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Lifestyle Intervention and Medical Management With vs Without Roux-en-Y Gastric Bypass and Control of Hemoglobin A_{1c}, LDL Cholesterol, and Systolic Blood Pressure at 5 Years in the Diabetes Surgery Study

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IMPORTANCE The Roux-en-Y gastric bypass is effective in achieving established diabetes treatment targets, but durability is unknown.

OBJECTIVE To compare durability of Roux-en-Y gastric bypass added to intensive lifestyle and medical management in achieving diabetes control targets.

DESIGN, SETTING, AND PARTICIPANTS Observational follow-up of a randomized clinical trial at 4 sites in the United States and Taiwan, involving 120 participants who had a hemoglobin A_{1c} (HbA_{1c}) level of 8.0% or higher and a body mass index between 30.0 and 39.9 (enrolled between April 2008 and December 2011) were followed up for 5 years, ending in November 2016.

INTERVENTIONS Lifestyle-intensive medical management intervention based on the Diabetes Prevention Program and LookAHEAD trials for 2 years, with and without (60 participants each) Roux-en-Y gastric bypass surgery followed by observation to year 5.

MAIN OUTCOMES AND MEASURES The American Diabetes Association composite triple end point of hemoglobin A_{1c} less than 7.0%, low-density lipoprotein cholesterol less than 100 mg/dL, and systolic blood pressure less than 130 mm Hg at 5 years.

RESULTS Of 120 participants who were initially randomized (mean age, 49 years [SD, 8 years], 72 women [60%]), 98 (82%) completed 5 years of follow-up. Baseline characteristics were similar between groups: mean (SD) body mass index 34.4 (3.2) for the lifestyle–medical management group and 34.9 (3.0) for the gastric bypass group and had hemoglobin A_{1c} levels of 9.6% (1.2) and 9.6% (1.0), respectively. At 5 years, 13 participants (23%) in the gastric bypass group and 2 (4%) in the lifestyle-intensive medical management group had achieved the composite triple end point (difference, 19%; 95% CI, 4%-34%; $P = .01$). In the fifth year, 31 patients (55%) in the gastric bypass group vs 8 (14%) in the lifestyle–medical management group achieved an HbA_{1c} level of less than 7.0% (difference, 41%; 95% CI, 19%-63%; $P = .002$). Gastric bypass had more serious adverse events than did the lifestyle–medical management intervention, 66 events vs 38 events, most frequently gastrointestinal events and surgical complications such as strictures, small bowel obstructions, and leaks. Gastric bypass had more parathyroid hormone elevation but no difference in B_{12} deficiency.

CONCLUSIONS AND RELEVANCE In extended follow-up of obese adults with type 2 diabetes randomized to adding gastric bypass compared with lifestyle and intensive medical management alone, there remained a significantly better composite triple end point in the surgical group at 5 years. However, because the effect size diminished over 5 years, further follow-up is needed to understand the durability of the improvement.

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Correcting the systemic disorder of type 2 diabetes to reduce microvascular and cardiovascular risks requires not only glycemic control but also management of blood pressure and lipids.[1] Clinical trials showing improved glycemic control without improved cardiovascular risk and pharmaceutical trials finding improved cardiovascular outcomes possibly unrelated to glycemic control have both emphasized end points beyond blood glucose control.[2] The value of a full range of clinical outcomes in treating diabetes has long been recognized by physicians and by the American Diabetes Association.[3]

Weight loss improves the diabetes metabolic disorder, but behavioral and pharmaceutical strategies have not been broadly successful. With bariatric surgery, it became possible to determine whether greater, more sustained weight loss could improve diabetes treatment. Some observations suggested that bariatric surgery might have salutary effects independent of weight loss.[4] Bariatric surgery has improved controlled glycemia in recent randomized trials and was associated with diabetes remission at 2 to 3 years.[5-10] However, the positive effect on remission resulting from surgery may wane with time.[5,6,10,11]

The Diabetes Surgery Study assesses the Roux-en-Y gastric bypass effect on attainment of the 2008 American Diabetes Association's (ADA's) composite triple end point for diabetes of hemoglobin A_{1c} (HbA_{1c}) <7.0%, low-density lipoprotein cholesterol (LDL-C) less than 100 mg/dL, and systolic blood pressure (BP)<130 mm Hg.[12] To increase generalizability, participants were enrolled from multiple sites with multiple treatment teams, including Taiwan.[13] Participants had poorly controlled diabetes and mild to moderate obesity. All participants received intensive lifestyle intervention, based on the Diabetes Prevention Program and LookAHEAD Study, and intensive medical management for the first 2 years. Results at 1 year,[12] 2 years,[14] and 3 years[10] have been published. Reported herein are the 5-year outcomes, focusing on durability of composite end point treatment effects, weight loss, diabetes remission, and adverse events.

Key Points

Question What are the 5-year outcomes of Roux-en-Y gastric bypass compared with lifestyle and medical management in obese adults with type 2 diabetes?

Findings This observational follow-up of a randomized clinical trial that included 120 participants, 5 years after the intervention found that significant improvement continued in a composite outcome that included glycosylated hemoglobin level, low-density lipoprotein level, and systolic blood pressure (23% vs 4%), but the magnitude of difference decreased over time in follow-up.

Meaning Roux-en-Y gastric bypass maintained significant differences from lifestyle and medical management in outcomes after 5-year, but with diminishing effectiveness.

Methods

The study was conducted at the University of Minnesota, Columbia University Medical Center, National Taiwan University Hospital and Min Sheng General Hospital (together called Taiwan), and the Mayo Clinic. Each site obtained institutional review board approval and written informed consent from each participant (the trial protocol is available in Supplement 1).

The complete list of inclusion and exclusion criteria has been published.[12] Briefly, key inclusion criteria included HbA_{1c} of 8.0% or higher despite having clinical care for at least 6 months for type 2 diabetes; body mass index (BMI) between 30.0 and 39.9, calculated as weight in kilograms divided by height in meters squared; and stated willingness and ability to accept randomization and follow the full treatment protocol (**Figure 1**). Details of the recruitment efforts are described elsewhere.[13]

Interventions

All participants were offered 2 years of lifestyle intervention and intensive medical management. Participants were randomized 1:1 (randomization details are described elsewhere[12]) to receive gastric bypass in addition to lifestyle and optimal medical treatment. Standardized Roux-en-Y bypass was performed.[12] The 2-year lifestyle intervention was based on protocols from 2 successful clinical trials: the Diabetes Prevention Program[15] and the Look AHEAD study.[16] Over the first year, the median number of lifestyle modules delivered was 32 for the lifestyle-medical management group and 27 for the gastric bypass group. Between years 1 and 2, the median number of modules was 5 and 7, respectively. Clinically important adverse event information was collected at each visit.

