Obesity Management and Treatment in Patients with Type 2 Diabetes

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Disclosure

Advisory Board: Biophytis; Eli Lilly; Keros; Pfizer Pharmaceuticals; Wave; Zyversa

Consultant: AstraZeneca

Data Safety Monitory Board: Advarra

Research Grant: Amgen; Cleerly; Ionis Pharmaceuticals; Kaneka; Novartis

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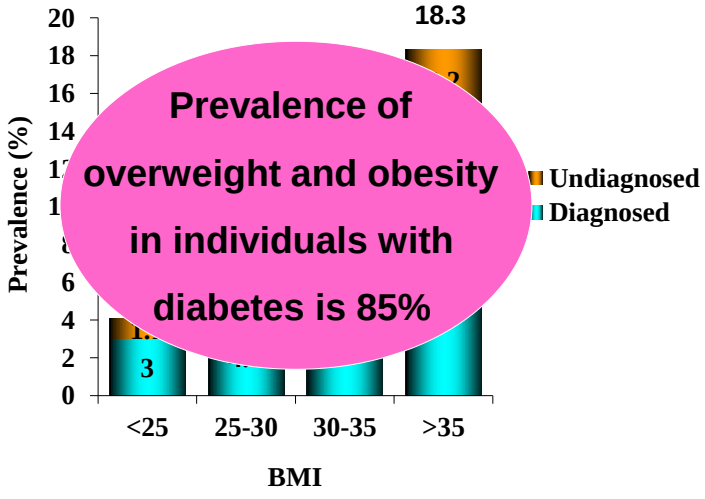
Objectives

- Examine the impact of obesity on diabetes
- Describe the effects of weight loss on diabetes and related outcomes
- Review weight management treatment options in patients with diabetes

3

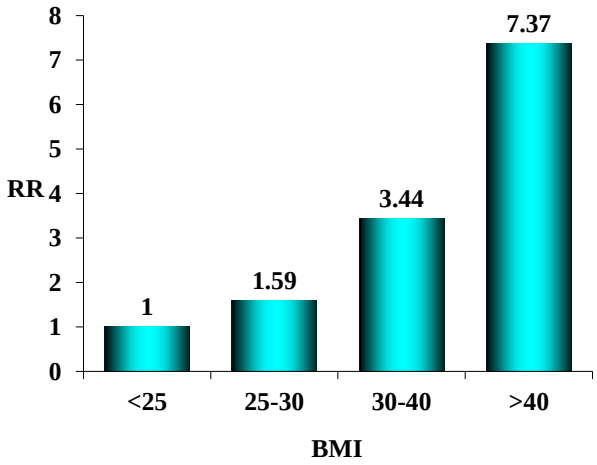
Prevalence of Diabetes According to BMI



Gregg, et al *Diabetes Care* 27:2806, 2004

4

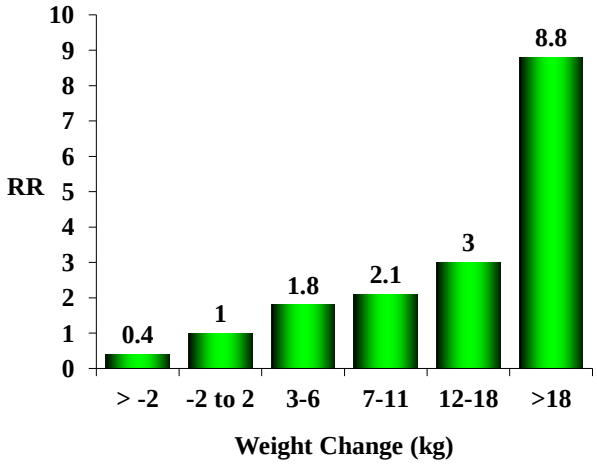
BMI and Relative Risk of Developing Diabetes



Mokdad, et al. *JAMA* 289:76, 2003

5

Weight Gain and Relative Risk of Developing Diabetes



Koh-Banerjee et al. *Am J Epidemiol* 159:1150, 2004

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Impact of Obesity on Diabetes

- Insulin Resistance
- “More difficult to treat”
- Gestational Diabetes
- Dyslipidemia
- Hypertension
- Cardiovascular Disease
- Mortality
- Others complications of obesity

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But Does Weight Loss Improve Outcomes in People with Diabetes?

