

BMJ Open Effects of gastric bypass surgery in patients with hypertension: rationale and design for a randomised controlled trial (GATEWAY study)

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ABSTRACT

Introduction: Obesity and overweight are becoming progressively more prevalent worldwide and are independently associated with a significant increase in the risk of cardiovascular diseases. Systemic arterial hypertension is frequently found in association with obesity and contributes significantly to increased cardiovascular risk. We hypothesise that Roux-en-Y gastric bypass (RYGB) surgery, a procedure that effectively reduces body weight, can also positively impact blood pressure control in obese and hypertensive individuals.

Methods and analysis: A unicentric, randomised, controlled, unblinded clinical trial. Sixty obese (body mass index between 30 and 39.9) and moderately well controlled hypertensive patients, in use of at least two antihypertensive medications at maximum doses or more than two in moderate doses, will be randomly allocated, using an online, electronic and concealed method, to receive either RYGB plus optimised clinical treatment (OCT) or OCT alone. The primary end point is the reduction of antihypertensive medication at 1 and 2 years of follow-up. Data analysis will primarily be conducted on an intention-to-treat basis.

Ethics and dissemination: The study was approved by the local institutional review board that works in total compliance with the latest version of the Helsinki Declaration, the Good Clinical Practices (GCP), the 'America's Document' and the national regulatory laws. Before the beginning of any study-related activities, each study participant is asked to provide a signed informed consent.

Trial registration number: NCT01784848.

BACKGROUND AND RATIONALE

Obesity and overweight are conditions of paramount relevance for public health worldwide, showing progressively increasing prevalence rates in developing and

Strengths and limitations of this study

- This is a randomised controlled trial designed to investigate a very important clinical question, namely the influence of a largely used surgical procedure to treat obesity on blood pressure control.
- The study was designed to be performed using optimised methodological resources such as an online randomisation system that ensures allocation concealment, intention-to-treat analysis of data and blinded adjudication of clinical events, in order to prevent systematic bias.
- The study is not blinded, given that the investigated procedure is a surgery.
- The number of patients in our sample is not sufficient to investigate hard outcomes (mortality, incidence of cardiovascular events, etc) but rather surrogate end points, such as blood pressure control and medication withdrawal.

developed countries in recent decades.^{1–5} The widespread epidemic of obesity occurs not only in adulthood but also in younger populations, which reinforces concerns that the problem is expected to become even worse along the upcoming years.¹ Obesity is currently defined by a body mass index (BMI, the body weight in kilograms divided by the square of the height in metres) equal to or larger than 30.¹ Among its most serious consequences, we can find an elevated risk for distinct diseases, especially those of cardiovascular nature. In addition, obesity is frequently observed in close association with other cardiovascular risk factors, such as diabetes or insulin resistance, hypertension and hyperlipidaemia, composing the so-called metabolic syndrome.⁶ A progressive enlargement in the burden of cardiovascular

mortality and morbidity with a direct impact on public health and healthcare systems all over the world is therefore expected, given the current scenario.¹

Although governments, as well as academic, profit and non-profit institutions, have conducted distinct initiatives in the search for better treatment options for obesity during the past few decades, virtually all the efforts have frequently resulted in disappointing results.^{1 4 7} Distinct approaches aiming at the change of nutritional habits and improvement of physical activity have been shown to be inefficient, as described by many clinical trials, with high failure rates and considerable weight regain over different follow-up periods.^{8 9} Similarly, the use of drugs to control appetite and nutrient absorption has shown far from successful results. Formerly promising medications are in some cases associated with significant adverse reactions and limited long-term benefits.^{10 11}

Bariatric surgery techniques were introduced in the 50s and evolved in subsequent decades as an invasive but efficient treatment for obesity. Some of these techniques have demonstrated results in terms of weight loss that are maintained over long periods.¹² Recent evidence suggests that surgical bariatric procedures can additionally improve metabolic profile, reducing lipid levels and leading to optimised glucose control in obese individuals with diabetes.^{13–18} Moreover, long-term mortality was reduced in the groups treated by surgery in comparison to those under intensive clinical treatment for obesity.¹⁹

Besides weight reduction, blood pressure is one of the multiple risk factors that seems to significantly change after surgery in comparison to optimised clinical treatment.^{13–15 20} Some studies have shown that a significant percentage of patients could discontinue blood pressure lowering medications in the post-operative period,^{15 17 20} although this effect was not consistently reproduced.¹⁴ Moreover, previous studies were not primarily designed to specifically address the question of blood pressure control. Consequently, current guidelines consider bariatric surgery only for patients who present a BMI higher than 40 or between 35 and 40 with coexisting medical conditions related to obesity and resistant to clinical interventions. The aim of the present study is therefore to investigate the long-term effects of Roux-en-Y gastric bypass (RYGB), in comparison to optimised clinical treatment, on blood pressure control, in a population of moderately hypertensive and obese participants.

