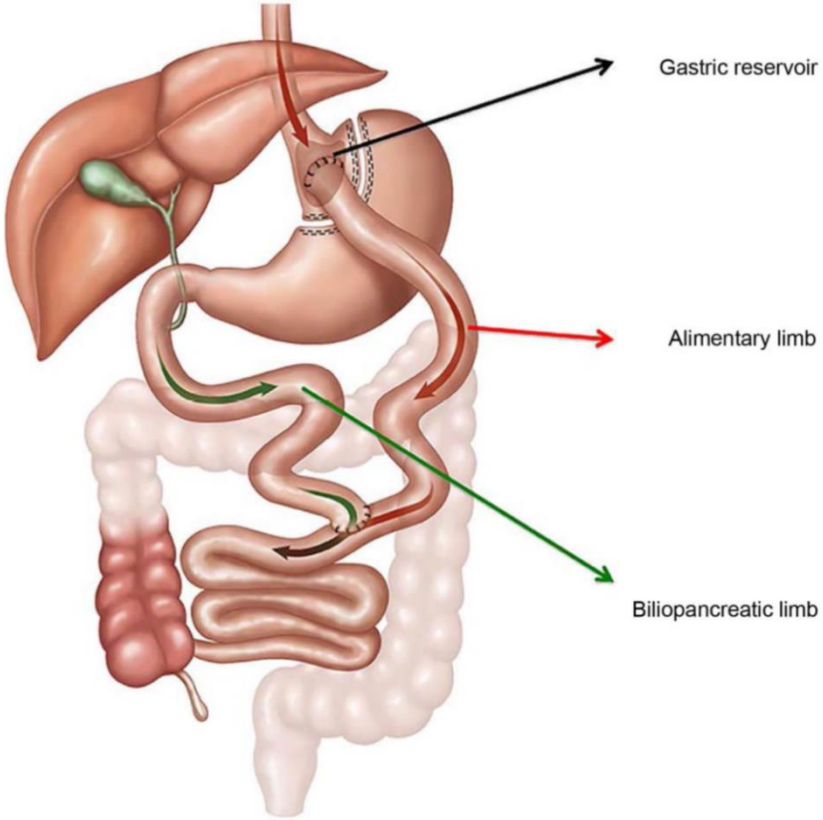
Supplementary Online Content

Cohen RV, Pereira TV, Aboud CM, et al. Effect of gastric bypass vs best medical treatment on early-stage chronic kidney disease in patients with type 2 diabetes and obesity: a randomized clinical trial. *JAMA Surg.* Published online June 3, 2020. doi:10.1001/jamasurg.2020.0420

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

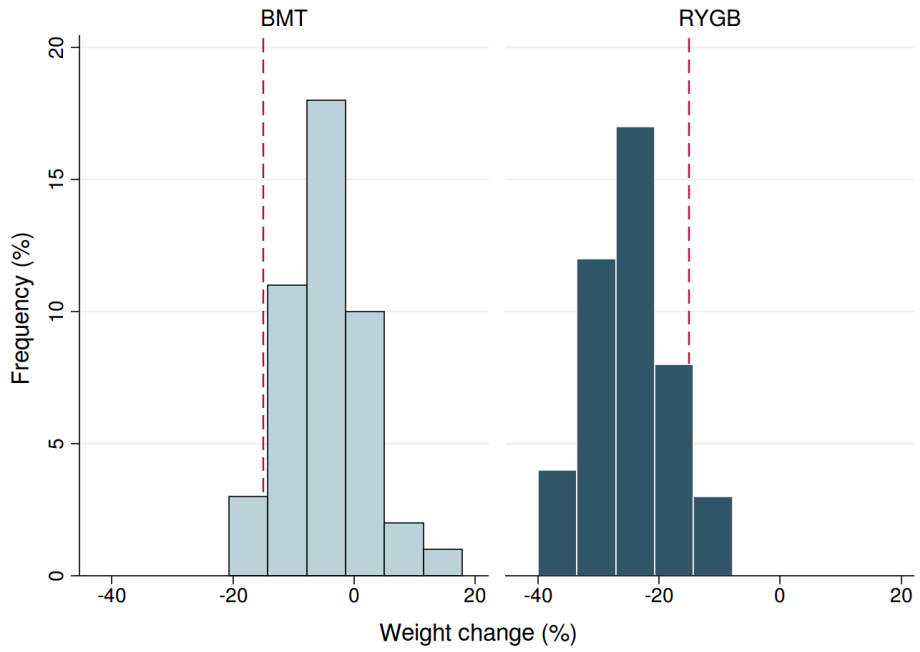
eFigure 1. RYGB Reconstruction



RYGB-Roux-en-Y gastric bypass.

eFigure 2. Patterns of Weight Change

A



Frequency histogram showing the percentage of weight loss after 2 years. BMT, best medical treatment. RYGB, Roux-en-Y Gastric Bypass. The panel depicts the complete case (no missing data) analysis: BMT (n = 45) and RYGB (n = 44). Vertical dashed lines represent the cuff-off of 15% reduction in body weight (measured in kilograms).

