Modern treatment of obesity pharmacotherapy & metabolic surgery: friend or foe?

RICARDO COHEN

Director, The Center for the treatment of Obesity and Diabetes Oswaldo Cruz German Hospital,

São Paulo Brazil

IFSO Global President-Elect

Past President SBCBM (2011-2012)

Past President IFSO LAC (2018-2019)

Disclosures

Research Grant, J&J Medical, Brasil

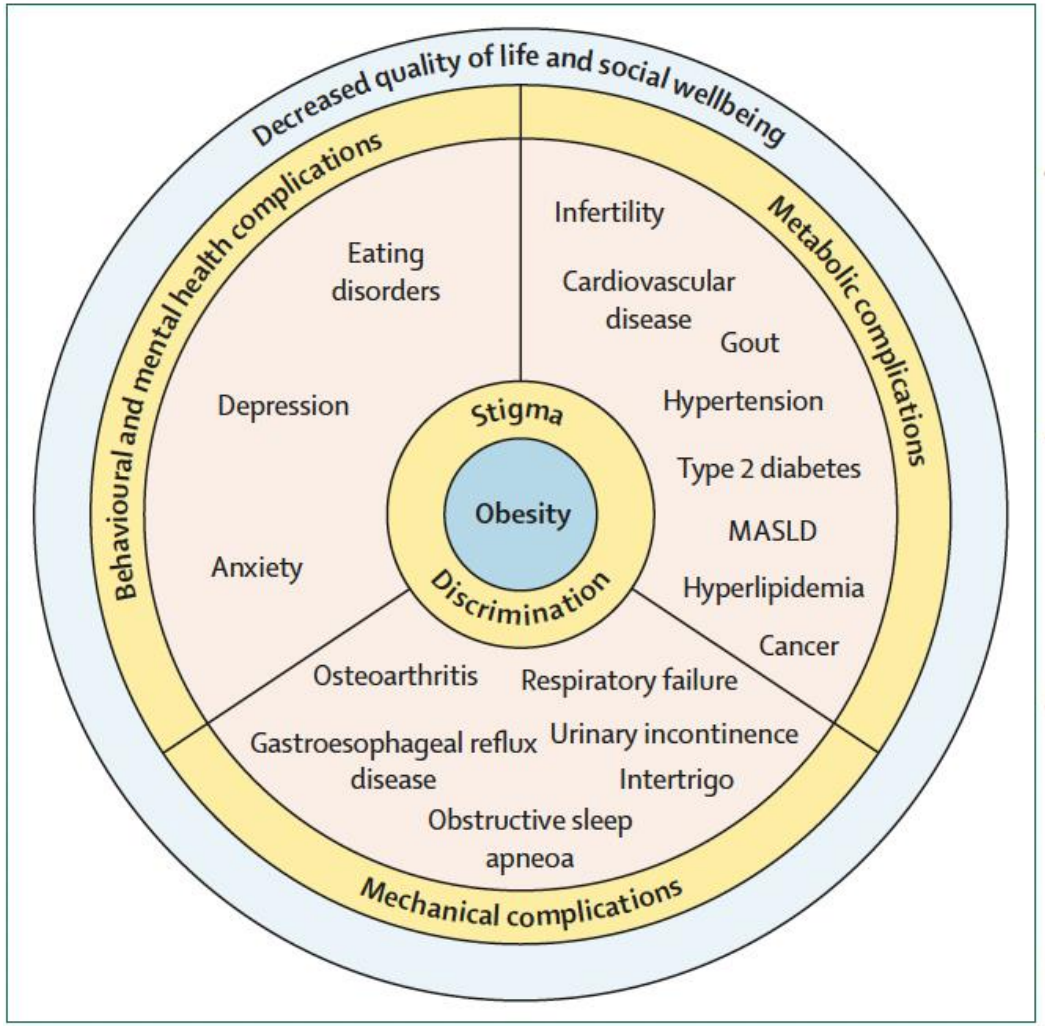
Research Grant, Medtronic

Research Grant, GI Dynamics

Research Grant, Hospital Oswaldo Cruz Bioscience Institute

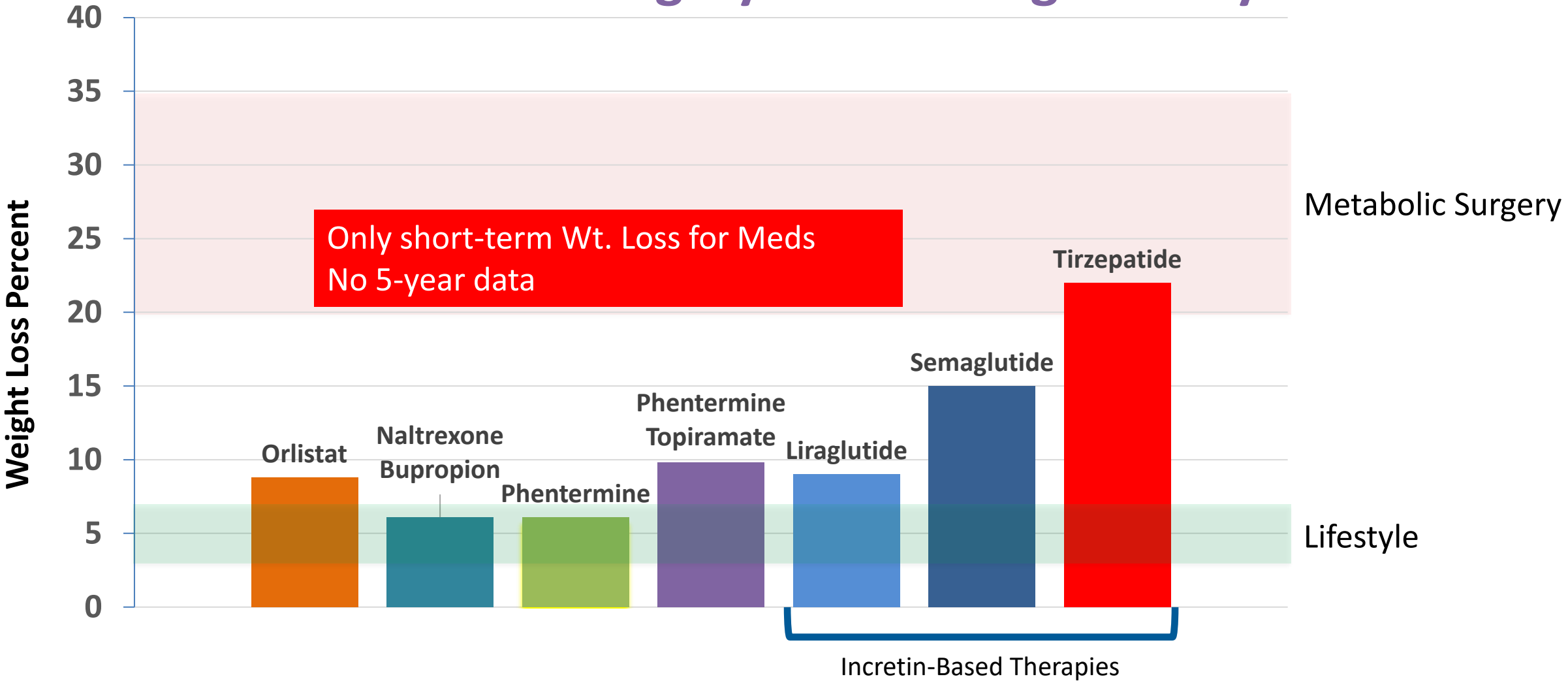
SAB: Morphic medical, JJ Medical, Medtronic

Speaker: J&J Medical, Medtronic, NovoNordisk

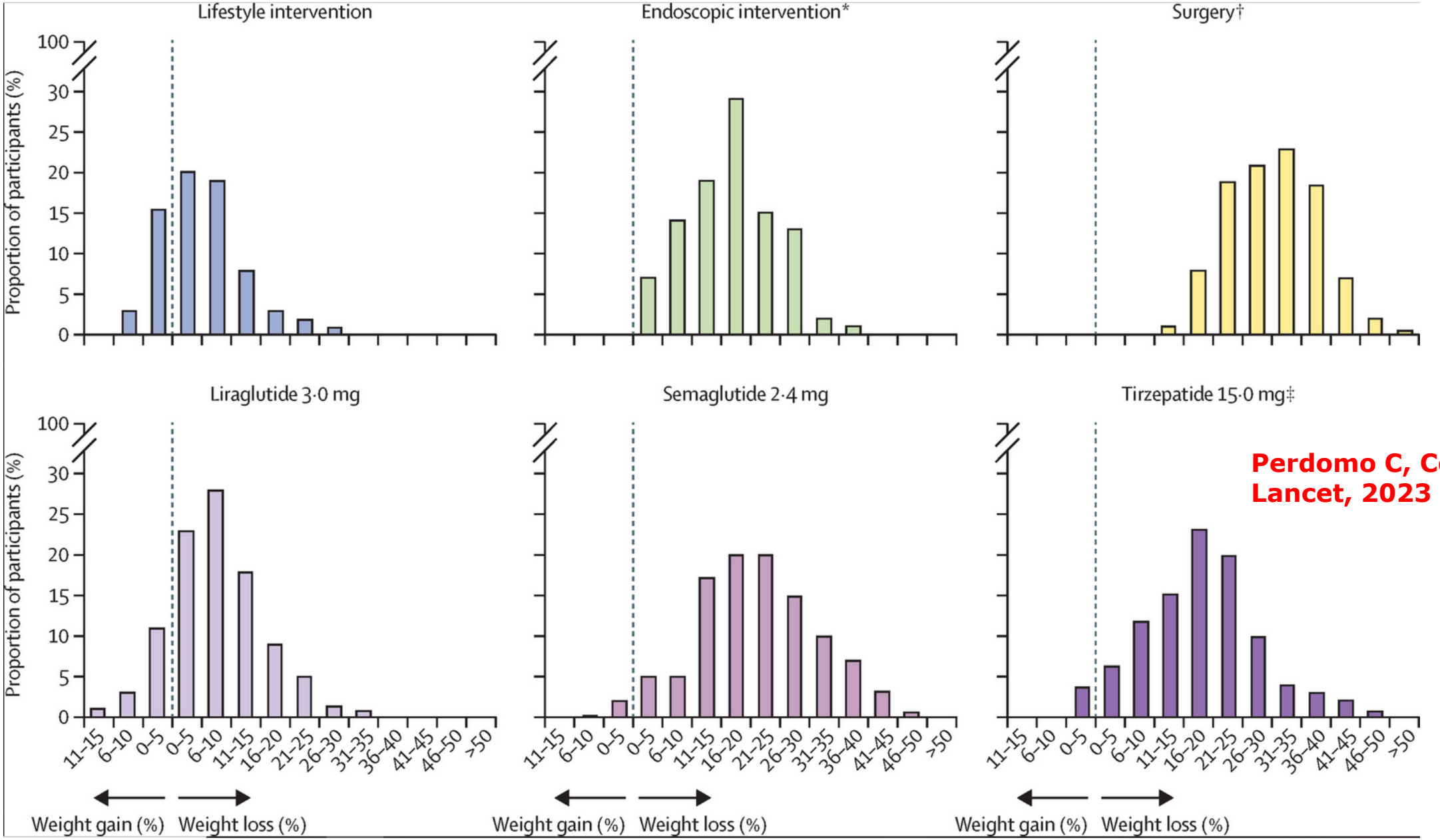


Lingvay I, Cohen RV et al, Lancet 2024

Effectiveness of Anti-obesity Medications vs. Lifestyle and Bariatric Surgery for Treating Obesity

