should record information about serious adverse events on medical and clinical records and complete the serious adverse event form. This form should be sent to the Research Ethics Committee within a maximum of 24 hours after being informed about the event.

4. STUDY POPULATION

4.1 Inclusion criteria

- Adults aged between 18 and 65 years.
- Patients with hypertension using at least 2 antihypertensive drugs at full doses or more than two in moderate doses.
- Grade 1 and Obesity: BMI between 30.0 and 39.9.

4.2 Exclusion criteria

- Patients with blood pressure levels ≥ 180/120 mmHg;
- Cerebrovascular disease (stroke) in the past 6 months.
- Cardiac disease (myocardial infarction, angina, coronary revascularization, heart failure) that occurred or were diagnosed in the past 6 months.
- Underlying psychiatric diseases: schizophrenia, bipolar disorder, severe depression, psychosis
- Kidney disease: diabetic nephropathy, creatinine clearance < 30 ml/min.
- Individuals with secondary hypertension, except due to sleep apnea.
- Advanced peripheral artery disease
- Patients with atrophic gastritis
- Type 1 diabetes; latent autoimmune diabetes of adults; type 2 diabetes mellitus with HbA1c >7.0%
- Alcoholism or use of illicit drugs
- Current tobacco smoking habit
- Previous abdominal surgery (except for MacBurney, Pfannenstiel, and video laparoscopic cholecystectomy)
- Severe hepatic disease
- Pregnant women or women at childbearing age not using effective contraceptive methods;
- Neoplasm occurring in the past 5 years
- Use of immunosuppressant drugs, chemotherapy or radiotherapy
- Inability to understand or to adhere to study procedures

4.3 Recruitment

Participants will be selected from hypertension outpatient clinics or doctor's offices. At this time, all participants will be investigated for compliance with eligibility criteria and those meeting these criteria will be asked to provide written consent to participate in the study by signing the informed consent form. Medical history and baseline clinical characteristics will be obtained through history taking, and baseline data will be collected through medical tests.

4.4 Losses to follow-up

All efforts will be made to ensure complete follow-up of study participants, whether they adhere or not to the procedures described in this protocol. However, patients who, for any reason, do not return to the scheduled visits according to the protocol or refuse follow-up will be classified as lost to follow-up.

4.5 Consent withdrawal

Withdrawal of consent occurs when a patient spontaneously decides, for whatever reason, whether specified or not and at any time during the study, that he/she does not want to participate in the study anymore and that he/she does not allow for his/her follow-up data to be collected.

5. STATISTICAL CONSIDERATIONS

5.1 Sample size calculation

The study was initially designed to enroll 60 patients. During the conduction of the trial, the Steering Committee decided to increase the sample size to 100 patients to improve precision around the effect estimate. This revised sample provides 90% power to detect an increase in the incidence of the primary end point from 10% in the medical therapy to 40% in the gastric bypass group, assuming a two-sided hypothesis test with a significance level of 5%.

5.2 Statistical analysis

Baseline characteristics will be reported as counts and percentages, mean and standard deviation (SD), or median and interquartile range (IQR), whenever appropriate.

Main analysis will be conducted according to the intention-to-treat principle; in case of missing values in 12-month visit we will use a simple carry-over imputation procedure. We will assess the effect of the trial treatments on the primary outcome using Fisher exact test and presented rate ratios with 95% confidence intervals (CIs).

We will conduct other five sensitivity analysis: complete-case analysis (without missing data imputation); per-protocol analysis (patients randomized from gastric bypass group who will not undergo surgery will be ignored), as-treated analysis (patients randomized to gastric bypass group who will not undergo surgery will be analyzed in the medical therapy group), worst-case scenario imputation analysis (missing end point data will be imputed as a positive result in the medical therapy group and negative result in the gastric bypass group), and adjusted analysis for BMI, number of medications at baseline, Framingham Risk Score, serum insulin level at baseline and duration of hypertension using Poisson regression analysis with robust error variance.. In all cases, rate ratio will be presented with 95% CIs.

Continuous secondary end points will be analyzed with adjustments for baseline values using repeated measure ANOVA models. Variables that do not

hold normal distribution assumption will be analyzed using generalized estimating equation models with distribution that fit better the data.

Analyses will be performed using R (R Core Team, 2016, Vienna, Austria) program. Results of diet recalls will be assessed using NutriQuanti®.

6. ADVERSE EVENTS

Physicians will complete adverse event forms or serious adverse event forms with the information provided by patient either at clinical visits or by telephone. The Research Ethics Committee should be immediately informed in case of a serious adverse event.

The physician must decide whether hospitalization, complementary tests, and early exclusion from the study are necessary. Medical care costs will be covered by the project.