eTable 1 Outcome Definitions

Blood pressure	Measurements was performed with a calibrated aneroid sphygmomanometer after at least 5 minutes of rest in a half-sitting position. Final systolic and diastolic blood pressure levels were obtained by the arithmetic mean of two readings measured at 5-minute intervals.
Biochemical parameters and imaging tests	Laboratory measurements were performed by the same central laboratory, certified by ISO 9001, ISO14001 and accredited by the College of American Pathologists (CAP). Imaging tests were performed according to standardized procedures of a local imaging diagnostic laboratory, equally certified and accredited. All biochemical and imagining measurements followed the same local standards and procedures. Blood and urine samples were obtained after a minimum 8-hour fast.
Microalbuminuria	Microalbuminuria was determined by the urine albumin-to-urine creatinine (uACR) ratio and was expressed in mg/g. An early morning spot urine sample was used. Urine albumin was quantified by an immunoturbidimetric assay (Roche), whereas creatinine was determined by a colorimetric assay (Roche). The lower limit of detection of albumin concentration was 3 mg/L. Urinary albumin levels below the detection limits were assigned the value of the respective detection limit. Conversion factor (mg/g to mg/mmol) is 0.113 (30mg/g =3.39mg/mmol)
Retinopathy	Eye examinations followed standardized procedures. Images were evaluated by one trained ophthalmologist masked to the allocation status of the patients. On the basis of the photographic standards defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) [1,2], patients were classified into one of the following categories: • No diabetic retinopathy • Non-proliferative diabetic retinopathy (mild) • Non-proliferative diabetic retinopathy (moderate) • Non-proliferative diabetic retinopathy (severe) • Proliferative diabetic retinopathy (low risk) • Proliferative diabetic retinopathy (high risk) The final retinopathy status for each participant was determined on the basis of the most severe level from both eyes. In 8 participants (five in the BMT and three in the medical gastric bypass), the severity of diabetic retinopathy in an eye could not be graded. For these patients, the eye with a missing classification received the same grade as the other eye. We considered three major main categories for statistical analysis: no diabetic retinopathy (none), non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).
Neuropathy	Monofilament and tuning fork tests were performed by diabetologists that were aware of the patient's allocation group. A standard monofilament (5.07/ 10-gram Semmes-Weinstein nylon monofilament) was employed to exert a gentle pressure on six sites of the patients' feet: hallux, three plantar metatarsal sites and ankle (bilateral). A random site order was used for application of stimulus in each participant. Each site was classified as “positive” if the patients perceived the stimulus normally, “positive, but with a reduced sensitivity” if the perception was reduced or “negative” if the patient did not perceive the stimulus at all. Vibration testing was carried out by a 128-Hz tuning fork applied to six sites of the patient's feet: hallux, three plantar metatarsal sites and ankle (bilateral). Patients were also classified into “positive”, “positive, but with reduced sensitivity” or “negative”. Neuropathy was defined as the presence of one or more sites being negative or “positive, but with reduced sensitivity” - either detected by the 10-g monofilament or tuning fork test.
ADA (2012) composite endpoint [3]	Glycated hemoglobin <7%, LDL-cholesterol <100 mg/dL, systolic blood pressure < 130 mmHg and diastolic blood pressure <80 mmHg.

eTable 2. Changes to Trial Nonprimary End Points After the Trial Commenced

N	Outcome	Status	Reason
1	ADA criteria composite	New. Non-prespecified in the protocol	Clinical relevance.
2	HbA1c: Estimated proportion of patients ≤7.0%	New. Non-prespecified in the protocol	Comparability with previous metabolic surgery trials.
3	HbA1c: Estimated proportion of patients ≤6.0%	New. Non-prespecified in the protocol	Comparability with previous metabolic surgery trials.
4	Estimated proportion of patients with ACR <10 mg/g	New. Non-prespecified in the protocol	Recent results (secondary analyses) from the SAVOR-TIMI 53 Trial [4].
5	Proportion of patients with >15% weight loss	New. Non-prespecified in the protocol	Clinical relevance.
6	Proportion of patients with a BMI <25 kg/m^2	New. Non-prespecified in the protocol	Clinical relevance.
7	Medications for hypertension	New. Non-prespecified in the protocol	Clinical relevance, since antihypertensive drugs affect directly the primary outcome.
8	Reduction in the degree of voiding dysfunction Symptoms	Prespecified and not reported.	Poor data quality. Voiding dysfunction was assessed by two questionnaires and one diary. There were several unanticipated limitations with these instruments. Firstly, questionnaires were applied simultaneously with other study forms, causing extremely low response rates. Secondly, the diary questionnaire has been considered too lengthy by the trial participants and some obstacles have been found in terms of user friendliness. Although several efforts have been made to guarantee the quality and completeness of data and procedures, the paucity of data prevented inclusion of this outcome at 12 months.
9	Reduction of hepatic elastographic resistance	Prespecified and not reported.	Outcome expected to change with longer follow-ups only. This outcome will be analyzed at 60 months.
10	Proportion of patients achieving a LDL <70 mg/dL in patients with previous cardiovascular events	Prespecified and not reported.	Few patients with previous cardiovascular events.
			This outcome was defined as a binary outcome at the study start. However, we judged that retinopathy as a categorical