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Weight Loss and Mortality in Diabetes

- "Intentional weight loss" is associated with a 25% reduction in total 12-year mortality among Individuals with overweight and diabetes

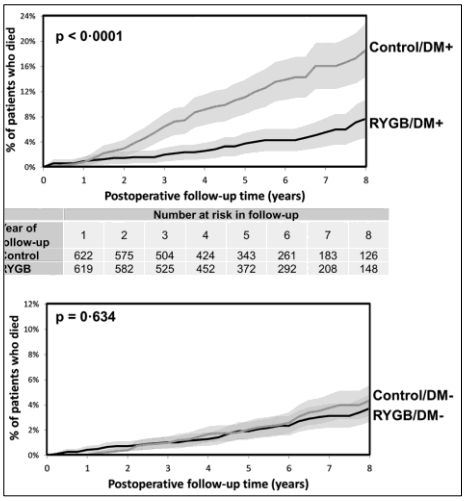
  Williamson, et al. *Diabetes Care,* 2000

- Just "trying to lose weight" is associated with a 23% reduction in 9-year mortality in adults with overweight and diabetes

  Gregg, et al. *Diabetes Care,* 2004

9

Mortality After Roux-en-Y Gastric Bypass in Patients With and Without Diabetes



Number at risk in follow-up

Year of follow-up	1	2	3	4	5	6	7	8
Control	622	575	504	424	343	261	183	126
RYGB	619	582	525	452	372	292	208	148

Lent et al. *Diabetes Care* 40:1379, 2017.

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Other Beneficial Effects of Weight Loss on Diabetes-Related Outcomes

- Diabetes prevention
- Improved glycemic control and resolution
- Improved insulin sensitivity
- Improved lipids
- Improved blood pressure
- Reduced cardiovascular disease
- Improved quality of life
- Improved costs of care

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We Should Thus Be More Aggressive in Recommending Weight Loss to Our Patients, But What Should Our Approach Be?

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American Diabetes Association
Standards of Medical Care in Diabetes

8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes–2025

*American Diabetes Association Professional Practice Committee**

Diabetes Care 2025;48(Suppl. 1):S167–S180 | https://doi.org/10.2337/dc25-S008

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Standards of Care in Diabetes 2025
Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes

- Use person-first and centered, nonjudgmental language fostering collaboration.
- Make and document the diagnosis of obesity (measure height, weight, BMI).
- Monitor weight and BMI at least annually and every 3 months during active weight management.
- Accommodations should be made to provide privacy during anthropometric measurements
- In people with diabetes and overweight/obesity, obesity management should represent a **primary goal** of treatment along with glycemic management.
- Individualize initial treatment approaches for obesity based on the person's medical history, life circumstances, preferences, and motivation. Consider combining treatment approaches if appropriate.

Diabetes Care, Suppl 1, 2025.

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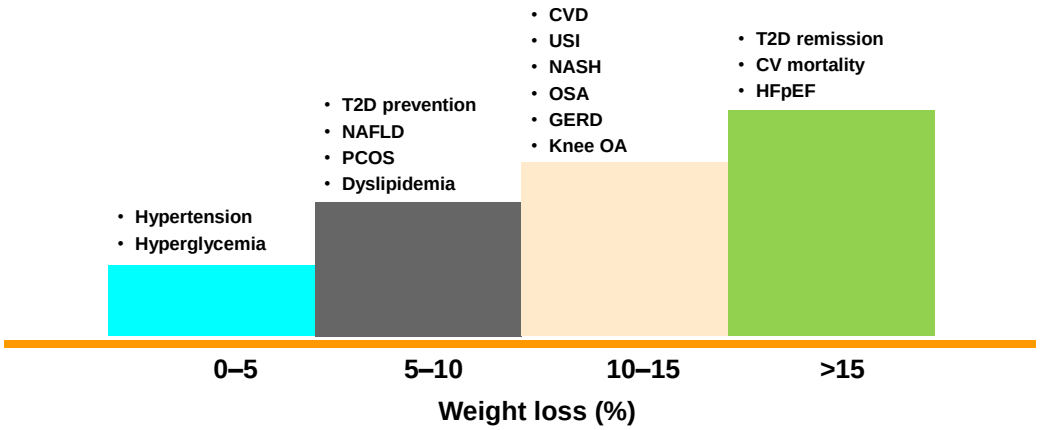
Greater Weight Loss Improves More Obesity-Related Complications



