

Gestione della terapia ipoglicemizzante nel post-operatorio

Chiara Dal Prà

Clinica Medica III

Unità bariatrica

Azienda Ospedaliera Padova

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ANTI-HYPERGLYCEMIC THERAPY

- Therapeutic options: Lifestyle

- Weight optimization



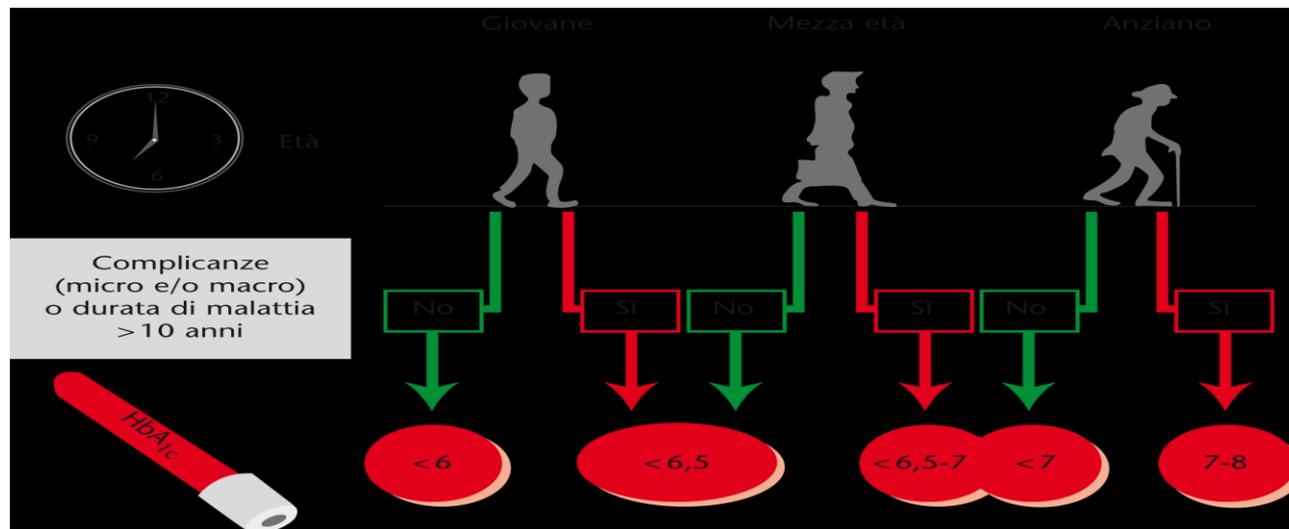
- Healthy diet

- Increased activity level



ANTI-HYPERGLYCEMIC THERAPY

- **Glycemic targets**
 - **HbA1c < 7.0%** (mean PG ~150-160 mg/dl [8.3-8.9 mmol/l])
 - Pre-prandial PG <130 mg/dl (7.2 mmol/l)
 - Post-prandial PG <180 mg/dl (10.0 mmol/l)
 - **Individualization is key:**



ANTI-HYPERGLYCEMIC THERAPY



- **Therapeutic options:**

- *Oral agents & non-insulin injectables*

- Metformin
 - Sulfonylureas
 - Thiazolidinediones
 - DPP-4 inhibitors
 - GLP-1 receptor agonists
 - Meglitinides
 - α -glucosidase inhibitors
 - Bile acid sequestrants
 - Dopamine-2 agonists
 - Amylin mimetics

Class	Mechanism	Advantages	Disadvantages	Cost
Biguanides	<ul style="list-style-type: none"> • Activates AMP-kinase • ↓ Hepatic glucose production 	<ul style="list-style-type: none"> • Extensive experience • No hypoglycemia • Weight neutral • ? ↓ CVD 	<ul style="list-style-type: none"> • Gastrointestinal • Lactic acidosis • B-12 deficiency • Contraindications 	Low
SUs / Meglitinides	<ul style="list-style-type: none"> • Closes KATP channels • ↑ Insulin secretion 	<ul style="list-style-type: none"> • Extensive experience • ↓ Microvasc. risk 	<ul style="list-style-type: none"> • Hypoglycemia • Weight gain • Low durability • ? Ischemic preconditioning 	Low
TZDs	<ul style="list-style-type: none"> • PPAR-γ activator • ↑ insulin sensitivity 	<ul style="list-style-type: none"> • No hypoglycemia • Durability • ↓ TGs, ↑ HDL-C • ? ↓ CVD (pio) 	<ul style="list-style-type: none"> • Weight gain • Edema / heart failure • Bone fractures • ? ↑ MI (rosi) • ? Bladder ca (pio) 	High
α -GIs	<ul style="list-style-type: none"> • Inhibits α-glucosidase • Slows carbohydrate absorption 	<ul style="list-style-type: none"> • No hypoglycemia • Nonsystemic • ↓ Post-prandial glucose • ? ↓ CVD events 	<ul style="list-style-type: none"> • Gastrointestinal • Dosing frequency • Modest ↓ A1c 	Mod.

Table 1. Properties of anti-hyperglycemic agents

Class	Mechanism	Advantages	Disadvantages	Cost
DPP-4 inhibitors	<ul style="list-style-type: none"> Inhibits DPP-4 Increases GLP-1, GIP 	<ul style="list-style-type: none"> No hypoglycemia Well tolerated 	<ul style="list-style-type: none"> Modest ↓ A1c ? Pancreatitis Urticaria 	High
GLP-1 receptor agonists	<ul style="list-style-type: none"> Activates GLP-1 R ↑ Insulin, ↓ glucagon ↓ gastric emptying ↑ satiety 	<ul style="list-style-type: none"> Weight loss No hypoglycemia ? Beta cell mass ? CV protection 	<ul style="list-style-type: none"> GI ? Pancreatitis Medullary ca  Injectable 	High
Amylin mimetics	<ul style="list-style-type: none"> Activates amylin receptor ↓ glucagon ↓ gastric emptying ↑ satiety 	<ul style="list-style-type: none"> Weight loss ↓ PPG 	<ul style="list-style-type: none"> GI Modest ↓ A1c Injectable Hypo w/ insulin Dosing frequency 	High
Bile acid sequestrants	<ul style="list-style-type: none"> Bind bile acids ↓ Hepatic glucose production 	<ul style="list-style-type: none"> No hypoglycemia Nonsystemic ↓ Post-prandial glucose ↓ CVD events 	<ul style="list-style-type: none"> GI Modest ↓ A1c Dosing frequency 	High
Dopamine-2 agonists	<ul style="list-style-type: none"> Activates DA receptor Modulates hypothalamic control of metabolism ↑ insulin sensitivity 	<ul style="list-style-type: none"> No hypoglycemia ? ↓ CVD events 	<ul style="list-style-type: none"> Modest ↓ A1c Dizziness/syncope Nausea Fatigue 	High

