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Three-Year Outcomes of Bariatric Surgery in Patients With Obesity and Hypertension

A Randomized Clinical Trial

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Background: Midterm effects of bariatric surgery on patients with obesity and hypertension remain uncertain.

Objective: To determine the 3-year effects of Roux-en-Y gastric bypass (RYGB) on blood pressure (BP) compared with medical therapy (MT) alone.

Design: Randomized clinical trial. (ClinicalTrials.gov: NCT01784848)

Setting: Investigator-initiated study at Heart Hospital (HCor), São Paulo, Brazil.

Participants: Patients with hypertension receiving at least 2 medications at maximum doses or more than 2 medications at moderate doses and with a body mass index (BMI) between 30.0 and 39.9 kg/m^2 were randomly assigned (1:1 ratio).

Intervention: RYGB plus MT or MT alone.

Measurements: The primary outcome was at least a 30% reduction in total number of antihypertensive medications while maintaining BP less than 140/90 mm Hg. Key secondary outcomes were number of antihypertensive medications, hypertension remission, and BP control according to current guidelines (<130/80 mm Hg).

Results: Among 100 patients (76% female; mean BMI, 36.9 kg/m^2 [SD, 2.7]), 88% from the RYGB group and 80% from the MT group completed follow-up. At 3 years, the primary outcome occurred in 73% of patients from the RYGB group compared with 11% of patients from the MT group (relative risk, 6.52 [95% CI, 2.50 to 17.03]; $P < 0.001$). Of the randomly assigned participants, 35% and 31% from the RYGB group and 2% and 0% from the MT group achieved BP less than 140/90 mm Hg and less than 130/80 mm Hg without medications, respectively. Median (interquartile range) number of medications in the RYGB and MT groups at 3 years was 1 (0 to 2) and 3 (2.8 to 4), respectively ($P < 0.001$). Total weight loss was 27.8% and −0.1% in the RYGB and MT groups, respectively. In the RYGB group, 13 patients developed hypovitaminosis B_{12} and 2 patients required reoperation.

Limitation: Single-center, nonblinded trial.

Conclusion: RYGB is an effective strategy for midterm BP control and hypertension remission, with fewer medications required in patients with hypertension and obesity.

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Hypertension is a leading cause of cardiovascular mortality (1). Its unfavorable impact is potentially explained by several factors, including the asymptomatic nature of this condition, poor medication adherence, and high burden of comorbid conditions, including obesity (1, 2). Hypertension occurs mostly in persons with excess weight and is often poorly controlled in patients with obesity (3, 4), and pharmacologic treatment of obesity has modest impact on blood pressure (BP) reduction (5).

Bariatric surgery is the most effective method to treat obesity (6–8). Although recent research efforts have focused on metabolic improvement and diabetes resolution (9–12), growing interest has been devoted to evaluating the effects of this surgery on hypertension (13–15). The GATEWAY (Gastric Bypass to Treat Obese Patients With Steady Hypertension) trial focused on hypertension and included patients with mild obesity (body mass index [BMI], 30 to 34.9 kg/m^2) and those with a BMI greater than 35 kg/m^2 per current guidelines. The 1-year results showed that patients with coexisting obesity and hypertension were able to reduce or completely discontinue their antihypertensive medications after surgery, while maintaining a controlled BP and a similar 24-hour BP profile (16, 17). However, midterm effects of bariatric surgery on office and 24-hour BP measurements in a broad population of patients with obesity and hypertension remain uncertain. Here, we present the 3-year results from the GATEWAY trial.

Methods

The GATEWAY trial is a randomized, nonblinded, single-center, investigator-initiated clinical trial performed at Heart Hospital in São Paulo, Brazil. Study design (18) and 1-year results (16) were previously pub-

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lished; the full protocol, approved by the Research Ethics Board at the Heart Hospital (HCor), and the statistical analysis plan are available in **Supplements 1** and **2** (available at Annals.org). The follow-up period for the primary end point was 12 months, but we prespecified that all patients would be scheduled for a 3-year and 5-year extension study. Here, we present the 3-year outcomes.

Study Participants

We included 100 patients followed from May 2013 to May 2016 who were aged 18 to 65 years with a BMI between 30.0 and 39.9 kg/m^2 and established hypertension treated with at least 2 antihypertensive drugs at maximum doses or more than 2 antihypertensive drugs at moderate doses (16, 18).

Main exclusion criteria included the following: mean systolic BP greater than or equal to 180 mm Hg or diastolic BP greater than or equal to 120 mm Hg; cardiovascular disease (myocardial infarction or stroke within 6 months, angina, coronary revascularization, heart failure); severe psychiatric disorders; secondary hypertension (except sleep apnea); type 1 diabetes, latent autoimmune diabetes of adults, or type 2 diabetes with glycated hemoglobin level greater than 7.0%; and current smoking (16, 18).

The trial was coordinated by the Research Institute (HCor). All authors had full and independent access to all data and vouch for the integrity and accuracy of the analysis.

Randomization

Patients were randomly assigned (1:1 ratio) to Roux-en-Y gastric bypass (RYGB) combined with medical therapy (MT) or MT alone. Randomization was performed in blocks containing 10 patients to guarantee equal group sizes and performed through a 24-hour central web-based automated system.

Interventions

Medical therapy was standardized for all patients on the basis of office BP. Patients were preferably treated with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, a calcium-channel blocker, and a diuretic, if necessary. Adherence to treatment was evaluated during the study only through active questions and continuous recommendations (17).

