

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery versus intensive medical therapy for diabetes — 3-year outcomes. *N Engl J Med* 2014;370:2002-13. DOI: 10.1056/NEJMoa1401329

**Supplementary Appendix**

Supplement to: Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery versus intensive medical therapy in obese diabetic patients: 3-year Outcomes. N Engl J Med 2014.

<b>Table of Contents</b>	<b>Page</b>
Author Contributions	3
Data and Safety Monitoring Board	4
Methods - Study Governance	4
Figure Legends	5
Figures 1-3	6-8
Tables 1-8	9-15
Background Material	16

**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

*Acquisition of data:* Schauer, Kashyap, Aminian, Kim, Pothier, Wolski

*Analysis and interpretation of data:* Schauer, Kashyap, Wolski, Bhatt, Nissen, Aminian, Navaneethan, Kirwan, Brethauer, Kim

*Drafting of the manuscript:* Schauer, Kashyap, Pothier, Wolski, Aminian, Navaneethan

*Critical revision of the manuscript for important intellectual content:* Nissen, Bhatt, Kirwan, Aminian, Navaneethan, Kashyap

*Statistical analysis:* Wolski

*Obtained funding:* Schauer, Kirwan, Kashyap

*Administrative technical or material support:* Schauer, Kashyap, Pothier, 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. 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**

J. Michael Henderson, MD (Chair); James B. Young, MD; Venu Menon, MD, Cleveland Clinic

**Study Governance**

Drs. Schauer, Kashyap, and Bhatt designed the trial with advice from Dr. Nissen. 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.