METHODS

Study design

This is a randomised, unicentre, phase III clinical trial, planned to be performed with concealed allocation of participants and intention-to-treat analyses. Patients allocated to both clinical and surgical groups are followed for a total of 24 months. An overview of the study design can be seen in the study flow chart (figure 1).

Aims

The primary aim of the study is to evaluate the efficacy of RYGB, as compared with OCT on the reduction of antihypertensive medication, over 12-month and 24-month periods. In parallel, we intend to investigate the effect of RYGB on the following secondary end points: (1) systemic blood pressure assessed through ambulatory blood pressure monitoring (ABPM) at 12 and 24 months; (2) central blood pressure, augmentation index and pulse wave velocity as measured by the SphygmoCor device²¹; (3) systolic and diastolic arterial blood pressure; (4) weight loss and BMI; (5) waist circumference; (6) fasting blood sugar, glycated haemoglobin (HbA1c) and insulin resistance; (7) lipid profile (low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol and triglyceride levels); (8) uric acid; (9) ultra-sensitive C reactive protein; (10) reduction of cardiovascular risk (Framingham risk score); (11) heart anatomy as evaluated by echocardiogram examination; (12) iron, calcium and vitamin B₁₂ metabolism; (m) main adverse events related to surgery.

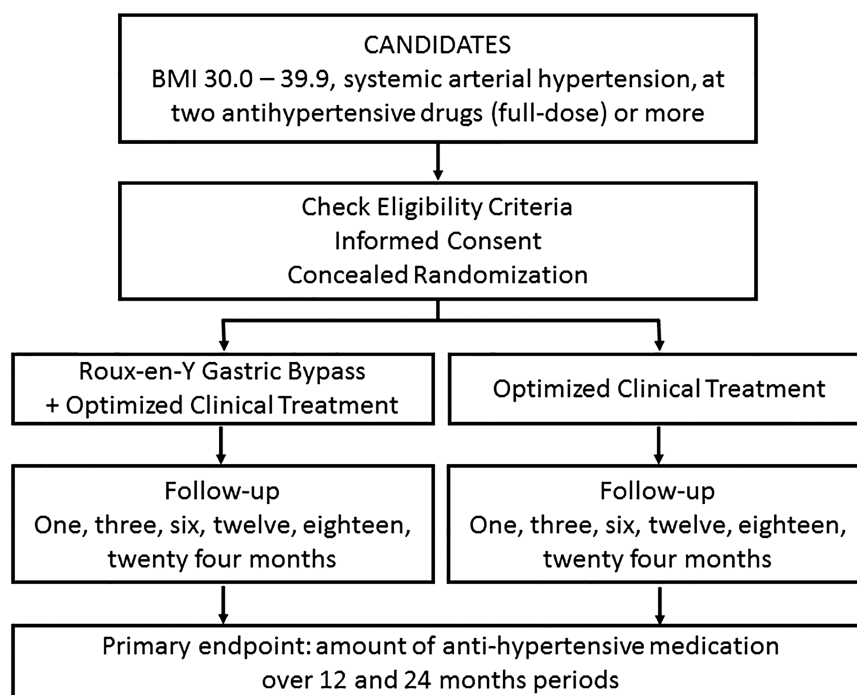
Eligibility

Patients of both genders, aged from 18 to 65 years, with previously diagnosed arterial hypertension (as defined by the current use of at least two full-dose antihypertensive drugs or more than two in moderate doses) and a BMI in the range from 30 to 39.9 are considered eligible for this study. Exclusion criteria are severe and uncontrolled arterial hypertension ($\geq 180/120$ mm Hg); cerebrovascular disease with acute events or alterations in the cognitive function in the past 6 months; heart diseases (myocardial infarction, angina, coronary revascularisation, heart failure) that occurred or were diagnosed in the past 6 months; severe psychiatric disorders: schizophrenia, bipolar disorder, severe depression, psychosis; severe kidney disease: diabetic nephropathy, important reduction of renal function (glomerular filtration rate <30 mL/min); diagnosed secondary hypertension, except due to sleep apnoea; advanced peripheral arterial disease; atrophic gastritis; type 1 (any) or uncontrolled type 2 (with HbA1c >7.0) diabetes mellitus or latent autoimmune diabetes of adults (LADA); alcoholism or use of illicit drugs; current tobacco smoking habit; previous abdominal surgery (except for MacBurney, Pfanneistil and laparoscopic cholecystectomy); severe hepatic diseases; pregnancy or women at childbearing risk who are not using effective contraceptive methods; cancer in the past 5 years; use of immunosuppressive drugs, chemotherapy or radiotherapy; inability to understand and adhere to the treatment or to the postsurgical instructions (box 1).