In addition to MT, patients randomly assigned to RYGB underwent laparoscopic RYGB performed by a single surgeon, with a 20- to 30-mL gastric pouch, an alimentary limb of 150 cm, and a biliopancreatic limb of 100 cm (18). All patients from both groups received medical, nutritional, and psychological advice aimed at weight reduction, reduction of salt intake, and increase in potassium intake. Physical exercises were also recommended in both groups.

Other comorbid conditions were treated according to current guidelines.

Data Collection

At baseline, we collected data on demographic information, comorbid conditions, anthropometric values, medication use, and laboratory values. We collected office BP measurements at all visits. Ambulatory BP monitoring (ABPM) was available to provide detailed 24-hour BP data. All ABPM analyses were performed according to the V Brazilian Guidelines for ABPM by a cardiologist with no access to the proposed interventions (19). Echocardiography and laboratory values were measured at baseline and at 12, 24, and 36 months.

Outcomes

The primary outcome was at least a 30% reduction in total number of antihypertensive medications (that is, reduction of ≥1 drug in patients taking 2 or 3 drugs or ≥2 drugs in patients taking 4 drugs), while maintaining BP less than 140/90 mm Hg. Secondary outcomes included number of antihypertensive drugs; systolic and diastolic BP; weight, percentage of total weight loss, and BMI; waist circumference; fasting plasma glucose and glycated hemoglobin levels; homeostatic model assessment of insulin resistance index; lipid profile; serum uric acid levels; high-sensitivity C-reactive protein levels; echocardiographic data; 10-year Framingham risk score; and adverse events.

In addition, we defined several post hoc outcomes: remission of hypertension (BP <140/90 mm Hg without medications), BP parameters during ABPM, resistant hypertension prevalence (defined as BP that remains above goal despite concurrent use of 3 antihypertensive agents of different classes, including a diuretic, with all agents at optimal doses; resistant hypertension also included patients whose BP was controlled with >3 medications) (20), at least 30% reduction in total antihypertensive medications and remission of hypertension while maintaining BP less than 130/80 mm Hg (21), and statin and glucose-lowering medication use at 3 years.

Statistical Analysis

One hundred patients were randomly assigned (16). Sample size was calculated to provide 90% power to detect an increase in the probability of the primary end point from 10% in the MT group to 40% in the RYGB group, assuming a 2-sided α level of 5% in 1 year.

Continuous variables with a normal distribution are reported as means and SDs. Variables with nonnormal distributions are reported as medians and interquartile ranges. Categorical variables are summarized as frequencies.

The 3-year main analysis followed the intention-to-treat principle with the assumption that missed follow-up visits were missing at random. The missing values for the number of medications and BP at the target visit were imputed with the multiple imputation technique by Gibbs sampling with the chain equation method (22), according to the number of medications and BP observed at previous visits, duration of hypertension, age, and sex. We conducted a sensitivity analysis of 84 patients using observed data from 76 patients present at the 3-year visit and imputing the information from 7 patients who attended the 30-month follow-up visit and 1 patient who attended the 42-month visit.

We used the log-binomial model to analyze the primary end point, and results are reported as relative risks and 95% CIs. We conducted other sensitivity analyses for the primary end point, assuming control of BP as systolic/diastolic less than 130/80 mm Hg: complete-case analysis; per protocol analysis; as-treated analysis; worst-case scenario; and multivariate model adjusted for BMI, number of medications at baseline, 10-year Framingham risk score, basal insulin level at baseline, and duration of hypertension.

Continuous end points were analyzed with mixed-effects models that included patient as a random effect and interaction between group and visit (baseline, 1 year, 2 year, and 3 year) as fixed effects.

Analyses were performed using R software, version 3.6.0 (R Foundation for Statistical Computing). Detailed presentations of statistical methods are available in Supplement 1 (Statistical Methods).

Role of the Funding Source

Ethicon provided unrestricted funding for this investigator-initiated trial but did not participate in study design; collection, management, analysis, or interpretation of data; or writing of publications or the decision to submit any report for publication. Also, the sponsor did not have authority over any of these activities.

RESULTS

Study Participants

Among 100 patients, 88% of the RYGB group and 80% of the MT group completed follow-up. One patient withdrew consent after randomization in the MT group, and an additional 9 patients in the MT group and 6 patients in the RYGB group missed follow-up visits (one patient died at the 13-month follow-up, and the cause of death was undetermined) (Figure 1). Thus, information on the primary end point at 3 years was available for 84 patients. The Appendix Table (available at Annals.org) shows baseline characteristics of the original 100 patients enrolled, which were generally balanced between the 2 intervention groups. Baseline characteristics of the 84 patients are shown in Table 1 of Supplement 1 (available at Annals.org) and were generally balanced between groups with the exception of a few comorbid conditions.