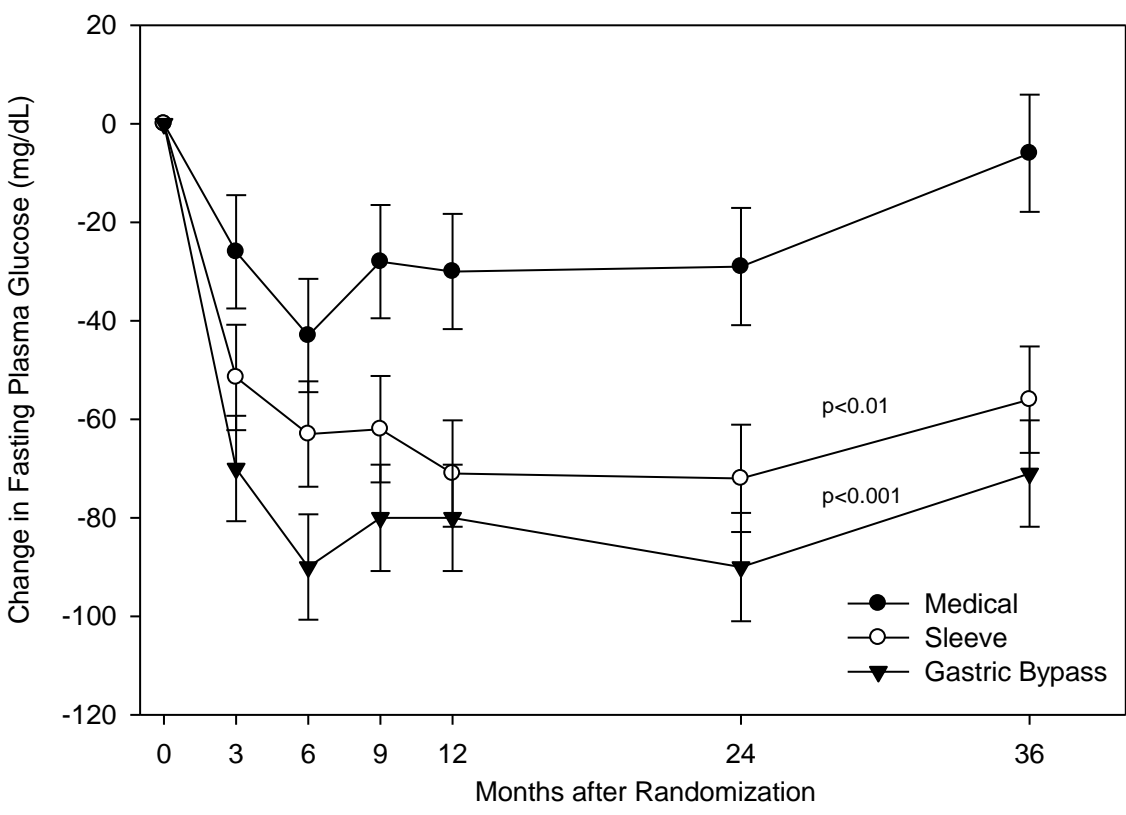
## Supplementary Figure Legends

**Figure S1. Change in Fasting Plasma Glucose.** Values for change in fasting plasma glucose over time.

**Figure S2. Change in Body Mass Index: Medical vs. Surgical by BMI Subgroup.** Change over time in BMI for the combined surgical groups (triangles) vs medical-therapy (circles) for BMI <35 (closed symbols) and BMI  $\geq$ 35 (open symbols)

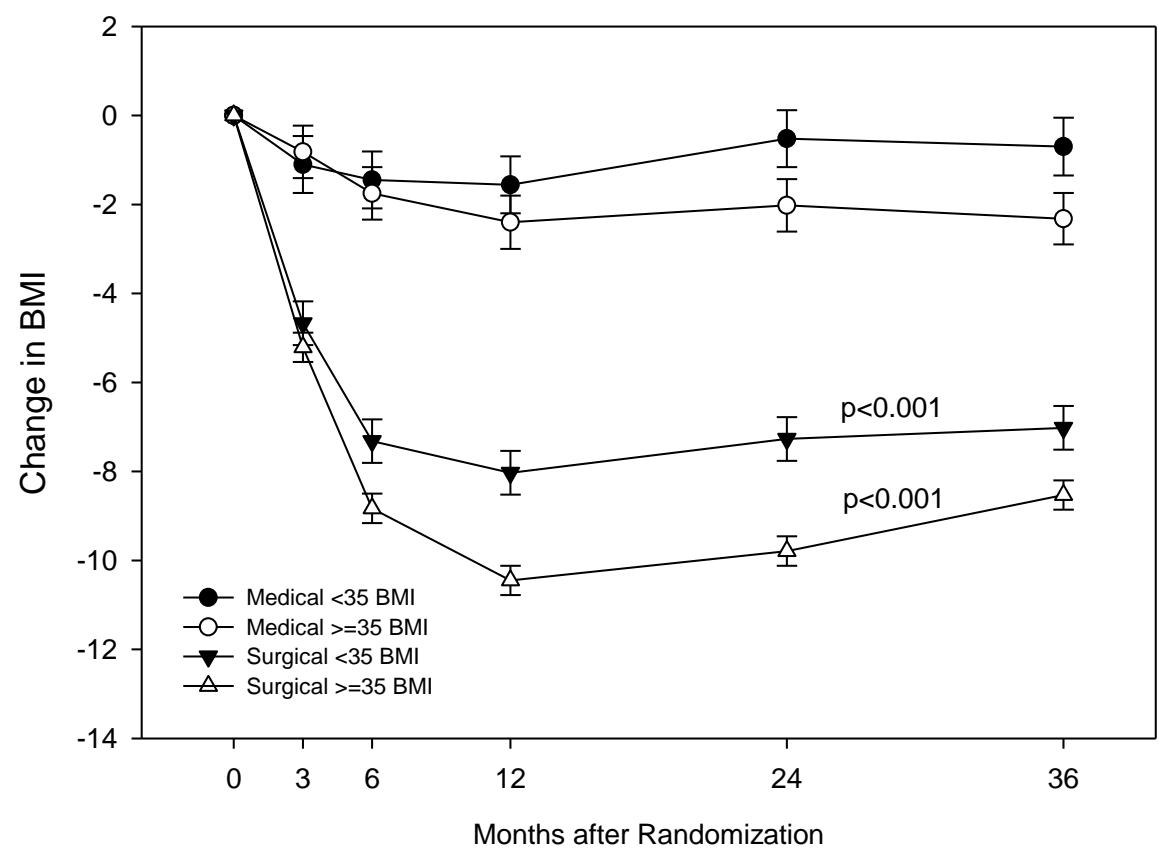
**Figure S3. Average Number of Diabetes Medications: Medical vs. Surgical by BMI Subgroup.** Change over time in average daily diabetes medication usage for the combined surgical groups (triangles) vs medical-therapy (circles) for BMI <35 (closed symbols) and BMI  $\geq$ 35 (open symbols).