Randomisation and allocation concealment

Participants who fulfil all the eligibility criteria and provide written informed consent are allocated to either RYGB combined with optimised clinical treatment (OCT) or OCT alone, in a 1:1 randomisation ratio basis, with a predicted sample size of 60 patients, 30 in each group. Randomisation is performed in blocks containing

Figure 1 Study flow chart.



Box 1 Criteria for eligibility

Inclusion criteria

Age: 18–65 years.

Body mass index (BMI) in the range from 30.0 to 39.9.

Previously diagnosed arterial hypertension (as defined by current use of at least two full-dose antihypertensive drugs or more than two in moderate doses).

Exclusion criteria

Severe and uncontrolled arterial hypertension ($\geq 180/120$ mm Hg).

Cerebrovascular disease with acute events or alteration in the cognitive function in the past 6 months.

Heart diseases (myocardial infarction, angina, coronary revascularisation, heart failure) that occurred or were diagnosed in the past 6 months.

Severe psychiatric disorders: schizophrenia, bipolar disorder, severe depression, psychosis.

Severe kidney disease: diabetic nephropathy, important reduction of renal function (glomerular filtration rate < 30 mL/min).

Diagnosed secondary hypertension, except due to sleep apnoea.

Advanced peripheral arterial disease.

Type I (any) or uncontrolled type II (with HbA1c > 7.0) diabetes mellitus or latent autoimmune diabetes of adults (LADA).

Atrophic gastritis.

Alcoholism or use of illicit drugs.

Current tobacco smoking habit.

Previous abdominal surgery (except for MacBurney, Pfanneistil and laparoscopic cholecystectomy).

Severe hepatic diseases.

Pregnancy or women at childbearing risk who are not using effective contraceptive methods.

Cancer in the past 5 years.

Current use of immunosuppressive drugs, chemotherapy or radiotherapy.

Inability to understand and adhere to the treatment or postsurgical instructions.

10 patients to guarantee equal group sizes. To assure concealment of the allocation list, randomisation is conducted through a 24-hour central web-based automated randomisation system.

Recruitment strategies

The recruitment process is conducted throughout two distinct strategies. First, candidates are referred from medical facilities and either private or public healthcare services located in the city of São Paulo to Hospital do Coração. Second, a press release containing the core information about the trial, as well as the eligibility criteria, was published in March 2013 in one of the most important Brazilian newspaper, and on that, further disseminated by other online Internet news websites and social websites. The second strategy resulted in an immediate and expressive interest of many participants who are currently being screened to participate.

Candidates are instructed to send email messages containing their personal information and recent anthropometric data to an institutional email account created for the purpose of study management. Those who are in accordance with eligibility criteria are invited to come to a screening visit at the hospital. On this occasion, they have their eligibility criteria verified. After a complete explanation of the study procedures, patients are asked to provide written informed consent.

Interventions

The randomisation process allocates patients to either one of two treatment groups:

1. Clinically optimised treatment alone (COT)

Treatment for hypertension: Treatment for hypertension is standardised for study patients, starting from 6 weeks

before the randomisation, according to the following recommendations: candidate patients preferably receive a renin-angiotensin blocking drug and a calcium-channel blocker, except if these are contraindicated or the patient has achieved good blood pressure control using other drugs prior to study recruitment. Whenever possible, other classes of drugs will be discontinued and changed considering the described scheme.

If the aforementioned association is already in use and the patient maintains blood pressure levels higher than 130×80 mm Hg, the combination with a thiazide diuretic is preferred. If the diuretic is contraindicated or if it is necessary to use other antihypertensive drugs to reach blood pressure control, spironolactone or clonidine is preferred. The decision to use different drugs is taken by the assistant physician.

Nutritional evaluation: In order to evaluate the average daily dietary intake, a 24 h reminder (24HR) is used. The patient is questioned about the types of food, preparations, servings, homely measures, quantities and the times at which they had their meals during the 24 h prior to the nutritional visit. A photo album showing pictures with distinct portions of food is used to help patients to better estimate the amounts they consumed over 24 hours. The 24HR enquiry is conducted at baseline, as well as after 6, 12, 18 and 24 months. An online computer program (Nutriquant, São Paulo, Brazil) is used to analyse the nutritional composition of energy and nutrients of the 24HR.²²

Nutritional advice. Patients from both groups receive nutritional advice that is based on national statements for hypertension and obesity.²³ A visit to a dietitian from the investigation team follows each medical visit at the hospital to reinforce the nutritional recommendations previously indicated. Nutritional advices in the clinical group are mainly directed at weight reduction and blood pressure control.^{23–25} Aiming at progressive weight loss over time, the total daily energy consumption calculated as 20 kcal/kg of ideal body weight per day is 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, are discouraged and the reduction of salt used for cooking at home or added to the already prepared food is encouraged. Consuming fruits and vegetables is stimulated also to increase potassium intake.