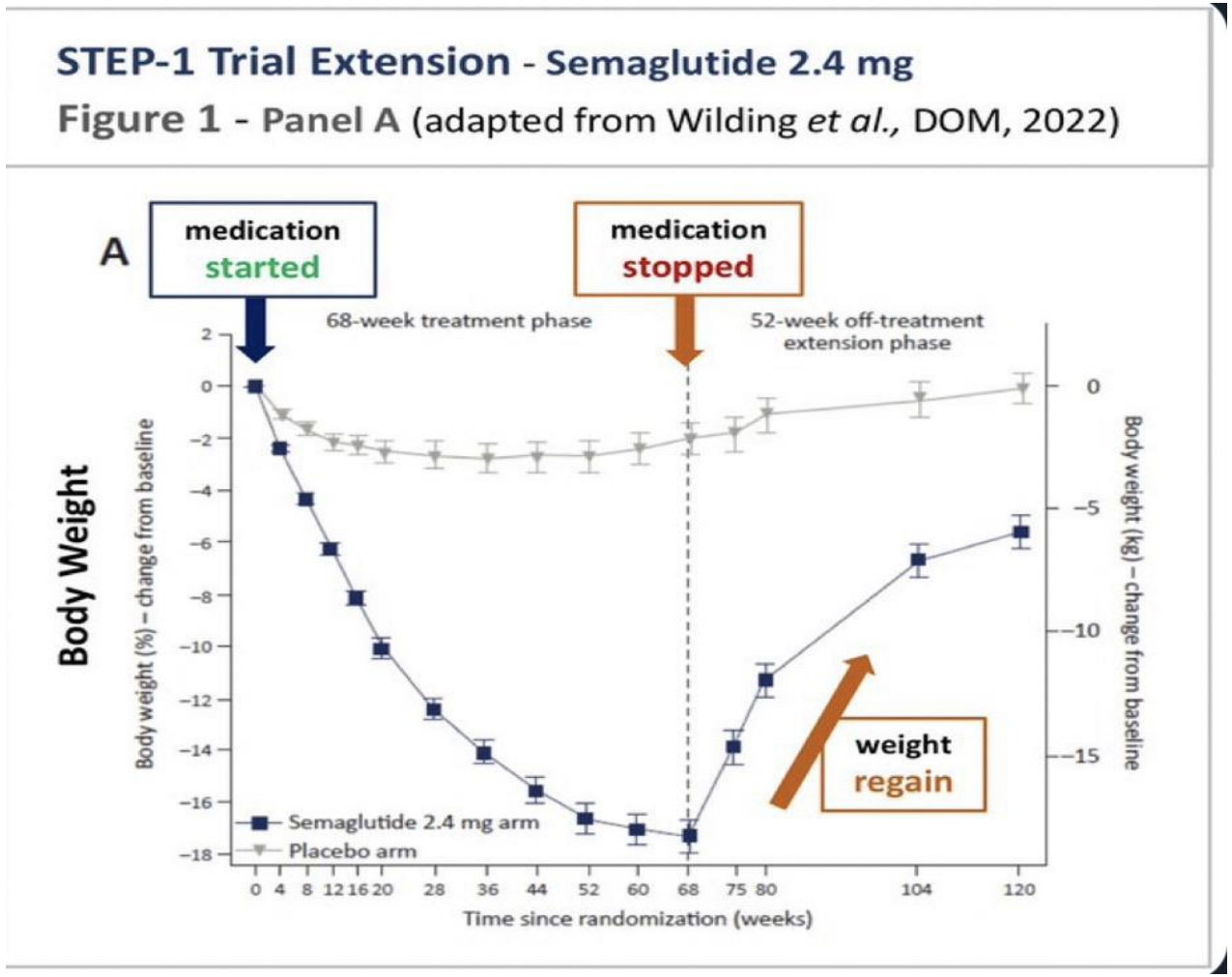


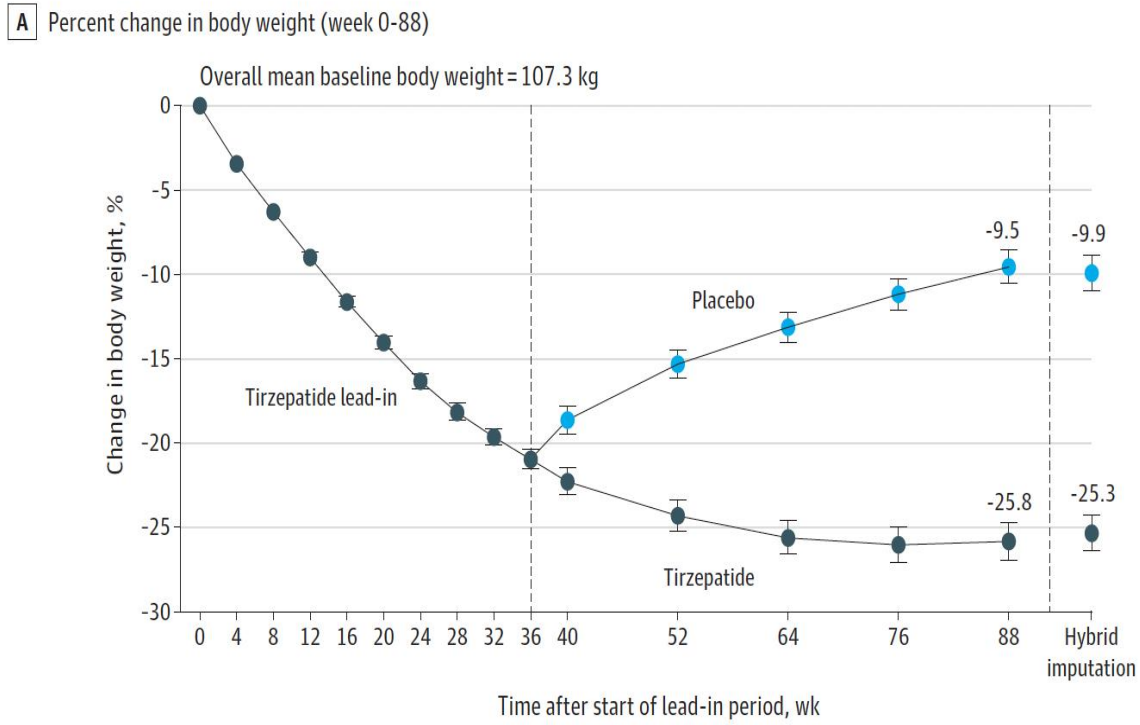
Heterogeneous response to obesity treatments



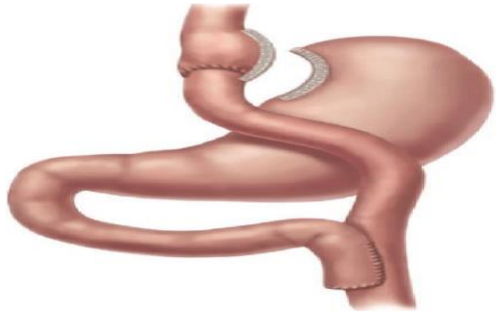
Perdomo C, Cohen RV et al, Lancet, 2023

Chronic illness,requires long-term treatment





Surmount 4-Aronne LJ et al NEJM, Dec 11, 2023



Metabolic Surgery

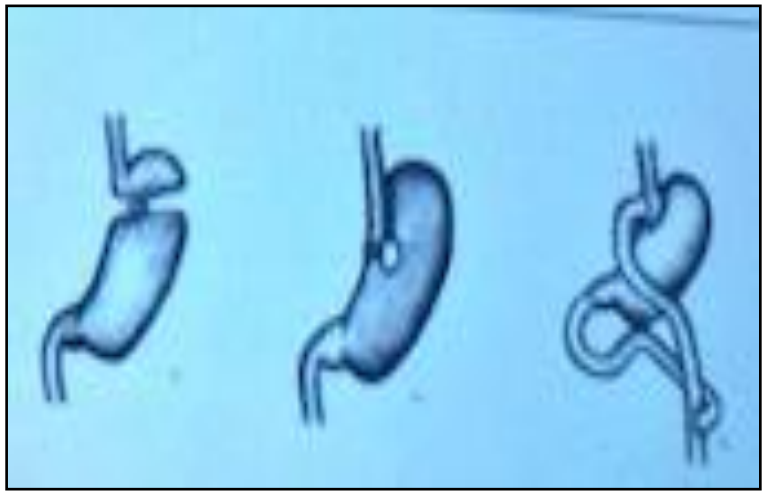
Prospective matched controlled

✓**Swedish Obese Subjects (SOS)**

✓Non RCT with over 20 years of follow-up

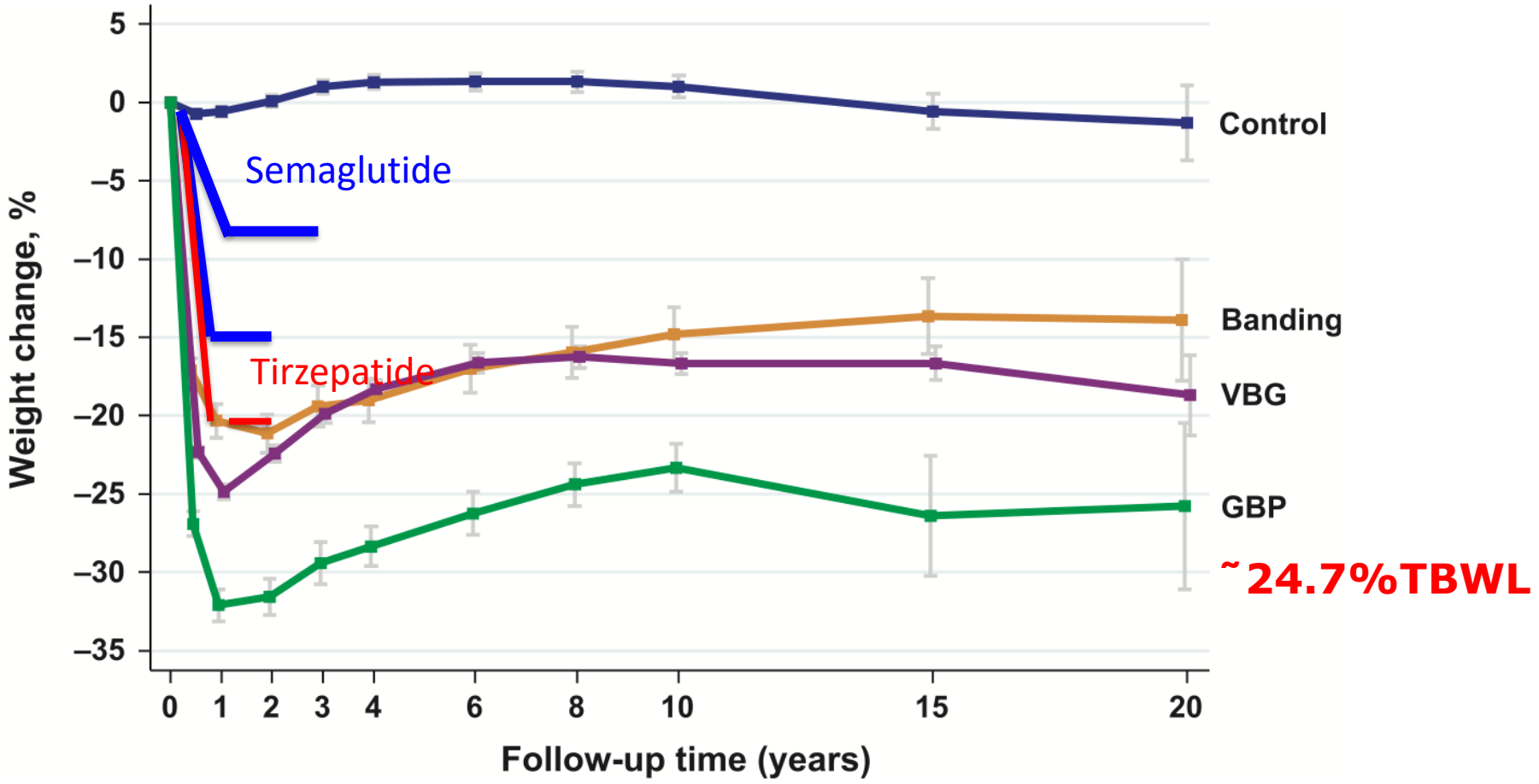
2039 PTS

X



2010 PTS, 11% with BMI < 35 kg/m²

Weight Loss After Bariatric Surgery Is Sustained for at Least 20 years-Superior to all other Treatments

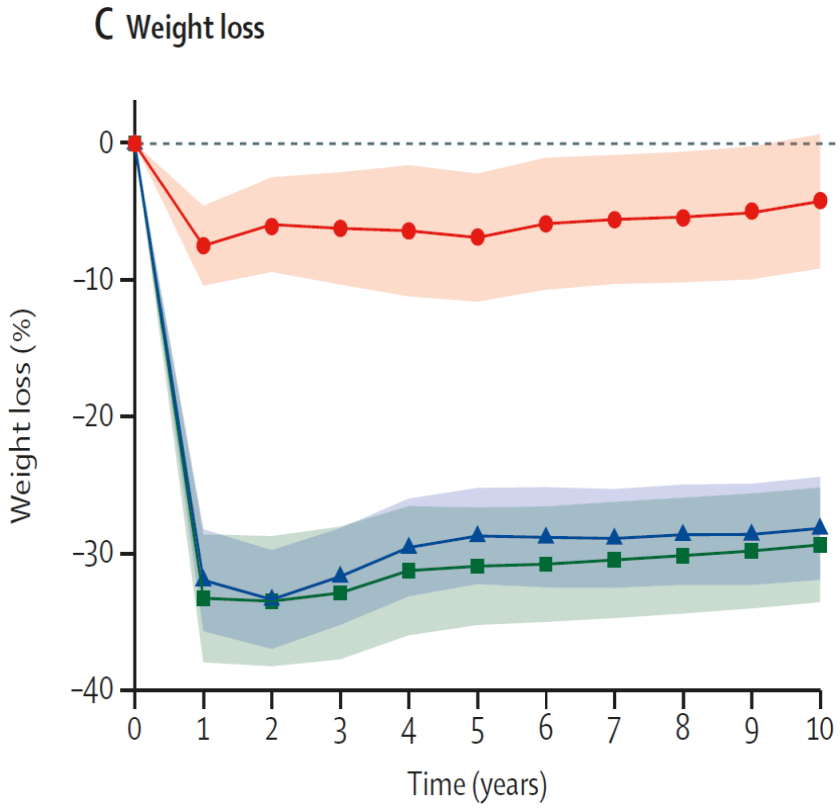


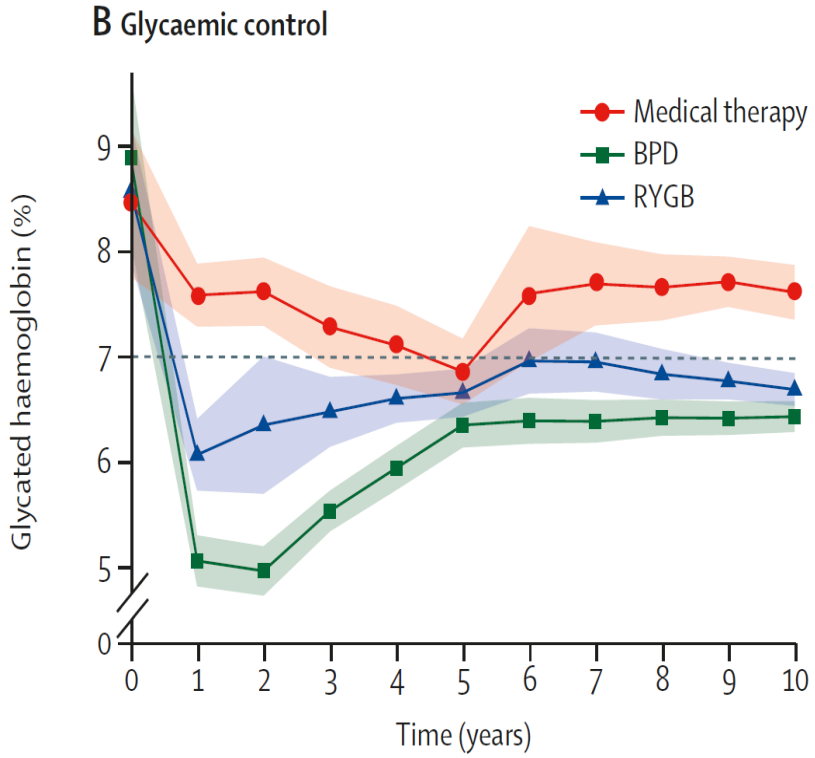
JAMA. 2012;307(1):56-65

Metabolic surgery versus conventional medical therapy in patients with type 2 diabetes: 10-year follow-up of an open-label, single-centre, randomised controlled trial

