VIII Convegno Nazionale
Fondazione AMD

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Surgery for Type 2 DM

Is it Metabolic or Bariatric surgery?

PALERMO, 17-19 NOVEMBRE 2016

Metabolic control after surgery is superior that after medical therapy

Consistently shown in 11 RCT

Patient characteristics and outcomes in 5 major RCTs

Author	Rx arms (n)	Follow up (years)	BMI (Kg/m²)	HbA1c	On insulin (%)	DM duration (years)	1ary aim	Main outcome
Schauer *STAMPEDE 2012, 2014*	ILMI ILMI+GBP ILMI+SG	3 (out to 5)	36.5	9.3	43%	8.3	**A1c<6% with or wo meds**	**ILMI: 5%** **GBP: 38%** **SG: 24%**
Mingrone *2012, 2015*	ILMI (15) ILMI+GBP (19) ILMI+BPD (19)	5 (out of 5)	45.0	8.7	47%	NA	**A1c<6%+ FPG<100, no meds**	**ILMI: 5%** **GBP: 38%** **BPD: 24%**
Ikkramudin *2013, 2015*	ILMI (60) ILMI+GBP (60)	2 (out of 5)	34.6	9.6	52%	NA	**A1c<7% + LDL<100 + SBP<130**	**ILMI: 14%** **GBP: 43%**
Courcalas *2014,2015*	LSI (23) LSI+GBP (24) LSI+AGB (23)	3 (out of 3)	35.7	7.8	40%	6.5	**A1c<6%+ FPG<100, no meds**	**ILMI: 0%** **GBP: 40%** **AGB: 29%**
Cummings *CROSSROADS 2016*	ILMI (17) ILMI+GBP (15)	1 (out to 1)	37.5	7.5	50%	9.0	**A1c<6% wo meds @ 1 y**	**ILMI: 5.9%** **GBP: 60%**

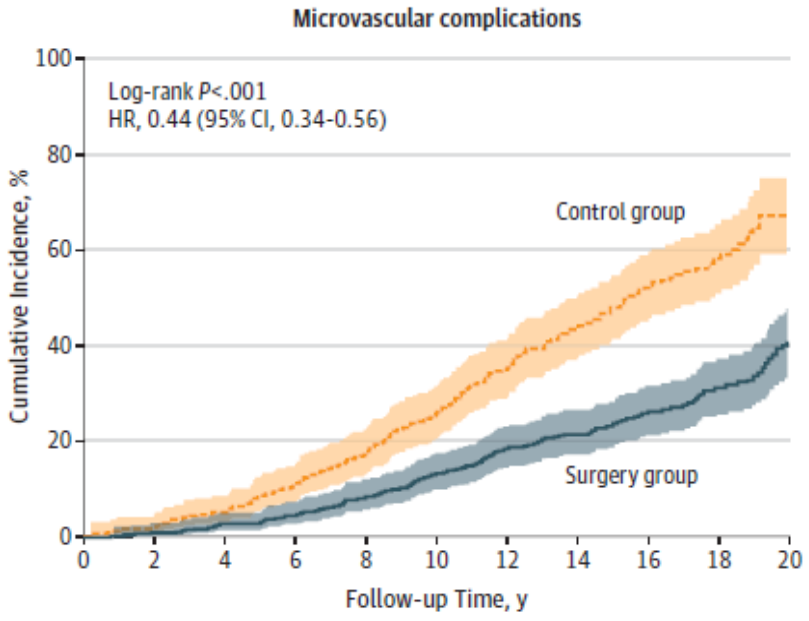
Surgical vs Medical therapy of T2DM

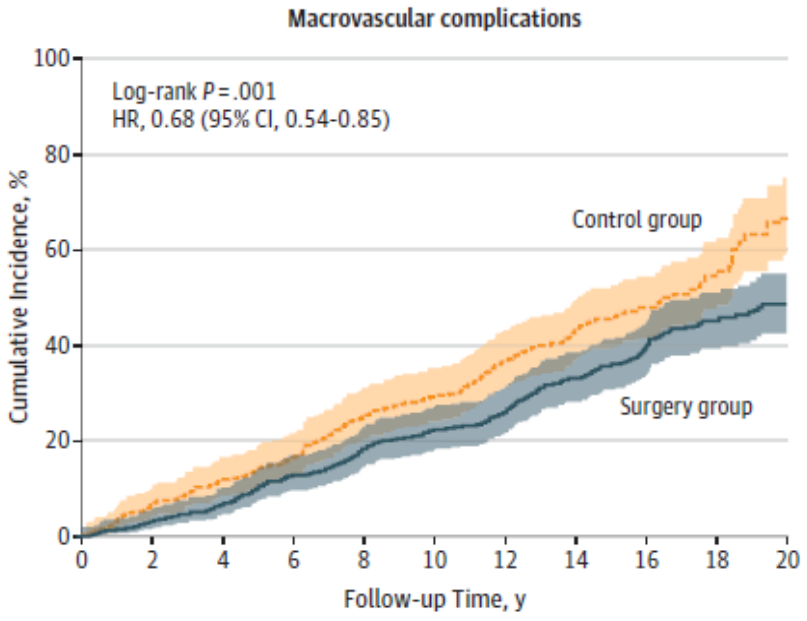
Postive Impact on chronic complications in a cohort-study

SWEDISH OBESE SUBJECTS STUDY- T2DM COHORT

N=607 (Bariatric surgery, n=345 --- Control, n= 262); Follow up: median 13.3 years (IQ range 10.2-16.4 y)

Figure 3. Cumulative Incidence of Microvascular and Macrovascular Diabetes Complications in the Surgery and Control Groups

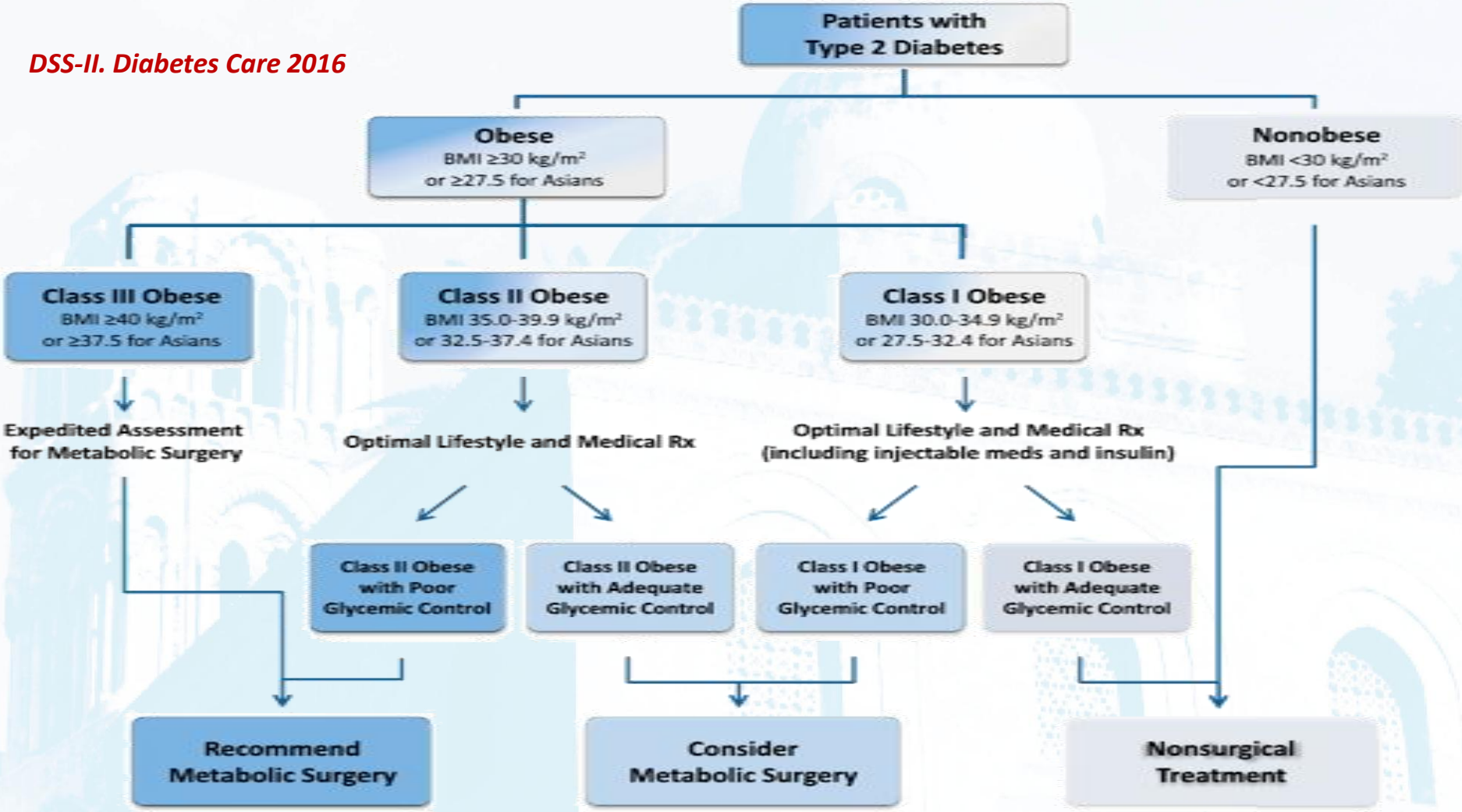




Sjostrom L et al, JAMA 2014

Surgery should be part of the therapeutic algorithm of T2D

DSS-II. Diabetes Care 2016



Should we call it "metabolic" or "bariatric" surgery"?

"bariatric"

American Society for Bariatric Surgery

"A set of gastrointestinal surgical procedures originally designed to induce weight reduction in morbidly obese patients»

"metabolic"

American Society for Metabolic and Bariatric Surgery

"Operative manipulation of a normal organ or organ system to achieve a biological result for a potential health gain»

RL Varco, Metabolic Surgery Book 1978

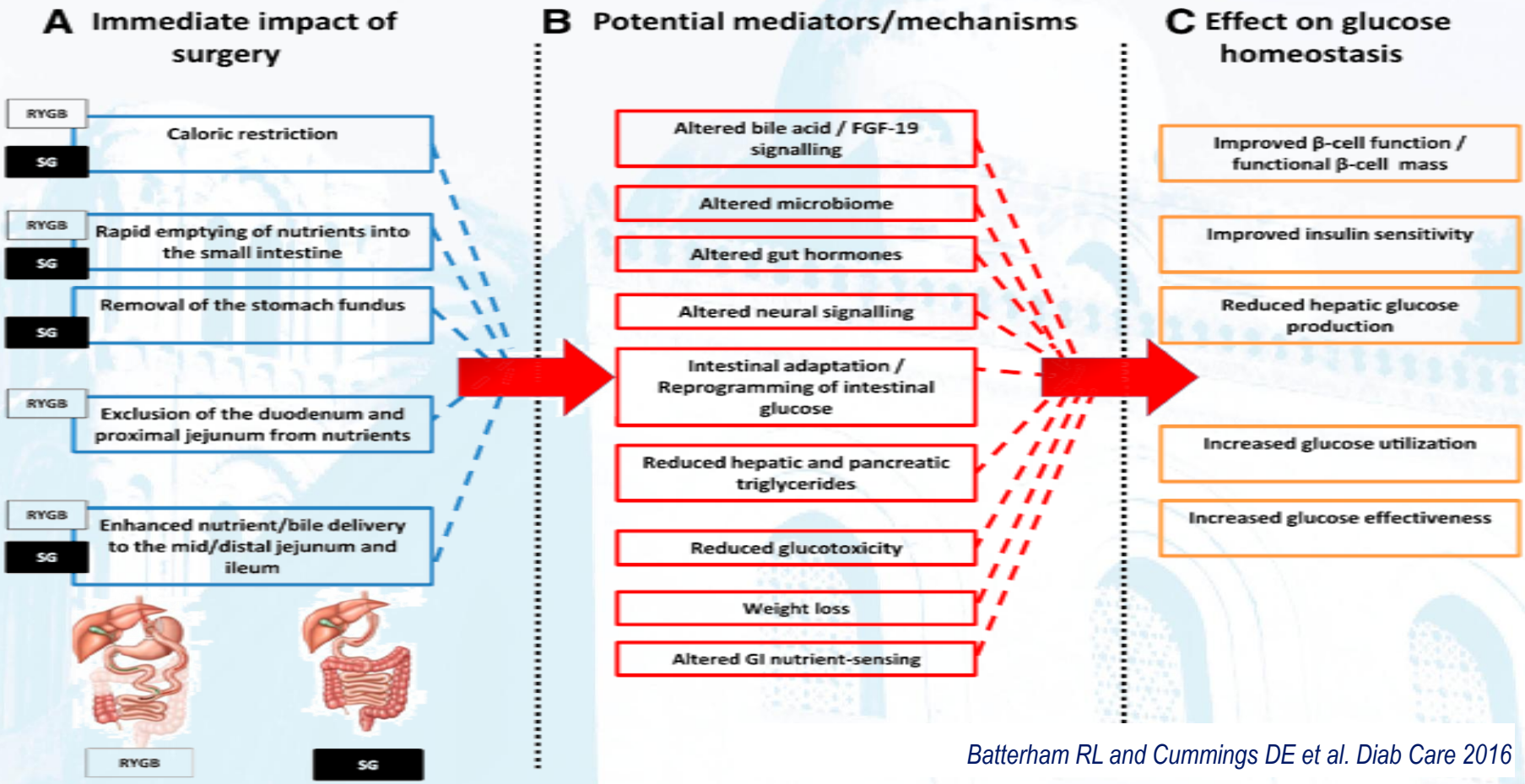
"a set of gastrointestinal operations used with the intent to treat diabetes ("diabetes surgery") and metabolic dysfunctions (which include obesity)"