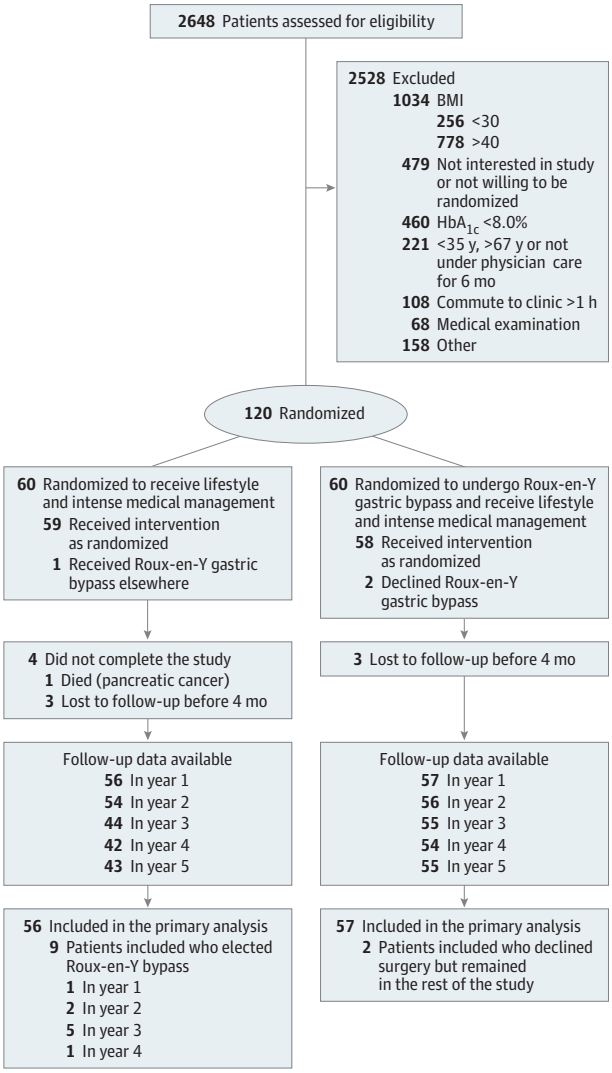
During the 2-year intervention period, participants were instructed to record weight, food intake, and daily exercise. Participants in both groups were prescribed 325 minutes of moderate-intensity physical activity per week and met regularly with a trained interventionist to facilitate weight management. Visits with an endocrinologist occurred monthly for 6 months, at least quarterly for the next 6 months, and quarterly through the second year. The intensive medical management protocol included the provision of a protocol-based optimal drug therapy to control hyperglycemia, cholesterol, and hypertension.

After 2 years, all study-supported interventions ceased and participants returned to usual care with their primary physician. Study endocrinologists evaluated participants during clinic visits at 3, 4, and 5 years and obtained interim histories of adverse events. Participants were encouraged to increase medications, nutritional supplementation, and dietary control if adherence or vitamin and mineral deficiency were deemed to be an issue. Prescriptions were written as necessary. During years 3 to 5, study coordinators contacted participants midyear to maintain their connection to the study and to obtain interim data on severe adverse events.

End Points

The primary outcome was attainment at the year-1 visit of a prespecified composite outcome: simultaneous achievement of HbA_{1c} of less than 7.0%, LDL-C of less than 100 mg/dL

Figure 1. Flow Diagram of Patients Through the Diabetes Surgery Study



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

(to convert cholesterol levels from mg/dL to mmol/L, multiply by 0.0259), and systolic BP of less than 130 mm Hg. Secondary outcomes included durability of achieving the composite triple end point and continuous measures of HbA_{1c}, LDL-C, and systolic BP; weight loss; high-density lipoprotein cholesterol (HDL-C), diastolic BP, medication usage, and adverse events.

Post hoc analyses were performed. Full diabetes remission was defined using the ADA consensus statement, which required HbA_{1c} levels of 6.0% at consecutive annual visits, and no use of antihyperglycemic medication at either visit.[17] The partial diabetes remission definition replaced HbA_{1c} levels of 6.0% with 6.5% at the same time points.[17]

This report at 5 years includes data on serious adverse events, elevated parathyroid hormone, vitamin B_{12} deficiencies, and anemia. Queries regarding possible serious adverse events (defined using standard US Food and Drug Administration criteria) were part of every study visit and telephone contact.

Statistical Analysis

The primary effectiveness analyses were based on an intention-to-treat longitudinal mixed model.[18] Secondary as-treated analyses were carried out for key end points to elucidate relationships between variables. A post hoc analysis of crossover participants was also performed.

A repeated-measures approach was used, using mixed models with a random intercept for participant. The repeated-measures approach uses all available follow-up data (including unbalanced data) and treats missing data as missing at random. All participants with at least 1 year of follow-up data are reflected in the estimates.

Dichotomous outcomes were analyzed using longitudinal logistic mixed models stratified by site; continuous outcomes were analyzed using linear mixed models adjusted for site. All models were adjusted for continuous baseline values, as appropriate. For dichotomous outcomes, the estimated log odds (95% CIs) for success were computed by SAS PROC GLIMMIX. For each treatment group separately, percent success and the upper and lower bounds for its 95% CI were obtained by applying an inverse logit transformation to the log odds supplied by PROC GLIMMIX. The estimated treatment difference was computed as the percentile difference between estimates. Approximate 95% CIs for the estimated percentile treatment difference were also computed assuming that the probabilities for success in each treatment group were independent, normally distributed random variables, with standard error equal to the width of their estimated 95% CIs divided by 2*1.96. A sensitivity test was performed for site effects by treating site as a random effect rather than as a fixed effect. Because fitted models were used to report the outcomes, estimated counts for outcome variables were computed as the estimated rate multiplied by the count of the base population, rounded to the nearest integer.

Secondary analyses excluded crossovers in years 2 to 4 and categorized first-year crossovers based on their chosen treatment, but otherwise used the same longitudinal mixed models as described above. Because the secondary analyses were unadjusted for multiple comparisons, these analyses should be interpreted as exploratory. Regressions were adjusted or stratified for use of bariatric surgery (as treated) and site.

The Clopper-Pearson method[19] (exact binomial CIs) was used to examine remission in the lifestyle-medical management group, where limited remissions made regressions unworkable. Exact binomial methods were also used to test for treatment differences in remission rates, and for indicator variables related to medication use.

Directly observed data for all 120 participants were included in the analysis of adverse events and are reported on an as treated basis. Recording of adverse events were as follows: Years 1 and 2: clinically important events; year 3 through 5: all serious adverse events. All serious adverse events are reported based on years since randomization, including those for all

participants who were randomized to lifestyle and medical management but later elected to undergo gastric bypass surgery.

All analyses were conducted using SAS/STAT (2014, SAS Institute Inc). All analyses were 2-sided and used a significance threshold of .05.

Results

Between April 2008 and December 2011, 120 participants were enrolled and were randomized 1:1 to receive either the lifestyle-medical management intervention alone (n = 60) or gastric bypass surgery plus the lifestyle intervention (n = 60). Excluding the 6 participants lost to follow-up prior to the 1-year visit and the 1 participant who died of pancreatic cancer, 56 participants in the lifestyle-medical management and 57 participants in the gastric bypass groups were included in the primary analysis (Figure 1). Baseline characteristics (**Table 1**) were similar between groups except that insulin usage was lower in the lifestyle-medical management group (43%) than in the gastric bypass (61%) group. A total of 11 participants crossed over (Figure 1). Two participants randomized to gastric bypass declined surgery but participated in the rest of the study. Nine participants randomized to the lifestyle-medical management group elected gastric bypass an average of 2 years after randomization and remained in the study. Five-year data were obtained from 43 participants (73%) randomized to lifestyle-medical management and 55 participants (92%) randomized to gastric bypass.

Primary End Point

In the first year after randomization, an estimated 28 participants (50%) in the gastric bypass group and 9 (16%) in the lifestyle-medical management group achieved the composite triple end point (difference, 34%; 95% CI, 14%-54%; $P = .003$). By 5 years, an estimated 13 participants (23%) in the gastric bypass group and 2 (4%) in the of lifestyle-medical management group achieved the composite triple end point (difference, 19%; 95% CI, 4%-34%; $P = .01$). Success in achieving the primary end point was reduced in both groups from year 1 to year 3, from 50% to 23% in gastric bypass group and from 16% to 4% in lifestyle-medical management group), but remained stable for years 3 through 5 (**Table 2**). There were no material differences in fitted outcomes when site was treated as a random effect rather than as a fixed effect. Results on an as-treated basis (eTable 2 in Supplement 2) were similar: 14 participants (26%) who had surgery during the first year and 3 participants (8%) who never had surgery achieved the triple end point at 5 years (difference, 18%; 95% CI, 6%-32%; $P = .04$).