Geltrude Mingrone, Simona Panunzi, Andrea De Gaetano, Caterina Guidone, Amerigo Iaconelli, Esmeralda Capristo, Ghassan Chamseddine, Stefan R Bornstein, Francesco Rubino

Feb, 2021





RCTs of metabolic surgery x BMT, at least 2 years of FU, glucocentric outcomes

	Surgical intervention	Follow-up duration, years	Glycaemic target	Proportion reaching glycaemic target (surgical intervention *vs* current medical treatment), %	Total bodyweight loss (surgical intervention *vs* current medical treatment), %
Dixon et al[37]	AGB	2	FPG <126 mg/dL and HbA_{1c} <6·2% (44·3 mmol/mol), without glucose-lowering agents	73% *vs* 13%	20% *vs* 1%
Cohen et al[21]	RYGB	2	HbA_{1c} <6·5% (47·5 mmol/mol), regardless of glucose-lowering agents	71% *vs* 51%	26% *vs* 5%
Simonson et al[38]	RYGB	3	FPG <126 mg/dL and HbA_{1c} <6·5% (47·5 mmol/mol) regardless of glucose-lowering agents	42% *vs* 0%	25% *vs* 5%
Ikramuddin et al[39]	RYGB	5	HbA_{1c} <7% (53·0 mmol/mol), regardless of glucose-lowering agents	55% *vs* 14%	22% *vs* 10%
Courcoulas et al[40]	RYGB *vs* AGB	5	HbA_{1c} <6·5 (47·5 mmol/mol) or FPG <126 mg/dL, without glucose-lowering agents	30% (RYGB) *vs* 19% (AGB) *vs* 0%	25% (RYGB) *vs* 15% (AGB) *vs* 6%
Wentworth et al[41]	AGB	5	FPG <126 mg/dL and 2 h blood glucose concentration <200 mg/dL (75 g glucose oral challenge test)	23% *vs* 9%	12% *vs* 2%
Schauer et al[42]	RYGB *vs* sleeve gastrectomy	5	HbA_{1c} <6% (42·1 mmol/mol), regardless of glucose-lowering agents	29% (RYGB) *vs* 23% (sleeve gastrectomy) *vs* 5%	23% (RYGB) *vs* 19% (sleeve gastrectomy) *vs* 5%
Mingrone et al[43]	RYGB *vs* biliopancreatic diversion	10	FPG <100 mg/dL and HbA_{1c} <6·5% (47·5 mmol/mol), without glucose-lowering agents	25% (RYGB) *vs* 50% (biliopancreatic diversion) *vs* 5%	37% (RYGB) *vs* 42% (biliopancreatic diversion) *vs* 7%

HbA_{1c}=glycated haemoglobin. FPG=fasting plasma glucose. AGB=adjustable gastric banding. RYGB=Roux-en-Y gastric bypass.

Table 1: **Randomised controlled trials with follow-up duration of at least 2 years comparing bariatric surgery with current medical treatment**

Lingvay ….Cohen Lancet 2022

Non- glucocentric endpoints

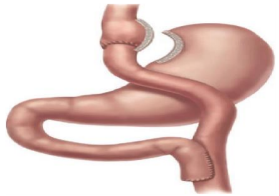
PUBLISHED BY ELSEVIER

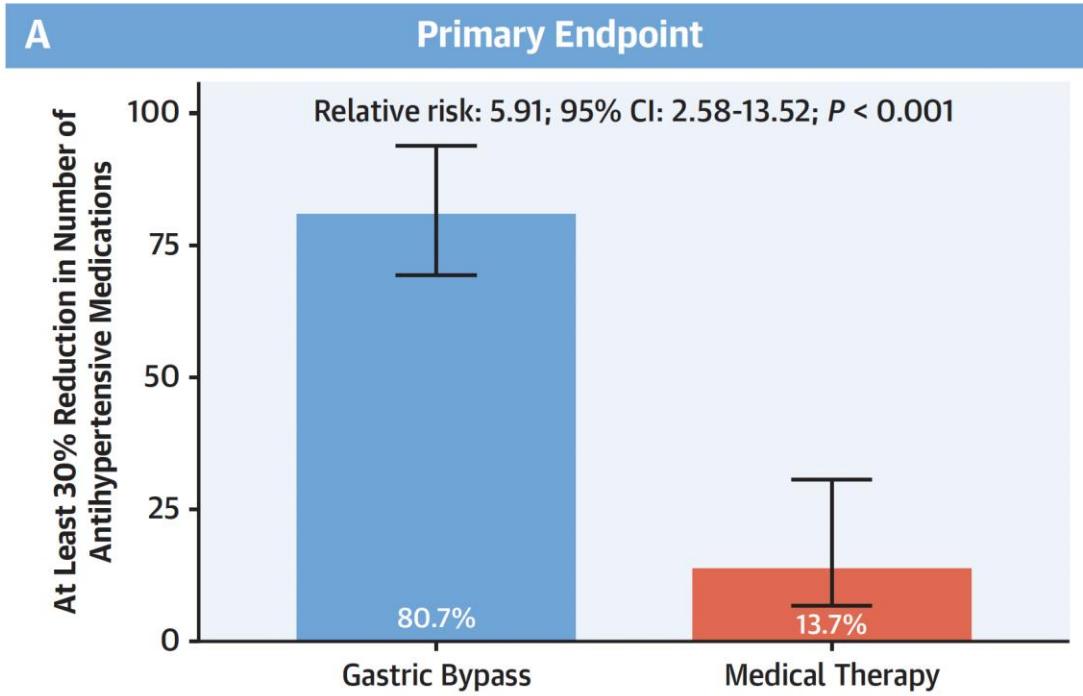
ORIGINAL RESEARCH

Randomized Trial of Effect of Bariatric Surgery on Blood Pressure After 5 Years

Carlos A. Schiavon, MD,[a,b] Alexandre B. Cavalcanti, MD,[a] Juliana D. Oliveira, CN,[a,b] Rachel H.V. Machado, CN,[a] Eliana V. Santucci, PT,[a] Renato N. Santos, STAT,[a] Julia S. Oliveira, STAT,[a] Lucas P. Damiani, STAT,[a] Débora Junqueira, MD,[a] Helio Halpern, MD,[c] Frederico de L.J. Monteiro, MD,[c] Patricia M. Noujaim, MD,[b] Ricardo V. Cohen, MD,[d] Marcio G. de Sousa, MD,[e] Luiz A. Bortolotto, MD,[f] Otavio Berwanger, MD,[g] Luciano F. Drager, MD[f,h,i]

Primary outcome was at least a 30% reduction in total number of antihypertensive medications



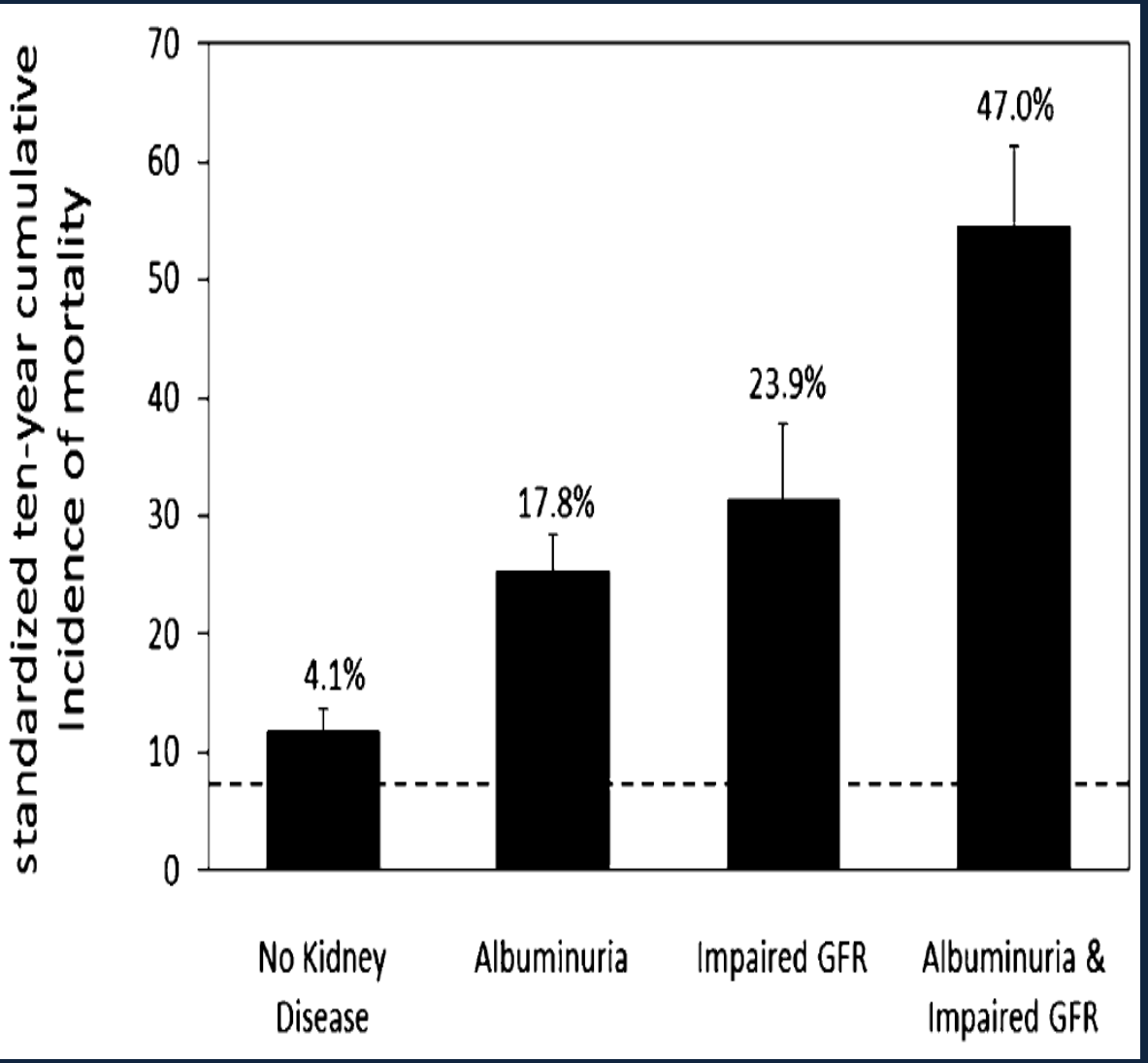


JACC,Feb 2024

Chronic Kidney Disease

Mortality of T2D kidney disease

Afkarian et al. JASN 2013



REVIEW

CURRENT OPINION

Bariatric surgery as a renoprotective intervention

Allon N. Friedman[a] *and Ricardo V. Cohen*[b]

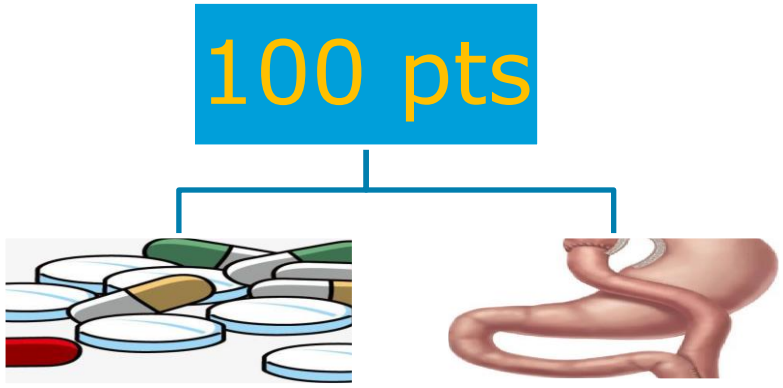
Current Opinion Hypertension and Nephrology, Oct 2019

MOMS TRIAL

Gastric bypass *versus* best medical treatment for diabetic kidney disease: 5 years follow up of a single-centre open label randomised controlled trial

Ricardo V. Cohen,[a,*] Tiago Veiga Pereira,[b,c] Cristina Mamédio Aboud,[a] Tarissa Beatrice Zanata Petry,[a] José Luis Lopes Correa,[a] Carlos Aurélio Schiavon,[d] Carlos Eduardo Pompílio,[a] Fernando Nogueira Quirino Pechy,[a] Ana Carolina Calmon da Costa Silva,[a] Lívia Porto Cunha da Silveira,[a] Pedro Paulo de Paris Caravatto,[a] Helio Halpern,[a] Frederico de Lima Jacy Monteiro,[a] Bruno da Costa Martins,[a] Rogerio Kuga,[a] Thais Mantovani Sarian Palumbo,[a] Allon N. Friedman,[e] and Carel W. le Roux[f,g]

The Lancet , online Nov 11,2022



T2D

uACR>30 mg/g **BMI 30-35 kg/m²**

Early stage kidney disease

MOMS trial

Endpoints

- **Primary endpoint**

➢uACR<30 mg/g

- Secondary endpoints

➢CKD remission

➢Metabolic control (A1c<6%;FPG<100 mg/dl;LDL<100mg/dl (<70 if CV+);HDL>50; TG<150mg/dl; SBP<130 mmHg ;DBP<80 mmHg

➢Weight-loss

➢Use of T2D medications

➢Neuropathy/Retinopathy

➢QOL

MOMS trial

- **Best Medical Treatment**

✓Metformin
✓**GLP1 RA**
✓**SGLT-2 i**
✓Glitazones
✓DPP4 i
✓ACEi/ARB
✓Statins
✓Diuretics
✓insulin