F Rubino, Ann Surg 2014

What's in the term "metabolic"?

Mechanism of resolution of T2DM following RYGB

BMI < 35 kg/m² ← **Metabolic Surgery** ← **Mainly WL independent**

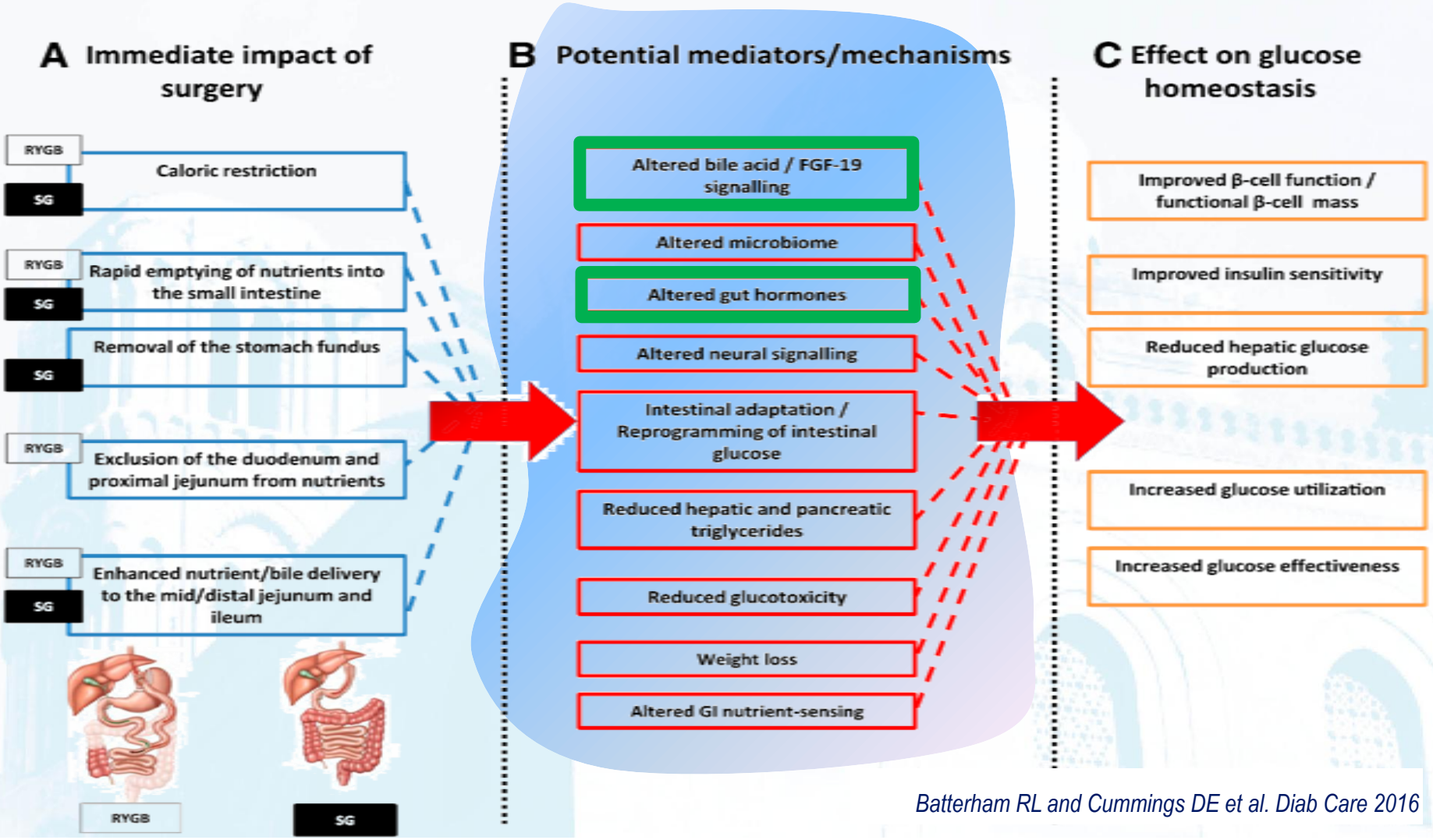


Batterham RL and Cummings DE et al. Diab Care 2016

What's in the term "metabolic"?

1. **The weight loss independent (metabolic) effects of surgery are "dominant".**
   - Is this supported by the evidence?
2. **Weight loss is just another metabolic outcome.**
   - Is WL simply a «good» side effect of surgery?
3. **The metabolic effect results in «universal» benefit**
   - Do all patients respond similarly?

1. WL independent effects as the dominant mechanism



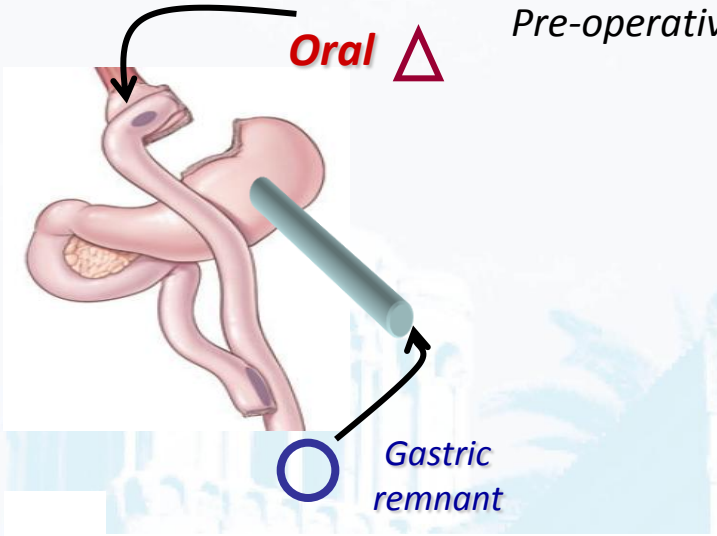
Batterham RL and Cummings DE et al. Diab Care 2016

The case of GLP-1: Glucose tolerance

Case report - Association Study

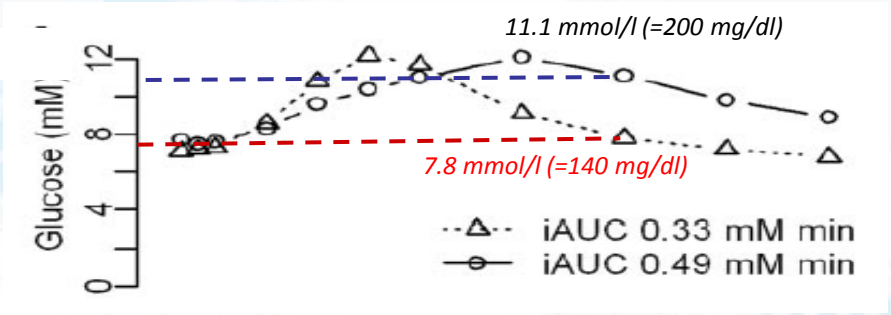
Admitted because of abdominal pain and fever following RYGBP

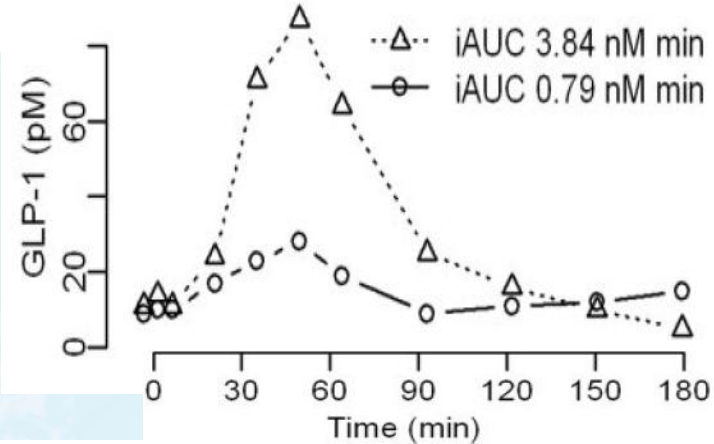
Pre-operatively: A1c 8%, Rx: Metformin + SU + insulin