ADA, American Diabetes Association. BMI, body mass index. CKD, chronic kidney disease

eTable 3. Variables With Missing Data

Variable – no. (%)	BMT (N = 49)		RYGB (N = 51)		Reasons for missing data	
	Baseline	2 years	Baseline	2 years	BMT	RYGB
Body-mass index	0	4 (8.1)	0	7 (13.7)	• 2 withdrew consent for not being satisfied with the randomization result (patients excluded from the trial). • 1 withdrew consent to undergo a cosmetic procedure (patient excluded). • 1 unable to attend follow-ups due to have moved to another state in our country (patient excluded).	• 2 withdrew consent unknown reasons (patients excluded). • 1 was diagnosed with Cushing's syndrome (patient excluded). • 1 had past history of psychiatric conditions (patient excluded). • 1 unable to attend follow-ups due to family and professional commitments (patient excluded). • 1 withdrew consent to undergo a non-approved procedure (endoscopic plasma argon coagulation). • 1 patient did not attend to study visit.
Urinary creatinine	0	6 (12.2)	0	7 (13.7)	• 2 withdrew consent for not being satisfied with the randomization result (patients excluded from the trial). • 1 withdrew consent to undergo a cosmetic procedure (patient excluded). • 1 unable to attend follow-ups due to have moved to another state in our country (patient excluded). • 2 patients did not provide urine samples.	• 2 withdrew consent unknown reasons (patients excluded). • 1 was diagnosed with Cushing's syndrome (patient excluded). • 1 had past history of psychiatric conditions (patient excluded). • 1 unable to attend follow-ups due to family and professional commitments (patient excluded). • 1 withdrew consent to undergo a non-approved procedure (endoscopic plasma argon coagulation). • 1 patient did not provide urine sample.
Albuminuria	0	5 (9.8)	0	8 (15.7)	• 2 withdrew consent for not being satisfied with the randomization result (patients excluded from the trial). • 1 withdrew consent to undergo a cosmetic procedure (patient excluded). • 1 unable to attend follow-ups due to have moved to another state in our country (patient excluded). • 1 sample was not processed by the central laboratory (unknown reasons).	• 2 withdrew consent unknown reasons (patients excluded). • 1 was diagnosed with Cushing's syndrome (patient excluded). • 1 had past history of psychiatric conditions (patient excluded). • 1 unable to attend follow-ups due to family and professional commitments (patient excluded). • 1 withdrew consent to undergo a non-approved procedure (endoscopic plasma argon coagulation). • 2 patients did not provide urine samples.
Glycated hemoglobin	0	4 (8.2)	0	7 (13.7)	• 2 withdrew consent for not being satisfied with the randomization result (patients excluded from the trial).	• 2 withdrew consent unknown reasons (patients excluded). • 1 was diagnosed with Cushing's syndrome (patient

					• 1 withdrew consent to undergo a cosmetic procedure (patient excluded). • 1 unable to attend follow-ups due to have moved to another state in our country (patient excluded).	excluded). • 1 had past history of psychiatric conditions (patient excluded). • 1 unable to attend follow-ups due to family and professional commitments (patient excluded). • 1 patient did not provide blood sample. • 1 withdrew consent to undergo a non-approved procedure (endoscopic plasma argon coagulation).
Fasting glucose	0	4 (8.2)	0	7 (13.7)	• 2 withdrew consent for not being satisfied with the randomization result (patients excluded from the trial). • 1 withdrew consent to undergo a cosmetic procedure (patient excluded). • 1 unable to attend follow-ups due to have moved to another state in our country (patient excluded).	• 2 withdrew consent unknown reasons (patients excluded). • 1 was diagnosed with Cushing's syndrome (patient excluded). • 1 had past history of psychiatric conditions (patient excluded). • 1 unable to attend follow-ups due to family and professional commitments (patient excluded). • 1 patient did not provide blood sample. • 1 withdrew consent to undergo a non-approved procedure (endoscopic plasma argon coagulation).
Total cholesterol	0	4 (8.2)	0	7 (13.7)		
HDL	0	4 (8.2)	0	7 (13.7)		
LDL	0	4 (8.2)	0	7 (13.7)		
Triglycerides	0	4 (8.2)	0	7 (13.7)		
Systolic blood pressure	0	4 (8.2)	2 (3.9)	8 (15.7)	• 2 withdrew consent for not being satisfied with the randomization result (patients excluded from the trial). • 1 withdrew consent to undergo a cosmetic procedure (patient excluded). • 1 unable to attend follow-ups due to have moved to another state in our country (patient excluded).	At baseline: • 2 patients had their blood pressure measured, but values not registered (unknown reasons). At 2 years of follow-up: • 2 withdrew consent unknown reasons (patients excluded). • 1 was diagnosed with Cushing's syndrome (patient excluded). • 1 had past history of psychiatric conditions (patient excluded). • 1 unable to attend follow-ups due to family and professional commitments (patient excluded). • 1 withdrew consent to undergo a non-approved procedure (endoscopic plasma argon coagulation). • 2 patients without blood pressure assessment.
Diastolic blood pressure	0	4 (8.2)	2 (3.9)	8 (15.7)		
Waist circumference	3 (6.1)	5 (10.2)	5 (9.98)	8 (15.7)	At baseline: • 3 patients failed to have their waist circumference measured	At baseline: • 5 patients failed to have their waist circumference measured