BP-Related End Points

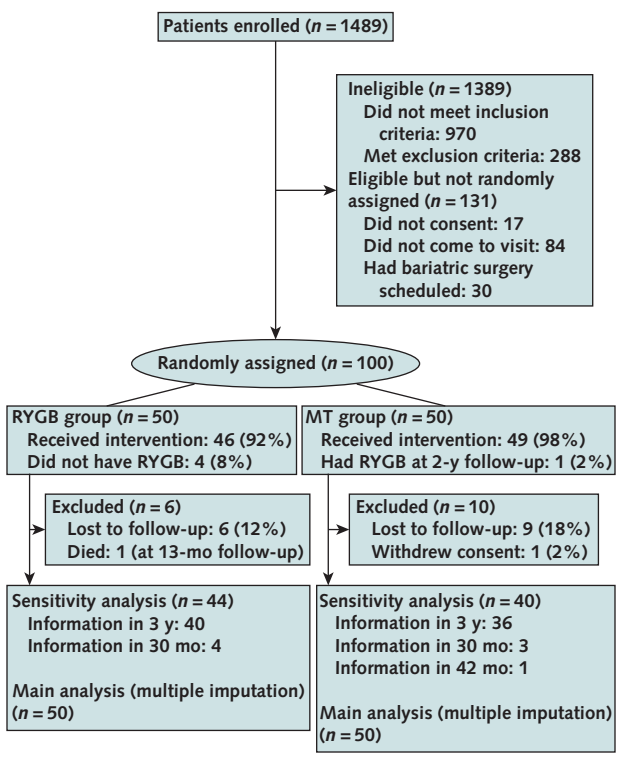
After multiple imputation, 88% of patients from the RYGB group and 72% of patients from the MT group maintained BP less than 140/90 mm Hg, regardless of the number of medications (relative risk, 1.21 [95% CI, 0.96 to 1.53]). Among patients in the RYGB group, 73% achieved the primary outcome; in contrast, only 11% of patients in the MT group achieved the primary outcome (relative risk, 6.52 [CI, 2.50 to 17.03]; $P < 0.001$) (Table 2 of Supplement 1, available at Annals.org). A total of 35% of patients from the RYGB group and 2% of patients from the MT group (1 patient who underwent RYGB at 24 months) achieved the secondary outcome of BP control without medications (relative risk, 17.35 [CI, 2.34 to 128.62]).

The complete-case analysis at 3 years with imputation of values from the 30-month follow-up visit for 7 patients and from the 42-month follow-up visit for 1 patient showed similar results for the primary outcome (relative risk, 5.82 [CI, 2.51 to 13.47]; $P < 0.001$); 86% (38 of 44) from the RYGB group and 70% (28 of 40) from the MT group maintained BP less than 140/90 mm Hg, regardless of the number of medications (relative risk, 1.23 [CI, 0.98 to 1.56]) (Figure 2). Other sensitivity analyses were consistent with those observed for the main analysis (Table 2 of Supplement 1).

At 3 years, there was a reduction in the secondary outcomes of the number of antihypertensive medications and in the use of most classes of BP medications (Table 3 of Supplement 1, available at Annals.org). The median number of drugs was 1 (0 to 2) for the RYGB group and 3 (2.8 to 4) for the MT group ($P < 0.001$).

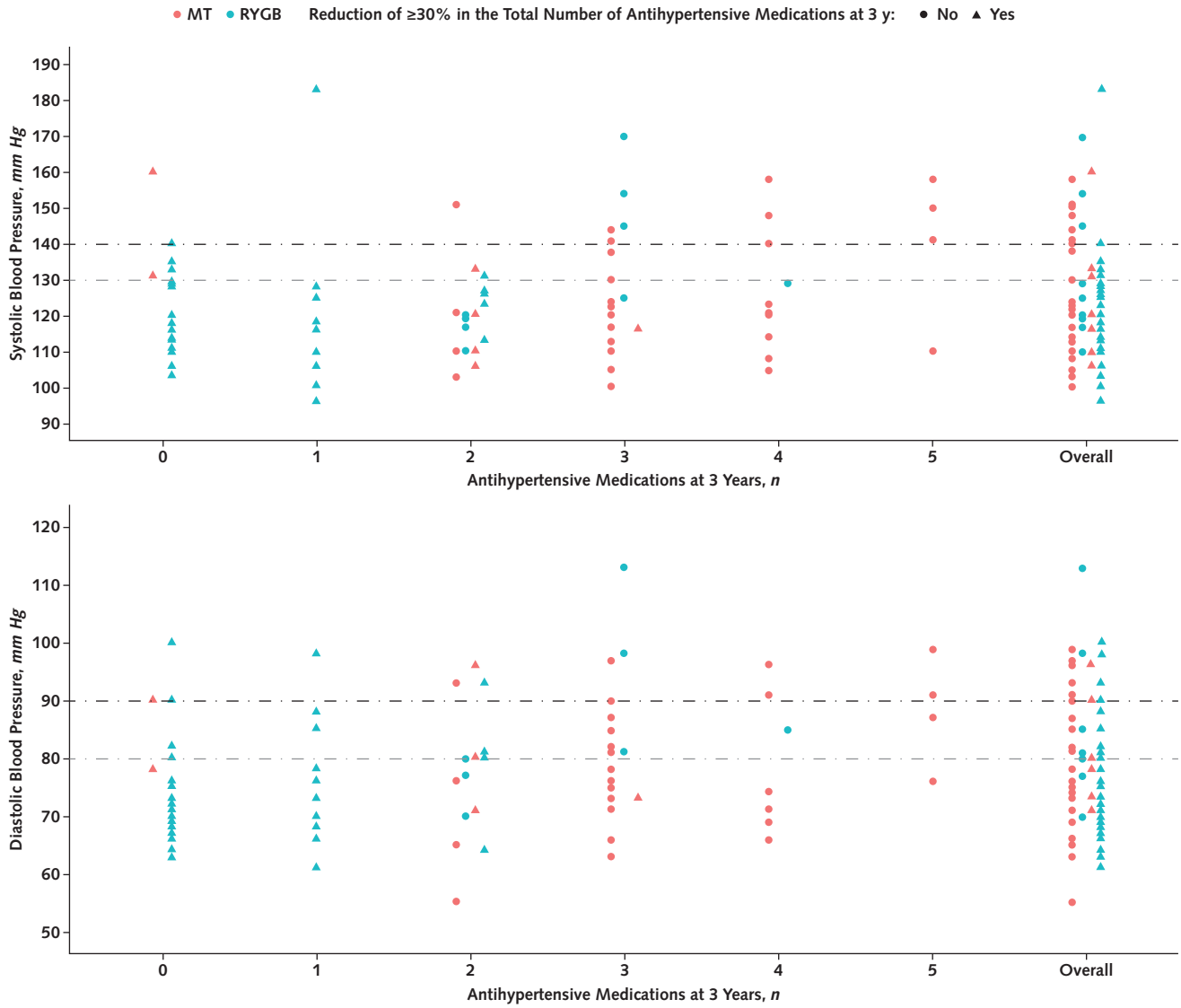
In post hoc analyses after multiple imputation, 68% of patients from the RYGB group and 58% of patients from the MT group maintained BP less than 130/80 mm Hg, independently of the number of medications (relative risk, 1.16 [CI, 0.81 to 1.65]); 58% of patients from the RYGB group and 8% of patients from the MT group (relative risk, 6.90 [CI, 2.22 to 21.46]) achieved at least 30% reduction in the

