What's New in Nutrition and Obesity

Highlights from the

AACE 28th Annual Clinical & Scientific Congress

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Diplomate of the American Board of Obesity Medicine

October 5, 2019

DISCLOSURE

- Slides for presentation courtesy of Dr. W. Timothy Garvey and presented to audience with permission

- No conflict of interest

OBJECTIVES

- Acknowledge proposed AACE framework for new diagnosis of Obesity
- Mention updates in the dietary recommendations for individuals with DM 2 and Obesity, as well as lifestyle interventions
- Recognized novel non surgical devices for weight reduction and maintenance
- Discuss emerging pharmacotherapy and cardiovascular outcome studies

AACE/ACE ALGORITHM FOR THE MEDICAL CARE OF PATIENTS WITH OBESITY

Garvey WT et al. Endocrine Practice 22(Suppl 3):1-203, 2016

Slide courtesy of W. Timothy Garvey, MD

DIAGNOSIS AND MEDICAL MANAGEMENT OF OBESITY

DIAGNOSIS		COMPLICATION-SPECIFIC STAGING AND TREATMENT		
Anthropometric Component (BMI kg/m²)	Clinical Component	Disease Stage	Chronic Disease Phase of Prevention	Suggested Therapy (based on clinical judgment)
<25 <23 in certain ethnicities waist circumference below regional/ ethnic cutoffs		Normal weight (no obesity)	Primary	• **Healthy lifestyle:** healthy meal plan/ physical activity
25–29.9 23–24.9 in certain ethnicities	Evaluate for presence or absence of adiposity-related complications and severity of complications • Metabolic syndrome • Prediabetes • Type 2 diabetes • Dyslipidemia • Hypertension • Cardiovascular disease • Nonalcoholic fatty liver disease • Polycystic ovary syndrome • Female infertility • Male hypogonadism • Obstructive sleep apnea • Asthma/reactive airway disease • Osteoarthritis • Urinary stress incontinence • Gastroesophageal reflux disease • Depression	Overweight stage 0 (no complications)	Secondary	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions
≥30 ≥25 in certain ethnicities		Obesity stage 0 (no complications)	Secondary	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Weight-loss medications:** Consider if lifestyle therapy fails to prevent progressive weight gain (BMI ≥27)
≥25 ≥23 in certain ethnicties		Obesity stage 1 (1 or more mild to moderate complications)	Tertiary	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Weight-loss medications:** Consider if lifestyle therapy fails to achieve therapeutic target or initiate concurrently with lifestyle therapy (BMI ≥27)
≥25 ≥23 in certain ethnicties		Obesity stage 2 (at least 1 severe complication)	Tertiary	• **Lifestyle therapy:** Reduced-calorie healthy meal plan/physical activity/ behavioral interventions • **Add weight-loss medication:** Initiate concurrently with lifestyle therapy (BMI ≥27) • **Consider bariatric surgery:** (BMI ≥35)

Lifestyle Interventions

Slide courtesy of W. Timothy Garvey, MD

Nutrition Therapy for Adults With Diabetes or **Prediabetes**: A Consensus Report. Diabetes Care. 2019

https://doi.org/10.2337/dci19-0014

Evert AB, Dennison D, Gardner CD, Garvey WT, Lau KHK, MacLeod J, Mitri J, Pereira RF, Rawlings K, Robinson S, Saslow L, Uelmen S,Urbansk PB, Yancy Jr WS

What's old (i.e., from 2014):

Evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all people with or at risk for diabetes; therefore, macronutrient distribution should be based on individualized assessment of current eating patterns, preferences, and metabolic goals.

Eating Patterns Reviewed: Mediterranean Style; Vegetarian or Vegan, Low Fat; Very Low Fat; Low Carbohydrate; Very Low Carbohydrate; DASH; Paleo, Very Low Calorie Diet

What's new:

1. Very low carbohydrate diet is recognized as a safe, viable, and important option as an eating pattern for patients with diabetes

2. Emphasis on weight loss in patients with overweight/obesity for treatment of diabetes and diabetes prevention

Slide courtesy of W. Timothy Garvey, MD

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Consensus recommendations

1. A variety of eating patterns are acceptable for the management of diabetes.

2. Health care providers should focus on the key factors that are common among the patterns:
    - Emphasize non-starchy vegetables.
    - Minimize added sugars and refined grains.
    - Choose whole foods over highly processed foods to the extent possible.

3. Reducing overall carbohydrate intake for individuals with diabetes has demonstrated the most evidence for improving glycemia and may be applied in a variety of eating patterns

4. For select adults with type 2 diabetes not meeting glycemic targets or where reducing antiglycemic medications is a priority, low- or very low carbohydrate eating plans are viable approaches. In general, replacing saturated fat with unsaturated fats reduces both total cholesterol and LDL-C and also benefits CVD risk.

Slide courtesy of W. Timothy Garvey, MD

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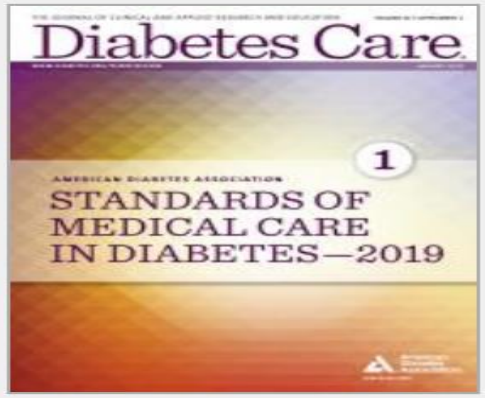
Consensus recommendations

1. In type 2 diabetes, 5% weight loss is recommended to achieve clinical benefit, and the benefits are progressive.
2. The goal for optimal outcomes is 15% or more when needed and can be feasibly and safely accomplished.
3. In prediabetes, the goal is 7–10% for preventing progression to type 2 diabetes.
4. In select individuals with type 2 diabetes, weight loss medications and/or metabolic surgery should be considered to help achieve weight loss and maintenance goals, lower A1C, and reduce CVD risk.
5. In conjunction with lifestyle therapy, medication-assisted weight loss can be considered for people at risk for type 2 diabetes when needed to achieve and sustain 7–10% weight loss.
6. People with prediabetes at a healthy weight should be considered for lifestyle intervention involving both aerobic and resistance exercise and a healthy eating plan such as a Mediterranean-style eating plan

5. Lifestyle Management: *Standards of Medical Care in Diabetes —2019*



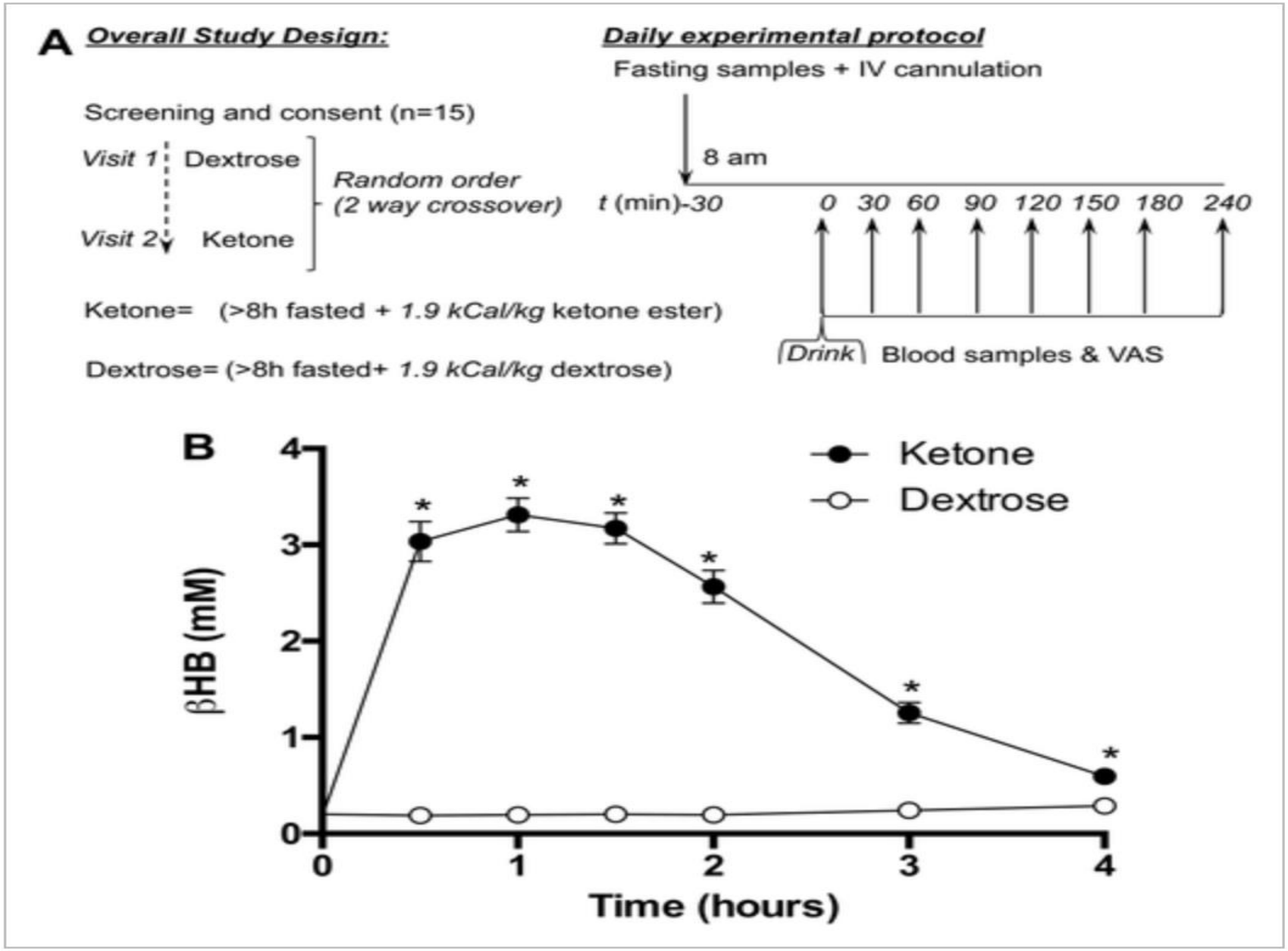
American Diabetes Association
Diabetes Care 2019 Jan; 42(Supplement 1): S46-S60.
https://doi.org/10.2337/dc19-S005

"For people with type 2 diabetes or prediabetes, low-carbohydrate eating plans show potential to improve glycemia and lipid outcomes for up to 1 year"

Obesity A Research Journal
OBESITY SOCIETY

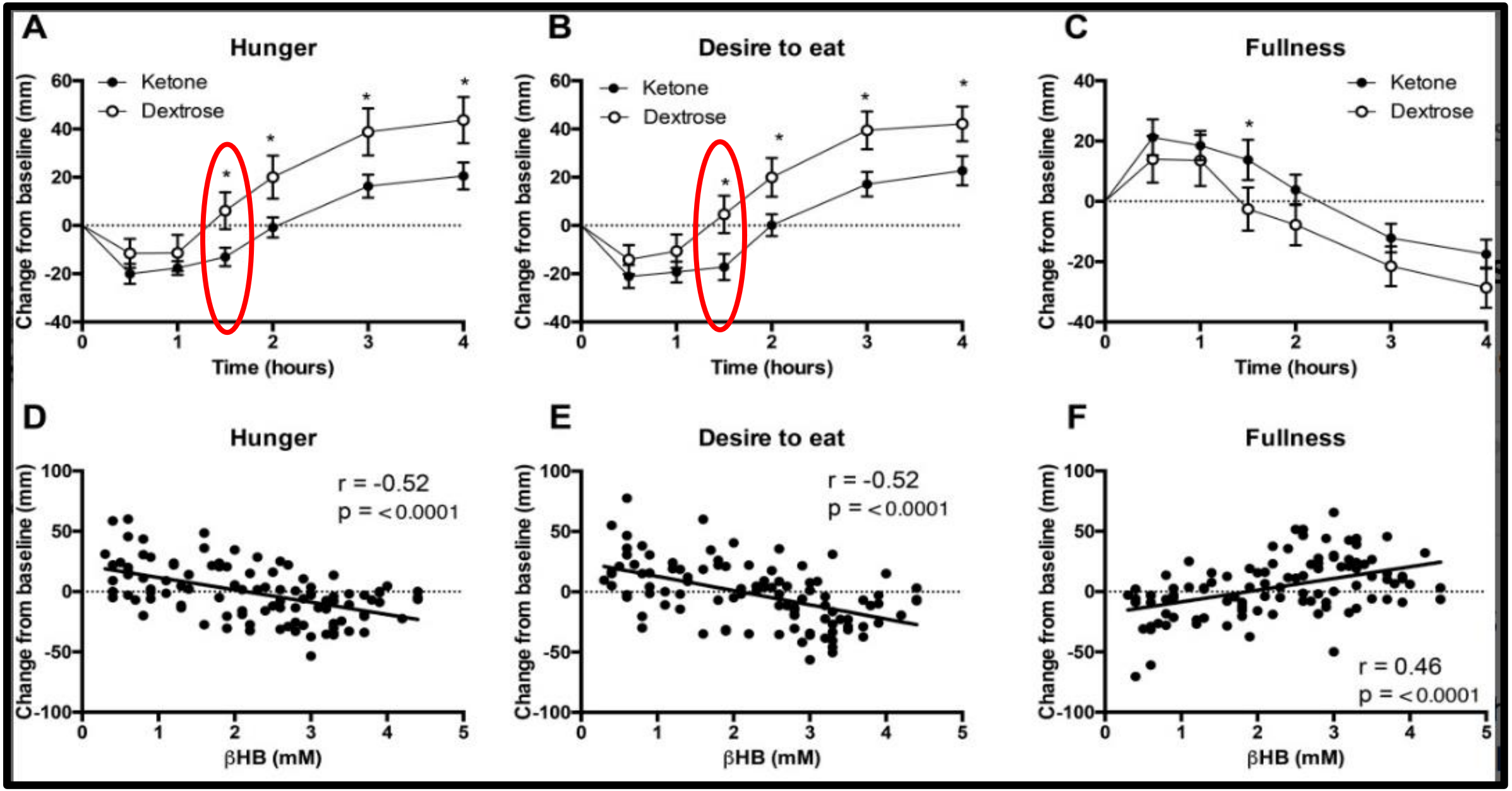
A Ketone Ester drink lowers Human Ghrelin and Appetite