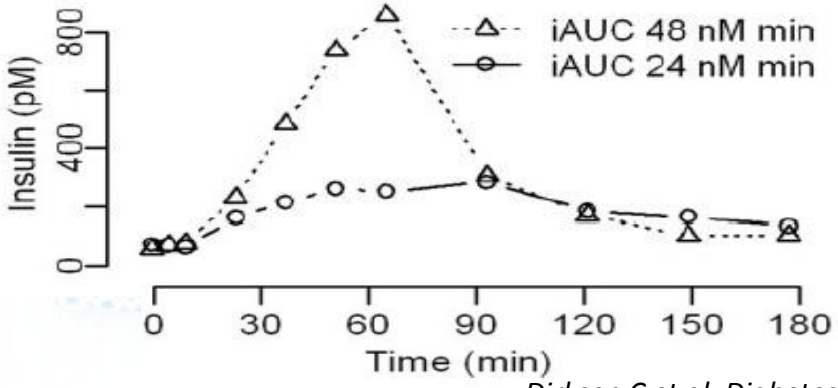


Evaluated at 5 weeks after surgery *(WL10kg= 10% of baseline BW)*

Standard Test Meal on 2 consecutive days







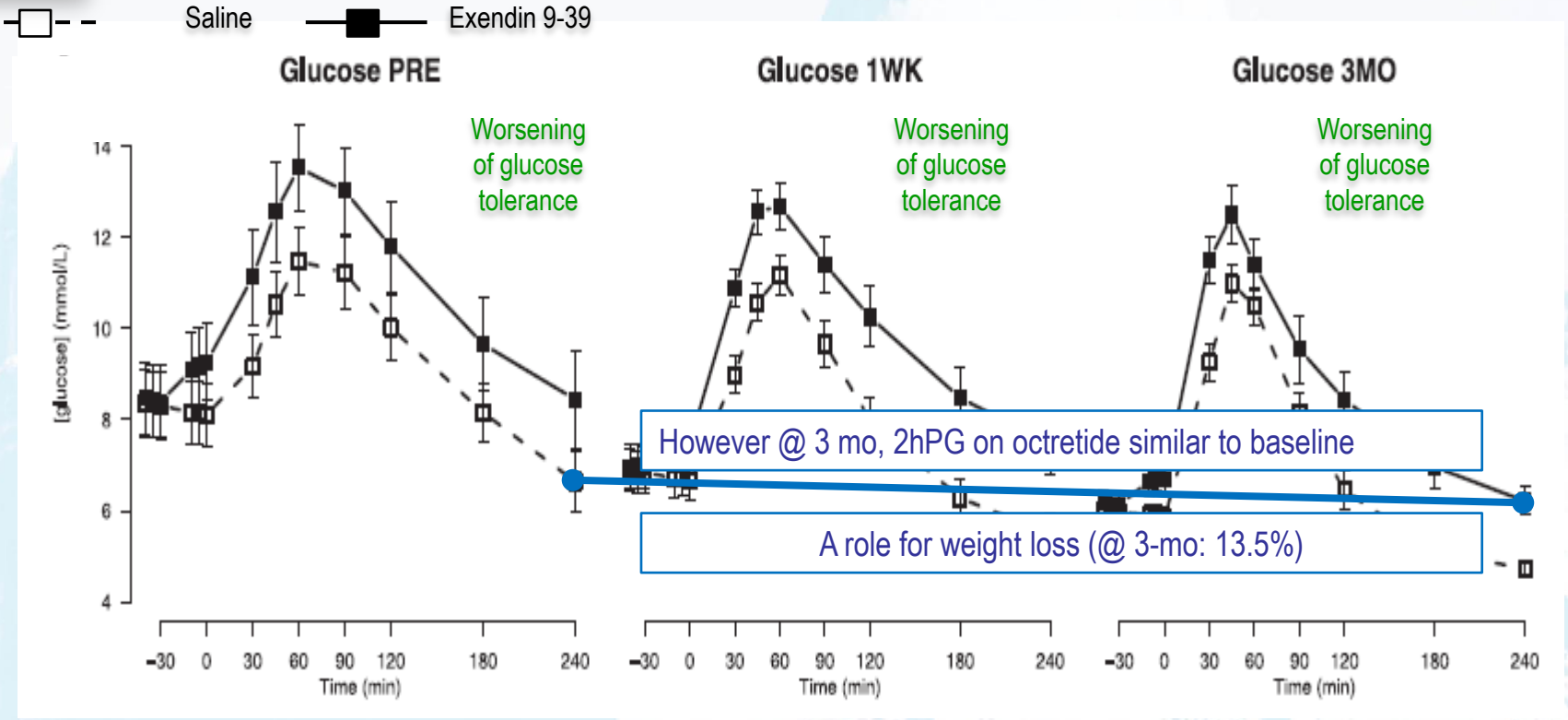
Dirksen C et al, Diabetes Care 2010

The case of GLP-1: Glucose tolerance

Causation in the case of GLP-1

Gastric bypass: T2DM prior to sugery short-term

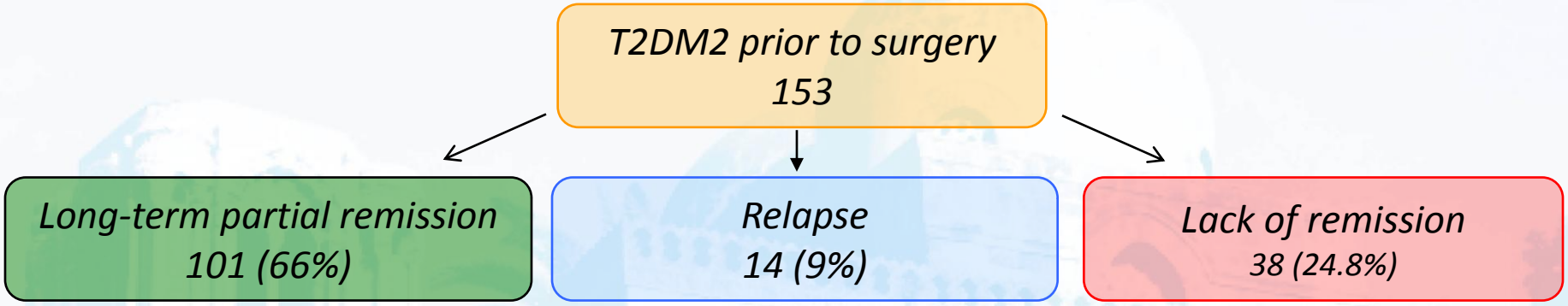
(n=9, 30% Female, DM duration prior to BS 5.7 y, 0% on insulin)



Jorgensen NB et al. Diabetes 2013

Is GLP-1 responsible for sustained remission?

Series of BS in subjects with T2D @ Hospital Clínic Barcelona

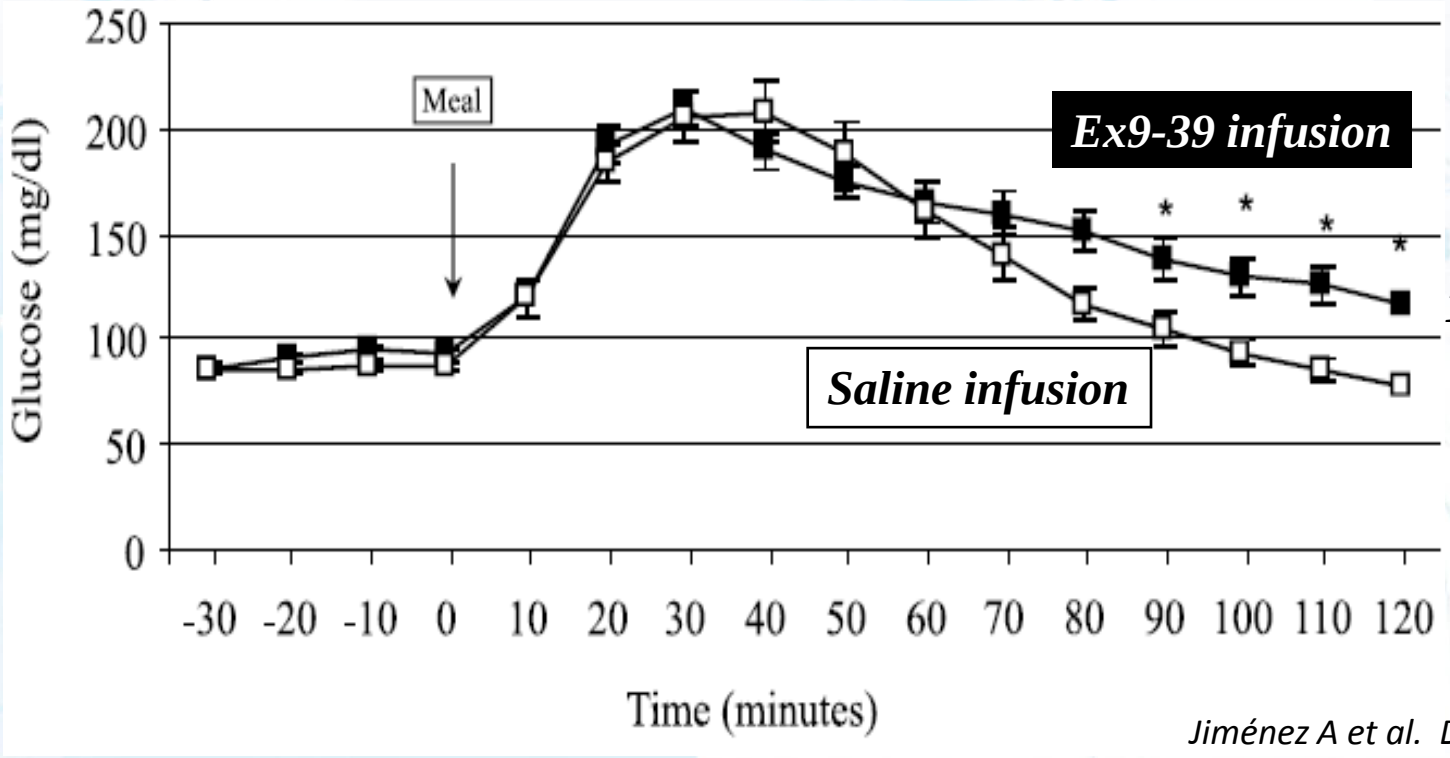


In those with remission of T2DM, does DM relapse upon blockade of endogenous GLP-1 action?

Is GLP-1 responsible for sustained remission?

Gastric bypass: T2DM prior to sugery with sustained post-surgical remission
(n=8, 100% Female, DM duration prior to BS 2.1 y, time after surgery 5.3 years, %WL relative to baseline: 34%;)

Effect of Exendin 9-39 Infusion on the Glucose Response to a Mixed Meal



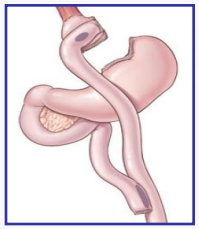
116.5±22.3mg/dl

78.4 ±15.1 mg/dl

Jiménez A et al. Diabetes Care 2013

Is GLP-1 responsible for sustained remission?

***RYGB** in subjects with T2DM prior to surgery but long-term resolution of T2DM*

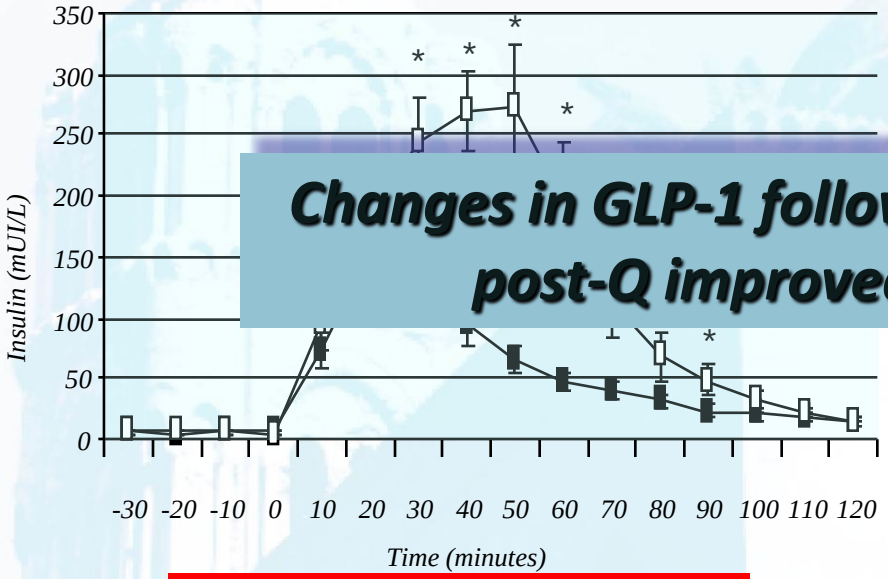


Effects of the blockade of GLP-1 receptor with Exendina 9-39

(n=8, women: 100%; time after surgery: 5.3 years)

