# 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

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**Importance** Controlling glycemia, blood pressure, and cholesterol is important for patients with diabetes. How best to achieve this goal is unknown.

**Objective** To compare Roux-en-Y gastric bypass with lifestyle and intensive medical management to achieve control of comorbid risk factors.

**Design, Setting, and Participants** A 12-month, 2-group unblinded randomized trial at 4 teaching hospitals in the United States and Taiwan involving 120 participants who had a hemoglobin $A_{1c}$ ($HbA_{1c}$) level of 8.0% or higher, body mass index (BMI) between 30.0 and 39.9, C peptide level of more than 1.0 ng/mL, and type 2 diabetes for at least 6 months. The study began in April 2008.

**Interventions** Lifestyle-intensive medical management intervention and Roux-en-Y gastric bypass surgery. Medications for hyperglycemia, hypertension, and dyslipidemia were prescribed according to protocol and surgical techniques that were standardized.

**Main Outcomes and Measures** Composite goal of $HbA_{1c}$ less than 7.0%, low-density lipoprotein cholesterol less than 100 mg/dL, and systolic blood pressure less than 130 mm Hg.

**Results** All 120 patients received the intensive lifestyle-medical management protocol and 60 were randomly assigned to undergo Roux-en-Y gastric bypass. After 12-months, 28 participants (49%; 95% CI, 36%-63%) in the gastric bypass group and 11 (19%; 95% CI, 10%-32%) in the lifestyle-medical management group achieved the primary end points (odds ratio [OR], 4.8; 95% CI, 1.9-11.7). Participants in the gastric bypass group required 3.0 fewer medications (mean, 1.7 vs 4.8; 95% CI for the difference, 2.3-3.6) and lost 26.1% vs 7.9% of their initial body weigh compared with the lifestyle-medical management group (difference, 17.5%; 95% CI, 14.2%-20.7%). Regression analyses indicated that achieving the composite end point was primarily attributable to weight loss. There were 22 serious adverse events in the gastric bypass group, including 1 cardiovascular event, and 15 in the lifestyle-medical management group. There were 4 perioperative complications and 6 late postoperative complications. The gastric bypass group experienced more nutritional deficiency than the lifestyle-medical management group.

**Conclusions and Relevance** In mild to moderately obese patients with type 2 diabetes, adding gastric bypass surgery to lifestyle and medical management was associated with a greater likelihood of achieving the composite goal. Potential benefits of adding gastric bypass surgery to the best lifestyle and medical management strategies of diabetes must be weighed against the risk of serious adverse events.

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THE FOUNDATION OF TREATment for type 2 diabetes mellitus is weight loss, achieved through reduction of energy intake and increased physical activity via lifestyle modification.[1] Results from the Look AHEAD (Action for Health in Diabetes) trial[2] show that sustained weight loss through lifestyle modification improves diabetes control, but this is difficult to achieve and maintain over time.

**See also pp 2250 and p 2274.**

**Author Video Interview available at www.jama.com.**

Medications to improve glycemia and control cardiovascular risk are also important, but up to 90% of patients with

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type 2 diabetes do not achieve treatment goals designed to reduce long-term risk of complications.[3]

The Swedish Obesity Subjects Study showed that patients who underwent bariatric surgery experienced greater weight loss, reduced incidence of type 2 diabetes, and lower mortality than obesity-matched control patients.[4,5] Randomized clinical trials evaluating bariatric surgery as treatment for type 2 diabetes have shown that laparoscopic adjustable gastric banding,[6] Roux-en-Y gastric bypass,[7,8] vertical sleeve gastrectomy,[8] and duodenal switch or biliopancreatic diversion[7] produced more weight loss and better glycemic control than typical medical therapy. These trials were limited by small numbers of participants for the various types of operations and were performed by single surgeons at each center, resulting in uncertain generalizability of their findings. The medical interventions used in these studies were not necessarily intensive.[9] Whether the surgical advantage remains when compared with optimal medical and lifestyle treatment is unknown.

The results of bariatric surgery must be balanced against adverse events. Operative mortality of bariatric surgery has decreased to between 0.1% and 1%, but other less severe adverse outcomes are common.[10] There is a need to better define the benefits and short-term risks of bariatric surgery compared with optimal medical treatment. The present study addresses several important aspects of bariatric surgery outcomes: (1) reported outcomes from recent randomized clinical trials of bariatric surgery[6-8] do not conform to diabetes treatment goals as expressed in clinical practice guidelines recommended by the American Diabetes Association (ADA)[1]; (2) weight loss in the medical control group of these trials was suboptimal relative to previous behavioral weight loss trials; (3) inclusion of different surgical procedures in single studies resulted in underpowered results precluding definitive conclusions about any single procedure ; and (4) to date, there are published data for only 14 patients with a body mass index (BMI) of less than 35 who had gastric bypass surgery as part of a controlled clinical trial. (BMI is calculated as weight in kilograms divided by height in meters squared.)[8]

The Diabetes Surgery Study addressed some of these limitations by conducting a prospective randomized clinical trial comparing a single operation, the Roux-en-Y gastric bypass, to intensive lifestyle modification in a cohort of patients with type 2 diabetes and inadequate glycemic control following treatment with standard medical therapy. Medical management of these obese patients was protocol driven and used a lifestyle intervention based on the Look AHEAD approach, which is known to result in weight loss.[2]

## METHODS

The study was conducted at 4 sites: the University of Minnesota (starting in 2008), Columbia University Medical Center (starting in 2009), 2 academic clinics in Taiwan (National Taiwan University Hospital and Min Sheng General Hospital, together called Taiwan, starting in 2009), and the Mayo Clinic in Rochester, Minnesota (starting in 2010). All sites had institutional review board (IRB) approval for the study and obtained written informed consent from each patient. The interventions included 3 components: lifestyle modification and intensive medical management for all participants and the addition of Roux-en-Y gastric bypass for half the participants. The intervention was provided without charge, except that participants at the New York site were required by law to make standard insurance copayments for medications. Compensation differed across sites, ranging from $25 to $400 for the 12-month visit.