Figure 1. Eligibility, randomization, and follow-up.



Of the ineligible candidates, 970 did not meet criteria mainly because of body mass index greater than 40 kg/m^2, uncontrolled blood pressure, or use of fewer than 2 medications at maximal doses. MT = medical therapy; RYGB = Roux-en-Y gastric bypass.

Figure 2. BP control and number of antihypertensive medications in use at 3 years.



Patients with BP control (<140/90 mm Hg), *n/N*							
RYGB	18/19	10/11	8/9	1/4	1/1	0/0	38/44
MT	1/2	0/0	6/8	14/17	6/9	1/4	28/40
Patients with reduction of ≥30% in the total number of antihypertensive medications, *n/N*							
RYGB	19/19	11/11	5/9	0/4	0/1	0/0	35/44
MT	2/2	0/0	4/8	1/17	0/9	0/4	7/40
Patients with reduction of ≥30% in the total number of antihypertensive medications while maintaining BP <140/90 mm Hg, *n/N*							
RYGB	18/19	10/11	4/9	0/4	0/1	0/0	32/44
MT	1/2	0/0	3/8	1/17	0/9	0/4	5/40

The values observed at 3 years were considered, and information was imputed on the number of medications and BP from 7 patients (4 RYGB and 3 MT) who attended the 30-month follow-up visit and 1 patient (MT) who attended the 42-month follow-up visit. BP = blood pressure; MT = medical therapy; RYGB = Roux-en-Y gastric bypass.

number of antihypertensive medications and maintained BP less than 130/80 mm Hg (**Table 4** of **Supplement 1**, available at Annals.org). A total of 31% of patients from the RYGB group and no patients in the MT group maintained BP less than 130/80 mm Hg without medications.

Changes in office BP and ABPM (including daytime and nighttime periods and nocturnal BP dipping) were

similar in both groups (Table 1). Compared with baseline, the percentage of patients with nondipping BP (characterized by <10% reduction during sleep compared with the awake period) was similar in both groups (Table 5 of Supplement 1, available at Annals.org). The prevalence of apparently resistant hypertension was 2.3% in the RYGB group and 15.0% in the MT group ($P = 0.07$) (Table 6 of Supplement 1, available at Annals.org).

Other Metabolic End Points

Patients in the RYGB group achieved greater weight loss and demonstrated greater improvements in the other non-BP metabolic parameters (Table 2; Tables 3 and 7 of Supplement 1, available at Annals.org) than patients in the MT group. Total weight loss was 27.8% and −0.1% in the RYGB and MT groups, respectively. No patients in the RYGB group and 26% of patients in the MT group ($P = 0.001$) had excessive weight gain (defined as an increase of >5% over the baseline value).

Adverse Events

Table 3 shows adverse events at 3 years. One patient from the RYGB group died at the 13-month follow-up, but the cause was not identified. Anemia was present in 11% of patients in the RYGB group and 10% of patients in the MT group ($P = 1.0$). Mean hemoglobin level was 140 g/L (SD, 14) and 134 g/L (SD, 13) ($P = 0.09$) in the MT and RYGB groups, respectively. In patients who presented with anemia, mean hemoglobin level was 113 g/L (SD, 9) and 112 g/L (SD, 8) ($P = 0.84$) in the MT and RYGB groups, respectively.

In the RYGB group, the serum parathyroid hormone level was elevated in 14% of patients and vitamin B_{12} was decreased in 30% of patients. During follow-up, 8 patients required laparoscopic cholecystectomy after RYGB. One patient had an anastomotic ulcer that was successfully treated clinically. One patient required a reoperation 4 months after surgery because of an abscess near the jejunal anastomosis and recovered uneventfully, and 1 patient had a perforated gastric ulcer (surgically treated) due to nonsteroidal anti-inflammatory drug use after 27 months of follow-up.

Discussion

Our results indicate that at 3 years, patients with obesity and hypertension who underwent RYGB plus MT were significantly more likely to reduce the number of antihypertensive medications by at least 30% while maintaining BP control than patients managed with MT alone. In addition, a significantly higher proportion of patients in the RYGB group achieved hypertension remission, whether defined as BP less than 140/90 mm Hg or less than 130/80 mm Hg. Although a slightly higher proportion of patients in the RYGB group overall achieved BP control compared with patients in the MT group, this difference did not achieve statistical significance and other measures of BP were neither statistically nor substantively different between the 2 groups. Nevertheless, these results support the effective role bariatric surgery plays in reducing the burden of polypharmacy for the treatment of hypertension.