For those patients subjected to RYGB, the nutritional advices include information about food consistency in the postoperative period. During nutritional visits, detailed evaluation regarding diet tolerance is performed.

Treatment for other risk factors and comorbid conditions: Patients participating in both groups are individually treated for the other associated comorbid conditions. The treatment for obesity includes dietary advices for the optimised clinical treatment group and the practice of physical activities. Specific drug treatments for diabetes and dyslipidaemias, if applicable, are performed in accordance with national and international guidelines and

recommendations.^{23 25–27} Adherence to treatment is registered during the follow-up visits, as reported by the patient.

2. COT plus RYGB:

Patients allocated to surgical treatment also receive treatment for optimised blood pressure reduction and control of other risk factors during 24-month follow-up, as previously described. In addition to that, they are subjected to RYGB, performed by one surgeon with experience in bariatric surgery. Patients are admitted to Hospital do Coração at least 12 h before the index procedure. On the day preceding surgery, patients receive a liquid diet, up to 10 h before the scheduled procedure, when a preoperative fasting period starts. All drugs taken by the patient are maintained along this period, except if expressly recommended by the attending physician. Patients are examined in a preanesthetic visit after admission and take the recommended drugs accordingly. General anaesthesia is performed for the surgery and the patient is positioned in horizontal dorsal recumbence, with the right arm placed close to the body.

In brief, the surgery consists of the following steps: (1) Five abdominal wall trocars—two 12 mm and three 5 mm; (2) biliopancreatic limb—100 cm; (3) alimentary limb (Roux Limb)—150 cm; (4) side-to-side jejunojejunal anastomosis between the biliopancreatic limb and alimentary limb; (5) creation of a 20–30 mL gastric pouch and (6) gastrojejunal anastomosis (alimentary limb) and (7) Final check of the abdominal cavity (figure 2). Patients with cholelithiasis, identified in the presurgical period, will undergo cholecystectomy at the same surgical time after the end of the RYGB. Prophylaxis for deep venous thrombosis is applied by the use of high compression elastic stockings and pneumatic compressors in the lower limbs during surgery and thereafter. Cephazolin 2 g at the induction stage of anaesthesia and 8 h thereafter is used as a prophylactic antibiotic.

Blinding

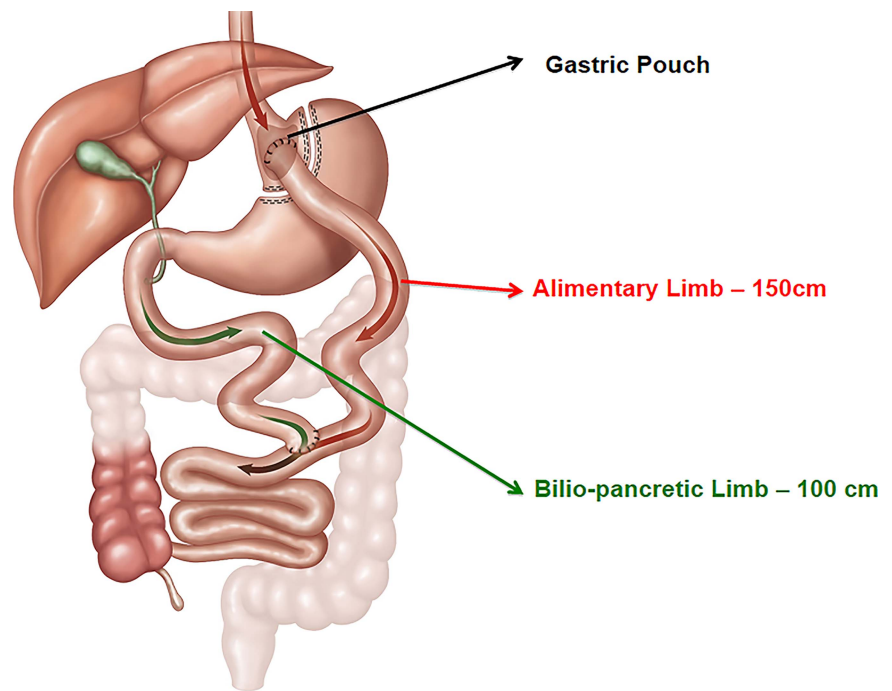
Since the study intervention is a surgical procedure, investigators and patients cannot be blinded for treatment allocation. Investigators who are responsible for the analysis of primary and secondary outcomes (adjudication of clinical events) are blinded for the treatment group.