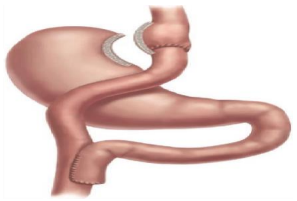
+

- **RYGB + BMT**

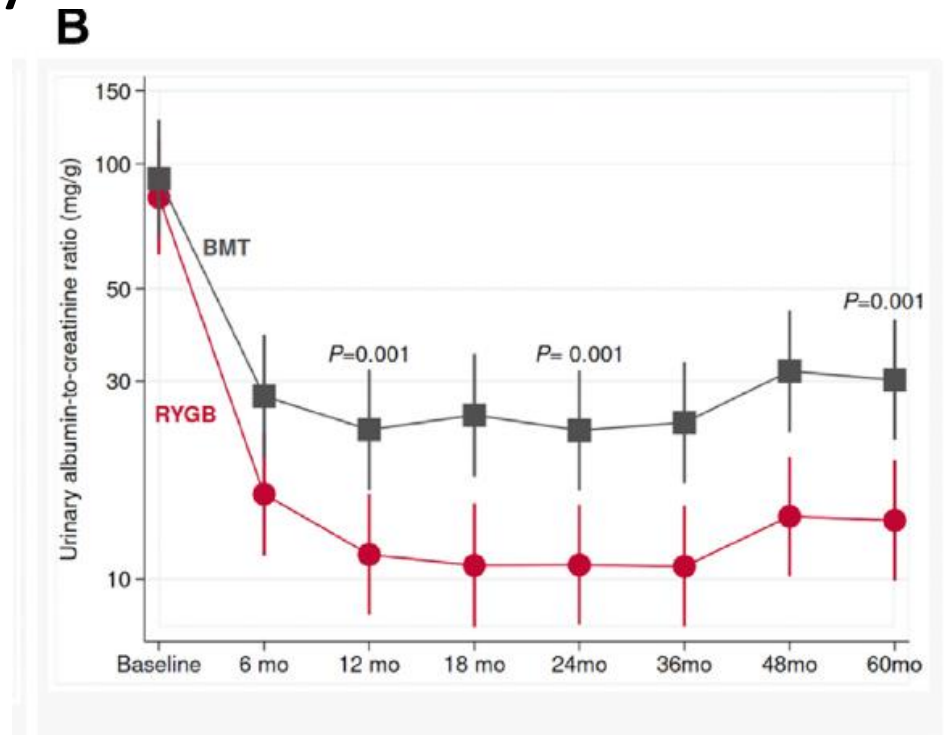
✓ACE/ARB
✓Statins
✓Metformin
✓Multivitamins

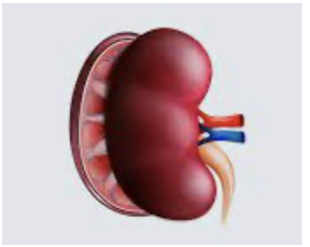
MOMS trial – 5 years outcomes

Primary outcome – uACR- continuous variable



+ BMT

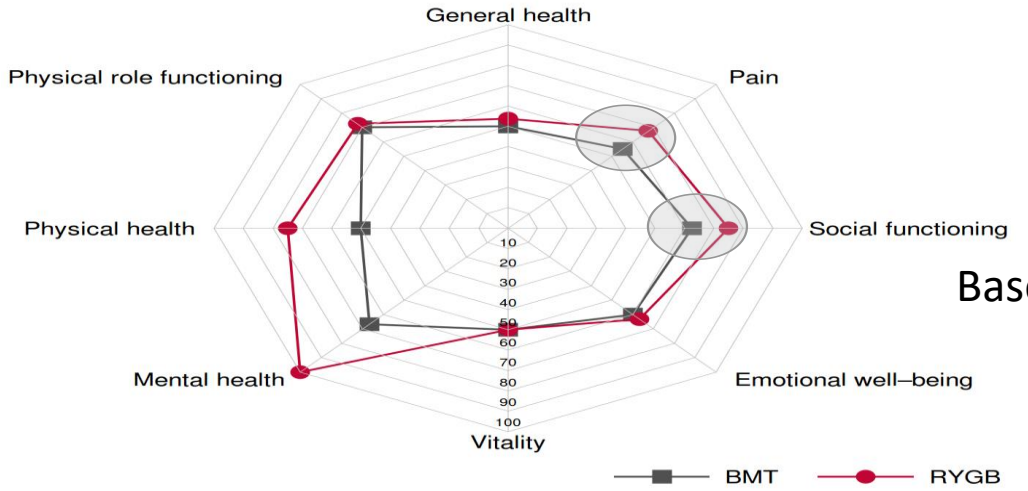




The geometric mean for albuminuria levels was 46% lower after RYGB (P = 0.001)

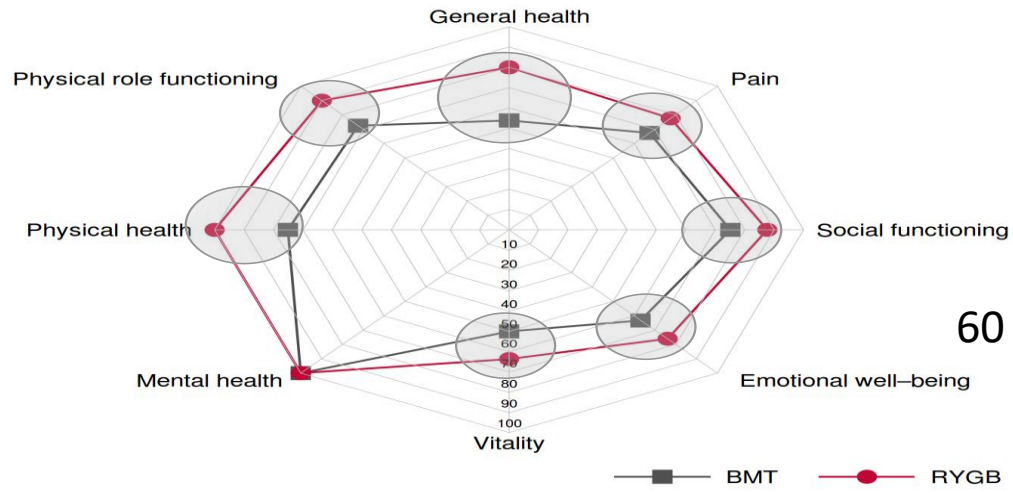
Quality of Life

A



Baseline

B

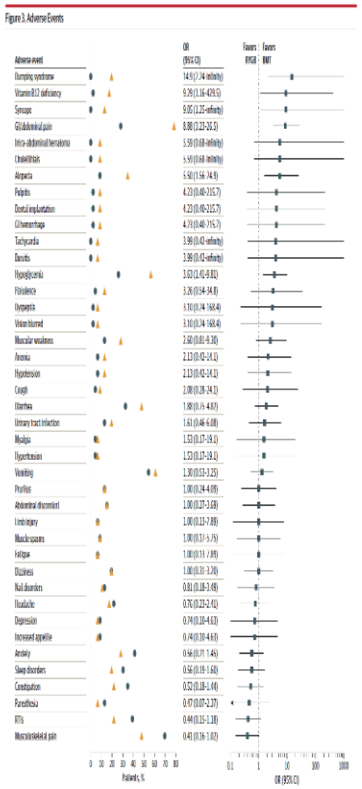


60 mo FU

MOMS trial

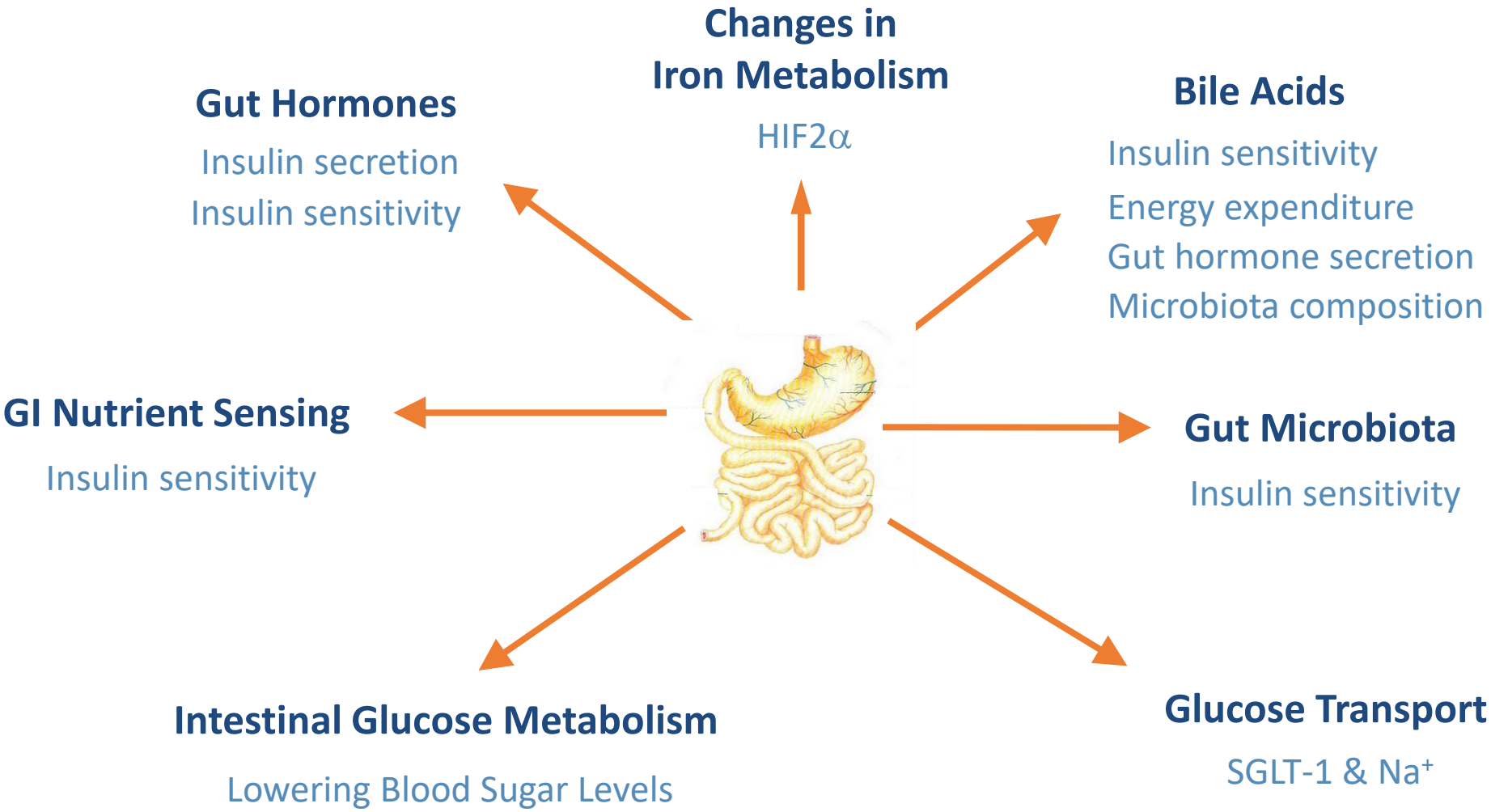
AEs & Safety

13% per arm



- No deaths
- 1 surgical complication managed by endoscopy
- No serious hypoglycemia
- No malnutrition
- No excessive weight-loss

MBS physiological Mechanisms



Complications and mortality continuous decrease

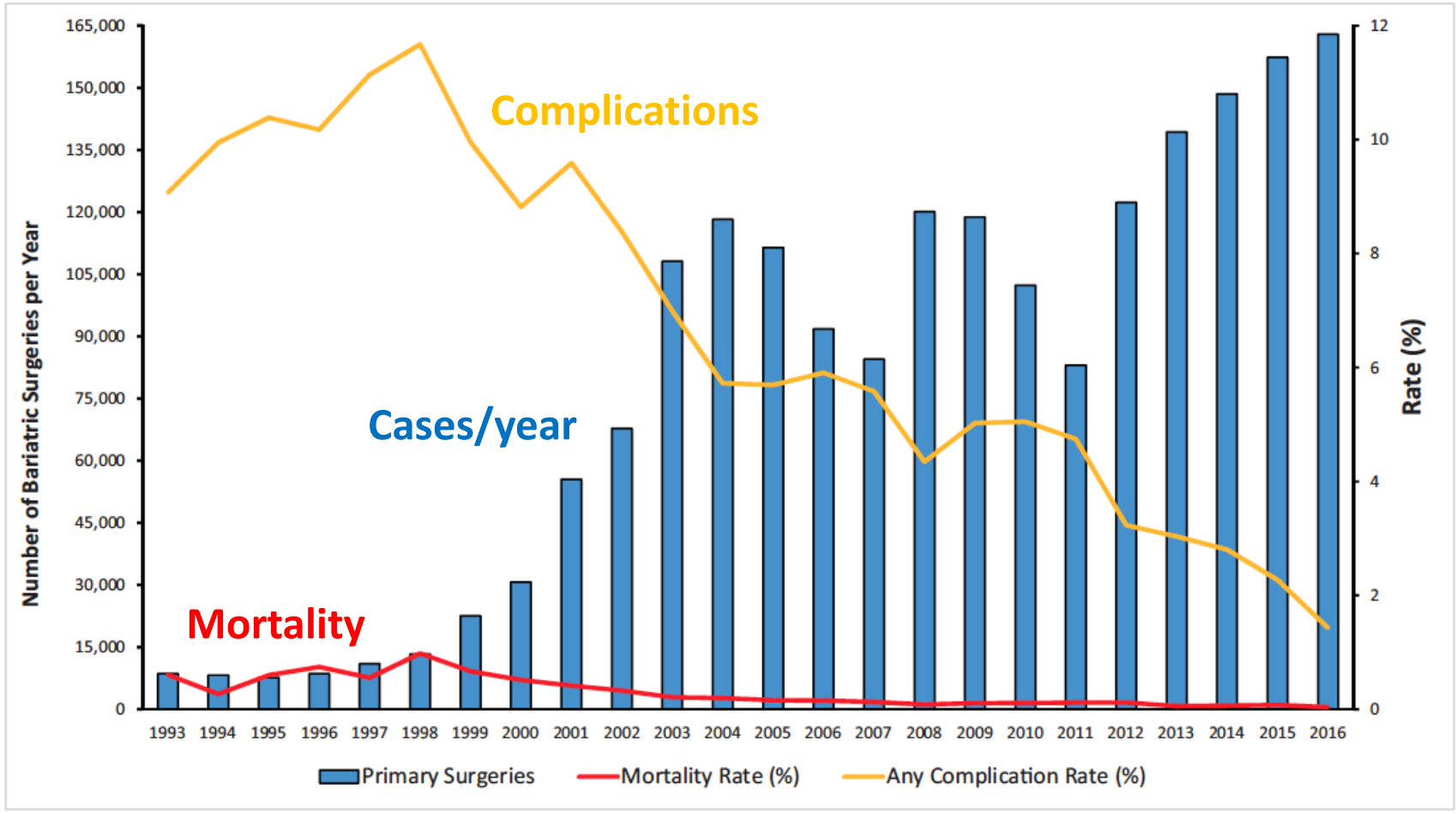


FIGURE 2. Number of inpatient primary bariatric surgery procedures and initial admission complication and mortality rates in the United States from 1993 to 2016.