The main results extend our previous findings, now demonstrating durability and consistent results with 3 years of follow-up after bariatric surgery (16, 19). Several observational studies had suggested long-term BP improvements and hypertension remission (up to 12

Table 1. Difference in the Number of Antihypertensive Drugs and BP-Related End Points Between Treatment Groups*

End Point	Baseline (95% CI)		3 Years (95% CI)		Change at 3 Years From Baseline (95% CI)		Difference Between Groups (95% CI)
	RYGB	MT	RYGB	MT	RYGB	MT	
Antihypertensive drugs in use, *n*†	2.8 (2.3 to 3.2)	3.1 (2.6 to 3.6)	1.0 (0.7 to 1.3)	3.2 (2.6 to 3.8)	−1.8 (−2.4 to −1.3)	0.1 (−0.7 to 0.9)	−1.9 (−2.9 to −1.0)
Office BP, *mm Hg*							
Systolic	123.0 (118.7 to 127.2)	122.8 (118.5 to 127.0)	122.8 (118.1 to 127.4)	125.4 (120.6 to 130.3)	−0.2 (−5.3 to 4.9)	2.7 (−2.6 to 8.0)	−2.9 (−10.2 to 4.4)
Diastolic	77.6 (74.7 to 80.5)	77.3 (74.5 to 80.2)	77.4 (74.2 to 80.6)	79.3 (76.0 to 82.6)	−0.2 (−3.9 to 3.5)	2.0 (−1.8 to 5.8)	−2.2 (−7.5 to 3.1)
Ambulatory BP monitoring							
24-h BP, *mm Hg*							
Systolic	118.9 (115.6 to 122.2)	122.6 (119.3 to 125.9)	118.4 (114.8 to 122.0)	123.8 (120.0 to 127.6)	−0.5 (−4.4 to 3.4)	1.2 (−2.8 to 5.2)	−1.7 (−7.2 to 3.9)
Diastolic	73.8 (71.0 to 76.6)	76.5 (73.7 to 79.3)	75.1 (72.1 to 78.1)	78.8 (75.7 to 82.0)	1.4 (−1.6 to 4.3)	2.4 (−0.7 to 5.4)	−1.0 (−5.3 to 3.3)
Daytime BP, *mm Hg*							
Systolic	122.4 (119.0 to 125.7)	125.0 (121.6 to 128.3)	121.1 (117.4 to 124.8)	126.3 (122.4 to 130.1)	−1.3 (−5.3 to 2.7)	1.3 (−2.9 to 5.4)	−2.6 (−8.4 to 3.2)
Diastolic	77.4 (74.5 to 80.4)	80.2 (77.3 to 83.1)	77.7 (74.5 to 80.9)	81.3 (77.9 to 84.6)	0.3 (−3.2 to 3.8)	1.1 (−2.6 to 4.7)	−0.8 (−5.8 to 4.3)
Nighttime BP, *mm Hg*							
Systolic	108.1 (103.8 to 112.3)	113.0 (108.8 to 117.3)	107.5 (102.8 to 112.2)	114.5 (109.5 to 119.4)	−0.5 (−5.9 to 4.8)	1.4 (−4.1 to 6.9)	−1.9 (−9.6 to 5.7)
Diastolic	61.6 (58.4 to 64.8)	66.4 (63.1 to 69.7)	64.2 (60.7 to 67.8)	68.4 (64.7 to 72.1)	2.7 (−1.1 to 6.4)	2.0 (−1.8 to 5.9)	0.6 (−4.7 to 6.0)
Nocturnal BP drop, %							
Systolic	11.6 (9.0 to 14.2)	9.2 (6.5 to 11.8)	11.1 (8.2 to 14.0)	9.1 (6.0 to 12.1)	−0.5 (−3.9 to 2.9)	−0.1 (−3.7 to 3.4)	−0.4 (−5.3 to 4.5)
Diastolic	20.4 (17.2 to 23.5)	16.3 (13.1 to 19.5)	17.3 (13.8 to 20.8)	15.9 (12.2 to 19.5)	−3.0 (−7.1 to 1.0)	−0.4 (−4.6 to 3.7)	−2.6 (−8.4 to 3.2)

BP = blood pressure; MT = medical therapy; RYGB = Roux-en-Y gastric bypass.
* The point estimates and 95% CIs were based on the linear mixed-effects model that included patient as a random effect and interaction between group and visit (baseline, 1 y, 2 y, and 3 y) as fixed effects.
† Poisson generalized linear mixed model with link log and that included the patient as a random effect and the interaction between group and visit (baseline, 1 y, 2 y, and 3 y). The 95% CI was obtained by using the delta method.

Table 2. Difference Between Treatment Groups for Anthropometric Measures, Laboratory Studies, Interventricular Septum Diastolic Thickness, and 10-Year Framingham Risk Score*