Figure S1. Change in Fasting Plasma Glucose.



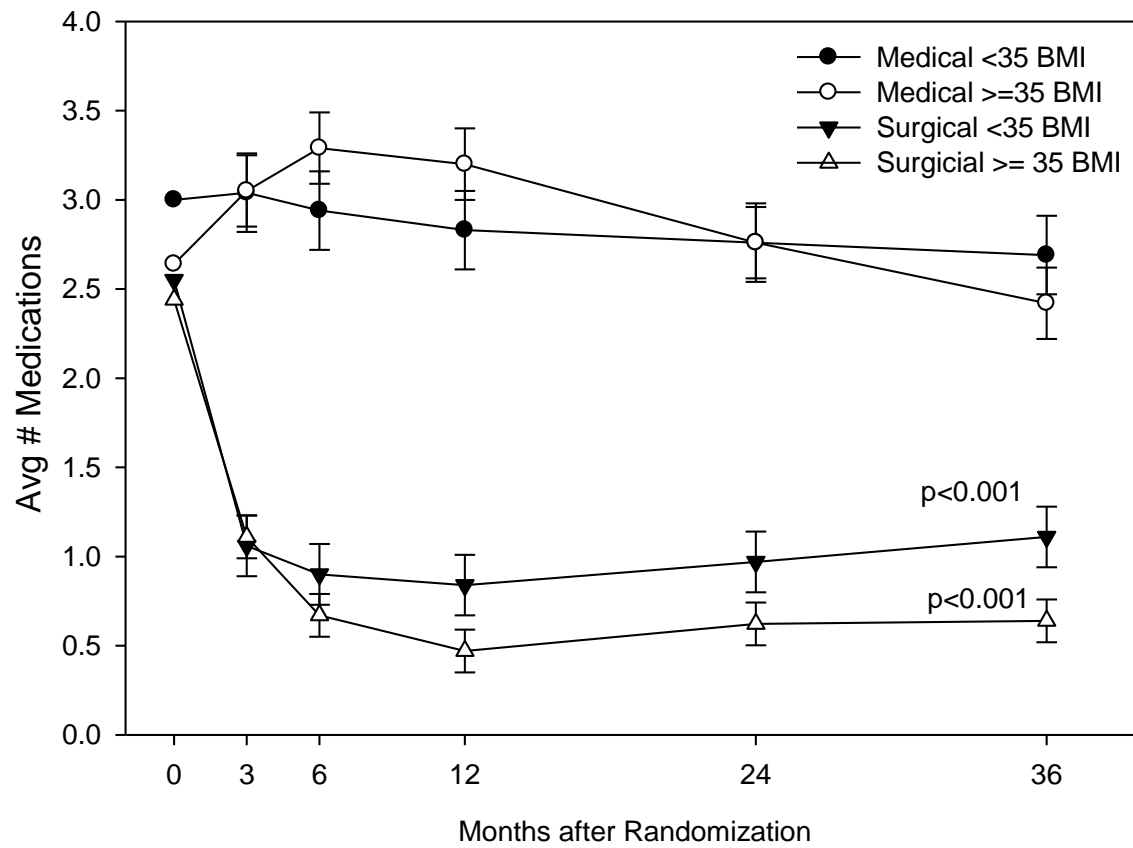
P-value is for each surgical group compared to intensive medical therapy