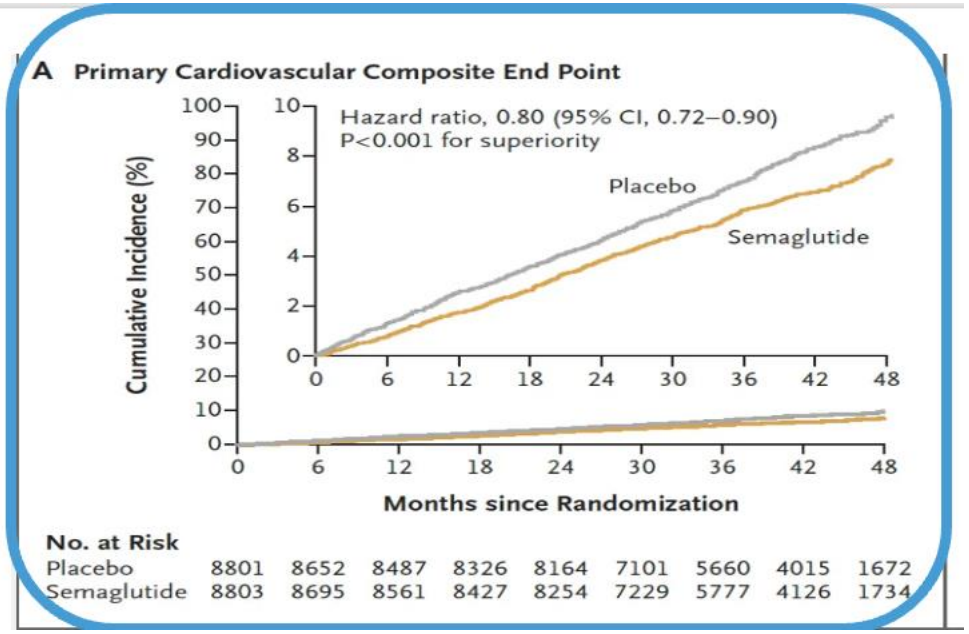
Cv events and mortality

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D., for the SELECT Trial Investigators*

NEJM, Nov 2023



Select RCT

20% CV events

Figure S2. Cumulative Proportion of Patients Who Permanently Prematurely Discontinued Treatment.

Semaglutide	8,803	8,051	7,671	7,365	7,022	5,587	4,591	2,609	712
Placebo	8,801	8,343	7,980	7,665	7,321	5,817	4,771	2,721	708

Discontinued treatment

27%

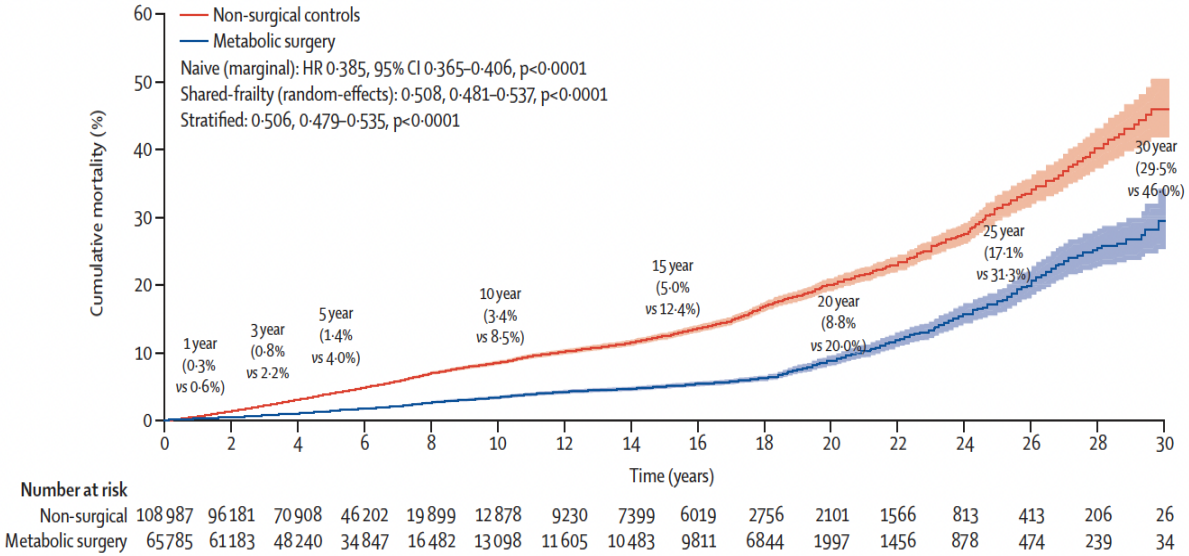
Select study

NEJM,2023

Association of metabolic–bariatric surgery with long-term survival in adults with and without diabetes: a one-stage meta-analysis of matched cohort and prospective controlled studies with 174 772 participants

Nicholas L Syn, David E Cummings*, Louis Z Wang*, Daryl J Lin*, Joseph J Zhao, Marie Loh, Zong Jie Koh, Claire Alexandra Chew, Ying Ern Loo, Bee Choo Tai, Guowei Kim, Jimmy Bok-Yan So, Lee M Kaplan, John B Dixon, Asim Shabbir*

Lancet, 05/21



Metanalysis

174.772 pts

✓**Reduction of all-cause mortality**

✓Overall ~ 50%

✓Pre-existing T2D ~ 60% reduction

✓No T2D @ baseline ~ 30% reduction

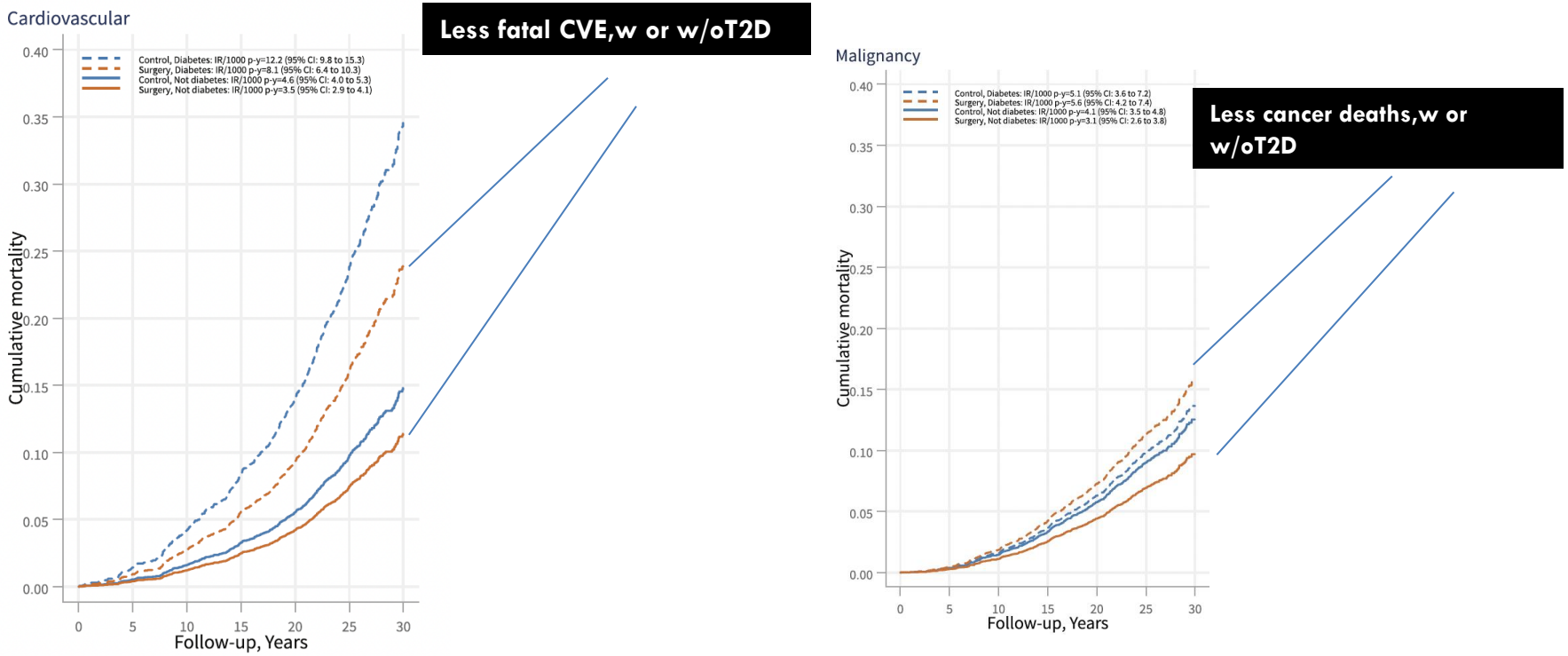
International Journal of Obesity www.nature.com/ijo

Life expectancy after bariatric surgery or usual care in patients with or without baseline type 2 diabetes in Swedish Obese Subjects

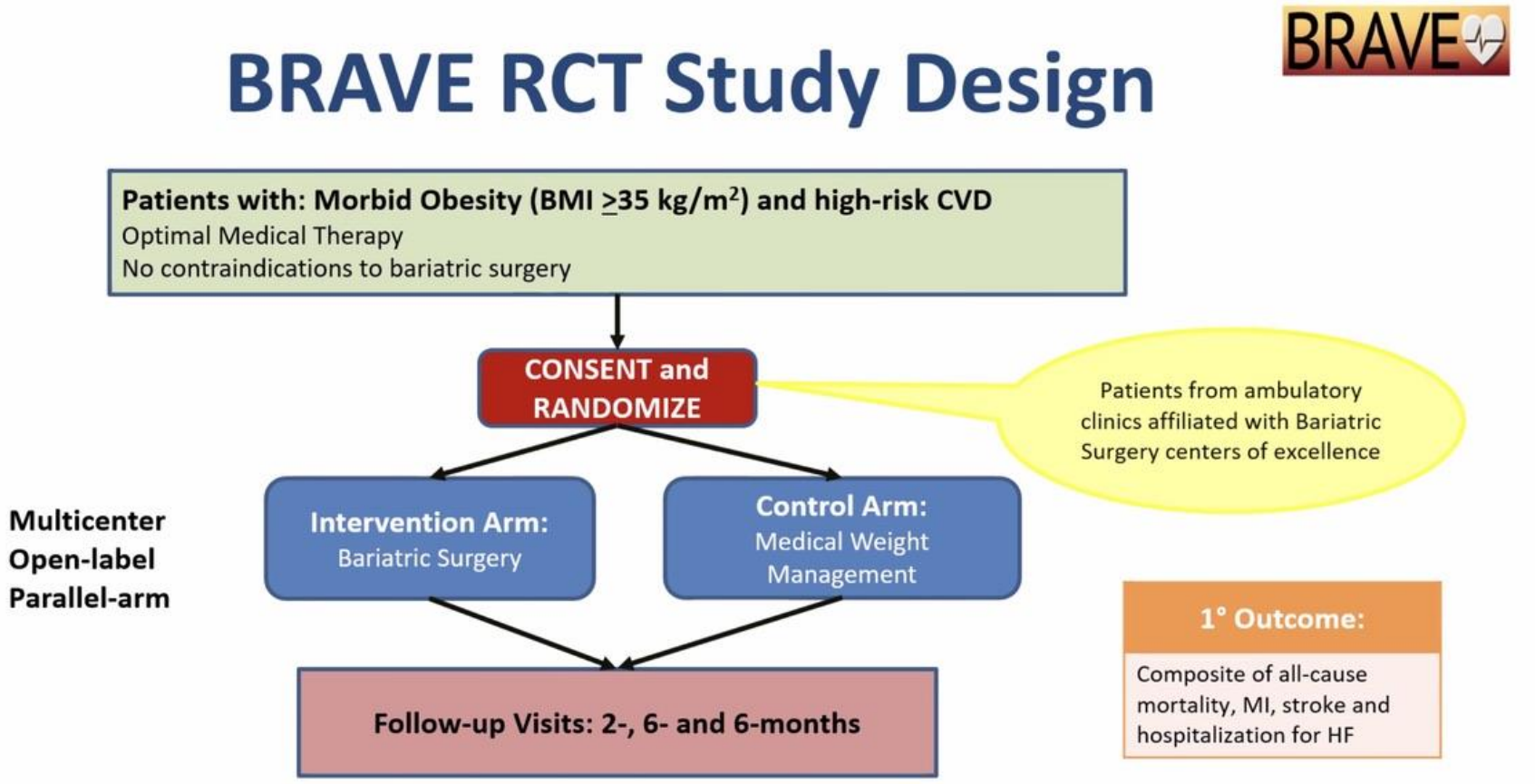
July12,2023

Lena M. S. Carlsson[1], Björn Carlsson[1,2], Peter Jacobson[1], Cecilia Karlsson[1,3], Johanna C. Andersson-Assarsson[1], Felipe M. Kristensson[1,4], Sofie Ahlin[1,5], Per-Arne Svensson[1,6], Magdalena Taube[1], Ingmar Näslund[7], Kristjan Karason[1], Markku Peltonen[8] and Kajsa Sjöholm[1]✉

26 years FU, SOS study



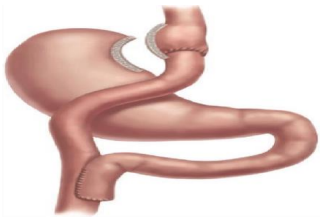
Level 1 evidence on its way



OSWALDO CRUZ
CENTRO ESPECIALIZADO EM OBESIDADE E DIABETES

Hamilton Health Sciences
McMaster University HEALTH SCIENCES

Bariatric/metabolic Surgery



- ✓ Long-term significant WL
- ✓ Physiologic mechanisms
- ✓ Durable T2D remission (glucocentric endpoints)
- ✓ Is renoprotective
- ✓ Decrease CV risk factors
- ✓ Decrease CV events and mortality (needs level 1 evidence)
- ✓ Safe

There is no magic bullet for obesity

*Ildiko Lingvay, Priya Sumithran, Carel W le Roux, *Ricardo V Cohen*
ricardo.cohen@haoc.com.br

Lancet DE, July 2023

There is no magic bullet for obesity

Treating obesity has wide-ranging benefits on health and wellbeing.[1] Advances in medications for obesity have sparked interest, and excessive unregulated media attention has driven unprecedented demand for these new agents. However, the media coverage risks propagating the view that there is a magic bullet treatment for obesity.