Table 1. Properties of anti-hyperglycemic agents

Class	Mechanism	Advantages	Disadvantages	Cost
Insulin	<ul style="list-style-type: none"> • Activates insulin receptor • ↑ peripheral glucose uptake 	<ul style="list-style-type: none"> • Universally effective • Unlimited efficacy • ↓ Microvascular risk 	<ul style="list-style-type: none"> • Hypoglycemia • Weight gain • ? Mitogenicity • Injectable • Training requirements • “Stigma” 	Variable

Table 1. Properties of anti-hyperglycemic agents

Diabetes Care, Diabetologia. 19 April 2012

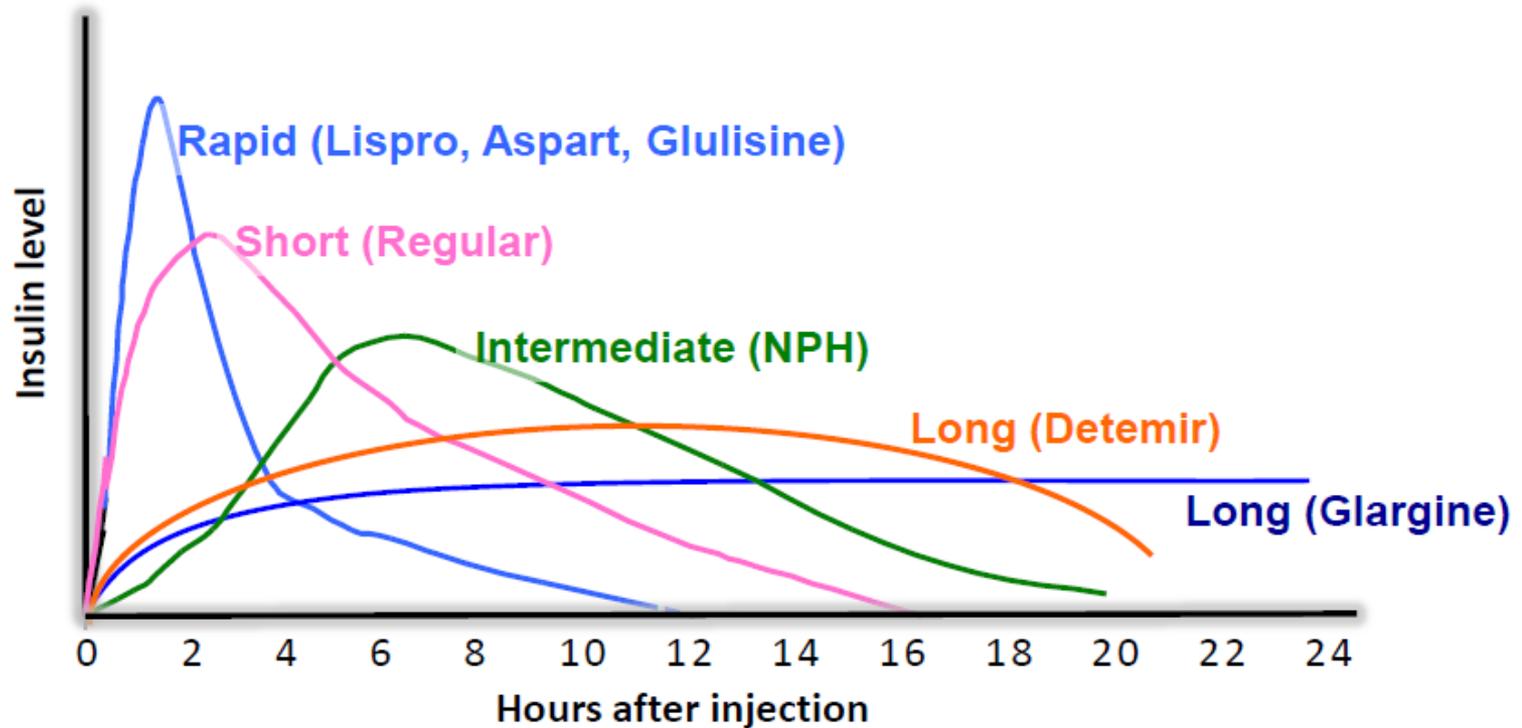
ANTI-HYPERGLYCEMIC THERAPY

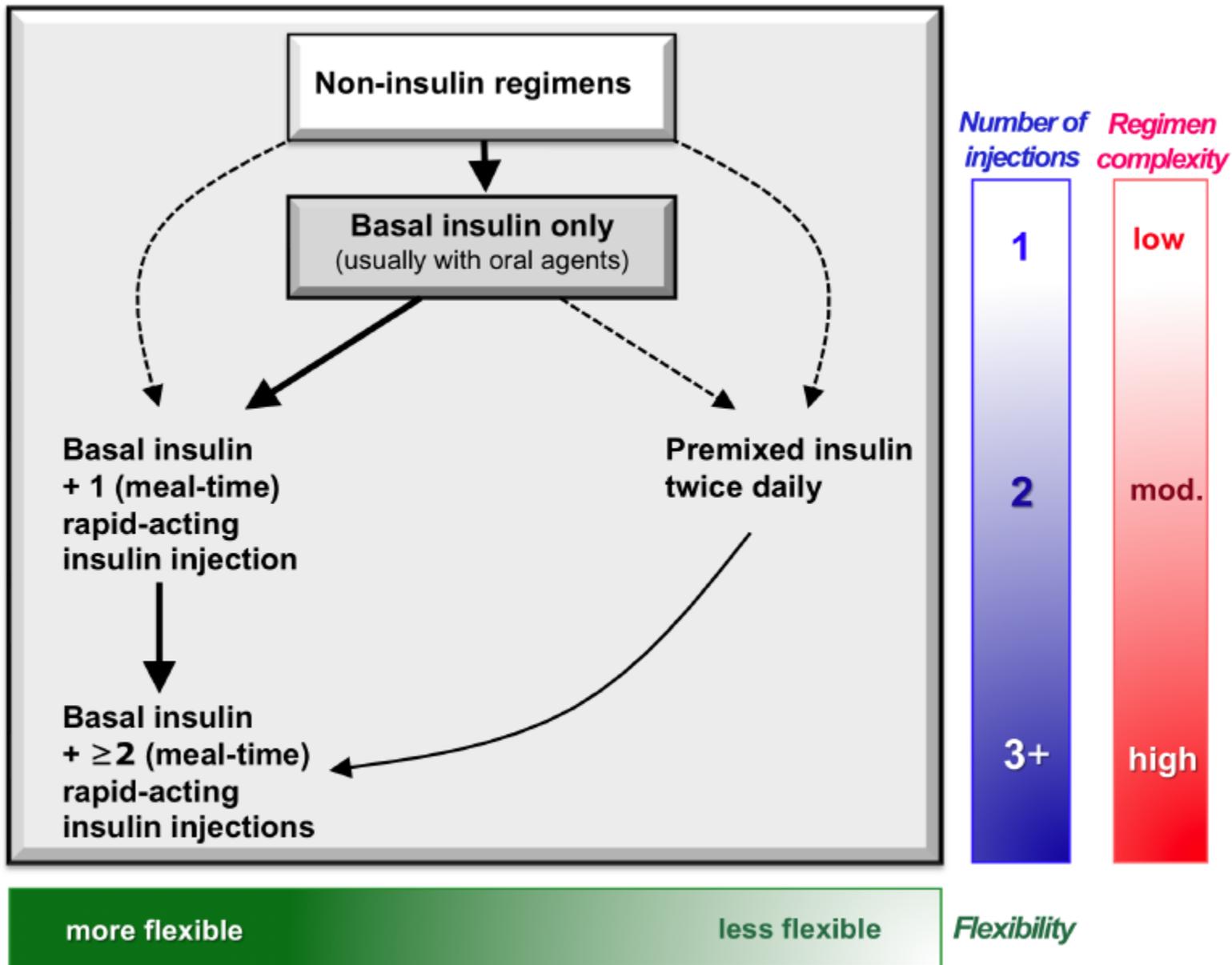
- Therapeutic options: Insulin
 - Neutral protamine Hagedorn (NPH)
 - Regular
 - Basal analogues (glargine, detemir)
 - Rapid analogues (lispro, aspart, glulisine)
 - Pre-mixed varieties

