Supplementary Appendix

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Supplement to: Schauer PR, Kashyap SR, Wolski K, et al. Bariatric Surgery vs Intense

Medical Therapy in Obese Diabetic Patients: STAMPEDE Trial – 1 year results

Author Contributions:

Drs Schauer, Kashyap, and Bhatt had full and independent access to all of the data and vouch for the integrity and the accuracy of the analysis.

Study concept and design: Schauer, Kashyap, Brethauer, Bhatt, Pothier, Thomas

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Obtained funding: Schauer

Administrative technical or material support: Schauer, Kashyap, Pothier, Abood, Bhatt

Study supervision: Schauer, Kashyap, Bhatt

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Role of the sponsor: The sponsor participated in discussions regarding study design and protocol development and provided logistical support during the trial. The database, statistical analysis, and monitoring were all performed by the Cleveland Clinic Coordinating Center for Clinical Research. The manuscript was prepared by the corresponding author and modified after consultation with co-authors. The sponsor was permitted to review the manuscript and suggest changes, but the final decision on content and submission was exclusively retained by the academic authors.

Data and Safety Monitoring Board

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Study Governance

Drs. Schauer, Kashyap, and Bhatt designed the trial. The study was approved by the Cleveland Clinic Institutional Review Board, and all subjects provided written informed consent. The Cleveland Clinic Coordinating Center for Clinical Research gathered and analyzed the data. An independent Data and Safety Monitoring Board reviewed the safety and conduct of the trial at confidential meetings held yearly. The first author vouches for the integrity of the data, wrote the first draft of the manuscript, and prepared subsequent drafts with input from all the coauthors. All the authors made the decision to submit the manuscript for publication. There were no agreements concerning confidentiality of the data between the funding sponsor and the authors or the institutions named in the credit lines.
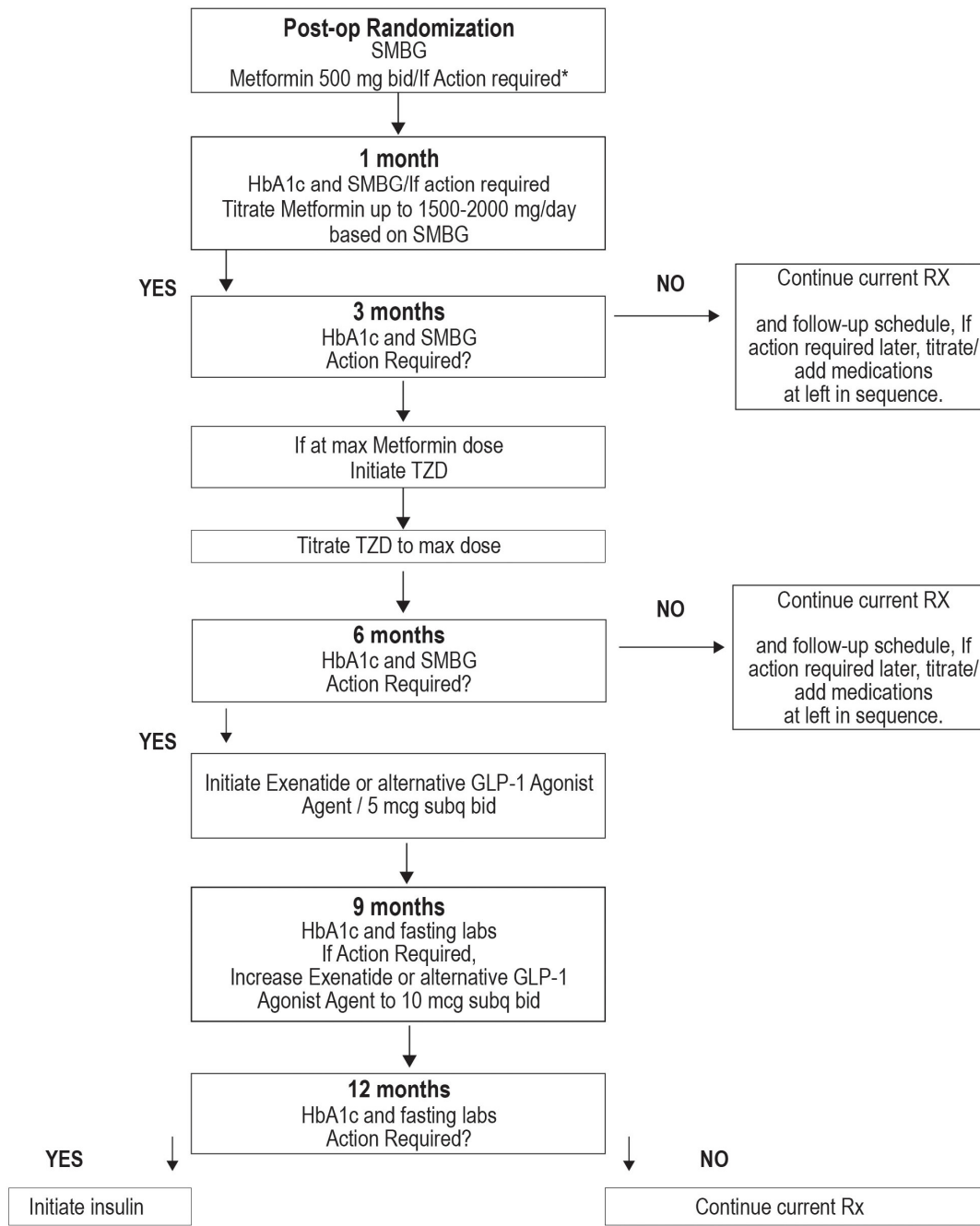
Supplementary Figure Legends