### Patient Eligibility and Enrollment

Between April 2008 and December 2011, 60 of the 120 patients participating in a intensive lifestyle and medically managed weight control program were randomized to receive Roux-en-Y gastric bypass surgery while continuing with the lifestyle-medical management protocol. Patients were recruited through mass media advertisements, contact with professional groups, presentations at public events, and a practice-based database. Patients were included if they were aged 30 through 67 years, under a physician's care for type 2 diabetes for at least 6 months before recruitment, had hemoglobin $A_{1c}$ ($HbA_{1c}$) levels of 8.0% or higher at the time of entry, and had a serum C-peptide level higher than 1.0 ng/mL (to convert C-peptide to nanomoles per liter, multiply by 0.331) 90 minutes after a liquid mixed meal (250 calories, 6 g fat, 40 g carbohydrate, and 9 g protein). Participants had a BMI of 30.0 to 39.9 and were willing to accept randomization to either treatment group and follow the full treatment protocol. Additional criteria included the absence of conditions that would contraindicate surgery, such as serious cardiovascular disease, previous gastrointestinal surgery, psychological concerns, or history of malignancy.

Randomization assignment was unblinded but allocation between treatment groups was concealed to the study staff until after randomization. The randomization schedule used permuted blocks of random length within each site so that each site would have nearly equal proportions in each group. Investigators, data collectors, and outcome adjudicators were blinded to aggregate outcomes until the final patient completed the 12-month follow-up.

### Intensive Medical Management

The lifestyle-medical management protocol consisted of 2 components—lifestyle modification designed to produce maximum achievable weight loss and medications to control glycemia and cardiovascular disease risk factors while facilitating weight loss. Only US Food and Drug Administration–approved medications were used.

**Lifestyle Modification.** The study lifestyle intervention was modeled on recent successful clinical trials, particularly the Diabetes Prevention Program[11] and the Look AHEAD protocol.[2] Participants were instructed to weigh them-

selves and to record eating and exercise behaviors on a daily basis. Both groups were advised to progressively increase their level of moderate-intensity physical activity (such as walking) to a total of 325 minutes per week. All lifestyle-medical management participants were given calorie intake targets of 1200, 1500, or 1800 kilocalories per day, depending on body weight, with the goal of producing a weight loss of 1 to 2 pounds per week. Portion-controlled diets using meal replacements, structured menus, and calorie counting were encouraged to help participants stay within calorie limits.

Both groups met regularly with a trained interventionist to discuss strategies for facilitating weight management and increasing physical activity, including self-monitoring, stimulus control, problem solving, social support, cognitive behavior modification, recipe modification, eating away from home, and relapse prevention. Counseling sessions comprised 24 weekly meetings over the first 6 months, biweekly meetings between months 7 and 9, and monthly meetings between months 10 and 12.

The lifestyle intervention protocol was similar for participants in both treatment groups. Patients assigned to the gastric bypass group, however, delayed initiation of the lifestyle intervention until they could tolerate solid foods (typically about 3 to 4 months after surgery), did not have calorie ceilings during the period of rapid weight loss, and received additional instruction regarding food volume and adequate protein intake.

**Medications.** When the intervention did not produce adequate weight loss among those in the lifestyle-medical management group, orlistat could be added to the treatment program. Sibutramine was also used for weight management until it was withdrawn from the US market. Medications for glycemic control were added in the following order: metformin, a glucagon-like peptide-1 analog or dipeptidyl peptidase 4 inhibitor, sulfonylurea or pioglitazone, and insulin. Low-density lipoprotein (LDL) cholesterol control was pursued with HMG-CoA reductase inhibitors first, followed by ezetimibe if necessary. Blood pressure medications were used in the following order: angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor II blocker (ARB), diuretic, β-blocker, and additional agents as necessary. The first approach to reducing elevated triglyceride levels was control of hyperglycemia; however, if triglycerides remained higher than 300 mg/dL (to convert to millimoles per liter, multiply by .0113), fenofibrate or fish oil was added. Smoking cessation was strongly recommended for all participants. An ACE or ARB inhibitor was provided for all participants with microalbuminuria or macroalbuminuria. Aspirin (81-100 mg daily) was added to be consistent with evolving recommendations from the American Diabetes Association and when not otherwise contraindicated.

All patients were given routine testing for nutritional deficiencies; supplements were prescribed accordingly. In addition, all patients in the gastric bypass group were prescribed multivitamin and mineral supplements, including calcium, iron, cholecalciferol (vitamin D), and cyanocobalamin (vitamin $B_{12}$) supplements regardless of routine test results.

The same medication treatment goals and algorithms were used for all participants with some qualifications. Occasionally, a participant refused or did not tolerate recommended medications or controlled their symptoms by taking medications differing from the algorithm and initiated before they entered the study. Medications for control of glycemia, dyslipidemia, and blood pressure were reduced or discontinued in gastric bypass participants immediately after surgery because of fluid and caloric decreases soon after surgery and were restarted as necessary to accomplish treatment goals.