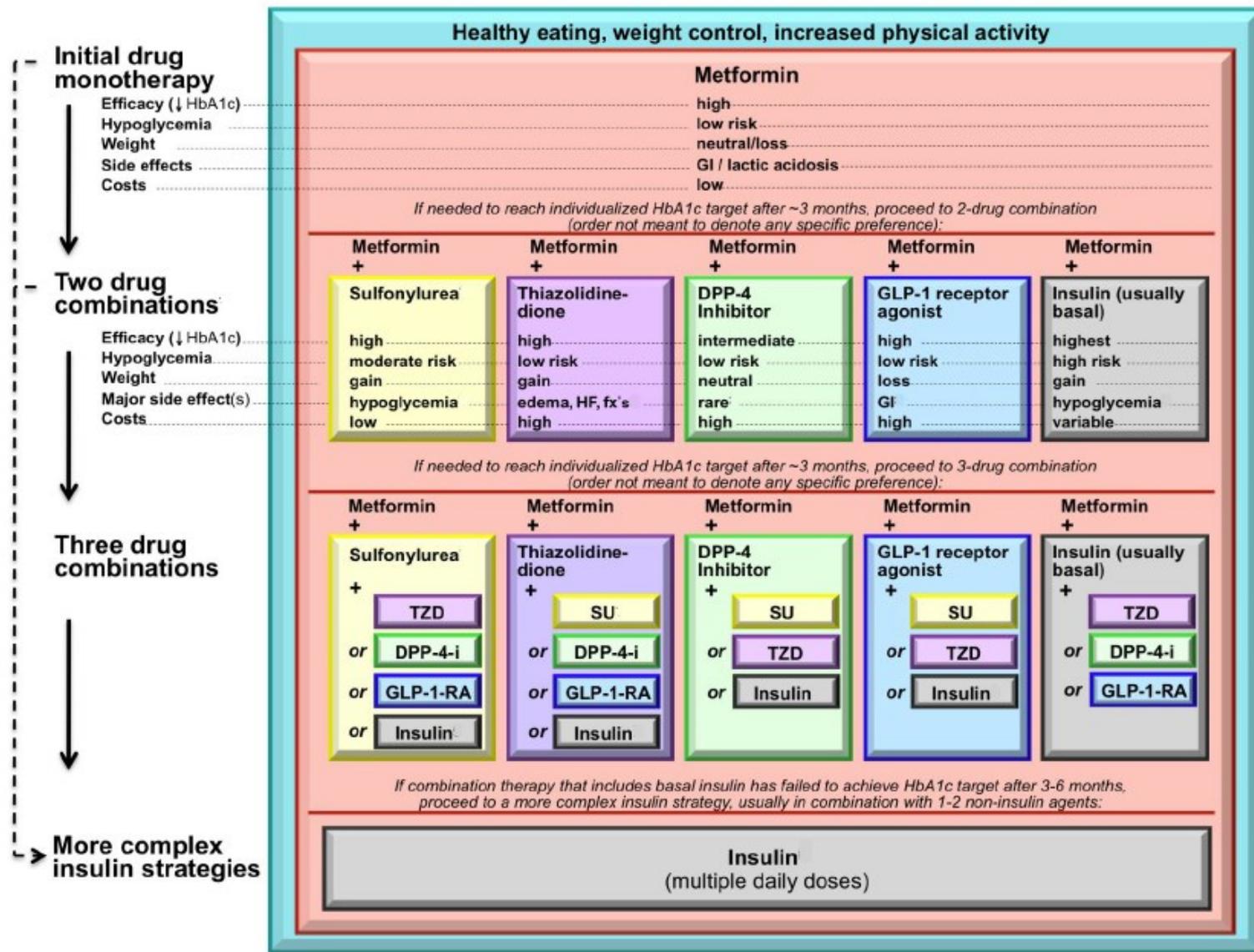


ANTI-HYPERGLYCEMIC THERAPY

- Therapeutic options: Insulin







T2DM Anti-hyperglycemic Therapy: General Recommendations

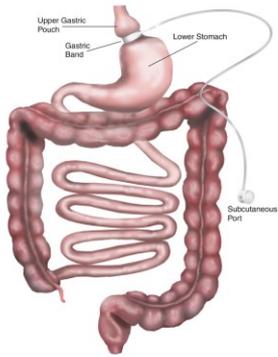
Tecniche chirurgiche bariatriche

Restrittive

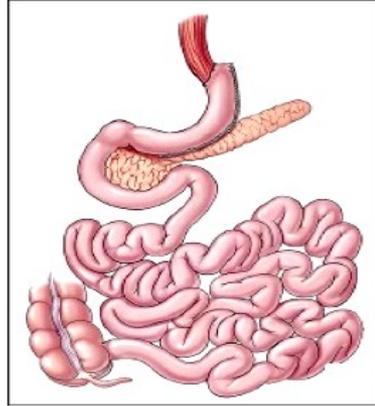
Malassorbitive

Miste

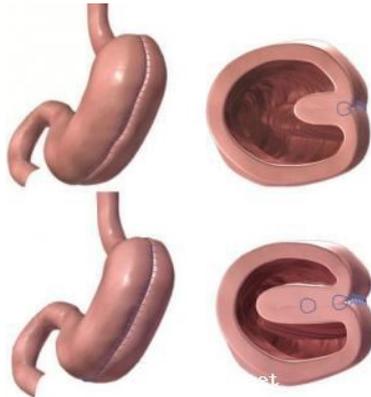
Figure 3. Anatomy of the Laparoscopic Adjustable Gastric Band (LAGB) procedure.



Bendaggio Gastrico (AGB)

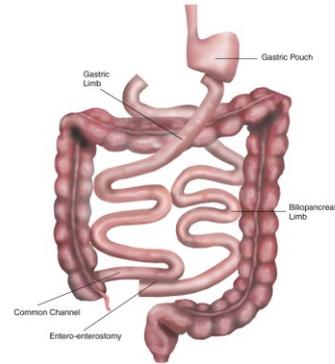


Sleeve Gastrectomy (SG)



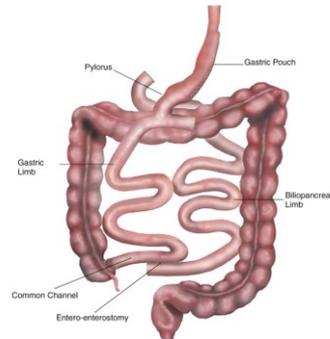
Plicatura Gastrica

Figure 4. Anatomy of Biliopancreatic Diversion (BPD).



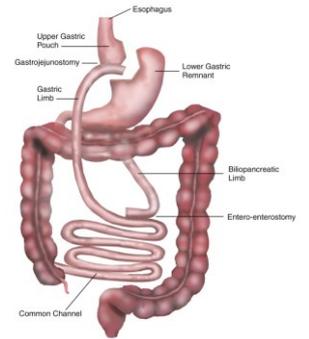
Diversione Bilio-Pancreatica (DBP)

Figure 5. Anatomy of Biliopancreatic Diversion with Duodenal Switch (BPD/DS).



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

Figure 2. Anatomy of the Roux-en-Y Gastric Bypass (RYGB).