Components of the Primary End Point

At 5 years, an estimated 31 participants (55%) in the gastric bypass group vs 8 participants (14%) in the lifestyle-medical management group achieved HbA_{1c} of less than 7.0% (difference, 41%; 95% CI, 19%-63%; $P = .002$; Table 2). Using directly observed data over the 5 years of follow-up, 29 of the 42 participants in the gastric bypass group who had achieved an HbA_{1c} of less than 7.0% at 1 year maintained that treatment goal at 5 years. Among the lifestyle-medical management group, 7 of the 18 who achieved the HbA_{1c} goal at year 1 were still at goal at year 5. For those participants achieving an HbA_{1c} of less than 7.0% at year 1, the odds ratio (OR) of durability at 5 years vs 1 year was 0.25 (95% CI 0.09, 0.68) for gastric bypass vs 0.41 (95% CI, 0.14-1.25) for the lifestyle-medical management

Table 1. Baseline Data

Demographics	Lifestyle and Intensive Medical Management (n = 56)	Roux-en-Y Gastric Bypass (n = 57)
Age, mean (SD), y	48 (8)	49 (9)
Women, No. (%)	31 (55)	37 (65)
Race/ethnicity (self-reported), No. (%)		
Non-Hispanic white	27 (48)	31 (54)
East Asian	17 (30)	16 (28)
Non-Hispanic black	6 (11)	5 (9)
Hispanic	3 (5)	3 (5)
Native American	1 (2)	2 (4)
Other	2 (4)	0 (0)
General medical		
BMI, mean (SD)	34.4 (3.2)	34.9 (3.0)
<35, No. (%)	32 (57)	35 (61)
Weight, mean (SD), kg	99 (14)	98 (17)
Waist circumference, mean (SD), cm	114 (12)	114 (10)
Blood pressure, mean (SD), mm Hg		
Systolic	132 (14)	127 (15)
Diastolic	79 (10)	78 (12)
Years since diabetes diagnosis	9.1 (5.6)	8.8 (6.1)
Laboratory values (serum), mean, (SD)		
HbA1c, %	9.6 (1.2)	9.6 (1.0)
Cholesterol, mg/dL		
LDL	102 (41)	102 (35)
HDL	41 (8)	41 (11)
Total	186 (42)	181 (38)
Triglycerides, mg/dL	211 (112)	200 (105)
Creatinine, mg/dL	0.80 (0.19)	0.81 (0.20)
Fasting C-peptide, ng/mL	3.0 (1.5)	2.8 (1.9)
Postmeal C-peptide, ng/mL	4.7 (2.2)	4.5 (2.6)
Fasting glucose, mg/dL	205 (54)	222 (75)
Medicines, No. (%)		
Insulin	24 (43)	35 (61)
Other glycemic medicines	53 (95)	49 (86)
Dyslipidemia medicines	38 (68)	36 (63)
Blood pressure medicines	41 (73)	38 (67)
Medications for control of glycemia, dyslipidemia, and blood pressure, mean (SD), No.	4.3 (1.5)	4.1 (1.9)
Clinical site, No. (%)		
University of Minnesota	24 (43)	24 (42)
National Taiwan University Hospital and Min-Sheng General Hospital	16 (29)	16 (28)
Columbia University Medical Center	13 (23)	13 (23)
Mayo Clinic	3 (5)	4 (7)

Abbreviations: BMI, body mass index; HbA_{1c}, Hemoglobin A_{1c}; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 2. Primary Outcomes in Years 1 Through 5[a]

Outcome, Follow-up y	Percent Success, % (95% CI)		Difference, % (95% CI)[b]	Estimated Odds Ratio (95% CI)[c]	*P* Value
	Lifestyle and Intensive Medical Management	Roux-en-Y Gastric Bypass			
Triple End Point[d]					
1[e]	16 (8 to 31)	50 (34 to 66)	34 (14-54)	5.13 (1.77 to 14.86)	.003
2	11 (5 to 24)	46 (30 to 63)	35 (16-54)	6.86 (2.18 to 21.59)	.001
3	6 (2 to 17)	23 (13 to 39)	17 (2-32)	5.12 (1.22 to 21.53)	.03
4	2 (0 to 11)	22 (11 to 37)	20 (6-34)	10.99 (1.84 to 65.57)	.01
5	4 (1 to 14)	23 (13 to 39)	19 (4-34)	7.45 (1.56 to 35.51)	.01
HbA_{1c} <7%					
1	29 (15 to 47)	83 (67 to 92)	54 (34 to 74)	12.29 (3.78 to 39.96)	<.001
2	18 (9 to 35)	85 (69 to 93)	67 (49 to 85)	24.42 (7.03 to 84.90)	<.001
3	14 (5 to 30)	58 (38 to 76)	44 (21 to 67)	8.89 (2.46 to 32.10)	.001
4	6 (2 to 18)	59 (39 to 76)	53 (33 to 73)	21.51 (5.00 to 92.57)	<.001
5	14 (6 to 31)	55 (36 to 73)	41 (19 to 63)	7.51 (2.07 to 27.28)	.002
Systolic BP <130 mm Hg					
0	45 (31 to 58)	51 (37 to 64)	6 (−13 to 25)	1.28 (0.61 to 2.69)	
1	85 (71 to 93)	89 (78 to 95)	4 (−10 to 18)	1.52 (0.46 to 4.98)	.49
2	78 (62 to 88)	88 (76 to 95)	10 (−6 to 26)	2.20 (0.70 to 6.95)	.18
3	56 (38 to 73)	79 (64 to 89)	23 (1 to 45)	2.90 (0.99 to 8.48)	.05
4	65 (45 to 80)	79 (63 to 89)	14 (−8 to 36)	2.04 (0.68 to 6.13)	.20
5	49 (31 to 68)	73 (56 to 85)	24 (0 to 48)	2.71 (0.95 to 7.78)	.06
LDL-C<100 mg/dL					
0	54 (40 to 67)	51 (37 to 64)	−3 (−21 to 16)	0.90 (0.43 to 1.88)	.78
1	74 (58 to 86)	84 (70 to 92)	10 (−8 to 28)	1.77 (0.60 to 5.20)	.30
2	77 (61 to 88)	81 (67 to 90)	4 (−14 to 22)	1.28 (0.43 to 3.79)	.65
3	56 (37 to 73)	73 (56 to 85)	17 (−6 to 40)	2.10 (0.72 to 6.09)	.17
4	54 (34 to 72)	69 (52 to 83)	15 (−10 to 40)	1.95 (0.66 to 5.78)	.23
5	47 (29 to 67)	77 (61 to 88)	30 (7 to 53)	3.66 (1.22 to 11.00)	.02

Abbreviations: HbA_{1c}, hemoglobin A_{1c}; LDL-C, low-density lipoprotein cholesterol; BP, blood pressure.

SI conversion factor: To convert LDL-C from mg/dL to mmol/L, multiply by 0.0259.

[a] For 113 patients (excluding 6 without 12-mo data and 1 who died), fitted values were derived from a longitudinal mixed model that was adjusted for baseline values and site. Treating patient as a random effect.

[b] For dichotomous variables in years 1 through 5, the percent risk (95% CI) is computed as the inverse logit of the estimated odds (95% CI). The percentile difference in risks is the estimated treatment difference. The estimated percentile difference is the difference in estimates. The estimated 95% CI for percentile differences requires 2 additional assumptions: the within-group estimated probability of success is normally distributed; and estimated probabilities for IMM lifestyle vs Roux-en-Y gastric bypass are statistically independent.