### Laparoscopic Roux-en-Y Gastric Bypass

Participants randomized to the gastric bypass group were placed on a low-calorie diet with meal replacements 2 weeks before the operation. Staff surgeons with extensive experience (>300 cases) performed the procedure. A single surgeon performed the surgeries at each of the 4 sites, except at 1 site, at which 2 surgeons performed the procedure. The technique was standardized across all sites and was performed with construction of a 20-mL lesser curvature gastric pouch, a 100-cm biliopancreatic limb, and an antecolic 150-cm Roux limb with closure of all mesenteric defects.[12] All surgeons committed to following this protocol, which was reviewed at an onsite meeting. The technical skill of each surgeon was established by personal observation of the principal investigator. On postoperative day 1, patients underwent a routine upper gastrointestinal contrast study and initiated a clear liquid diet if the study showed no leak. Participants were typically discharged 2 days after surgery. At home, participants remained on a clear liquid diet for 1 week, gradually advancing to pureed foods until they could tolerate solid foods.

### Outcomes

The primary outcome was considered successful if patients achieved the composite of the triple end point: an $HbA_{1c}$ of less than 7.0%, an LDL cholesterol level of less than 100 mg/dL (to convert to millimoles per liter, multiply by 0.0259), and systolic blood pressure less than 130 mm Hg, at the 12-month visit. The triple end point was specified based on diabetes treatment guidelines at study onset.[13] Secondary outcome measures included weight loss, adverse events, fasting glucose, $HbA_{1c}$ levels less than 6.0%, high-density lipoprotein (HDL) cholesterol and triglycerides levels, diastolic blood pressure, waist circumference, and medications.

### Measurement and Data Collection

Data were collected at baseline, medical visits (monthly for the first 6 months and then quarterly thereafter), and lifestyle intervention visits. Collected data included height, weight, blood pres-

sure, pulse rate, medications used, and adverse events. Laboratory measurements collected included blood levels of $HbA_{1c}$, fasting lipid profile, complete blood count, electrolytes, hepatic panel, ferritin, vitamin $B_1$, vitamin $B_{12}$, vitamin D, parathyroid hormone, fasting and 90-minute postmeal glucose and C-peptide concentrations, and urine microalbumin to creatinine ratios were obtained at baseline and 1 year following randomization.

### Statistical Design and Analysis

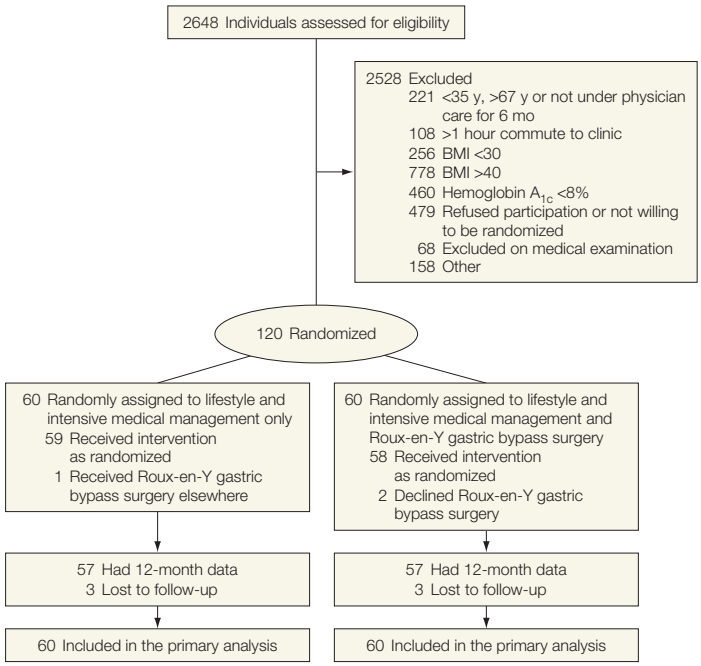
The primary analysis was intention to treat. For participants who did not have data for the composite triple end point at 12 months, methods of multiple imputation[14] based on all prior data were applied. Logistic regressions stratified by site were used to compare proportions of success in the 2 groups (SAS PROC MI and SAS PROC MIANALYZE, SAS 9.2, SAS Institute Inc).

Estimates of sample size were based on the following assumptions: a 2-sided significance level of $P \leq .05$ and a standard superiority trial design; 95% power; and an alternative hypothesis of success rates on the 3 end points of 65% in the gastric bypass group vs 30% in the lifestyle-medical management group. These estimates were derived from previous studies. Schauer et al[15] reported that 83% of participants with type 2 diabetes undergoing Roux-en-Y gastric bypass succeeded in obtaining $HbA_{1c}$ levels that were lower than 6.0% when evaluated more than 12 months after surgery. Because gastric bypass is less effective in reducing serum LDL cholesterol levels and systolic blood pressure to the targets established by the triple end point of <100 mg/dL for LDL cholesterol and 130 mm Hg for systolic blood pressure, we decreased the estimated success rate for the gastric bypass group from the 83% that was set by Schauer et al to 65%. The other reason we lowered the estimated success rate is because the participants in our study had higher $HbA_{1c}$ levels than did the patients involved in the study by Schauer et al. Establishing the 30% success rate in the lifestyle-medical management group was based on studies used to generate the American Diabetes Association Standards of Care.[13,16] This alternative hypothesis resulted in a sample-size estimate of 108 participants (54 in each group). An inflation factor of 12% was included to account for possible crossovers and losses to follow-up. *Crossover* participants were either randomized to gastric bypass, declined surgery, and continued to have contact with the study or randomized to the lifestyle-medical management group and obtained bariatric surgery elsewhere, but continued to have contact with the study.

Multiple imputation was used to address the issue of missing outcome data[14] for participants missing the 12-month visit with PROC MI in SAS. The following baseline covariates were used: clinic; age; sex; $HbA_{1c}$; C-peptide, LDL, HDL, total cholesterol, and triglyceride levels; systolic and diastolic blood pressure; blood glucose measures; weight; waist circumference; and medication count to construct the imputations. Information on crossover was also used but no other postrandomization information. Analysis of the imputed data set was based on logistic regression, carried out using PROC MIANALYZE in SAS. The regressions were stratified by site. Graphs indicate means and 95% CIs. A test for whether the odds ratios (ORs) for the gastric bypass vs lifestyle-medical management treatment effect differed between clinics was carried out using the Breslow-Day test for homogeneity of the odds ratio in PROC FREQ in SAS version 9.3.