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

Meccanismi ipotizzati

- Alterazioni anatomiche e funzionali indotte dall'intervento:
 - Alimenti indigeriti che dallo stomaco passano direttamente alle porzioni distali del tenue → aumento di *GLP-1*, *PYY* e ossintomodulina
 - Ridotta secrezione di *GIP* e *Ghrelina* (ruolo ancora non chiarito)
- Rapido bilancio calorico negativo (giorni)
- Effetto insulino-sensibilizzante del calo ponderale (long term)

Prompt Reduction in Use of Medications for Comorbid Conditions After Bariatric Surgery

Jodi B. Segal • Jeanne M. Clark • Andrew D. Shore • Francesca Dominici •
Thomas Magnuson • Thomas M. Richards • Jonathan P. Weiner • Eric B. Bass •
Albert W. Wu • Martin A. Makary

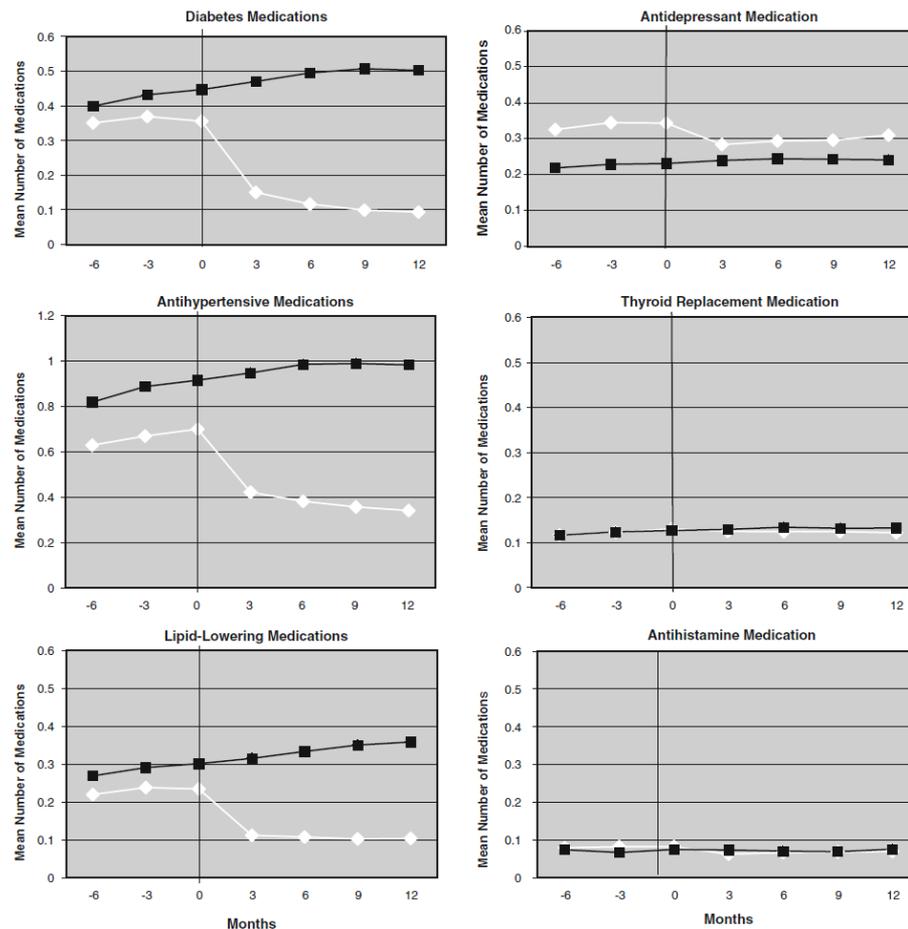


Fig. 1 White diamonds = surgical group, black squares = nonsurgical group of individuals predicted to be obese