Figure S1. Algorithm for all Patients Requiring Medical Therapy. The intensive medical algorithm included lifestyle modification as the foundation of anti-diabetic therapy based on the current American Diabetes Association practice guidelines, while pharmacologic recommendations were stratified to target HbA1c ≤ 6% and facilitate weight management. Upon randomization, monotherapy with metformin was initiated and maximized, followed by initiation of thiazoledinediones (pioglitazone) as tolerated. GLP-1 analogs (exenatide/liraglutide) or mimetics were added to intensify therapy if treatment goal of ≤ 6% was not met in patients pre-treated with insulin sensitizers.[2] Patients pre-treated with sulfonylureas at time of randomization were titrated up or down or, changed to incretin analogs based on home glucose monitoring and study target HbA1c levels.

Figure S2. Use of Insulin for Patients on Maximum Oral Agents and GLP-1 Agonist Therapy. Basal insulin was initiated in individuals who did not meet the target HbA1c ≤ 6% with combination of oral agents and incretin analogs at 0.5-1.0 units/kg that was titrated to achieve fasting target glucose levels of 70-120 mg/dl. Prandial insulin coverage was provided with rapid acting insulin analogs to target daytime glucose levels < 160 mg/dl. Glargine was initially dosed based on weight (0.6-1.0 unit/kg) in single or divided doses and titrated up and down with further correspondence with the subject to review home glucose readings.

Figure S3. Bariatric surgery: Roux-en-Y Gastric Bypass and Sleeve Gastrectomy. Roux-en-Y Gastric Bypass consists of 15 ml gastric pouch, 150 cm Roux-Limb, and 50 cm biliopancreatic limb. Sleeve Gastrectomy consists of a 75-80% gastric volume reduction by vertical stapling along a 30 French endoscope beginning 3cm from the pylorus and extending to the angle of His.

Figure S4. Patient flow diagram. Two hundred and eighteen eligible patients enrolled and underwent the screening protocol for the trial. There were 68 screen failures as indicated. There were 13 initial screen failures that were eventually re-screened and later randomized in the trial. All were because they met the HbA1c inclusion criteria. Of the 218 patients, 150 were randomized to the designated treatment intervention. There were a total of 140 patients who completed the primary analysis; 41 patients in the medical therapy group, 50 in the gastric bypass group and 49 in the sleeve gastrectomy group. The number of patients that withdrew consent or missed visits is indicated in the flow diagram.