[c] Baseline values and 95% CIs were computed assuming normality. Odds ratios (95% CIs) were computed using an unadjusted logistic regression and compare Roux-en-Y against lifestyle and medical management.

[d] The triple end point indicates simultaneous achievement of HbA_{1c} concentration of less than 7.0%, systolic BP of less than 130 mm Hg, and LDL-C levels of less than 100 mg/dL.

[e] This article reports fitted values based on data from all 5 years, and thus differs from what was reported in the first-year article, which was based on data available at the time. Fitted values take into account missing data and are thus consistent with an intent-to-treat analysis. The 5-year article is based on the patients with 1-year visits, excluding 1 patient who died shortly after the year-1 visit. The longitudinal mixed model that formed the backbone for this article modeled changes from the year-1 visit; it was not practical to include patients without year-1 data. The 1-year article focused on early outcomes in the 120 randomized patients, using multiple imputation to fill in data for any missing 12-month visits. See eTable 2A for observed date in the Supplement 2.

group. Attainment of the goal of systolic BP of less than 130 mm Hg in the gastric bypass group dropped from 89% (95% CI, 78%-95%) to an estimated 42 participants (73%; 95% CI, 56%-85%), while systolic BP goal attainment in the lifestyle-medical management group fell from 85% (95% CI, 71%-93%) at 1 year to an estimated 27 participants (49%; 95% CI, 31%-68%) at 5 years (Table 2). Recognizing the greater emphasis being placed on individualized targets for diabetes management, a goal of systolic BP of less than 140 mm Hg was also assessed; 92% of gastric bypass and 86% of lifestyle-medical management participants met that target at 5 years (OR, 1.92; 95% CI, 0.47-7.91; no significant difference; **Table 3**). There was a significant difference in achievement of LDL-C of less than 100 mg/dL only in the fifth year, estimated 44 (77%) in gastric bypass and 26 (47%) in lifestyle-medical management (OR, 3.66; 95%, CI; 1.22-11.00; P = .02) but not at other time points (Table 2).

Group differences between components of the composite triple end point were also examined as continuous variables instead of evaluating achievement of threshold values (**Figure 2** and **Table 4**). At 5 years, the mean HbA_{1c} was 7.1% (95% CI, 6.7%-7.5%) in the gastric bypass group compared with 8.7%

Table 3. Post Hoc Outcomes in Years 1 Through 5

Outcome[a]	Success or Yes, % (95% CI)		Difference, % (95% CI)	Estimated Odds Ratio (95% CI)[b]	*P* Value
	Lifestyle and Intensive Medical Management	Roux-en-Y Gastric Bypass			
HbA_{1c} <6.0%					
1	5 (2 to 16)	45 (26 to 65)	40 (19 to 61)	13.94 (3.17 to 61.28)	.001
2	3 (1 to 11)	35 (18 to 57)	32 (12 to 52)	18.25 (3.32 to 100.4)	.001
3	4 (1 to 16)	20 (9 to 39)	16 (−1 to 33)	5.52 (0.97 to 31.49)	.05
4	3 (1 to 13)	15 (6 to 32)	12 (−2 to 26)	6.51 (0.92 to 46.06)	.06
5	3 (0 to 13)	11 (4 to 26)	8 (−5 to 21)	4.62 (0.64 to 33.13)	.13
Remission					
Full or partial[c]					
2	0 (0 to 7)	36 (16 to 61)	36 (13 to 59)	Not available	<.001
3	0 (9 to 8)	35 (16 to 60)	35 (13 to 57)	Not available	<.001
4	5 (1 to 16)	32 (14 to 57)	27 (4 to 50)	Not available	<.001
5	5 (1 to 16)	16 (6 to 36)	11 (−6 to 28)	Not available	.003
Full[c]					
2	0 (0 to 7)	16 (7 to 33)	16 (3 to 29)	Not available	<.001
3	0 (9 to 8)	12 (5 to 28)	12 (0 to 24)	Not available	.002
4	0 (0 to 8)	11 (4 to 25)	11 (0 to 22)	Not available	.004
5	0 (0 to 8)	7 (2 to 19)	7 (−2 to 16)	Not available	.02
Fasting Glucose <100 mg/dL					
0	2 (−2 to 5)	0	−2 (−5 to 2)	Not available	
1	11 (5 to 24)	44 (28 to 62)	33 (14 to 52)	6.52 (1.98 to 21.46)	.002
2	8 (3 to 20)	31 (18 to 49)	23 (5 to 41)	5.30 (1.42 to 19.81)	.01
3	7 (2 to 21)	20 (10 to 39)	13 (−4 to 30)	3.61 (0.73 to 17.96)	.12
4	4 (1 to 16)	12 (5 to 26)	8 (−5 to 21)	3.39 (0.55 to 21.03)	.19
5	4 (1 to 15)	25 (13 to 43)	21 (4 to 38)	8.78 (1.52 to 50.61)	.02
Using Insulin					
0	43 (29 to 56)	61 (48 to 74)	19 (0 to 37)	2.12 (1.00 to 4.50)	
1	43 (30 to 57)	18 (9 to 30)	−25 (−42 to −8)	0.10 (0.02 to 0.54)	.004
2	44 (31 to 59)	18 (9 to 30)	−26 (−44 to −9)	0.08 (0.01 to 0.46)	.004
3	45 (30 to 61)	15 (6 to 27)	−30 (−49 to −11)	0.04 (0.01 to 0.28)	.001
4	36 (22 to 52)	13 (5 to 25)	−23 (−41 to −5)	0.06 (0.01 to 0.41)	.01
5	37 (23 to 53)	15 (6 to 27)	−22 (−40 to −4)	0.07 (0.01 to 0.44)	.02
Using Noninsulin Diabetes Medication					
0	95 (89, 100)	86 (77 to 95)	−9 (−20,2)	0.35 (0.09 to 1.38)	
1	98 (90 to 100)	35 (23 to 49)	−63 (−77 to −49)	0.00 (0.00 to 0.02)	<.001
2	93 (82 to 98)	43 (30 to 57)	−50 (−66 to −34)	0.02 (0.00 to 0.12)	<.001
3	84 (70 to 93)	42 (29 to 56)	−42 (−60 to −24)	0.06 (0.01 to 0.27)	<.001
4	90 (77 to 97)	41 (28 to 55)	−49 (−66 to −32)	0.02 (0.00 to 0.14)	<.001
5	88 (75 to 96)	42 (29 to 56)	−46 (−63 to −29)	0.04 (0.01 to 0.19)	<.001
Systolic BP <140 mm Hg					
0	70 (57 to 82)	81 (70 to 91)	11 (−5 to 27)	1.82 (0.76 to 4.35)	
1	96 (87 to 99)	97 (89 to 99)	1 (−7 to 9)	1.49 (0.24 to 9.07)	.67
2	92 (81 to 97)	97 (88 to 99)	5 (−5 to 15)	2.38 (0.44 to 12.71)	.31
3	82 (65 to 92)	97 (88 to 99)	15 (0 to 30)	5.90 (1.17 to 29.76)	.03
4	81 (63 to 92)	97 (88 to 99)	16 (0 to 32)	6.39 (1.25 to 32.61)	.03
5	86 (69 to 94)	92 (80 to 97)	6 (−9 to 21)	1.92 (0.47 to 7.91)	.37

(continued)

Table 3. Post Hoc Outcomes in Years 1 Through 5 (continued)