Medication Utilization and Annual Health Care Costs in Patients With Type 2 Diabetes Mellitus Before and After Bariatric Surgery

Martin A. Makary, MD, MPH; Jeanne M. Clarke, MD; Andrew D. Shore, PhD; Thomas H. Magnuson, MD; Thomas Richards, MS; Eric B. Bass, MD; Francesca Dominici, PhD; Jonathan P. Weiner, DrPH; Albert W. Wu, MD, MPH; Jodi B. Segal, MD, MPH

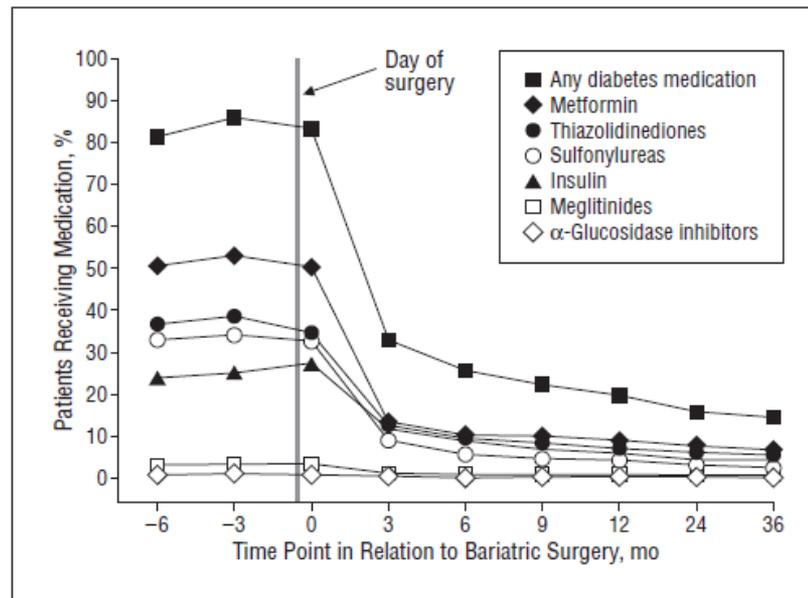
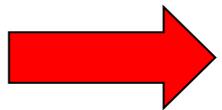


Figure. Use of diabetes medication before and after bariatric surgery.

Terapia ipoglicemizzante dopo chirurgia bariatrica

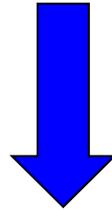
La gestione della terapia ipoglicemizzante dei pazienti affetti da diabete mellito dopo chirurgia bariatrica varia enormemente nei diversi centri.

Non esistono degli algoritmi di trattamento universalmente approvati e accettati....

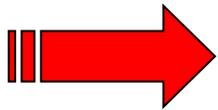


LE NOSTRE "LINEE GUIDA" INTERNE

METFORMINA



Reintrodurre alla dimissione la dose precedentemente assunta



Solo con $GFR > 50$ ml (min/1.73 m²)

Effect of Gastric Bypass Surgery on the Absorption and Bioavailability of Metformin

RAJ S. PADWAL, MD, MSC¹
RANIAH Q. GABR, MSC²
ARYA M. SHARMA, MD, PHD¹
LEE-ANN LANGKAAS, LPN³

DAN W. BIRCH, MD⁴
SHAHZEER KARMALI, MD⁴
DION R. BROCKS, PHD²

Aumento dell'assorbimento dopo RYGB :

- ritardando lo svuotamento gastrico per i cibi solidi aumenta l'esposizione del farmaco alla mucosa del piccolo intestino;
- marcata riduzione della produzione dell'acido gastrico (ambiente alcalino aumenta assorbimento di farmaci acidi come la metformina)
- Up-regolazione di OCT (organic cation transporters)
- adattamento del piccolo intestino che porta a iperplasia villosa

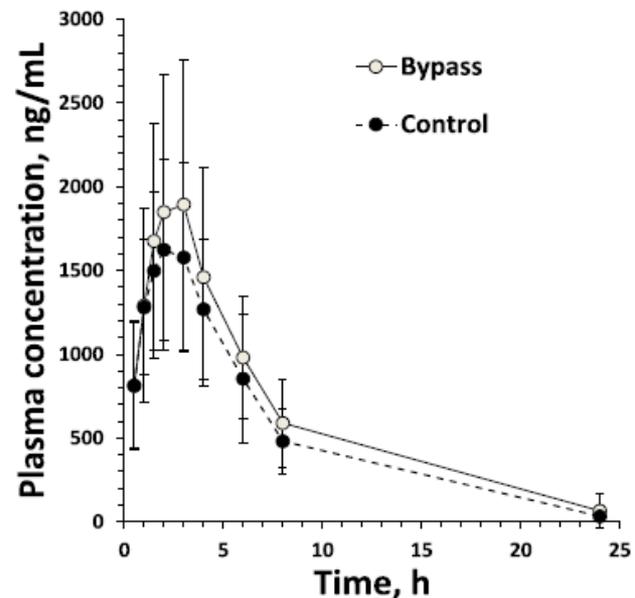
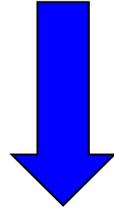


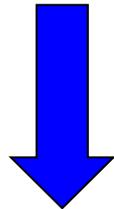
Figure 1—Plasma concentration time curve.

SULFANILUREE



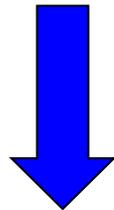
Sospensione della terapia!!!!!!!