Figure S1. Algorithm for all Patients Requiring Medical Therapy.


```
┌─────────────────────────────────────┐
│         Post-op Randomization       │
│                SMBG                 │
│  Metformin 500 mg bid/If Action required* │
└─────────────────────────────────────┘
                  │
                  ▼
┌─────────────────────────────────────┐
│              1 month                │
│    HbA1c and SMBG/If action required │
│  Titrate Metformin up to 1500-2000 mg/day │
│            based on SMBG            │
└─────────────────────────────────────┘
                  │ YES
                  ▼                          NO    ┌─────────────────────────────┐
┌─────────────────────────────────────┐  ──────▶  │     Continue current RX      │
│              3 months               │           │                             │
│          HbA1c and SMBG             │           │  and follow-up schedule, If │
│          Action Required?           │           │ action required later, titrate/ │
└─────────────────────────────────────┘           │       add medications        │
                  │                                │       at left in sequence.   │
                  ▼                                └─────────────────────────────┘
┌─────────────────────────────────────┐
│       If at max Metformin dose      │
│            Initiate TZD             │
└─────────────────────────────────────┘
                  │
                  ▼
┌─────────────────────────────────────┐
│       Titrate TZD to max dose       │
└─────────────────────────────────────┘
                  │                          NO    ┌─────────────────────────────┐
                  ▼                       ──────▶  │     Continue current RX      │
┌─────────────────────────────────────┐           │                             │
│              6 months               │           │  and follow-up schedule, If │
│          HbA1c and SMBG             │           │ action required later, titrate/ │
│          Action Required?           │           │       add medications        │
└─────────────────────────────────────┘           │       at left in sequence.   │
                  │ YES                            └─────────────────────────────┘
                  ▼
┌─────────────────────────────────────┐
│ Initiate Exenatide or alternative GLP-1 Agonist │
│        Agent / 5 mcg subq bid       │
└─────────────────────────────────────┘
                  │
                  ▼
┌─────────────────────────────────────┐
│              9 months               │
│       HbA1c and fasting labs        │
│         If Action Required,         │
│  Increase Exenatide or alternative GLP-1 │
│    Agonist Agent to 10 mcg subq bid │
└─────────────────────────────────────┘
                  │
                  ▼
┌─────────────────────────────────────┐
│              12 months              │
│       HbA1c and fasting labs        │
│          Action Required?           │
└─────────────────────────────────────┘
        │ YES                    │ NO
        ▼                        ▼
┌─────────────────┐    ┌─────────────────────┐
│ Initiate insulin │   │  Continue current Rx │
└─────────────────┘    └─────────────────────┘
```
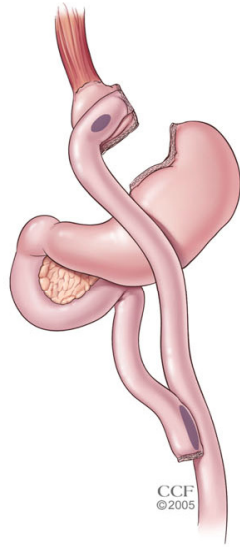
*SMBG: Self-Monitoring Blood Glucose; Action Required if HbA1c > 6%