Data collection and management

Time schedule and study visits: The study started in March 2013 and is already recruiting candidate patients under a time schedule that was previously defined by the investigation team. The study was planned to stop recruitment procedures by July 2014 and close follow-up procedures by July 2016.

Screening visit: During the screening visit that takes place 6 weeks before randomisation, each candidate is informed by one of the medical investigators (CAS or DTI) about the study methods and all the procedures they will be subjected to during the observation period, as well as the risks implicated in each procedure. Patients are then evaluated, regarding the inclusion and

Figure 2 Schematic view of the aspect of the Roux-en-Y gastric bypass surgery.



exclusion criteria and the antihypertensive drugs currently in use. Those who are not using the drugs according to the study treatment protocol might have their treatment modified at this time following the specified treatment protocol described in the intervention section. When a candidate agrees to participate, and is in accordance with the eligibility criteria, he or she is asked to sign the informed consent form (ICF).

Randomisation visit: A detailed clinical evaluation is carried out to confirm the eligibility criteria in the randomisation visit, 6 weeks after the screening visit. At this point, if a patient's evaluation is not adequate according to the study eligibility criteria, she or he will not be randomised. Those patients who fulfil the eligibility criteria are randomised at a 1:1 ratio, to be subjected to the RYGB or to receive optimised clinical treatment, as previously described. After randomisation, patients receive an identification number that will be used, in addition to their initials, in all participants' documents, such as clinical records, correspondence and any other elements that require patient identification.

Blood samples are collected to carry out patients' baseline laboratory tests. Those patients allocated to surgery are subjected to additional specific preoperative tests in order to identify any contraindication to the procedure and also to evaluate the risk of associated adverse events. The tests should include total abdominal ultrasound, high digestive endoscopy with *Helicobacter pylori* testing, coagulation screening tests and a parasitological stool test. These patients are evaluated by a psychologist to determine whether their psychological conditions are adequate to deal with the changes resulting from the intervention. Also, at this time, a multivitamin preparation will be prescribed and maintained until the day preceding the surgery.

Patients in both groups are seen by a dietitian to take the baseline anthropometric measurements and receive dietary advice on weight control and salt intake, and to create a baseline nutritional reminder. The in-office blood pressure measurements are made, and the central blood pressure, pulse rate and increment rate are measured using the SphygmoCor device. The ABPM, echocardiogram and electrocardiogram tests are scheduled to be performed within the following days.

Surgery visit: Surgical procedures are planned to be performed within 2 weeks from the randomisation visit. On this occasion, the coagulation parameters and blood counts shall be checked to verify the risks of bleeding and transfusion. If the *H. pylori* test is positive, the patients are prescribed a threefold therapeutic scheme for 10 days (2 g/day amoxicillin, 1 g/day clarithromycin and 80 mg/day pantoprazole). If an intestinal parasitosis is identified, a specific treatment should be administered. If a test result contraindicates the surgery, the patient will be excluded from the study and considered as a failure in randomisation.

Follow-up visits—general: Follow-up visits are scheduled after 2 weeks, and at 1, 3, 6, 12, 18 and 24 months after the index procedure in the surgery group, or at the same intervals in the clinical group after the baseline interview, for general clinical examination, during which the following procedures are made: measurement of systemic blood pressure and heart rate; check the need to increase, maintain or discontinue antihypertensive medication; weight measurement; reports of any adverse events, related or not to the study treatments; information related to treatment compliance is obtained; nutritional advice after anthropometric measurements, by a dietitian; prescribe and check the use of multivitamin treatment for the surgery group. Concomitant care or

procedures suggested by other physicians will be analysed for each individual patient by the investigators and allowed if considered necessary.

Follow-up visits—measurement procedures: Patients allocated to the surgery group who still maintain their gallbladder will be subjected to an abdominal ultrasound examination at the 3 month follow-up visit. If the examination demonstrates the presence of gallstones in the biliary tree, the patient shall be subjected to an elective cholecystectomy.

Central blood pressure, pulse speed and increment rate (using the SphygmoCor device), as well as an echocardiography and ECG will be performed at the 12-month and 24-month regular visits. Blood sampling is planned to be performed at the 12-month and 24-month visits. The analytes to be measured at these specific time points are: fasting glucose tolerance, HbA1c, insulin, ultra-sensitive PCR, lipid profile, uric acid, complete blood count, creatinine and potassium. Plasmatic iron, ferritin, vitamin B₁₂, total and fraction proteins and parathyroid hormone will also be measured for the surgery group.