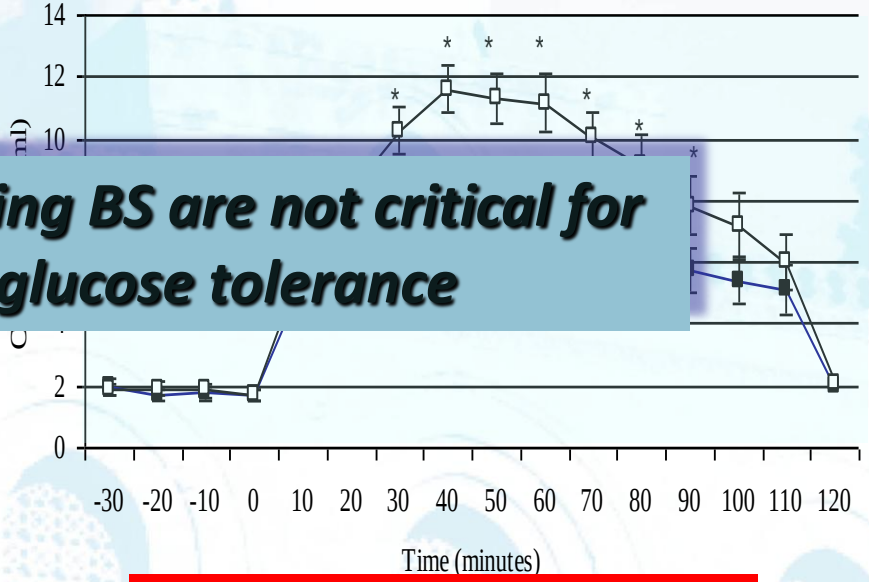
■ *Ex 9-39* □ *Saline*

Insulin response to a SLM



Delta AUC insulin response: -52.1%
P<0.001 relative to baseline

C-peptide response to a SLM



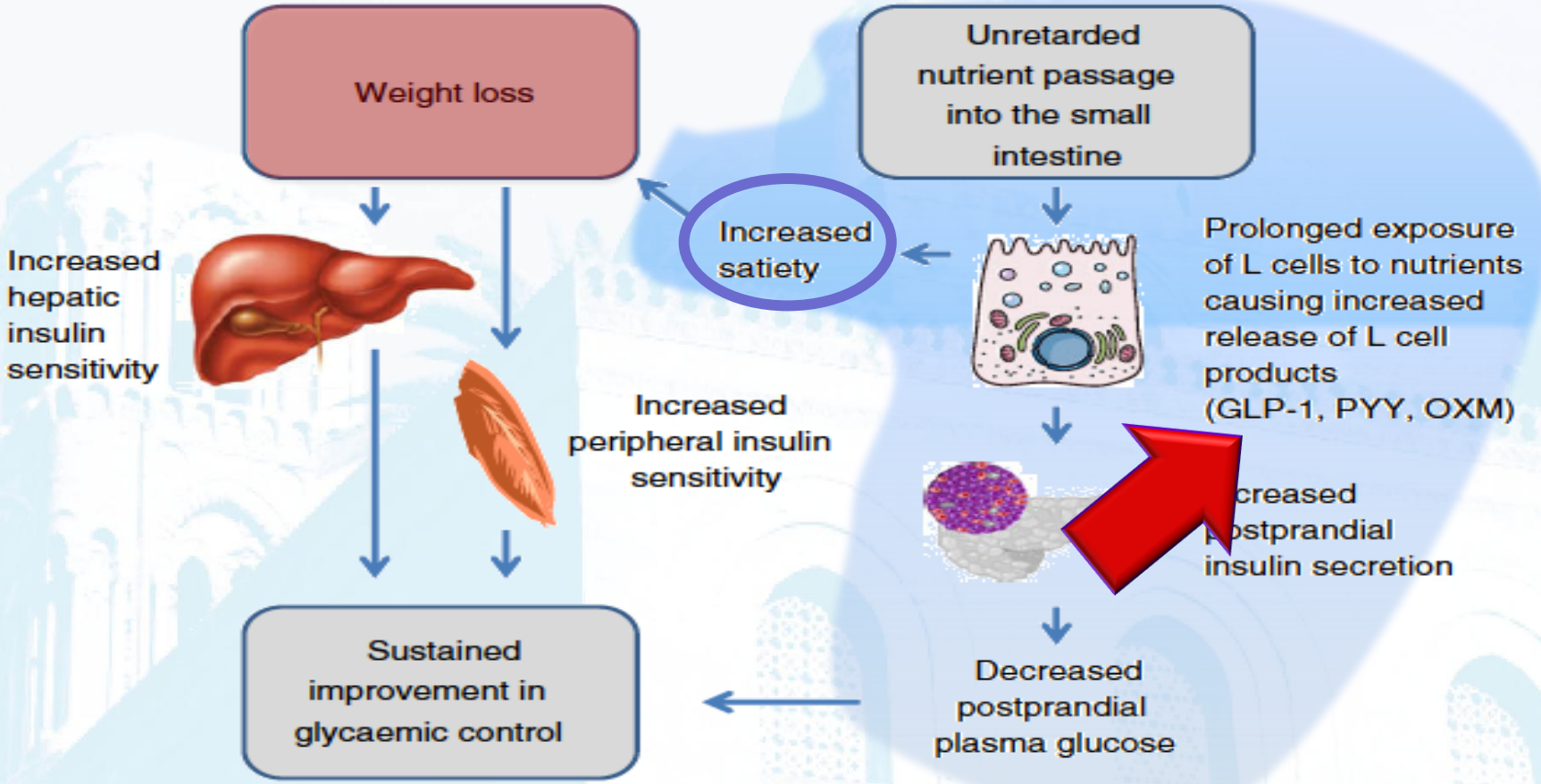
Delta AUC C-peptide response: -24.1%
P<0.001 relative to baseline

Changes in GLP-1 following BS are not critical for post-Q improved glucose tolerance

Jiménez A et al, Diabetes Care 2013

The case of GLP-1: food intake

Mechanism of sustained weight loss RYGB



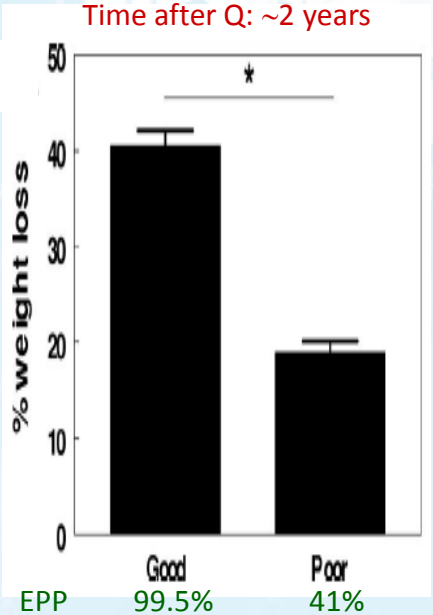
Dirksen et al, Diabetologia 2012

The case of GLP-1: food intake

A limited response of anorexigenic GI hormones has been proposed as mechanism for the poor WL after GBP

GLP-1 and PYY response to a mixed meal challenge
According to Weight Loss Outcome Following Roux-en-Y Gastric Bypass
(Good WL: n=13, Poor WL: n=7)

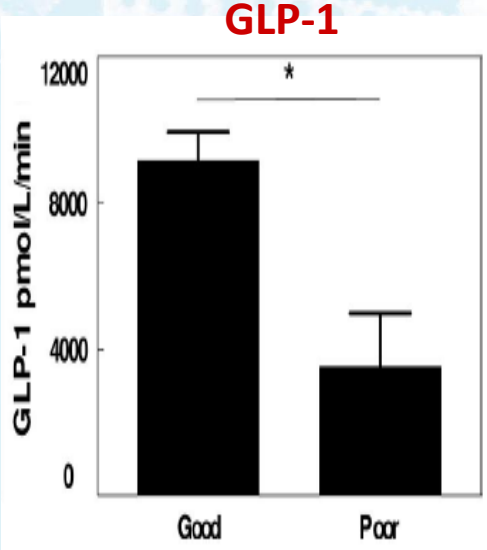
WL at evaluation
(% relative to baseline)
Time after Q: ~2 years



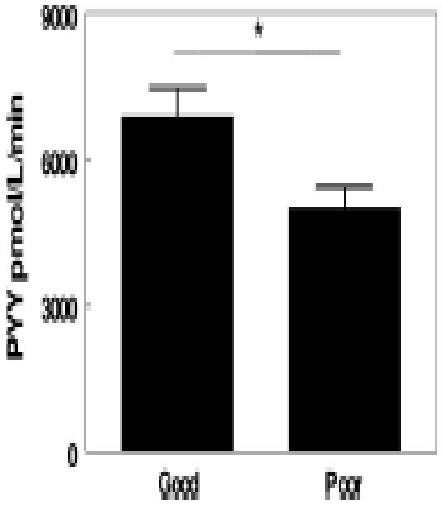
EPP 99.5% 41%

Hormonal response to MMT

GLP-1



PYY



Le Roux CW et al. Ann Surgery 2007

The case of GLP-1: food intake

Hypothesis

Shall a less anorexigenic hormonal response account for larger food intake in subjects with secondarily poor-weight loss after GBP , such differences shall vanish upon blockade of GI-hormonal secretion with octreotide

The case of GLP-1: food intake

Comparison of cumulative FI of a SMLM over 60 minutes with or without the blockade of GI hormonal secretion with sc injection of octretide (100 μg)

SC Injection of (random order)
Day 1: Octreotide (100 μg)
Day 2: Saline (same volume)

Patient offered 50 ml of a mixed liquid meal every 5'
(50% CCHH, 35% fat, 15% protein)

-60 0 30 60

Measurement of:

Gastrointestinal GI hormones (GLP-1, PYY, Ghrelin)

-60 0 30 60

Food intake

Satiety, Fullness, Hunger (VAS)

Main Outcome Variable

-60 0 5 10 15 20 25 30 35 40 45 50 55 60

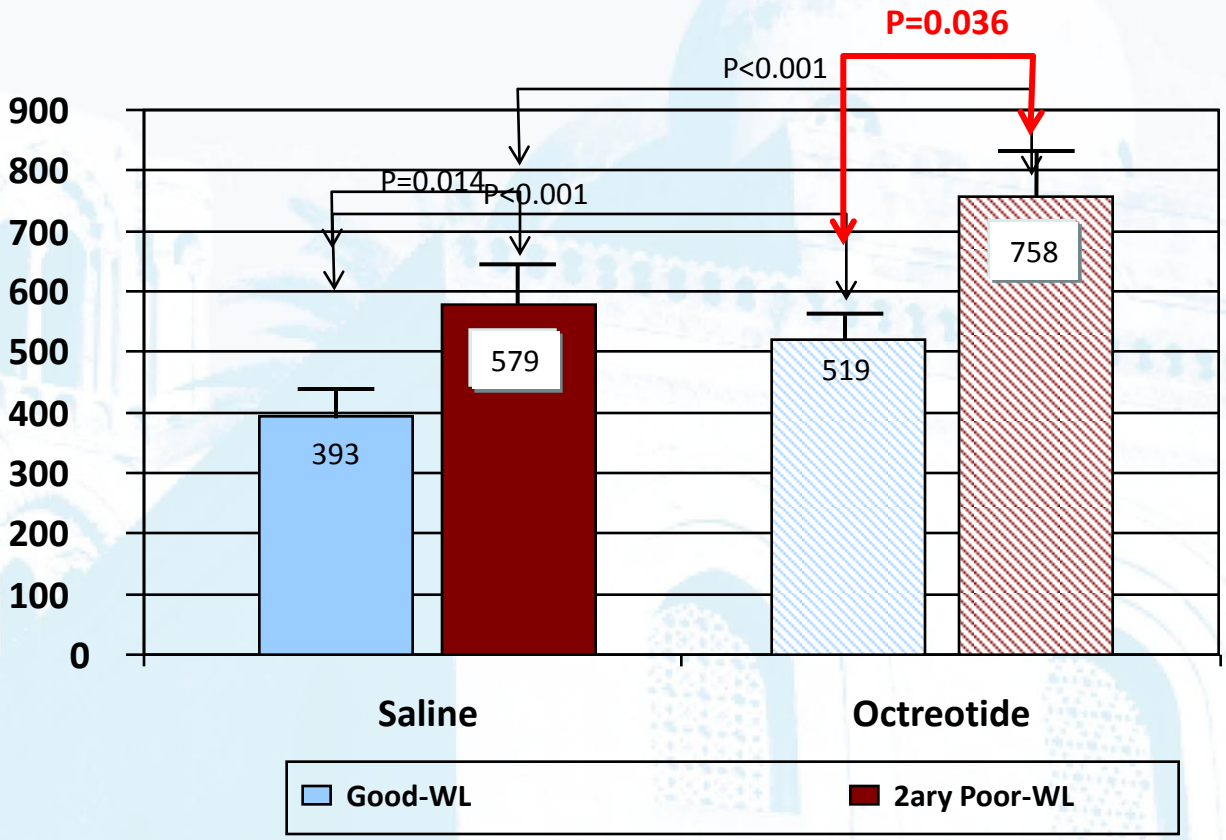
Patients maintained in recumbent position, with upper part of bed inclined at 45º