6.1 Adverse event definitions

According to the Document of the Americas, adverse event is defined as any adverse medical occurrence in a patient or clinical research participant who underwent an intervention. This occurrence does not necessarily have a causal relationship with the treatment. Thus, an adverse event may be any unfavorable and unintentional sign, symptom, or disease (including abnormal laboratory findings), whether related or not to study interventions.

6.2 Unexpected adverse events

This is an adverse reaction whose nature, severity, or outcome is not consistent with information described in the package leaflet. It should be monitored according to guidelines for adverse reactions and, if applicable, according to guidelines for serious adverse reactions.

6.3 Definition of serious adverse events

A serious adverse event is any event that is fatal, life-threatening, debilitating or incapacitating or resulting in hospitalization (not relevant to the study), an event that causes longer hospital stay (relevant to the study and longer hospital stay than the length planned in the study protocol) or is associated with congenital abnormality. In addition, any event that the investigator considers serious or that may suggest any significant risk, contraindication, side effect, or prevention measure that may be associated with the use of the drug should be reported as a serious event.

An event should be considered as life threatening if it poses the patient at immediate risk of death. An event should be considered as disabling or incapacitating if it causes significant and/or permanent impairment of the patient's ability to perform normal life activities.

6.4 Evaluation of adverse event intensity

Adverse events should be classified as to their severity into mild, moderate, or severe. The following table describes the definitions:

Mild	Adverse event easily tolerated by the patient, causing minimal discomfort, not interfering with his activities.
Moderate	Adverse event sufficiently discomforting to interfere with the patient's normal activities.
Serious	Any fatal, life-threatening, debilitating event, or an event leading to hospitalization, according to item 6.3

7. ADMINISTRATIVE PROCEDURES

7.1 Electronic case report forms (e-CRF)

Electronic reports forms will be accessed through the System of Clinical Studies of IEP-HCor (Sistema de Estudos Clínicos do IEP-HCor). They should be completed within a maximum of 5 days after visiting the patient. The electronic system for the development of informative reports on the completion status of forms and shows whether the completion of some of these forms is delayed and the duration of such delay, enabling the study team to manage participants in all research sites.

All security recommendations set out by international guidelines for the use of e-CRFs are ensured by the system. In this sense, any changes of data made by the team and the reasons for the changes are recorded in the system, thus ensuring data accuracy and quality.

7.2 Monitoring report

The researcher must submit a study monitoring report every six months to Research Ethics Committee informing status of inclusion, safety data, and study schedule.

7.3 Filing of records

The Research Center will keep confidentiality of all study documentation, taking the appropriate measures to prevent premature or accidental destruction of such documents. The study documentation must be kept for at least 5 years after completion or discontinuation of the study.

7.4 Publication

We expect to publish at least four manuscripts related to this study: a design paper and main manuscripts describing study results at one, three and five years.

Study findings will be published regardless of results.

7.5 Confidentiality

The investigator should ensure the privacy and confidentiality of study participants. In the e-CRFs and in any documents sent to the sponsor, only their identification number and name initials will identify participants.

The investigator should provide direct access to patient records and source document for monitoring, audit, or inspection by the sponsor, authorized representatives of the sponsor, and regulatory authorities.

7.6 Data protection

Personal information of investigators and patients enrolled in the study that may be included in the database will be treated according to applicable laws and regulations.

When filling or processing personal data from investigators and/or participants, all necessary measures will be taken to safeguard and prevent unauthorized third parties to have access to these data.

7.7 Audits and inspections of regulatory agencies

In order to ensure protocol compliance with good clinical practices and applicable legal requirements, investigators will be obliged to allow for audits and inspections of applicable regulatory agencies if necessary. The confidentiality of the obtained data and participant anonymity will be respected during these inspections. Any results and information from inspections of regulatory authorities will be immediately communicated by the investigation to the sponsor.

Investigators should take all the required appropriate measures to implement corrective actions for all the issues raised during audits or inspections.

8. RESPONSIBILITIES

It is important to emphasize that all the procedures to be executed during the study period will be based on the guidelines described in Document of the Americas, Good Clinical Practice handbook, and related laws.

8.1 Investigator Responsibilities

The investigator should ensure the completion of all the procedures described in this protocol. The investigator is also responsible to report reliable data in an accurate and legible manner according to the provided instructions and provide study monitors with direct access to source documents if requested so.

These are the responsibilities of the principal investigator:

- Submitting the trial project proposal to the REC of the study site and executing the study according to the Declaration of Helsinki, good clinical practices, and guidelines outlined in the Document of the Americas and in compliance with all laws and regulations applicable;
- Starting the study only after the protocol and the **written informed consent** are reviewed and approved by the **REC** where the study will be conducted and all local institutional requirements are complied;
- Ensuring that every patient and/or legal representative (or caregiver) reads, understands, and signs an informed consent form.