Regression analyses, stratified by site, were carried out to examine whether the gastric bypass effect on triple end point success was mediated primarily by weight loss. These were exploratory analyses designed to elucidate the mechanism of the treatment effect, not intention-to-treat analyses.

**Figure 1.** Flow Diagram of Patients in the Diabetes Surgery Study




BMI indicates body mass index, calculated as weight in kilograms divided by height in meters squared.

## RESULTS

### Participant Characteristics

The methodology of recruitment and screening is summarized in FIGURE 1. A total of 2648 candidates for the study were screened to attain 120 random-

ized patients. Racial and ethnic information was determined by patient report and collected related to possible influence on triple end point outcomes. Patient characteristics at baseline are summarized in TABLE 1. Participants had diabetes for an average of 9.0 years (95% CI, 7.9-10.0 years) at enrollment. Mean (SD) BMI was 34.6 (3.1) with 71 participants (59%) having a BMI of less than 35. Mean (SD) $HbA_{1c}$ was 9.6% (1.1%). Baseline characteristics were similar across randomized groups. One participant in the gastric bypass group was later determined to have type 1 diabetes. The data from this participant were included in the analyses.

**Table 1.** Baseline Data by Treatment Group

| | Lifestyle and Medical Management (n = 60) | Roux-en-Y Gastric Bypass (n = 60) |
|---|---|---|
| Demographics | | |
| Age, mean (SD), y | 49 (8) | 49 (9) |
| Women, No. (%) | 34 (57) | 38 (63) |
| Race/ethnicity, No. (%) | | |
| Non-Hispanic white | 30 (50) | 33 (55) |
| East Asian | 17 (28) | 16 (27) |
| Non-Hispanic black | 6 (10) | 5 (8) |
| Hispanic | 4 (7) | 4 (7) |
| Native American | 1 (2) | 2 (3) |
| Other | 2 (3) | 0 (0) |
| General medical | | |
| Body mass index[a] | | |
| Mean (SD) | 34.3 (3.1) | 34.9 (3.0) |
| 30.0-34.9, No. (%), | 35 (58) | 36 (60) |
| Body size measures, mean (SD) | | |
| Height, cm | 168 (10) | 168 (9) |
| Weight, kg | 97.9 (17.0) | 98.8 (14.0) |
| Waist circumference, cm | 113 (12) | 114 (10) |
| Blood pressure, mean (SD), mm Hg | | |
| Systolic | 132 (14) | 127 (15) |
| Diastolic | 79 (10) | 78 (12) |
| Years since diabetes diagnosis, mean (SD) | 9.1 (5.6) | 8.9 (6.1) |
| Laboratory values, serum, Mean (SD) | | |
| $HbA_{1c}$ (%) | 9.6 (1.2) | 9.6 (1.0) |
| Cholesterol, mg/dL | | |
| Low-density lipoprotein | 105 (43) | 103 (36) |
| High-density lipoprotein | 42 (9) | 41 (1) |
| Total | 189 (46) | 182 (39) |
| Triglycerides, mg/dL | 249 (213) | 255 (383) |
| Creatinine, mg/dL | 0.79 (0.19) | 0.81 (0.20) |
| Fasting C-peptide, ng/mL | 3.0 (1.5) | 2.9 (1.9) |
| Postmeal C-peptide, ng/mL | 4.8 (2.2) | 4.4 (2.6) |
| Fasting glucose, mg/dL | | |
| Mean (SD) | 207 (57) | 222 (77) |
| <100, No. (%) | 1 (2) | 1 (2) |
| Alanine aminotransferase, U/L | 37 (22) | 36 (23) |
| Alkaline phosphatase, U/L | 84 (32) | 88 (39) |
| Serum albumin, g/dL | 4.3 (0.3) | 4.3 (0.4) |
| Medicines, No. (%) | | |
| Taking insulin | 26 (43) | 37 (62) |
| Taking other glycemic medicines | 57 (95) | 52 (87) |
| Taking dyslipidemia medicines | 41 (68) | 39 (65) |
| Taking blood pressure medicines | 44 (73) | 41 (68) |
| No. needed to control glycemia, dyslipidemia, and blood pressure, mean (SD) | 4.4 (1.5) | 4.1 (1.9) |

Abbreviations: $HbA_{1c}$, hemoglobin $A_{1c}$.
SI conversion factors: To convert alanine aminotransferase from U/L to μkat/L; multiply by 0.0167; alkaline phosphatase from U/L to μkat/L, multiply by 0.0167; low- and high-density lipoprotein and total cholesterol from mg/dL to mmol/L, multiply by 0.0259; C-peptide from ng/dL to nmol/L; multiply by 0.331; creatinine from mg/dL to μmol/L, multiply by 88.4; glucose from mg/dL to mmol/L, multiply by 0.0555; and tryglycerides from mg/dL to mmol/L, multiply by 0.0113.
[a]Body mass index is calculated as weight in kilograms divided by height in meters squared.

Six (5%) of the 120 enrolled participants were lost to follow-up, 3 from each group. There were also 3 crossovers: 1 participant randomized to the lifestyle-medical management group underwent gastric bypass elsewhere, and 2 participants randomized to gastric bypass declined the operation. A sensitivity analysis was carried out under the assumption that in the gastric bypass group all of the participants with missing 12-month data (n = 3) did not achieve the triple end point, whereas in the lifestyle-medical management group all of the participants with missing 12-month data (n = 3) were successful in achieving the triple end point. The results with regard to significance of the gastric bypass vs the lifestyle-medical management treatment effect were in agreement with analyses based on completely observed data and with those based on multiple imputation. Because of the high level of participant adherence and follow-up, there were no material differences in *P* values.