					At 2 years of follow-up: • 2 withdrew consent for not being satisfied with the randomization result (patients excluded from the trial). • 1 withdrew consent to undergo a cosmetic procedure (patient excluded). • 1 unable to attend follow-ups due to have moved to another state in our country (patient excluded). • 1 patient failed to have his/her waist circumference measured.	At 2 years of follow-up: • 2 withdrew consent unknown reasons (patients excluded). • 1 was diagnosed with Cushing's syndrome (patient excluded). • 1 had past history of psychiatric conditions (patient excluded). • 1 unable to attend follow-ups due to family and professional commitments (patient excluded). • 2 patients did not provide blood samples. • 1 withdrew consent to undergo a non-approved procedure (endoscopic plasma argon coagulation).
36-Item Short Form Health Survey	0	6 (12.2)	3 (5.9)	8 (15.7)	At 2 years of follow-up: • 2 withdrew consent for not being satisfied with the randomization result (patients excluded from the trial). • 1 withdrew consent to undergo a cosmetic procedure (patient excluded). • 1 unable to attend follow-ups due to have moved to another state in our country (patient excluded) - #091 • 2 patients did not answer the SF-36 questionnaire.	At baseline: • 3 patients did not answer the SF-36 questionnaire. At 2 years of follow-up: • 2 withdrew consent unknown reasons (patients excluded). • 1 was diagnosed with Cushing's syndrome (patient excluded). • 1 had past history of psychiatric conditions (patient excluded). • 1 unable to attend follow-ups due to family and professional commitments (patient excluded). • 1 withdrew consent to undergo a non-approved procedure (endoscopic plasma argon coagulation). • 2 patients did not answer the SF-36 questionnaire.
Retinopathy	6 (12.2)	10 (20.4)	3 (5.9)	12 (23.5)	At baseline: • 6 patients did not attend the scheduled visits. At 2 years of follow-up: • 2 withdrew consent for not being satisfied with the randomization result (patients excluded from the trial). • 1 withdrew consent to undergo a cosmetic procedure (patient excluded). • 1 unable to attend follow-ups due to have moved to another state in our country (patient excluded). • 6 patients did not attend the scheduled visits.	At baseline: • 3 patients did not attend the schedule visits. At 2 years of follow-up: • 2 withdrew consent unknown reasons (patients excluded). • 1 was diagnosed with Cushing's syndrome (patient excluded). • 1 had past history of psychiatric conditions (patient excluded). • 1 unable to attend follow-ups due to family and professional commitments (patient excluded). • 1 withdrew consent to undergo a non-approved

						procedure (endoscopic plasma argon coagulation). • 6 patients did not attend the scheduled visits.
Neuropathy	1 (2)	6 (12.2)	3 (5.9)	9 (17.6)	At baseline: • 1 patient did not attend the scheduled visit. At 2 years of follow-up: • 2 withdrew consent for not being satisfied with the randomization result (patients excluded from the trial). • 1 withdrew consent to undergo a cosmetic procedure (patient excluded). • 1 unable to attend follow-ups due to have moved to another state in our country (patient excluded). • 2 patients did not attend the scheduled visits.	At baseline: • 3 patients did not attend the scheduled visits. At 2 years of follow-up: • 2 withdrew consent unknown reasons (patients excluded). • 1 was diagnosed with Cushing's syndrome (patient excluded). • 1 had past history of psychiatric conditions (patient excluded). • 1 unable to attend follow-ups due to family and professional commitments (patient excluded). • 1 withdrew consent to undergo a non-approved procedure (endoscopic plasma argon coagulation). • 3 patients did not attend the scheduled visits.

eTable 4. Clinical Variables by Quartile

Variables at base line	Arm	25th percentile	Median	75th percentile
Albuminuria (mg/g of creatinine)	BMT	52	73	168
	RYGB	53	72	143
EGFR (ml/min/1.73m^2)	BMT	89.04	100.98	108.75
	RYGB	84.11	98.11	105.39
HbA1c (%)	BMT	7.5	8.9	10
	RYGB	7.5	8.4	10.4
Fasting plasma glucose (mg/dL)	BMT	142	174	232
	RYGB	145	167	208
Total Cholesterol (mg/dL)	BMT	163	185	226
	RYGB	153	180	204
HDL (mg/dL)	BMT	30	37	46
	RYGB	33	38	47
LDL (mg/dL)	BMT	79	103	135
	RYGB	74	101	125
Triglycerides (mg/dL)	BMT	150	214	334
	RYGB	145	195	293
Systolic blood pressure (mmHg)	BMT	125	135	145
	RYGB	130	140	150
Diastolic blood pressure (mmHg)	BMT	80	85	90
	RYGB	80	90	95

BMT, best medical treatment (n = 49). RYGB, Roux-en-Y gastric bypass (n = 51).

eTable 5. Minor Protocol Deviations (Eligibility Waivers)

Based on clinical grounds, the principal investigator granted eligibility waivers for 21 patients that that did not meet all inclusion/exclusion criteria. All events were due to circumstances that were under the PI's control and did not involve potential risks to the participants or affect subject's right, safety or welfare. All waivers were later submitted to the Brazilian national research ethics commission (Comissão Nacional de Ética em Pesquisa, CONEP) for approval. As of August 3, 2018, since CONEP does not give retroactive approvals of eligibility waivers, a report has been issued (number 2.796.501) explicitly recommending to continue the trial without modification. All protocol deviations are described below:

BMT, best medical treatment. RYGB, Roux-en-Y Gastric Bypass. BMI, body mass index. PDR, proliferative diabetic retinopathy.