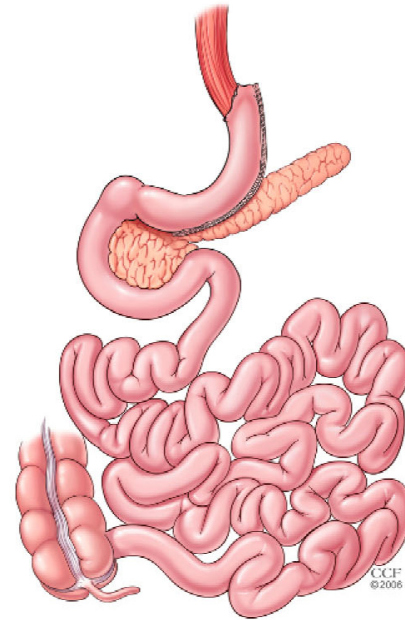**Figure S2. Use of Insulin for Patients on Maximum Oral Agents and GLP-1 Agonist Therapy.**
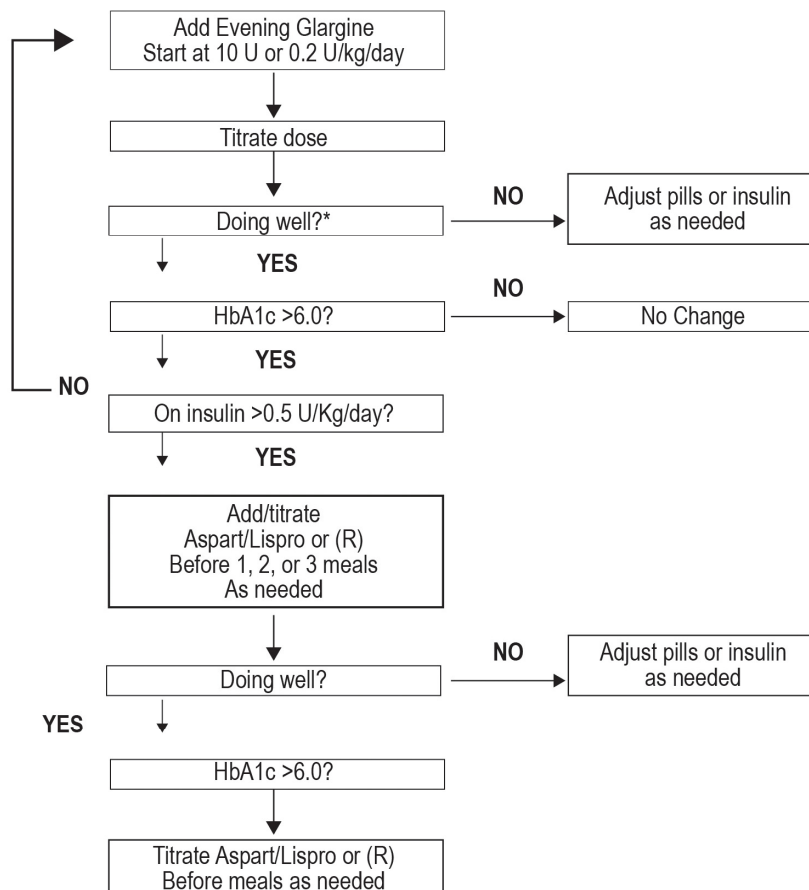