GLITAZONI



Reintrodurre dal giorno successivo
alla dose precedentemente assunta

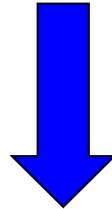
ANALOGHI GLP-1 INIBITORI DDP-IV



Reintrodurre con la ripresa
dell'alimentazione post-intervento
(solitamente il giorno successivo)

TERAPIA INSULINICA 1

INSULINA BASALE (Glargine, Detemir)



da non sospendere mai
di solito dose ridotta del 50% rispetto al pre-intervento.
Correggere secondo schemi di titolazione

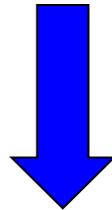
Basalizzazione

Dose iniziale	<ul style="list-style-type: none">• 40-50% del fabbisogno insulinico giornaliero calcolato• 0,2-0,4 U/Kg/die• 10 U/die (dose prudenziale, pazienti anziani, fragili o in pazienti in terapia con ipoglicemizzante orale)
Titolazione	<ul style="list-style-type: none">• Dose corretta se la glicemia a digiuno è più o meno uguale alla glicemia bedtime (ore 22)• +/- 2 U ogni 2-3 giorni se glicemia a digiuno >150/<100 mg/dl
Gestione	<p>Non sospendere l'insulina basale se la glicemia bedtime è bassa:</p> <ol style="list-style-type: none">1. se glicemia bedtime > 130 → somministra basale prescritta2. se glicemia bedtime 100-130 → somministra spuntino + basale prescritta3. se glicemia bedtime <100 → spuntino e/o eventuale riduzione basale (circa 2 unità) (controllo h 02:00)4. se glicemia bedtime <70 → trattamento ipoglicemia "bedtime" ed eventuale riduzione basale (controllo h 02:00)

TERAPIA INSULINICA 2

insulina rapida umana
(Actrapid/Humulin R)

analogo ultrarapido
(Humalog-Lispro; Apidra-Glulisina; Novorapid-Aspart)



Reintrodurre in terapia se glicemie preprandiali >200 mg/dL
generalmente a una dose ridotta del 50% rispetto alla dose
pre-intervento.

Adeguare secondo schemi di correzione

Tabelle di correzione della dose di insulina prandiale secondo la glicemia preprandiale

☐ <i>algoritmo basso dosaggio</i>		☐ <i>algoritmo medio dosaggio</i>		☐ <i>algoritmo alto dosaggio</i>		☐ <i>algoritmo personalizzato</i>	
<i>≤50 U insulina/die</i>		<i>50-90 U insulina/die</i>		<i>>90 U insulina/die</i>			
Glicemia pre-prandiale	Unità da aggiungere	Glicemia pre-prandiale	Unità da aggiungere	Glicemia pre-prandiale	Unità da aggiungere	Glicemia pre-prandiale	Unità da aggiungere
70-90	- 1	70-90	- 2	70-90	- 2	70 - _____	- _____
150-199	1	150-199	1	150-199	2	150-199	
200-249	2	200-249	3	200-249	4	200-249	
250-299	3	250-299	5	250-299	7	250-299	
300-349	4	300-349	7	300-349	10	300-349	
>349	5	>349	8	>349	12	>349	

Sig.....

Tabelle di correzione della dose di insulina prandiale secondo la glicemia pre-prandiale

<i>algoritmo medio dosaggio</i>	
<i>50-90 U insulina/die</i>	
Glicemia pre-prandiale	Unità da aggiungere
70-90	- 2
150-199	1
200-249	3
250-299	5
300-349	7
>349	8

Tabella per la basalizzazione (LANTUS)

Titolazione	•Dose corretta se la glicemia a digiuno è più o meno uguale alla glicemia bedtime •+/- 2 U ogni 2-3 giorni se glicemia a digiuno >150/<100 mg/dl
Gestione	Non sospendere l'insulina basale se la glicemia bedtime è bassa: 1.se glicemia bedtime >130 → somministra basale prescritta 2.se glicemia bedtime 100-130 → somministra spuntino + basale prescritta 3.se glicemia bedtime <100 → spuntino e/o eventuale riduzione basale (circa 2 unità) (controllo h 02:00) 4.se glicemia bedtime <70 → trattamento ipoglicemia "bedtime" ed eventuale riduzione basale (controllo h 02:00)

Digiuno per esami

La sera precedente	se Lantus → mantieni la dose. Valuta riduzione della dose se glicemie <70 mg/dl nelle 24 ore precedenti il giorno dell'esame
Il giorno del digiuno	correggere le iperglicemie con analogo rapido (Humalog) secondo algoritmo

TRATTAMENTO DELL'IPOGLICEMIA (<70 mg/dl)

Somministrare 15 grammi di zucchero pari a:

4 zollette di zucchero o tre bustine di zucchero o ½ succo di frutta zuccherato (100 ml)
150 ml (1 bicchiere) di coca cola, aranciata o altra bibita zuccherata

Ricontrollare la glicemia dopo 15 minuti. Ripetere il trattamento fino a glicemia >70 mg/dl.

Per glicemia <40 mg/dl e ipoglicemie "bedtime" far assumere anche 15-20 gr di carboidrati a più lento assorbimento: 25-30 gr di pane, crackers, fette biscottate oppure 300 ml di latte.

Can a Protocol for Glycaemic Control Improve Type 2 Diabetes Outcomes After Gastric Bypass?

Wiebke K. Fenske • Dimitri J. Pournaras •
Erlend T. Aasheim • Alexander D. Miras •
Nicola Scopinaro • Samantha Scholtz • Carel W. le Roux

Table 1 Daily insulin titration schedule in insulin-requiring type 2 diabetes after gastric bypass surgery

Start with dose equivalent to the insulin required in the previous 24 h prior to discharge and adjust it daily

Self-monitored fasting glucose values	Adjustment of insulin dosage (IU/day)
≥12 mmol/L (220 mg/dL)	6 ↑
>10 mmol/L (180 mg/dL)	4 ↑
>8 mmol/L (144 mg/dL)	2 ↑
≥7 mmol/L (120 mg/dL)	1 ↑
5.5–6.9 mmol/L (100–120 mg/dL)	No change in insulin dosage
<5.5 mmol/L (100 mg/dL)	2 ↓
<4.5 mmol/L (81 mg/dL)	4 ↓
<4.0 mmol/L (72 mg/dL)	6 ↓