Outcome[a]	Success or Yes, % (95% CI)		Difference, % (95% CI)	Estimated Odds Ratio (95% CI)[b]	*P* Value
	Lifestyle and Intensive Medical Management	Roux-en-Y Gastric Bypass			
Using Antihypertensives					
0	73 (61 to 85)	67 (54 to 79)	−7 (−24 to 11)	0.73 (0.33 to 1.64)	
1	71 (58 to 83)	37 (24 to 51)	−34 (−52 to −16)	0.02 (0.00 to 0.13)	<.001
2	63 (49 to 76)	39 (26 to 53)	−24 (−43 to −5)	0.11 (0.02 to 0.55)	.01
3	61 (45 to 76)	38 (25 to 52)	−23 (−44 to −2)	0.14 (0.03 to 0.73)	.03
4	62 (46 to 76)	44 (31 to 59)	−18 (−39 to 3)	0.19 (0.03 to 1.08)	.10
5	67 (51 to 81)	47 (34 to 61)	−20 (−40 to 0)	0.14 (0.02 to 0.84)	.06
Using Dyslipidemia Medication					
0	68 (55 to 80)	63 (50 to 76)	−5 (−23 to 130)	0.81 (0.37 to 1.77)	
1	64 (50 to 77)	37 (24 to 51)	−27 (−46 to −8)	0.17 (0.04 to 0.61)	.005
2	69 (54 to 80)	43 (30 to 57)	−26 (−45 to −7)	0.17 (0.04 to 0.63)	.01
3	48 (32 to 63)	36 (24 to 50)	−12 (−32 to 8)	0.40 (0.10 to 1.58)	.31
4	45 (30 to 61)	43 (29 to 57)	−2 (−23 to 19)	0.76 (0.19 to 3.03)	.84
5	53 (38 to 69)	40 (27 to 54)	−13 (−34 to 8)	0.34 (0.09 to 1.36)	.22

Abbreviations: BP, blood pressure; HbA_{1c} to hemoglobin A_{1c}.

[a] For 113 patients (excluding 6 without 12-month data and 1 who died), values were fitted from a longitudinal mixed model and were adjusted for baseline values and site, treating patient as a random effect (eTable 2C in Supplement 2).

[b] Compares Roux-en-Y against lifestyle and medical management.

[3] Full diabetes remission is defined as an HbA_{1c} level of less than 6.0% at the 4- and 5-year visits and no use of antihyperglycemic medication at either visit. Partial diabetes remission definition replaced the HbA_{1c} level of 6.0% with 6.5% at the same time points.

(95% CI, 8.3%-9.1%) in the lifestyle-medical management group (Figure 2). The net treatment difference in HbA_{1c} at 5 years was 1.6% (95% CI, 1.0%-2.2%; $P < .001$) lower HbA_{1c} in the gastric bypass group. Both groups had a substantial decrease in HbA_{1c} in the first year, more so in the gastric bypass group, followed by gradual rebounds that were nearly equal between groups. Differences in fasting glucose levels (Table 4) were observed at all time points between the 2 groups, for example, a 41-mg/dL difference in year 1 and a 36-mg/dL difference in year 5. Both groups had some reduction of treatment effect in years 2 and 3, followed by stable mean values in years 4 and 5.

There were no significant differences in systolic blood pressure over the 5 years (Figure 2). There were statistically significant differences in mean LDL-C (Figure 2), HDL-C, and total cholesterol levels and triglycerides in each case favoring the gastric bypass group (Table 4). Differences emerged at 2 and 3 years for total cholesterol and LDL-C levels, respectively. For the other lipids, differences were present at each year of follow-up (Table 4).

Medications

At baseline, gastric bypass and lifestyle-medical management participants required a mean (SD) number of medications of 4.1 (1.9) and 4.3 (1.5), respectively, to control glucose, lipid levels, and blood pressure. At 5 years, medications for the composite triple end point had been reduced to 2.0 in the gastric bypass group compared with an increase to 4.4 in the lifestyle-medical management group (difference, 2.4; 95% CI, 1.7-3.0; $P < .001$). Insulin use was less common in the gastric bypass group at 5 years than in the lifestyle-medical management group: 15% vs 37% (difference, 22%; 95% CI, 4%-40%; $P = .02$), with similar differences in each previous year of follow-up (Table 3). One participant randomized to the gastric bypass group was later found to have adult-onset type 1 diabetes. At 5 years, noninsulin diabetes medications were used in an estimated 24 participants (42%) in the gastric bypass group compared with 49 participants (88%) in the lifestyle-medical management group (difference, 46%; 95% CI, 29%-63%; $P < .001$; Table 4).

Estimated antihypertensive medication use was approximately 20 to 30 percentage points less in the gastric bypass group at all time points, but not significantly different by the fifth year. Use of dyslipidemia medications followed a pattern similar to antihypertensive medications.