Figure S2. Change in Body Mass Index: Medical vs. Surgical by BMI Subgroup



P-value is for surgical vs intensive medical therapy for each BMI subgroup

**Figure S3. Average Number of Diabetes Medications: Medical vs. Surgical by BMI Subgroup.**



P-value is for surgical vs intensive medical therapy for each BMI subgroup



### Supplementary Tables

<b>Table S1 – Demographics*</b>				
Parameter	Intensive Medical Therapy (N=40)	Gastric Bypass (N=48)	Sleeve Gastrectomy (N=49)	p-value
Duration of diabetes - yrs	8.8 ± 5.38	8.0 ± 5.36	8.3 ± 4.49	0.62
Insulin Users - no. (%)	17 (42.5)	21 (43.8)	21 (42.9)	0.99
Age - yrs	50.3 ± 7.51	48.0 ± 8.45	47.8 ± 8.08	0.27
Female sex - no. (%)	27/40 (67.5)	28/48 (58.3)	38/49 (77.6)	0.13
Body-mass index - (kg/m <sup>2</sup> )	36.4 ± 2.99	37.1 ± 3.39	36.1 ± 3.91	0.36
Body-mass index <35	18 (45.0)	13 (27.1)	18 (36.7)	0.21
Body weight - kg	104.5 ± 14.20	106.8 ± 14.90	100.6 ± 16.51	0.14
Waist circumference - cm	113.3 ± 9.33	116.6 ± 9.25	113.6 ± 10.21	0.19
Waist to hip ratio	0.949 ± 0.0854	0.964 ± 0.0684	0.951 ± 0.0830	0.63
Caucasian race - no. (%)	29 (72.5)	36 (75.0)	36 (73.5)	0.96

\* Plus-minus values are means ±SD.

<b>Table S2. Predictors of primary endpoint at 36 months</b>				
	<b>Whole Cohort (n=137)</b>		<b>Surgical Groups (n=97)</b>	
	<b>Odds Ratio (95% CI)</b>	<b>P value</b>	<b>Odds Ratio (95% CI)</b>	<b>P value</b>
Change in BMI (per unit decrease)	1.41 (1.22, 1.64)	<0.001	1.33 (1.15, 1.56)	<0.001
Duration of diabetes < 8 years	2.42 (0.84, 7.01)	0.10	3.27 (1.18-9.07)	0.02
Female	0.60 (0.22, 1.62)	0.31	0.69 (0.24, 1.97)	0.48
Insulin Use	0.58 (0.20, 1.72)	0.33	0.63 (0.21, 1.93)	0.42
Baseline BMI	0.91 (0.79, 1.06)	0.22	0.89 (0.76, 1.04)	0.15
Baseline HbA1c	0.94 (0.67, 1.31)	0.71	0.95 (0.68,1.34)	0.79
Baseline C-peptide	1.02 (0.74, 1.39)	0.92	1.08 (0.77, 1.50)	0.67
Age	0.95 (0.89, 1.01)	0.08	0.95 (0.89, 1.00)	0.10
Baseline LDL	1.01 (0.99, 1.03)	0.13	1.01 (0.99, 1.03)	0.11
Baseline HDL	0.99 (0.95, 1.03)	0.60	0.90 (0.95, 1.03)	0.57
Baseline FPG	1.00 (0.99, 1.01)	0.56	1.00 (0.99, 1.01)	0.69
Baseline Triglycerides	1.00 (0.99, 1.003)	0.82	1.00 (0.99, 1.003)	0.81
Baseline SBP	0.99 (0.96, 1.01)	0.29	0.98 (0.96, 1.01)	0.24
Baseline DBP	0.98 (0.93, 1.02)	0.30	0.96 (0.92, 1.01)	0.11
Change in LDL	0.99 (0.98, 1.00)	0.18	0.99 (0.98, 1.00)	0.21
Change in HDL	1.04 (0.99, 1.09)	0.06	1.04 (0.99, 1.08)	0.10
Change in SBP	1.01 (0.99, 1.03)	0.41	1.01 (0.99, 1.04)	0.28