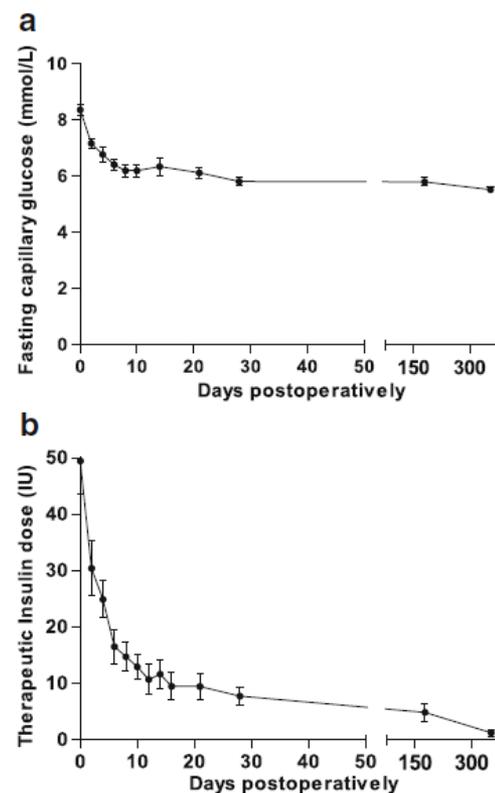


Fig. 1 Fasting plasma glucose levels (a) and therapeutic insulin doses in units per day (b) during protocol-driven insulin management in 50 patients over a period of 379 ± 4.5 days. Data are presented as mean \pm SEM of fasting capillary concentration and daily insulin dose

Remissione del diabete

COMPLETA

- HbA1c < 6%
- Glicemia a digiuno < 5.6 mmol/L (100 mg/dL)
per almeno un anno senza assunzione di alcuna terapia ipoglicemizzante

PARZIALE

- HbA1c < 6.5%
- Glicemia a digiuno 5.6-6.9 mmol/L (100-125 mg/dL)
per almeno un anno senza assunzione di alcuna terapia ipoglicemizzante

ORIGINAL ARTICLE

Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes

Geltrude Mingrone, M.D., Simona Panunzi, Ph.D., Andrea De Gaetano, M.D., Ph.D.,
Caterina Guidone, M.D., Amerigo Iaconelli, M.D., Laura Leccesi, M.D.,
Giuseppe Nanni, M.D., Alfons Pomp, M.D., Marco Castagneto, M.D.,
Giovanni Ghirlanda, M.D., and Francesco Rubino, M.D.

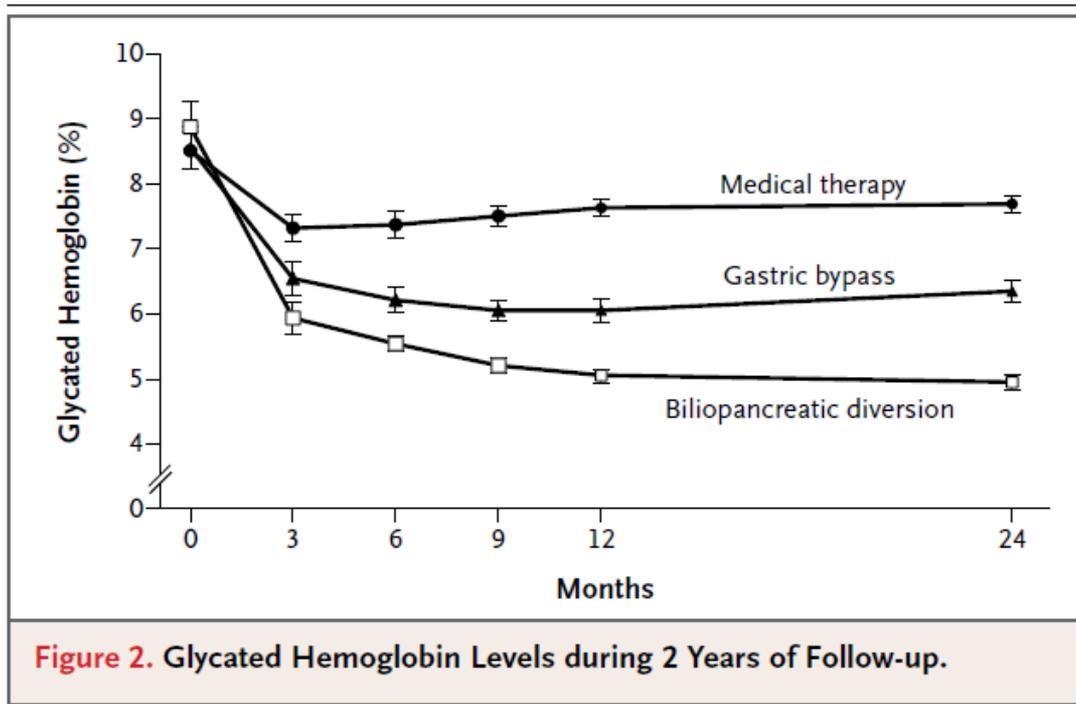


Table 2. Average Absolute Values and Percentage Changes at 2 Years.*

Variable	Medical Therapy (N=18)	Biliopancreatic		Overall	P Value†		
		Diversion (N=19)	Gastric Bypass (N=19)		Biliopancreatic Diversion vs. Medical Therapy	Gastric Bypass vs. Medical Therapy	Gastric Bypass vs. Bilio- pancreatic 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				

* Plus-minus values are means ±SD.

† P values for the overall comparisons were calculated with the use of analysis of variance. P values for the comparisons between each of the two surgical procedures and medical therapy and for the comparison between the two types of surgery were calculated with the use of the Bonferroni method in post hoc analyses.

Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes

Philip R. Schauer, M.D., Sangeeta R. Kashyap, M.D., Kathy Wolski, M.P.H., Stacy A. Brethauer, M.D.,
John P. Kirwan, Ph.D., Claire E. Pothier, M.P.H., Susan Thomas, R.N., Beth Abood, R.N., Steven E. Nissen, M.D.,
and Deepak L. Bhatt, M.D., M.P.H.

