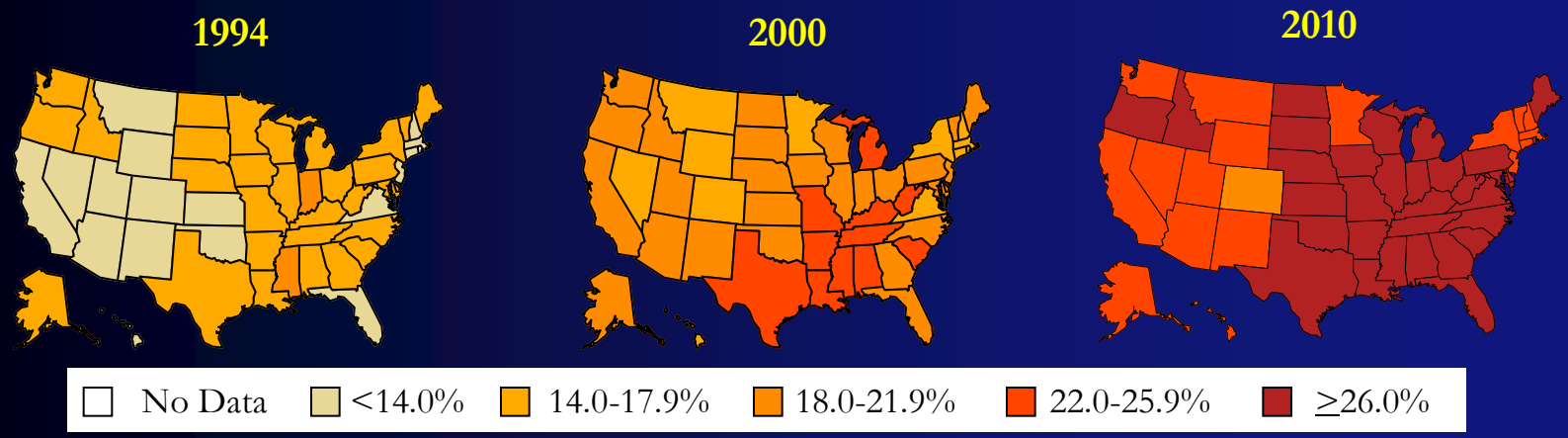
3° WORKSHOP CONGIUNTO SICOb – SID – SIO
L'integrazione tra terapia medica e chirurgica nel trattamento del paziente obeso diabetico
7 marzo 2014

Reversibilità delle complicanze nel diabete tipo 2

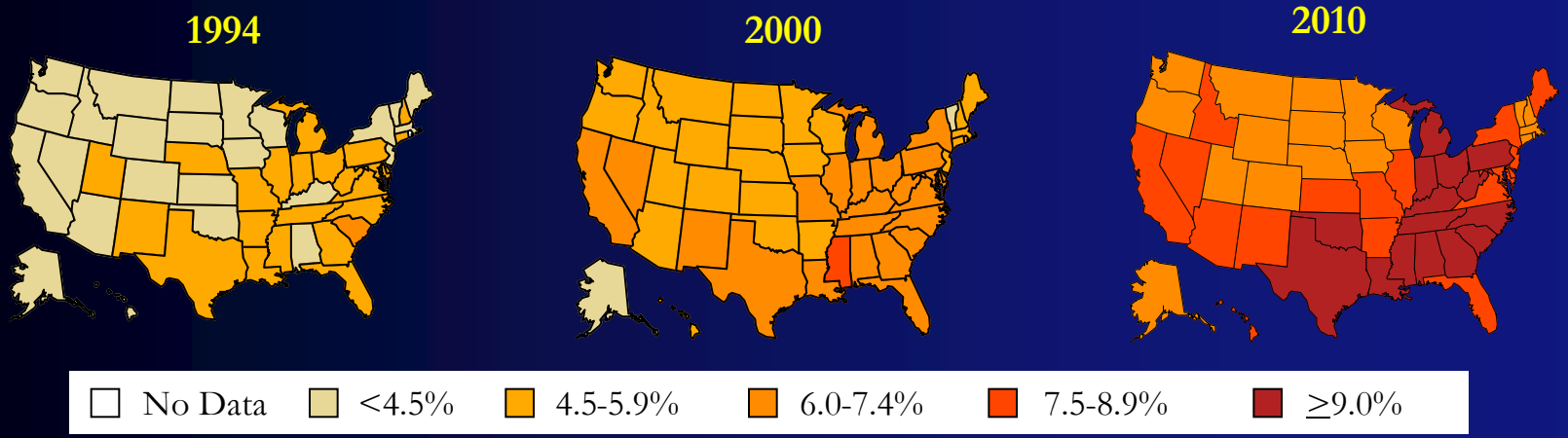
Roberto Fabris
Unità Bariatrica - Clinica Medica III
Azienda Ospedaliera di Padova

Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among U.S. Adults Aged 18 Years or older

Obesity (BMI ≥30 kg/m^2)

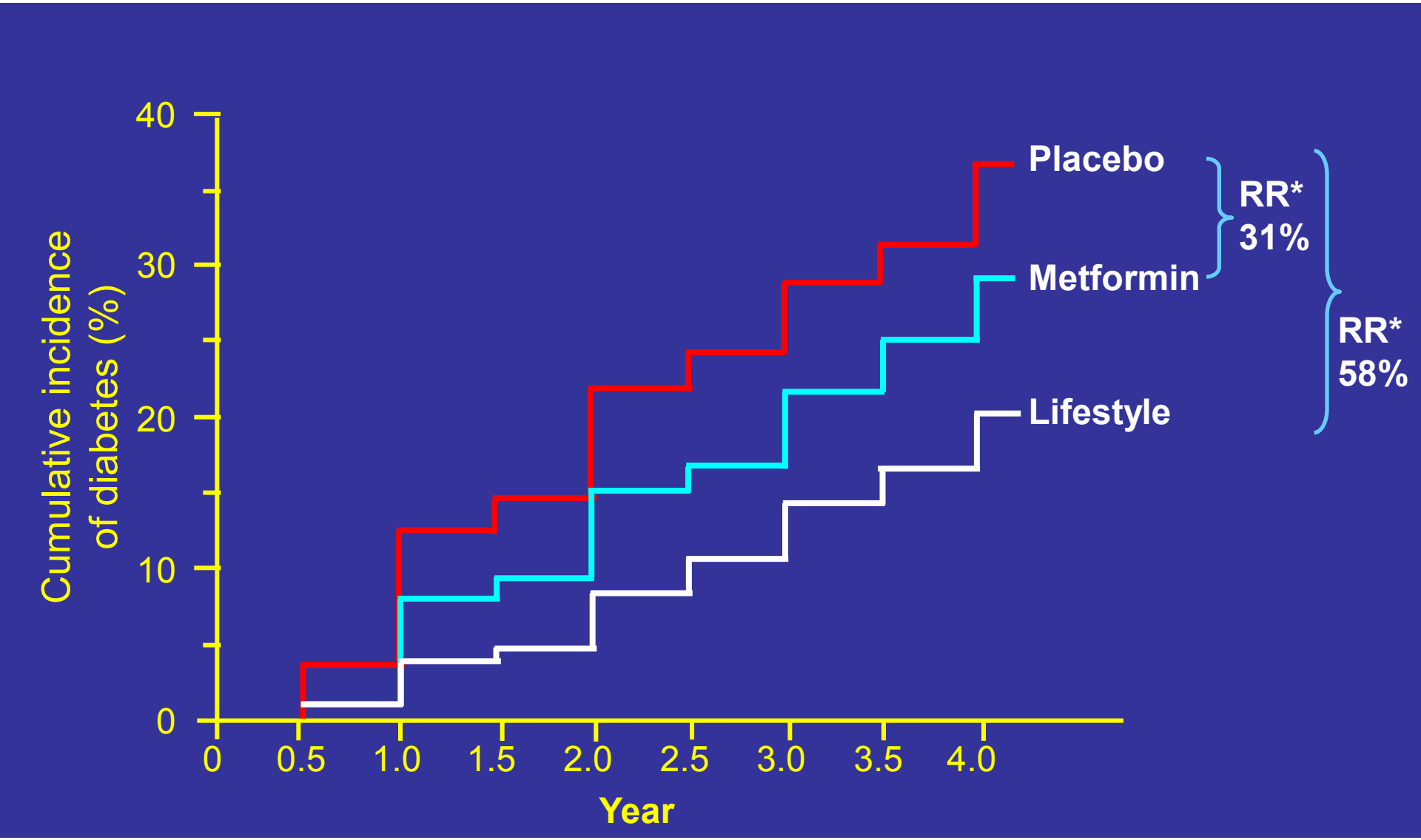


Diabetes



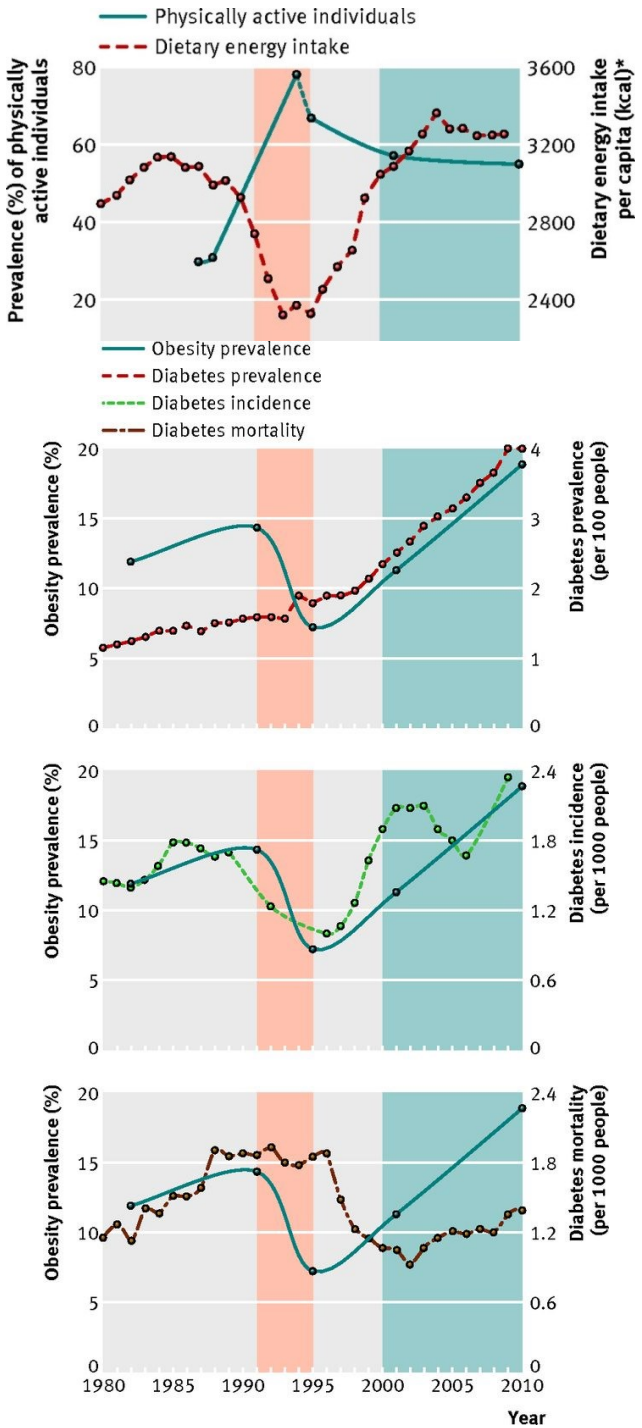
CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

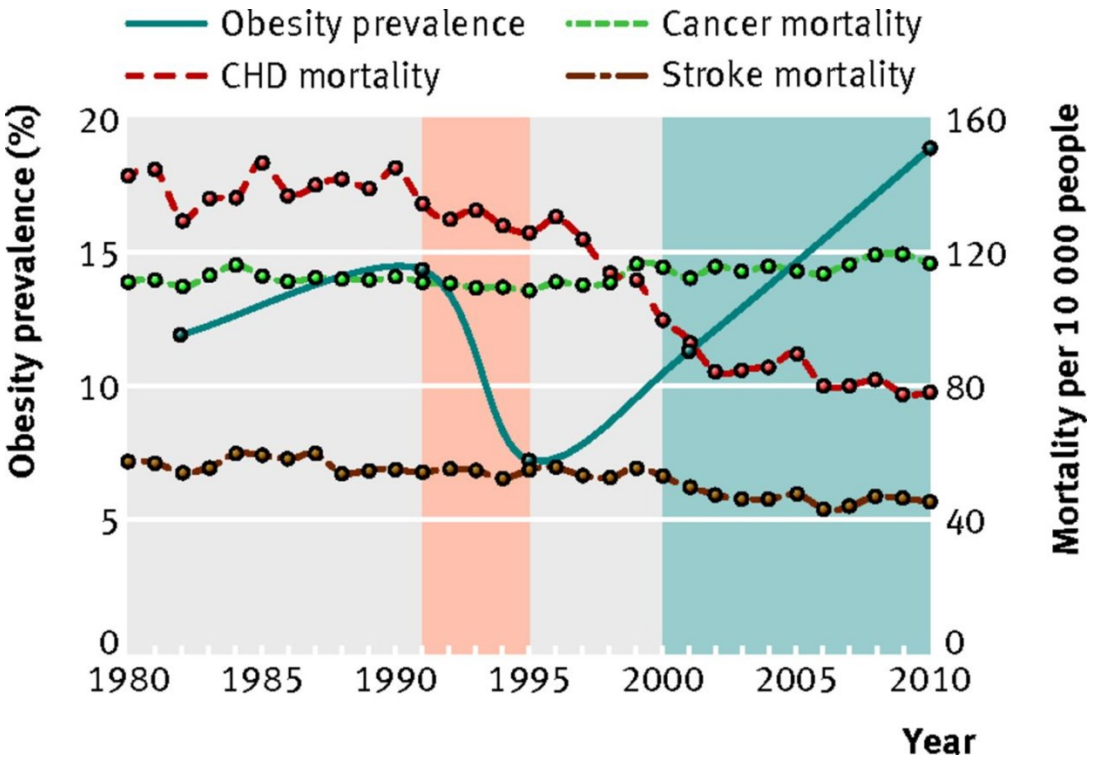
Diabetes Prevention Program



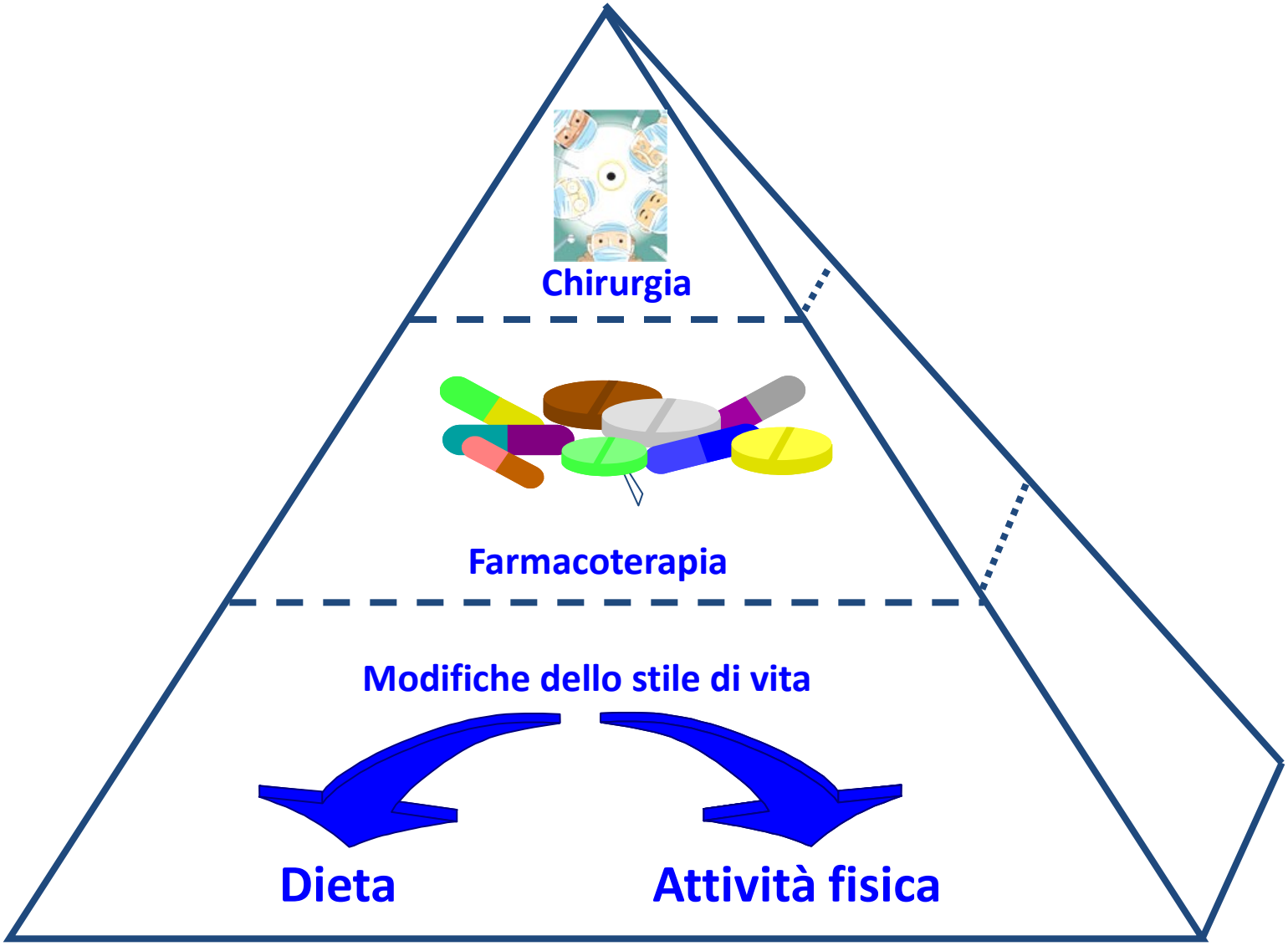
*Reduction in risk of progressing to type 2 diabetes versus placebo