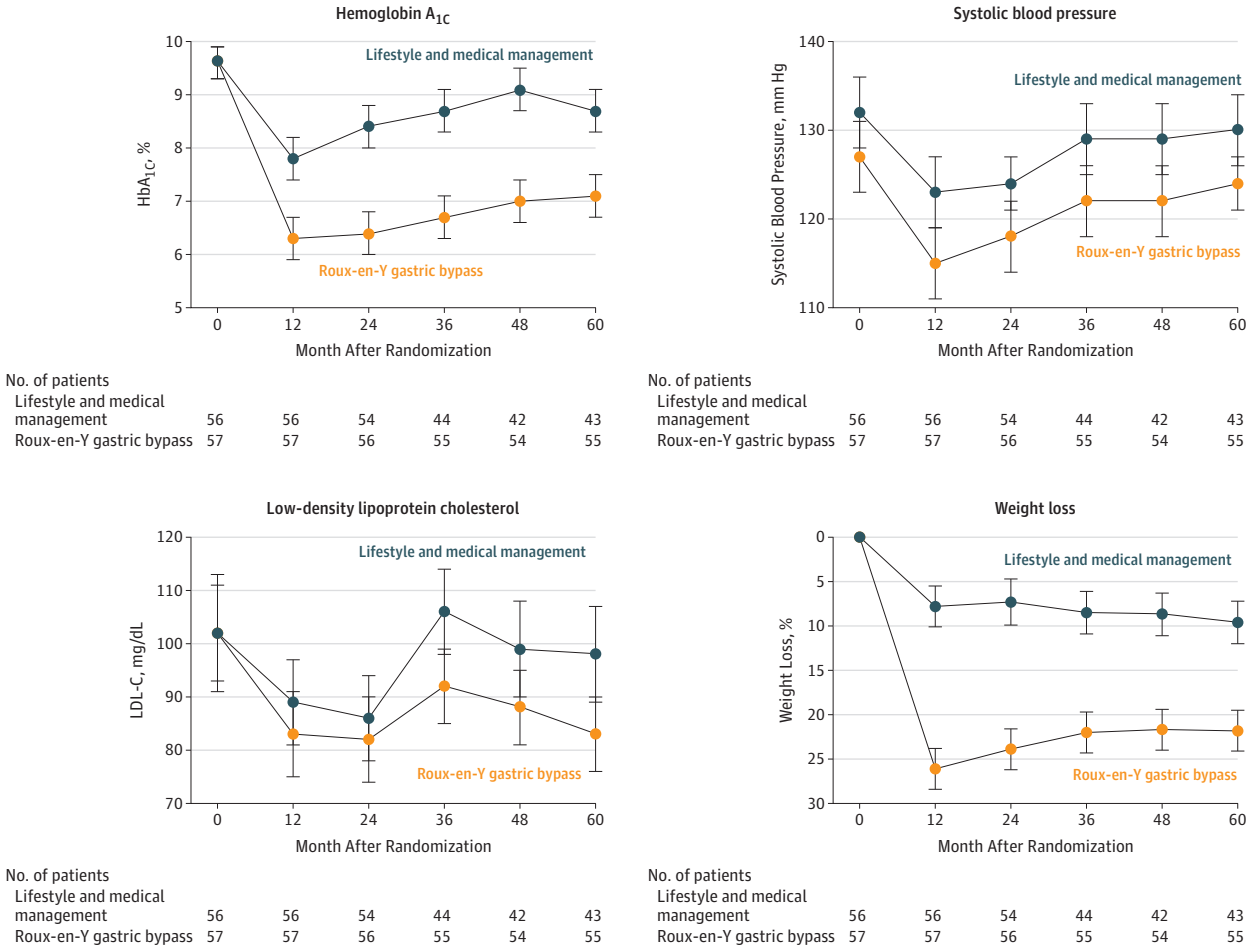
Weight Loss

At 5 years, participants in the gastric bypass group had a mean weight loss of 21.8% vs 9.6% in lifestyle-medical management group (difference, 12.2%; 95% CI, 8.9%-15.5%; **Figure 3**). Weight loss in the gastric bypass was 26.1% at 1 year (95% CI, 23.8%-28.4%), and decreased to 21.8% at 5 years (95% CI, 19.5%-24.1%). By randomization assignment, the lifestyle-medical management group mean weight loss increased from 7.8% at 1 year (95% CI, 5.5%-10.1%) to 9.6% at 5 years (95% CI, 7.2%-12.0%). In a post hoc analysis, crossovers in the first year were categorized with their chosen treatment and crossovers in later years were removed from the analysis. With these adjustments, cumulative percent weight loss at 5 years was 22.9% (95% CI, 21.1%-24.8%) in gastric bypass and 6.3% (95% CI, 4.2%-8.4%) in the lifestyle-medical management group.

Diabetes Remission

Neither partial nor full remission occurred with the lifestyle-medical management group at any time, except for 2 participants who elected gastric surgery during the third year (Table 3). Partial remission, defined as an HbA_{1c} level of less than 6.5% at all visits for 1 year without taking any glycemic medications, occurred in estimated 21 participants (35%) in the gastric bypass group at 2 years, but the rate of partial remission decreased to 9 (16%) by year 5. Full remission, defined as an HbA_{1c} level of less than 6.0% at all visits for 1 year without

Figure 2. Outcomes Over Time



Point estimates represent fitted values from longitudinal mixed models. The 0 time point represents randomization. Error bars indicate 95% CI; LDL-C, low-density lipoprotein cholesterol (to convert from mg/dL to mmol/L, multiply by 0.0259). The *P* value for difference is .01.

taking any glycemic medications, was achieved in an estimated 9 participants (16%) in the gastric bypass group at 2 years but declined to 4 (7%) at year 5.

Adverse Events

Adverse events in years 1 to 3 were previously reported in detail.[10,14] Assigning complications as treated and including crossovers in the as-treated group, the gastric bypass group experienced 16 additional adverse events from years 3 to 5 and an additional 14 adverse events occurred among participants who did not undergo gastric bypass, for a total of 66 and 38 events at 5 years in each group, respectively (**Table 5**). The most common adverse events were 14 episodes of surgical complications in the gastric bypass group, and 15 and 16 gastrointestinal events in the gastric bypass and lifestyle-medical management groups, respectively. Bone fractures had been previously reported in the gastric bypass group but were not seen in years 3 to 5. Details of the types of adverse events are reported in eTable 4 in Supplement 2.

Parathyroid hormone, vitamin B_{12}, and hemoglobin values were available at 5 years. Data were missing for 14 of 98 participants who had other 5-year data. For the remaining 84 participants, elevated parathyroid hormone was present in 24 participants (46%) in the gastric bypass group and 6 (19%) in the lifestyle-medical management group (*P* = .02). Vitamin B_{12} deficiency was present in 2 participants (4%) in the gastric bypass group and 1 (3%) in the lifestyle-medical management group. Three participants (6%) in the gastric bypass group had anemia vs none in the lifestyle-medical management group.

Crossover Data

Outcomes for participants who did not maintain their randomization assignment for the duration of the study are summarized in the appendix (eTable 3 in the Supplement 2). A total of 9 of 60 participants (15%) randomized to the intensive medical management group elected to have bariatric surgery elsewhere, 8 of whom elected to do so after the first year. Of those, 1 met the composite end point at 5 years. By 5 years, their mean (SD) HbA_{1c} concentration was 7.2% (1.3); LDL-C levels, 104 mg/dL (32 mg/dL); systolic BP, 127 mm Hg (24 mm Hg); and percent weight loss, 22% (8.5%). In addition, 2 of 60

Table 4. Secondary Outcomes in Years 1 Through 5

Outcomes[a]	Mean (95% CI)[b] Lifestyle and Intensive Medical Management	Mean (95% CI)[b] Roux-en-Y Gastric Bypass	Difference (95% CI)[c]	*P* Value
BMI				
0	34.4 (33.5 to 35.2)	34.9 (34.1 to 35.7)	0.5 (−0.6 to 1.7)	
1	31.6 (30.8 to 32.4)	25.8 (25.09 to 26.6)	−5.8 (−7.0 to −4.7)	<.001
2	31.9 (31.0 to 32.7)	26.8 (25.7 to 27.4)	−5.3 (−6.5 to −4.1)	<.001
3	31.5 (30.7 to 32.4)	27.3 (26.5 to 28.1)	−4.2 (−5.4 to −3.0)	<.001
4	31.5 (30.6 to 32.3)	27.5 (26.5 to 28.3)	−4.0 (−5.2 to −2.8)	<.001
5	31.1 (30.3 to 32.0)	27.4 (26.5 to 28.2)	−3.7 (−4.9 to −2.5)	<.001
Fasting Glucose, mg/dL				
0	205 (190 to 219)	222 (202 to 241)	17 (−8 to 41)	
1	153 (138 to 167)	111 (97 to 125)	−41 (−61 to −21)	<.001
2	172 (157 to 186)	113 (100 to 127)	−58 (−78 to −38)	<.001
3	179 (163 to 196)	131 (116 to 146)	−49 (−71 to −26)	<.001
4	182 (167 to 198)	129 (114 to 143)	−54 (−76 to −32)	<.001
5	168 (152 to 183)	132 (117 to 146)	−36 (−58 to −15)	.001
Diastolic BP, mm Hg				
0	79 (76 to 82)	78 (74 to 81)	−1 (−5 to 3)	
1	74 (72 to 76)	68 (66 to 71)	−6 (−9 to −3)	<.001
2	75 (73 to 78)	70 (67 to 72)	−6 (−9 to −2)	.001
3	77 (74 to 79)	71 (69 to 73)	−5 (−9 to −2)	.002
4	76 (74 to 79)	72 (70 to 74)	−4 (−8 to −1)	.01
5	77 (74 to 80)	73 (70 to 75)	−4 (−8 to −1)	.01
Cholesterol, mg/dL				
HDL				
0	41 (39 to 43)	41 (38 to 44)	0 (−4 to 3)	
1	42 (39 to 44)	50 (48 to 53)	9 (5 to 13)	<.001
2	43 (40 to 45)	50 (48 to 53)	8 (4 to 12)	<.001
3	46 (43 to 49)	53 (50 to 56)	7 (3 to 11)	<.001
4	45 (42 to 48)	54 (51 to 57)	9 (5 to 13)	<.001
5	45 (42 to 48)	53 (50 to 56)	8 (4 to 12)	<.001
Total				
0	186 (175 to 197)	181 (170 to 191)	−6 (−21 to 9)	
1	162 (153 to 172)	153 (144 to 163)	−9 (−22 to 5)	.20
2	169 (160 to 179)	154 (145 to 164)	−15 (−29 to −2)	.03
3	191 (180 to 201)	165 (155 to 174)	−26 (−40 to −12)	<.001
4	179 (168 to 190)	162 (153 to 172)	−16 (−31 to −2)	.02
5	179 (168 to 189)	160 (151 to 169)	−19 (−33 to −4)	.01
Triglycerides, mg/dL				
0	250 (191 to 309)	258 (154 to 362)	8 (−111 to 127)	
1	181 (140 to 222)	104 (64 to 144)	−77 (−134 to −19)	.01
2	258 (217 to 299)	109 (68 to 149)	−149 (−207 to −92)	<.001
3	237 (192 to 282)	110 (70 to 151)	−127 (−187 to −66)	<.001
4	196 (150 to 242)	111 (70 to 152)	−85 (−147 to −23)	.01
5	183 (137 to 228)	116 (75 to 157)	−66 (−127 to −6)	.03
No. of Triple End Point Medications[d]				
0	4.3 (3.9 to 4.7)	4.1 (3.6 to 4.6)	−0.3 (−0.9 to 0.4)	
1	4.9 (4.4 to 5.3)	1.7 (1.3 to 2.2)	−3.1 (−3.7 to −2.5)	<.001
2	4.7 (4.2 to 5.1)	1.9 (1.5 to 2.4)	−2.7 (−3.4 to −2.1)	<.001
3	3.9 (3.4 to 4.4)	1.7 (1.3 to 2.2)	−2.2 (−2.8 to −1.5)	<.001
4	4.1 (3.6 to 4.5)	1.9 (1.5 to 2.3)	−2.2 (−2.8 to −1.5)	<.001
5	4.4 (3.9 to 4.9)	2.0 (1.6 to 2.5)	−2.4 (−3.0 to −1.7)	<.001