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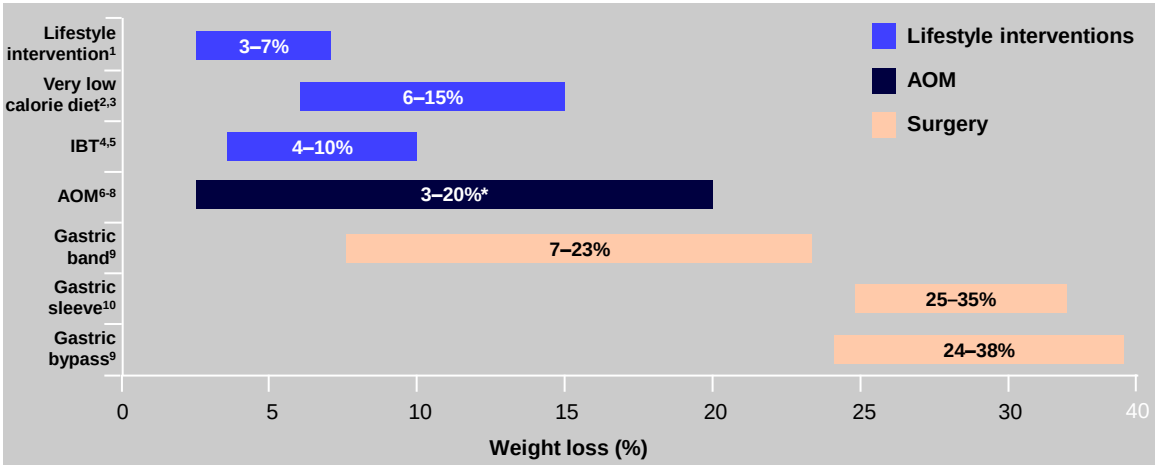
Efficacy of Existing Weight Loss Interventions



*Based on mean weight loss achieved by the completer populations in the largest phase 3 clinical trial of each respective product's clinical development program as reported in the AACE Guidelines (2016).
AACE, American Association of Clinical Endocrinology; AOM, anti-obesity medications; IBT, intensive behavioral therapy.
1. le Roux CW et al. Lancet 2017;389:1399–409; 2. Lean ME et al. Lancet 2018;391:541–51; 3. Tsai AG and Wadden TA. Obesity 2006;14:1283–93; 4. Wadden TA et al. Obesity 2011;19:1987–98; 5. Wadden TA et al. Obesity 2019;27:75–86; 6. Garvey WT et al. Endocr Pract 2016;22(Suppl 3):1–203; 7. Tak YJ and Lee SY. Curr Obes Rep 2021;10:14–30; 8. 10. Novo Nordisk. Wegovy (semaglutide). Package Insert. Available at: https://www.novo-pi.com/wegovy.pdf. Accessed August 2022; 9. Courcoulas AP et al. JAMA 2013;310:2416–25; 10. IFSO Sleeve Gastrectomy. Available at: https://ifso.com/patient-sleeve-gastrectomy/. Accessed August 2022;

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Guide to Selecting Treatment

	BMI					
Treatment	**<25**	**25-26.9**	**27-29.9**	**30-35**	**35-40**	**>40**
Diet Exercise		+	+	+	+	+
Pharmacology			w/ co-morbidities	+	+	+
Surgery					w/ co-morbidities	+

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Guide to Selecting Treatment

	BMI					
Treatment	**<25**	**25-26.9**	**27-29.9**	**30-35**	**35-40**	**>40**
Diet Exercise		+	+	+	+	+
Pharmacology			w/ co-morbidities	+	+	+
Surgery					w/ co-morbidities	+