	No. of deviations		Detailed values	
Deviation	BMT	RYGB	BMT	RYGB
Microalbuminuria outside the range 30-300 mg/g of creatinine	3	1	359,383,344 mg/g of creatinine	387 mg/g of creatinine
BMI outside the range of 30-35 kg/m^2	4	6	29,36,38,38 kg/m^2	28,29,36,36,36,36 kg/m^2
Taking no anti-diabetic drugs	-	1		
Age at enrolment outside the range of 18-65 years	1	-	66 years	
Diabetes duration longer than 15 years	-	3	-	16,20,20 years
Fasting C peptide below 1 ng/mL and appropriate postprandial C peptide response after a 500 kcal mixed meal challenge	2	4	0.34, 0.65 ng/mL	0.80, 0.54, 0.76 ng/mL and one laboratory test not performed.
Positive glutamic acid decarboxylase autoantibodies test	1	-		
History of PDR	1	-		

eTable 6. Chronic Kidney Disease Assessment According KDIGO Criteria

		Baseline (n=92)		24 months (n=89)	
CKD equation for estimated GFR		BMT (n=46)	RYGB (n=46)	BMT (n=45)	RYGB (n=44)
CKD-Epi					
	G1, n(%)	35 (76.1)	33 (71.7)	31 (67.4)	34 (73.9)
	G2, n(%)	9 (19.6)	11 (23.9)	9 (19.6)	9 (19.6)
	G3a, n(%)	0 (0.0)	2 (4.3)	3 (6.5)	1 (2.2)
	G3b, n(%)	2 (4.3)	0 (0.0)	2 (4.3)	0 (0.0)

KDIGO, Kidney Disease Improving Global Outcomes. CKD, chronic kidney disease. GFR, glomerular filtration rate. BMT, best medical treatment. RYGB, Roux-en-Y gastric bypass. CKD-Epi, Chronic Kidney Disease Epidemiology Collaboration. All results are expressed in mL/min/1,73m^2.

eTable 7. Medication Use at Baseline and 24 Months

	Baseline		24 months		Difference between groups	
	BMT (N = 49)	RYGB (N = 51)	BMT (N = 46)	RYGB (N = 46)	Baseline	24 months
Diabetes and obesity medications						
Biguanides						
No. of patients using – no. (%)	45 (91.8)	40 (78.4)	45 (97.8)	35 (76.1)	0.092	0.004
Median no. of drugs (IQR)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	0.411	0.113
Thiazolidinediones						
Patients using – no. (%)	4 (8.2)	2 (3.9)	31 (67.4)	9 (19.6)	0.432	<0.001
Median no. of drugs (IQR)	0 (0-0)	0 (0-0)	1 (0-1)	0 (0-0)	0.377	<0.001
Incretin mimetics/enhancers						
Patients using – no. (%)	13 (27)	23 (45)	46 (100)	19 (41.3)	0.063	<0.001
Median no. of drugs (IQR)	0 (0-1)	0 (0-1)	2 (1-3)	0 (0-1)	0.259	<0.001
SGLT2 Inhibitors						
Patients using – no. (%)	2 (4.1)	2 (3.9)	41 (89.1)	21 (45.7)	>0.999	<0.001
Median no. of drugs (IQR)	0 (0-0)	0 (0-0)	1 (1-1)	0 (0-1)	0.968	<0.001
Insulin						
Patients using – no. (%)	12 (24.5)	20 (39.2)	25 (54.3)	5 (10.9)	0.115	<0.001
Median no. of drugs (IQR)	0 (0-0)	0 (0-1)	1 (0-3)	0 (0-0)	0.352	0.004
Secretagogues						
Patients using – no. (%)	20 (40.8)	21 (41.2)	2 (4.3)	0	>0.999	0.495
Median no. of drugs (IQR)	0 (0-1)	0 (0-1)	0 (0-0)	0 (0-0)	0.672	>0.999
Antiobesity drugs						
Patients using – no. (%)	1 (2)	1 (2)	6 (13.0)	1 (2.2)	>0.999	0.111
Median no. of drugs (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.977	0.156
Cardiovascular medications						
Lipid lowering agents						
Patients using – no. (%)	18 (36.7)	30 (58.8)	38 (82.6)	33 (71.7)	0.03	0.321
Median no. of drugs (IQR)	0 (0-1)	0 (0-1)	1 (1-2)	0 (0-1)	0.009	0.061
Beta-blockers						
Patients using – no. (%)	6 (12.2)	8 (15.7)	10 (21.7)	6 (13)	0.775	0.410
Median no. of drugs (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.624	0.175
Calcium channel blockers						
Patients using – no. (%)	7 (14.3)	13 (25.5)	10 (21.7)	5 (10.9)	0.213	0.259
Median no. of drugs (IQR)	0 (0-0)	0 (0-1)	0 (0-0)	0 (0-0)	0.165	0.079

ACE-inhibitor or ARB						
Patients using – no. (%)	30 (61.2)	37 (72.5)	40 (87)	41 (89.1)	0.289	>0.999
Median no. of drugs (IQR)	1 (0-1)	0 (0-1)	1 (1-1)	1 (1-2)	0.346	0.110
Diuretics						
Patients using – no. (%)	17 (34.7)	15 (29.4)	14 (30.4)	5 (10.9)	0.669	0.038
Median no. of drugs (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-0)	0.606	0.014
Anticoagulants						
Patients using – no. (%)	16 (32.7)	17 (33.3)	13 (28.3)	6 (13.0)	>0.999	0.121
Median no. of drugs (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-0)	0.660	0.045