*Doing well: no severe hypoglycemic or adverse event or not reason to reduce therapy
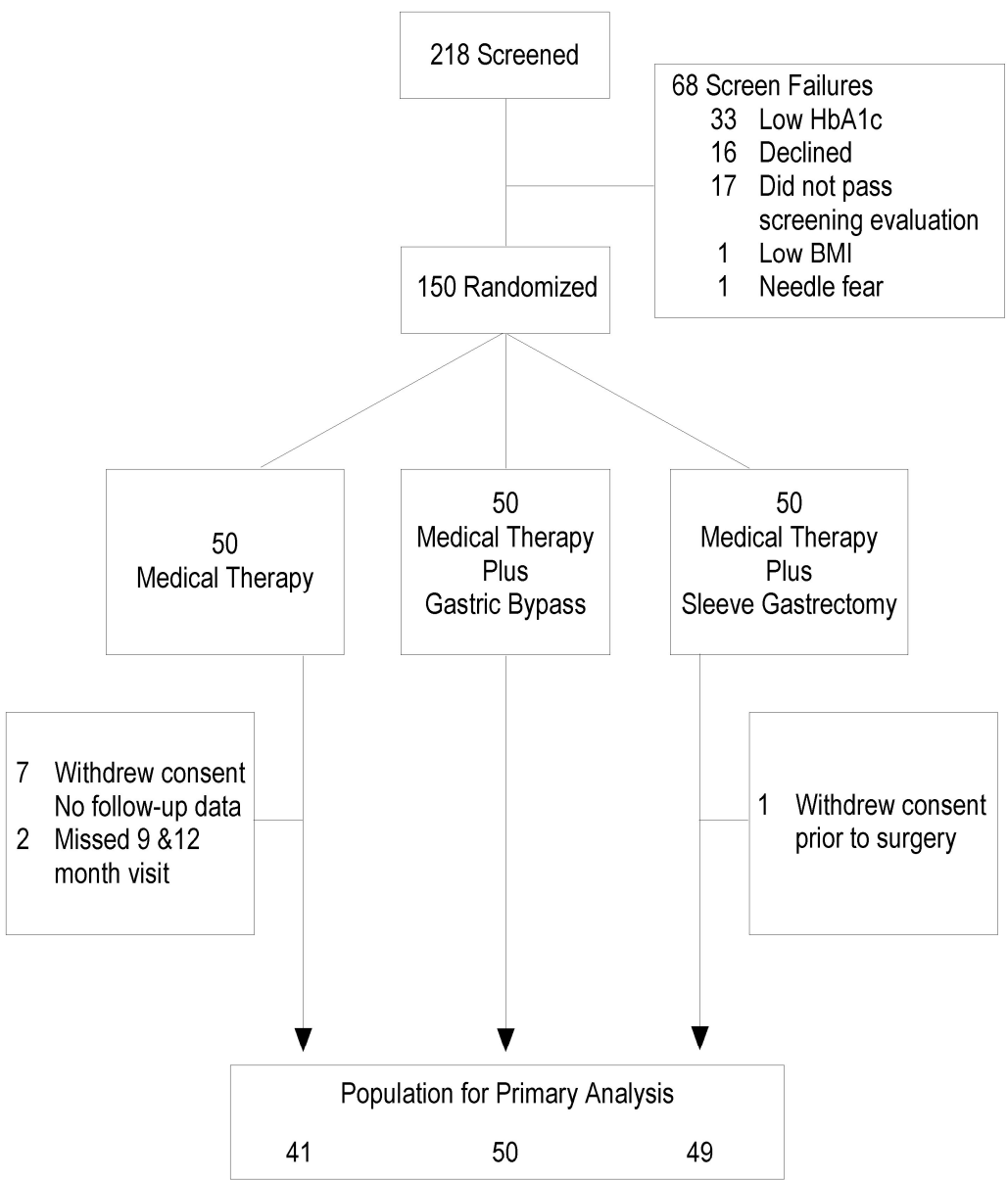
Figure S3. Bariatric surgery.