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Standards of Care in Diabetes 2025
Lifestyle Therapy

- Lifestyle-Behavioral Therapy are recommended for people with T2D and overweight or obesity to achieve both weight and health outcome goals.
  - Interventions including high frequency of counseling (≥16 sessions in 6 months) with focus on nutrition changes, physical activity, and behavioral strategies to achieve a 500–750 kcal/day energy deficit should be recommended for weight loss and should be considered when available
  - If access to such interventions is limited, consider alternative structured programs delivering behavioral counseling (face-to-face or remote).
  - For those who achieve weight loss goals, continue to monitor progress, provide ongoing support, and recommend continuing interventions to maintain weight goals long term. Effective long-term (≥1 year) weight maintenance programs provide monthly contact and support, include frequent self-monitoring of body weight (weekly or more frequently) and other self-monitoring strategies (e.g., food diaries or wearables), and encourage regular physical activity (200–300 min/week).

Diabetes Care, Suppl 1, 2025.

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Standards of Care in Diabetes 2025
Nutrition Therapy

- When developing a plan of care, consider systemic, structural, cultural, and socioeconomic factors that may impact nutrition patterns and food choices, such as food insecurity and hunger, access to healthful food options, and other social determinants of health.
- Short-term nutrition intervention using structured, very-low-calorie meals (800–1,000 kcal/day) should be prescribed only to carefully selected individuals by trained practitioners in medical settings with close monitoring.
- Long-term, comprehensive weight maintenance strategies and counseling should be integrated to maintain weight loss.
- Nutritional supplements have not been shown to be effective for weight loss and are not recommended

Diabetes Care, Suppl 1, 2025.

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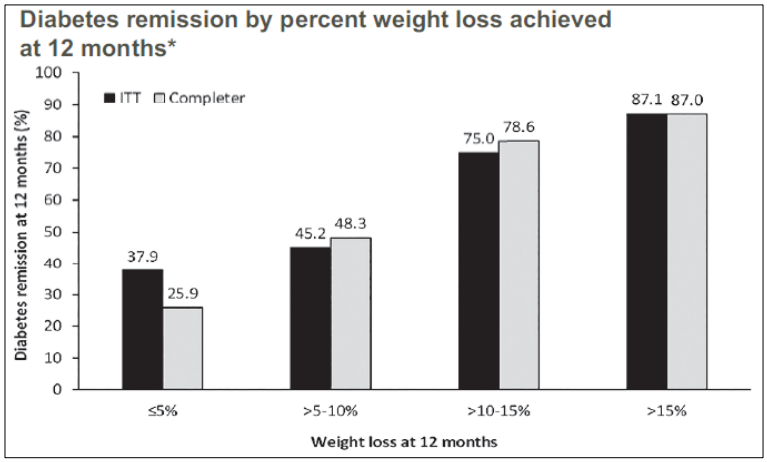
DiRECT-Aus: Intensive Lifestyle Intervention for Remission of Early Type 2 Diabetes



Hocking et al *Diabetes Care* 2024;47:66-70.

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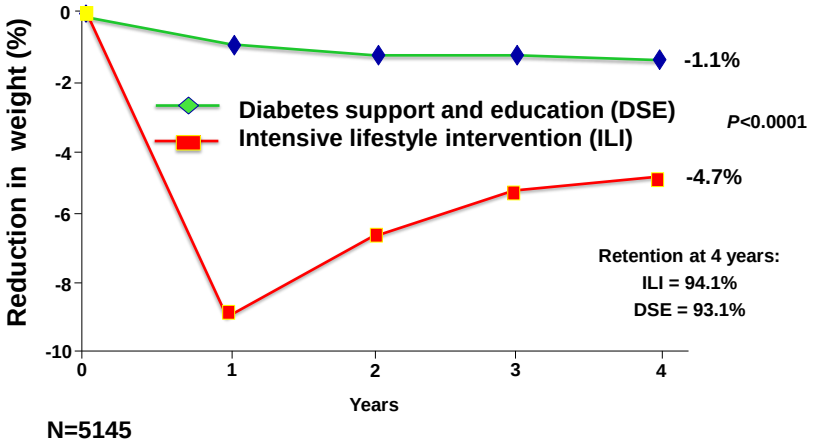
Look AHEAD: Intensive Lifestyle Intervention in Type 2 Diabetes



Look AHEAD Research Group. *Arch Intern Med* 170:1566-1575, 2010.