Considering that Resolution No. 251 of the Brazilian National Health Council, dated of August 7, 1997, restates the non-transferable responsibility of investigators under the terms of Resolution No. 196/96, the principal researcher is responsible for:

- Submitting the complete research project to the REC under the terms of Resolutions No. 196/96 and 251/97.
- Filing clinical records of all research subjects for 5 years after study completion, respecting data confidentiality.
- If the investigator leaves the institution where the study was conducted, the documents should remain under the custody of the person who will occupy his/her position.
- Providing a detailed report, whenever requested or established by the

REC, the National Research Ethics Committee (Comissão Nacional de Ética em Pesquisa, CONEP) or by the Brazilian Health Surveillance Agency (Secretaria de Vigilância Sanitária, SVS/MS).

- Communicating the occurrence of serious adverse events to the REC.
- Communicating proposals of possible changes in the project and/or justification for interruption and awaits for appraisal of the REC, except for urgent cases to safeguard the protection of study participants, when the REC should be informed a posteriori as soon as possible.
- Providing the REC, CONEP, and SVS/MS with all appropriately requested information.
- Proceeding with the continuous analysis of results throughout study execution, in order to detect as early as possible the benefits of one treatment over the other and to avoid adverse effects in study participants.
- Sending periodic reports within the deadlines established by the REC, providing at least a semi-annual report and a final report.
- Providing access to test and treatment results to patient's physician and to the patient whenever requested and/or indicated.
- Recommending that the same person will not participate in a new research project within the first year after participating in the previous research, unless the participant may directly benefit from the research.

8.2 Sponsor responsibilities

The sponsor of this study is obliged by the health authorities to implement all reasonable measures to ensure the adequate development of the study in terms of ethics and compliance with all items of the protocol.

According to the Document of the Americas, sponsor responsibilities include:

- Quality assurance and control;
- Management of research, handling of data, keeping of records; Selection of a qualified team to conduct the study;
- Compensation of study participants and researchers; Research funding;
- Notification/submission of the research to regulatory authorities; Provide all information on research product(s);
- Manufacturing, packing, labeling, and promoting the coding of research

product(s) according to good manufacturing practices;

- Provision and handling of research product(s); Providing of safety information;
- Ensuring that all drug adverse reactions are appropriately reported and reporting the notified events to the regulatory agency;
- Ensuring appropriate research monitoring.

9. ETHICAL CONSIDERATIONS

9.1 Approval from independent Research Ethics Committees (REC)

The study should be started only after being approved by the Research Ethics Committee of *Hospital do Coração* (HCor), which should grant the approval and provide one copy to the research investigator.

9.2 Standards for conducting the study

9.2.1 Declaration of Helsinki

The present study will be conducted in full compliance with the current version of the Declaration of Helsinki.

9.2.2 Good Clinical Practices

The study will be conducted in accordance with the research protocol and to good clinical practices (GCP) guidelines. All study sites will be responsible for adhering to GCP principles and local study requirements. Institutions with no experienced in clinical research will receive specific training on GCP guidelines provided by the coordinating center.

9.2.3 National clinical trials norms

This study will be conducted in compliance with local regulations, Resolution RDC No. 196/96, Resolution RDC No. 251/97 and complementary resolutions from the Ministry of Health and National Health Council.

9.2.4 Obtainment of consent

According to the Document of the Americas, the administration of the informed consent form is a process through which the study participant voluntarily confirms his/her desire to participate in the study, particularly after being informed on all aspects relevant to his/her decision to participate.

The informed consent form is a document that will be signed and dated by the research subject or his/her legal representative and the witness (if applicable) and will be used as documentary evidence that participants received

enough information on the clinical trial, possible study intervention, and theirs rights as a research subjects, and that they voluntarily agreed to participate in the study.

Before signing the Informed Consent form the investigator or his/her designated representative must provide all relevant information and give the participant or his/her legal representative enough time and opportunity to ask questions about the details of the study so that the patients can decide on their participation.

The patients should also be informed that they can freely withdraw their consent and discontinue their participation in the study at any time, with the only responsibility of communicating this decision, without any damage to their treatment.

If the participant or his/her legally authorized representative are unable to read or understand the study information, the participation of an impartial and independent witness is requested. This witness preferably should not be familiar with the clinical study. Fingerprints can be used if the subject or his/her legal representative is unable to sign the form.

The research subject or his/her legal representative and the witness (when necessary) must sign and date two copies of the document. Similarly, the researcher who administers the Informed Consent form must also date and sign the two copies. One copy should be filed in the study center and the other copy should be provided to the participant.

Note: All pages of the Informed Consent form must be initialed by the research subject, the legal representative and/or the witness (if applicable), and the researcher.

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