1.9 kcal/kg ketone ester
VS
isocaloric dextrose



Stubbs BJ et al. A Ketone Ester Drink Lowers Human Ghrelin and Appetite. Obesity. 2018; 26(2):269-273

Slide courtesy of W. Timothy Garvey, MD



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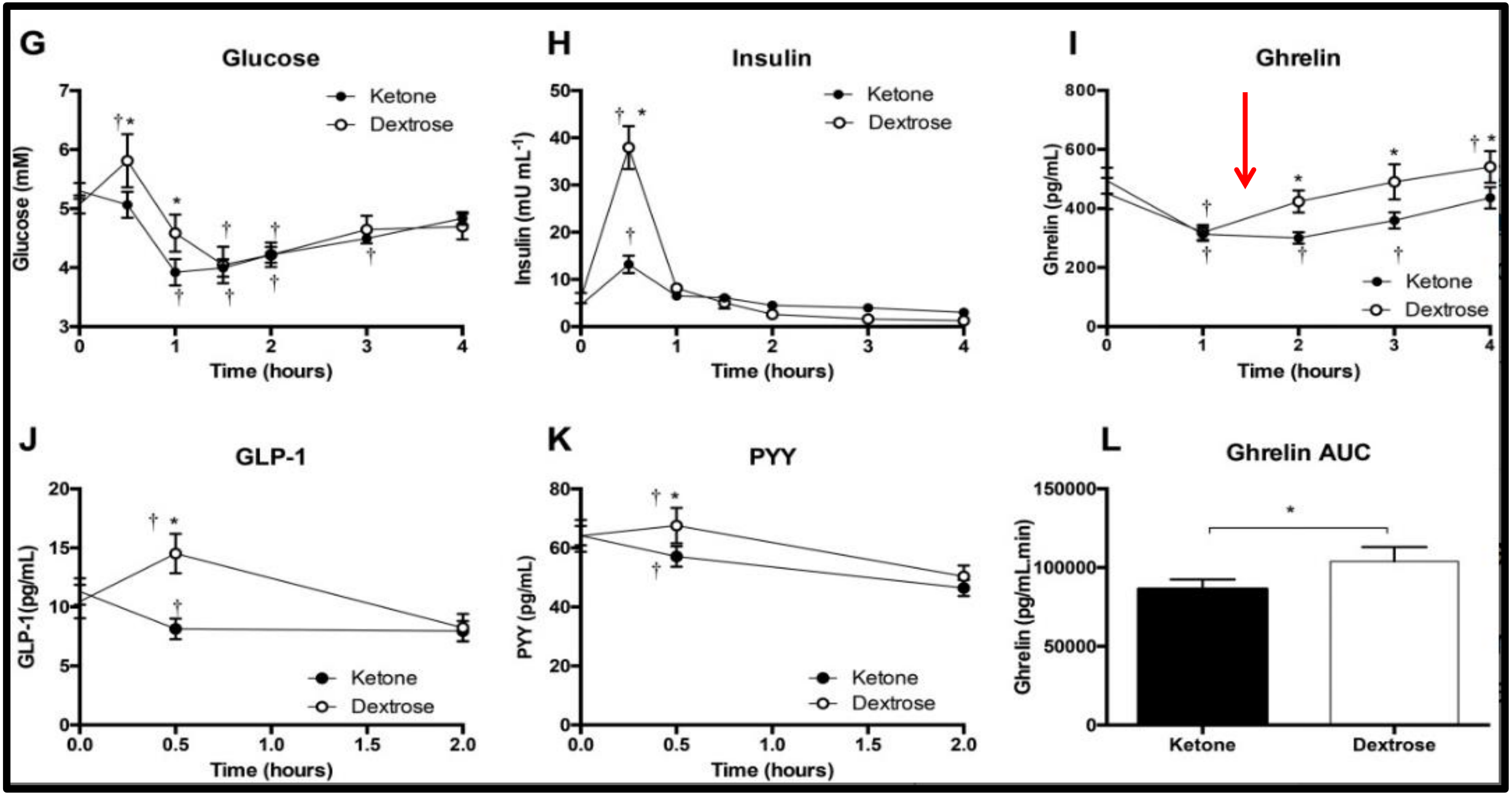

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Obesity. 2018; 26(2):269-273

Time Restricted Feeding and Intermittent Fasting

Continuous dietary restriction

This eating pattern involves a continuous reduction in caloric intake without malnutrition.

Time Restricted Feeding

Daily calories are consumed over a restricted time frame each day (e.g., 8AM to 2PM).

Intermittent Fasting

This eating pattern involves fasting for varying periods of time, typically for 12 hours or longer.

Alternate Day Fasting.

This eating pattern involves consuming no calories on fasting days and alternating fasting days with a day of unrestricted food intake.

➔ Alternate-day modified fast (ADMF)

Anton SD, et al. Obesity. 2018 Feb;26(2):254-268.

Flipping the Metabolic Switch…

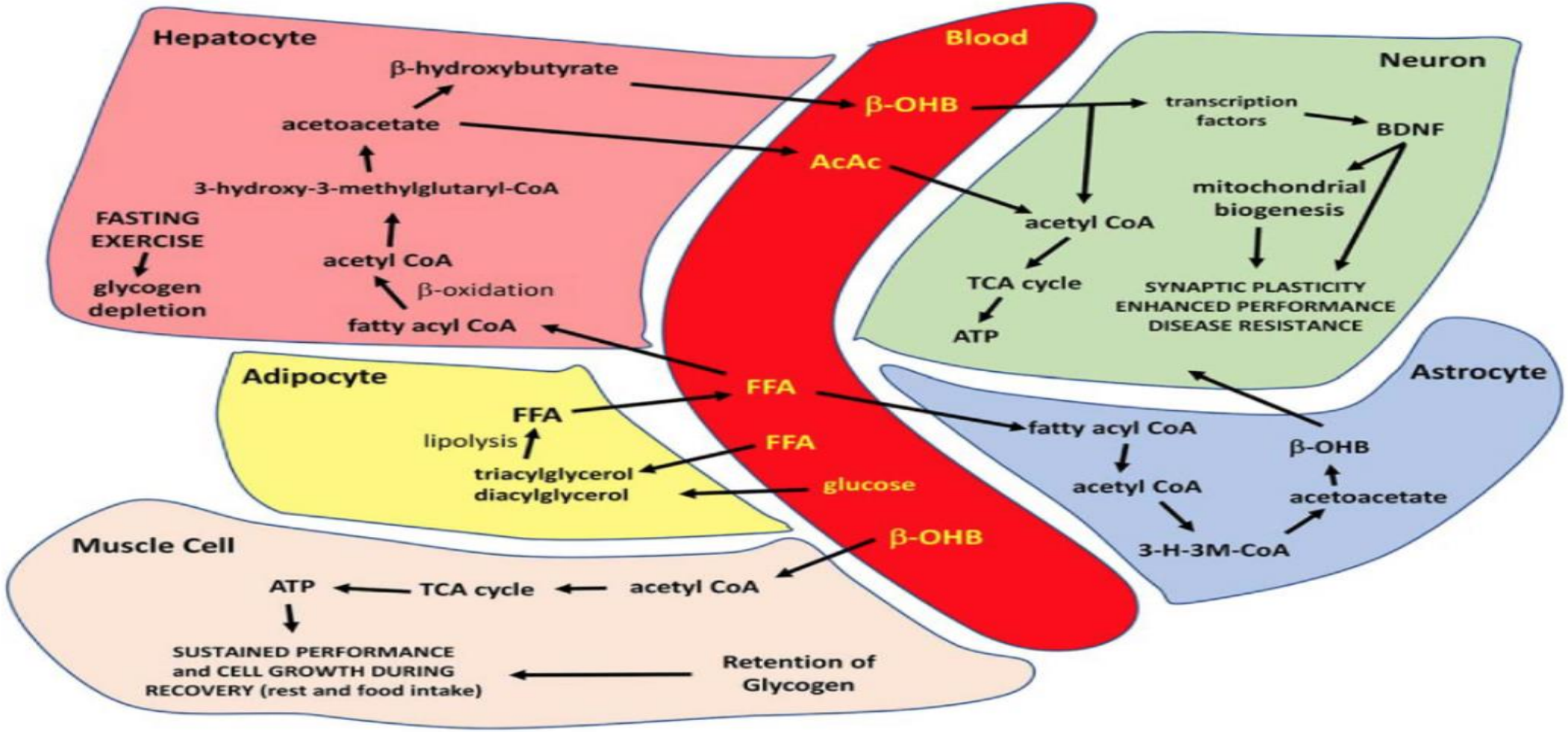


Figure 1 Summary of the major metabolic pathways involved in the metabolic switch and responses of excitable cells to the ketone β-hydroxybutyrate (β-OHB). AcAc, acetoacetate; ATP, adenosine triphosphate; FFA, free fatty acids; TCA, tricarboxylic acid.

Anton SD, et al. Obesity. 2018 Feb;26(2):254-268.

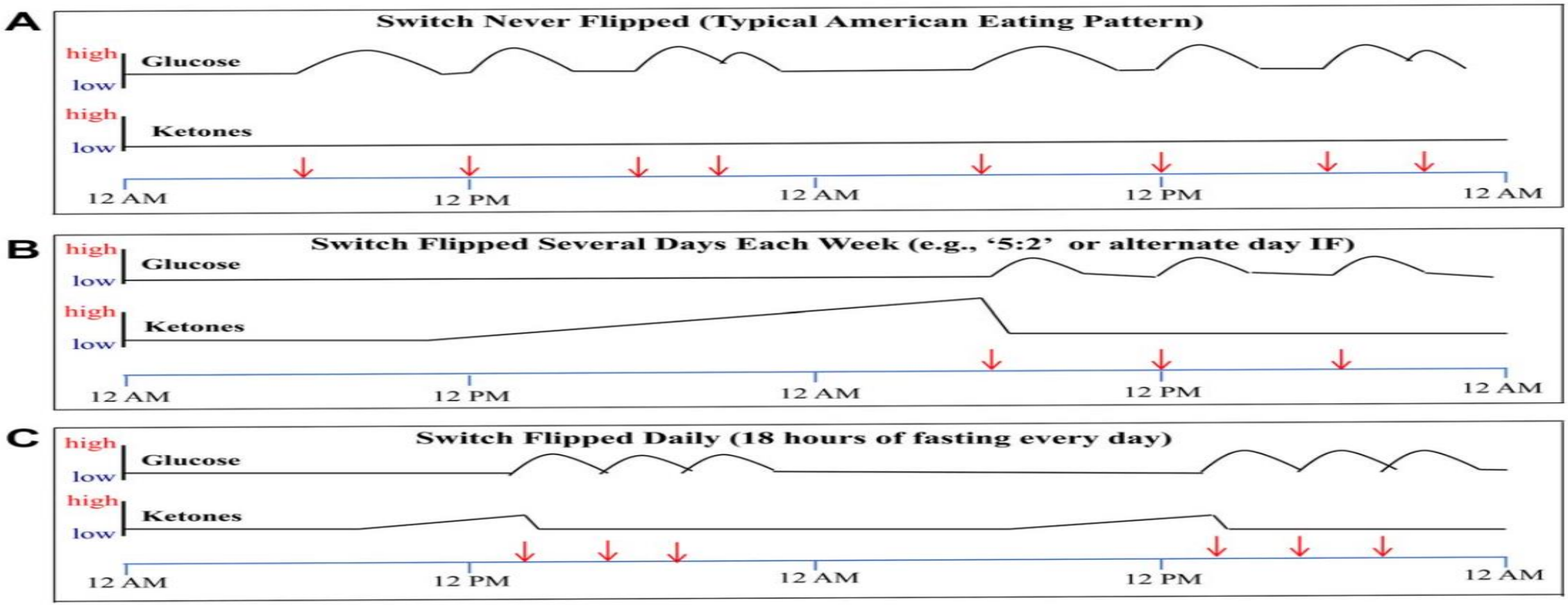
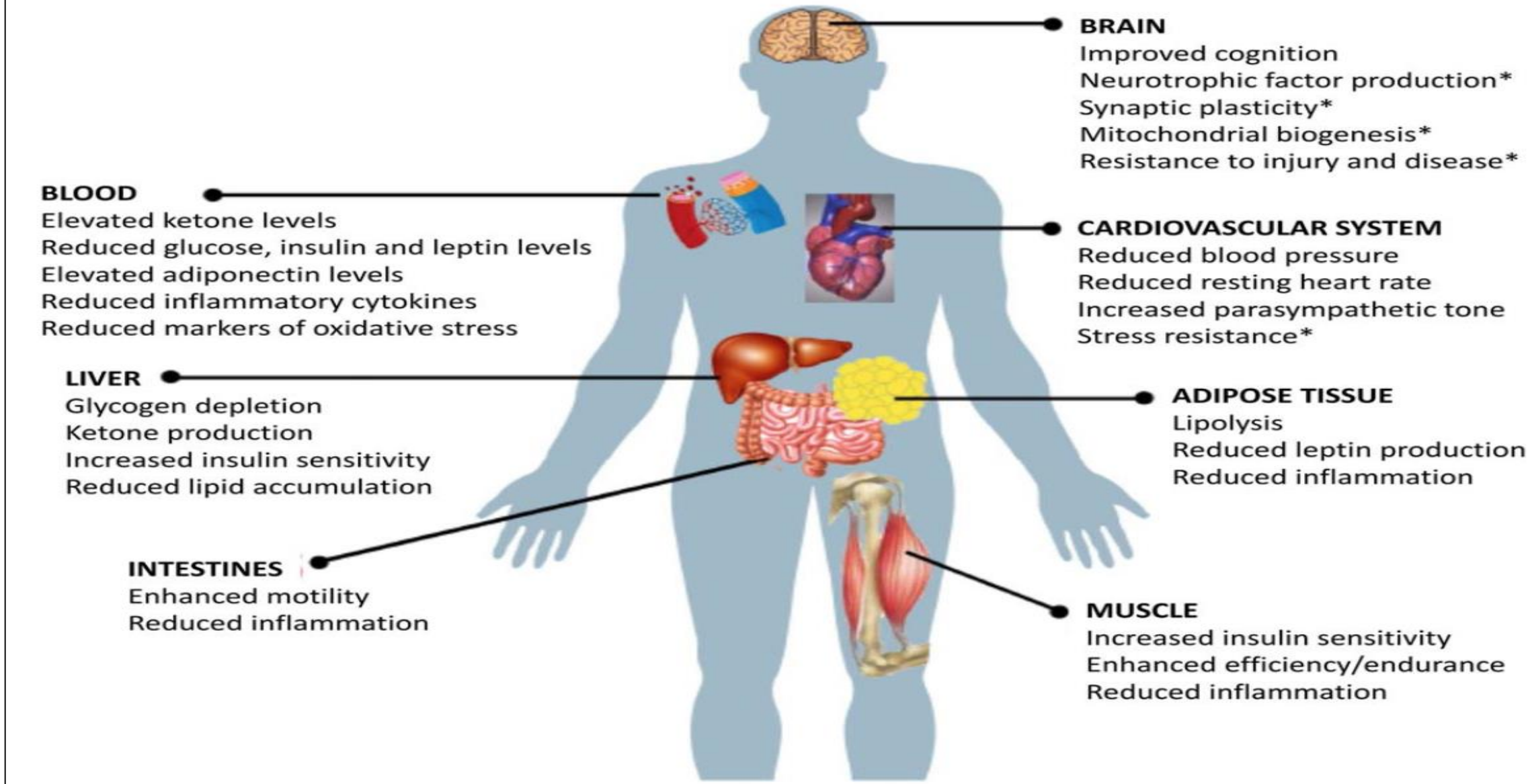