Outcomes: Primary outcome is defined as a reduction of at least 30% in the total antihypertensive drugs in relation to the baseline medical prescription at 12 months following the index procedure. The same level of drug reduction is considered a secondary outcome for the 6-month and the 24-month follow-up intervals. Significant changes in the other previously described measurements (see the aims section) are also considered as secondary outcomes.

Adverse events: Adverse events are medical conditions not considered as study end points and must be registered during the study period. Serious adverse events correspond to any adverse event which is fatal, poses a risk to life, is debilitating or disabling, or results in hospital admission (not concerning the predefined study procedures), increase in the hospital length of stay (pertinent to the study and beyond the planned procedures), or is associated with induction of congenital abnormalities (in study descents). In addition, any event considered serious by the investigator or that adds any significant risk, contraindication, side effect or precaution that may be connected with the study intervention should be reported as a serious event. A life-threatening risk should be recognised as such, in the case of an adverse event that causes the patient to be at immediate risk of death due to the event. An event should be considered as debilitating or disabling if it causes a substantial and/or permanent rupture in the patient's capacity to perform regular activities.

Criteria for study withdrawal: Individuals who decide to no longer participate in the study or who are lost to follow-up (failure to attend the prescheduled visits or cannot be reached by telephone call) can be withdrawn from the study.

Statistical considerations: Statistical analysis will be performed at the three prespecified time points as chosen for the adjudication of primary and secondary end

points. The study is conducted on an intention-to-treat basis, meaning that data from all patients who complete follow-up will be analysed according to the group to which they were originally allocated, regardless of having adhered to the treatment and study procedures. Additionally, we will conduct per protocol and on treatment analysis at the end of the study. Comparison of proportions of patients experiencing primary outcomes in both groups will be carried out using the Fisher exact test. Additionally, the relative risk with its respective 95% CIs will be used as measures of effect size and the trends for each variable over time will be analysed using generalised estimation equation (GEE) models. For continuous variables, the differences between the average variations from baseline values, with their respective 95% CIs, will be calculated and, in addition, repeated measurements over time will be analysed using analysis of variance (ANOVA for repeated measures). A list of outcomes and plan for statistical analysis is provided as supplementary material (see online supplementary table S1). All analyses will be performed using the SAS software, V.9.3 (Cary, North Carolina, 2012) or R (<http://www.R-project.org>, 2014, Vienna, Austria).

Sample size: In the study from Dixon,²⁰ a 49% reduction in the incidence of patients using antihypertensive medication was observed in surgically treated patients over a 2 year follow-up. Considering that our study should be able to detect at least 40% difference in the incidence of the primary binary outcome (reduction of at least 30% of the drug prescription for each patient), a sample size of 60 patients (30 in either group) will be needed, assuming a two-tailed α of 5% and 90% power. This 40% absolute difference represents the difference between the assumed 50% proportion of outcome incidence in the surgery group and 10% incidence in the clinical treatment group.

Trial organisation and management: All data from medical visits and procedures are registered in electronic case report forms, accessed by the system of IEP HCor Clinical Studies. They are filled out within a period of no longer than 5 days after the study patient's visit, but preferentially during the visit or procedure to be performed. Security measures as recommended by international guidelines are applied to the electronic case report form. Thus, any changes in data made by the team and the reasons for the alteration are registered in the system, ensuring data quality and reliability.

The study investigators are responsible for providing all resources to guarantee privacy and confidentiality of data of study patients and to prevent their being prematurely or accidentally destroyed. Only the investigators will have access to the final data set. The study documentation will be maintained for at least 2 years after the end of the study so that they can be monitored, audited or inspected by the sponsor, the sponsor's authorised representatives or local regulatory authorities.

Quality control and data management: Besides concealed randomisation, the online management system ensures

data entry, data cleaning and exportation for analysis, as well as reports of the status of the study forms. Several procedures are performed to assure data quality, including periodic checkout of missing data and plausible, possible and non-permitted value ranges and logic checks. Problems of data consistency are informed by the system at the time of data entry. In addition, statistical techniques to identify inconsistencies and completeness of data are applied periodically to ensure correction of possible mistakes.