## Composite and Other End Points

At 12 months, 11 participants (19%; 95% CI, 10%-32%) in the lifestyle-medical management group and 28 (49%; 95% CI, 36%-63%) in the gastric bypass group achieved the primary composite end point (OR, 4.8; 95% CI, 1.9-11.7; TABLE 2). Among the composite end point components, the only significant treatment effect was for $HbA_{1c}$: 18 participants (32%) in the lifestyle-medical management group vs 43 (75%) in the gastric bypass group achieved an $HbA_{1c}$ level of less than 7% (OR, 6.0; 95% CI, 2.6-13.9).

Emerging evidence about risks and benefits of blood pressure control has led the American Diabetes Association to recommend less aggressive goals.[1] By

these new standards, 31 participants (54%) who underwent gastric bypass and 15 (26%) in the lifestyle-medical management group achieved the triple end point (OR, 3.8;, 95% CI, 1.6-8.7).

The lifestyle-medical management group lost a mean (SD) of 7.9% (7.8%) of initial body weight at 1 year. Most of the weight loss occurred in the first 6 months (FIGURE 2). The mean (SD) weight loss in the gastric bypass group was 26.1% (8.7%) of starting weight at 1 year (difference, 17.5%; 95% CI, 14.2%-20.7%). Although the rate of weight loss was greater in the first 6 months, weight loss continued during months 6 through 12.

On average, the gastric bypass group used 3.0 fewer medications to manage glycemia, dyslipidemia, and hypertension than did those in the lifestyle-medical management group (95% CI, 2.3-3.6). The gastric bypass group also had significantly better results for the secondary outcomes of glycemia, HDL cholesterol, triglycerides, and diastolic blood pressure.

A sensitivity analysis was performed to determine whether there were important clinic differences in treatment effect. The Breslow-Day test for homogeneity across sites of the ORs for the primary end point yielded a *P* value of .75. There was, therefore, no significant interaction between treatment group and clinic.

Gastric bypass status was a significant predictor of triple end point success (OR, 4.7; 95% CI, 1.9-11.2) in as-treated models adjusted only for site. When both gastric bypass and weight loss are present in a logistic regression model stratified by clinic, the OR for gastric bypass becomes nonsignificant (OR, 0.96; 95% CI, 0.22-4.24), whereas the OR for triple end point success associated with a 10% weight loss is significant (OR, 2.3; 95% CI, 1.2-4.5). In regression analyses performed separately within each treatment group, the effect of 10% weight loss was significant and similar in the lifestyle-medical management group (OR, 2.6; 95% CI, 1.1-5.9) and gastric bypass groups (OR, 2.2; 95% CI, 1.1-4.7), indicating a consistent effect of weight loss (*P* = .80 for difference). This implies that weight loss explains most of the diabetes treatment benefit of gastric bypass.

**Table 2.** Twelve-Month Outcomes

| End Points | Lifestyle and Medical Management | Roux-en-Y Gastric Bypass | OR (95% CI)[a] |
|---|---|---|---|
| | Dichotomous Outcomes | | |
| | No. (%) of Patients | | |
| Meets primary outcome triple end point | 11 (19) | 28 (49) | 4.8 (1.9-11.7) |
| $HbA_{1c}$ <7.0% | 18 (32) | 43 (75) | 6.0 (2.6 to 13.9) |
| LDL cholesterol <100 mg/dL | 38 (70) | 45 (79) | 1.6 (0.7 to 3.8) |
| Systolic blood pressure <130 mm Hg | 44 (79) | 48 (84) | 1.7 (0.6 to 4.6) |
| $HbA_{1c}$ <6.0% | 5 (9) | 25 (44) | 7.9 (2.7 to 23.4) |
| Fasting glucose <100, mg/dL | 7 (14) | 25 (44) | 5.8 (2.1 to 15.9) |
| | Continuous Outcomes | | |
| | Mean (SD) | | Difference (95% CI)[a] |
| Glycemia | | | |
| $HbA_{1c}$, % | 7.8 (1.5) | 6.3 (0.9) | −1.4 (−1.9 to −0.9) |
| Fasting glucose, mg/mL | 153 (59) | 111 (34) | −42 (−60 to −24) |
| Serum lipids, mg/dL | | | |
| Cholesterol | | | |
| LDL | 89 (31) | 83 (25) | −5 (−16 to 5) |
| HDL | 42 (9) | 50 (14) | 7.5 (3 to 12) |
| Total | 162 (40) | 153 (32) | −10 (−23 to 4) |
| Triglycerides | 182 (151) | 104 (48) | −78 (−119 to −36) |
| Blood pressure, mm Hg | | | |
| Systolic | 124 (12) | 115 (14) | −9 (−13 to −4) |
| Diastolic | 74 (9) | 68 (9) | −6 (−9. to −4) |
| Weight | | | |
| Weight, kg | 90.1 (17.0) | 73.0 (13.6) | −16.0 (−21.1 to −10.8) |
| BMI, | 31.6 (3.7) | 25.8 (3.5) | −5.5 (−6.8 to −4.2) |
| Percent weight change (%) | −7.9 (7.8) | −26.1 (8.7) | −17.5 (−20.7 to −14.2) |
| Waist circumference, cm | 105 (11) | 90 (11) | −15 (−18 to −11) |
| Other | | | |
| Medications for control of glycemia, dyslipidemia and blood pressure (n) | 4.8 (2.1) | 1.7 (1.8) | −3.0 (−3.6 to −2.3) |

[a] ORs, Differences, and their 95% CIs are computed using multiple imputations. Logistic regressions are stratified by site; linear regressions are adjusted for site.