Figure 2 Profiles of circulating glucose and ketone levels over 48 hours in individuals with a typical American eating pattern or two different IF eating patterns. (**A**) In individuals who consume three meals plus snacks every day, the metabolic switch is never "flipped," their ketone levels remain very low, and the area under the curve for glucose levels is high compared with individuals on an IF eating pattern. (**B**) In this example, the person fasts completely on the first day and then at three separate meals on the subsequent day. On the fasting day, ketones are progressively elevated and glucose levels remain low, whereas on the eating day, ketones remain low and glucose levels are elevated during and for several hours following meal consumption. (**C**) In this example, the person consumes all food within a 6-hour time window every day. Thus, the metabolic switch is flipped on following 12 hours of fasting and remains on for approximately 6 hours each day, until food is consumed after approximately 18 hours of fasting. Modified from Mattson et al. (2016) (9).

Anton SD, et al. Obesity. 2018 Feb;26(2):254-268.

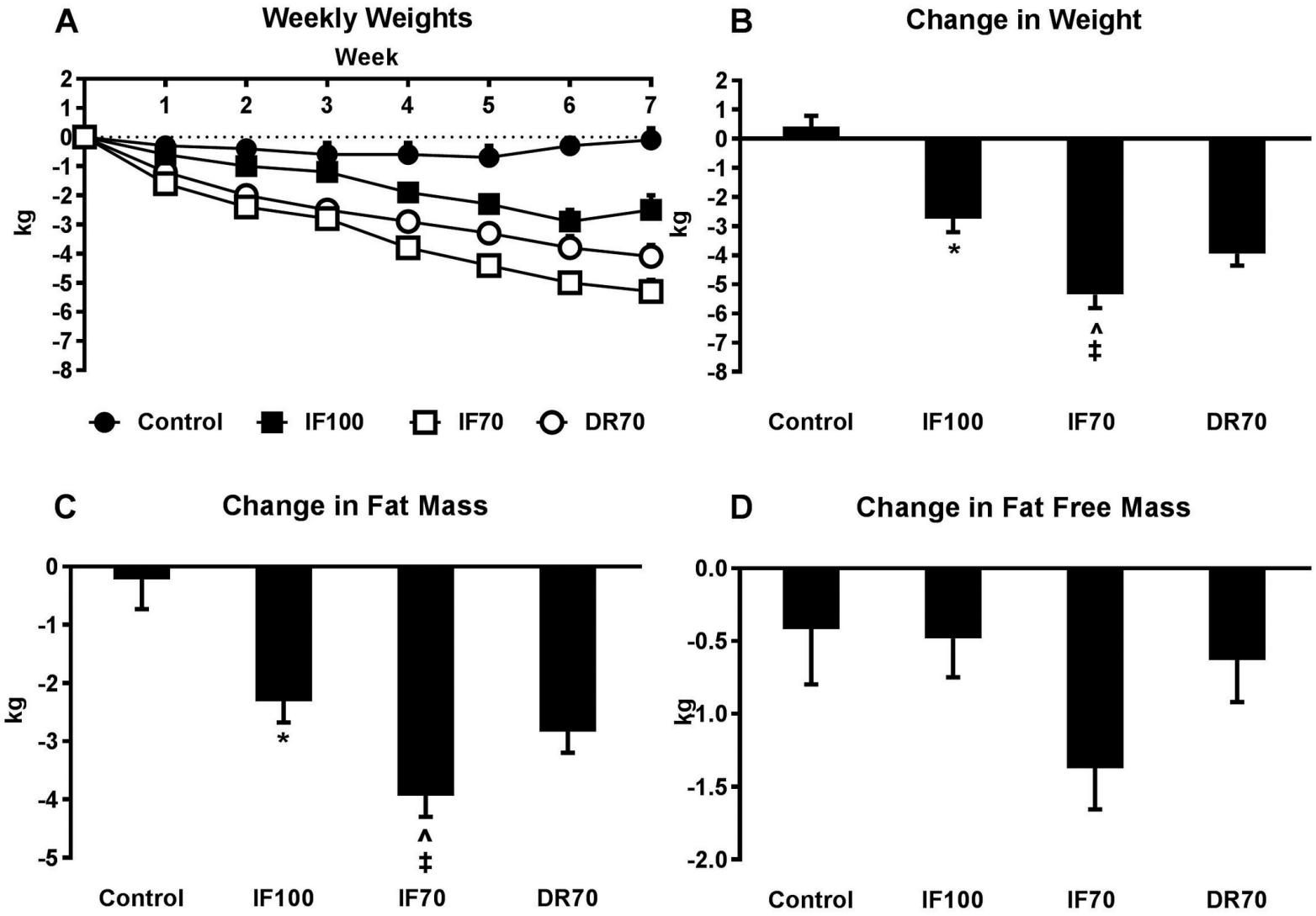


Anton SD, et al. Obesity. 2018 Feb;26(2):254-268.

Effects of Intermittent Fasting on Body Weight and Composition

Slide courtesy of W. Timothy Garvey, MD

- Women (n=88) with overweight (BMI 25-42kg/m^2 nondiabetic)
- DR = dietary restriction 70% of isocaloric
- IF100= Intermittent fasting 100% of isocaloric
- IF70 = Intermittent fasting at 70% of isocaloric

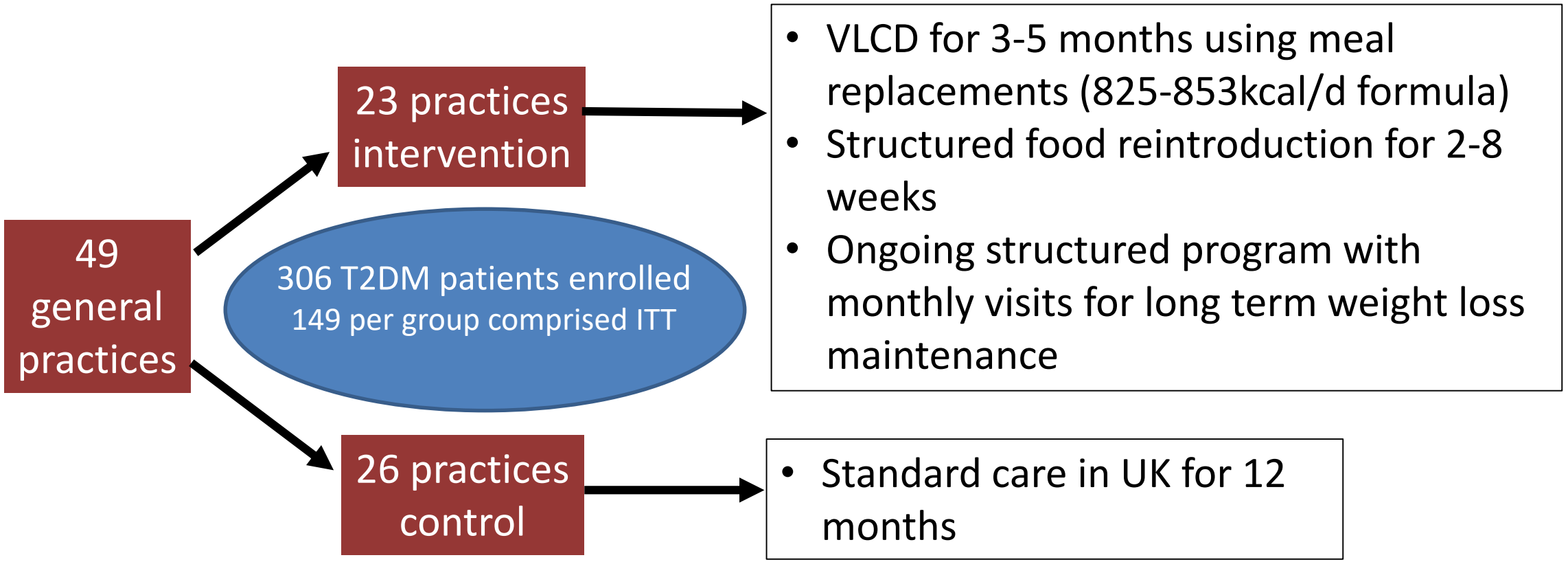


Hutchison AT et al. Effects of Intermittent Versus Continuous Energy Intakes on Insulin Sensitivity and Metabolic Risk in Women with Overweight. 2019; Obesity, 27(1):50-58,

THE LANCET

Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial

Michael EJ Lean*, Wilma S Leslie, Alison C Barnes, Naomi Brosnahan, George Thom, Louise McCombie, Carl Peters, Sviatlana Zhyzhneuskaya, Ahmad Al-Mrabeh, Kieren G Hollingsworth, Angela M Rodrigues, Lucia Rehackova, Ashley J Adamson, Falko F Sniehotta, John C Mathers, Hazel M Ross, Yvonne McIlvenna, Renae Stefanetti, Michael Trenell, Paul Welsh, Sharon Kean, Ian Ford, Alex McConnachie, Naveed Sattar, Roy Taylor*



Lean ME et al. Lancet 391(10120):541-551, 2018

Slide courtesy of W. Timothy Garvey, MD

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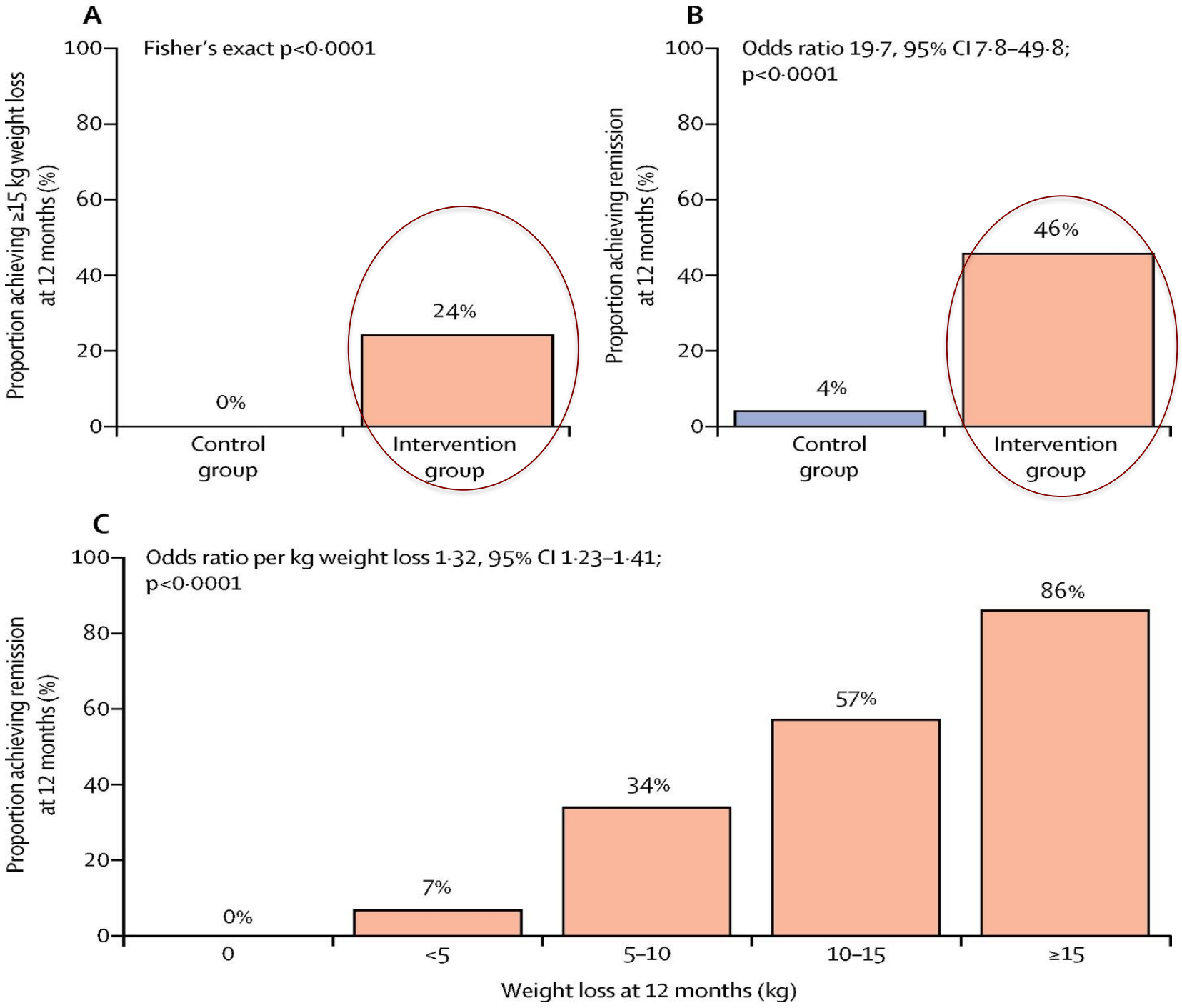
- Recruited individuals: 20-65 years
  Type 2 Diabetes diagnosis within the past 6 years
  BMI 27-45 kg/m^2
  Not on insulin