DPP. N Engl J Med. 2002; 346: 393-403



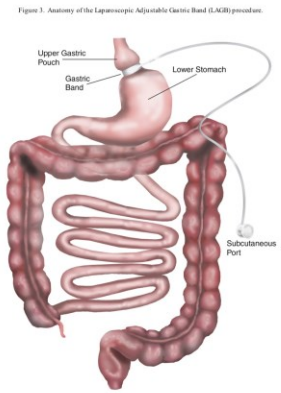


Franco M et al., BMJ 2013

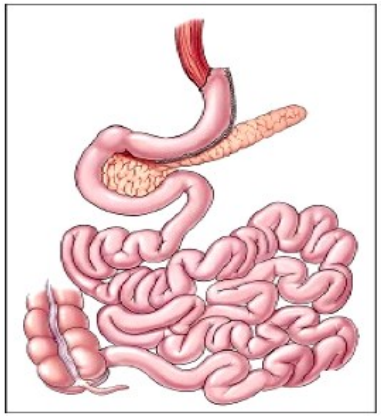

Chirurgia
Farmacoterapia
Modifiche dello stile di vita
Dieta
Attività fisica

Tecniche chirurgiche bariatriche

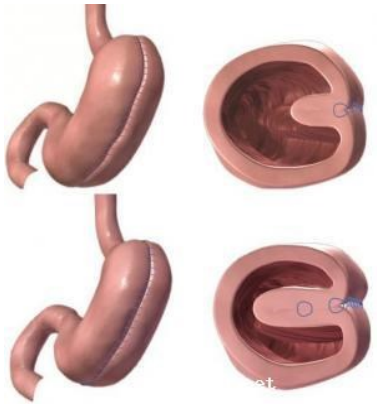
Restrittive



Bendaggio Gastrico (AGB)

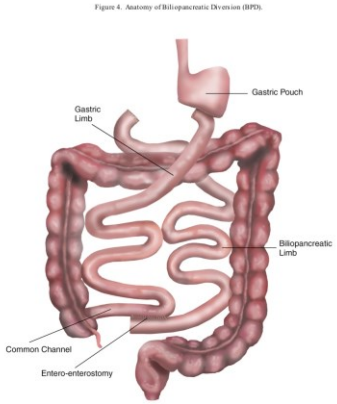


Sleeve Gastrectomy (SG)

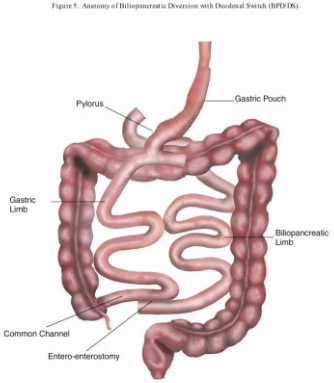


Plicatura Gastrica

Malassorbitive

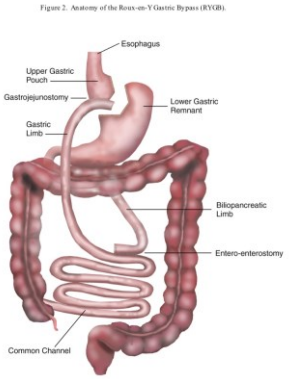


Diversione Bilio-Pancreatica (DBP)



Diversione Bilio-Pancreatica con switch duodenale (DBP+DS)

Miste



By-Pass Gastrico Roux-en-Y (GBP)

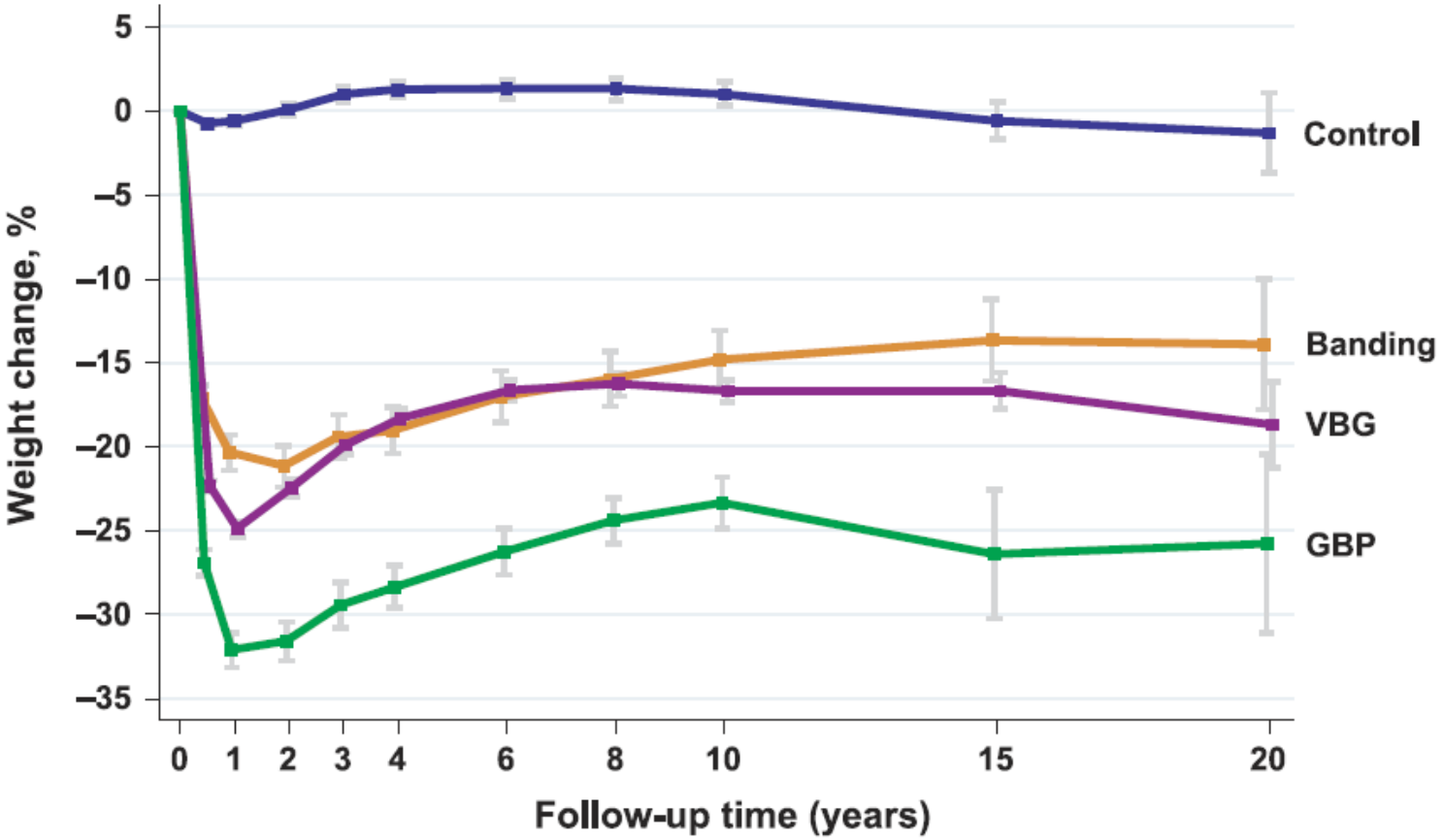
Indicazioni alla Chirurgia Bariatrica

- BMI > 40 kg/m^2 (3° grado)
- BMI > 35 kg/m^2 (2° grado) in presenza di comorbilità associate all'obesità (Diabete mellito tipo 2, Ipertensione arteriosa, Cardiopatia ischemica, OSAS, patologie da sovraccarico scheletrico)
- Età compresa tra 18 e 60 anni *;
- Obesità di durata superiore ai 5 anni;
- Dimostrato fallimento di precedenti tentativi di perdere peso e/o di mantenere la perdita di peso con tecniche non chirurgiche;
- Piena disponibilità ad eseguire controlli medici per tutta la vita dopo l'intervento chirurgico.

Controindicazioni alla Chirurgia Bariatrica

- Obesità secondaria a causa endocrinologia suscettibile di trattamento specifico;
- Rischio operatorio troppo alto;
- Presenza di patologie gravi non legate all'obesità;
- Malattie psichiatriche severe;
- Abuso di alcol o di droghe;
- Bulimia Nervosa.

Swedish Obese Subjects (SOS) trial

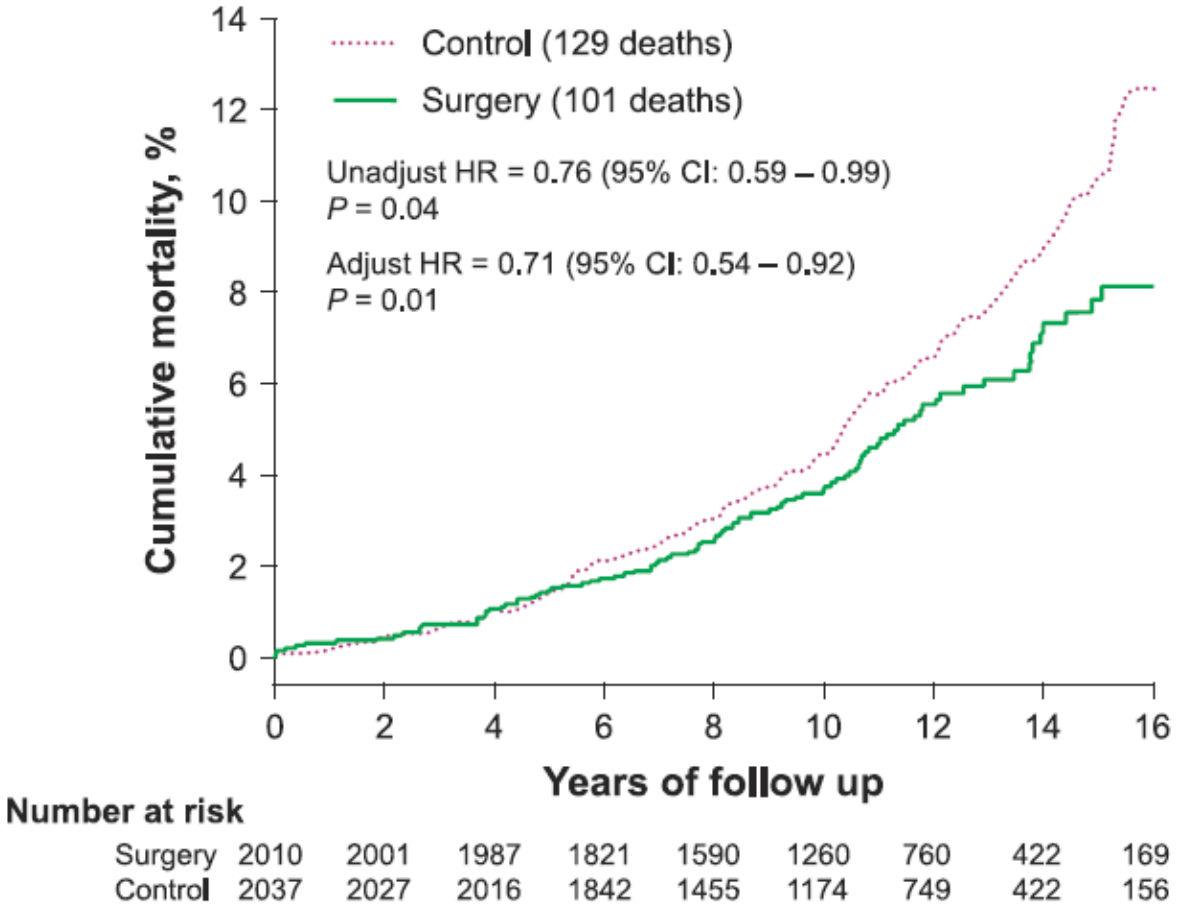


No. examined

Control	2037	1490	1242	1267	556	176
Banding	376	333	284	284	150	50
VBG	1369	1086	987	1007	489	82
GBP	265	209	184	180	37	13

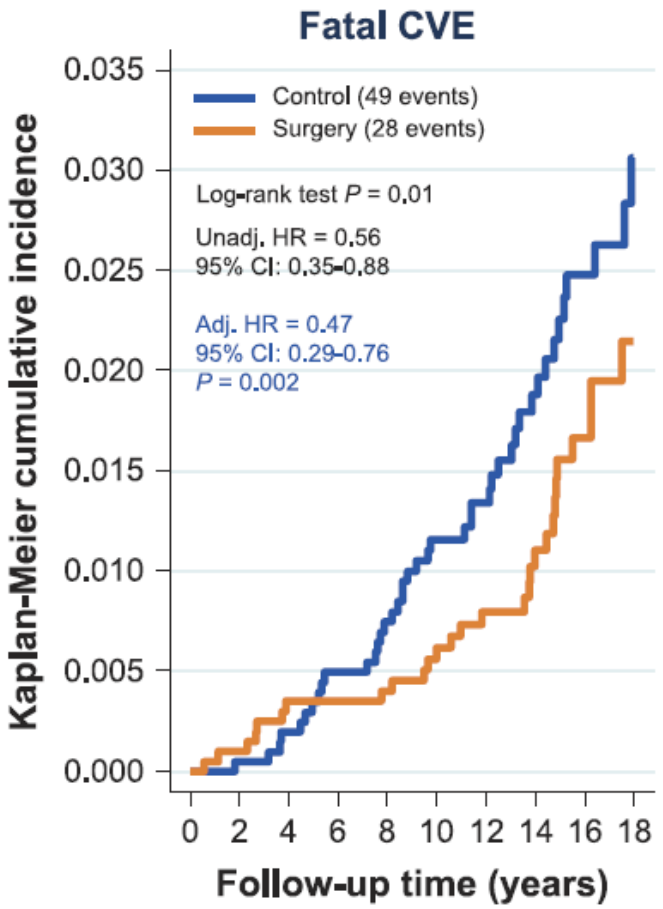
Sjöström L et al., JAMA 2012

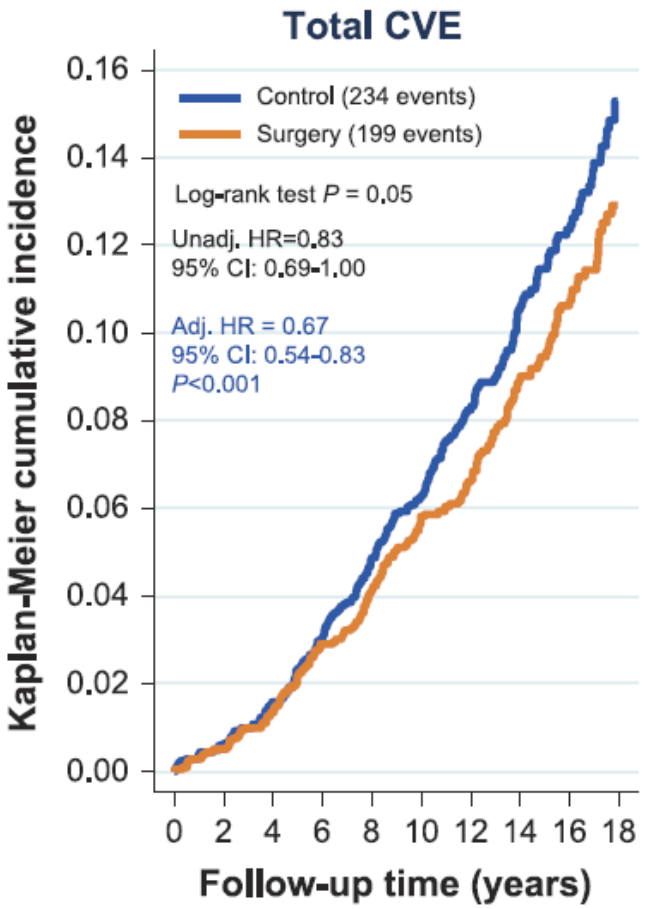
Swedish Obese Subjects (SOS) trial



Sjöström L et al., New Engl J Med 2007

Swedish Obese Subjects (SOS) trial





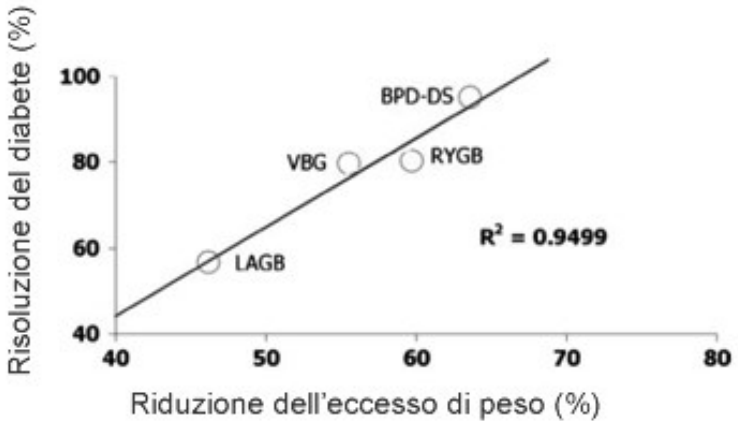
Number at risk:

Control	2037	1993	1423	405
Surgery	2010	1970	1557	412

Control	2037	1945	1326	361
Surgery	2010	1921	1468	375

Sjöström L et al., JAMA 2012

Remissione del DM tipo 2 dopo chirurgia bariatrica



Busetto L et al, Obesity Surgery 2011

Criteria for assessment of the effect of bariatric surgery on remission of T2DM

- **Partial remission**: hyperglycaemia below diagnostic thresholds for diabetes (HbA1c >6%, but < 6.5%, FPG 100–125 mg/dl), at least 1-year duration, no active pharmacological therapy or on-going procedures.
- **Complete remission**: Normal glycaemic measures (HbA1c normal range (<6%), FPG <100 mg/dl), at least 1-year duration, no active pharmacological therapy or on-going procedures.
- **Prolonged remission**: Complete remission of at least 5-year duration.

Surgically induced improvement of T2DM may be considered effective if:

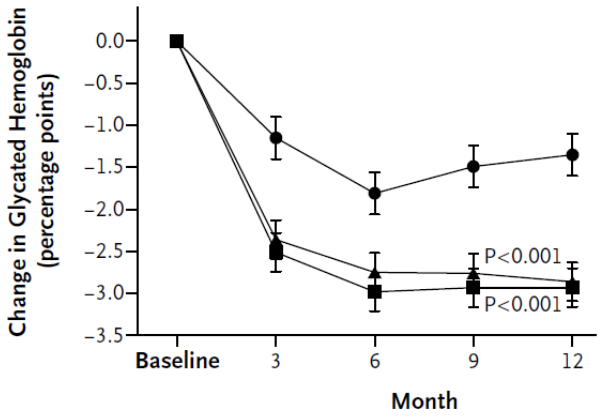
- Post-operative insulin dose ≤ 25% of the pre-operative one
- Post-operative oral anti-diabetic treatment dose ≤ 50% of the pre-operative one
- Post-operative reduction in HbA1c > 0.5% within 3 months or reaching < 7.0%.

Criteria for assessment of effect of bariatric surgery on optimization of metabolic status and some other co-morbid conditions

- HbA1c ≤ 6%, no hypoglycaemia, total cholesterol < 4 mmol/l, LDL-cholesterol < 2 mmol/l, triglycerides < 2.2 mmol/l, blood pressure < 135/85 mmHg, >15% weight loss,
- or lowering of HbA1c by >20%, LDL< 2.3 mmol/l, blood pressure < 135/85 mm Hg with reduced medication from pre-operative status

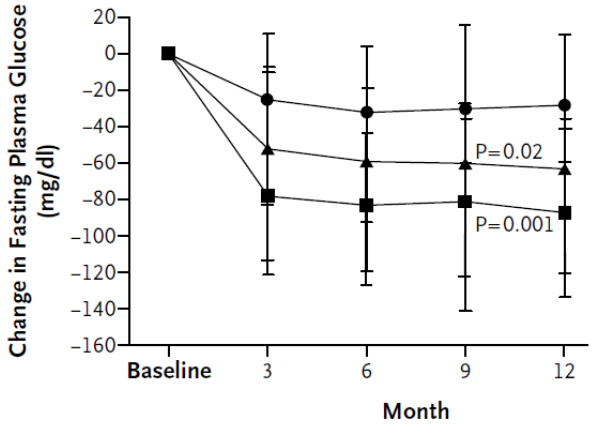
● Intensive medical therapy ■ Roux-en-Y gastric bypass ▲ Sleeve gastrectomy

A Change in Glycated Hemoglobin



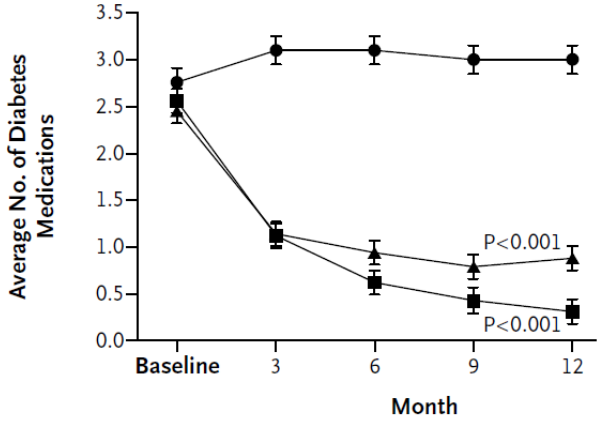
Value at Visit					
Intensive medical therapy	8.9	7.7	7.1	7.4	7.5
Roux-en-Y gastric bypass	9.3	6.8	6.3	6.4	6.4
Sleeve gastrectomy	9.5	7.1	6.7	6.7	6.6

B Change in Fasting Plasma Glucose



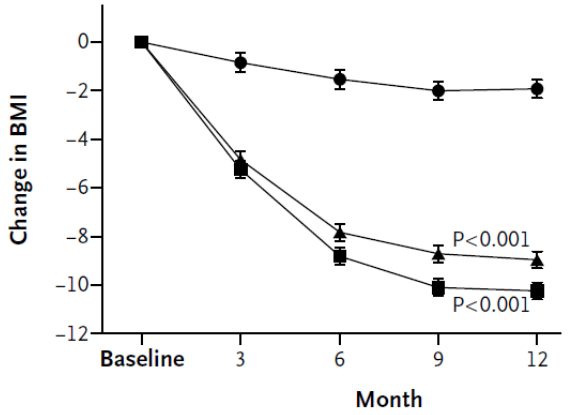
Value at Visit					
Intensive medical therapy	155	122	113	120	120
Roux-en-Y gastric bypass	193	109	96	96	99
Sleeve gastrectomy	164	118	104	102	97

C Average No. of Diabetes Medications



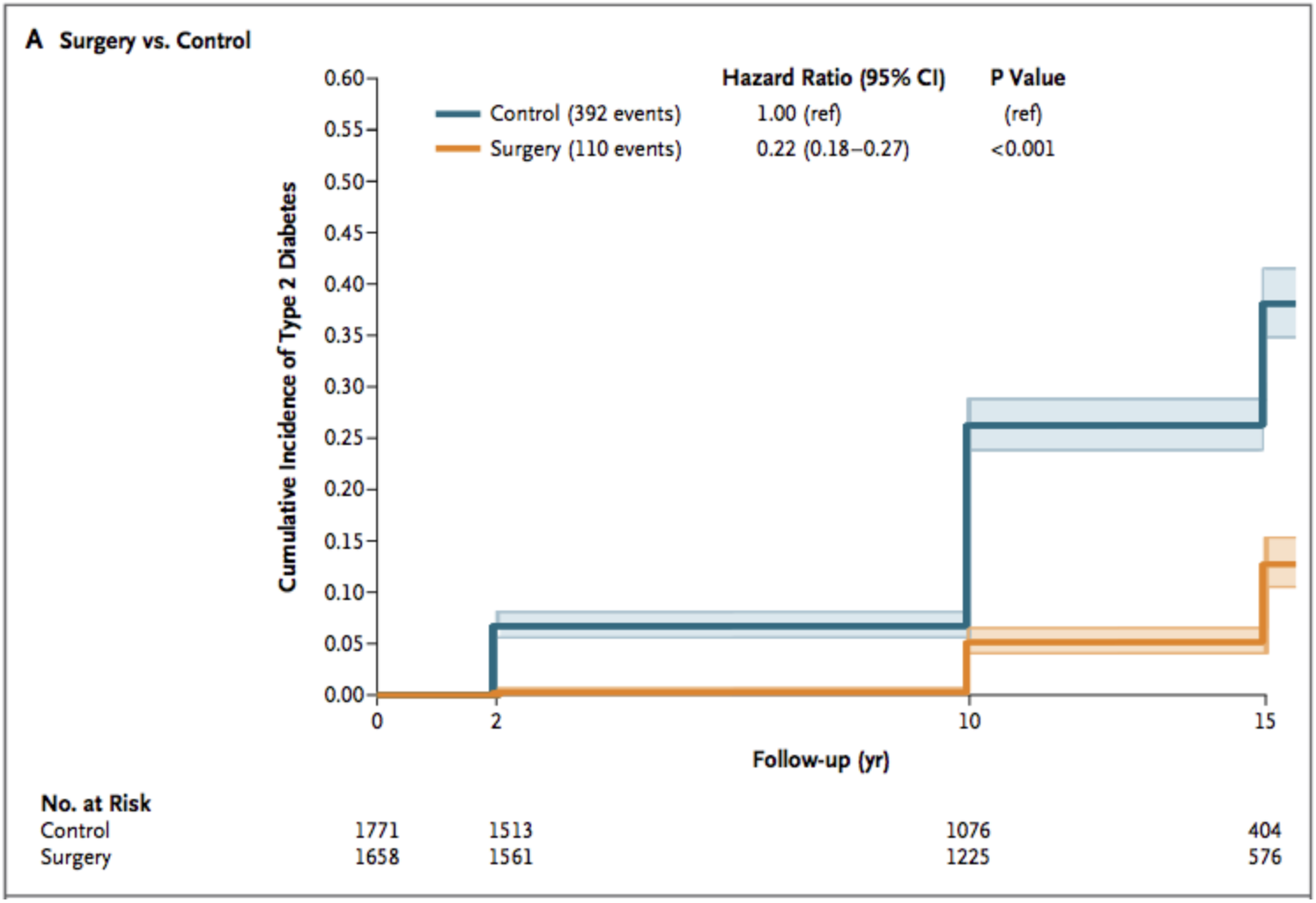
Value at Visit					
Intensive medical therapy	2.8	3.1	3.1	3.0	3.0
Roux-en-Y gastric bypass	2.6	1.1	0.6	0.4	0.3
Sleeve gastrectomy	2.4	1.1	0.9	0.8	0.9

D Change in BMI

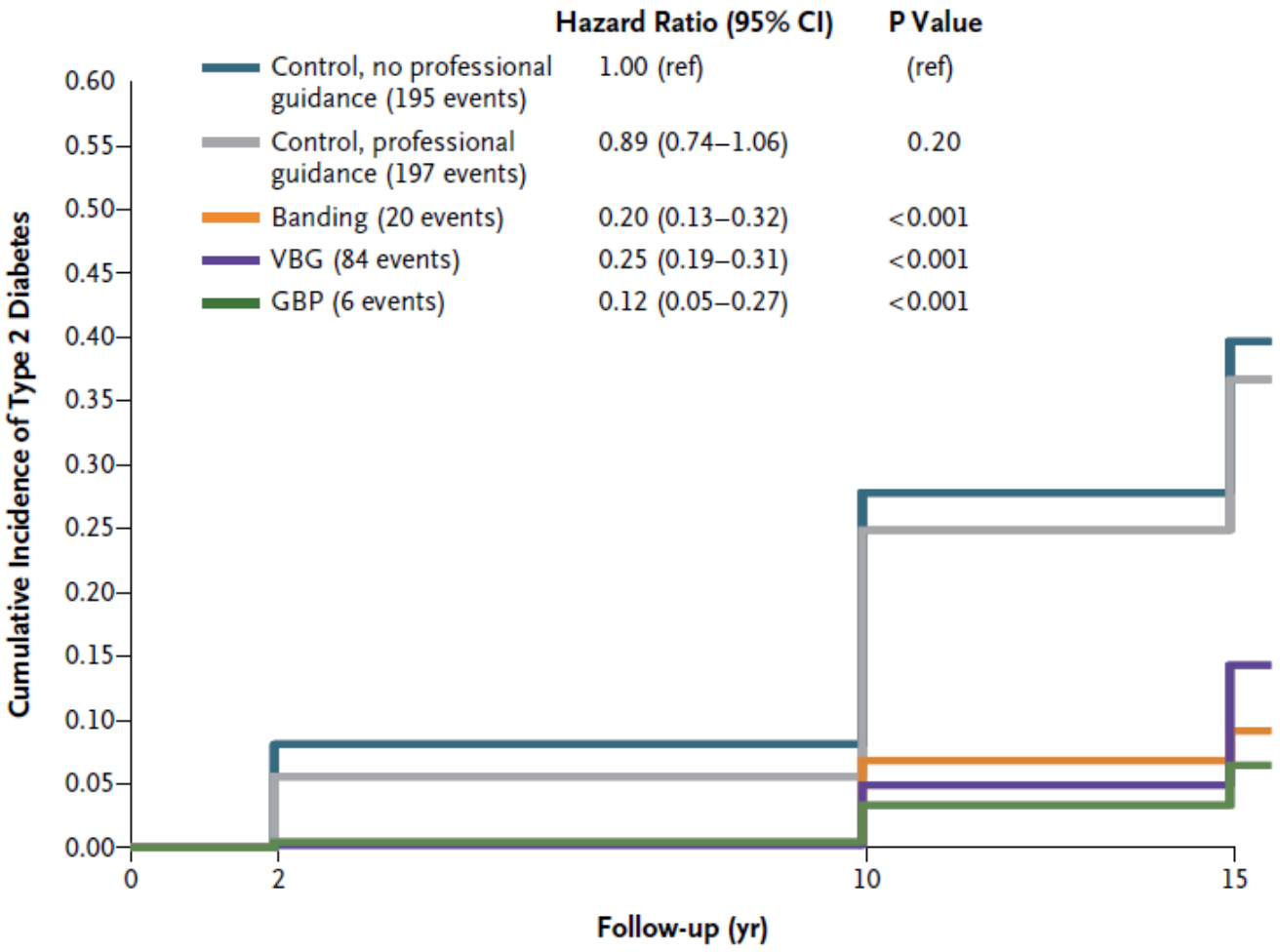


Value at Visit					
Intensive medical therapy	36.3	35.4	34.8	34.5	34.4
Roux-en-Y gastric bypass	37.0	31.8	28.2	26.9	26.8
Sleeve gastrectomy	36.1	31.3	28.3	27.3	27.2

Schauer et al, NEJM 2012



SOS Study, Carlsson et al, NEJM 2012



No. at Risk

Control, no professional guidance	871	691	489	207
Control, professional guidance	900	822	587	197
Banding	311	302	244	121
VBG	1140	1064	841	424
GBP	207	195	140	31

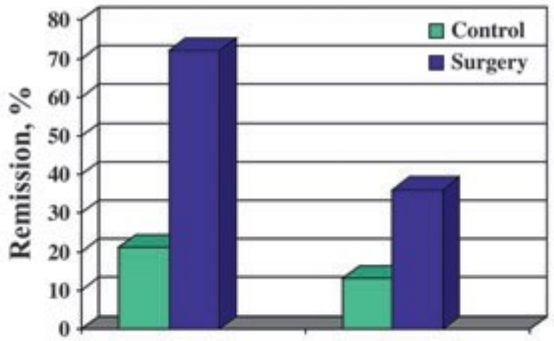
SOS Study, Carlsson et al, NEJM 2012

Weight and Type 2 Diabetes after Bariatric Surgery: Systematic Review and Meta-analysis