Table 2. Primary and Secondary End Points at 12 Months.*

End Point	Medical Therapy (N=41)	Gastric Bypass (N=50)	Sleeve Gastrectomy (N=49)	P Value		
				Gastric Bypass vs. Medical Therapy	Sleeve Gastrectomy vs. Medical Therapy	Gastric Bypass vs. Sleeve Gastrectomy
Glycated hemoglobin						
≤6% — no. (%)	5 (12)	21 (42)	18 (37)	0.002	0.008	0.59
≤6% with no diabetes medications — no. (%)	0	21 (42)	13 (27)	<0.001	<0.001	0.10
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 — percentage points	-1.4±1.5	-2.9±1.6	-2.9±1.8	<0.001	<0.001	0.85
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
High-density lipoprotein cholesterol						
Percent change from baseline	11.3±25.7	28.5±22.7	28.4±21.9	0.001	0.001	0.98
Triglycerides						
Median percent change from baseline (interquartile range)	-14 (-40 to 3)	-44 (-65 to -16)	-42 (-56 to 0)	0.002	0.08	0.17
High-sensitivity C-reactive protein						
Median percent change from baseline (interquartile range)	-33.2 (-71 to 0)	-84 (-91 to -59)	-80 (-90 to -63)	<0.001	<0.001	0.59

* Plus-minus values are means ±SD. Post-randomization data were not available for nine patients in the medical-therapy group and one patient in the sleeve-gastrectomy group. P<0.05 for the comparisons with baseline values in all listed categories. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

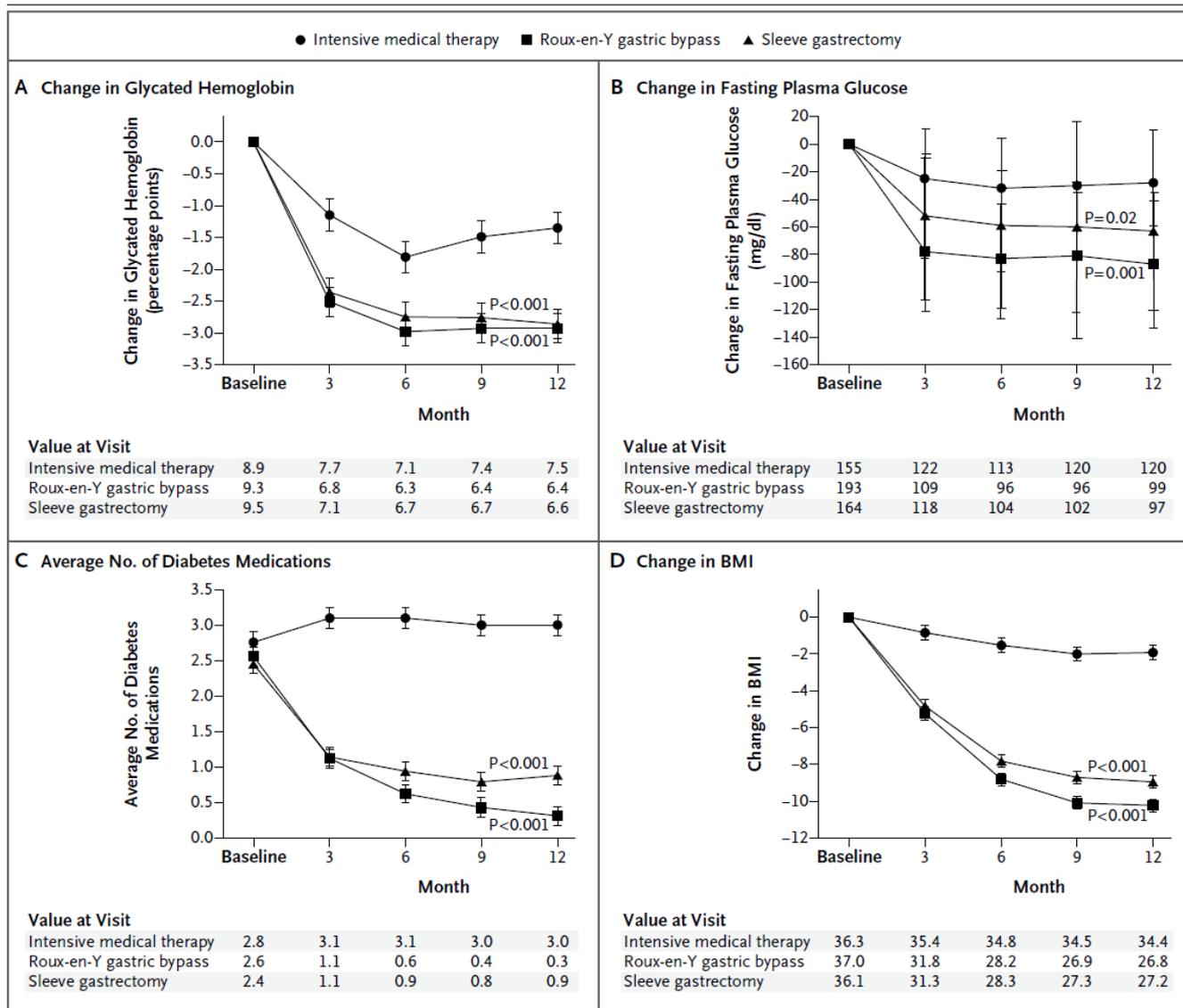


Figure 1. Changes in Measures of Diabetes Control from Baseline.

Values for change in glycated hemoglobin (Panel A), change in fasting plasma glucose (Panel B), the average number of diabetes medications (Panel C), and change in body-mass index (BMI) (Panel D) were plotted at 3, 6, 9, and 12 months. Least-square means and standard errors from a repeated measures model are plotted for glycated hemoglobin, average number of medications, and BMI; medians and interquartile ranges are plotted for fasting plasma glucose. P values are for the comparison between each surgical group and the medical-therapy group and were calculated from a repeated-measures model that considers data over time.

Guidelines for Glycemic, BP, & Lipid Control

	American Diabetes Assoc. Goals
HbA1C	< 7.0% (<i>individualization</i>)
Preprandial glucose	70-130 mg/dL (3.9-7.2 mmol/l)
Postprandial glucose	< 180 mg/dL
Blood pressure	< 130/80 mmHg
Lipids	<p>LDL: < 100 mg/dL (2.59 mmol/l) < 70 mg/dL (1.81 mmol/l) (with overt CVD)</p> <p>HDL: > 40 mg/dL (1.04 mmol/l) ♂ > 50 mg/dL (1.30 mmol/l) ♀</p> <p>TG: < 150 mg/dL (1.69 mmol/l)</p>

HDL = high-density lipoprotein; LDL = low-density lipoprotein; PG = plasma glucose; TG = triglycerides.

ADA. *Diabetes Care*. 2012;35:S11-63



**GRAZIE PER
L'ATTENZIONE!!!!**