ETHICAL ASPECTS

The study protocol was approved by the institutional review board of the Hospital do Coração which works in consonance with the latest version of the Helsinki Declaration, the Good Clinical Practices statements, the 'Americas' Document' and the national regulatory laws. Any changes in the protocol will be first submitted to the local review board that might approve it before we put it into practice. Before the beginning of any study-related activities, each study participant is asked to provide a signed ICF in order to produce documentary evidence that the participants received enough information about the clinical trial, the possible study interventions, their rights as research participants and that he or she freely and voluntarily wishes to participate in the study. Patients are also informed that they may freely withdraw their consent and discontinue their participation in the study at any moment, only by communicating this decision, without affecting their treatment. If the participants or their authorised legal representatives cannot read or understand the information related to the study, an impartial witness not connected to the team of the study centre and who preferably is unaware of the clinical study is asked to participate. Fingerprints may be used when the participants or their legal representatives cannot sign the document. The participants themselves or their legal representatives and the witness (when necessary) sign and date the document in two counterparts. The investigator who applies the Free and Informed Consent Term also dates and signs the two copies. One of the copies is maintained in the patient's file at the investigator centre and the other is given to the research participant.

Dissemination

The main publication will be released in the name of the Study Steering Committee, mentioning the study sponsor. Four manuscripts are planned to be published: design paper, patients' baseline characteristics and the main manuscripts containing the results of the study in 12 months and in 24 months. The study results will be published regardless of whether the analysis performed shows positive outcomes for the tested intervention or not.

DISCUSSION

This is, to the best of our knowledge, the first randomised controlled trial designed to specifically test the potential

benefit of bariatric surgery on blood pressure control. Previously published studies have shown evidence of blood pressure reduction following surgical approach, in comparison to the optimised clinical treatment, at least in the short term. Buchwald *et al*²⁸ observed, in a meta-analysis of clinical trials, a significant reduction in blood pressure over the first two postoperative years, but such effect was not sustained in subsequent years. In the Swedish Obese Study, a 6-month progressive decrease in blood pressure in the operated individuals in comparison to controls was reported. However, after this period, a new increase in blood pressure was registered and further maintained up to 8 years.²⁹ In one recent study, Schauer *et al*¹⁵ report that patients were able to reduce the amount of antihypertensive drugs, after 12 months of either RYGB or sleeve gastrectomy. One previous publication observed a similar effect on blood pressure control for gastric banding procedure.²⁰ Former trials have also shown conflicting results. In the study from Mingrone *et al*,¹⁴ for instance, no significant effect of bariatric procedures on blood pressure was observed at all, in comparison to the clinical approach. Moreover, the majority of the trials in this regard did not address the specific question of blood pressure control.

Considering the current evidence, the question regarding control of arterial hypertension in obese patients subjected to bariatric procedures remains still open. The reasons for this lack of evidence are related first to the absence of studies designed for this specific purpose; second, there is no agreement among previous studies concerning the antihypertensive effect of surgery; and third, there is no clear answer to whether any observed blood pressure reduction could be maintained in the long term.

Former trials that investigate populations of more severely obese patients (grade III) were largely responsible for the current indications for bariatric surgery. More recently, however, investigations have been extended for less obese (grade I) patients, or even for patients who were not subjected to any previous weight reduction therapy, since it is not clear that these groups are under less severe risk for cardiovascular events. Taking into consideration the eligibility criteria of the present study, we are selecting patients of elevated potential for cardiovascular events in the long term, given that, besides the obesity and hypertension diagnosis, many of them display features of metabolic syndrome, such as dyslipidaemia, insulin resistance and diabetes.

Finally, a theoretical discussion can also arise in terms of the pathophysiological causes of blood pressure reduction after bariatric surgery, since weight loss achieved by means of clinical treatment has been previously demonstrated to positively influence blood pressure control. Whether it can be an effect of weight loss per se or rather a direct effect of surgery on blood pressure will not be possible to be investigated by the present study. Nonetheless, consistent evidence does show that other effects of bariatric surgery, for example, insulin resistance and glycaemic control, might be

explained beyond the reduction of body weight, being at least partially related by an influence on a few gut secreted mediators.³⁰ Eventually, mechanistic explanations for such phenomena deserve deeper and further consideration by studies using appropriate methodology.

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Contributors CAS conceived the study, participated in the design of the study and performed bariatric surgeries and surgical follow-up. DTI participated in the design of the study, drafted the manuscript and performed clinical follow-up. MGdS performed blood pressure measurements using the SphygmoCor technology. CRAS participated in trial management and helped to draft the manuscript. ACBF participated in trial management, nutritional advice for the clinically treated patients and drafting of the paper. JDdO participated in trial management, nutritional advice for the surgically-treated patients and helped to draft the manuscript. PMN and RVC performed bariatric surgeries and surgical follow-up. CA participated in the design of the study and clinical follow-up. OB participated in the study concept, design and coordination and helped to draft the manuscript. All authors read and approved the final version of the manuscript.