IQR, interquartile range. ACE inhibitor, angiotensin-converting enzyme (ACE) inhibitor. ARB, angiotensin receptor blocker. SGLT2, sodium-glucose co-transporter 2. BMT, best medical treatment. RYGB, Roux-en-Y Gastric Bypass

eTable –8. SF-36 Scores

Domain	BMT (n = 49)									RYGB (n = 51)									P-value (between group difference)		
	Baseline			12 mo			24 mo			Baseline			12 mo			24 mo					
	Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI		Baseline	12 mo	24 mo
General health	49.69	44.4	54.99	61.06	55.44	66.68	60.3	54.76	65.83	54.17	48.81	59.52	77.63	72.12	83.14	78.15	72.6	83.7	0.244	<0.001	<0.001
Pain	54.54	47.61	61.47	56.99	49.57	64.42	60.14	52.84	67.43	65.68	58.68	72.68	75.64	68.4	82.87	74.91	67.61	82.21	0.027	<0.001	0.005
Social functioning	63.78	56.57	70.98	65.28	57.56	73.01	65.48	57.89	73.07	76.04	68.77	83.32	78.65	71.12	86.18	82.51	74.91	90.1	0.019	0.015	0.002
Emotional well–being	62.53	57.05	68.01	59.93	54	65.85	63.04	57.23	68.84	63.25	57.72	68.78	71.23	65.48	76.98	71.97	66.17	77.78	0.856	0.007	0.033
Vitality	48.88	43.3	54.45	56.04	50.04	62.05	55.1	49.21	60.99	52.81	47.18	58.44	66.42	60.58	72.26	69.51	63.62	75.4	0.330	0.015	0.001
Mental health	56.46	45.11	67.81	61.79	49.52	74.06	62.64	50.61	74.66	69.44	57.97	80.91	75.54	63.63	87.45	73.53	61.5	85.55	0.115	0.115	0.209
Physical health	54.59	43.58	65.6	61.39	49.54	73.24	60.52	48.89	72.14	58.85	47.73	69.98	74.32	62.79	85.85	80.42	68.79	92.06	0.594	0.125	0.018
Physical role functioning	64.39	58.24	70.54	73.99	67.51	80.48	70.15	63.75	76.55	68.75	62.54	74.96	84.6	78.22	90.97	84.3	77.89	90.72	0.328	0.022	0.002

Results are presented as mean (95% confidence intervals, CI). Scores range (0-100). The higher the score, the better the quality of life. BMT, best medical treatment. RYGB, Roux-en-Y Gastric Bypass. 12 mo, 12 months. 24 mo, 24 months.

eTable 9. Adverse Events

	BMT (n=46)	RYGB (n=46)	OR (95% CI)
Abdominal hernias and other abdominal wall conditions			
Inguinal hernia	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Umbilical hernia	2 (4.3)	1 (2.2)	0.49 (0.01,9.78)
Allergic conditions			
Allergic reaction	2 (4.3)	0 (0.0)	0.41 (0.00,5.31)
Alopecia			
Alopecia	4 (8.7)	16 (34.8)	5.50 (1.56,24.9)
Anal and rectal conditions NEC			
Proctalgia	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Angioedema and urticaria			
Urticaria	1 (2.2)	0 (0.0)	1.0 (0.00,39.0)
Anterior eye structural change, deposit and degeneration			
Cataract	1 (2.2)	2 (4.3)	2.03 (0.10,123.3)
Anxiety disorders and symptoms			
Anxiety	19 (41.3)	13 (28.3)	0.56 (0.21,1.45)
Appetite and general nutritional disorders			
Food intolerance	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Pica	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Decreased appetite	1 (2.2)	1 (2.2)	1.00 (0.01,80.2)
Increased appetite	4 (8.7)	3 (6.5)	0.74 (0.10,4.63)
Arteriosclerosis, stenosis, vascular insufficiency and necrosis			
Intermittent claudication	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Bacterial infectious disorders			
Erysipelas	1 (2.2)	0 (0.0)	1.00 (0.00,39.0)
Body temperature conditions			
Pyrexia	0 (0.0)	2 (4.3)	2.45 (0.19,+Inf)
Bone and joint injuries			
Joint dislocation	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Bone disorders (excl congenital and fractures)			
Osteoporosis	0 (0.0)	2 (4.3)	2.45 (0.19,+Inf)
Exostosis	1 (2.2)	0 (0.0)	1.00 (0.00,39.0)
Cardiac arrhythmias			
Tachycardia	0 (0.0)	3 (6.5)	3.99 (0.42,+Inf)
Dental and gingival conditions			
Noninfective gingivitis	1 (2.2)	0 (0.0)	1.00 (0.00,39.0)
Depressed mood disorders and disturbances			
Depression	4 (8.7)	3 (6.5)	0.74 (0.10,4.63)