## Adverse Events

TABLE 3 presents serious adverse events for both treatment groups, as well as the incidence of hypoglycemia and nutritional deficiencies. Overall, there were 22 serious adverse events in the gastric bypass group and 15 in the lifestyle-medical management group. There were 4 perioperative complications and 6 late postoperative complications in the gastric bypass group. Although there was no mortality, 2 postoperative complications merit particular attention. One participant who had undergone gastric bypass surgery developed a leak from the jejuno-jejunostomy with severe systemic consequences. The leak was not evident in the patient's routine postoperative upper gastrointestinal contrast study; it was detected hours later based on patient symptoms. Ultimately, this participant required extracorporeal membrane oxygenation and suffered anoxic brain injury, lower extremity amputation, and long-term disability. Another participant in the gastric bypass group developed a leak from the gastrojejunostomy. The intraoperative leak test was negative, but a leak was detected in the immediate postoperative period using the upper gastrointestinal tract contrast study, and the patient underwent another laparo-

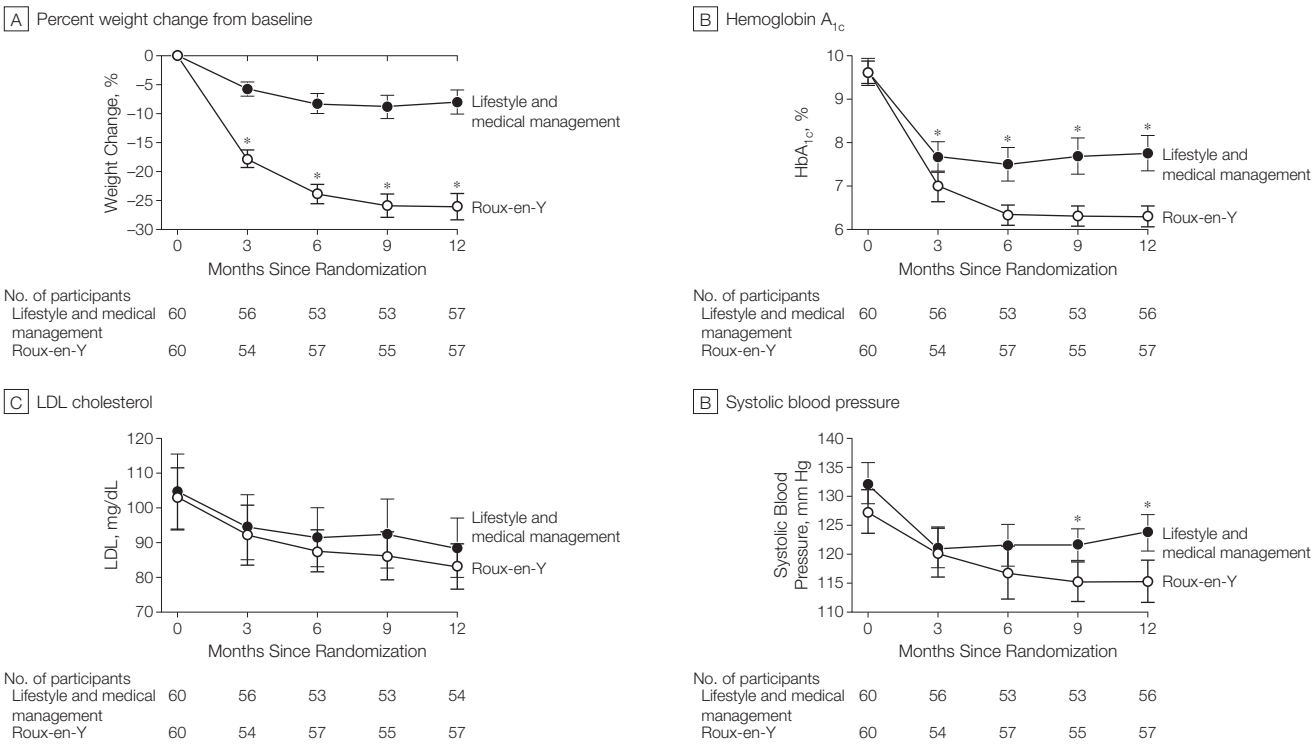
scopic procedure and was discharged without further sequelae. One participant in the lifestyle-medical management group experienced pancreatitis. Two other participants were diagnosed with pancreatic cancer well into the first year of enrollment; one had received treatment with glucagon-like peptide-1 analog mimetics. Symptomatic hypoglycemia with neuroglycopenia was reported by 2 participants in the lifestyle-medical management group and by 5 patients in the gastric bypass group (one of whom had declined surgery; TABLE 4). Nutrient deficiencies in the participants (gastric bypass vs lifestyle-medical management) included iron deficiency (13 vs 0), hypoalbuminemia (4 vs 0), one or more vitamin B deficiencies (11 vs 2), and low serum vitamin D (4 vs 5). The adverse events are reported based on original treatment assignment. There were no deaths reported in either group, but as discussed above, a cerebrovascular event occurred in one gastric bypass patient as a complication of surgery.

## DISCUSSION

Of the patients with suboptimally controlled type II diabetes and a BMI that ranged from 30.0 through 39.9 who underwent Roux-en-Y gastric bypass surgery, 49% achieved established diabetes management goals compared with 19% of patients in the lifestyle-medical management group. Only about half of the participants achieved the composite treatment goal despite surgery and their simultaneous participation in intensive medical and lifestyle therapy; however, the patients in the gastric bypass group who achieved the composite goal took 66% fewer medications than did those in the lifestyle-medical management group.