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Competing interests None.

Ethics approval Ethics Committee from HCor—Hospital do Coração—São Paulo, Brazil.

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REFERENCES

- [No authors listed]. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000;894:i–xii, 1–253
- Haidar YM, Cosman BC. Obesity epidemiology. *Clin Colon Rectal Surg* 2011;24:205–10.
- Mendis S, Lindholm LH, Mancia G, et al. World Health Organization (WHO) and International Society of Hypertension (ISH) risk prediction charts: assessment of cardiovascular risk for prevention and control of cardiovascular disease in low and middle-income countries. *J Hypertens* 2007;25:1578–82.
- Chopra M, Galbraith S, Darnton-Hill I. A global response to a global problem: the epidemic of overnutrition. *Bull World Health Organ* 2002;80:952–8.
- Monteiro CA, Moura EC, Conde WL, et al. Socioeconomic status and obesity in adult populations of developing countries: a review. *Bull World Health Organ* 2004;82:940–6.
- Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;120:1640–5.
- Mauro M, Taylor V, Wharton S, et al. Barriers to obesity treatment. *Eur J Inter Med* 2008;19:173–80.
- Lepe M, Bacardi Gascon M, Jimenez Cruz A. Long-term efficacy of high-protein diets: a systematic review. *Nutr Hosp* 2011;26:1256–9.
- Schwingshackl L, Hoffmann G. Long-term effects of low-fat diets either low or high in protein on cardiovascular and metabolic risk factors: a systematic review and meta-analysis. *Nutr J* 2013;12:48.
- Cheung BM. Drug treatment for obesity in the post-sibutramine era. *Drug Saf* 2011;34:641–50.
- Siebenhofer A, Jeitler K, Horvath K, et al. Long-term effects of weight-reducing drugs in hypertensive patients. *Cochrane Database Sys Rev* 2013;3:CD007654.
- Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med* 2007;357:753–61.
- Ikramuddin S, Korner J, Lee WJ, et al. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. *JAMA* 2013;309:2240–9.
- Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med* 2012;366:1577–85.
- Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med* 2012;366:1567–76.
- Cazzo E, Gestic MA, Utrini MP, et al. Impact of Roux-en-Y gastric bypass on metabolic syndrome and insulin resistance parameters. *Diabetes Technol Ther* 2014;16:262–5.
- Chang SH, Stoll CR, Song J, et al. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003–2012. *JAMA Surg* 2014;149:275–87.
- Vest AR, Heneghan HM, Agarwal S, et al. Bariatric surgery and cardiovascular outcomes: a systematic review. *Heart* 2012;98:1763–77.
- Adams MH, Carter TM, Lammon CA, et al. Obesity and blood pressure trends in rural adolescents over a decade. *Pediatr Nurs* 2008;34:381–6, 94
- Dixon JB, O'Brien PE, Playfair J, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *JAMA* 2008;299:316–23.
- Ding FH, Fan WX, Zhang RY, et al. Validation of the noninvasive assessment of central blood pressure by the SphygmoCor and Omron devices against the invasive catheter measurement. *Am J Hypertens* 2011;24:1306–11.
- Weber B, Galante AP, Bersch-Ferreira AC, et al. Effects of Brazilian Cardioprotective Diet Program on risk factors in patients with coronary heart disease: a Brazilian Cardioprotective Diet randomized pilot trial. *Clinics* 2012;67:1407–14.
- Nobre F. Introduction: Brazilian guidelines on hypertension VI. Brazilian Society of Cardiology, Brazilian Society of Hypertension, Brazilian Society of Nephrology. *J Bras Nefrol* 2010;32(Suppl 1):III.
- ABESO ABpoEdOedSM-. Diretrizes Brasileiras e Obesidade. In: ABESO, ed. 3rd ed. Itapevi—SP—Brazil, 2009.
- Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560–72.
- American Diabetes A. Standards of medical care in diabetes—2013. *Diabetes Care* 2013;36(Suppl 1):S11–66.
- Sposito AC, Caramelli B, Fonseca FA, et al. IV Brazilian guideline for dyslipidemia and atherosclerosis prevention: department of Atherosclerosis of Brazilian Society of Cardiology. *Arq Bras Cardiol* 2007;88(Suppl 1):2–19.
- Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA* 2004;292:1724–37.
- Sjostrom CD, Peltonen M, Wedel H, et al. Differentiated long-term effects of intentional weight loss on diabetes and hypertension. *Hypertension* 2000;36:20–5.
- Ashrafian H, le Roux CW. Metabolic surgery and gut hormones—a review of bariatric entero-humoral modulation. *Physiol Behav* 2009;97:620–31.