Ear diseases			
Ear diseases	5 (10.9)	2 (4.3)	0.38 (0.03,2.46)
Electrolyte and fluid balance conditions			
Fluid retention	1 (2.2)	0 (0.0)	1.00 (0.00,39.0)
Epidermal and dermal conditions			
Dermatitis	1 (2.2)	2 (4.3)	2.03 (0.10,123.3)
Pruritus	6 (13.0)	6 (13.0)	1.00 (0.24,4.09)
Photosensitivity reaction	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Skin diseases	6 (13.0)	1 (2.2)	0.15 (0.00,1.32)
Eye disorders NEC			
Eye pain	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Eye therapeutic procedures			
Eye operation	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Glaucoma surgery	1 (2.2)	0 (0.0)	1.00 (0.00,39.0)
Cataract operation	1 (2.2)	0 (0.0)	1.00 (0.00,39.0)
Fungal infectious disorders			
Candidiasis	2 (4.3)	0 (0.0)	0.41 (0.00,5.31)
Gallbladder disorders			
Cholelithiasis	0 (0.0)	4 (8.7)	5.59 (0.68,+Inf)
Gastrointestinal disorders			
GI/abdominal pain	13 (28.3)	36 (78.3)	8.88 (3.23,26.5)
GI hemorrhage	1 (2.2)	4 (8.7)	4.23 (0.40,215.7)
Flatulence	2 (4.3)	6 (13.0)	3.26 (0.54,34.8)
Diarrhoea	15 (32.6)	22 (47.8)	1.88 (0.75,4.82)
Vomiting	25 (54.3)	28 (60.9)	1.30 (0.53,3.25)
Abdominal discomfort	7 (15.2)	7 (15.2)	1.00 (0.27,3.69)
Constipation	16 (34.8)	10 (21.7)	0.52 (0.18,1.44)
Gastrointestinal haemorrhages NEC			
Intra-abdominal. hematoma	0 (0.0)	4 (8.7)	5.59 (0.68,+Inf)
Gastrointestinal inflammatory conditions			
Gastritis	1 (2.2)	0 (0.0)	1.00 (0.00,39.0)
Gastrointestinal motility and defaecation conditions			
Gastrooesophageal reflux disease	1 (2.2)	1 (2.2)	1.00 (0.01,80.2)
Gastrointestinal signs and symptoms			
Dyspepsia	1 (2.2)	3 (6.5)	3.10 (0.24,168.4)
Eructation	0 (0.0)	2 (4.3)	2.45 (0.19,+Inf)
Dumping syndrome	0 (0.0)	9 (19.6)	14.91 (2.24,+Inf)
Acute abdomen	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Nausea	6 (13.0)	2 (4.3)	0.31 (0.03,1.84)
General system disorders NEC			
Fatigue	3 (6.5)	3 (6.5)	1.00 (0.13,7.89)

Xerosis	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Microlithiasis	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Pain	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Chest pain	3 (6.5)	0 (0.0)	0.25 (0.00,2.39)
Oedema peripheral	4 (8.7)	0 (0.0)	0.18 (0.00,1.47)
Head and neck therapeutic procedures			
Dental implantation	1 (2.2)	4 (8.7)	4.23 (0.40,215.7)
Headaches			
Headache	10 (21.7)	8 (17.4)	0.76 (0.23,2.41)
Hepatic and hepatobiliary disorders			
Hepatitis	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Hypoglycaemia			
Hypoglycaemia	12 (26.1)	26 (56.5)	3.63 (1.41,9.81)
Hypotension			
Hypotension	3 (6.5)	6 (13.0)	2.13 (0.42,14.1)
Infections - pathogen unspecified			
Peritonsillar abscess	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Cystitis	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Localised infection	1 (2.2)	1 (2.2)	1.00 (0.01,80.2)
Injuries NEC			
Limb injury	3 (6.5)	3 (6.5)	1.00 (0.13,7.89)
Epicondylitis	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Fall	2 (4.3)	1 (2.2)	0.49 (0.01,9.78)
Joint disorders			
Arthritis	1 (2.2)	1 (2.2)	1.00 (0.01,80.2)
Arthralgia	10 (21.7)	0 (0.0)	0.06 (0.00,0.38)
Menstrual cycle and uterine bleeding disorders			
Menorrhagia	1 (2.2)	1 (2.2)	1.00 (0.01,80.2)
Mental impairment disorders			
Memory impairment	2 (4.3)	2 (4.3)	1.00 (0.07,14.4)
Movement disorders (incl parkinsonism)			
Movement disorder	1 (2.2)	0 (0.0)	1.00 (0.00,39.0)
Muscle disorders			
Muscular weakness	6 (13.0)	13 (28.3)	2.60 (0.81,9.30)
Myalgia	2 (4.3)	3 (6.5)	1.53 (0.17,19.1)
Muscle spasms	4 (8.7)	4 (8.7)	1.00 (0.17,5.75)
Musculoskeletal and connective tissue disorders NEC			
Plantar fasciitis	1 (2.2)	0 (0.0)	1.00 (0.00,39.0)
Musculoskeletal pain	32 (69.6)	22 (47.8)	0.41 (0.16,1.02)
Neurological disorders NEC			
Syncope	0 (0.0)	6 (13.0)	9.05 (1.25,+Inf)

Dizziness	9 (19.6)	9 (19.6)	1.00 (0.31,3.20)
Neuralgia	1 (2.2)	0 (0.0)	1.00 (0.00,39.0)
Neuromuscular disorders			
Hypotonia	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Nutritional disorders			
Anaemia	3 (6.5)	6 (13.0)	2.13 (0.42,14.1)
Ocular neuromuscular disorders			
Eye diseases	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Ocular structural change, deposit and degeneration NEC			
Macular degeneration	1 (2.2)	0 (0.0)	1.00 (0.00,39.0)
Paraesthesia			
Paraesthesia	6 (13.0)	3 (6.5)	0.47 (0.07,2.37)
Penile and scrotal disorders (excl infections and inflammations)			
Penile pain	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Personality disorders and disturbances in behaviour			
Aggression	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Procedural related injuries and complications NEC			
Seroma	0 (0.0)	2 (4.3)	2.45 (0.19,+Inf)
Incision site pain	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Prostatic disorders (excl infections and inflammations)			
Benign prostatic hyperplasia	1 (2.2)	1 (2.2)	1.00 (0.01,80.2)
Psychiatric disorders NEC			
Organic brain syndrome	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Pulpitis			
Pulpitis	1 (2.2)	4 (8.7)	4.23 (0.40,215.7)
Renal and urinary tract disorders congenital			
Renal aplasia	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Respiratory disorders NEC			
Cough	2 (4.3)	4 (8.7)	2.08 (0.28,24.1)
Hiccups	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Choking	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Oropharyngeal pain	1 (2.2)	1 (2.2)	1.00 (0.01,80.2)
Dyspnoea exertional	1 (2.2)	0 (0.0)	1.00 (0.00,39.0)
Pulmonary mass	1 (2.2)	0 (0.0)	1.00 (0.00,39.0)
Respiratory tract infections			
RTIs	18 (39.1)	10 (21.7)	0.44 (0.15,1.18)
Salivary gland conditions			
Dry mouth	2 (4.3)	1 (2.2)	0.49 (0.01,9.78)
Seizures (incl subtypes)			
Partial seizures	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)