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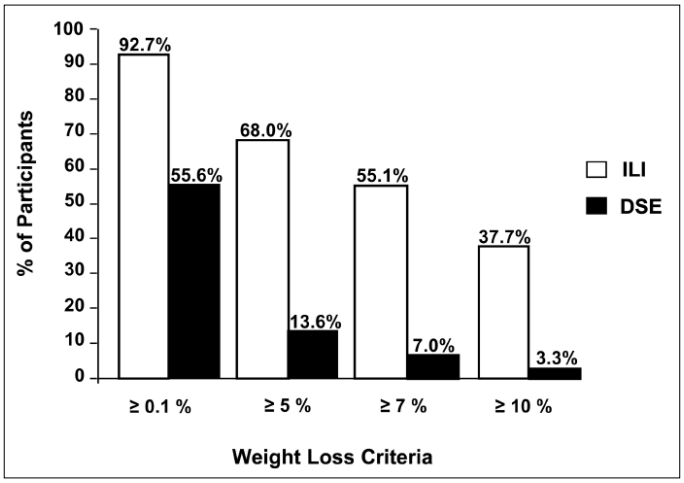
Look AHEAD: 1-Year Weight Loss Data



Wadden et al *Obesity* 2009;17:713

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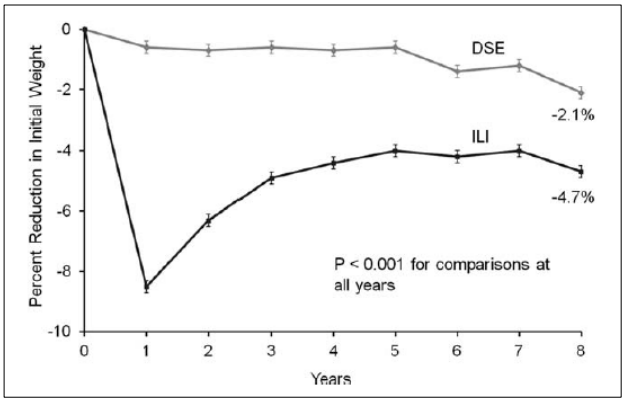
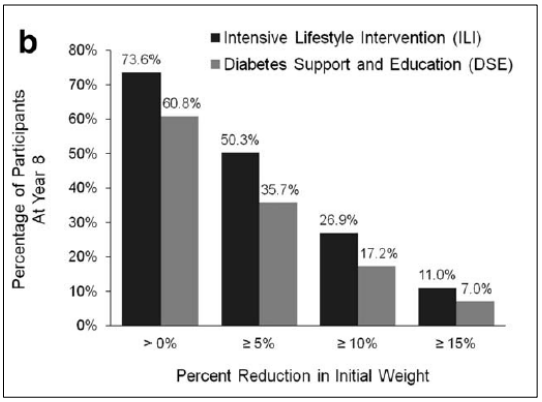
Look AHEAD: 8-year Results





Look AHEAD Research Group. *Obesity* 22:5-13, 2013.

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Look AHEAD 1-year results: Glycemia and CVD Risk Factors

	ILI*	DSE
n	2496	2463
Use of diabetes meds (%)	-7.8	2.2
Fasting BG (mg/dl)	-21.5	-7.2
A1c (%)	-0.64	-0.14
SBP (mmHg)	-6.8	-2.8
HDL-C (mg/dl)	3.4	1.4
TG (mg/dl)	-30.3	-14.6
Albumin/Cr > 30 (%)	-3.9	-1.5
Metabolic Syndrome (%)	-14.7	-7.1

*p<0.001 for all

Diabetes Care 30:1374, 2007.