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; BP, blood pressure; HDL, high-density lipoprotein.

SI conversion factors: To convert cholesterol from mg/dL to mmol/L, multiply by 0.0259; glucose from mg/dL to mmol/L, multiply by 0.0555; triglycerides from mg/dL to mmol/L, multiply by 0.0113.

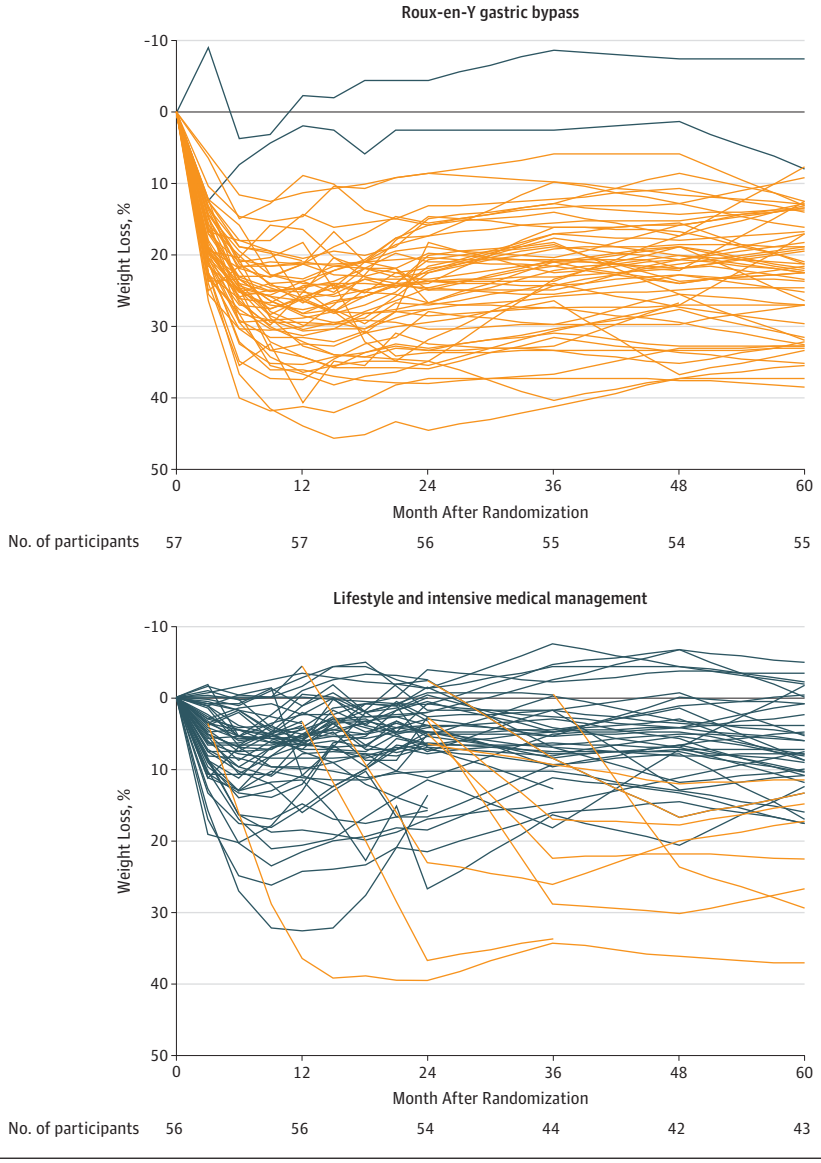
[a] For 113 patients (excluding 6 without 12-month data and 1 who died), fitted values were derived from a longitudinal mixed model that was adjusted for baseline values and site, treating patients as a random effect.

[b] Baseline values and 95% CIs were computed assuming normality. Odds ratios (95% CIs) were computed using an unadjusted logistic regression.

[c] For dichotomous variables in years 1 through 5, the percent risk (95% CI) is computed as the inverse logit of the estimated odds (95% CI). The percentile difference in risks is the estimated treatment difference. The estimated percentile difference is the difference in estimates. The estimated 95% CI for percentile differences requires 2 additional assumptions: the within-group that estimates the probability of success is normally distributed; and estimated probabilities for lifestyle-medical management vs Roux-en Y gastric bypass interventions are statistically independent. For observed data, see eTable 2B in Supplement 2.

[d] Triple end point medications are those taken for control of blood glucose, blood pressure, or LDL cholesterol.

Figure 3. Weight Loss Over Time



For Roux-en-Y gastric bypass, the 0 time point represents randomization. For both groups, blue indicates that the participant did not have bariatric surgery. Two patients were randomized to the Roux-en-Y gastric bypass group and are represented in blue based on their decision to decline surgery. Orange indicates that the participant did have bariatric surgery (as-treated basis). Some patients randomized to the intensive medical management group later obtained gastric bypass surgery outside of the study. They are reported on the intensive medical management graph (based on their randomization assignment), but their line turns from blue to orange at their approximate surgery date.

participants (3%) randomized to undergo gastric bypass declined surgery but participated in the rest of the intervention and contributed data.