**Table S3 - Additional Secondary Endpoints\***

	Intensive Medical Therapy (N=40)*	Gastric Bypass (N=48)	Sleeve Gastrectomy (N=49)	P Value		
				Gastric Bypass vs. Medical Therapy	Sleeve Gastrectomy vs. Medical Therapy	Gastric Bypass vs. Sleeve Gastrectomy
Waist - cm						
Baseline	113.3 ± 9.33	116.6 ± 9.25	113.6 ± 10.21			
Month 36	111.9 ± 12.73	97.2 ± 9.96	98.8 ± 10.00	<0.001	<0.001	0.44
% Change	-1.5 ± 8.00	-16.5 ± 6.97	-12.8 ± 8.72	<0.001	<0.001	0.03
Within-group p-value	0.25	<0.001	<0.001			
Waist:Hip Ratio						
Baseline	0.9 ± 0.09	1.0 ± 0.07	1.0 ± 0.08			
Month 36	1.0 ± 0.10	0.9 ± 0.07	0.9 ± 0.07	0.168	0.05	0.50
%Change from baseline	0.4 ± 6.97	-3.8 ± 5.35	-3.1 ± 7.95	0.003	0.04	0.61
Within-group p-value	0.71	<0.001	0.006			
LDL, mg/dL						
Baseline	100.9 ± 36.18	92.4 ± 29.03	105.8 ± 39.50			
Month 36	99.7 ± 35.42	96.3 ± 27.16	108.1 ± 35.19	0.61	0.26	0.07
%Change from baseline	2.5 ± 29.91	16.9 ± 54.47	14.5 ± 52.16	0.14	0.20	0.82
Within- group p-value	0.83	0.12	0.16			
HDL, mg/dL						
Baseline	48.8 ± 12.95	45.4 ± 13.01	44.5 ± 12.01			
Month 36	49.7 ± 12.14	60.0 ± 19.14	59.2 ± 17.21	0.004	0.004	0.81
%Change from baseline	4.6 ± 20.68	34.7 ± 27.29	35.0 ± 30.98	<0.001	<0.001	0.96
Within-group p-value	0.16	<0.001	<0.001			
Triglycerides, median (IQR) - mg/dL						
Baseline	162 (94.5, 233.5)	179 (126.0, 258.5)	160 (120.0, 211.0)			
Month 36	121.0 (92.5, 158.0)	103.0 (76.0, 149.0)	103.0 (74.0, 135.0)	0.19	0.10	0.89
%Change from baseline	-21.5 (-45.4, 16.4)	-45.9 (-61.0, -7.5)	-31.5 (-52.1, -6.9)	0.01	0.01	0.18
Within group p-value	0.03	<0.001	<0.001			
Systolic blood pressure - mmHg						
Baseline	135.3 ± 17.35	135.0 ± 19.05	135.8 ± 18.82			
Month 36	136.0 ± 16.80	136.3 ± 22.32	131.4 ± 17.21	0.94	0.21	0.23
Change from baseline	0.63 ± 22.63	1.29 ± 20.38	-4.43 ± 20.69	0.88	0.27	0.17
Within-group p-value	0.99	0.72	0.14			
Diastolic blood pressure - mmHg						
Baseline	82.08 ± 11.15	81.85 ± 10.18	82.18 ± 11.59			
Month 36	75.60 ± 10.43	77.60 ± 10.42	75.92 ± 12.57	0.37	0.90	0.47
Change from baseline	-6.48 ± 12.33	-4.25 ± 10.57	-6.27 ± 13.30	0.36	0.94	0.41
Within- group p-value	0.002	0.008	0.002			

\* Plus-minus values are means ±SD unless otherwise stated.