Roux-en-Y Gastric Bypass   Sleeve Gastrectomy

Figure S4.

Patient Flow Diagram

218 Screened

68 Screen Failures
33 Low HbA1c
16 Declined
17 Did not pass screening evaluation
1 Low BMI
1 Needle fear

150 Randomized

50 Medical Therapy

50 Medical Therapy Plus Gastric Bypass

50 Medical Therapy Plus Sleeve Gastrectomy

7 Withdrew consent No follow-up data
2 Missed 9 &12 month visit

1 Withdrew consent prior to surgery

Population for Primary Analysis
41   50   49

Supplementary Tables

Table S1. Baseline Characteristics of Randomized Population

Parameters	Intensive Medical Therapy (N=50)	Gastric Bypass (N=50)	Sleeve Gastrectomy (N=50)	P-Value
Duration of diabetes - yrs	8.9 ± 5.8	8.2 ± 5.5	8.5 ± 4.8	0.72
Insulin Users – no. (%)	22 (44.0)	22 (44.0)	22 (44.0)	1.0
Age – yrs	49.7 ± 7.4	48.3 ±8.4	47.9 ± 8.0	0.46
Female sex – no. (%)	31 (62.0)	29 (58.0)	39 (78.0)	0.08
Body-mass index – (kg/m^2)	36.8 ± 3.0	37.0 ± 3.3	36.2 ± 3.9	0.42
Body-mass index <35	19 (38.0)	14 (28.0)	18 (36.0)	0.54
Body weight - kg	106.5 ± 14.7	106.7± 14.8	100.8 ± 16.4	0.10
Waist circumference - cm	114.5 ± 9.4	116.4 ± 9.2	114.0 ± 10.4	0.43
Waist to hip ratio	0.95 ± 0.09	0.96 ± 0.07	0.96 ± 0.09	0.88
Caucasian race – no. (%)	37 (74.0)	37 (74.0)	36 (72.0)	0.97
Smoker – no. (%)	15/42 (35.7)	20 (40.0)	11 (22.0)	0.14
Metabolic syndrome – no. (%)	46 (92.0)	45 (90.0)	47 (94.0)	1.0
History of dyslipidemia – no. (%)	36/43 (85.7)	44 (88.0)	40 (80.0)	0.55
History of hypertension – no. (%)	26/43 (60.5)	35 (70.0)	30 (60.0)	0.51
Retinopathy – no. (%) *				0.36
None	43 (86.0)	39 (78.0)	41 (82.0)	
Background diabetic retinopathy	7 (14.0)	11 (22.0)	7 (14.0)	
Proliferative diabetic retinopathy	0 (0)	0 (0)	2 (4.0)	
C-peptide – ng/mL	2.3 (1.5, 3.3)	2.5 (1.9, 3.1)	2.0 (1.2, 2.7)	0.32
Microalbuminuria†	7 (14.0)	14 (28.6)	11 (22.0)	0.21
Macroalbuminuria†	3 (6.0)	3 (6.0)	1 (2.0)	0.63
NASH‡				0.25
Normal	NA	6/47 (12.8)	7/45 (15.6)	
Mild		5/47 (10.6)	10/45 (22.2)	
Moderate		8/47 (17.0)	10/45 (22.2)	
Severe		28/47 (59.6)	18/45 (40.0)	
Gastroesophogeal reflux	17/43 (39.5)	17 (34.0)	19 (38.0)	0.85
Depression	14/43 (32.6)	18 (36.0)	23 (46.0)	0.38
Arthritis	15/43 (34.9)	16 (32.0)	14 (28.0)	0.77
Sleep apnea	14/43 (32.6)	11 (22.0)	12 (24.0)	0.48