De Hollanda A et al. J Clin Endocrinol Metab 2015

The case of GLP-1: food intake

Causation: cumulative FI of a SMLM over 60' with or without blockade of GI hormonal secretion with octreotide @ ~72 mo after GBP

Cumulative food intake over the course of the test (kcal)

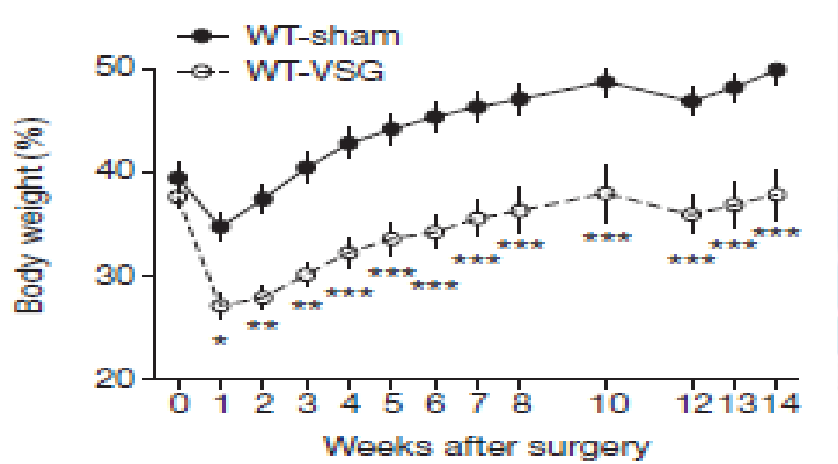


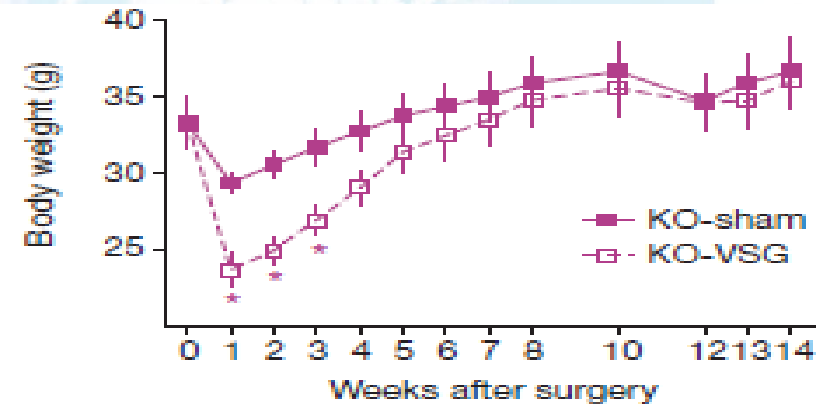
De Hollanda A et al. J Clin Endocrinol Metab 2015

The case of bile acids

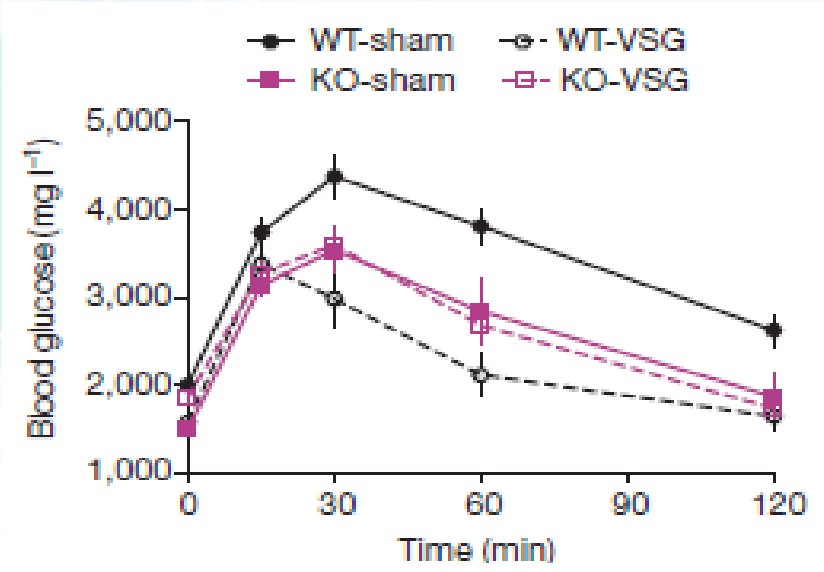
Lack of efficacy of SG in a mouse model lacking FXR

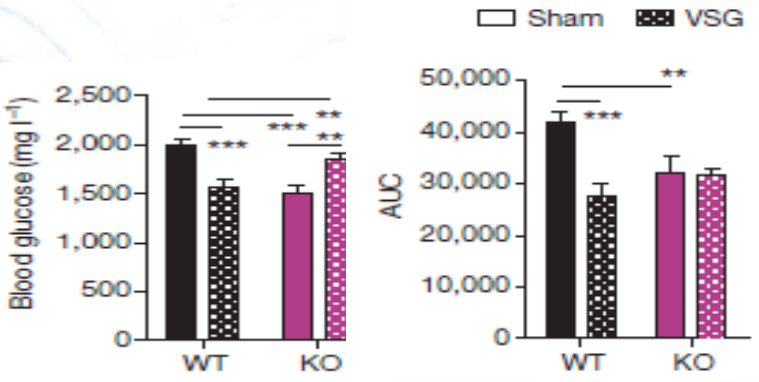
Weight loss





Glycemic control





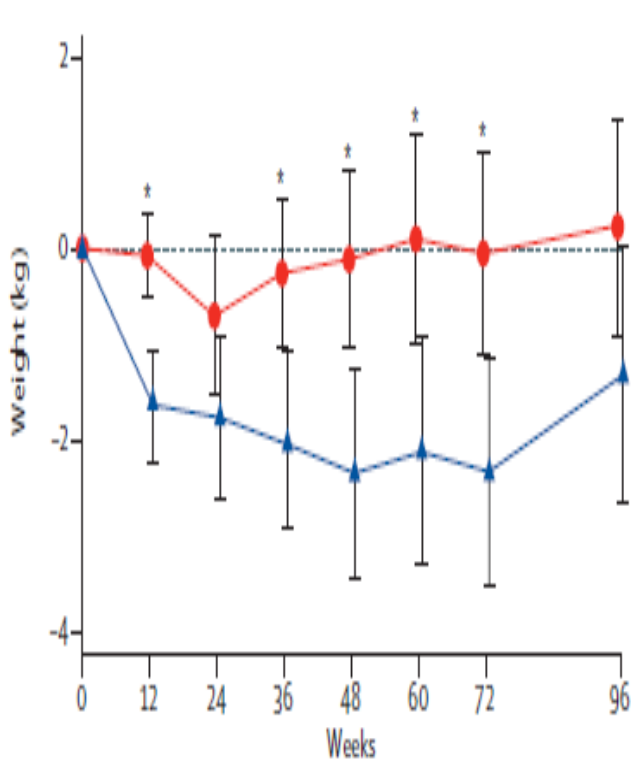
Ryan KK et al, Nature 2014

The case of bile acids

Efficacy of the FXR activator obethicolic acid in humans

(RCT: n= 283, age 52 y, BMI 35 kg/m2, 53% T2DM)

Weight loss



Glucose metabolism

	Change from baseline to 72 weeks (mean [SD])		Mean changes from baseline* (obeticholic acid vs placebo) (95% CI)	p value*
	Obeticholic acid (n=126)	Placebo (n=131)		
Metabolic factors				
Fasting serum glucose (mmol/L)	0·4 (2·1)	0·2 (2·3)	0·3 (-0·2 to 0·8)	0·26
Insulin (pmol/L)	29 (159)	10 (111)	38 (6 to 69)	0·02
HOMA-IR (glucose [mmol/L] x insulin [pmol/L] / 22·5)	15 (50)	4 (29)	13 (3 to 23)	0·01
Glycated haemoglobin A_{1c} (mmol/mol)	0·5 (9·7)	0·4 (8·3)	0·4 (-1·7 to 2·6)	0·71

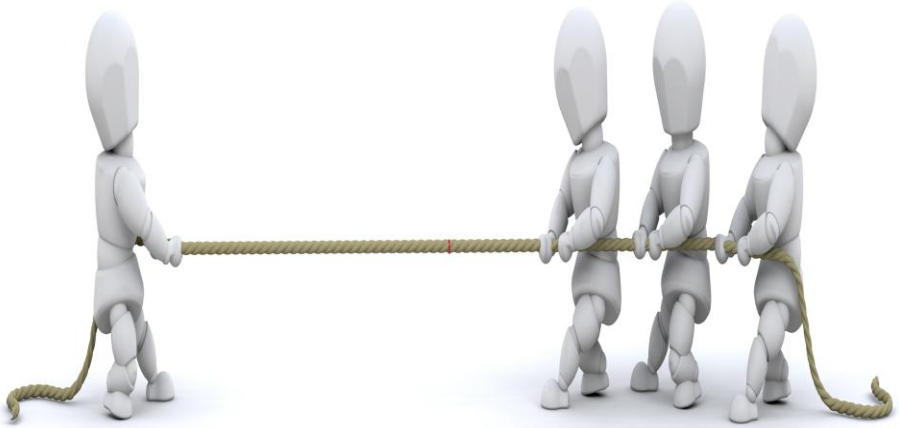
Neuschwander-Tetri BA et al. Lancet 2015

1. WL independent effects as the dominant mechanism

Evaluation of Weight Loss Independent Effects

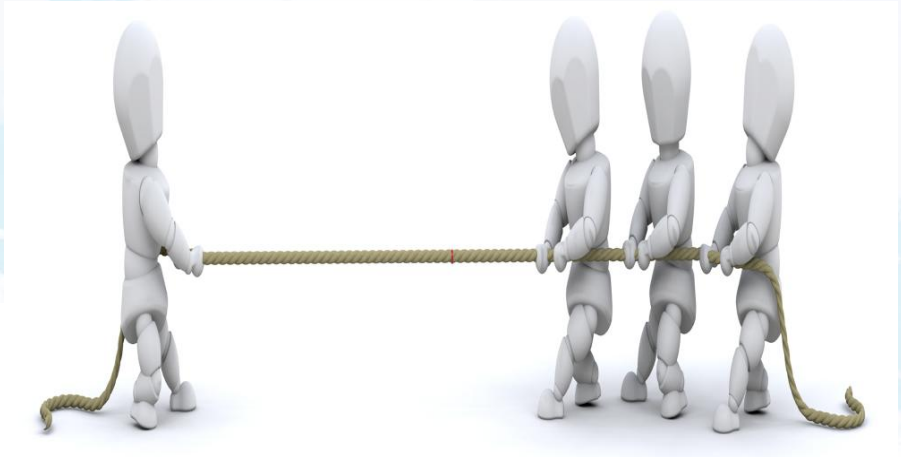
For most WL- independent factors evidence is based on association, and are mainly of research interest