- Primary Outcomes: Reduction in weight of ≥ 15kg
  Remission of DM (HbgA1c < 6.5% after at least 2 mo off all antidiabetic meds)

Lean ME et al. Lancet 391(10120):541-551, 2018

DiRECT Study:

Primary outcomes and remission of diabetes in relation to weight loss at 12 months



Lean ME et al. Lancet 391(10120):541-551, 2018

Slide courtesy of W. Timothy Garvey, MD

DiRECT Study: Results

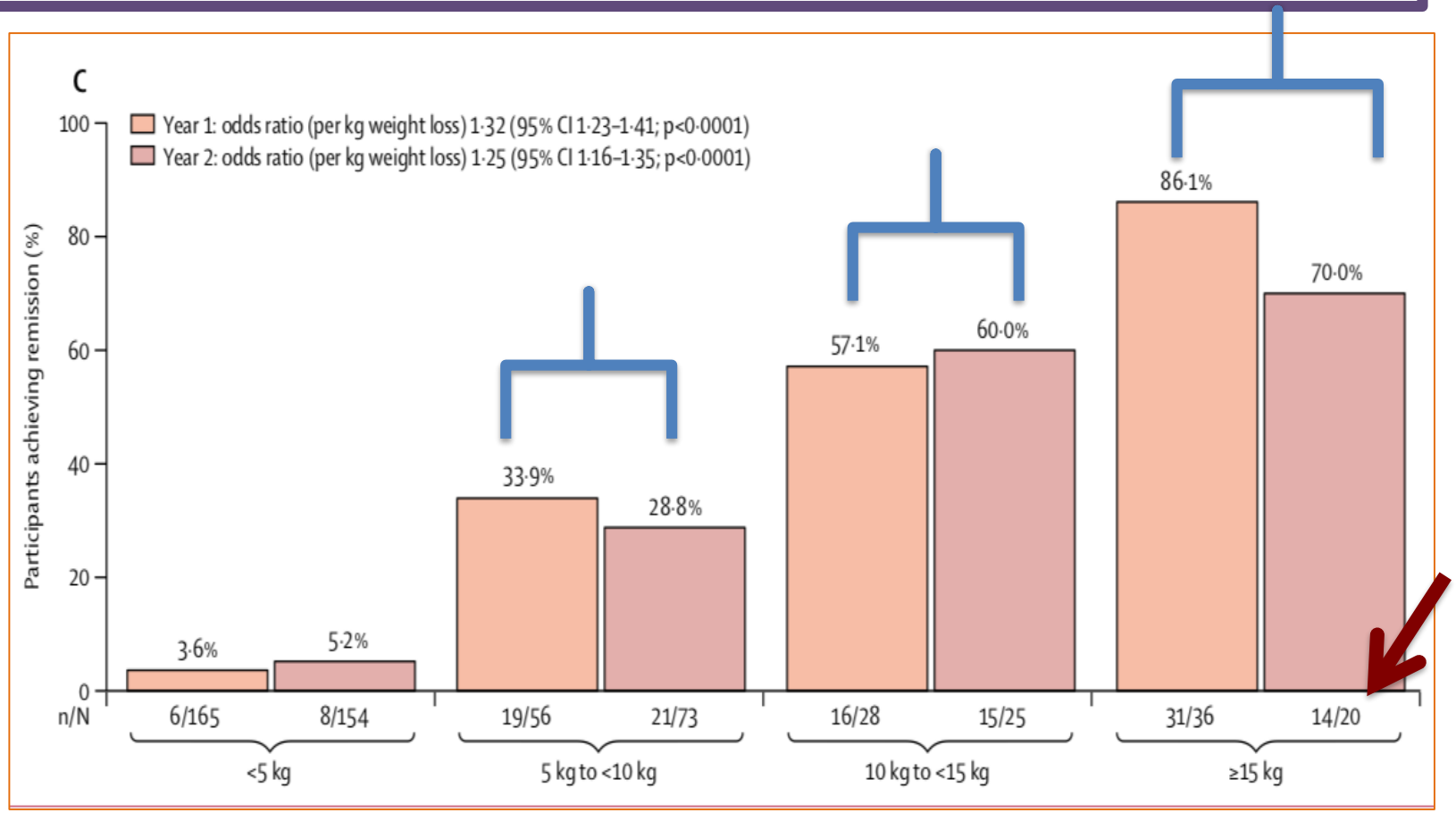
Parameter/Outcome	Intervention Group	Control Group
Weight	↓ 10.0 kg	↓ 1.0 kg
HbA1c	↓ 0.9%	↑ 0.1%
Number Diabetes Medications	↓ 0.8	↑ 0.2
Number Blood Pressure Medications	↓ 0.6	↑ 0.1
Triglycerides	↓ 0.31 mmol/L	↑ 0.09 mmol/L
Quality of Life	↑ 7.2	↓ 2.9

Lean ME et al. Lancet 391(10120):541-551, 2018
Slide courtesy of W. Timothy Garvey, MD

Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial

Michael E J Lean, Wilma S Leslie, Alison C Barnes, Naomi Brosnahan, George Thom, Louise McCombie, Carl Peters, Sviatlana Zhyzhneuskaya, Ahmad Al-Mrabeh, Kieren G Hollingsworth, Angela M Rodrigues, Lucia Rehackova, Ashley J Adamson, Falko F Sniehotta, John C Mathers, Hazel M Ross, Yvonne McIlvenna, Paul Welsh, Sharon Kean, Ian Ford, Alex McConnachie, Claudia-Martina Messow, Naveed Sattar, Roy Taylor**

- Aim was to assess the durability of the intervention effect at 2 years
- Intention to treat population consisted of 149 participants

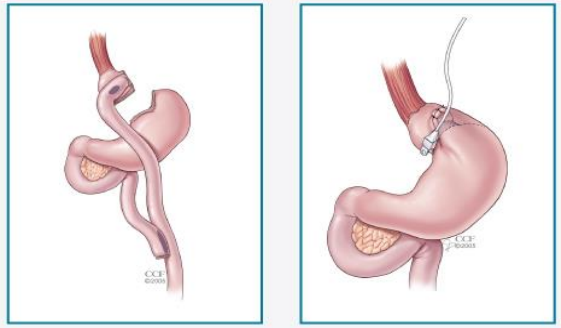


Lean ME et al. Lancet May 2019; 7:344-55

Medical Devices for Weight Loss

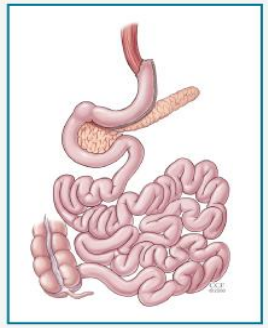
Surgical and Endoscopic Therapies for Treatment of Obesity

SURGICAL PROCEDURE

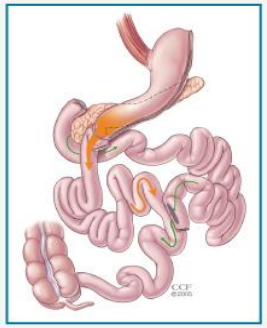


Gastric Bypass

Band



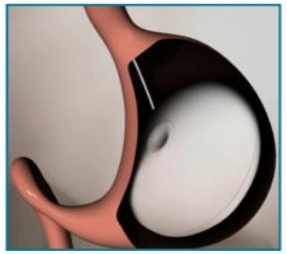
Sleeve



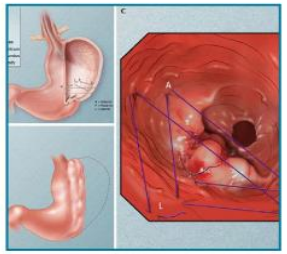
DS

NON-SURGICAL PROCEDURE

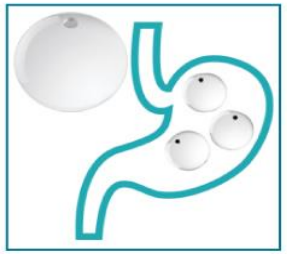
Aspire Assist



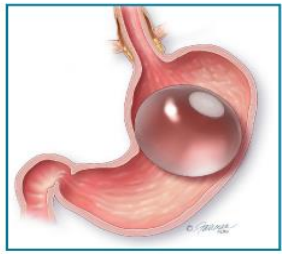
Ellipse Balloon



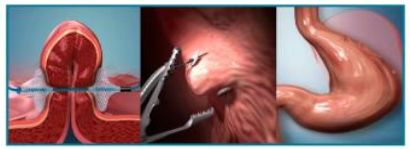
Endoscopic Sleeve Gastoplasy Apollo Device



Obalon Balloon

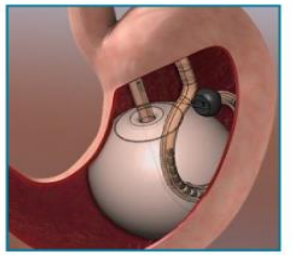


Orbera

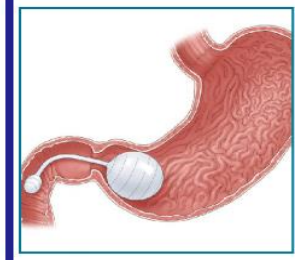


POSE Procedure

Reshape



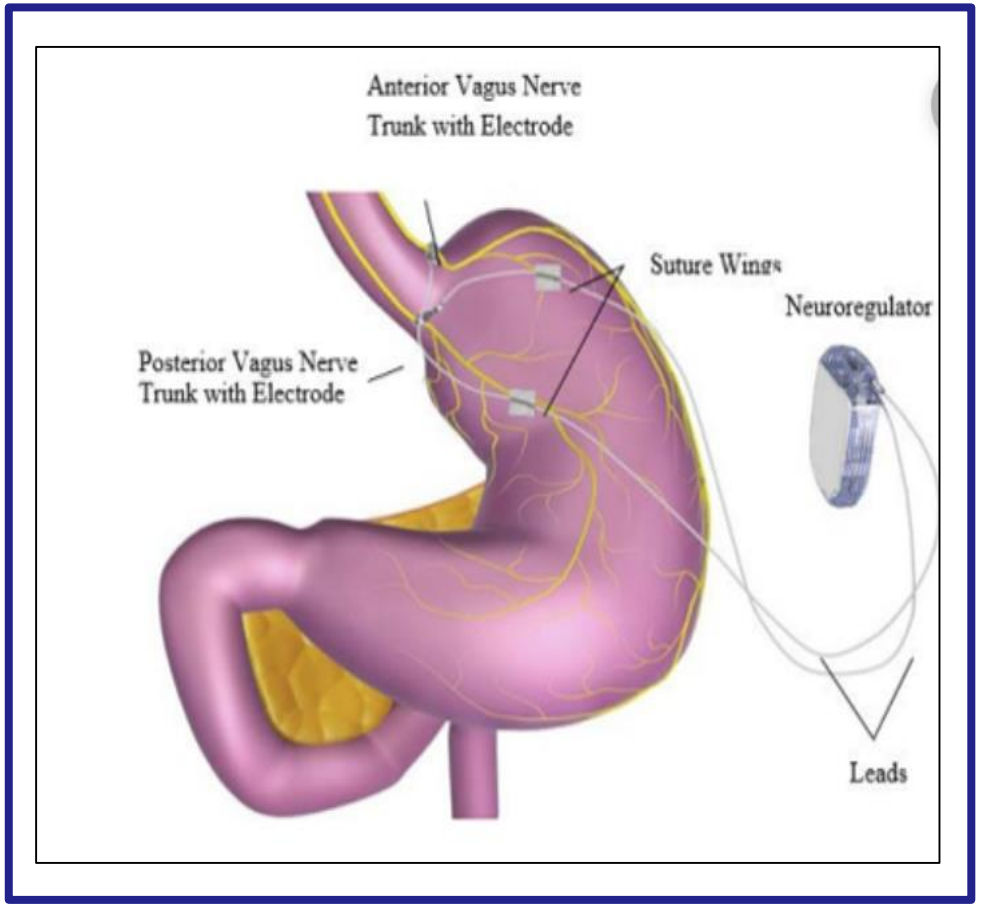
Spatz Balloon



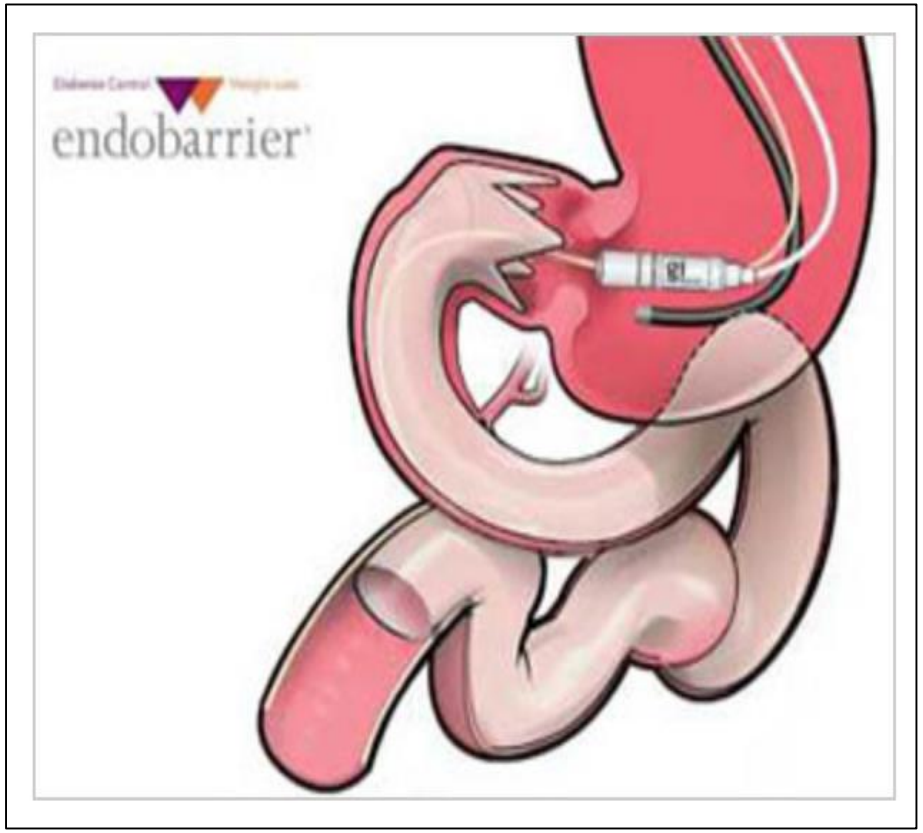
Transpyloric Shuttle

2019

Slide courtesy of W. Timothy Garvey, MD



VBLOC Maestro Rechargable System[1]