*Definition based on American Academy of Ophthalmology (AAO) (2002) International clinical diabetic retinopathy severity scale.[1]
† Defined as the albumin/creatinine ratio ≥300mg albumin per gram creatinine for macroalbuminuria (≥ 30 for microalbuminuria) in a random urine sample. ‡ NASH, non-alcoholic steato-hepatitis. Based on liver biopsy in surgical patients and defined using NASH Clinical Research Network criteria.[2]   NA=Not applicable.

1. Wilkinson CP, Ferris FL, 3rd, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1677-82.
2. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41:1313-21.

Table S2. Primary and Efficacy Endpoints at 12 Months

Parameters	Intensive Medical Therapy (N=41)€	Gastric Bypass (N=50)	Sleeve Gastrectomy (N=49)€	P-Value[1]	P-Value[2]	P-Value[3]
HbA1c ≤ 6% - no. (%)	5 (12.2)	21 (42.0)	18 (36.7)	0.002	0.008	0.59
HbA1c ≤ 6% - no diabetes medications	0 (0)	21 (42.0)	13 (26.5)	<0.001	<0.001	0.10
HbA1c - %						
Baseline	8.9 ± 1.4	9.3 ± 1.4	9.5 ± 1.7			
Month 12	7.5 ± 1.8	6.4 ± 0.9	6.6 ± 1.0	<0.001	0.003	0.23
Change from baseline	-1.4 ± 1.5*	-2.9 ± 1.6*	-2.9 ± 1.8*	<0.001	<0.001	0.85
Fasting Plasma Glucose, median (IQR) – mg/dL						
Baseline	155 (120, 206)	193 (141, 231)	164 (132, 224)			
Month 12	120 (97, 154)	99 (83, 121)	97 (84, 114)	0.004	0.003	0.86
Change from baseline	-28 (-58, 11)*	-87 (-135, -37)*	-63 (-121, -41)*	<0.001	0.003	0.62
Insulin, median (IQR) – uU/ml†						
Baseline	17.3 (7.7, 22.3)	18.4 (11.7, 25.8)	13.6 (9.3, 17.4)			
Month 12	12.7 (9.9, 20.3)	5.4 (4.0, 8.1)	5.4 (4.4, 9.3)	<0.001	<0.001	0.77
Change from baseline	0.0 (-4.7, 3.3)	-11.8 (-17.8, -6.0)*	-6.0 (-12.0, -2.9)*	<0.001	0.003	0.02
HOMA-IR, median (IQR) †‡						
Baseline	5.6 (2.6, 8.6)	8.9 (4.3, 13.5)	5.2 (3.1, 8.8)			
Month 12	3.7 (2.5, 6.4)	1.4 (0.9, 1.7)	1.3 (1.0, 2.6)	<0.001	<0.001	0.88
Change from baseline	-0.4 (-4.6, 0.6)	-6.7 (-11.7, -2.1)*	-3.4 (-7.0, -1.7)*	<0.001	0.010	0.09
Body weight - kg						
Baseline	104.4 ± 14.5	106.7 ± 14.8	100.6±16.5			
Month 12	99.0 ± 16.4	77.3 ±13.0	75.5 ± 12.9	<0.001	<0.001	0.50
Change from baseline	-5.4 ± 8.0*	-29.4 ± 8.9*	-25.1 ± 8.5*	<0.001	<0.001	0.02
BMI – kg/m²						
Baseline	36.3±3.0	37.0±3.3	36.1±3.9			
Month 12	34.4 ± 3.7	26.8 ± 3.2	27.2 ± 3.5	<0.001	<0.001	0.61
Change from baseline	-1.9 ± 2.9*	-10.2 ± 3.1*	-9.0 ± 2.7*	<0.001	<0.001	0.03
% Excess weight loss, median (IQR)	13 (0.8, 23)*	88 (72, 101)*	81 (65, 97)*	<0.001	<0.001	0.32
Systolic BP – mmHg						
Baseline	135.5 ± 17.0	134.6 ± 18.7	135.8 ± 18.8			
Avg. post baseline	131.4 ± 14.0	132.3 ± 15.5	130.8 ± 14.3	0.77	0.85	0.62
Change from baseline	-3.9 ±14.7*	-2.4 ± 18.7	-5.1 ± 17.0*	0.87	0.67	0.46
LDL – mg/dL						
Baseline	101.0 ± 37.3	91.8 ± 28.8	105.8 ± 39.5			
Month 12	98.7 ± 36.6	93.7 ± 27.1	110.0 ± 30.9	0.46	0.12	0.01
% Change	3.3 ± 38.0	12.3 ± 48.6	17.2 ± 52.9	0.33	0.16	0.63
HDL – mg/dL						
Baseline	48.4 ± 13.1	46.2 ± 13.4	44.5 ± 12.0			
Month 12	52.8 ± 14.3	58.8 ± 18.0	56.1 ± 13.7	0.09	0.27	0.41
% Change	11.3 ± 25.7*	28.5 ± 22.7*	28.4 ± 21.9*	0.001	0.001	0.98
Triglycerides, median (IQR) – mg/dL						
Baseline	166 (97, 232)	167 (125, 257)	160 (120, 211)			
Month 12	111 (88, 173)	95 (70, 124)	101 (78, 131)	0.09	0.23	0.47
% Change	-14 (-40, 3)*	-44 (-65, -16)*	-42 (-56, 0)*	0.002	0.08	0.17
HS-CRP, median (IQR) – mg/L						
Baseline	4.2 (1.8, 5.8)	4.3 (2.0, 8.8)	6.3 (2.9, 11.9)			
Month 12	2.0 (0.8, 5.5)	0.6 (0.4, 1.2)	1.1 (0.6, 2.1)	<0.001	0.006	0.02
% Change	-33.2 (71, 0)*	-84 (91, -59)*	-80 (-90, -63)*	<0.001	<0.001	0.59