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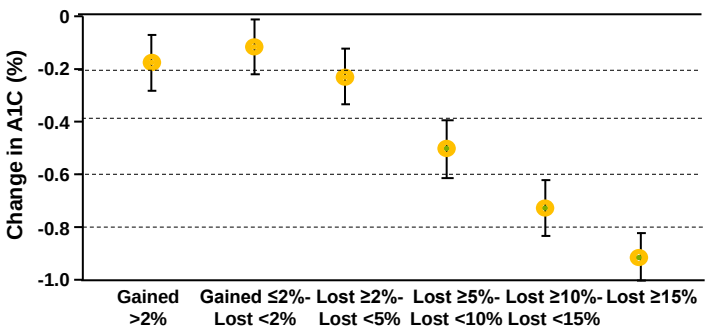
Look AHEAD: Weight Loss and Glycemic Control

Change in A1C (%) by Weight-Loss Category



Wing, et al. *Diabetes Care* 34:1481-1486, 2011.

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Look AHEAD: CVD Data

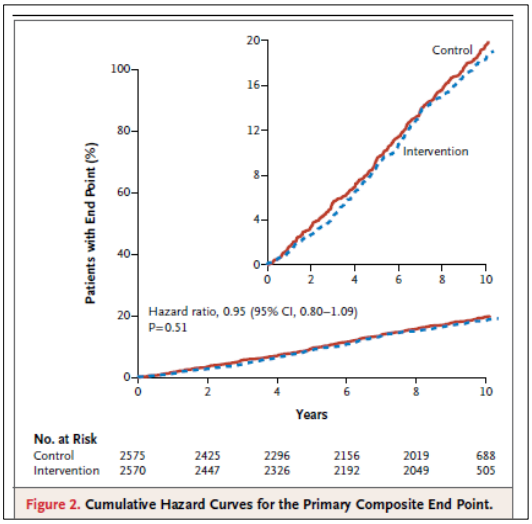

Figure 2. Cumulative Hazard Curves for the Primary Composite End Point.

An intensive lifestyle intervention did not reduce rate of CVD events despite significant improvements in CVD risk factors

N Engl J Med 369:145-154, 2013.

**Lancet Diabetes Endocrinol* 4:913-921, 2016.

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Look AHEAD: CVD Data

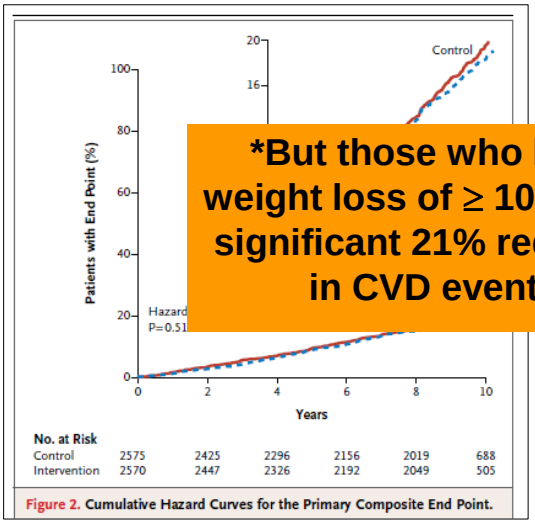

Figure 2. Cumulative Hazard Curves for the Primary Composite End Point.

***But those who had a weight loss of ≥ 10% had a significant 21% reduction in CVD events!**

sive lifestyle
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VD events despite
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k factors

N Engl J Med 369:145-154, 2013.

**Lancet Diabetes Endocrinol* 4:913-921, 2016.

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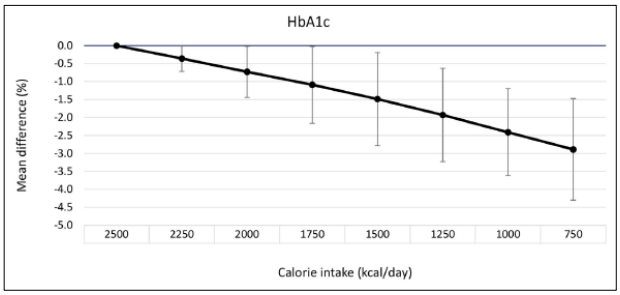
Meta-Analysis of Calorie Restriction vs "Usual" Diet or Care