Endobarrier Sleeve (Duodenal Endoluminal Sleeve)[2]

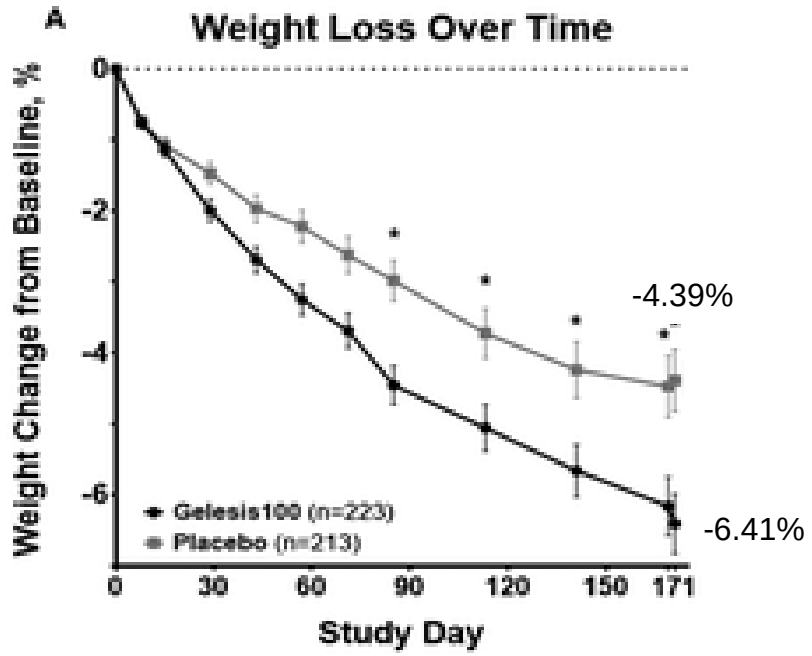
[1]https://www.obesityhelp.com/articles/should-vbloc-neurometabolic-therapy-ever-be-performed

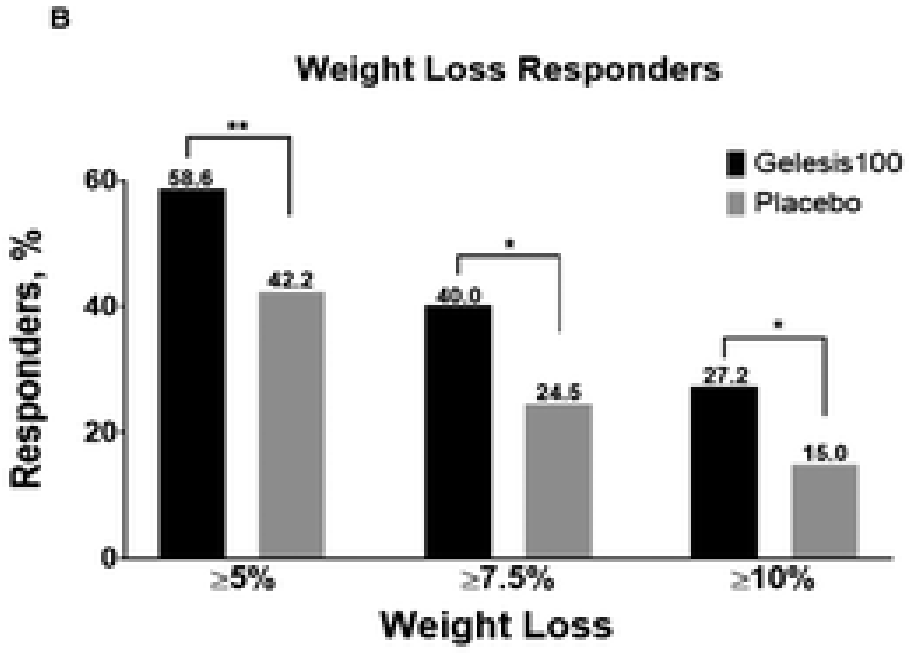
[2]http://www.weightlosssurgeryscotland.com/mobile/services/treatment-prices/duodenal-liner-sleeve

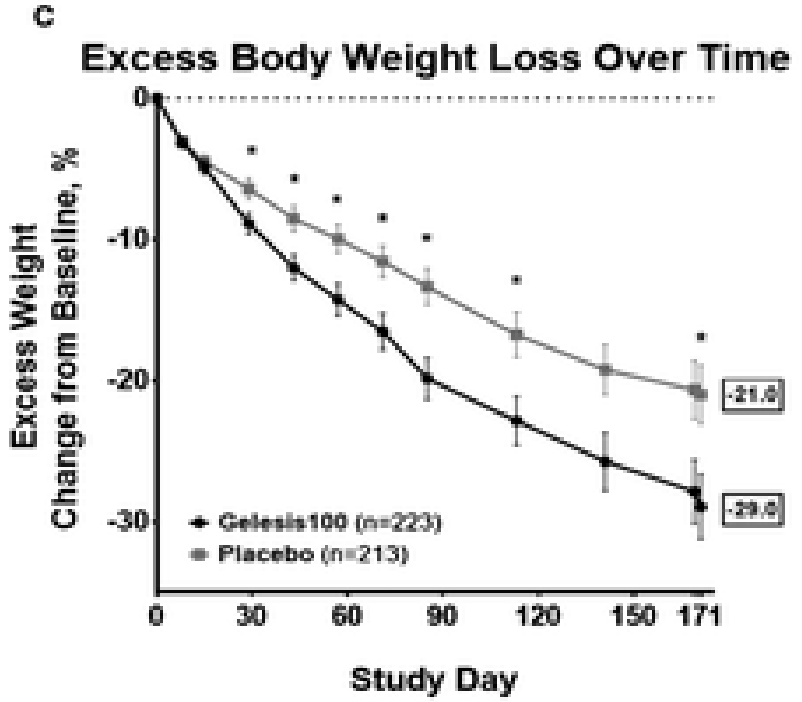
Oral Hydrogel Approach to Treatment of Obesity: Gelesis 100

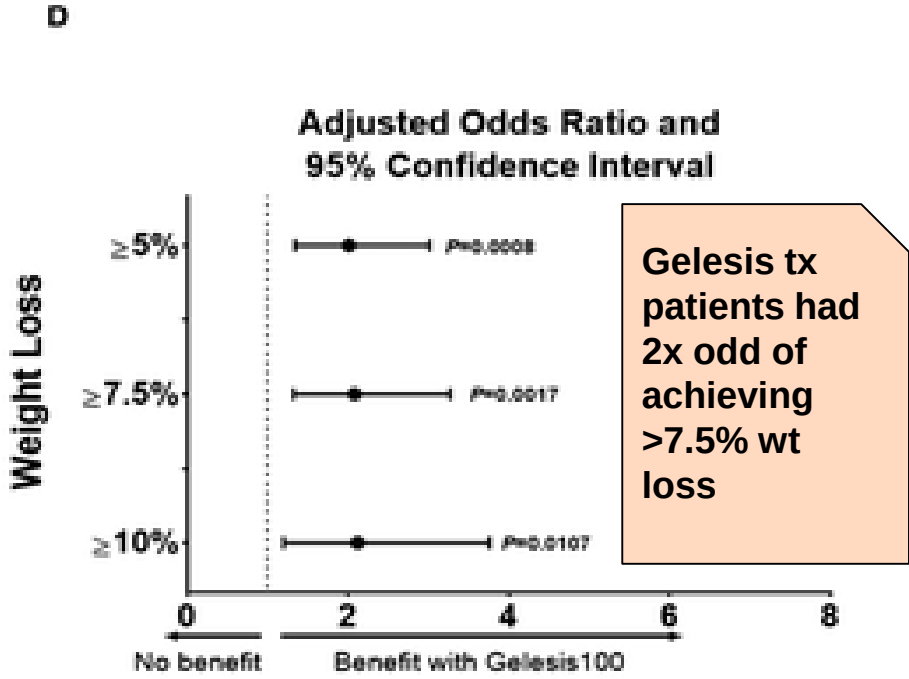
FDA Cleared April 2019

- GLOW study
- Multicenter, randomized, double blind
- 24 weeks
- BMI ≥ 27-40kg/m^2







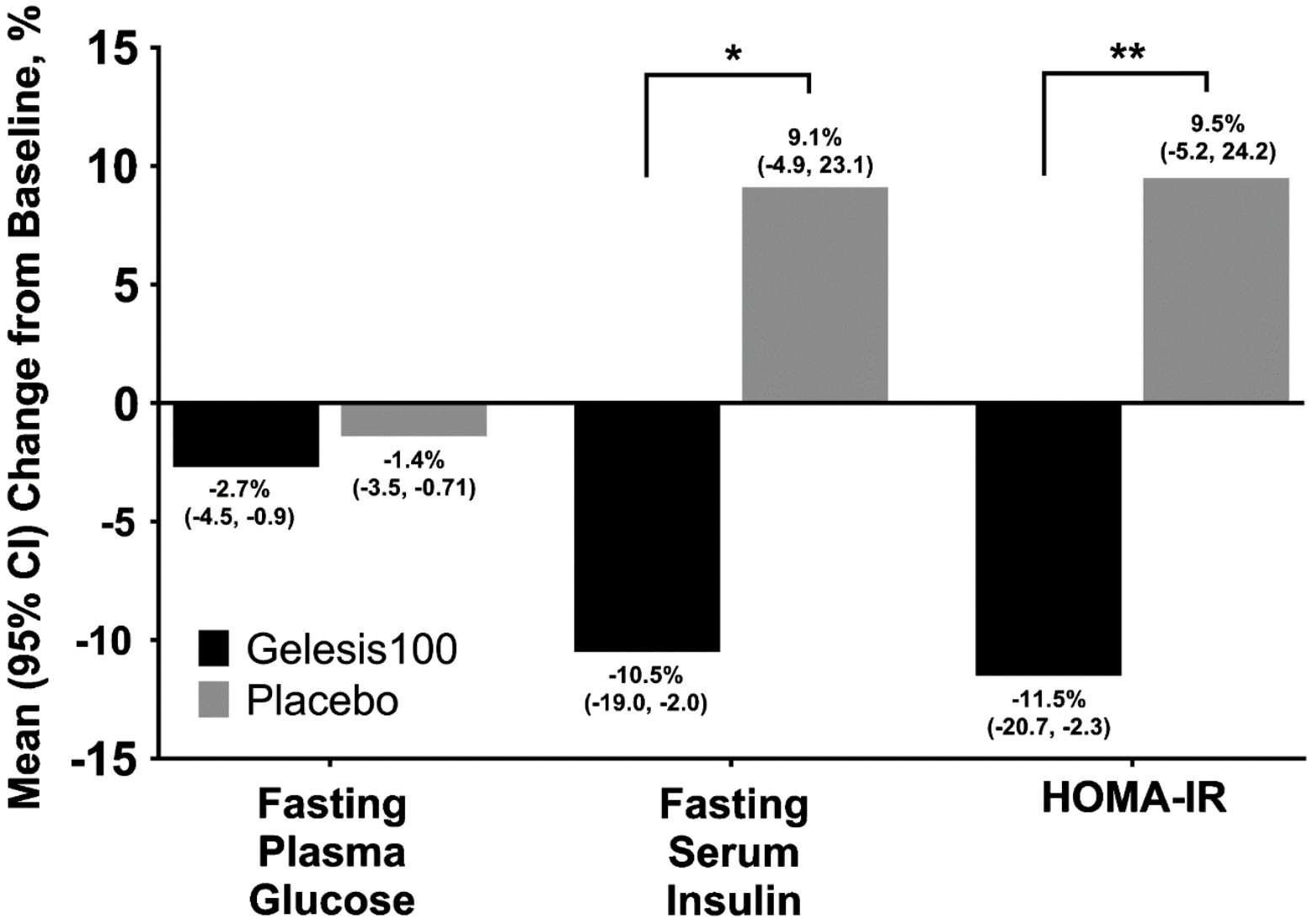


Gelesis tx patients had 2x odd of achieving >7.5% wt loss

Greenway FL et al. A Randomized, Double-Blind, Placebo-Controlled Study of Gelesis100: A Novel Nonsystemic Oral Hydrogel for Weight Loss. Obesity. 27(2):205-216, 2019

Slide modified from W. Timothy Garvey, MD

Oral Hydrogel Approach to Treatment of Obesity: Gelesis 100



Greenway FL et al. A Randomized, Double-Blind, Placebo-Controlled Study of Gelesis100: A Novel Nonsystemic Oral Hydrogel for Weight Loss. Obesity. 27(2):205-216, 2019