End Point	Baseline (95% CI)		3 Years (95% CI)		Change at 3 Years From Baseline (95% CI)		Difference Between Groups (95% CI)
	RYGB	MT	RYGB	MT	RYGB	MT	
Body mass index, *kg/m²*	37.4 (36.4 to 38.3)	36.4 (35.5 to 37.4)	26.8 (25.8 to 27.9)	36.4 (35.3 to 37.4)	−10.5 (−11.5 to −9.6)	−0.1 (−1.0 to 0.9)	−10.5 (−11.8 to −9.1)
Body weight, *kg*	102.0 (98.1 to 105.8)	100.1 (96.3 to 103.9)	73.1 (69.1 to 77.1)	99.8 (95.8 to 103.9)	−28.9 (−31.4 to −26.3)	−0.3 (−2.9 to 2.3)	−28.6 (−32.2 to −24.9)
Waist circumference, *cm*	112.2 (109.7 to 114.8)	111.1 (108.5 to 113.6)	86.4 (83.6 to 89.3)	110.4 (107.3 to 113.5)	−25.8 (−28.2 to −23.3)	−0.7 (−3.5 to 2.1)	−25.1 (−28.8 to −21.4)
Fasting plasma glucose							
mmol/L†	5.46 (5.17 to 5.75)	5.47 (5.20 to 5.75)	4.73 (4.48 to 4.99)	5.57 (5.28 to 5.87)	−0.73 (−0.87 to −0.58)	0.10 (−0.06 to 0.26)	−0.83 (−1.05 to −0.61)
mg/dL†	98.4 (93.2 to 103.6)	98.6 (93.7 to 103.6)	85.3 (80.7 to 89.9)	100.4 (95.1 to 105.7)	−13.1 (−15.7 to −10.5)	1.8 (−1.1 to 4.8)	−14.9 (−18.9 to −11.0)
Glycated hemoglobin, %†	5.70 (5.53 to 5.88)	5.73 (5.56 to 5.90)	5.21 (5.04 to 5.37)	5.69 (5.51 to 5.86)	−0.50 (−0.58 to −0.42)	−0.04 (−0.13 to 0.05)	−0.46 (−0.57 to −0.34)
Insulin, *pmol/L*†	125.6 (102.3 to 148.8)	128.6 (105.2 to 151.9)	36.9 (29.7 to 44.2)	120.0 (96.1 to 143.8)	−88.6 (−108.0 to −69.3)	−8.6 (−28.6 to 11.4)	−80.0 (−107.8 to −52.2)
HOMA-IR index‡	4.98 (4.27 to 5.70)	4.69 (4.08 to 5.29)	1.60 (1.05 to 2.15)	4.70 (4.01 to 5.39)	−3.38 (−3.90 to −2.87)	0.01 (−0.74 to 0.76)	−3.39 (−4.30 to −2.48)
Low-density lipoprotein cholesterol							
mmol/L	3.15 (2.91 to 3.38)	3.13 (2.90 to 3.36)	2.25 (2.00 to 2.50)	3.29 (3.03 to 3.55)	−0.89 (−1.15 to −0.64)	0.16 (−0.11 to 0.43)	−1.05 (−1.42 to −0.68)
mg/dL	121.5 (112.5 to 130.5)	120.8 (111.8 to 129.8)	87.0 (77.3 to 96.7)	127.0 (116.9 to 137.0)	−34.5 (−44.4 to −24.5)	6.2 (−4.1 to 16.4)	−40.7 (−54.9 to −26.4)
High-density lipoprotein cholesterol							
mmol/L	1.20 (1.10 to 1.31)	1.25 (1.15 to 1.35)	1.64 (1.53 to 1.75)	1.35 (1.23 to 1.46)	0.44 (0.34 to 0.54)	0.09 (−0.01 to 0.19)	0.35 (0.21 to 0.48)
mg/dL	46.4 (42.4 to 50.4)	48.3 (44.3 to 52.3)	63.4 (59.2 to 67.6)	51.9 (47.6 to 56.3)	17.0 (13.3 to 20.7)	3.6 (−0.2 to 7.5)	13.4 (8.0 to 18.7)
Triglycerides							
mmol/L†	1.72 (1.48 to 1.97)	1.63 (1.40 to 1.85)	0.95 (0.81 to 1.09)	1.58 (1.34 to 1.81)	−0.77 (−0.95 to −0.60)	−0.05 (−0.24 to 0.14)	−0.72 (−0.98 to −0.47)
mg/dL†	152.5 (130.5 to 174.4)	143.9 (123.7 to 164.1)	84.0 (71.4 to 96.6)	139.4 (118.3 to 160.6)	−68.5 (−84.2 to −52.8)	−4.4 (−20.8 to 12.0)	−64.0 (−86.8 to −41.3)
Serum uric acid, *mmol/L*	0.34 (0.32 to 0.37)	0.34 (0.31 to 0.36)	0.26 (0.23 to 0.28)	0.36 (0.33 to 0.38)	−0.08 (−0.11 to −0.06)	0.02 (−0.00 to 0.04)	−0.10 (−0.14 to −0.07)
High-sensitivity C-reactive protein, *mg/L*†	10.53 (7.25 to 13.82)	7.54 (5.24 to 9.85)	0.81 (0.55 to 1.08)	4.84 (3.21 to 6.47)	−9.72 (−12.85 to −6.59)	−2.70 (−4.54 to −0.87)	−7.01 (−10.64 to −3.39)
Interventricular septum diastolic thickness, *mm*	9.4 (9.0 to 9.7)	9.8 (9.4 to 10.2)	8.7 (8.3 to 9.0)	9.4 (9.0 to 9.8)	−0.7 (−1.1 to −0.3)	−0.4 (−0.8 to 0.1)	−0.3 (−0.9 to 0.3)
10-year Framingham risk score†§	5.2 (4.0 to 6.5)	5.1 (3.9 to 6.3)	3.3 (2.5 to 4.1)	3.8 (2.9 to 4.8)	−1.9 (−2.6 to −1.3)	−1.3 (−1.9 to −0.7)	−0.7 (−1.6 to 0.2)
Serum creatinine							
µmol/L	64.5 (61.0 to 68.1)	70.7 (67.2 to 74.3)	57.5 (53.9 to 61.0)	71.6 (68.1 to 75.1)	-6.2 (-9.7 to -3.5)	0.9 (−1.8 to 3.5)	−8.0 (−11.5 to −3.5)
mg/dL	0.73 (0.69 to 0.77)	0.80 (0.76 to 0.84)	0.65 (0.61 to 0.69)	0.81 (0.77 to 0.85)	−0.07 (−0.11 to −0.04)	0.01 (−0.02 to 0.04)	−0.09 (−0.13 to −0.04)
Glomerular filtration rate, *mL/min/1.73 m²*‖	103.6 (98.2 to 109.1)	98.5 (93.0 to 103.9)	114.3 (108.6 to 120.0)	93.3 (87.5 to 99.2)	10.6 (6.1 to 15.1)	−5.1 (−9.8 to −0.4)	15.7 (9.2 to 22.3)