Association



Causation

Research interest

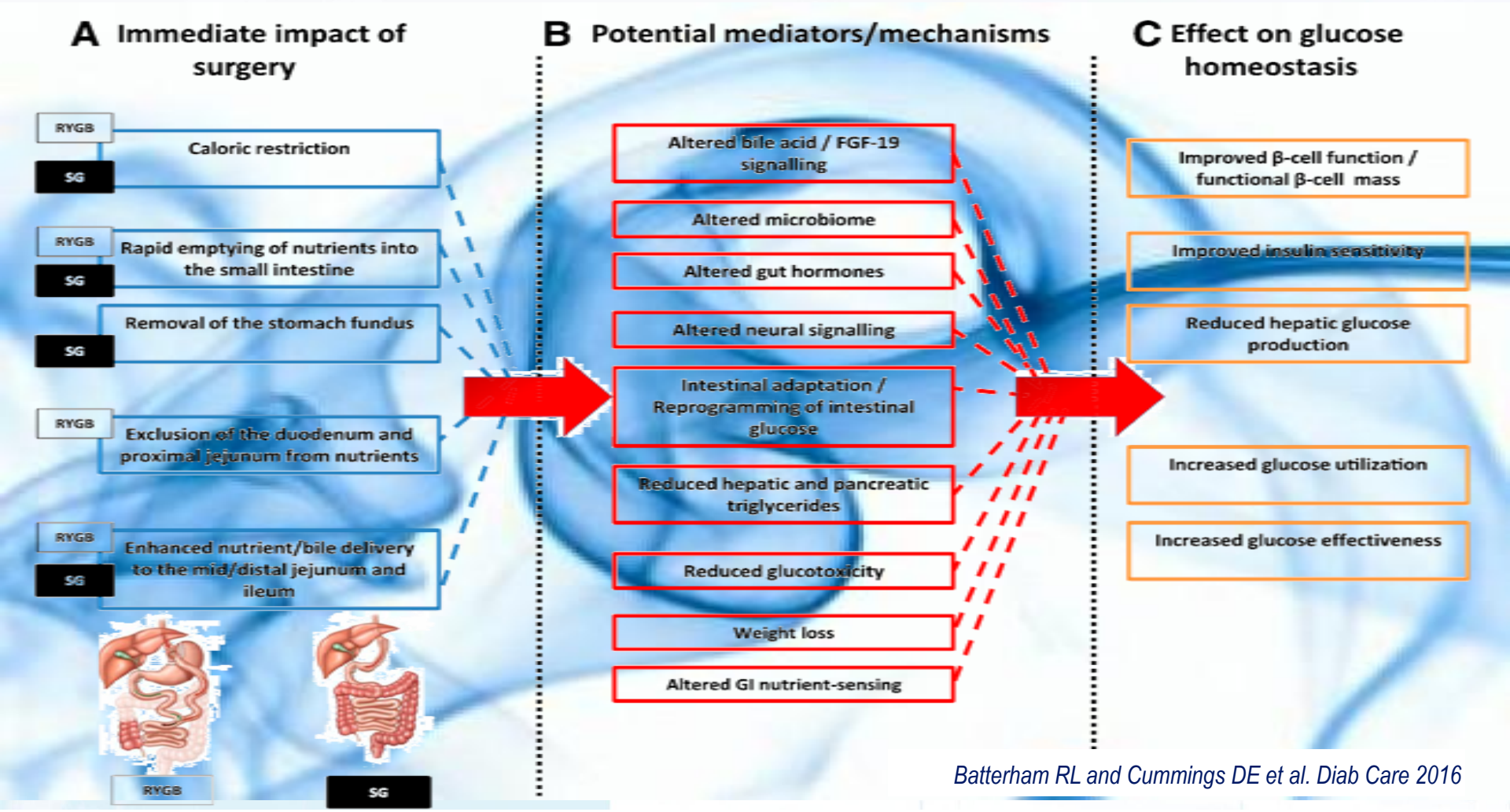


Clinically applicable

2. Weight loss is not important?

Back to the basics: Isn't this mainly WL surgery?

(be it mediated or not by non-mechanical mechanisms!)



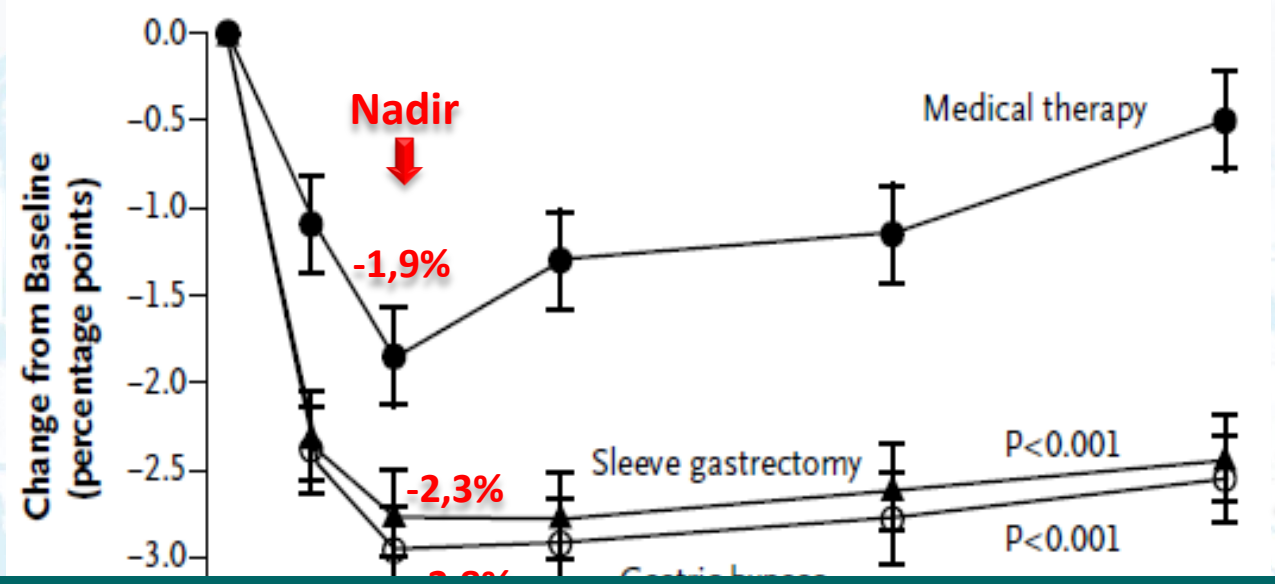
Batterham RL and Cummings DE et al. Diab Care 2016

The case of the STAMPEDE Trial

STAMPEDE Trial-Cleveland Clinic: 3 years FU

(n=137, Age 48 y, BMI 36,5 kg/m2, HbA1c preQ 9,3%, DM *duration* 8,3 *y*, Insulin Rx 43%)

Time course of HbA1c



- **In the whole population:**
  Change in BMI was the only predictor for 1^{ary} aim [OR 1.41 (95%CI 1.22-1.64)]
- **In the surgical groups:**
  Change in BMI and T2D duration <8 years

Schauer et al. N Eng J Med 2014

The case of the STAMPEDE Trial

STAMPEDE Trial-Cleveland Clinic: 5 years FU

Highlights presented at the American College Cardiologists – April 2016

1. **Attainment of A1C levels (6.0% or less) ± meds. @ 5 years:**

ILMI+ GBP	29%
ILMI+ SG	23%
ILMI	5%

2. **Those who had surgery—GBP>SG—sustained weight loss more than patients who controlled diabetes with medication**
3. **Weight loss was the primary reason their blood glucose remained in control.**

http://www.acc.org/latest-in-cardiology/articles/2016/03/23/18/25/mon-2pm-stampede-bariatric-surgery-vs-intensive-medical-therapy-for-long-term-glycemic-control-and-complications-of-diabetes-acc-2016

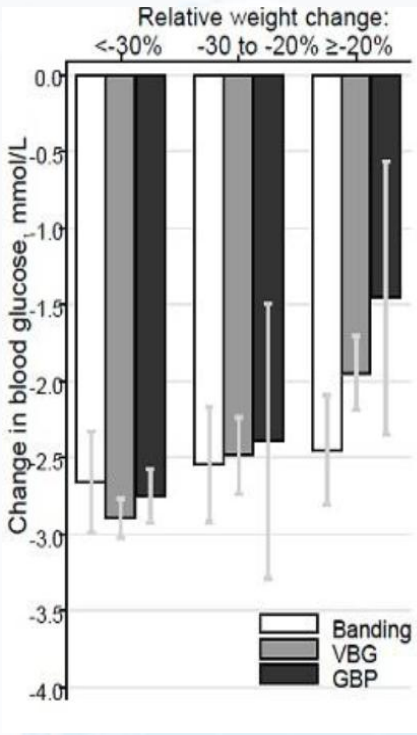
The case of the SOS Study

Swedish Obese Subjects

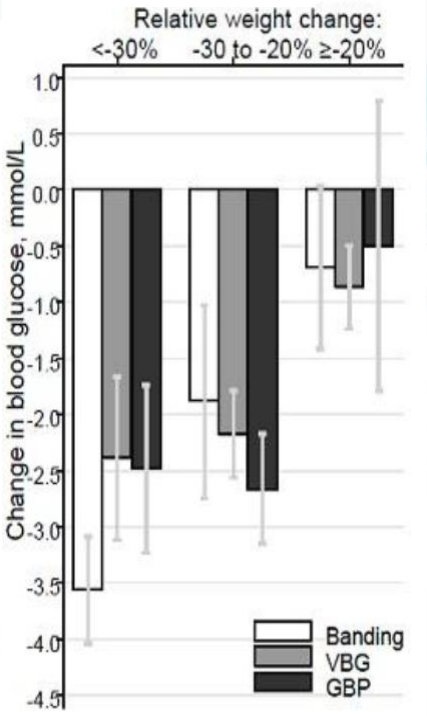
FPG and Insulin weight-adjusted changes at 2 and 10 years in IFG/T2D subjects

Fasting plasma glucose

2 years

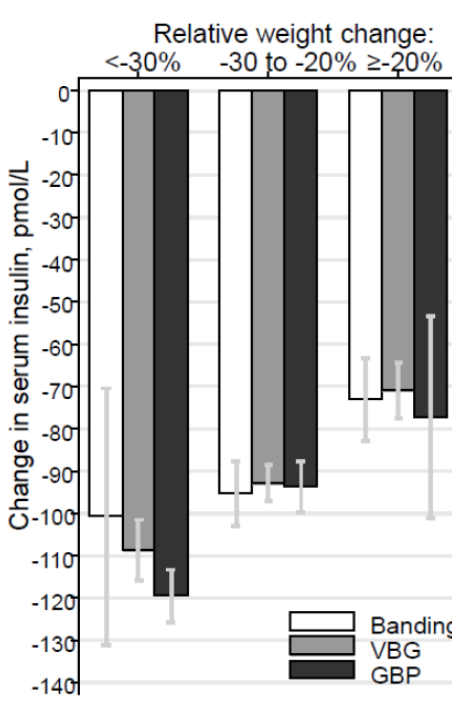


10 years

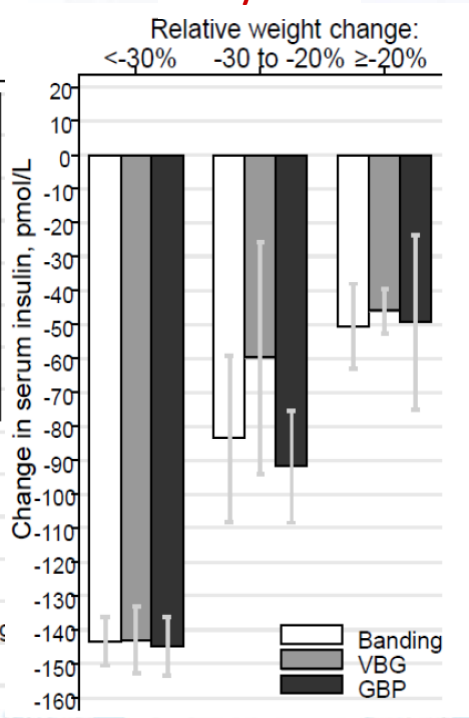


Fasting Insulin

2 years



10 years



Sjokholm et al. Diab Care 2016

The importance of weight regain

Long term remission and recurrence of T2DM following BS

	N	Follow up	Remission criteria	Type of surgery	Initial remission	Relapse	Long-term remission
Jiménez et al	153	≥ 2 years (2.9±1.1 y)	A1c<6.5%+ FPG<126 mg/dL + off medication	GBP/SG (64/36%)	75% (115/153)	12% (14/115)	*Weight regain*
Di Giorgi et al	42	≥ 3 years (5.0±1.9 y)	A1c<6.0%+ FPG<126 mg/dL+off medication	GBP	64% (27/42)	26% (7/27)	*Weight regain*
Adams et al	88	6 years	FPG +A1c in the normal range + off meds	GBP	75% (66/88 at 2y)	14% (12/87)	**62%**
Brethauer et al	217	>5 years (median 6y)	A1c<6.5%+ FPG<126 mg/dL + off medication	GBP/SG/GB	59% (127/217 at 2y)	19% (24/127)	*Weight regain*
Arterburn et al	4434	>5 years	A1c<6.5%+ FPG<126 mg/dL + off medication	GBP	84.3% (at 1 y)	40.2%	**50%**
Chikunguwo et al	177	≥ 5 years 8.6 (5-16 y)	Off medication	GBP	88.7% (157/177)	43% (68/157)	*Weight regain*
Sjostrom et al	342	10 years	FPG<126 mg/dL+off medication	GBP/GB/VBG	72% At 2 years	50%	**36%**

Jiménez , Ann Surg 2012; Vidal, unpublished; Di Giorgi , SOARD 2010; Adams, JAMA 2012; Chikunguwo, SOARD 2010; Sjostrom, N Eng J Med 2004.