Sexual function and fertility disorders			
Sexual dysfunction	4 (8.7)	1 (2.2)	0.24 (0.00,2.52)
Skin and subcutaneous tissue disorders NEC			
Diabetic foot	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Skin appendage conditions			
Hidradenitis	1 (2.2)	0 (0.0)	1.00 (0.00,39.0)
Nail disorders	6 (13.0)	5 (10.9)	0.81 (0.18,3.49)
Sleep disorders and disturbances			
Sleep disorders	14 (30.4)	9 (19.6)	0.56 (0.19,1.60)
Soft tissue neoplasms benign			
Leiomyoma	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Synovial and bursal disorders			
Bursitis	0 (0.0)	3 (6.5)	3.99 (0.42,+Inf)
Tendon, ligament and cartilage disorders			
Tendonitis	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Thyroid gland disorders			
Thyroide nodule	2 (4.3)	2 (4.3)	1.00 (0.07,14.4)
Hypothyroidism	1 (2.2)	0 (0.0)	1.00 (0.00,39.0)
Urinary tract signs and symptoms			
Urinary tract infection	6 (13.0)	9 (19.6)	1.61 (0.46,6.08)
Renal colic	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Haematuria	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Urinary tract disorders	2 (4.3)	0 (0.0)	0.41 (0.00,5.31)
Urolithiases			
Nephrolithiasis	2 (4.3)	2 (4.3)	1.00 (0.07,14.4)
Vascular disorders			
Varicose vein	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Vascular disorders NEC			
Peripheral vascular disorder	1 (2.2)	0 (0.0)	1.00 (0.00,39.0)
Hyperaemia	1 (2.2)	0 (0.0)	1.00 (0.00,39.0)
Vascular hypertensive disorders			
Hypertension	2 (4.3)	3 (6.5)	1.53 (0.17,19.1)
Viral infectious disorders			
Viral infection	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Dengue fever	2 (4.3)	0 (0.0)	0.41 (0.00,5.31)
Vision disorders			
Vision blurred	1 (2.2)	3 (6.5)	3.10 (0.24,168.4)
Visual acuity reduced	1 (2.2)	1 (2.2)	1.00 (0.01,80.2)
Diplopia	2 (4.3)	0 (0.0)	0.41 (0.00,5.31)
Vitamin related disorders			
Vit. B12 deficiency	1 (2.2)	8 (17.4)	9.29 (1.16,429.5)

Vitamin D deficiency	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)
Vulvovaginal disorders (excl infections and inflammations)			
Vulvovaginal dryness	0 (0.0)	1 (2.2)	1.00 (0.03,+Inf)

OR denotes odds ratio and CI confidence interval. OR estimates are based on an exact logistic regression model. BMT denotes best medical treatment. RYGB denotes Roux-en-Y Gastric Bypass. GI denotes gastrointestinal. Reported adverse events encompass all the recorded adverse events. NEC denotes not elsewhere classified.

eMethods. Statistical Analysis Missing Data Approach

The reporting of the statistical approach for missing data of this study followed the recommendations by Sterne et al. [5]. A total of eight participants (three in the best medical treatment group and five in the medical gastric bypass arm) did not receive the allocated intervention due to several reasons (see Cohen et al. [6] and Supplementary Table S2) and were excluded from the trial. However, all available data were used throughout the statistical analysis in a full intention-to-treat analysis, incorporating data from all participants.

Statistical analysis

Microalbuminuria (mg/g) was statistically evaluated on a log scale. Mean (standard deviation) or mean (95% confidence intervals, CI) were used for approximately normally distributed variables. Median (interquartile range) was used for variables with skewed distributions.

eReferences

[1] Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98:786-806.

[2] Classification of diabetic retinopathy from fluorescein angiograms. ETDRS report number 11. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98:807-22

[3] American Diabetes Association. Standards of medical care in diabetes--2012. Diabetes Care. 2012 Jan;35 Suppl 1:S11-63.

[4] Scirica BM, Mosenzon O, Bhatt DL, Udell JA, Steg PG, McGuire DK, Im K, Kanevsky E, Stahre C, Sjöstrand M, Raz I, Braunwald E. Cardiovascular Outcomes According to Urinary Albumin and Kidney Disease in Patients With Type 2 Diabetes at High Cardiovascular Risk: Observations From the SAVOR-TIMI 53 Trial. JAMA Cardiol. 2018;3(2):155-163.

[5] Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. Bmj. 2009 Jun 29;338:b2393.

[6] Cohen RV, Pereira TV, Aboud CM, de Paris Caravatto PP, Petry TB, Correa JL, Schiavon CA, Correa M, Pompílio CE, Pechy FN, le Roux C. Microvascular Outcomes after Metabolic Surgery (MOMS) in patients with type 2 diabetes mellitus and class I obesity: rationale and design for a randomised controlled trial. BMJ open. 2017 Jan 1;7(1):e013574.