**Table S4 - Medication Use at Baseline and Month 36\***

	Baseline			Month 36		
	Intensive Medical Therapy (n=40)	Gastric Bypass (n=48)	Sleeve Gastrectomy (n=49)	Intensive Medical Therapy (n=40)	Gastric Bypass (n=48)	Sleeve Gastrectomy (n=49)
Diabetes medications – no. (%)						
Biguanides	37 (92.5)	40 (83.3)	41 (83.7)	34 (85.0)	13 (27.1) <sup>†</sup>	23 (46.9) <sup>†δ</sup>
TZD's	18 (45.0)	23 (47.9)	17 (34.7)	11 (27.5)	0 (0.0) <sup>†</sup>	1 (2.0) <sup>†</sup>
Incretin mimetics	19 (47.5)	18 (37.5)	21 (42.9)	22 (55.0)	1 (2.1) <sup>†</sup>	13 (26.5) <sup>†δ</sup>
Secretagogues	16 (40.0)	16 (33.3)	18 (36.7)	14 (35.0)	6 (12.5)	9 (18.4)
Insulin	21 (52.5)	22 (45.8)	22 (44.9)	22 (55.0)	3 (6.3) <sup>†</sup>	4 (8.2) <sup>†δ</sup>
Injectables‡	27 (67.5)	28 (58.3)	30 (61.2)	29 (72.5)	3 (6.3) <sup>†</sup>	9 (18.4) <sup>†</sup>
Number of diabetes medications – no. (%)						
0	1 (2.5)	1 (2.1)	1 (2.0)	1 (2.5)	32 (69.6) <sup>€</sup>	19 (40.4) <sup>€δ</sup>
1	4 (10.0)	10 (20.8)	11 (22.4)	6 (15.0)	7 (15.2)	9 (19.1)
2	10 (25.0)	13 (27.1)	14 (28.6)	11 (27.5)	6 (13.0)	16 (34.0)
≥3	25 (62.5)	24 (50.0)	23 (46.9)	22 (55.0)	1 (2.2)	3 (6.4)
Cardiovascular medications – no. (%)						
Lipid lowering agents	34 (85.0)	41 (85.4)	38 (77.6)	33 (82.5)	15 (32.6) <sup>†</sup>	20 (42.6) <sup>†</sup>
Beta-blocker	7 (17.5)	8 (16.7)	6 (12.2)	9 (22.5)	6 (13.0)	3 (6.4) <sup>¶</sup>
Calcium channel blocker	4 (10.0)	4 (8.3)	2 (4.1)	2 (5.0)	1 (2.2)	1 (2.1)
ACE-inhibitor or ARB	25 (62.5)	36 (75.0)	30 (61.2)	22 (55.0)	11 (23.9) <sup>¶¶</sup>	13 (27.7) <sup>¶</sup>
Diuretics	12 (30.0)	17 (35.4)	14 (28.6)	15 (37.5)	7 (15.2) <sup>¶¶</sup>	17 (36.2) <sup>δ</sup>
Anticoagulant	22 (55.0)	21 (43.8)	16 (32.7)	21 (52.5)	2 (4.3) <sup>†</sup>	10 (21.3) <sup>†δ</sup>
Number of CV medications – no. (%)						
0	0 (0.0)	3 (6.3)	2 (4.1)	1 (2.5)	33 (68.8) <sup>€</sup>	21 (42.9) <sup>€</sup>
1	6 (15.0)	5 (10.4)	12 (24.5)	6 (15.0)	8 (16.7)	9 (18.4)
2	13 (32.5)	12 (25.0)	16 (32.7)	12 (30.0)	6 (12.5)	16 (32.7)
≥3	21 (52.5)	28 (58.3)	19 (38.8)	21 (52.5)	1 (2.1)	3 (6.1)

\*All p-values were calculated on the basis of the 36-month data with the medical-therapy group as the comparator.

Values are means (%).

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker. ‡ Injectables includes insulin