If WL matters, what are the implications?

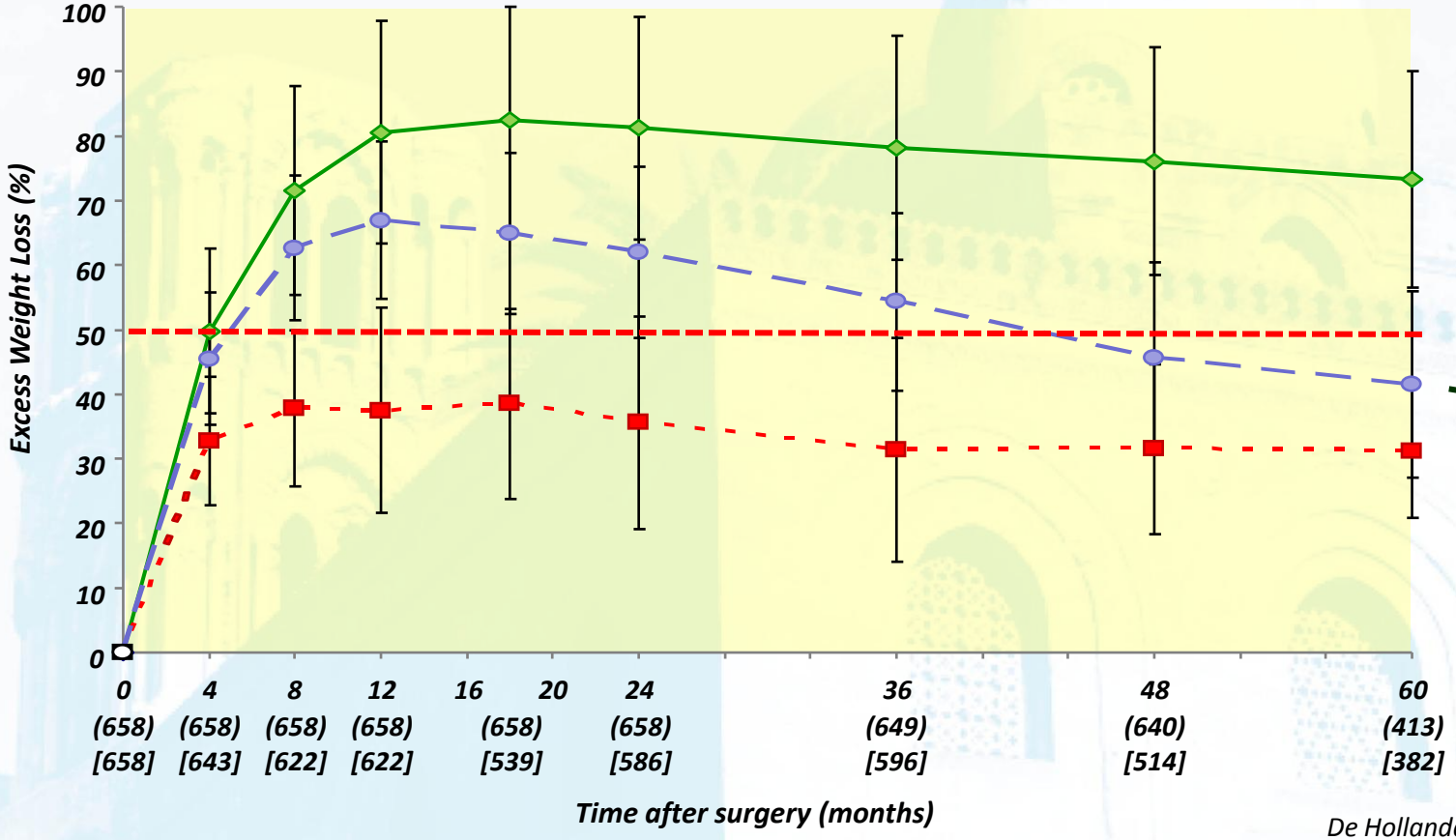
After Bariatric/metabolic surgery,
we should be paying more attention to weight loss!!

If WL matters, what are the implications?

Variability of the weight loss response following BS in morbidly obese subjects

Hospital Clinic, University of Barcelona

N=658 subjects with at least 24 mo follow up. GBP (70%) y SG (30%)



Good-WL 72.3%

2ary poor-WL (poor WL maintenance) 23.0%

1ary poor-WL 4.7%

De Hollanda A et al. Ob Surgery 2014

If WL matters, what are the implications?

The importance of post-Q factors

Curr Obes Rep (2015) 4:198–206
DOI 10.1007/s13679-015-0146-y

OBESITY PREVENTION (A MUST, SECTION EDITOR)

Prevention of Weight Regain Following Bariatric Surgery

Robert F. Kushner[1] · Kirsten Webb Sorensen[2]

We need to better understand the critical factors, and improve care for sustained WL after surgery:

- Nutritional non-adherence
- Sedentarism
- Mental health/psychological
- Anatomical/surgical failure

Specific programs
The WL that is required is achievable

3. Is the effect "universal"?

Patient characteristics in subjects seeking Metabolic vs Bariatric surgery in

	Metabolic cohort	Bariatric cohort
Age (y)	45.8±13.4	41.8±11.7
Gender (female), %	58	74
Diabetes, %	62	35
Patients with ≥3 comorbidities, %	57	27
Duration of DM, y	9.0±7.6	N/A
Baseline A1c, %	8.1±1.7	7.3±1.5
Insulin usage, %	47	28

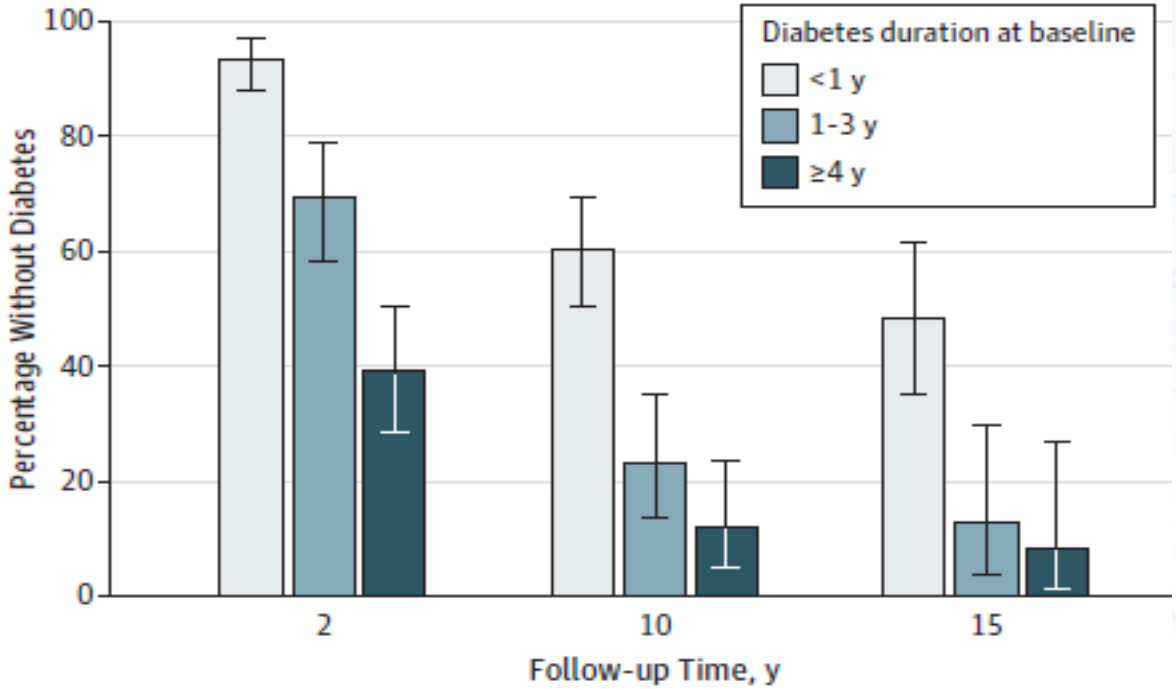
Adpated from Rubino F et al, Ann Surg 2014

3. Is the effect "universal"?

The importance of patient selection

SOS Study

Diabetes Duration and percentage without T2DM after BS



Total participants			
<1 y	139	113	60
1-3 y	82	65	31
≥4 y	82	58	24

Sjostrom L et al. JAMA 2014

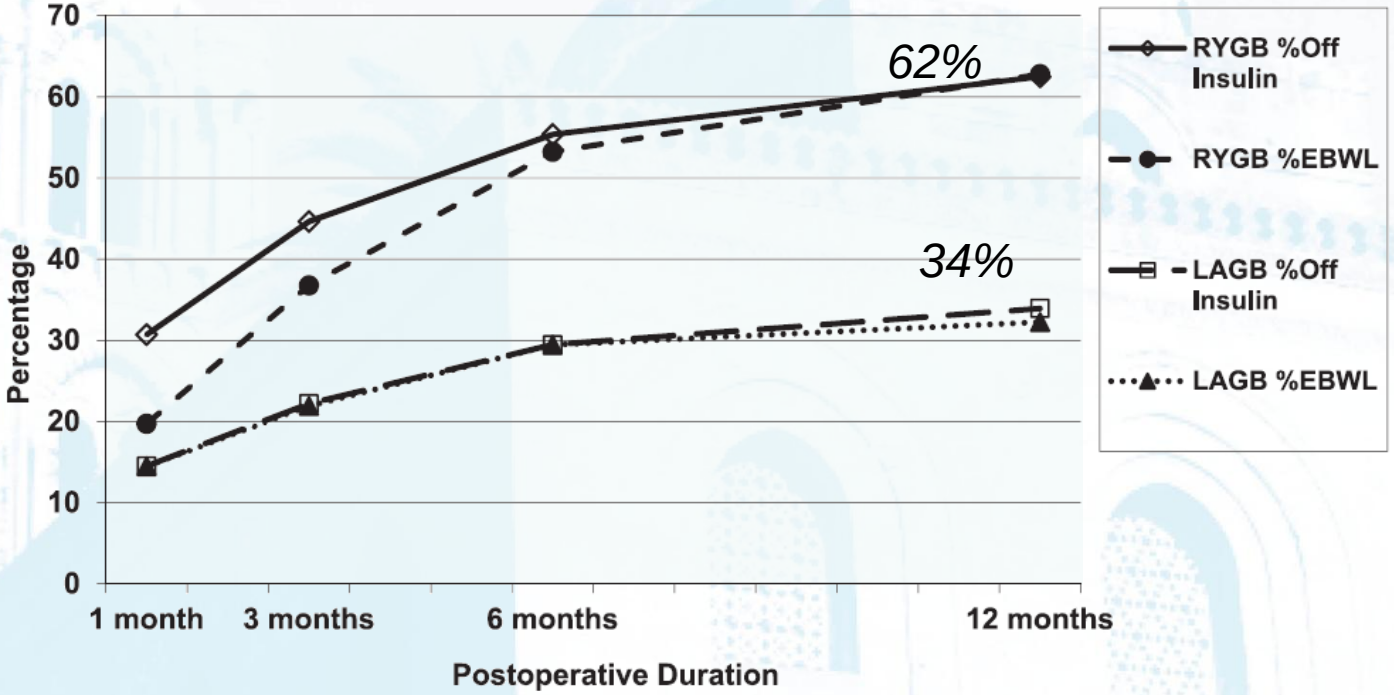
3. Is the effect "universal"?