	Total	Gastric Banding	Gastroplasty	Gastric Bypass	BPD/DS
% EBWL	55.9	46.2	55.5	59.7	63.6
% Resolved overall	78.1	56.7	79.7	80.3	95.1
% Resolved<2 y	80.3	55.0	81.4	81.6	94.0
% Resolved≥2 y	74.6	58.3	77.5	70.9	95.9

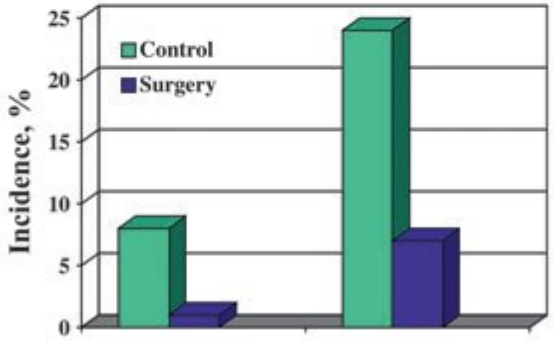
Buchwald et al, The American Journal of Medicine 2009

(a) **SOS. Remission from diabetes over 2 and 10 years**



Number of subjects:	2 year	10 year
Control	248	84
Surgery	342	118
Adjusted Odds ratio	8.42	3.45
95% CI	5.68 - 12.5	1.64 - 7.28
P value	<0.001	<0.001

(b) **SOS. Incidence of diabetes over 2 and 10 years**



Number of subjects:	2 year	10 year
Control	1402	539
Surgery	1489	517
Adjusted Odds ratio	0.14	0.25
95% CI	0.08 - 0.24	0.17 - 0.38
P value	<0.001	<0.001

Sjöström L, J Intern Med 2013

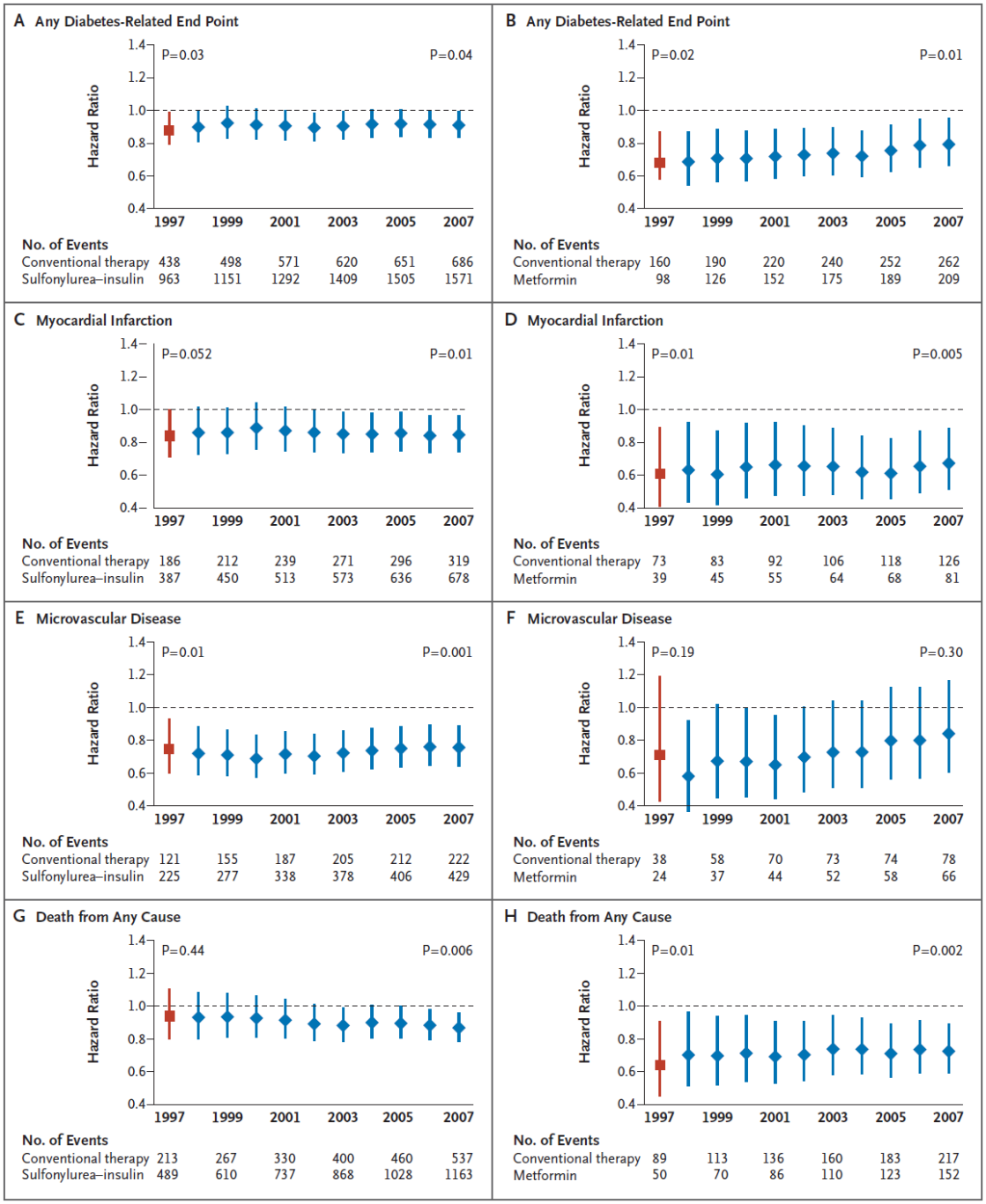
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

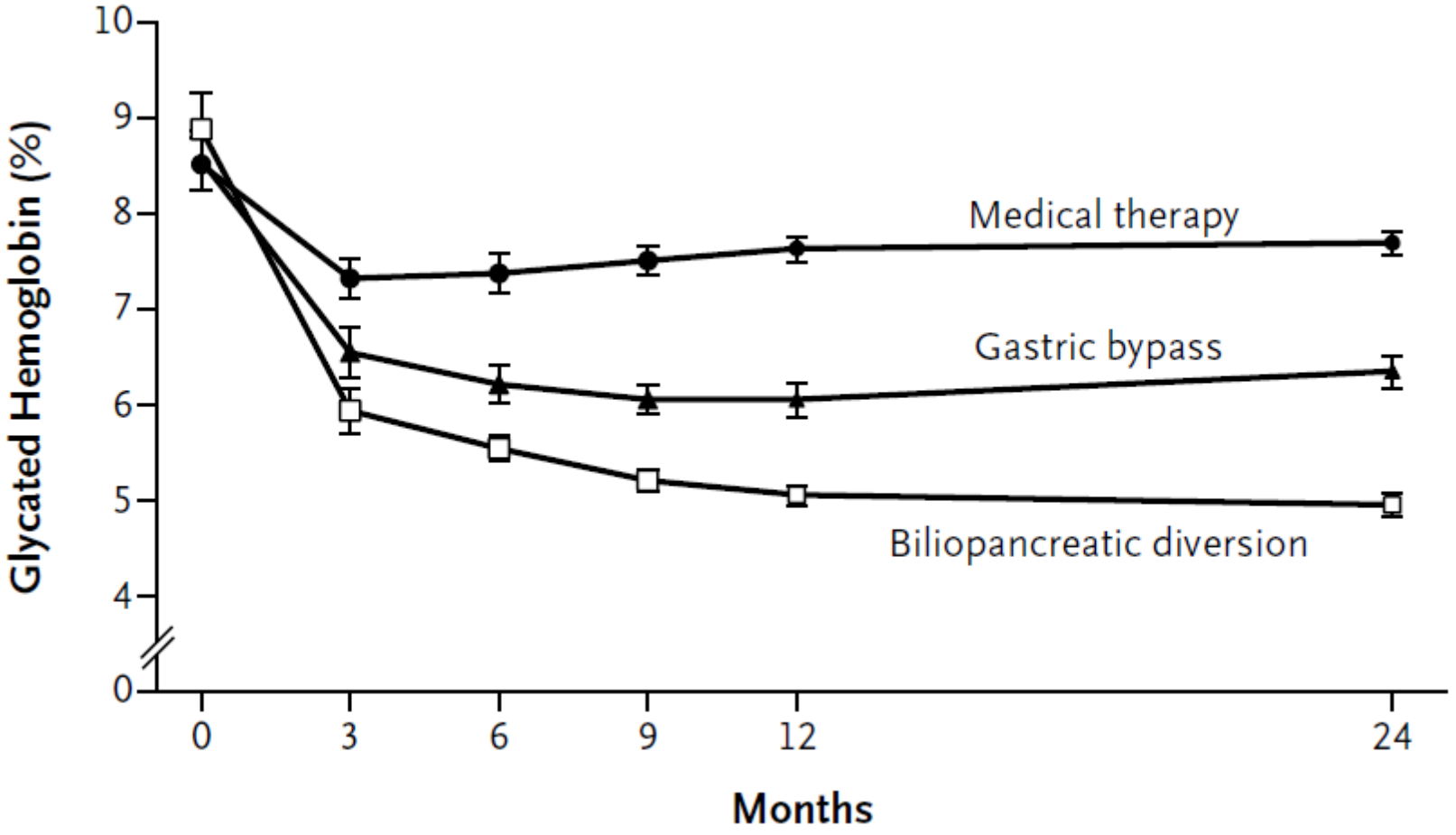
10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes

Rury R. Holman, F.R.C.P., Sanjoy K. Paul, Ph.D., M. Angelyn Bethel, M.D., David R. Matthews, F.R.C.P., and H. Andrew W. Neil, F.R.C.P.

Rury et al, N Engl J Med 2008



Glycated Hemoglobin Levels during 2 Years of Follow-up

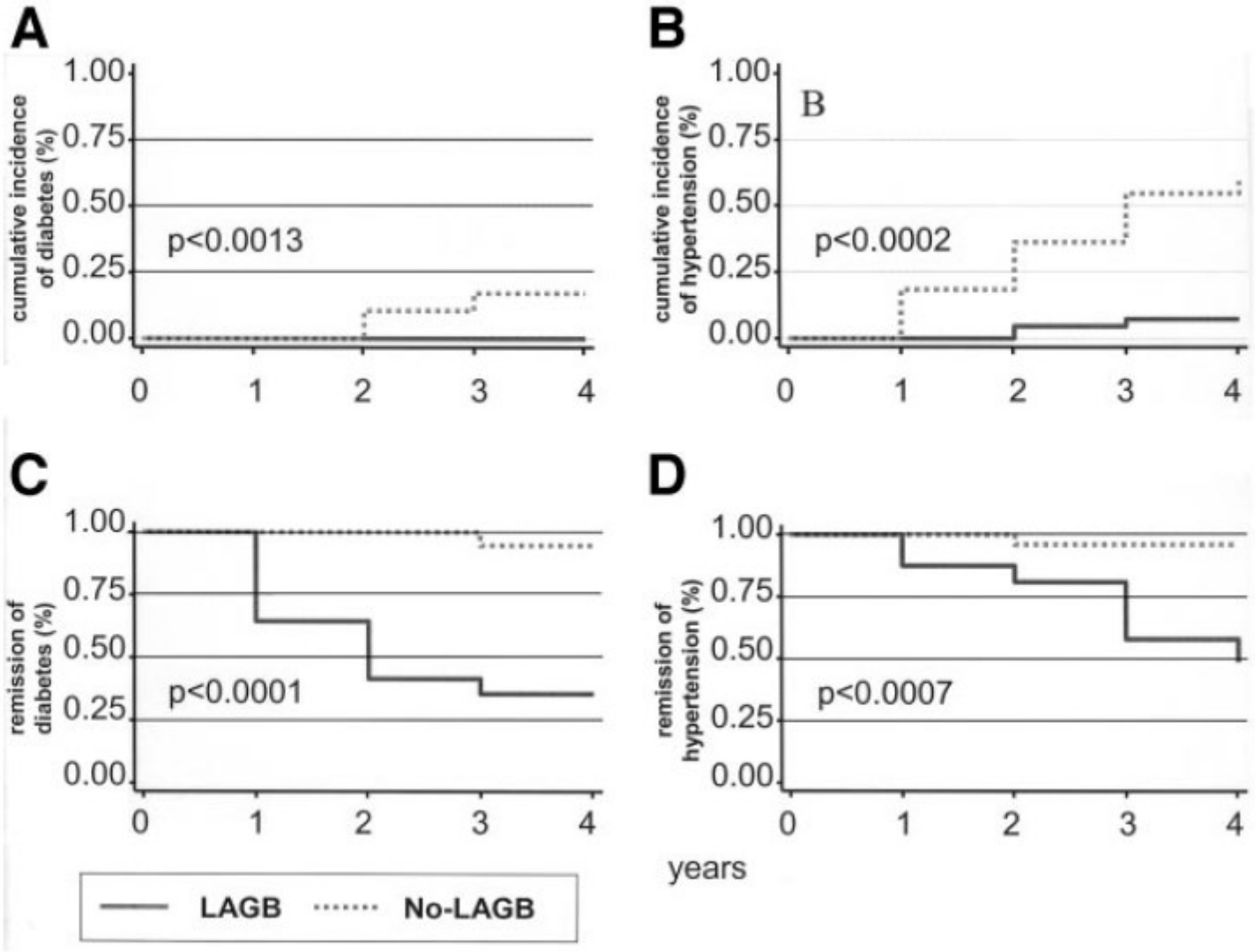


Mingrone et al, NEJM 2012

Table 2. Average Absolute Values and Percentage Changes at 2 Years.*

Variable	Medical Therapy (N=18)	Biliopancreatic Diversion (N=19)	Gastric Bypass (N=19)	P Value†			
				Overall	Biliopancreatic Diversion vs. Medical Therapy	Gastric Bypass vs. Medical Therapy	Gastric Bypass vs. Biliopancreatic Diversion
Glucose (mmol/liter)	7.83±1.66	3.89±0.67	5.69±3.07	<0.001	<0.001	0.005	0.03
Change from baseline (%)	−14.37±11.93	−56.23±10.01	−37.81±33.75				
Glycated hemoglobin (%)	7.69±0.57	4.95±0.49	6.35±1.42	<0.001	<0.001	0.003	0.001
Change from baseline (%)	−8.39±9.93	−43.01±9.64	−25.18±20.89				
Cholesterol (mmol/liter)							
Total	4.91±0.87	2.77±0.81	4.27±0.77	<0.001	<0.001	0.31	<0.001
Change from baseline (%)	−16.82±11.60	−49.25±11.52	−6.83±27.03				
High-density lipoprotein	1.05±0.20	1.08±0.16	1.47±0.31	<0.001	0.61	<0.001	0.01
Change from baseline (%)	6.03±6.25	12.98±20.66	29.66±18.21				
Low-density lipoprotein	2.98±0.83	1.25±0.71	2.20±0.72	<0.001	<0.001	1.00	<0.001
Change from baseline (%)	−20.31±15.24	−64.63±15.93	−17.21±36.21				
Triglycerides (mmol/liter)	1.91±0.39	0.96±0.32	1.15±0.48	<0.001	<0.001	1.00	0.001
Change from baseline (%)	−18.28±7.84	−56.79±16.70	−21.17±41.23				
Blood pressure (mm Hg)							
Systolic	134.44±10.97	129.21±8.04	132.11±10.45	0.32	1.00	1.00	0.40
Change from baseline (%)	−11.15±12.71	−14.55±12.63	−9.02±7.51				
Diastolic	87.28±9.32	82.37±4.21	84.21±4.79	0.13	0.23	1.00	0.24
Change from baseline (%)	−7.14±11.51	−13.06±8.97	−7.30±9.42				
Weight (kg)	128.06±19.77	89.53±17.84	84.29±13.35	<0.001	<0.001	<0.001	1.00
Change from baseline (%)	−4.74±6.37	−33.82±10.17	−33.31±7.88				
Excess weight lost (%)	9.29±12.94	69.36±17.60	68.08±12.70	<0.001	<0.001	<0.001	1.00
Body-mass index	43.07±6.44	29.19±4.90	29.31±2.64	<0.001	<0.001	<0.001	1.00
Change from baseline (%)	−4.73±6.37	−33.82±10.17	−33.31±7.88				
Waist (cm)	116.33±12.14	103.53±16.94	98.58±13.06	<0.001	<0.001	<0.001	1.00
Change from baseline (%)	−7.69±7.80	−20.70±8.34	−19.91±8.44				

Mingrone et al, NEJM 2012



Pontiroli et al, Diabetes Care 2005

ELSEVIER

Surgery for Obesity and Related Diseases 9 (2013) 498–502

SURGERY FOR OBESITY AND RELATED DISEASES

Original article

Long-term remission of type 2 diabetes in morbidly obese patients after sleeve gastrectomy

Francesca Abbatini, M.D.[a], Danila Capoccia, M.D.[b], Giovanni Casella, M.D.[a], Emanuele Soricelli, M.D.[a], Frida Leonetti, M.D., Ph.D.[b], Nicola Basso, M.D.[a,*]

[a]*Surgical-Medical Department for Digestive Diseases, Policlinico "Umberto I," University of Rome "Sapienza," Italy*
[b]*Department of Clinical Sciences, Policlinico "Umberto I," University of Rome "Sapienza," Italy*

Background: The aim of this study was to evaluate the long-term effects of laparoscopic sleeve gastrectomy (LSG) on type 2 diabetes mellitus (T2DM) and other related co-morbidities in severely obese patients.