HOMA-IR = homeostatic model assessment-insulin resistance; MT = medical therapy; RYGB = Roux-en-Y gastric bypass.
* The point estimates and 95% CIs were based on the linear mixed-effects model that included patient as a random effect and interaction between group and visit (baseline, 1 y, 2 y, and 3 y) as fixed effects unless indicated otherwise.
† Mixed-effects model that included the patient as a random effect and the interaction between group and visit (baseline, 1 y, 2 y, and 3 y) with distribution gamma and link log. The 95% CI was obtained using the delta method.
‡ An indirect measure of insulin resistance calculated from levels of fasting plasma glucose and insulin.
§ Estimative of 10-y risk for cardiovascular disease by the Framingham risk score.
‖ Calculated using the MDRD (Modification of Diet in Renal Disease) study equation.

years) after bariatric surgery (7, 8, 23, 24). Although important, observational data are subject to residual confounding that cannot be fully controlled. A few randomized trials (primarily designed to evaluate the effects of bariatric surgery on diabetes) also assessed BP in follow-up. In the STAMPEDE (Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently) trial, the authors observed a reduction in the number of antihypertensive medications after surgery in patients with diabetes and obesity but no significant differences in BP per se (9, 25–27). The Diabetes Surgery Study, consisting of patients with diabetes and obesity, also demonstrated a reduction in the number of antihypertensive medications and a lower systolic BP in patients

Table 3. Adverse Events at 3 Years Across Treatment Groups

Nutritional and Metabolic Events*	RYGB, *n/N (%)*	MT, *n/N (%)*	*P* Value
Anemia†	5/47 (11)	4/41 (10)	1
Secondary hyperparathyroidism‡	6/43 (14)	NA	NA
Hypovitaminosis B_{12}§	13/44 (30)	NA	NA
Hypoalbuminemia‖	0/44 (0)	NA	NA
Iron deficiency¶	0/44 (0)	NA	NA
Ferritin deficiency**	2/44 (5)	NA	NA

MT = medical therapy; NA = not applicable; RYGB = Roux-en-Y gastric bypass.
* Metabolic laboratory studies were performed only in the group undergoing RYGB.
† Hemoglobin levels <120 g/L in women and <130 g/L in men.
‡ Serum parathyroid hormone levels >69 ng/L.
§ Serum vitamin B_{12} levels <142.4 pmol/L.
‖ Serum albumin levels <35 g/L.
¶ Serum iron levels <8.8 µmol/L.
** Serum ferritin levels <9 µg/L in women and <28 µg/L in men.

who underwent gastric bypass for up to 5 years of follow-up (11). Similar results were also observed with 2 other trials focusing on diabetes (10, 13). The 3-year GATEWAY trial results add to the literature by focusing specifically on hypertension as the end point among patients with mild to moderate obesity. The MT group consisted of a standardized approach for BP control. In addition, the availability of ABPM data allowed us to determine the 3-year effects of bariatric surgery on the 24-hour BP profile.

Our secondary end points and post hoc analyses are hypothesis generating and need to be confirmed in future investigation. A total of 35% of patients from the RYGB group achieved hypertension remission; this was observed in only 1 patient from the MT group who underwent RYGB outside the trial. Similar results were obtained in a post hoc analysis using the current BP cutoff (<130/80 mm Hg) (21). However, we did not demonstrate improved BP control across multiple measures of BP control. On the basis of ABPM data, we found consistent BP maintenance during the 24-hour period for both treatments, although the RYGB group required a median of 2 fewer antihypertensive drugs for achieving this BP control. Another important variable associated with poor prognosis is the presence of a nondipping BP pattern (28). In our study, the percentage of nondipping status was numerically higher in the control group but did not reach statistical significance. This finding is consistent with our previous investigation (17). Another potentially important end point is the prevalence of apparently resistant hypertension, a challenging condition to treat for which there are relatively few therapies (29, 30). Its prevalence was numerically lower in the RYGB group and approached but did not reach statistical significance, potentially because of the small sample size overall and the particularly small number of patients with resistant hypertension in our trial.

These promising results do not minimize the potential adverse risks of bariatric surgery and the tradeoffs between cardiovascular and metabolic benefits and adverse risks and greater costs. Bariatric surgery seems to be safe and effective (31). We did not have any 30-day mortality or surgical morbidity in our trial; however, 1 patient in the RYGB group died of undetermined cause during the follow-up. Anemia is common after bariatric surgery, but it was present in both groups. Hypovitaminosis B_{12} was common in the RYGB group but could be potentially mitigated by better vitamin supplementation.

Obesity is a growing challenge to health care systems around the world. Data from the World Health Organization show that worldwide obesity has nearly tripled since 1975. Although newer weight loss pharmacotherapeutic agents have been developed (5, 32), some have been problematic; in the past decade, 3 drugs (rimonabant, sibutramine, and lorcaserin) were withdrawn from the market because of safety concerns (33–35).