To our knowledge, this is the first trial comparing Roux-en-Y gastric bypass surgery with intense lifestyle and medical management to treat type 2 diabetes using composite specified therapeutic goals. The rationale for these end points is that achieving a $HbA_{1c}$ of 7.0% or less protects against vascular complications of type 1 diabetes.[17,18] Decreasing LDL cholesterol and blood pressure reduce the risk of macrovascular events in populations of patients with diabetes.[1] Previous randomized trials involving patients with diabetes who underwent gastric bypass reported effects on glycemia, and sometimes on blood pressure and lipids, as individual variables but not as a composite end point. The proportion of participants in both groups who achieved the composite goal was greater than the 10.2% cross-sectional rates reported in the National Health and Nutrition Survey database[3] and the 10.1% in the baseline Look AHEAD study population.[19] The Look AHEAD intensive lifestyle intervention improved achievement of the composite goal from 10.8% to 23.6% of participants at 1 year,[16] similar to the

**Figure 2.** Outcomes Over Time




Error bars indicate 95% CIs; LDL, low-density lipoprotein (to convert from mg/dL to mmol/L, multiply by 0.0259). *$P$ value for difference is $<.01$.

19% (95% CI, 10%-32%) achieved by those participating in the current lifestyle-medical management group. In our trial, the proportion of patients in both groups who achieved the composite goal was less than we projected in our power analysis. This was because of the smaller than expected improvements in systolic blood pressure and serum LDL cholesterol levels. Between-group differences in the triple end point were consistent with our projections.

Glycemic control results are comparable with the experience of other controlled trials testing bariatric surgery treatment of diabetes. In the current study, the mean (SD) $HbA_{1c}$ at baseline was 9.6% (1.1%), substantially greater than the baseline reported in the Look AHEAD trial,[16] the gastric band trial of Dixon et al,[6] and the bariatric surgery study by Mingrone et al,[7] but similar to the trial by Schauer and colleagues.[8] The generally greater mean $HbA_{1c}$ likely reflects our entry criteria requiring an $HbA_{1c}$ higher than 8.0% and is relevant to balancing the risks of poorly controlled diabetes with surgical risks. The glycemic goal of an $HbA_{1c}$ lower than 7.0%, achieved by 75% of those in the gastric bypass group cannot be directly compared with the other randomized trials of bariatric surgery involving patients with diabetes because the current study target was different. The mean (SD) $HbA_{1c}$ in our gastric bypass group was 6.3% (0.9%) at 1 year, comparable with 6.4% for those undergoing Roux-en-Y gastric bypass surgery in the Schauer et al study and 6.3% at 2 years in the Mingrone et al study. The lifestyle-medical management group improved its mean $HbA_{1c}$ to 7.8% (1.5%), similar to the 7.2% achieved in the Look AHEAD intense treatment group and the medical treatment groups of the other 3 studies.[6-8,16] Overall, both of the treatment groups in the current study were congruent with our prior hypotheses on glycemic control.

The gastric bypass procedure did not significantly improve LDL cholesterol or blood pressure outcomes with more than 70% of both groups having achieved these goals. The mean (SD) 1-year LDL cholesterol concentration of 89 mg/dL (31 mg/dL) among those in the lifestyle-medical management group was lower than among patients who had participated in the Look AHEAD intense treatment group and the Mingrone et al study medical group. The mean (SD) LDL of 83 mg/dL (25 mg/dL) among patients in the gastric bypass group was similar to what was reported by Mingrone et al. The 84% rates in the gastric bypass and the 79% rates in lifestyle-medical management groups of achieving the blood pressure goal approximate what was achieved in the Look AHEAD and other diabetes-focused bariatric surgery studies.[6-8,16]

Compared with previous randomized surgical studies, we pursued optimal medical management including the use of weight-lowering medications. In addition to lifestyle modification, sibutramine (until removed from the market) and orlistat were used to facilitate weight loss. Glucagon-like peptide-1 analog mimetics, known to produce sustained weight loss in this population, were used early in the diabetes treatment algorithm. Weight loss in the lifestyle-medical management group averaged 7.9% at 1 year compared with 5.4% in Schauer et al,[6] 4.7% at 2 years in Mingrone et al,[7] and 1.4% at 2 years in Dixon et al.[8] Interestingly, all metabolic benefits in the lifestyle-medical management group were realized by 6 months with subsequent decrease in the number meeting composite goal by 12 months. In contrast, treatment benefits continued to increase in the gastric bypass group throughout the year.

The mechanisms responsible for improvement in diabetes and cardiovascular risk factors in this study cannot be determined with certainty. The underlying assumption for the original application of bariatric surgery to treat type 2 diabetes was that greater sustained weight loss would benefit patients. In other studies, weight loss among patients who had gastric band surgery correlated with improvement in type 2 diabetes control,[6] but other bariatric surgery studies have not found a correlation with weight loss or reduction of BMI.[7,8,20] Regression