Methods: From May 2003 to July 2008, 33 morbidly obese diabetic patients (20 with body mass index [BMI] >50 kg/m^2) underwent LSG. A total of 23 females and 10 males participated, with a mean age of 49.3 $\pm$ 8 years, mean preoperative BMI of 52.1 $\pm$ 8.5 kg/m^2, mean fasting plasma glucose (FPG) of 143.2 $\pm$ 47.9 mg/dL, mean glycosylated hemoglobin (HbA_{1c}) of 7.3% $\pm$ 1.4%, and a mean T2DM duration of 7 years. All patients had a 36-month follow-up, and 13 had a 60-month follow-up.

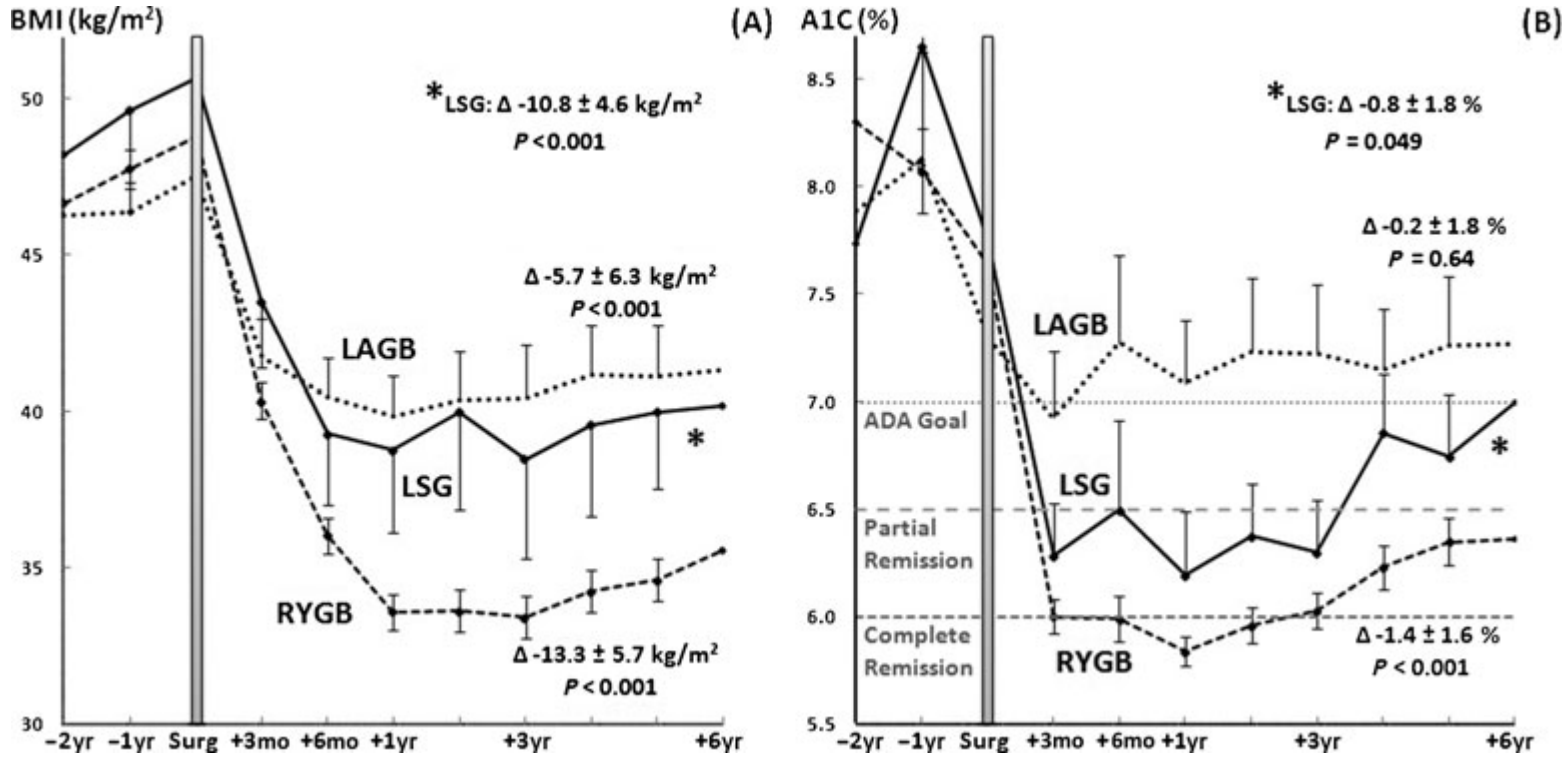
Results: Twenty-nine patients (87.8%) discontinued antidiabetic medications 3 months after LSG, (mean BMI of 42.8 $\pm$ 7.8 kg/m^2; FPG of 104.5 $\pm$ 22.1 mg/dL; HbA_{1c} of 5.3% $\pm$ .4%). At 36 months, 22 of 26 LSG patients (84.6%) had normal FPG and HbA_{1c} values without antidiabetic therapy. At the 60-month follow-up, 10 of 13 patients (76.9%) had normal FPG and HbA_{1c} values without antidiabetic therapy. The Framingham risk score decreased significantly from 9.7% preoperatively to 4.7% postoperatively. No new diabetic retinopathy occurred during the whole period of observation.

Conclusions: This study confirms the efficacy of LSG in the treatment of T2DM and indicates that, at both 36- and 60-month follow-ups, LSG can provide a significant percentage of treated patients with a prolonged remission of T2DM, with diminished cardiac risk factors and no development of diabetic retinopathy. These results compare favorably with those reported after standard medical therapy. (Surg Obes Relat Dis 2013;9:498–502.)

Can Diabetes Be Surgically Cured?

Long-Term Metabolic Effects of Bariatric Surgery in Obese Patients with Type 2 Diabetes Mellitus

Stacy A. Brethauer, MD, Ali Aminian, MD,* Héctor Romero-Talamás, MD,* Esam Batayyah, MD,* Jennifer Mackey, RN,* Laurence Kennedy, MD,† Sangeeta R. Kashyap, MD,† John P. Kirwan, PhD,† Tomasz Rogula, MD,* Matthew Kroh, MD,* Bipan Chand, MD,‡ and Philip R. Schauer, MD**

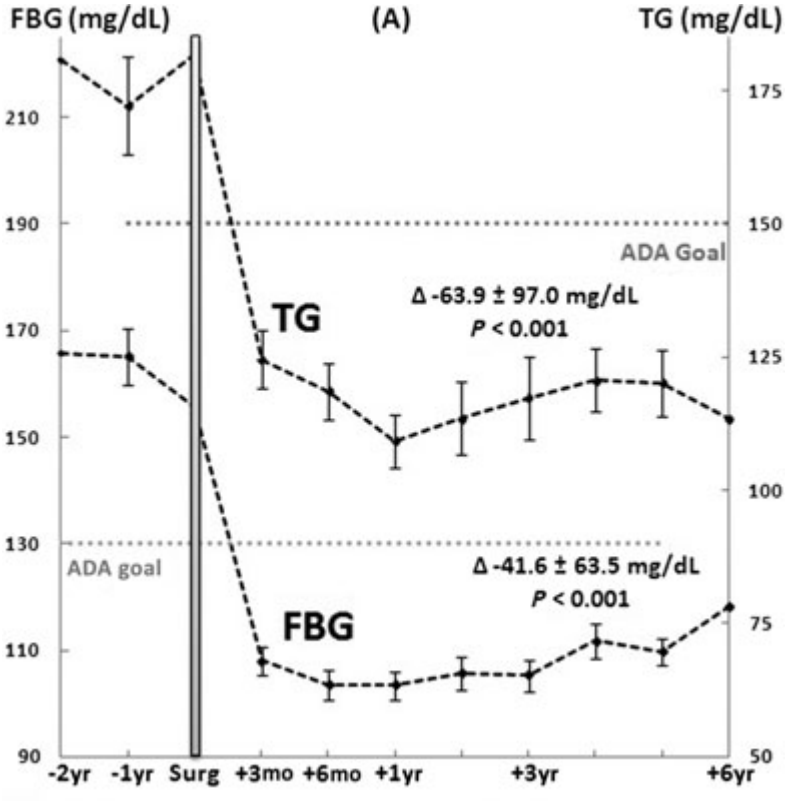


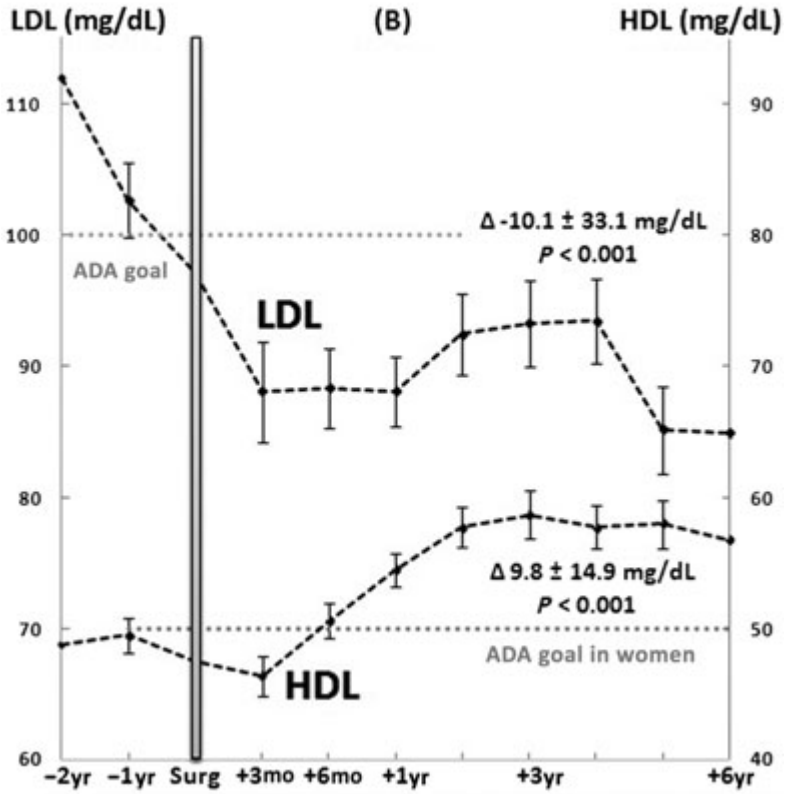
Brethauer et al, Ann Surg 2013

Can Diabetes Be Surgically Cured?

Long-Term Metabolic Effects of Bariatric Surgery in Obese Patients with Type 2 Diabetes Mellitus

Stacy A. Brethauer, MD, Ali Aminian, MD,* Héctor Romero-Talamás, MD,* Esam Batayyah, MD,* Jennifer Mackey, RN,* Laurence Kennedy, MD,† Sangeeta R. Kashyap, MD,† John P. Kirwan, PhD,† Tomasz Rogula, MD,* Matthew Kroh, MD,* Bipan Chand, MD,‡ and Philip R. Schauer, MD**



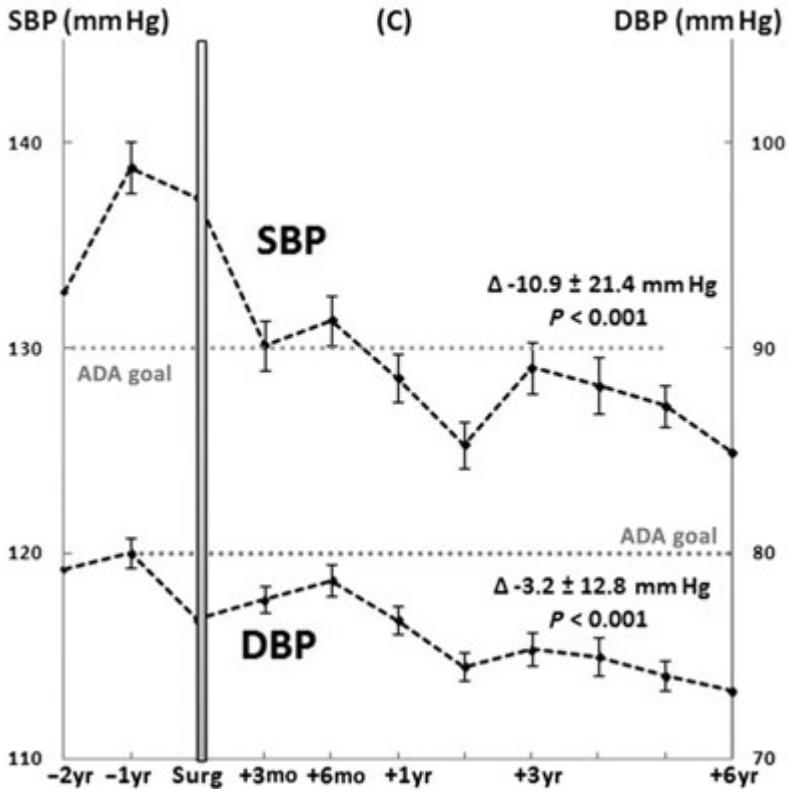


Brethauer et al, Ann Surg 2013

Can Diabetes Be Surgically Cured?