† P-value <0.001

¶ P-value <0.01

€ P-value <0.05 for categorical comparison to intensive medical therapy

δ P-value <0.05 for comparison between gastric bypass and sleeve gastrectomy

**Table S5 - Renal and Macrovascular Endpoints through 36 Months\***

	Intensive Medical Therapy (n=40)	Gastric Bypass (n=48)	Sleeve Gastrectomy (n=49)	P Value		
				Gastric Bypass vs. Medical Therapy	Sleeve Gastrectomy vs. Medical Therapy	Gastric Bypass vs. Sleeve Gastrectomy
<b>Albumin/creatinine ratio</b>						
Baseline	6.5 (5.0, 13.5)	9.0 (5.0, 41.5)	12.0 (7.0, 23.0)			
Change from baseline	-1.0 (-4.5, 3.5)	-3.0 (-30.5, 0.0)	-5.0 (-13.0, -2.0)	0.03	0.002	0.65
% change from baseline	-8.6 (-53.9, 67.5)	-40.0 (-70.3, 0.0)	-52.4 (-76.5, -16.7)	0.06	0.003	0.36
Within-group p-value	0.77	0.08	<0.001			
<b>Serum creatinine (mg/dL)</b>						
Baseline	0.70 (0.60, 0.80)	0.69 (0.59, 0.81)	0.68 (0.57, 0.82)			
Change from baseline	0.03 (-0.04, 0.11)	0.07 (-0.07, 0.17)	0.05 (-0.02, 0.12)	0.38	0.38	0.75
Within-group p-value	0.08	0.01	0.001			
<b>Glomerular filtration rate<sup>†</sup></b>						
Baseline	105.2 (96.7, 111.7)	107.6 (98.3, 117.9)	108.7 (96.5, 118.7)			
% change from baseline	-2.5 (-6.1, 2.1)	-4.8 (-14.8, 5.1)	-3.5 (-8.7, 1.5)	0.48	0.38	0.77
Within-group p-value	0.04	0.04	0.002			
<b>Albuminuria<sup>‡</sup></b>						
Baseline	4 (10.0)	13 (27.1)	10 (20.4)	0.04	0.18	0.44
No. resolved by 36 months	1/4 (25.0)	8/13 (61.50)	8/10 (80.0)	0.30	0.10	0.41
Within-group p-value <sup>δ</sup>	1.0	0.04	0.11			
<b>Maximum Carotid Intima Medial Thickness (CIMT), mm<sup>#</sup></b>						
Baseline	0.99 (0.88, 1.10)	0.96 (0.86, 1.14)	0.99 (0.88, 1.11)			
Change from baseline	0.048 (-.04, 0.09)	0.013 (-.06, 0.07)	0.017 (-.08, 0.10)	0.36	0.99	0.49

\*Values are median (IQR)

For skewed data, such as the albumin/creatinine ratio, the median of the percentage change is not the numerical difference between the group-level medians at baseline and at 3 years.

<sup>†</sup> calculated using the CKD-EPI formula.  $GFR = 141 \times \min(Scr/\kappa, 1)^\alpha \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993 \text{Age} \times 1.018$  [if female]  $\times 1.159$  [if black]; where Scr is serum creatinine (mg/dL),  $\kappa$  is 0.7 for females and 0.9 for males,  $\alpha$  is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/ $\kappa$  or 1, and max indicates the maximum of Scr/ $\kappa$  or 1.

<sup>‡</sup> Albuminuria defined as urine albumin/creatinine ratio >30 mg/g

<sup>δ</sup> McNemar's test for paired pre-post evaluation of albuminuria

<sup>#</sup> Mean and maximal carotid intima-media thickness (CIMT) values of the far wall of the bilateral distal common carotid arteries were measured using duplex ultrasound at baseline and after 2 years follow up.

**Table S6 - RAND-36 Questionnaire Responses at Baseline and Month 36\***

	Intensive Medical Therapy (n=40)	Gastric Bypass (n=48)	Sleeve Gastrectomy (n=49)	P Value		
				Gastric Bypass vs. Medical Therapy	Sleeve Gastrectomy vs. Medical Therapy	Gastric Bypass vs. Sleeve Gastrectomy
<b>Physical Health Components</b>						
Physical Functioning						
Baseline	78.0 ± 18.34	76.9 ± 19.56	79.6 ± 17.99			
Change from baseline	1.0 ± 21.63	14.8 ± 16.28	9.9 ± 23.35	0.003	0.11	0.28
Role Limitations due to Physical Health						
Baseline	75.0 ± 36.77	81.2 ± 31.98	78.5 ± 31.55			
Change from baseline	-2.6 ± 45.49	6.5 ± 36.82	5.2 ± 43.19	0.36	0.47	0.88
Bodily Pain						
Baseline	80.6 ± 17.77	79.0 ± 20.97	79.0 ± 20.06			
Change from baseline	-8.7 ± 16.62	4.9 ± 24.09	-2.7 ± 33.11	0.011	0.373	0.24
General Health						
Baseline	52.2 ± 19.76	54.2 ± 16.39	53.3 ± 21.61			
Change from baseline	-0.4 ± 19.54	23.7 ± 19.69	17.6 ± 22.96	<0.001	0.001	0.20
<b>Mental Health Components</b>						
Role Limitations due to Emotional Problems						
Baseline	90.7 ± 25.23	92.0 ± 22.90	88.7 ± 27.45			
Change from baseline	-11.5 ± 41.09	1.6 ± 19.65	-5.8 ± 43.29	0.08	0.59	0.34
Energy/Fatigue						
Baseline	51.8 ± 21.73	53.3 ± 20.50	48.8 ± 25.77			
Change from baseline	-2.2 ± 21.70	21.6 ± 18.35	12.8 ± 30.23	<0.001	0.03	0.12
Emotional Well Being						
Baseline	80.5 ± 13.21	84.3 ± 10.60	80.0 ± 14.88			
Change from baseline	-7.0 ± 16.17	0.6 ± 12.14	-6.3 ± 21.76	0.03	0.88	0.08
Social Functioning						
Baseline	86.8 ± 18.28	87.5 ± 16.94	82.0 ± 21.89			
Change from baseline	-5.6 ± 20.48	3.4 ± 17.68	-2.5 ± 36.05	0.055	0.678	0.36