Obesity is a chronic and relapsing condition with a complex multifactorial pathophysiology that spans genetics, metabolic maladaptation, neuroendocrine abnormalities, and major shifts in lifestyle, food composition, and societal inequities. An effective approach to obesity treatment must be multifactorial, individualised, and adaptable over time. The treatment will often require a combination of modalities and long-term therapy, akin to the accepted approach for other chronic diseases. The new medications will neither cure obesity nor render other approaches obsolete, including lifestyle interventions and metabolic surgery.

Although the latest generation of medications for obesity shows average results of 15–20% body weight loss per patient, seemingly even without major lifestyle interventions,[2] a few points are worth noting. First, weight loss observed in clinical trials using any obesity treatment has a Gaussian distribution, and up to 20% of participants do not experience clinicaly significant weight loss. Additionally, up to 10% of patients will struggle to tolerate the side effects from the medications.[2] Second, even people who meet the treatment goals with obesity pharmacotherapy might decide to explore metabolic surgery for long-term maintenance of weight loss and health gains. Third, the benefits of obesity medications cease if the medications are stopped.[3] Fourth, regardless of the weight loss method or its effect on bodyweight, a healthy lifestyle remains the cornerstone of optimising health.

Lifestyle interventions also are a valid and independent obesity management strategy. For up to 20% of patients, optimising nutritional quality, eating habits, eradicating maladaptive behaviours, and incorporating physical activity will successfully sustain weight loss and health gains.

Metabolic surgery also remains an effective therapy for obesity, reducing cardiovascular events, microvascular complications, some types of cancer, and all-cause deaths. As obesity is progressive, 10–20% of patients might regain a substantial amount of weight after surgery, often resulting in suboptimal control or relapses of the health issues related to obesity, and necessitate additional weight loss interventions (eg, use of medications). The inverse is also likely to be true for pharmacotherapy.

Combining surgical and medical approaches is standard practice in chronic disease management (eg, coronary disease). In oncology, a range of adjunctive treatments (eg, chemotherapy, radiotherapy, or immunotherapy) might be used in addition to surgery to improve outcomes. Likewise, in the treatment of type 2 diabetes and obesity, a combination of metabolic surgery and medications is associated with excellent glycaemic control, weight loss, and even reversal of diabetic complications.[5] Patients with advanced forms of obesity often have suboptimal responses to lifestyle, medical, or surgical interventions alone; thus, combination treatment might be necessary.

A chronic multifactorial disease requires an approach that is long term, multifactorial, flexible over time, and tailored to the individual. We should not promote one form of treatment by dismissing the other options. We need to combine our efforts and use the right tools, at the right time, and for the right person to achieve optimal care and maximise health benefits for our patients.

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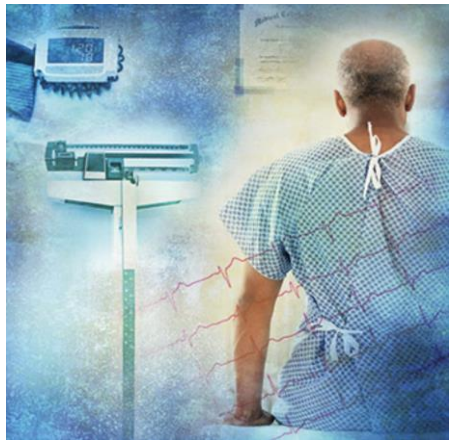
*Ildiko Lingvay, Priya Sumithran, Carel W le Roux, *Ricardo V Cohen*
ricardo.cohen@haoc.com.br

University of Texas Southwestern Medical Center, Dallas, TX, USA (IL); Monash University, Central Clinical School, Melbourne, VIC, Australia (PS); Diabetes Complications Research Centre, University College Dublin, Ireland (CIWR); Diabetes Research Centre, Ulster University, Coleraine, UK (CIWR); The Center for the Treatment of Obesity and Diabetes, Oswaldo Cruz German Hospital, São Paulo 01327–001, Brazil (RVC)

1 Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. *Lancet* 2022; **399:** 394–405.
2 Perdomo CM, Cohen RV, Sumithran P, Clément K, Frühbeck G. Contemporary medical, device, and surgical therapies for obesity in adults.*Lancet* 2023; **401:** 1116–30.
3 Wilding JPH, Batterham RL, Davies M, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. *Diabetes Obes Metab* 2022; **24:** 1553–64.
4 Look ARG. Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. *Obesity* 2014; **22:** 5–13.
5 Cohen RV, Pereira TV, Aboud CM, et al. Gastric bypass *versus* best medical treatment for diabetic kidney disease: 5 years follow up of a single-centre open label randomised controlled trial. *EClinicalMedicine* 2022; **53:** 101725.

DECISIONS ARE MORE IMPORTANT THAN INCISIONS

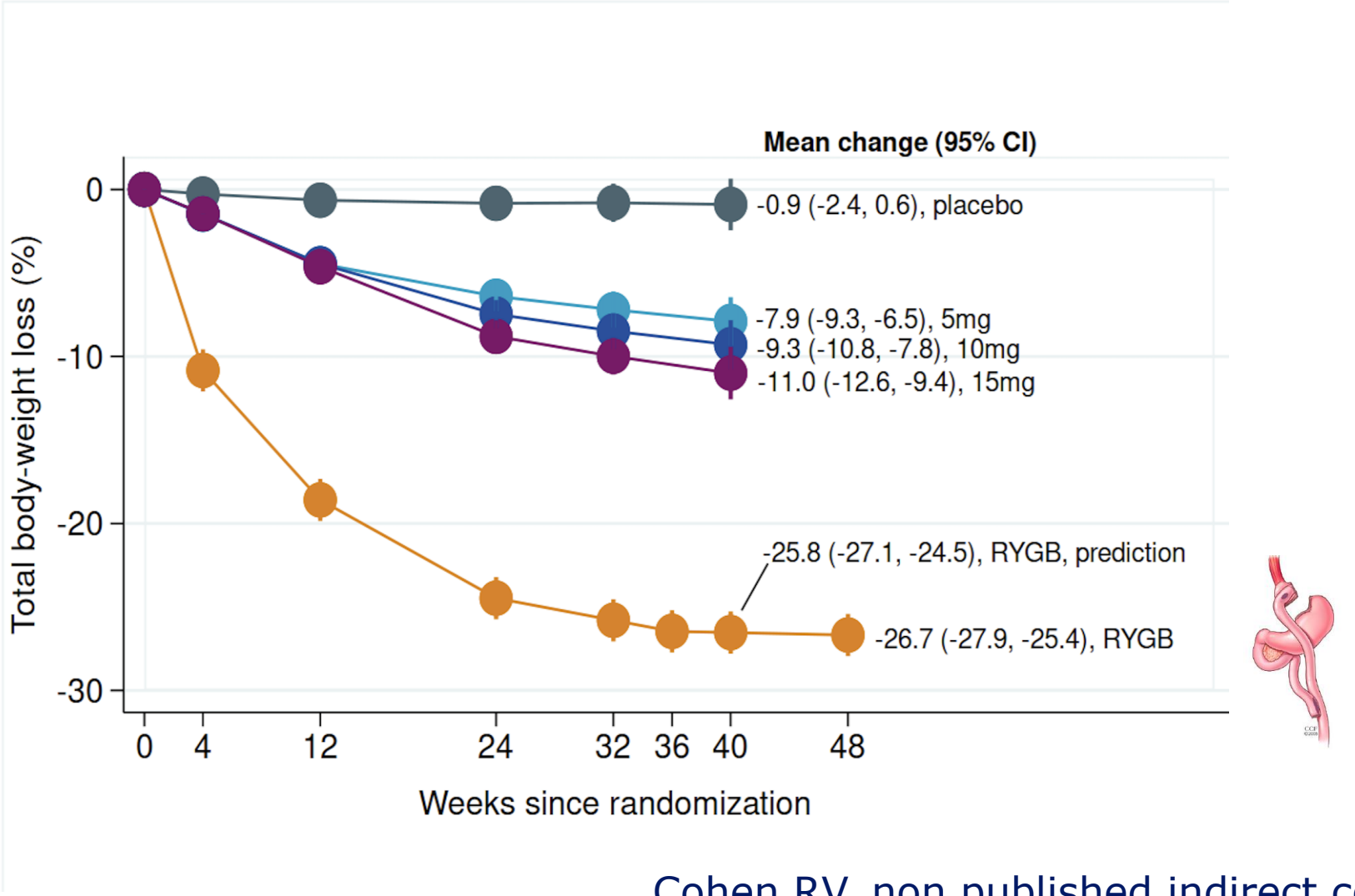


BEST OUTCOMES

Metabolic surgery
&
Pharmacotherapy

MOMS X SURPASS 1

RYGB x Tirzepatide in people with obesity and T2D



Cohen RV, non published indirect comparison

Obesity Surgery
https://doi.org/10.1007/s11695-020-04934-1

BRIEF COMMUNICATION

Bariatric Surgery: There Is a Room for Improvement to Reduce Mortality in Patients with Type 2 Diabetes

Carel W. le Roux [1] · Johan Ottosson [2,3] · Erik Näslund [2,4] · Ricardo V. Cohen [5] · Erik Stenberg [2,3] · Magnus Sundbom [2,6] · Ingmar Näslund [2,3]

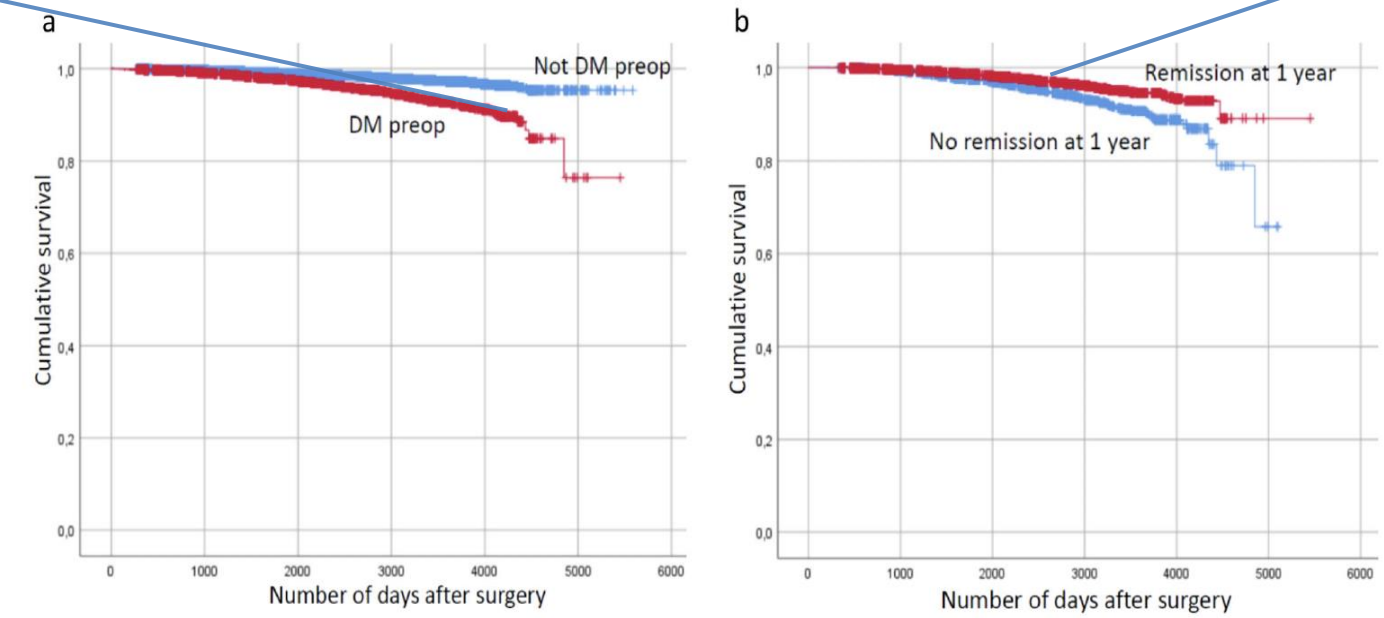
Received: 6 July 2020 / Revised: 13 August 2020 / Accepted: 14 August 2020

SoReg, Scandinavian Obesity Surgery Registry

65,345 pts up to 10y FU, all after RYGB

Operated pts with uncontrolled T2D @ 1 year have higher mortality during FU

Adjuctive pharmacotherapy



JAMA | Original Investigation

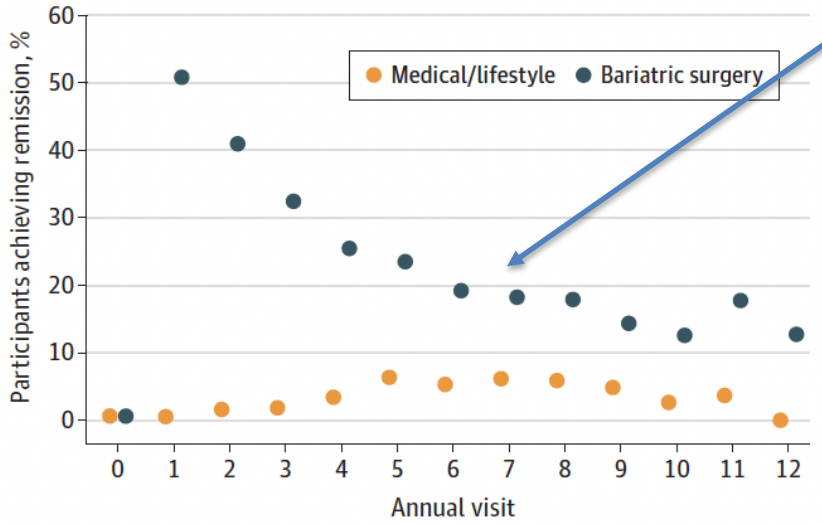
Long-Term Outcomes of Medical Management vs Bariatric Surgery in Type 2 Diabetes