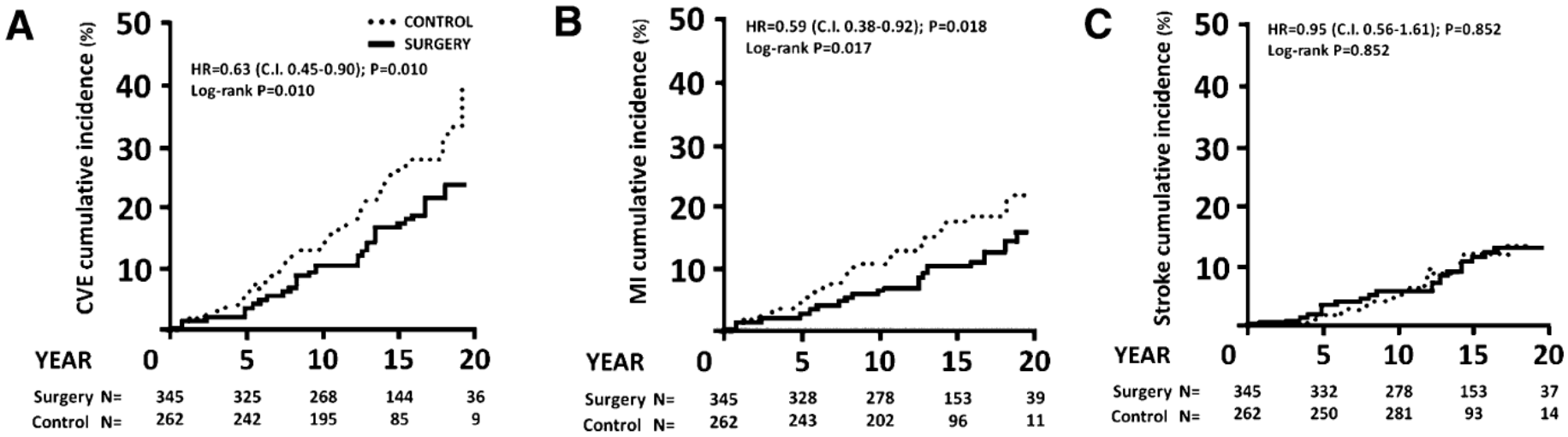
Long-Term Metabolic Effects of Bariatric Surgery in Obese Patients with Type 2 Diabetes Mellitus

Stacy A. Brethauer, MD, Ali Aminian, MD,* Héctor Romero-Talamás, MD,* Esam Batayyah, MD,* Jennifer Mackey, RN,* Laurence Kennedy, MD,† Sangeeta R. Kashyap, MD,† John P. Kirwan, PhD,† Tomasz Rogula, MD,* Matthew Kroh, MD,* Bipan Chand, MD,‡ and Philip R. Schauer, MD**



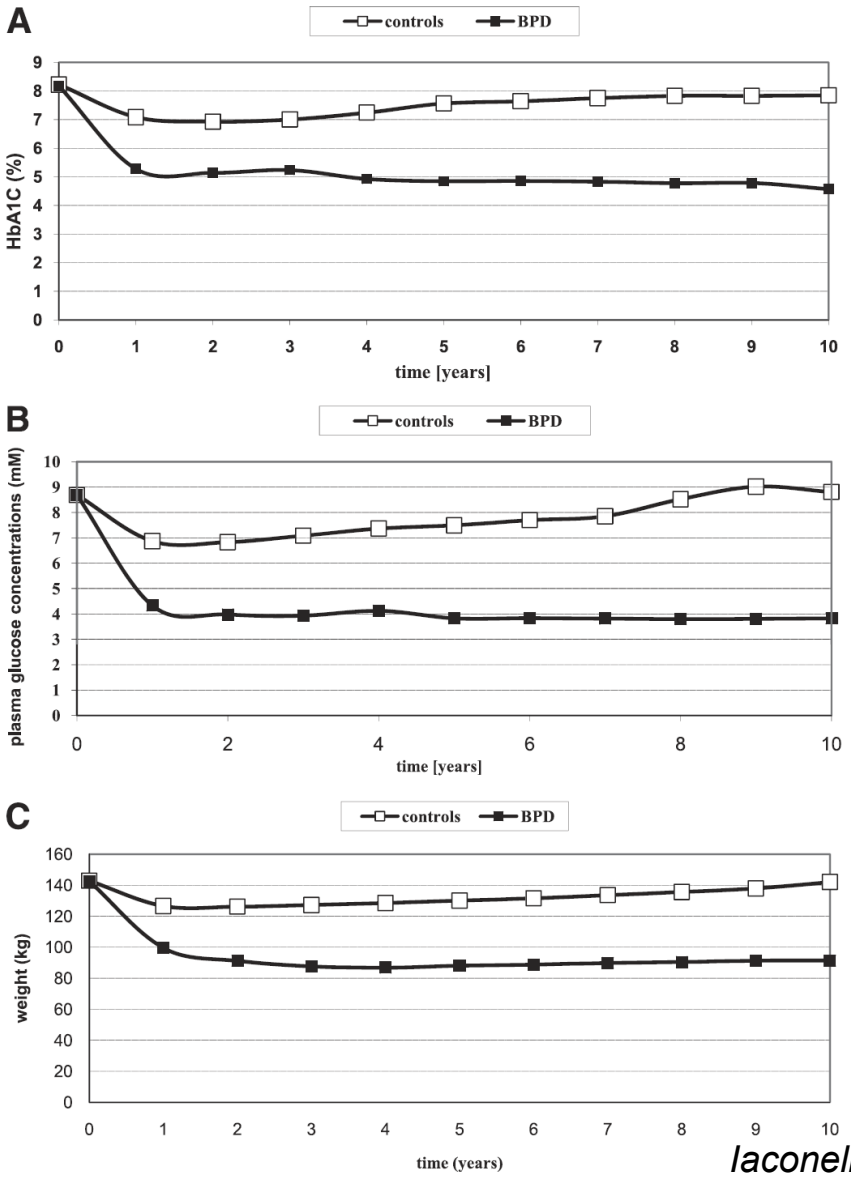
Brethauer et al, Ann Surg 2013

Bariatric Surgery and Cardiovascular Events in Diabetic Subjects (SOS)



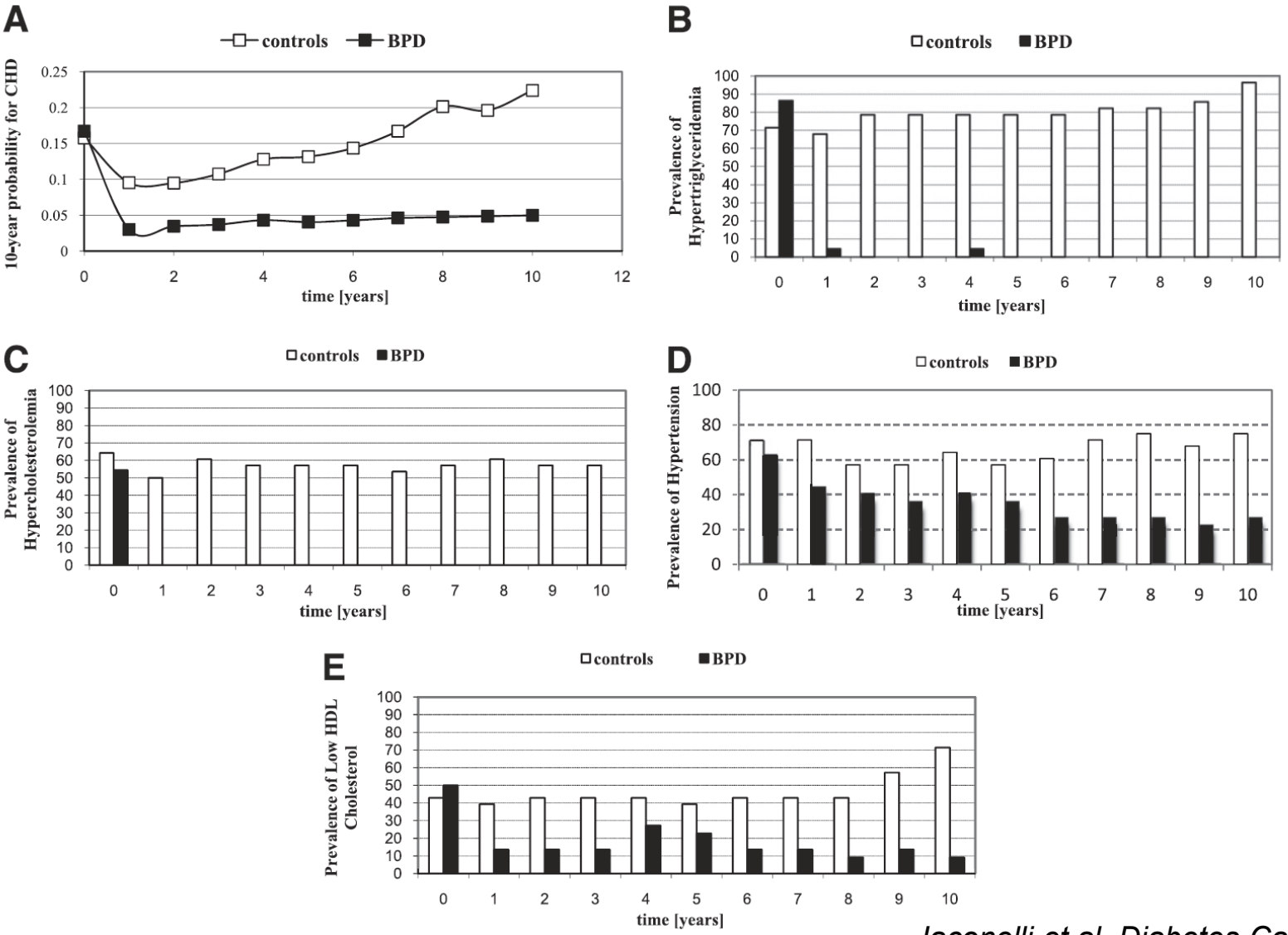
Romeo et al, Diabetes Care 2012

Effects of Bilio-Pancreatic Diversion on Diabetic Complications



Iaconelli et al, Diabetes Care 2011

Effects of Bilio-Pancreatic Diversion on Diabetic Complications



Iaconelli et al, Diabetes Care 2011

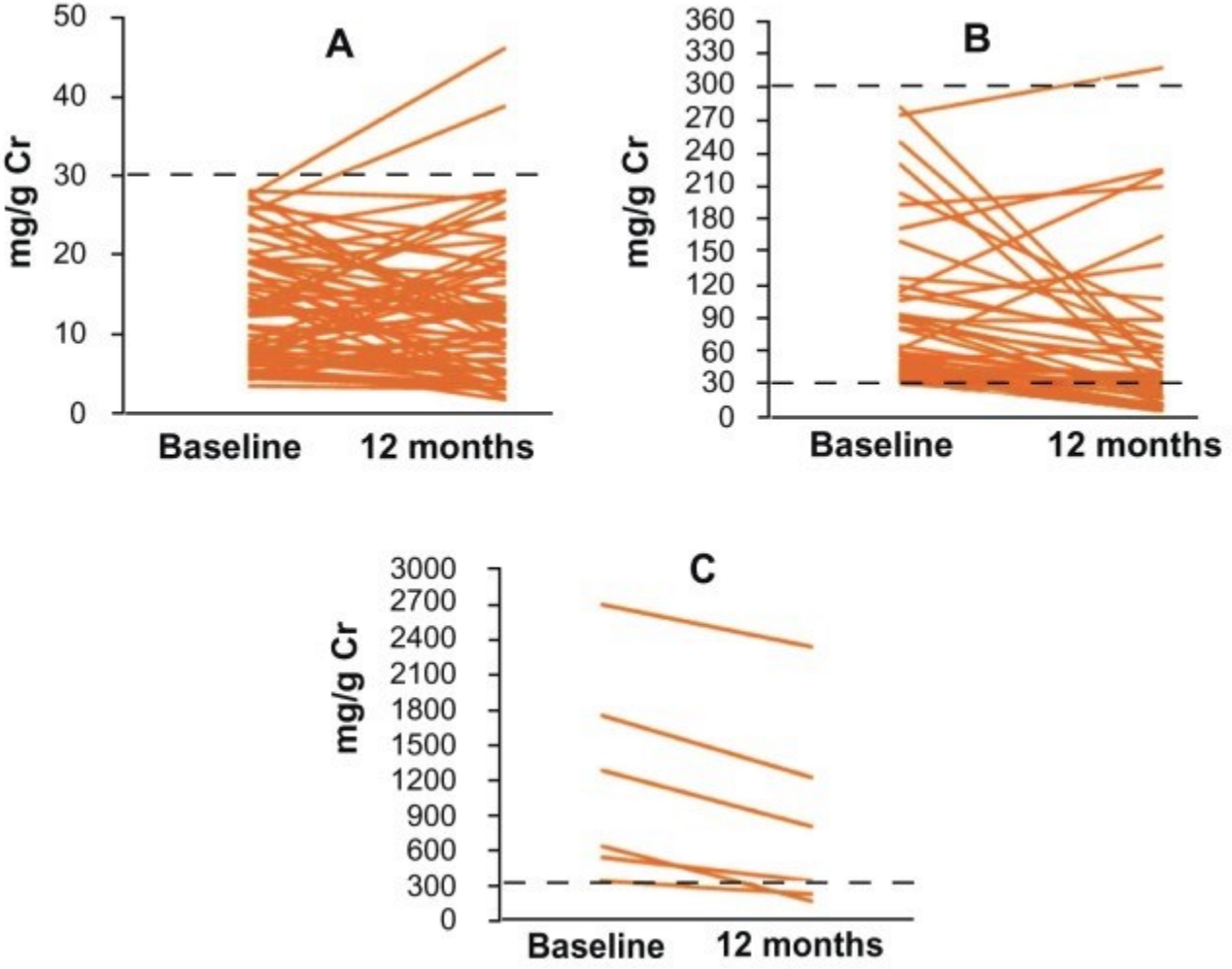
Table III
Carotid intima media thickness before and after bariatric surgery

	C-IMT before	*C-IMT after*	*p*
Gastric bypass (n = 14)	0.565 ± 0.17	0.497 ± 0.10	< 0.05
Sleeve gastrectomy (n = 13)	0.593 ± 0.10	0.476 ± 0.05	< 0.05
Both (n = 27)	0.578 ± 0.14	0.487 ± 0.08	< 0.05

C-IMT (mm).
p for paired simple t test.

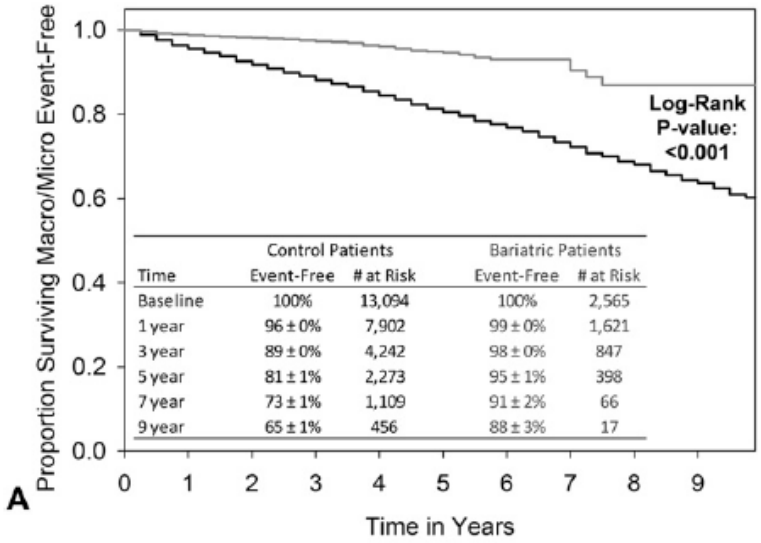
García G et al, Nutr Hosp. 2013

Reduction in urinary albumin excretion with a moderate low-carbohydrate diet

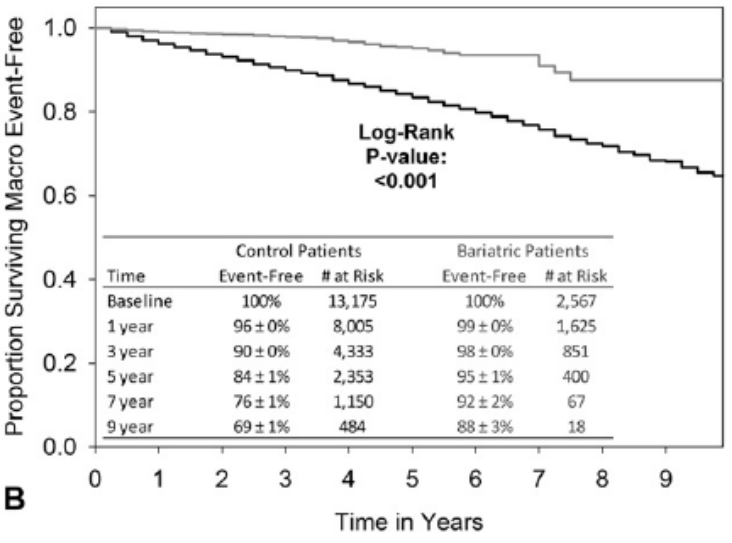


Haimoto et al., Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2012

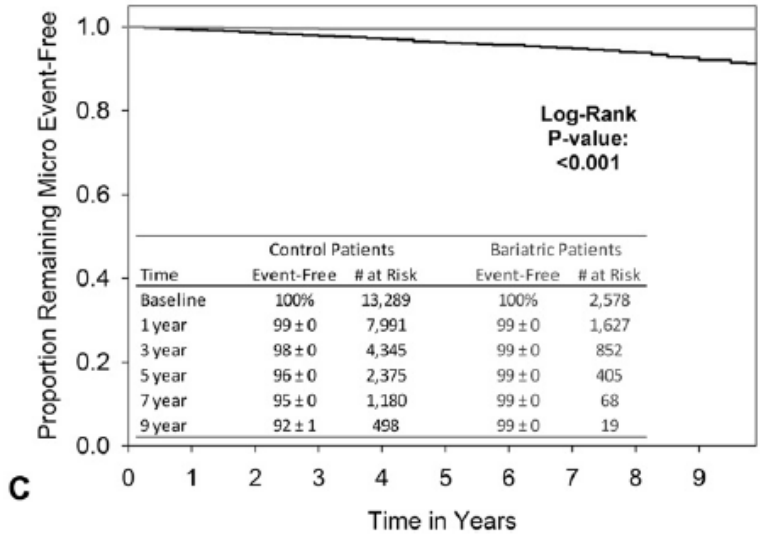
Effects of Bariatric Surgery on micro- and macrovascular complications