Discussion

In the 5-year follow-up, adding gastric bypass to intense lifestyle and medical management continued to show improved attainment of the triple diabetes end point goal. However, the 5-year results for gastric bypass of 23% and lifestyle plus intense medical management of 4% maintaining the end point goal were significantly lower than the first-year rates of 50% and 16%. Most of the reduction in the proportion of participants achieving the primary end point was between years 2 and 3, after which the effects of both strategies remained relatively constant. Although Roux-en-Y gastric bypass provided significant benefit, the overall achievement was modest at 23% compared with averages ranging from 7% to 14% in the diabetes population.[20-23]

Because the key treatment goals for patients with diabetes are the prevention of long-term complications,[2] this triple end point finding is important. Although the Diabetes Surgery Study ideally would have been designed to study the cardiovascular effects of gastric bypass in persons with diabetes, the size and scope required was prohibitive. Power analyses indicated that control of cardiovascular risk factors would be an achievable target. The integrated triple end point provides a more comprehensive view of changes in cardiovascular risk than evaluations of each variable alone. With this broader goal, the Diabetes Surgery Study aimed to test the value of adding gastric bypass to intense diabetes management on prevention of cardiovascular complications. The results indicate that gastric bypass provides significant benefit but with a smaller

Table 5. Adverse Events on an As-treated Basis[a]

	Clinically Significant		Serious			All
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Lifestyle and Intensive Medical Management						
Surgical complications	0	0	0	0	0	0
Gastrointestinal	7	2	2	3	2	16
Cardiovascular	0	1	1	1	1	4
Renal	1	0	0	1	0	2
Metabolic	0	1	0	0	1	2
Musculoskeletal	0	0	0	1	0	1
Neurologic	1	0	0	0	0	1
Psychiatric	1	1	0	0	0	2
Miscellaneous	4	0	2	2	2	10
Total	14	5	5	8	6	38
Roux-en-Y Gastric Bypass						
Surgical complications	10	3	0	0	1	14
Gastrointestinal	4	8	2	1	0	15
Cardiovascular	0	1	1	2	0	4
Renal	1	0	2	1	0	4
Metabolic	0	0	0	1	0	1
Musculoskeletal	2	0	2	2	0	6
Neurologic	1	1	0	0	1	3
Psychiatric	0	0	0	0	1	1
Miscellaneous	5	4	3	5	1	18
Total	**23**	**17**	**10**	**12**	**4**	**66**

[a] Adverse events were counted on an as-treated basis for years 1 and 2: Clinically Significant Events; Year 3-5: Serious Events

and less durable effect size than what is seen in the evaluation of glycemic control alone.

Glycemic control at 5 years was significantly better in the surgical group with HbA_{1c} concentrations of less than 7.0% achieved by 55% compared with 14% in lifestyle-medical management group. These achievement rates are higher than for the primary composite triple end point but were also significantly reduced from the corresponding 1-year values of 83% in the surgical group and 29% in the lifestyle-medical management group. Because most participants had good baseline control of blood pressure and LDL-C and because the treatment effect on these variables was weaker, glycemic control is likely the primary contributor to the surgical composite triple end point improvement. Some participants may also benefit from reductions in medications for glucose control, particularly insulin, and hypertension. Better glucose control was the primary outcome sought and observed in other controlled trials of bariatric surgery for diabetes, and the rates of improvement seen in this study are similar to those outcomes.[5-9]

Weight loss was durable in both groups. Following cessation of intensive lifestyle-medical management modification at the end of 2 years, weight loss remained around 21% in the surgical group and 6.3% in the lifestyle-medical management group on an as-treated basis. These weight loss results in both groups are similar to the weight loss seen at 5 years in the single-site, single-surgeon STAMPEDE trial.[6] Compared with the current study, the single-site study in Italy found a slightly greater amount of 5-year weight loss of 28.4% in the gastric bypass, while the medical treatment group at 6.9% was similar.[5] A recent prospective observational study of patients with diabetes who had undergone gastric bypass found a mean weight loss of 28% at 6 years.[24] The size of the treatment effect on weight appears relatively comparable across these studies, but the 2 studies with less weight loss, the Diabetes Surgery Study and STAMPEDE study included participants with higher baseline HbA_{1c} values, possibly indicating that greater diabetes-related illness could lessen gastric bypass weight loss.

Durability of weight loss in the both groups of the Diabetes Surgery Study contrasts sharply with lack of durability in metabolic control of diabetes. Weight loss was thought to be one of the principal goals of the gastric bypass approach based on expectations that weight loss would improve diabetes control, and some previous studies including earlier reports of the Diabetes Surgery Study had shown weight loss as a predictor of improved diabetes control.[6,10] Worsening metabolic control over 5 years despite weight loss durability, particularly in the gastric bypass group with greater weight loss, indicates that improving diabetes control for the long-term may involve other factors, notably the health of pancreatic beta cells.[25] There may have been insufficient beta cell function in some participants to maintain long-term diabetes improvement. Whether such a possibility supports earlier surgical intervention for diabetes will need to be evaluated in other studies.

In evaluating the post hoc outcomes of either full or partial remission, which occurred only in the surgical group, the remission rates seen in this study at year 2 were reduced by 50%. At 5 years, 16% of participants had partial remission and 7% of participants had full remission. This partial remission rate for gastric bypass was lower than the 37% rate at 5 years in a single-site study with a treatment population of 20

participants with a baseline HbA_{1c} concentration of 8.7% in each group, but that study also found no full remissions at 5 years.[5] A recent report from the STAMPEDE trial found partial remission rate in 30.6% and full remission in 22.4% 5 years following gastric bypass.[6] Accounting for these differences is uncertain, but the Diabetes Surgery Study was different from other surgical diabetes treatment studies in severity of pretreatment diabetes, with baseline HbA_{1c} concentration of 9.6%, and the multisite program with participation of several racial/ethnic groups.

It is important to consider the adverse events associated with surgical treatment. There were 104 total adverse events through 5 years. On an as-treated basis, there were 66 in the gastric bypass group and 38 in the lifestyle-medical management group. Surgical complications were among the most common adverse events in the gastric bypass group, including 1 complication that occurred in year 5. Surgical complications included 1 catastrophic outcome, a cerebrovascular event. Malabsorptive complications were also more common among in the gastric bypass group. Significant elevations of parathyroid hormone were observed among participants in the gastric bypass group, potentially indicating a long-term negative effect on bone health. The earlier report about increased fractures in the gastric bypass group was not observed beyond 3 years. Although B_{12} deficiency is a common concern after gastric bypass, B_{12} deficiency was not different between the 2 groups, suggesting effective supplementation, in accordance with the study protocol. Overall, adverse events and nutritional deficiencies were seen in substantially greater numbers in the gastric bypass group through 5 years.

Strengths of the study include generalizability conveyed by larger group sizes than previous randomized studies of gastric bypass for diabetes,[5-9] the participation of multiple sites and surgeons, and greater range of race/ethnic groups including an East Asian cohort. More than 50% of the participants had an initial BMI less than 35, further improving generalizability. In addition, the primary end point incorporated the full range of established diabetic treatment goals instead of glucose control alone.

Limitations

This study has several limitations. The mean baseline HbA_{1c} concentration of 9.6% indicates that this was a group of participants with relatively poorly controlled glycemia, so whether the results would be different with better controlled glycemia at baseline cannot be determined. Similarly, the participants had diabetes for a mean of 9 years at study entry, so treatment effect on diabetes of lesser duration could be different. Conversely, blood pressure and LDL-C levels were relative well controlled among the study participants, so it is possible that individuals with less control might receive greater treatment benefit. Follow-up was incomplete (82% at 5 years), creating an opportunity for bias. Statistical analyses assumed missing data were missing at random, which may not have been true. Crossovers, which were analyzed on an intention-to-treat basis, may have reduced observed treatment differences. The study tested a single type of bariatric surgery, the gastric bypass procedure which was most common at study initiation, so whether these conclusions apply to other surgical approaches will have to be assessed.

Conclusions

In extended follow-up of obese adults with type 2 diabetes randomized to adding gastric bypass compared with lifestyle-medical management and intensive medical management alone, there remained a significantly better composite triple end point in the surgical group at 5 years. However, because the effect size diminished over 5 years, further follow-up is needed to understand the durability of the improvement.

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Supervision: Ikramuddin, Korner, Lee, Chuang, Vella, Billington.

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