Anita P. Courcoulas, MD; Mary Elizabeth Patti, MD; Bo Hu, PhD; David E. Arterburn, MD; Donald C. Simonson, MD, ScD; William F. Gourash, PhD; John M. Jakicic, PhD; Ashley H. Vernon, MD; Gerald J. Beck, PhD; Philip R. Schauer, MD; Sangeeta R. Kashyap, MD; Ali Aminian, MD; David E. Cummings, MD; John P. Kirwan, PhD

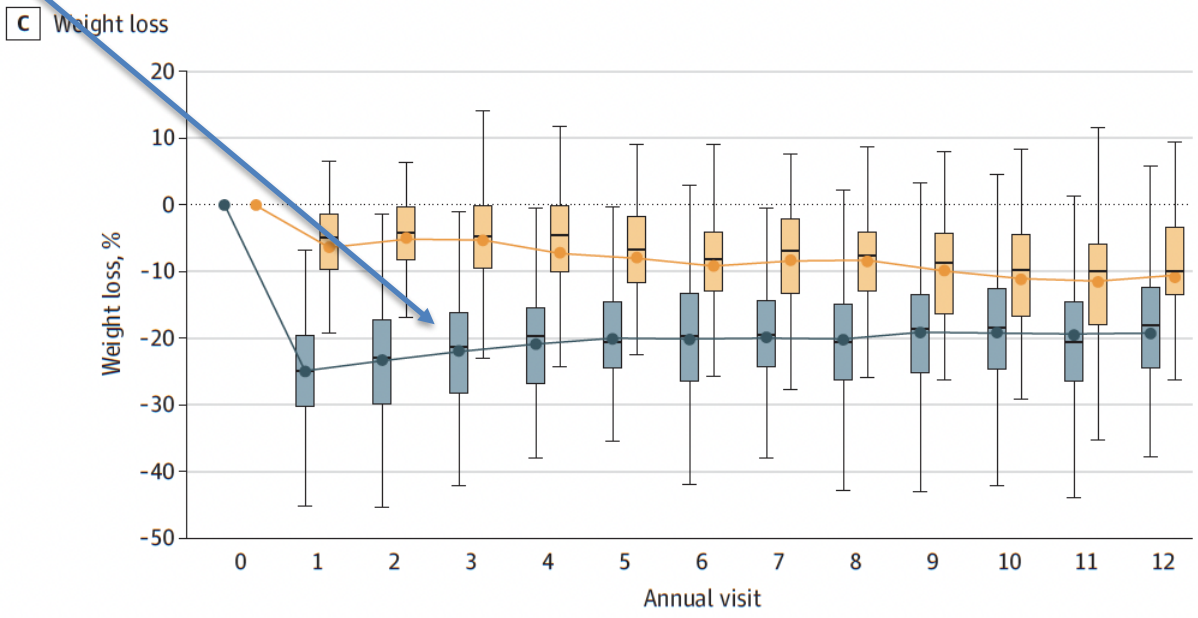
2024

Addition of pharmacotherapy

Figure 3. Diabetes Remission



No. of participants													
Medical/lifestyle	96	92	87	82	78	84	76	79	72	70	67	55	31
Bariatric surgery	166	164	151	149	140	146	108	131	116	125	117	99	82



No. at risk													
Bariatric surgery	166	164	161	158	144	149	122	139	121	126	121	106	85
Medical/lifestyle	96	91	84	86	79	78	77	75	73	73	70	60	34

Remission was defined as hemoglobin A_{1c} less than 6.5% and not receiving any medications for diabetes.

Medications are as effective in operated x non operated patients, ⬆ WL

Adjunctive liraglutide treatment in patients with persistent or recurrent type 2 diabetes after metabolic surgery (GRAVITAS): a randomised, double-blind, placebo-controlled trial

Alexander Dimitri Miras, Belén Pérez-Pevida*, Madhawi Aldhwayan, Anna Kamocka, Emma Rose McGlone, Werd Al-Najim, Harvinder Chahal, Rachel L Batterham, Barbara McGowan, Omar Khan, Veronica Greener, Ahmed R Ahmed, Aviva Petrie, Samantha Scholtz, Stephen R Bloom, Tricia M Tan*

Research

JAMA Surgery | Original Investigation

Safety and Efficacy of Liraglutide, 3.0 mg, Once Daily vs Placebo in Patients With Poor Weight Loss Following Metabolic Surgery
The BARI-OPTIMISE Randomized Clinical Trial

Jessica Mok, BMBS, MPhil; Mariam O. Adeleke, PhD; Adrian Brown, PhD; Cormac G. Magee, MBBChir, MA; Chloe Firman, MRes; Christwishes Makahamadze, MRes; Friedrich C. Jassil, PhD; Parastou Marvasti, PhD; Alisia Carnemolla, PhD; Kalpana Devalia, MBBS, MS; Naim Fakih, MD; Mohamed Elkalaawy, MRCSEd, MS, MD; Andrea Pucci, MD, PhD; Andrew Jenkinson, MBBS, MS; Marco Adamo, MD; Rumana Z. Omar, PhD; Rachel L. Batterham, MBBS, PhD; Janine Makaronidis, MBChB, PhD

Received: 31 October 2022 | Revised: 4 January 2023 | Accepted: 6 January 2023
DOI: 10.1002/oby.23736

Obesity THE OBESITY SOCIETY WILEY

ORIGINAL ARTICLE
Clinical Trials and Investigations

Effectiveness of semaglutide versus liraglutide for treating post-metabolic and bariatric surgery weight recurrence

Natia Murvelashvili[1] | Luyu Xie[2,3] | Jeffrey N. Schellinger[1] | M. Sunil Mathew[2,3] | Elisa Morales Marroquin[2,3] | Ildiko Lingvay[1,4] | Sarah E. Messiah[2,3,5] | Jaime P. Almandoz[1]

CONCLUSION 1

Modern pharmacotherapy may be a good “adjunctive” friend of MBS

Pending questions of modern pharmacotherapy

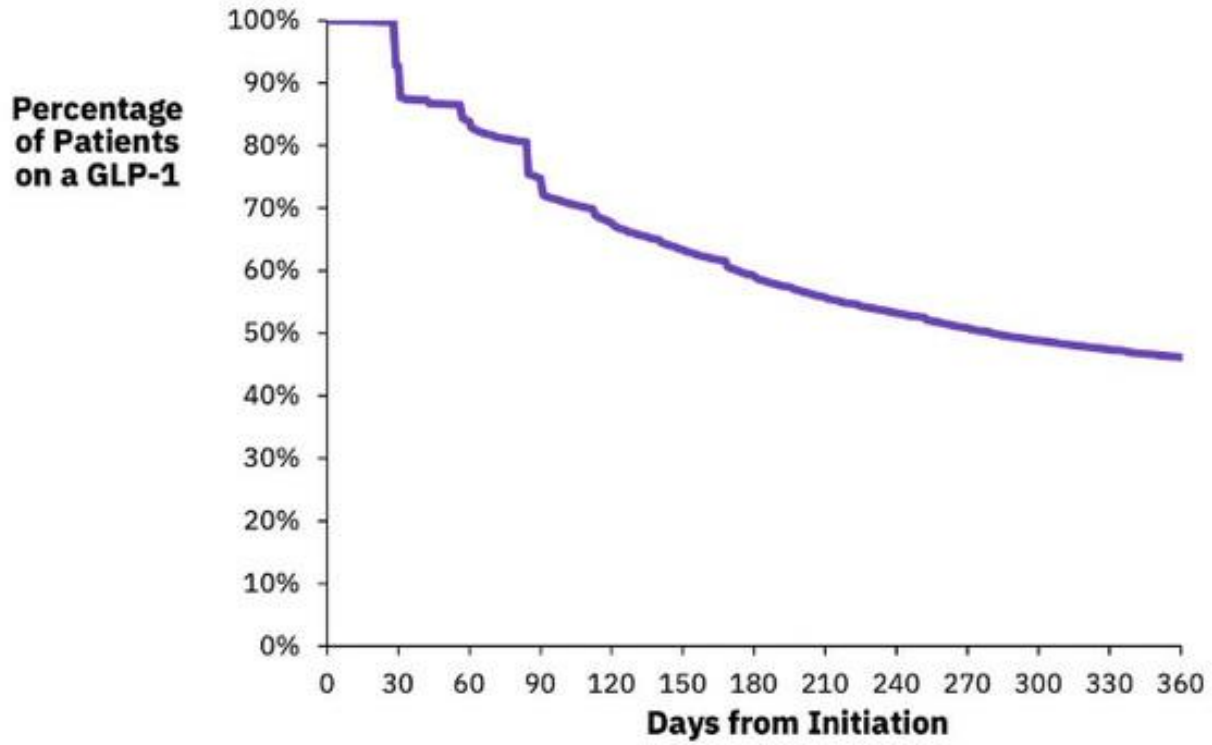
- **Real world**
- Long-term adherence
  - $$
  - Access
  - Polypharmacy
  - Tolerability (short and long-term 27% de dropout in Select)
- Long-term efficacy
- Extreme obesity

Updated

Majority of people who adopt GLP-1s do not stay on therapy for 12 months

55% of patients discontinue GLP-1 use within 12 months of initiation; 28% within 90 days

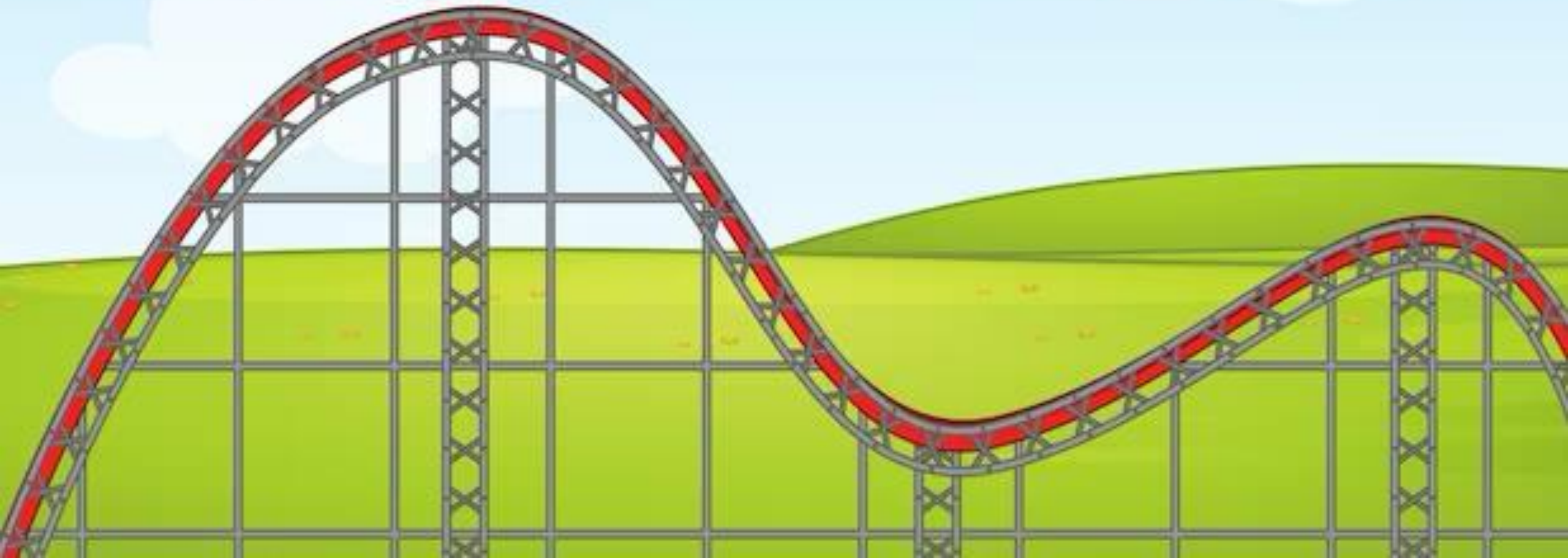
Proportion of new GLP-1 patients remaining on therapy[1], n=54,379

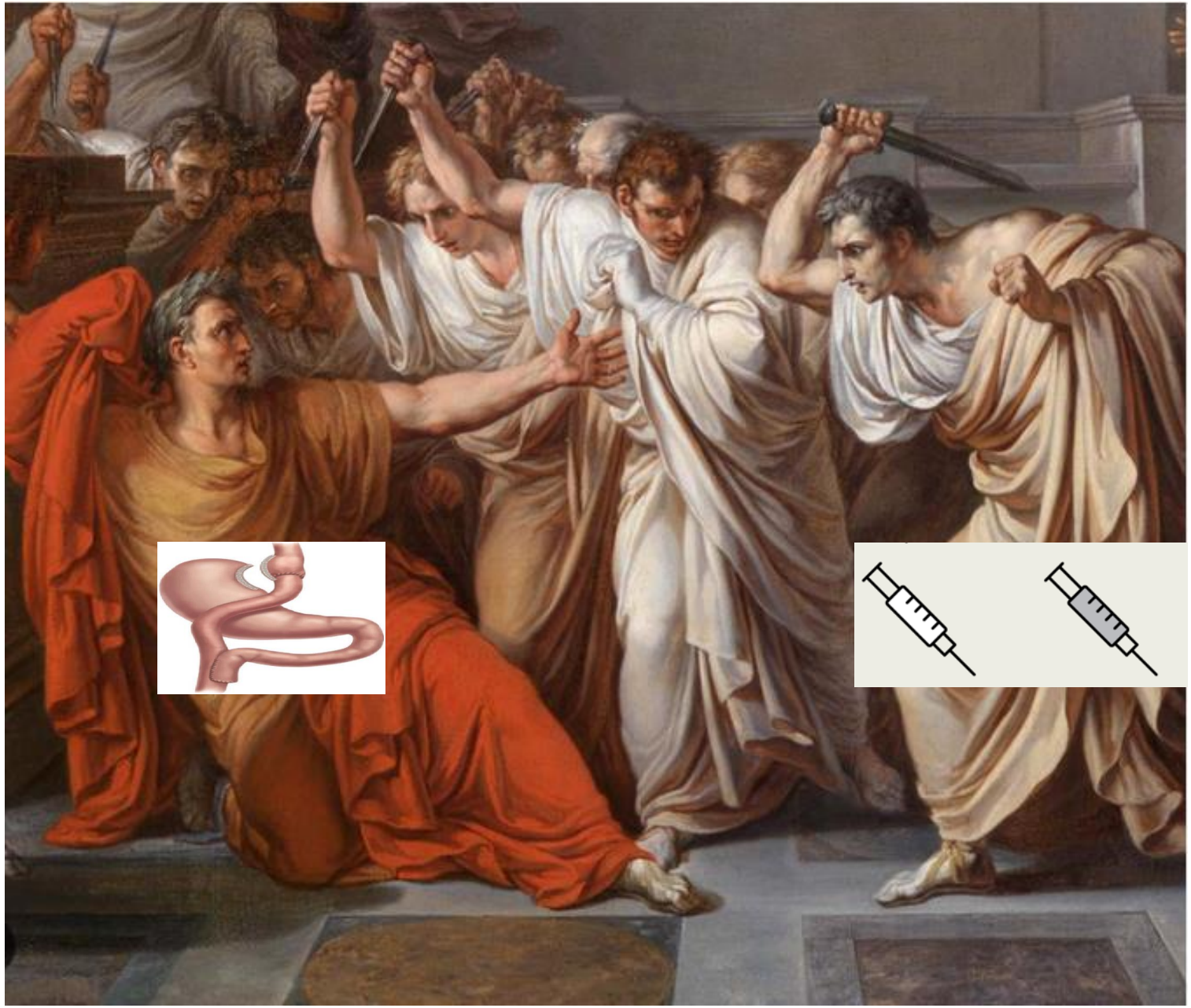


1. Analysis of treatment duration for patients new to GLP-1 therapy. GLP-1 discontinuation based on the time from the date of first pharmacy claim with an NDC code for a GLP-1 medication (Index date between 7/21 to 6/22) to the earliest of: end of continuous enrollment or a gap of more than 60 days in treatment.