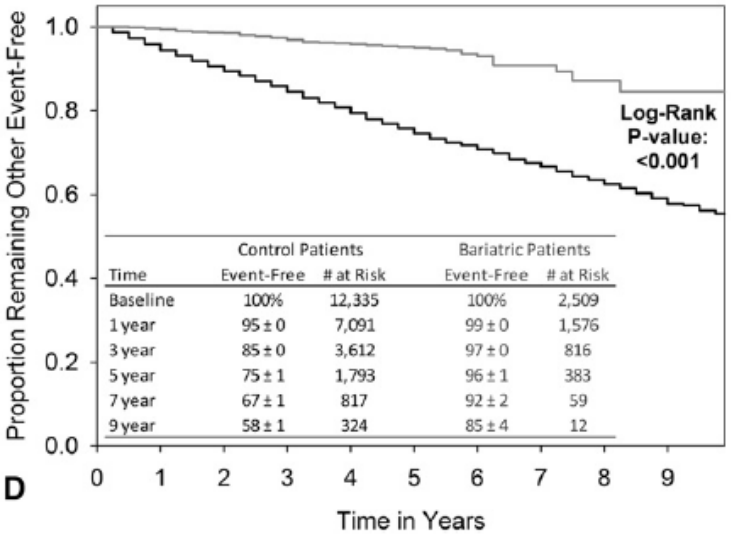
Time	Control Patients Event-Free	Control Patients # at Risk	Bariatric Patients Event-Free	Bariatric Patients # at Risk
Baseline	100%	13,094	100%	2,565
1 year	96 ± 0%	7,902	99 ± 0%	1,621
3 year	89 ± 0%	4,242	98 ± 0%	847
5 year	81 ± 1%	2,273	95 ± 1%	398
7 year	73 ± 1%	1,109	91 ± 2%	66
9 year	65 ± 1%	456	88 ± 3%	17



Time	Control Patients Event-Free	Control Patients # at Risk	Bariatric Patients Event-Free	Bariatric Patients # at Risk
Baseline	100%	13,175	100%	2,567
1 year	96 ± 0%	8,005	99 ± 0%	1,625
3 year	90 ± 0%	4,333	98 ± 0%	851
5 year	84 ± 1%	2,353	95 ± 1%	400
7 year	76 ± 1%	1,150	92 ± 2%	67
9 year	69 ± 1%	484	88 ± 3%	18



Time	Control Patients Event-Free	Control Patients # at Risk	Bariatric Patients Event-Free	Bariatric Patients # at Risk
Baseline	100%	13,289	100%	2,578
1 year	99 ± 0	7,991	99 ± 0	1,627
3 year	98 ± 0	4,345	99 ± 0	852
5 year	96 ± 0	2,375	99 ± 0	405
7 year	95 ± 0	1,180	99 ± 0	68
9 year	92 ± 1	498	99 ± 0	19



Time	Control Patients Event-Free	Control Patients # at Risk	Bariatric Patients Event-Free	Bariatric Patients # at Risk
Baseline	100%	12,335	100%	2,509
1 year	95 ± 0	7,091	99 ± 0	1,576
3 year	85 ± 0	3,612	97 ± 0	816
5 year	75 ± 1	1,793	96 ± 1	383
7 year	67 ± 1	817	92 ± 2	59
9 year	58 ± 1	324	85 ± 4	12

Johnson et al, J Am Coll Surg 2013

Can Diabetes Be Surgically Cured?

Long-Term Metabolic Effects of Bariatric Surgery in Obese Patients with Type 2 Diabetes Mellitus

Stacy A. Brethauer, MD, Ali Aminian, MD,* Héctor Romero-Talamás, MD,* Esam Batayyah, MD,* Jennifer Mackey, RN,* Laurence Kennedy, MD,† Sangeeta R. Kashyap, MD,† John P. Kirwan, PhD,† Tomasz Rogula, MD,* Matthew Kroh, MD,* Bipan Chand, MD,‡ and Philip R. Schauer, MD**

Objective: Evaluate the long-term effects of bariatric surgery on type 2 diabetes (T2DM) remission and metabolic risk factors.

Background: Although the impressive antidiabetic effects of bariatric surgery have been shown in short- and medium-term studies, the durability of these effects is uncertain. Specifically, long-term remission rates following bariatric surgery are largely unknown.

Methods: Clinical outcomes of 217 patients with T2DM who underwent bariatric surgery between 2004 and 2007 and had at least 5-year follow-up were assessed. Complete remission was defined as *glycated hemoglobin* (A1C) less than 6% and fasting blood glucose (FBG) less than 100 mg/dL off diabetic medications. Changes in other metabolic comorbidities, including hypertension, dyslipidemia, and diabetic nephropathy, were assessed.

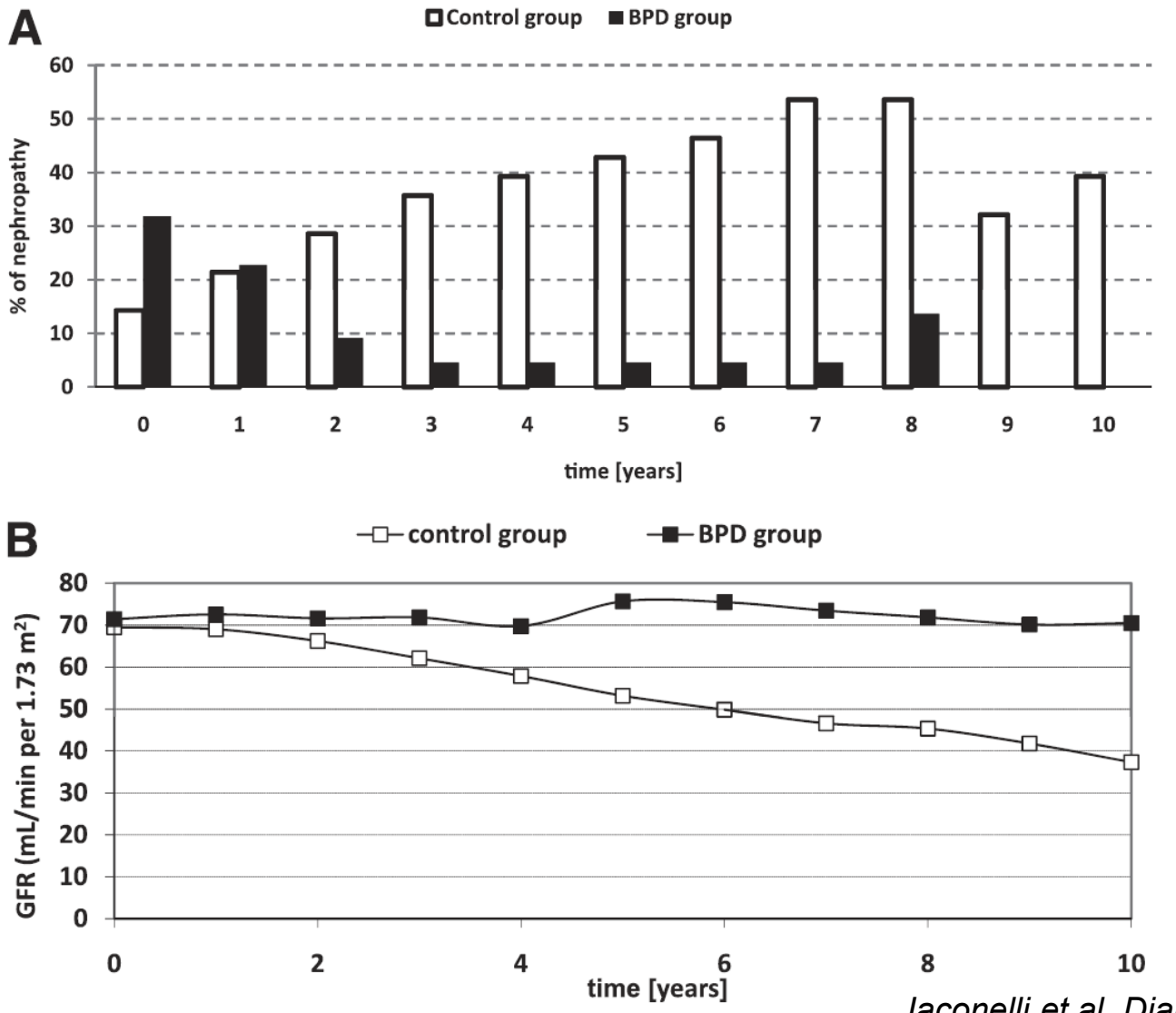
Results: At a median follow-up of 6 years (range: 5–9) after surgery (Roux-en-Y gastric bypass, $n = 162$; gastric banding, $n = 32$; sleeve gastrectomy, $n = 23$), a mean excess weight loss (EWL) of 55% was associated with mean reductions in A1C from 7.5% ± 1.5% to 6.5% ± 1.2% ($P < 0.001$) and FBG from 155.9 ± 59.5 mg/dL to 114.8 ± 40.2 mg/dL ($P < 0.001$). Long-term complete and partial remission rates were 24% and 26%, respectively, whereas 34% improved (>1% decrease in A1C without remission) from baseline and 16% remained unchanged. Shorter duration of T2DM ($P < 0.001$) and higher long-term EWL ($P = 0.006$) predicted long-term remission. Recurrence of T2DM after initial remission occurred in 19% and was associated with longer duration of T2DM ($P = 0.03$), less EWL ($P = 0.02$), and weight regain ($P = 0.015$). Long-term control rates of low high-density lipoprotein, high low-density lipoprotein, high triglyceridemia, and hypertension were 73%, 72%, 80%, and 62%, respectively. Diabetic nephropathy regressed (53%) or stabilized (47%).

Conclusions: Bariatric surgery can induce a significant and sustainable remission and improvement of T2DM and other metabolic risk factors in severely obese patients. Surgical intervention within 5 years of diagnosis is associated with a high rate of long-term remission.

Keywords: bariatric, diabetes, gastric banding, gastric bypass, LAGB, long term, metabolic, nephropathy, RYGB, sleeve gastrectomy

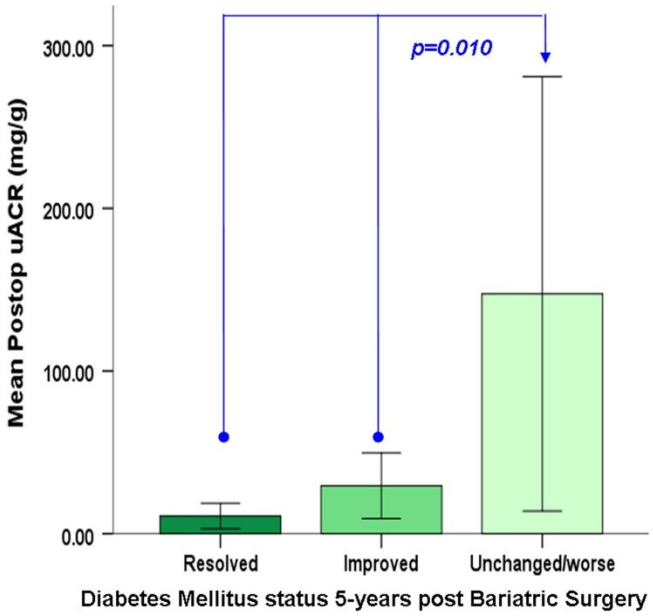
Brethauer et al, Ann Surg 2013

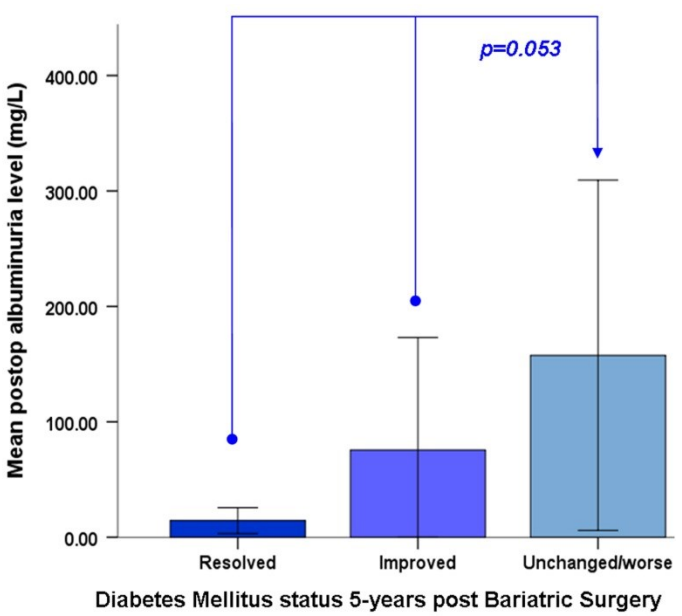
Effects of Bilio-Pancreatic Diversion on Diabetic Complications



Iaconelli et al, Diabetes Care 2011

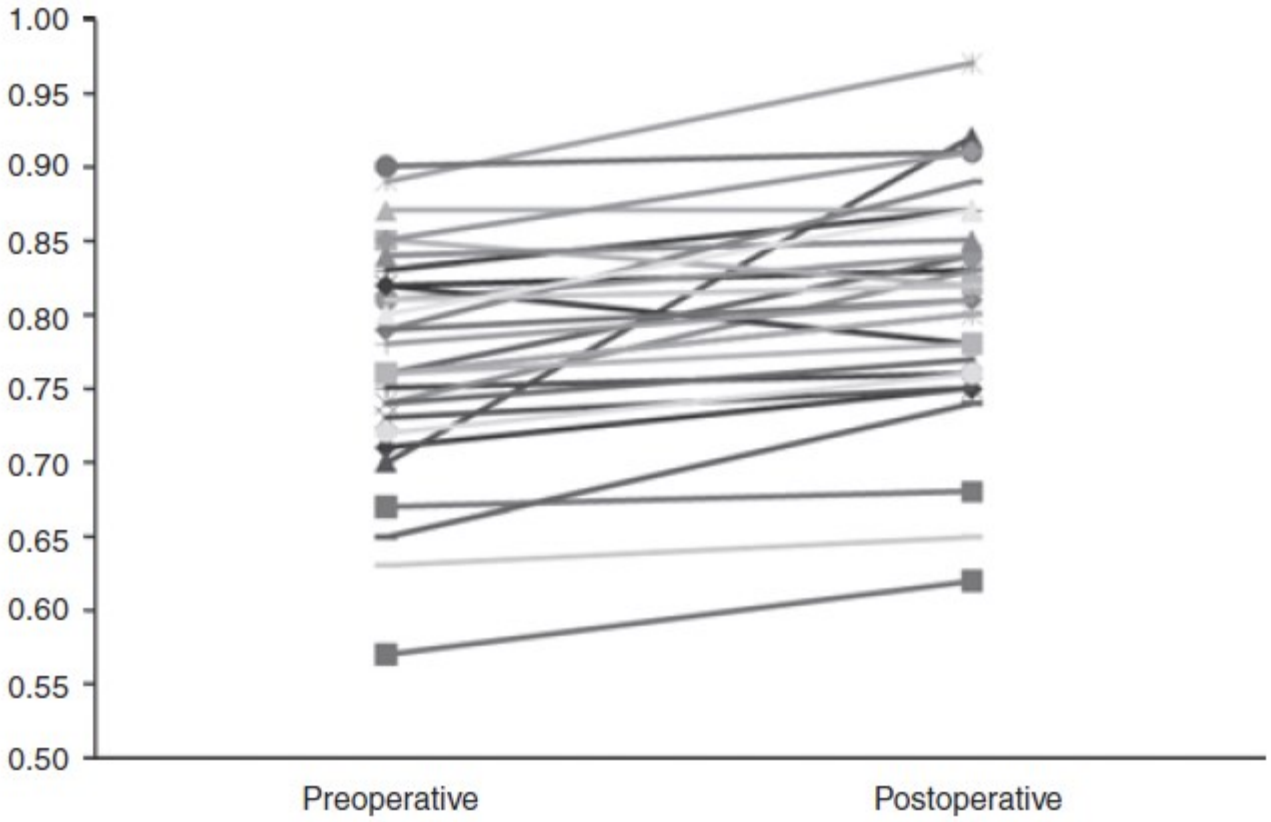
Retrospective study
52 obese T2DM patients (RYGB, LAGB, LSG), mean follow up 66 months
DN 37,6% (microalbuminuria 31,3%, macroalbuminuria 6,3%)
DN remission : 58,3%
DN progression: 25% after 66 months (vs 10-20%/year)