**Table 3.** Adverse Events

| Serious Adverse Events | Medical Management | Roux-en-Y Gastric Bypass |
|---|---|---|
| Postoperative Complications | | |
| Anastomotic leak | | 2[a] |
| Wound infection | | 1 |
| Wound hematoma | | 1 |
| Late surgical Complications | | |
| Stricture | | 2 |
| Bleeding anastomotic ulcer | | 1 |
| Gastritis proximal pouch | | 1 |
| Small bowel obstruction | | 2 |
| Gastrointestinal disorders | | |
| Diarrhea | 0 | 1 |
| Abdominal pain | 0 | 1 |
| Duodenitis | 1 | 0 |
| Acute pancreatitis | 1 | 0 |
| Infections | | |
| Urinary tract infection | 0 | 1 |
| Buttock abscess | 0 | 1 |
| Pyelonephritis | 1 | 0 |
| Bronchitis | 1 | 0 |
| Neurologic | | |
| Herniated disc | 1 | 1 |
| Foot drop | 0 | 1 |
| Third cranial nerve palsy | 1 | 0 |
| Bell palsy | 1 | 0 |
| Suicide attempt | 1 | 0 |
| Vascular-toe amputation | 0 | 1 |
| Nonoperative trauma | | |
| Motor vehicle crash | 2 | 0 |
| Ankle burn from a motorcycle accident resulting in a below-the-knee amputation | 0 | 1 |
| Other | | |
| Hypertension/ headache | 0 | 1 |
| Back pain | 0 | 1 |
| Pregnancy | 0 | 1 |
| Chest pain | 1 | 0 |
| Uterine bleeding | 1 | 0 |
| Uretal stone | 1 | 1 |
| Pancreatic cancer | 2 | 0 |
| **Total serious adverse events** | **15** | **22** |

[a] Complications for one patient with anastomotic leak included sepsis, stroke, leg amputation, renal failure, other organ failures, coma, and extensive blood loss/clotting disorder.

**Table 4.** Selected Nonserious Adverse Events Commonly Associated With Diabetes or Procedure

| Nonserious Adverse Events | Medical Management | Roux-en-Y Gastric Bypass |
|---|---|---|
| Cataract (severe) | 0 | 1 |
| Nephrolithiasis | 2 | 1 |
| Peripheral neuropathy | 2 | 2 |
| Hypoglycemia without need for assistance | 2 | 7[a] |
| Nutritional | | |
| Iron deficiency | 0 | 13 |
| Hypoalbuminemia | 0 | 4 |
| Vitamin B deficiency[b] | 2 | 11 |
| Vitamin D drop to ≤30 ng/dL | 5 | 4 |
| Electrolyte/fluid disorder | 0 | 1 |
| Hypertriglyceridemia | 5 | 1 |

[a] Adverse events are reported based on randomization assignment. Two of the hypoglycemic incidents were in a patient randomized to gastric bypass who declined surgery.
[b] Includes vitamins $B_1$, $B_6$, and $B_{12}$.

analyses of the present data indicate that the effect of gastric bypass on achieving the composite end point is attributable to weight loss. This finding does not preclude the possible contribution of changes in the secretion of gastrointestinal hormones to glucose control improvement,[21] nor does it take into account between-group differences in medication use.

There was substantial difference in the frequency of serious adverse events between groups. Patients in the gastric bypass group experienced 50% more serious and 55% more nonserious adverse events than did those in the lifestyle-medical management group (Table 4). The 2 most serious complications of gastric bypass were related to problems with gastrointestinal anastomotic leakage. All surgeons performing gastric bypass in this study were experts, thus the occurrence of serious complications must be factored into the design of larger trials of effectiveness for patients with moderate obesity. Although the published incidence of anastomotic leakage after gastric bypass has decreased from as high as 5%[22] to 0.8%,[10] even in the hands of experienced surgeons serious complications occur at a modest rate. Our leak rate of 3% is likely a function of random effects, but it is important to emphasize the differences in our patient population compared with other reported complications. The reported complication rates reflect data to 1 year and do not reflect internal hernias, the potential for later development of anastomotic ulcers, suicide, substance addiction, and failure of maintenance of weight loss known to occur beyond the first year after gastric bypass. As expected, the number of nutritional deficiencies was greater in the gastric bypass group despite monitoring of laboratory values and prescription of appropriate nutritional supplements.

Proponents have suggested that bariatric surgery for type 2 diabetes be considered earlier and for patients with lower BMIs, based on evidence of lower mortality, decreased rate of malignancy, and better glycemic control durability.[23,24] Others hesitate to recommend widespread use of a costly surgical procedure with inherent risks without support from large, prospective randomized clinical trials. The American Diabetes Association and the National Institutes of Health have been conservative about application of bariatric surgery in treatment algorithms for type 2 diabetes.[1] Emerging data suggest that recurrence of type 2 diabetes is associated with weight regain after bariatric surgery.[25] This study provides an indication of the potential benefit as well as the risks of adding gastric bypass to best lifestyle and medical management for diabetes. However, to determine the long-term cardiovascular effects of bariatric surgery would require a large-scale, multiinstitutional study.

Strengths of this study include randomized design, multiple sites, surgeons, and an intention-to-treat comparison to a group treated with best practices for lifestyle and pharmacological management, as well as examining gastric bypass in combination with existing best medical practices. A high level of participant follow-up was obtained. Weaknesses include relatively small sample size, use of surrogate end points for cardiovascular disease, and evaluation of the primary outcome at 1 year. Because recruitment emphasized participants with suboptimally controlled diabetes among patients whose BMI ranged from 30 to 40 and who were willing to attend the lifestyle program, generalizability of the study to patients with better control of their diabetes, those in other BMI ranges, or those less able to engage with lifestyle change treatment is uncertain.

It is important to comment that recruitment for the study with 4 participating clinical centers proved to be considerably more difficult than anticipated: for every patient enrolled in the study, an additional 21 potential candidates were screened.

## CONCLUSIONS

The Diabetes Surgery Study examined Roux-en-Y gastric bypass surgery as an adjunct to intensive behavioral intervention and intensive medical management using a composite primary end point of cardiovascular disease risk factors in the treatment of diabetes. This trial provides data about efficacy and safety for the first year of treatment.

The merit of gastric bypass treatment of moderately obese patients with type 2 diabetes depends on whether potential benefits make risks acceptable. Bariatric surgery can result in dramatic improvements in weight loss and diabetes control in moderately obese patients with type 2 diabetes who are not successful with lifestyle changes or medical management. The benefits of applying bariatric surgery must be weighed against the risk of serious adverse events.

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