Unless otherwise specified, data are expressed as mean and standard deviation. Abbreviations: BP, blood pressure, LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range.
€Nine patients in the intensive medical therapy group and 1 patient in the sleeve gastrectomy group did not have post-randomization data collected. [1] Gastric bypass vs. intensive medical therapy; [2] Sleeve gastrectomy vs intensive medical therapy; [3] Gastric bypass vs sleeve gastrectomy. * p<0.05 for comparison with baseline.
† Calculated for the non-insulin users only. ‡ An indirect measure of insulin resistance calculated as fasting glucose (mmol/L) x fasting insulin (µU/ml)/22.5 .

Table S3. Additional Secondary Endpoints

	Intensive Medical Therapy (N=41)*	Gastric Bypass (N=50)	Sleeve Gastrectomy (N=49)*	P-Value[1]	P-Value[2]	P-Value[3]
HbA1c categorization – no. (%)				0.005	0.01	0.85
≤ 6%	5 (12.2)	21 (42.0)	18 (36.7)			
>6% to ≤7%	18 (43.9)	18 (36.0)	20 (40.8)			
>7%	18 (43.9)	11 (22.0)	11 (22.4)			
HbA1c ≤ 7% without diabetes medications	0 (0.0)	34 (68.0)	22 (44.9)	<0.001	<0.001	0.02
Resolution of Metabolic Syndrome – no. (%)	13 (35.1)	30 (65.2)	27 (58.7)	0.01	0.03	0.52
Waist – cm						
Baseline	112.9 ± 8.4	116.4±9.2	113.6±10.2			
Month 12	108.8 ± 10.8	93.4 ± 9.0	93.5 ± 8.8	<0.001	<0.001	0.96
Change from baseline	-4.1 ± 8.5	-23.0 ± 8.3	-20.1 ± 9.0	<0.001	<0.001	0.11
% Change	-3.6 ± 7.4	-19.6 ± 6.5	-17.5 ± 7.1	<0.001	<0.001	0.12
Waist:Hip Ratio						
Baseline	0.95 ± 0.08	0.96 ± 0.07	0.95 ± 0.08			
Month 12	0.93 ± 0.08	0.91 ± 0.06	0.92 ± 0.07	0.12	0.07	0.71
Change from baseline	-0.01 ± 0.04	-0.05 ± 0.06	-0.05 ± 0.07	<0.001	0.02	0.68
Diastolic BP – mmHg						
Baseline	82.6 ± 11.0	81.8 ± 10.2	82.2 ±11.6			
Avg. post baseline	78.2 ± 10.6	78.3 ± 10.0	78.6 ± 8.9	0.97	0.84	0.86
Change from baseline	-4.5 ±8.5	-3.5 ± 9.0	-3.6 ± 9.6	0.98	0.64	0.70
Total Cholesterol – mg/dL						
Baseline	183.6 ± 42.1	180.2 ± 43.4	187.3 ± 46.8			
Avg. post baseline	179.7 ± 46.0	173.6 ± 35.3	187.9 ± 37.0	0.48	0.35	0.05
Change from baseline	-3.9 ± 42.2	-6.6 ± 46.6	0.6 ± 43.9	0.78	0.62	0.43
% Change	-0.3 ± 23.7	0.7 ± 27.3	4.3 ± 24.1	0.85	0.37	0.49
LDL – mg/dL						
Change from baseline	-2.3 ± 35.2	1.9 ± 35.4	4.2 ± 42.3	0.57	0.44	0.77
HDL – mg/dL						
Change from baseline	4.4 ± 9.3	12.6 ± 10.5	11.6 ± 9.5	<0.001	<0.001	0.62
Triglycerides, median (IQR) – mg/dL						
Change from baseline	-24 (-70, 2.0)	-73 (-135, -17)	-61 (-120, 0)	0.01	0.17	0.25
HS-CRP, median (IQR) – mg/L						
Change from baseline	-0.8 (-3.1, 0.2)	-3.6 (-6.9, -0.9)	-3.6 (-9.4, -1.4)	0.002	<0.001	0.22

Unless otherwise specified, data are expressed as mean and standard deviation. Abbreviations: BP, blood pressure, LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range.
* Nine patients in the intensive medical therapy group and 1 patient in the sleeve gastrectomy group did not have post-randomization data collected. [1] Gastric bypass vs. intensive medical therapy; [2] Sleeve gastrectomy vs intensive medical therapy; [3] Gastric bypass vs sleeve gastrectomy.

Table S4. Cardiovascular Medication Use at Baseline and Month 12

	Baseline			Month 12		
	Intensive Medical Therapy (N=41)	Gastric Bypass (N=50)	Sleeve Gastrectomy (N=49)	Intensive Medical Therapy (N=39)	Gastric Bypass (N=49)	Sleeve Gastrectomy (N=49)
Number of CV medications – no. (%)						
None	0 (0)	3 (6.0)	2 (4.1)	0 (0.0)	24 (49.0) ¶	20 (40.8) ¶
1	7 (17.1)	5 (10.0)	12 (24.5)	3 (7.7)	13 (26.5)	17 (34.7)
2	15 (36.6)	12 (24.0)	16 (32.7)	13 (33.3)	10 (20.4)	5 (10.2)
≥3	19 (46.3)	30 (60.0)	19 (38.8)	23 (59.0)	2 (4.1)	7 (14.3)

¶ P-value <0.001 for categorical comparison of number of medications using the intensive medical therapy group as the comparator. Data for the 12-month analysis were missing for two patients in the medical-therapy group and for one patient in the gastric-bypass group.

Table S5. Subgroups Stratified by BMI, Age, Duration of Diabetes, and Insulin Use

Subgroups				
	Medical	Gastric Bypass	Sleeve	Interaction p-value
BMI < median†	3 (13.6)	5 (23.8)	8 (29.6)	0.60
BMI ≥ median	2 (10.5)	16 (55.2)	10 (45.5)	
Age < median‡	2 (12.5)	11 (45.8)	13 (41.9)	0.84
Age ≥ median	3 (12.0)	10 (38.5)	5 (27.8)	
Duration DM <= 8 yrs	4 (19.1)	16 (53.3)	12 (46.2)	0.73
Duration DM > 8 yrs	1 (5.0)	5 (25.0)	6 (26.1)	
Non-insulin users	3 (15.0)	12 (44.4)	11 (40.7)	0.95
Insulin users	2 (9.5)	9 (39.1)	7 (31.8)	

† Median BMI is 36.7; ‡ Median Age is 50 yrs.