Slide courtesy of W. Timothy Garvey, MD

Pharmacotherapy

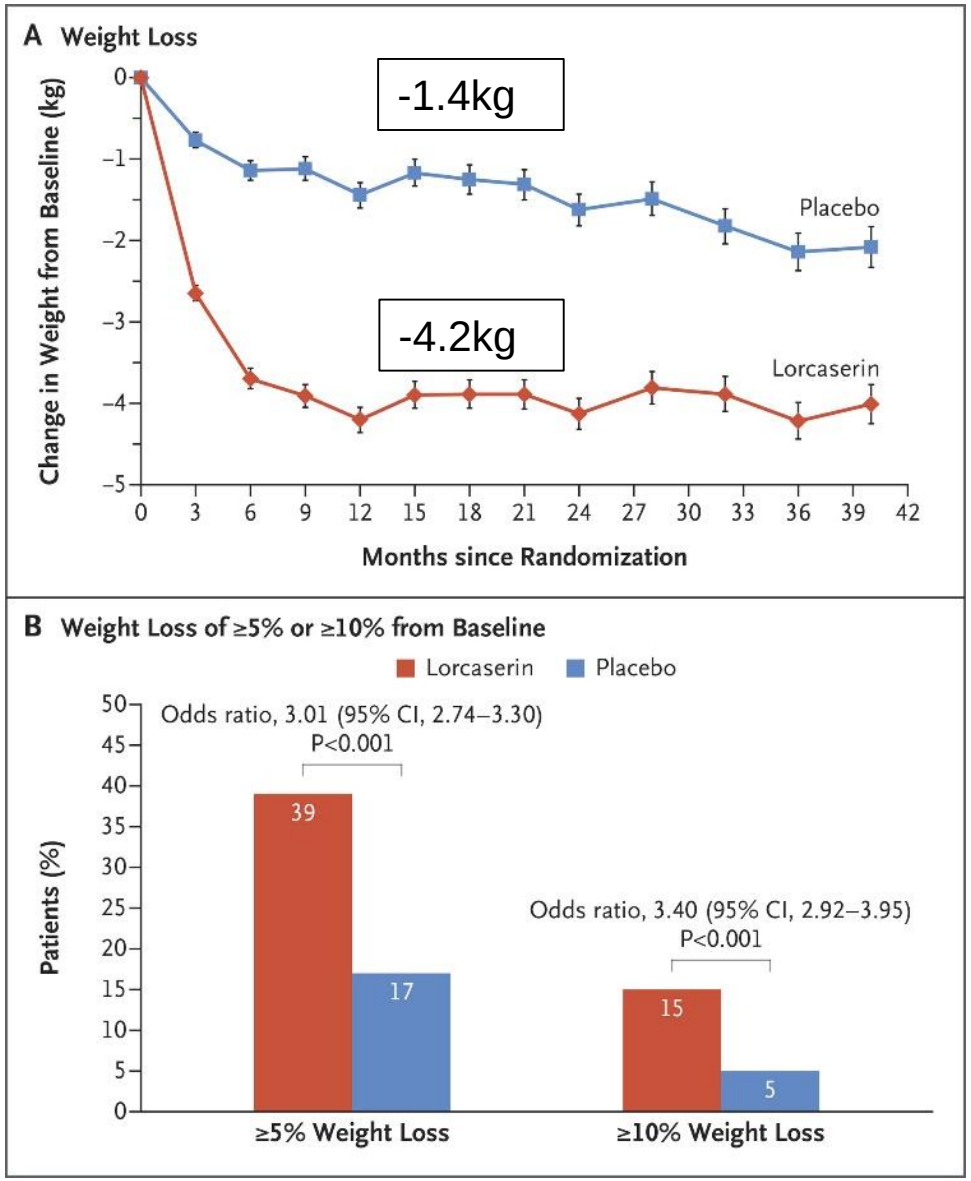
Obesity Pharmacotherapy

Agents	Action	Approval
Previously available		
Phentermine	• Sympathomimetic	• 1959
Orlistat	• GI lipase inhibitor	• 1997
Recently Approved		
Phentermine/ Topiramate ER	• Sympathomimetic/Anticonvulsant (GABA receptor modulation?)	• Approved, Summer 2012
Lorcaserin	• 5-HT_{2C} serotonin receptor agonist	• Approved, Summer 2012
Naltrexone ER/ Bupropion ER	• Dopamine/noradrenaline reuptake inhibitor/Opioid receptor antagonist	• Approved, September 2014
Liraglutide 3 mg	• GLP-1 receptor agonist	• Approved, December 2014

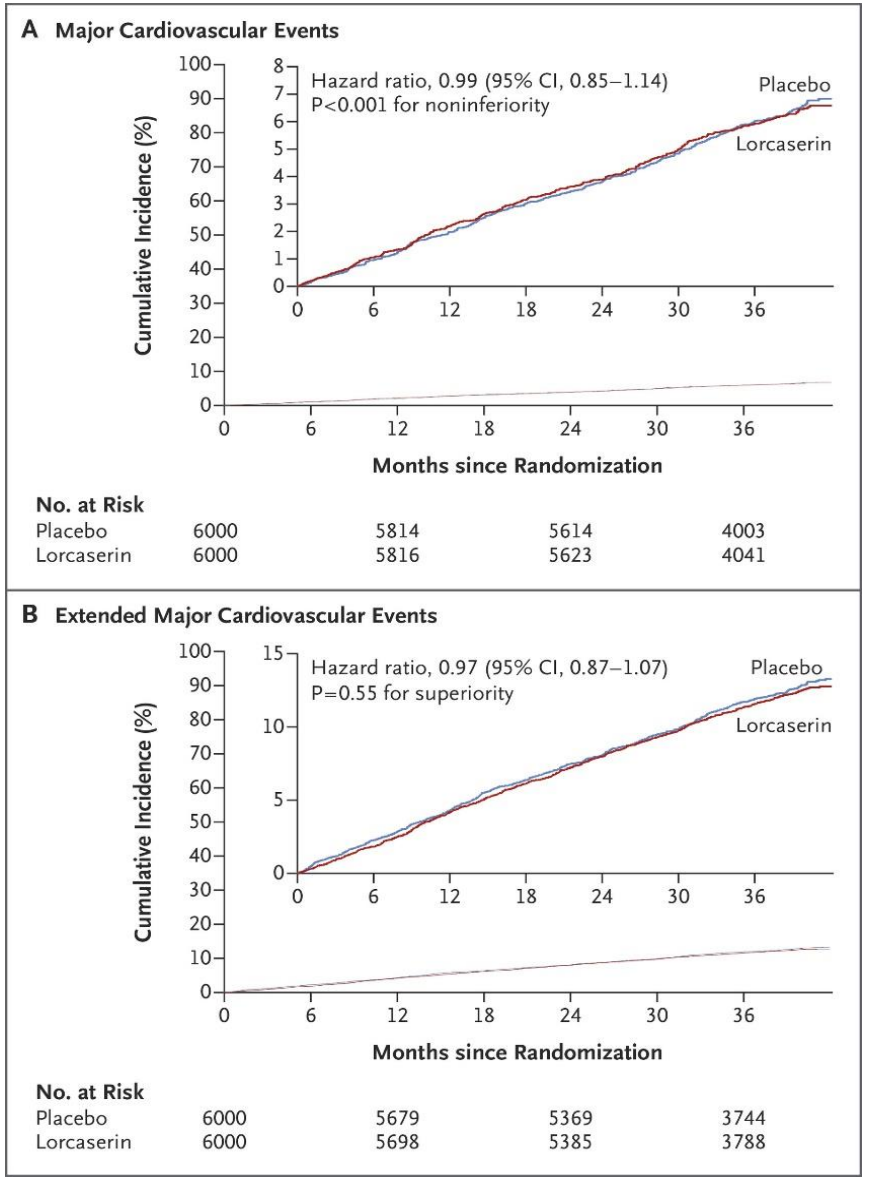
US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.

Slide courtesy of W. Timothy Garvey, MD

Cardiovascular Outcome Study for Lorcaserin: CAMELLIA



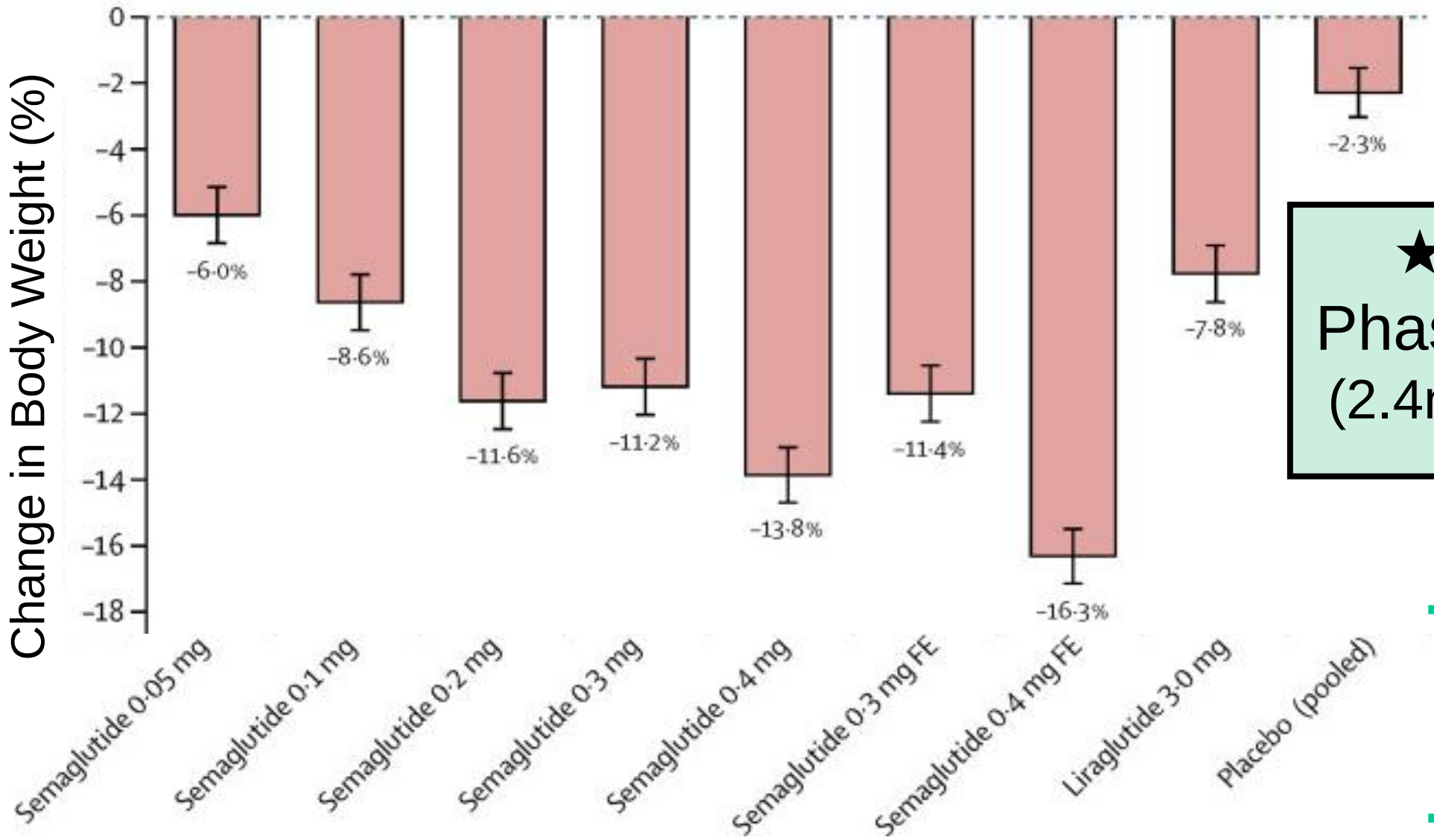
- 12,000 overweight or obese patients
- 3.3 years
- With atherosclerotic CVD or multiple risk factors
- Lorcaserin 10 mg bid or placebo
- 3 point MACE.



Bohula EA et al. Cardiovascular Safety of Lorcaserin in Overweight or Obese PatientsN Engl J Med 2018; 379:1107-1117

Slide courtesy of W. Timothy Garvey, MD

Semaglutide for Weight Loss: Dose Ranging for Efficacy and Safety



★Now in Phase 3 study (2.4mg weekly)

O'Neil PM et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity Lancet. 2018; 392:25-31.

Slide modified from W. Timothy Garvey, MD

SELECT Study - Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity

- International study to enroll 17,500 patients, begin Oct 2018 and end Sept 2023
- Semaglutide 2.4 mg/week VS placebo
- Time to first occurrence of CV death, non-fatal MI, non-fatal stoke (3point MACE)

Inclusion Criteria:

1. Age ≥ 45 years; BMI ≥ 27 kg/m^2
2. Established CVD as evidenced by prior MI; or symptomatic peripheral arterial disease (PAD)

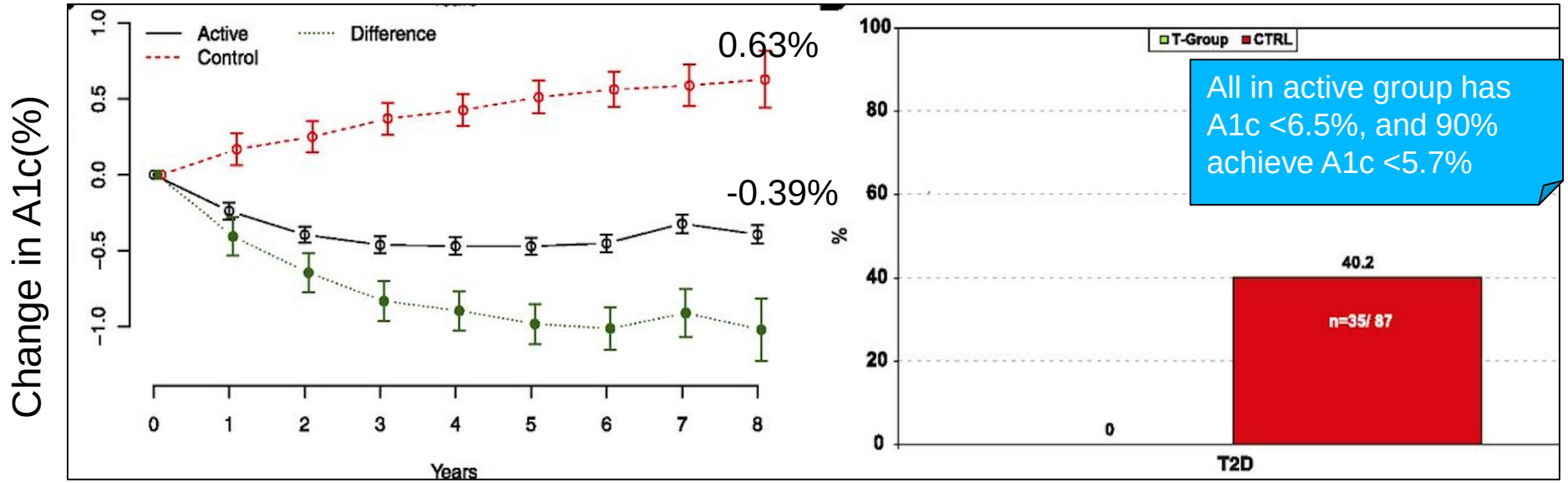
Exclusion Criteria:

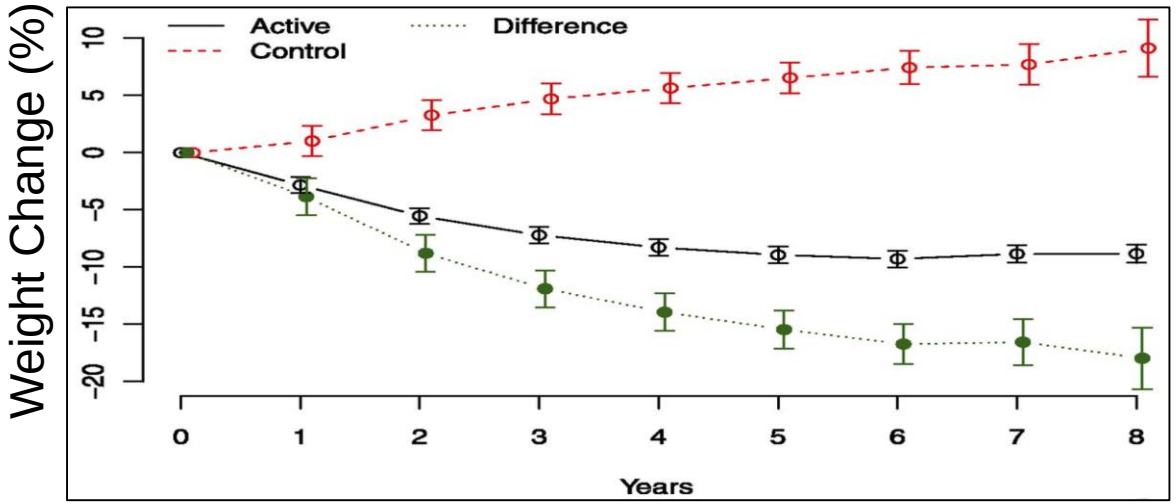
1. CVD events within past 60 days.
2. HbA1c ≥ 6.5%
3. History of T1DM or T2DM

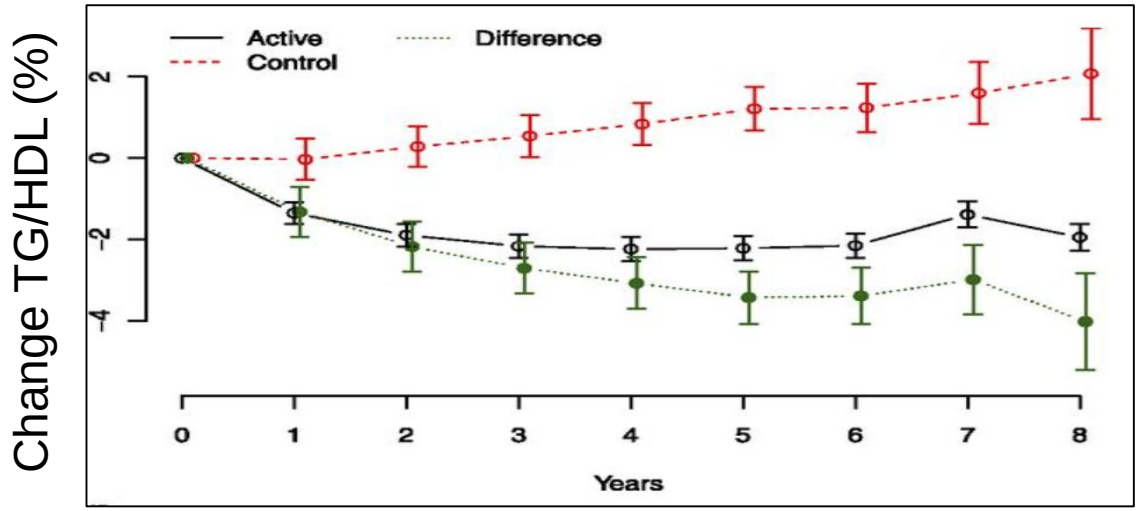
https://clinicaltrials.gov/ct2/show/study/NCT03574597?term=select&cond=obesity&rank=2
Slide courtesy of W. Timothy Garvey, MD

Testosterone Therapy in Men With Hypogonadism Prevents Progression From Prediabetes to Type 2 Diabetes

- 316 men with prediabetes and hypogonadism
- 8 year prospective cohort study
- Aging Males Symptoms Scale
- Decreased HbA1c,lipids,weight, and symptoms
- Diabetes prevention







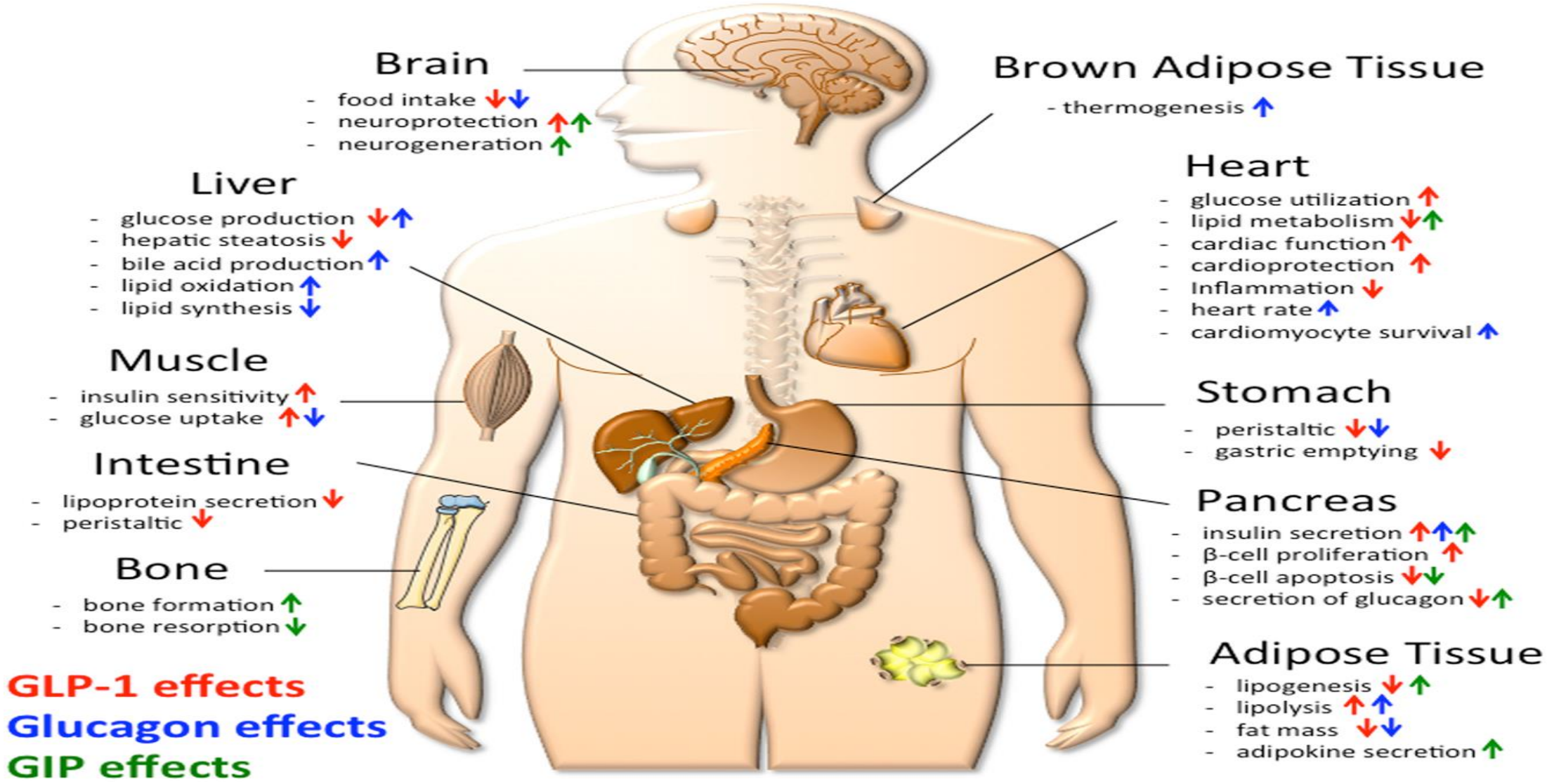
Yassin A, Haider A, Haid KS, Caliber M, Doros G, Saad F, Garvey WT. Diabetes Care 2019; Epub Mar 12; dc182388
Slide courtesy of W. Timothy Garvey, MD

Emerging Pharmacotherapy for Obesity

- Long-acting high-dose GLP-1 receptor agonists
- MC4R Agonist
- Y5 Receptor Inhibitor
- Zonisamide/bupropion
- Triple monoamine reuptake inhibitor (dopamine/NE/serotonin)
- Cannabinoid 1 receptor blocker
- Anti-gherlin vaccine
- Leptin analog
- GDF15 mimetics
- PYY analog
- GPR55 and GPR 40 receptor (GPCR) modulation
- Oxyntomodulin
- Dual GLP-1/glucagon receptor agonist
- Triple agonist GLP-1/glucagon/GIP
- GIP analog
- Amylin mimetics
- Dual amylin and calcitonin receptor agonist
- Methionine amino-peptidase 2 inhibitor
- Neuregulin-4
- Farnesoid X receptor agonist
- FGF21 receptor agonists
- FGF4 inhibitor
- AMPK activators
- Adenovirus 36 vaccine
- Lipase inhibitor
- Gastric Hydrogels