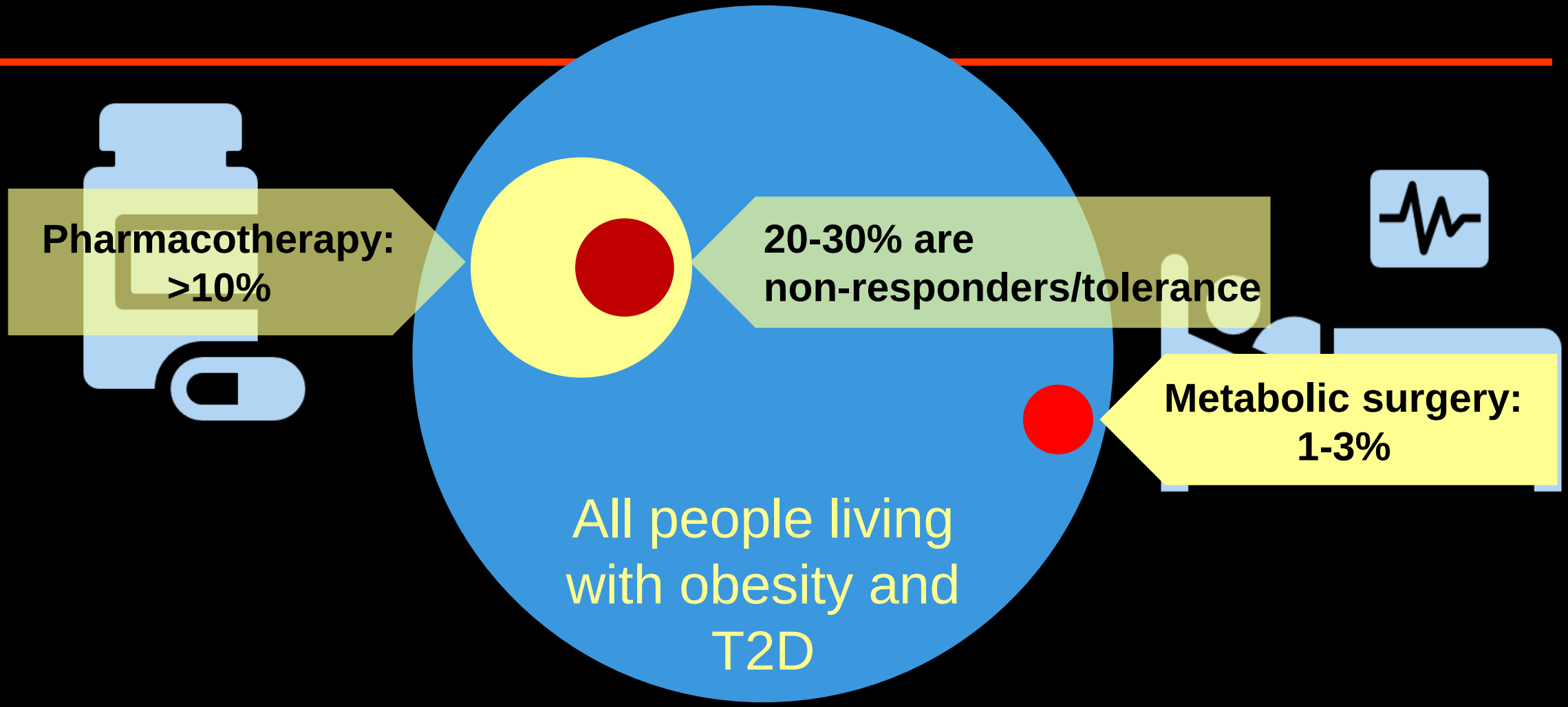
Insulet

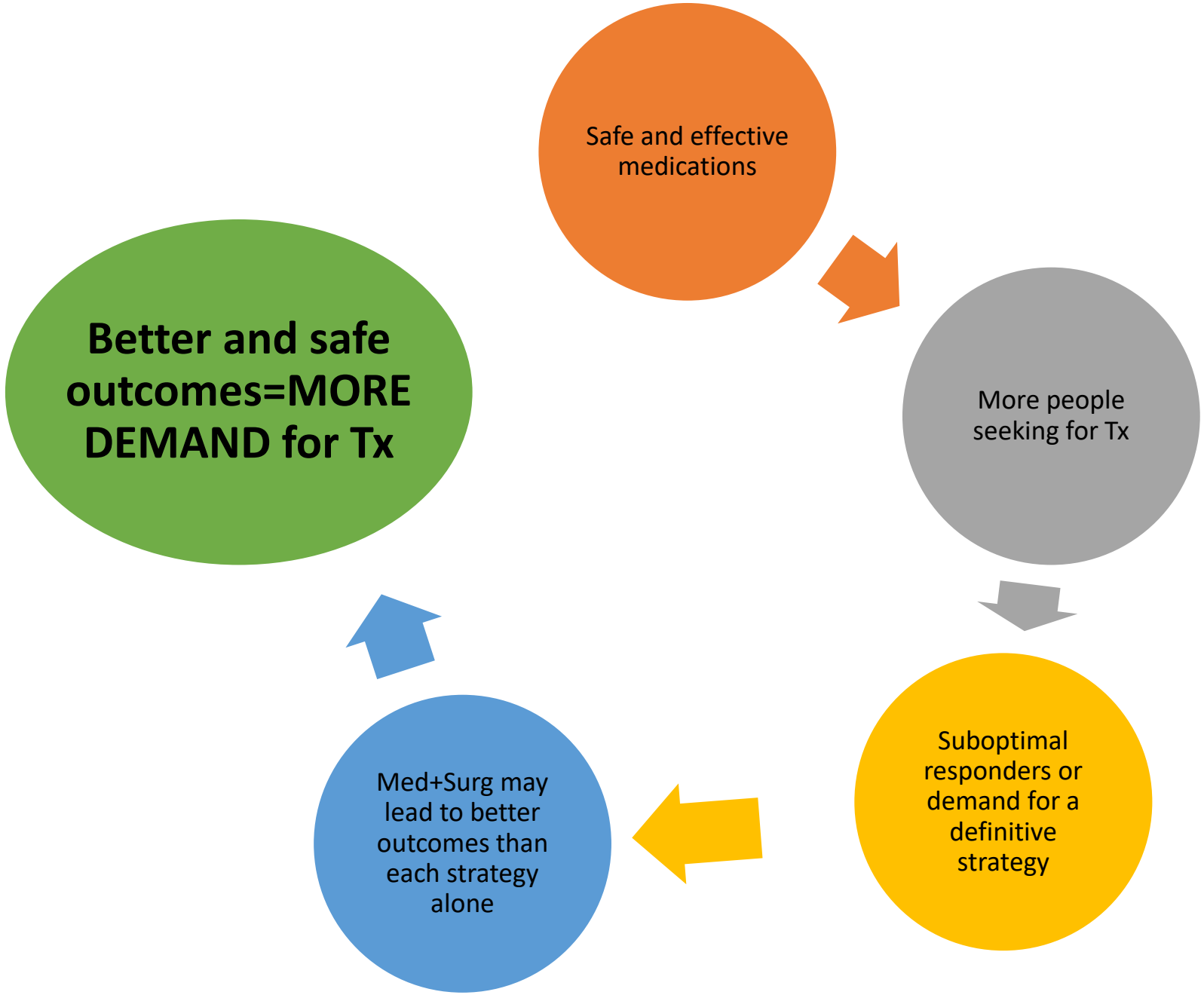
How modern pharmacotherapy may affect surgical indications?





The Death of Julius Caesar (1806) by Vincenzo Camuccini in the National Museum of Capodimonte, in Naples


Pharmacotherapy:
>10%
20-30% are
non-responders/tolerance
Metabolic surgery:
1-3%
All people living
with obesity and
T2D


Safe and effective medications
More people seeking for Tx
Suboptimal responders or demand for a definitive strategy
Med+Surg may lead to better outcomes than each strategy alone
Better and safe outcomes=MORE DEMAND for Tx

Metabolic surgery in era of modern pharmacotherapy

- ✓ Advancements in CV medications and PCI did not kill CABG
- ✓ Advancements in chemo, radio and immunotherapy did not kill cancer surgery
- ✓ Multifactorial disease, no magic bullet

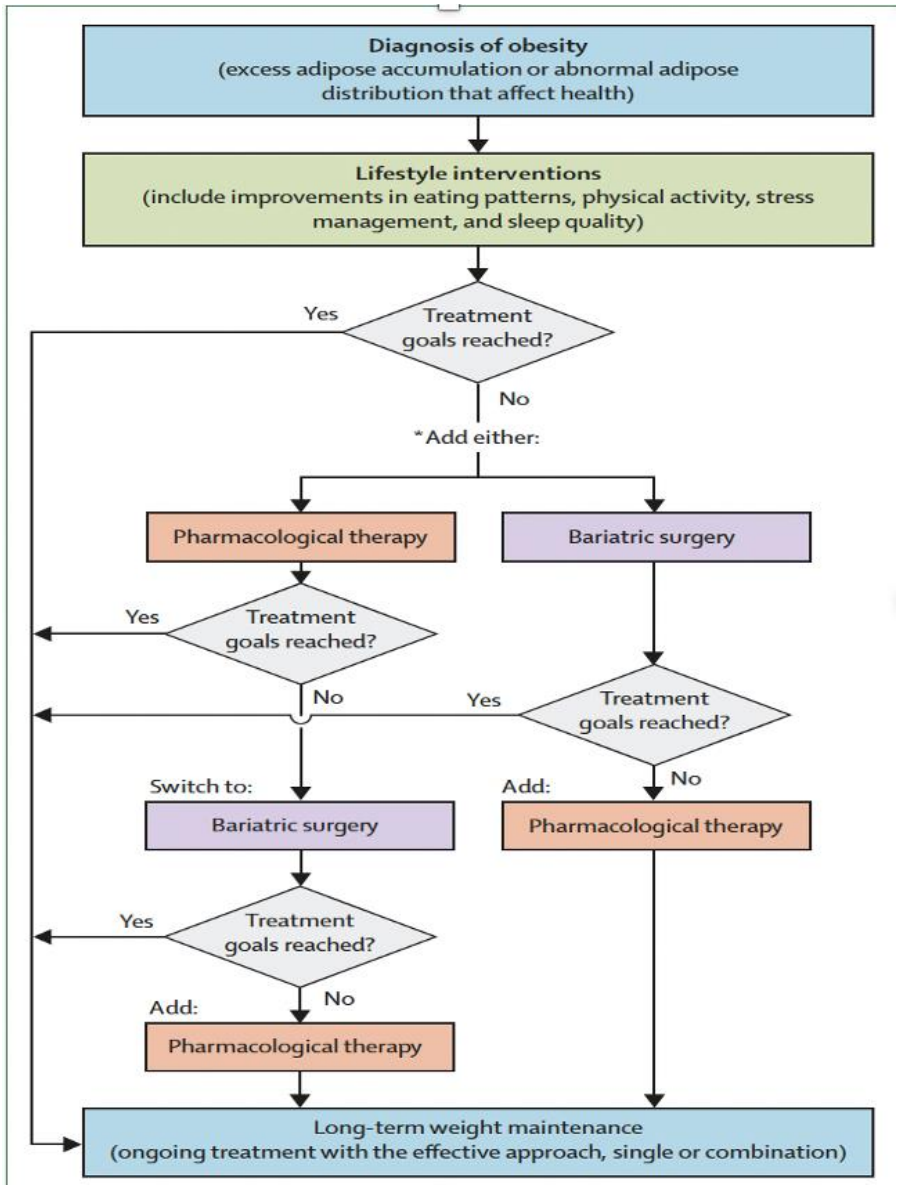
Candidates in the new obesity treatment era

- Pts preference
- Extreme Obesity BMI > 45-50
- Suboptimal response to med tx
- Intolerance to pharmacotherapy

Candidates in the new obesity treatment era

Contraindications to medicines

Cost



Oncology model

What would an oncologist do ?

Access to full spectrum of therapies

- Lingvay I, Cohen RV et al, Lancet 2024


Thank you
ricardo.cohen@haoc.com.br
@rvcohen (X)