We did not evaluate cost-effectiveness, but studies suggest economic benefits from bariatric surgery. Although not the main focus of our study, our findings also suggest that RYGB produces other cardiometabolic benefits, as demonstrated in prior work (8, 11, 16), which contribute to potential cost savings. In 2 studies from England and Sweden, the authors found that bariatric surgery may lead to significant cost savings to health care systems in addition to the known clinical benefits (36, 37).

Our study has several strengths. To our knowledge, the GATEWAY trial is the first study primarily devoted to evaluating the effects of BP after bariatric surgery. We carefully standardized hypertension management and the decision to reduce or withdraw antihypertensive medications. Second, ABPM was available to provide detailed 24-hour BP data. Finally, the GATEWAY trial included patients with obesity and hypertension, most of whom did not have diabetes. Therefore, our results complement the findings from the available randomized evidence.

There are important limitations, however. First, this is a small, single-center, open-label study, although ABPM analysis was performed in a blinded manner. Moreover, the results of the primary end point were robust to all sensitivity analysis assumptions. Second, our study was not powered to adequately assess the effect of RYGB on our secondary outcomes and did not examine hard outcomes, such as mortality and major cardiovascular events. Third, the MT group primarily focused on BP and does not represent the standard of care for nonsurgical obesity management and treatment. For example, we did not include pharmacologic obesity treatment as part of the MT group because at the time the GATEWAY trial was designed (18), the only drug approved in Brazil for obesity treatment was sibutramine, which was not appropriate for patients with hypertension (34); the behavioral component was also not more intense in the MT group than in the RYGB group. Fourth, although physical activity was encouraged in all patients, we did not measure adherence to and the relative impact of physical activity. Finally, 16 patients were lost to follow-up, mainly in the MT group.

Bariatric surgery is an effective and durable strategy for reducing the number of antihypertensive drugs at 3 years in patients with obesity and hypertension while maintaining well-controlled BP; however, we did not demonstrate superior BP control with RYGB. Nevertheless, RYGB may be an attractive option in patients with refractory hypertension or for whom nonadherence to MT and its related consequences (38) are major concerns.

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Data Sharing Statement: Six months after completion of the trial, the database will be publicly available upon request by e-mail (cschiavon@hcor.com.br) and will be considered on an individual basis. The request must include a scientific proposal, including objectives. Statistical code will be publicly available upon request by e-mail (cschiavon@hcor.com.br) and will be considered on an individual basis. The request must include a scientific proposal, including objectives. The protocol and statistical analysis plan are immediately available as **Supplement 2** (available at Annals.org).

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Appendix Table. Baseline Characteristics of Study Participants*

Characteristic	RYGB (n = 50)	MT (n = 50)	Total (n = 100)
Mean age (SD), *y*	43.1 (9.2)	44.6 (9.2)	43.8 (9.2)
Female	41 (82)	35 (70)	76 (76)
Mean duration of hypertension (SD), *y*	9.4 (7.5)	9.4 (6.7)	9.4 (7.1)
Black or Brown race/ethnicity†	19 (38)	16 (32)	35 (35)
Mean body mass index (SD), kg/m^2	37.4 (2.4)	36.4 (2.9)	36.9 (2.7)
Previous smoker‡	9 (18)	12 (24)	21 (21)
Dyslipidemia	20 (40)	16 (32)	36 (36)
Diabetes	4 (8)	4 (8)	8 (8)
Family history of coronary artery disease	14 (28)	20 (40)	34 (34)
Personal history			
Heart failure	0 (0)	0 (0)	0 (0)
Atrial fibrillation	0 (0)	0 (0)	0 (0)
Valve disease	1 (2)	0 (0)	1 (1)
Chronic obstructive pulmonary disease	0 (0)	1 (2)	1 (1)
Asthma	2 (4)	7 (14)	9 (9)
Gout	1 (2)	1 (2)	2 (2)
Hypothyroidism	5 (10)	9 (18)	14 (14)
Obstructive sleep apnea	11 (22)	9 (18)	20 (20)
Median insulin level (IQR), *pmol/L*	122.2 (89.6–163.9)	136.5 (84.7–178)	127.1 (86.1–174.7)
10-year Framingham risk score (IQR)§	4.5 (2.9–7.3)	5 (2.8–6.7)	4.5 (2.9–7.1)
Mean creatinine level (SD)			
µmol/L	64.4 (12.7)	70.8 (14.7)	67.6 (14.0)
mg/dL	0.73 (0.14)	0.80 (0.17)	0.76 (0.16)
Mean glomerular filtration rate (SD), $mL/min/1.73\ m^2$‖	103.6 (18.8)	98.5 (23.3)	101 (21.2)
Median antihypertensive medications (IQR), *n*	3 (2–3)	3 (3–3)	3 (3–3)
Antihypertensive medications			
β-Blocker	18 (36)	23 (46)	41 (41)
Angiotensin-converting enzyme inhibitor	21 (42)	11 (22)	32 (32)
Calcium-channel blocker	29 (58)	33 (66)	62 (62)
Angiotensin-receptor blocker	28 (56)	38 (76)	66 (66)
Diuretic	40 (80)	46 (92)	86 (86)
Thiazide diuretic	40 (80)	45 (90)	85 (85)
Other	4 (8)	5 (10)	9 (9)

IQR = interquartile range; MT = medical therapy; RYGB = Roux-en-Y gastric bypass.
* Values are numbers (percentages), unless otherwise stated.
† Race/ethnicity was self-reported.
‡ Enrolled patients either had never smoked or were previous smokers. Current smokers were excluded.
§ Estimative of 10-y risk for cardiovascular disease by the Framingham risk score.
‖ Calculated using the MDRD (Modification of Diet in Renal Disease) study equation.

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