The case of patients on insulin therapy

Bariatric Outcomes Longitudinal Database (BOLD)

N=5225 Insulin-treated T2D subjects (pre-op BMI 45 kg/m^2)

Percentage of subjects off insulin in the 1st year after surgery



Ardestani A et al. Diabetes Care 2015

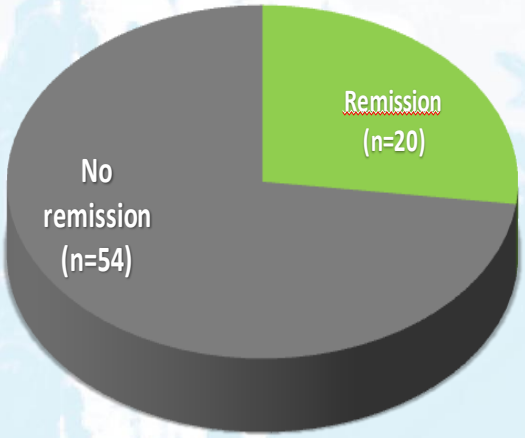
3. Is the effect "universal"?

The case of patients on insulin therapy

Hospital Clinic of Barcelona cohort

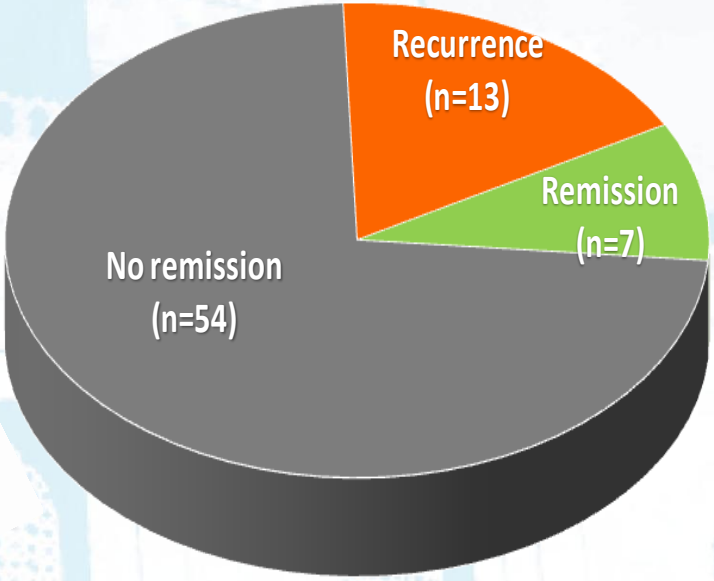
N=74 Insulin-treated T2D subjects (SG or GBP)

Remission rate (n=74)



12 m FU

Remission and relapse rates (n=74)



Mean FU 4.9±1.9 years

Vidal J et al. Submitted

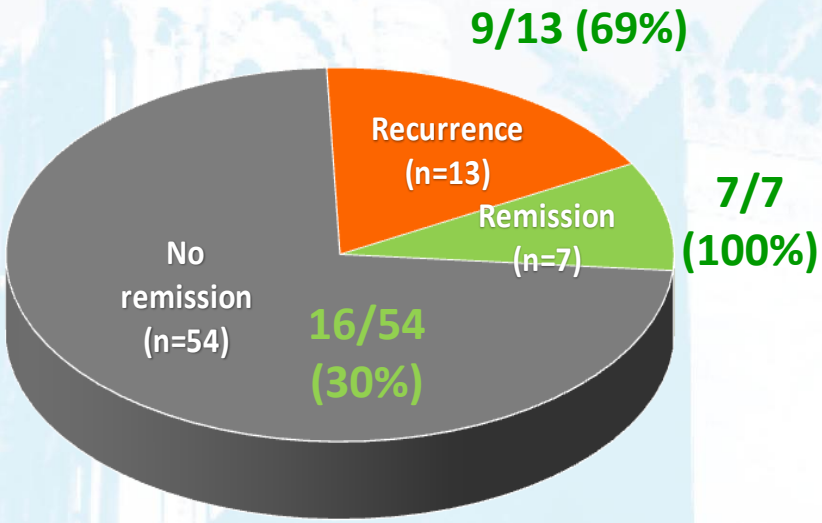
3. Is the effect "universal"?

The case of patients on insulin therapy

Hospital Clinic of Barcelona cohort

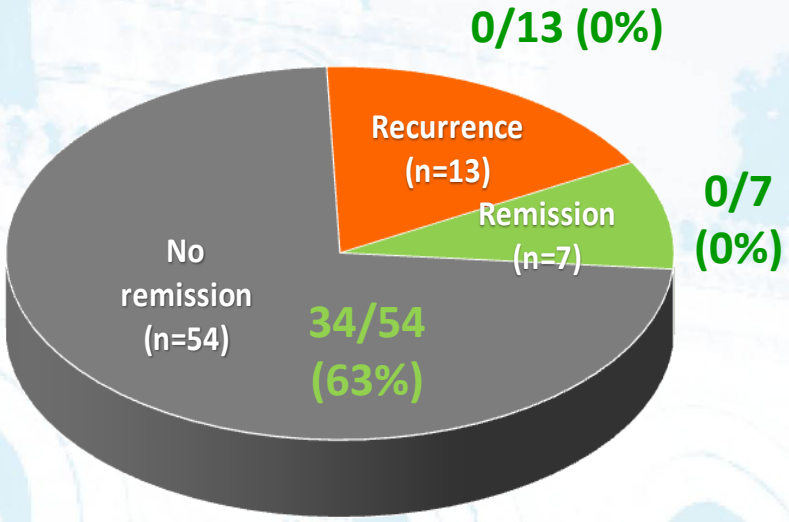
N=74 Insulin-treated T2D subjects (SG or GBP)

HbA1c <7% at last FU visit



Overall: 32/74 (43%)

Insulin therapy at last FU visit



Overall: 34/74 (46%)

Vidal J et al. Submitted

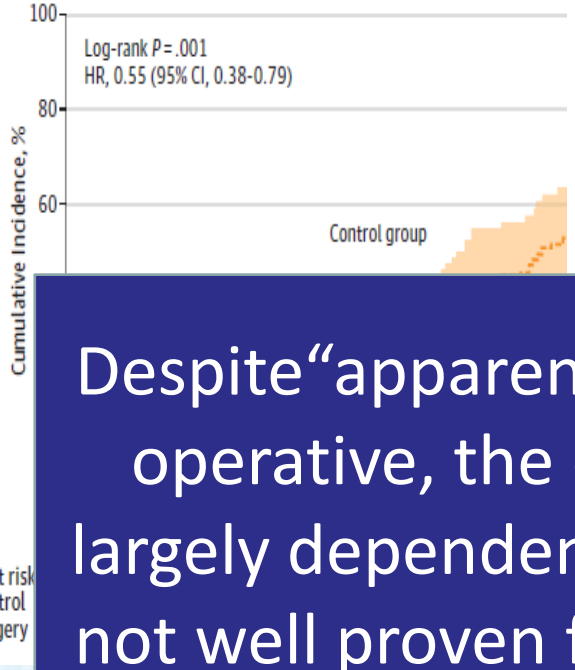
3. Is the effect "universal"?

SWEDISH OBESE SUBJECTS STUDY- T2DM COHORT

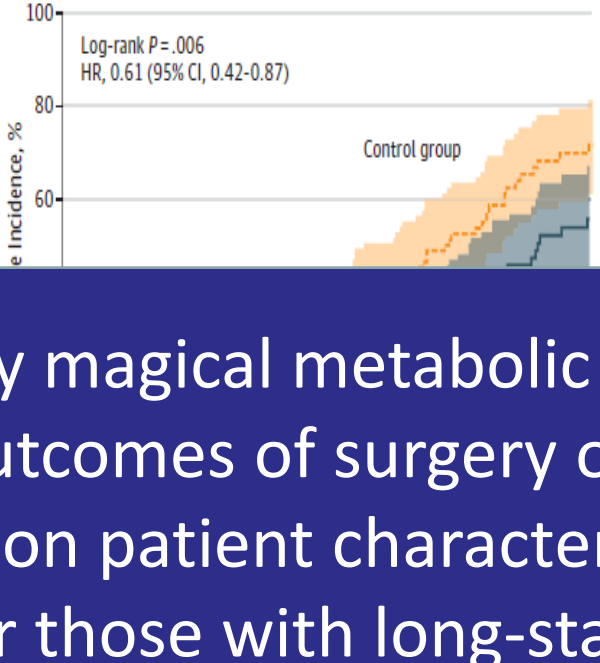
N=607 (Bariatric surgery, n=345 --- Control, n= 262)

COMPOSITE OF MICRO & MACROVASCULAR COMPLICATIONS ACCORDING TO DURATION OF T2DM

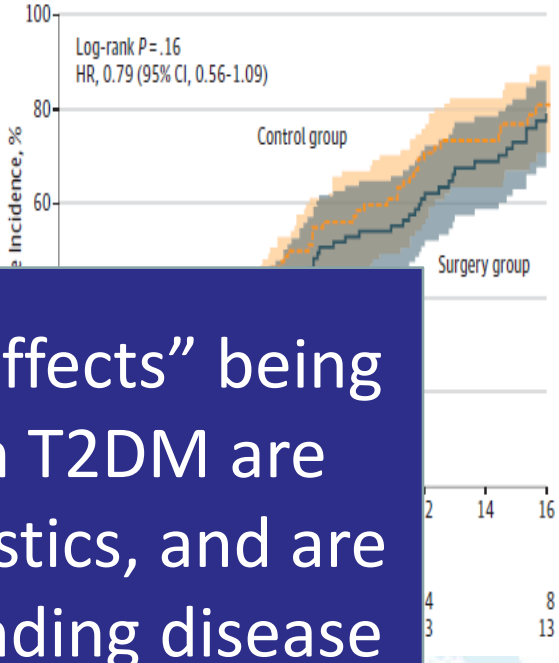
DM duration <1y



DM duration 1-3y



DM duration >4y



Despite"apparently magical metabolic effects" being operative, the outcomes of surgery on T2DM are largely dependent on patient characteristics, and are not well proven for those with long-standing disease

Sjostrom L et al, JAMA 2014

Summary

1. No matter how we call it, "bariatric/metabolic surgery", should be part of the therapeutic algorithm of T2DM.
2. The term metabolic surgery comes with a sense of "magical-" or "universal-" beneficial effect that is not supported by research nor by clinical findings.
3. Weight loss (WL) is a major determinant of the outcomes of "metabolic surgery". Thus,
   - WL should be considered a major outcome rather than a side-effect.
   - Research and clinical efforts should be placed on better understanding of the mechanisms that result on sustained WL after "metabolic surgery".
   - For now, lets call "bariatric" this powerful for patients with T2D.

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Thank you for your attention