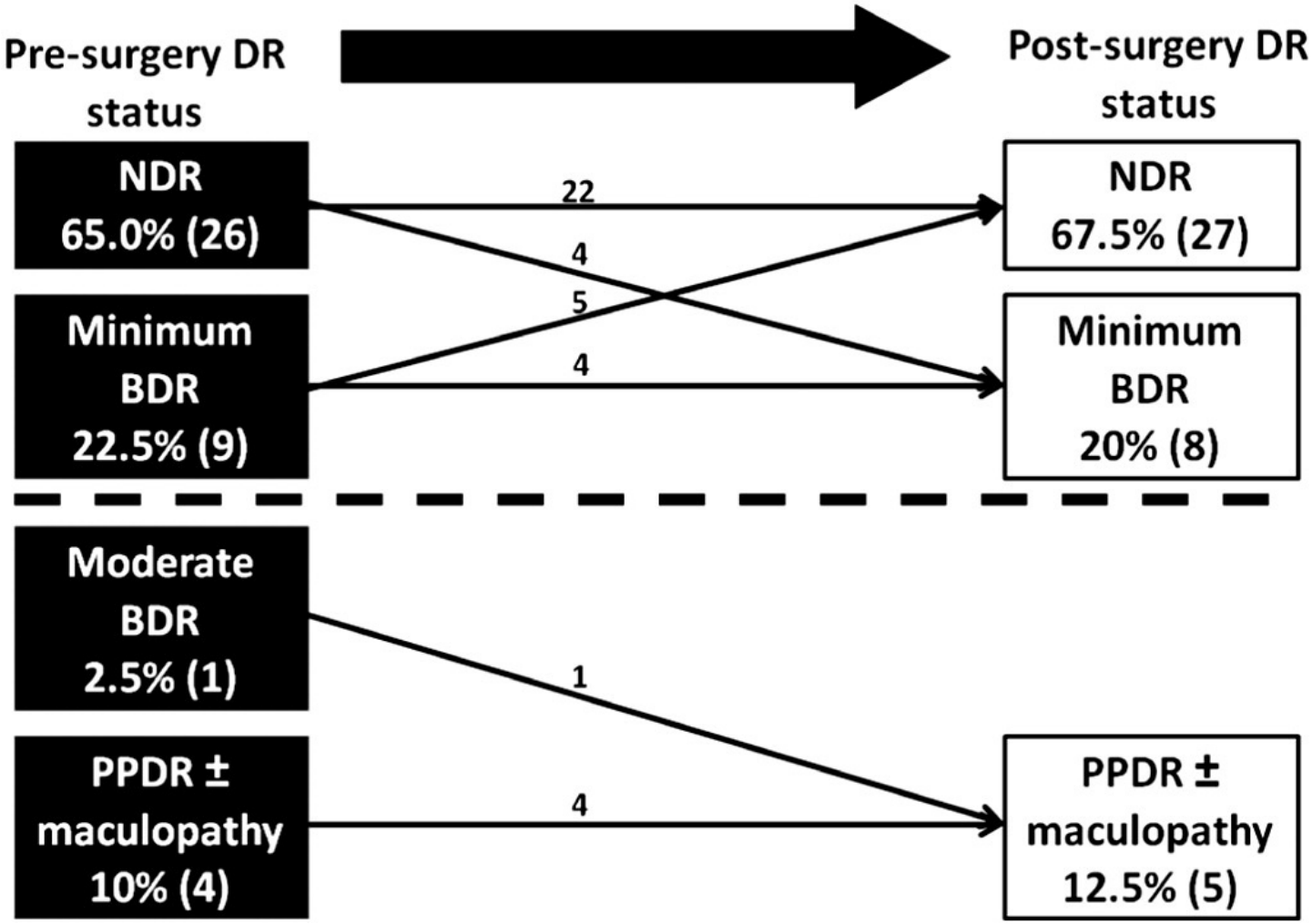
Heneghan et al, Surgery for Obesity and Related Diseases 2013

Improvement of endothelial function (Arteriole-to-venule ratio of retinal vessels) after bariatric surgery.



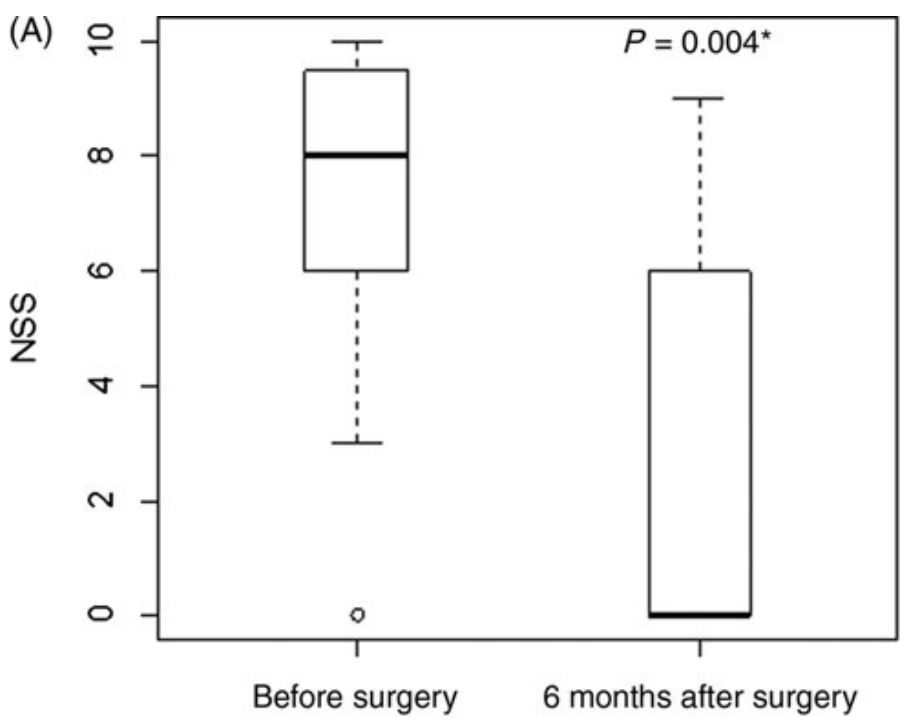
Lammert et al, Obesity 2012

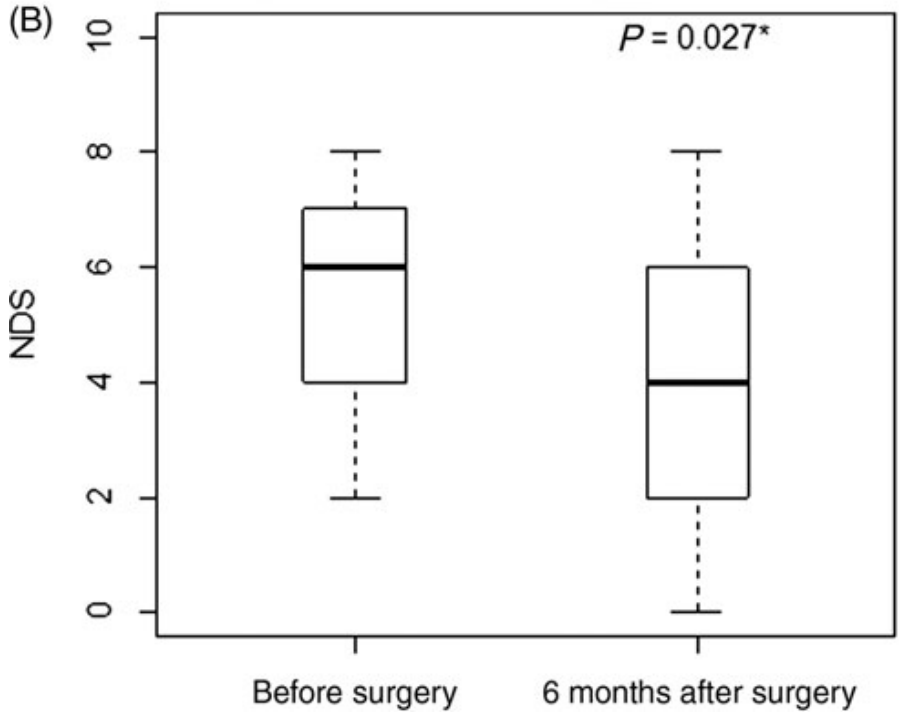
Effects of Bariatric Surgery on diabetic retinopathy



Thomas et al., J Diabetes Complications 2013

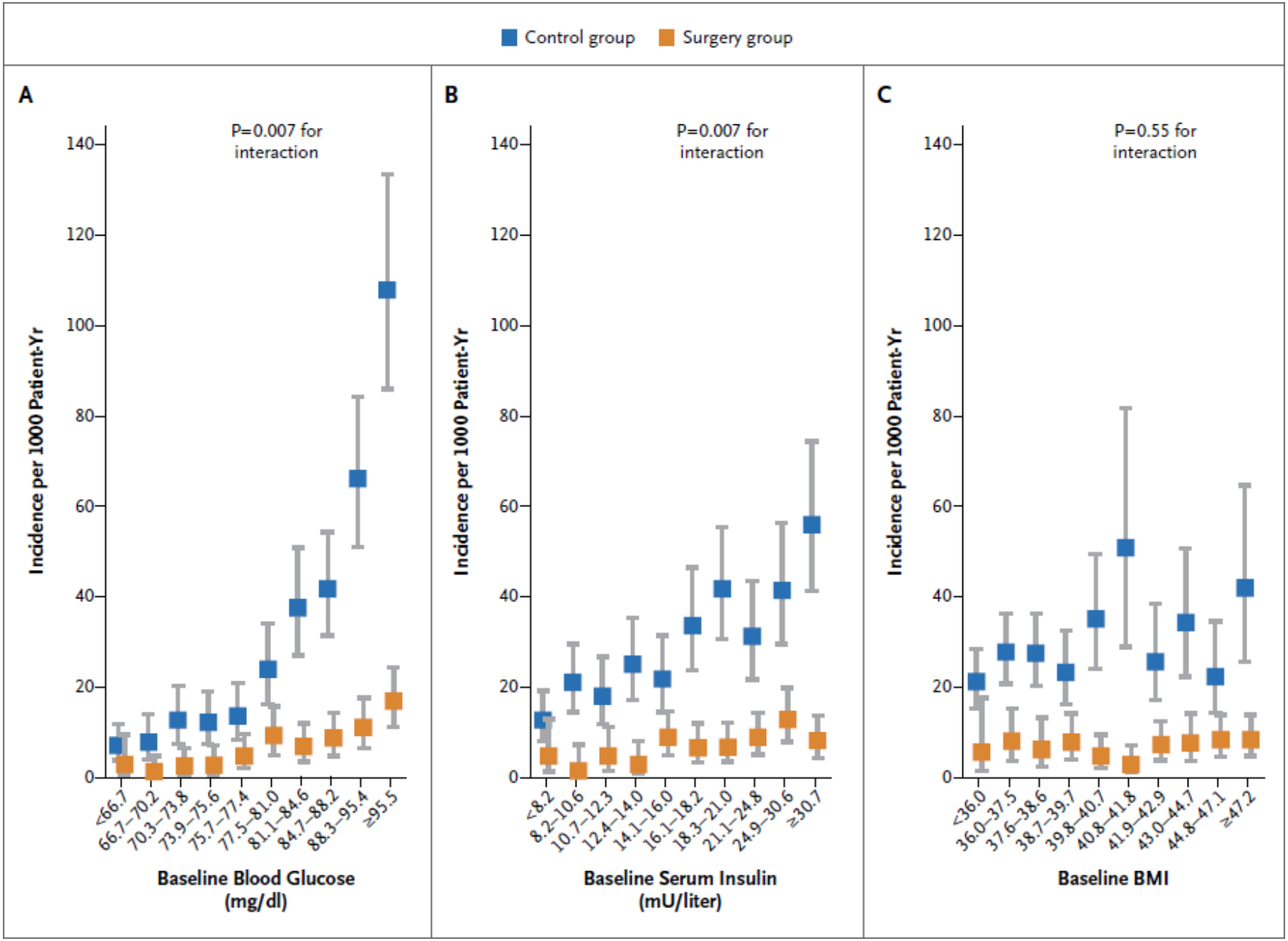
Neuropathy scores before and 6 months after RYGB.





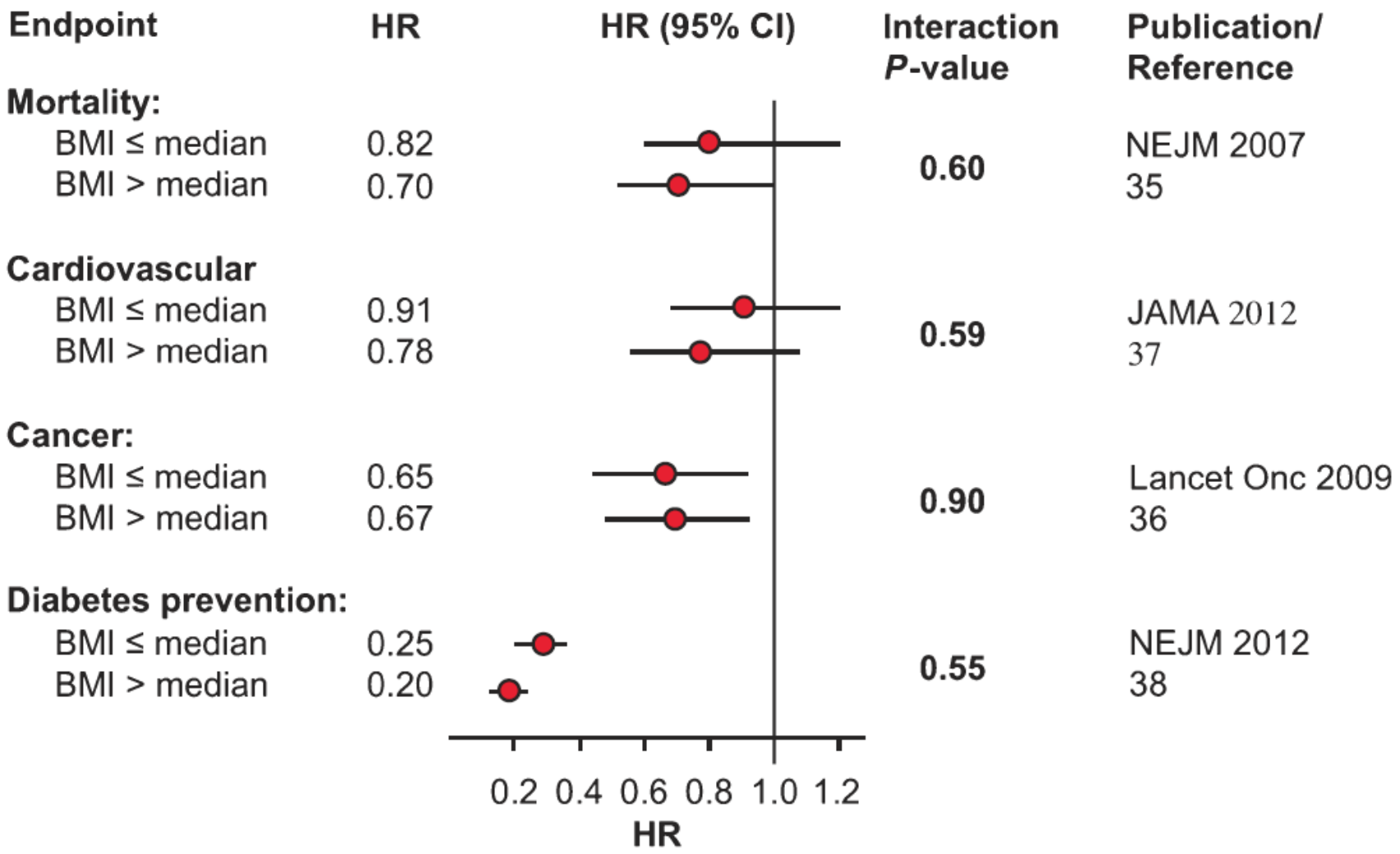
A: Neuropathy Symptom Score (NSS)
B: Neuropathy Deficit Score (NDS)

Müller-Stich et al, Ann Surg 2013



NNT: **1.3 (IFG)**
7.0 (NFG)

SOS Study, Carlsson et al, NEJM 2012



Sjöström L, J Intern Med 2013

Conclusioni

- La chirurgia bariatrica è in grado di ottenere un calo ponderale significativo e sostenuto nel tempo e la rapida remissione del diabete o il significativo miglioramento del compenso glicemico, con riduzione del numero e della posologia dei farmaci ipoglicemizzanti
- Lo stato di remissione si accompagna alla riduzione del profilo di rischio cardiovascolare e dell'incidenza di complicanze macrovascolari
- I dati finora disponibili suggeriscono un vantaggio anche sulle complicanze microvascolari