\* Plus-minus values are means ±SD. The RAND-36 scores are standardized, with the worst score of 0 (poor health) and the best score of 100 (good health).

<b>Table S7 - Types of new cancers through 36 Months (n=6)</b>		
<b>Intensive Medical Therapy</b>	<b>Gastric Bypass</b>	<b>Sleeve Gastrectomy</b>
Ovarian cancer (stage 2b)	Papillary thyroid cancer (stage 1)	Breast cancer (stage 2)
Basal cell carcinoma (skin)	Malignant melanoma (skin)	Basal cell carcinoma (skin)

<b>Table S8 - Characteristics of foot ulcers</b>	
<b>Patient</b>	<b>Onset</b>
Left metatarsal foot osteomyelitis from unhealing foot ulcer resulting from trauma 2 years after surgery	Developed after randomization
Plantar foot ulcer from ill-fitting shoes 2 years after surgery	Developed after randomization
Chronic foot ulcer 2 years after surgery	Developed after randomization

## **Background Material**

### **1. *Exclusion of type 1 diabetes or MODY:***

No individual randomized had absence of fasting c-peptide levels or phenotypic features suggesting type 1 diabetes, LADA, MODY. Individuals with clinical suspicion for either of these conditions had further evaluation with autoimmune antibodies in select cases and were screened out.

### **2. *Presence of insulin secretion failure:***

Clinical indicators of poor insulin secretion at baseline include long-standing duration of disease (8 yrs median with Q1: 4 years; Q4: 12 years), exogenous use of insulin (approximately 44%), and low c-peptide (40% below 1 ng/mL). Based on the prevalence of insulin use and those with long-standing duration of disease at baseline, we suspect that a considerable proportion of patients likely had poor residual pancreatic beta cell function.

### **3. *Characteristics of a patient who developed severe hypoglycemia after surgery:***

She had residual diabetes after RYGB and was on 3 oral antidiabetics (Glyburide, Metformin, Precose) when she developed symptomatic hypoglycemia. She was on insulin, GLP-1 agonist, and 2 oral antidiabetics before RYGB.

### **4. *Characteristics of retinopathy:***

Retinopathy was primarily background non-proliferative and was reported in our previous report (14% in IMT, 22% in RYGB and 14% in SG group).

### **5. *Correlation analysis shows that among surgical groups, both a reduction in BMI and duration of diabetes <8 years predicted achievement of the primary endpoint. Is this true also within individual surgical groups?***

We performed an analysis to determine whether the factors related to glycemic control at 3 years differ within each surgical group. We evaluated the following factors: age, gender, insulin use, duration of diabetes, c-peptide level, baseline HbA1c, baseline glucose, baseline lipids and triglycerides, body weight and blood pressure. We ran models for each surgical group separately and also tested interactions in a model for both surgical groups combined. None of the interactions were significant in the overall model. In the separate models for each surgical group, the only significant factor related to glycemic control at 36 months was reduction in BMI.