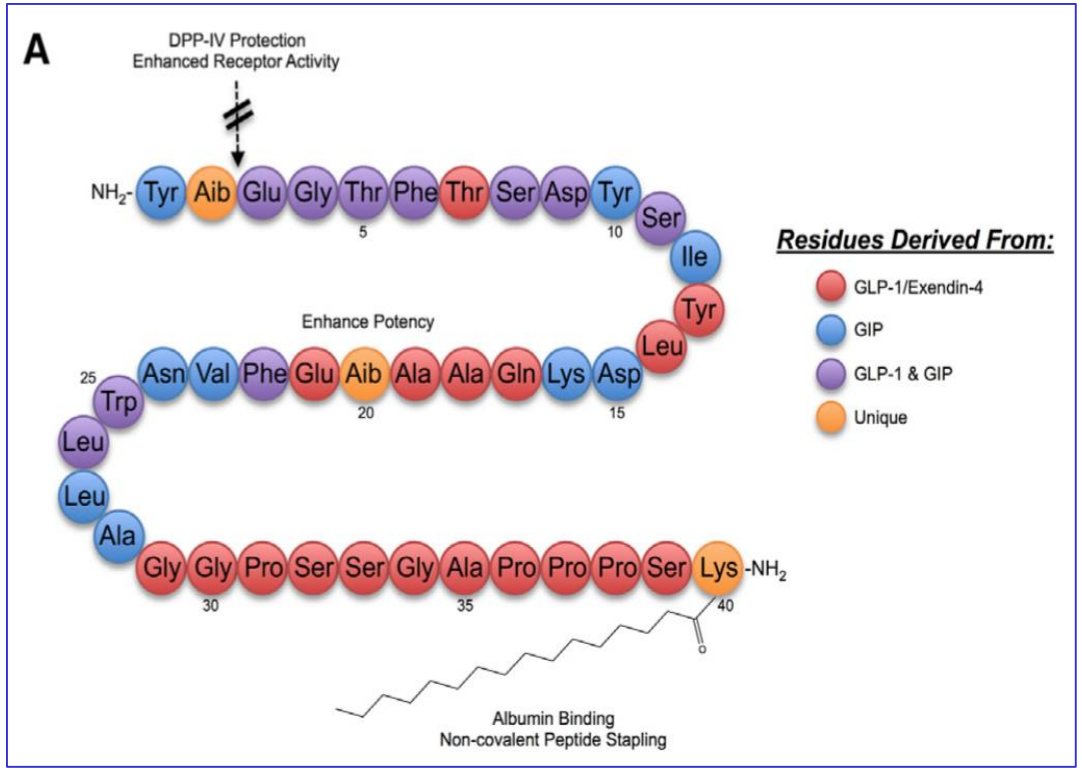
Slide courtesy of W. Timothy Garvey, MD

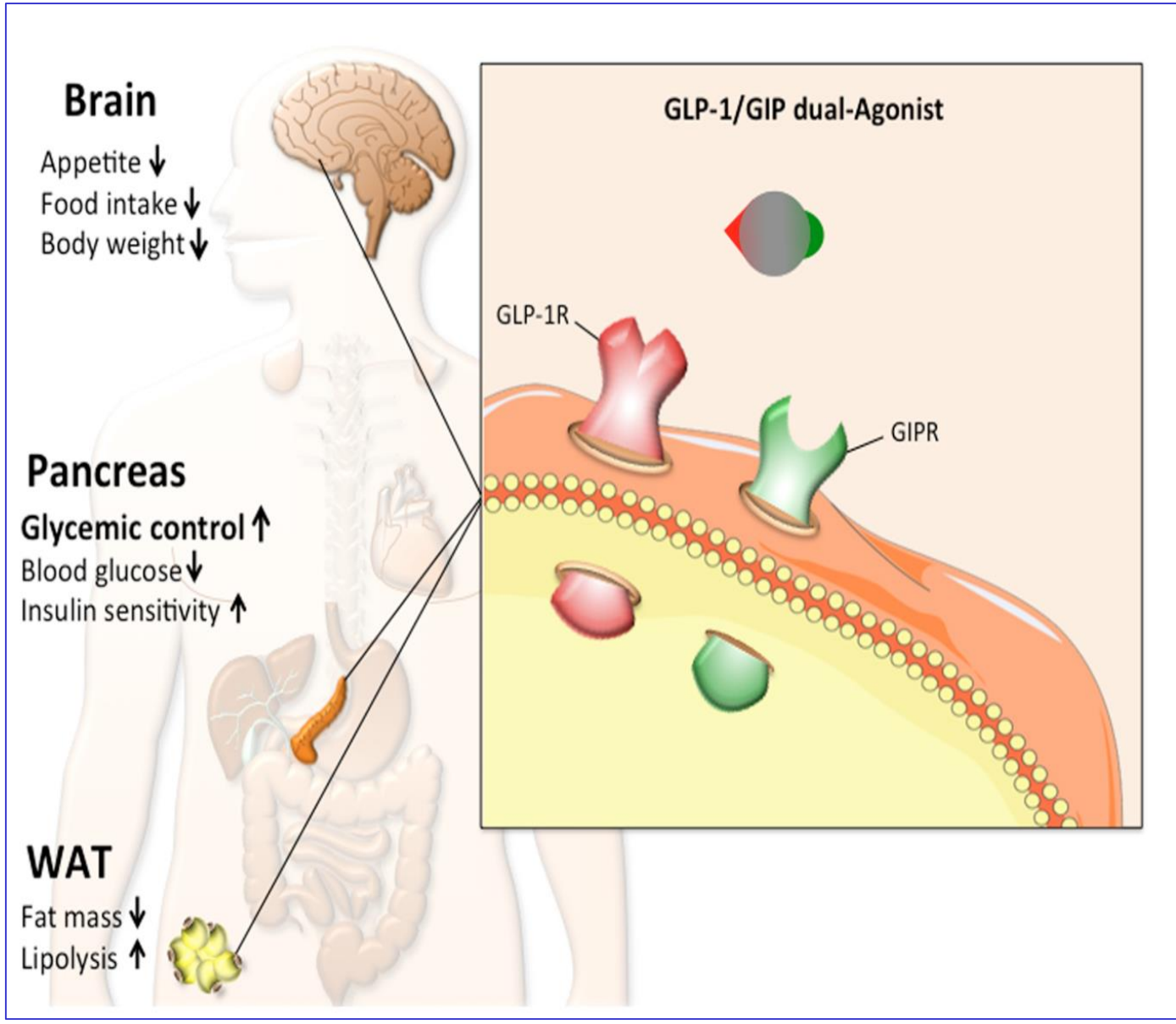
Single Molecule –Dual/triple action



Brandt, S., Kleinert, M., Tschöp, M., & Müller, T. (2018). Are peptide conjugates the golden therapy against obesity?, *Journal of Endocrinology*, *238*(2), R109-R119. Retrieved Oct 2, 2019, from https://joe.bioscientifica.com/view/journals/joe/238/2/JOE-18-0264.xml

Dual agonist



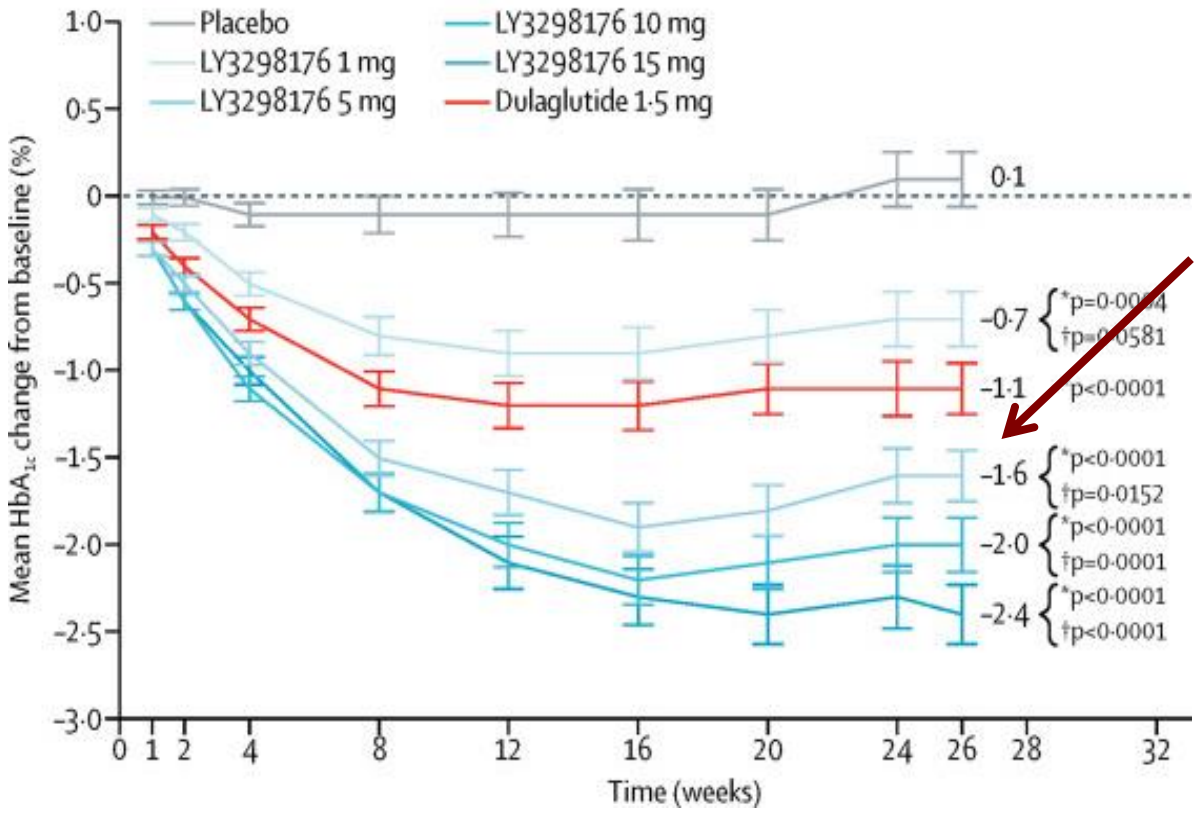


https://www.cell.com/cell-metabolism/pdf/S1550-4131(16)30307-2.pdf

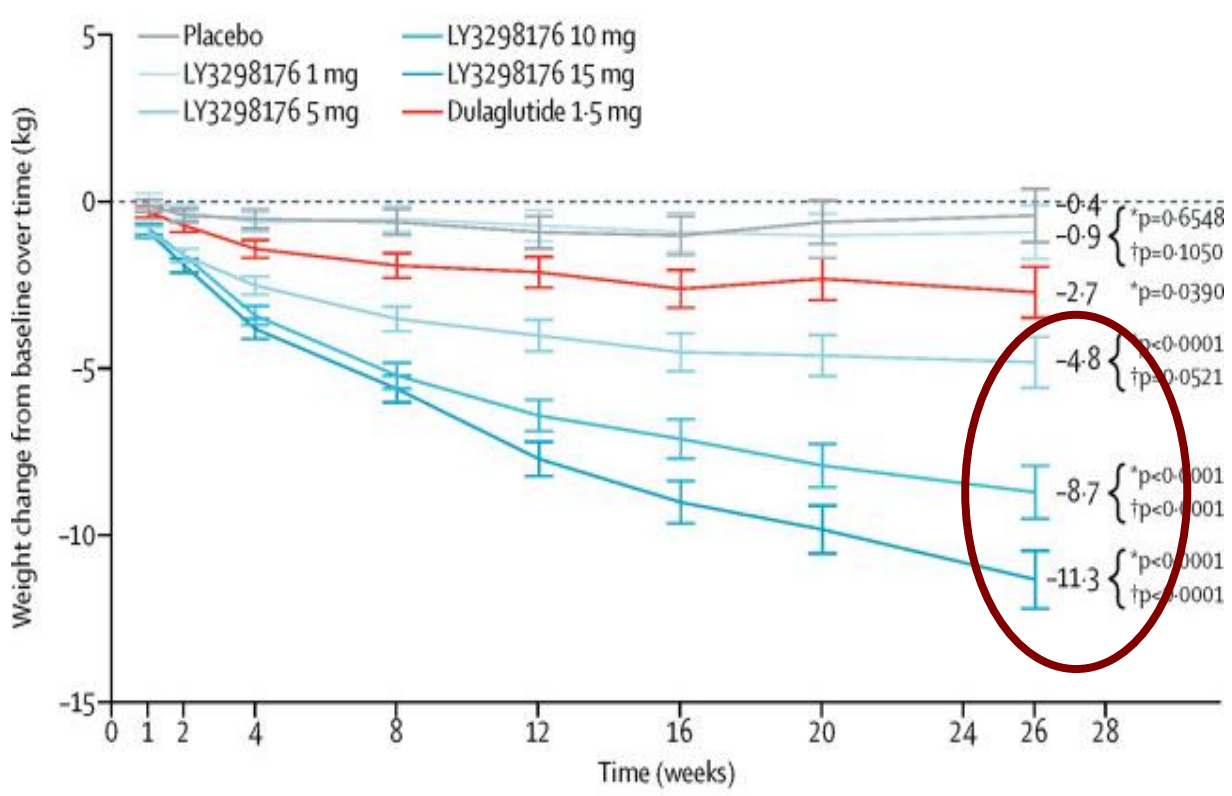
http://joe.endocrinology-journals.org
https://doi.org/10.1530/JOE-18-0264

Effects of Dual GIP / GLP-1 Agonist (LY3298176) on HbA1c and Weight in T2DM: Dose Ranging and Comparison with Dulaglutide

HbA1c (%)



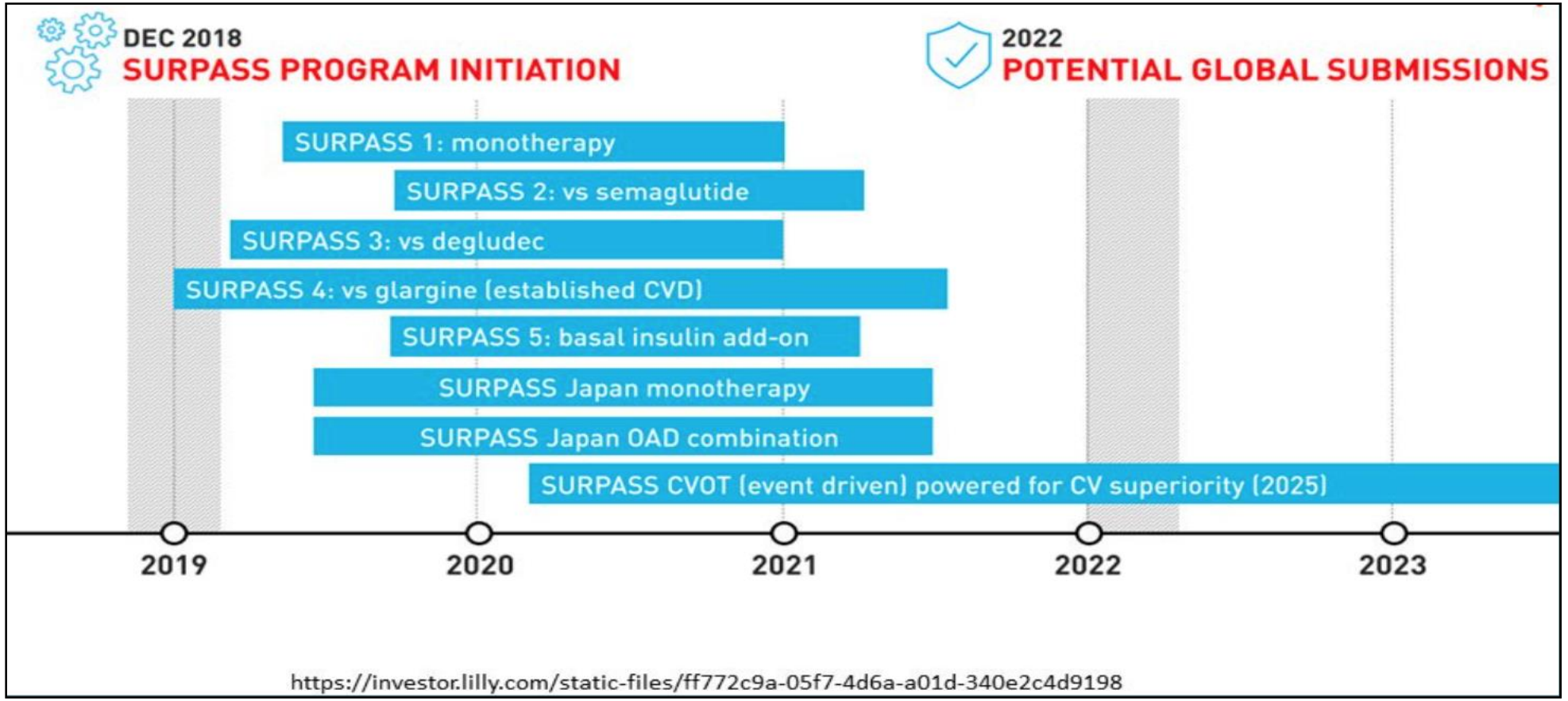
Body Weight (kg)



Frias JP et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. Frias JP et al. Lancet. 2018 Nov 17;392(10160):2180-2193

Slide courtesy of W. Timothy Garvey, MD

Tirzepatide Phase 3: Type 2 Diabetes Clinical Program



T2DM Phase 3 start 2018
Obesity Phase 3 start 2019
NASH Phase 2 start 2019

https://twitter.com/DanielJDrucker/status/1075377630839480320

Key Points

- Recognize there is a variety of eating patterns that are acceptable for the management of diabetes mellitus, as well as acknowledging low carb diet as a viable option for patients with Type 2 DM
- Identify FDA-approved non surgical devices for weight reduction and maintenance
- Understand new concepts pharmacotherapy for the management of obesity
- Be familiar with cardiovascular outcome results in anti-obesity medications


Thank You !