Jayedi et al *Am J Clin Nutr* 2023

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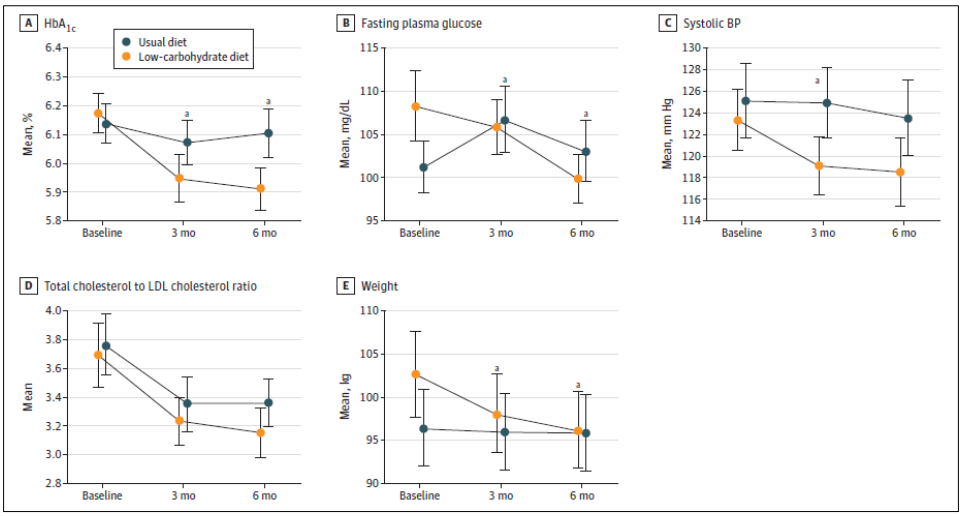
Effects of a Low Carb vs "Usual" Diet on A1c



Dorans, et al. *JAMA Network Open* 2022.

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Keto-Med Trial: Ketogenic vs Mediterranean Diet

No differences seen in:
- HbA1c, glucose, insulin
- Lipids
- Transaminases

Gardner, et al. *Am J Clin Nutr* 2022.

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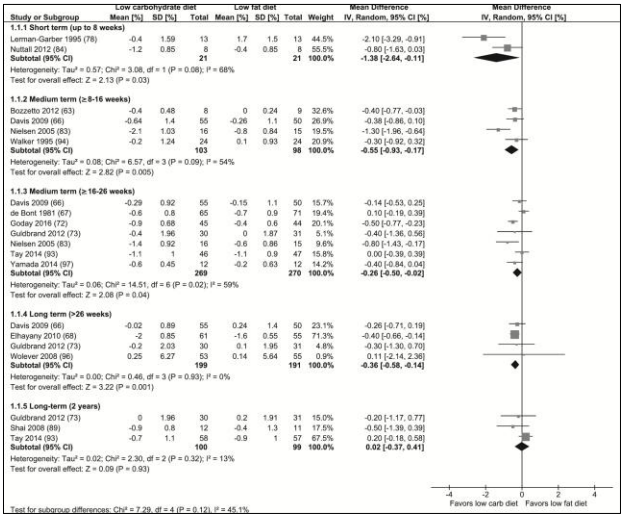
Meta-Analysis: Low Carb vs Low Fat Interventions in Type 2 Diabetes



Van Zuuren, et al. *Am J Clin Nutr* 2022.

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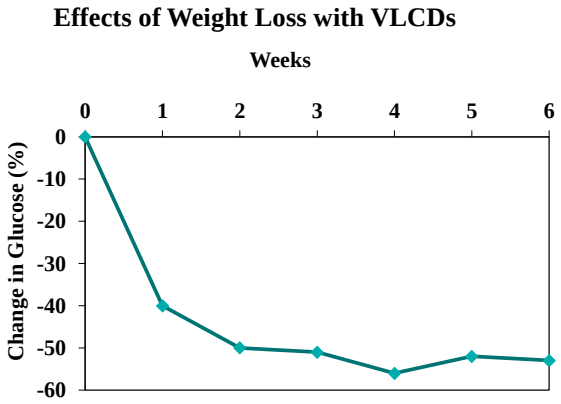
Beneficial Effects of Aggressive Calorie Restriction on Diabetes



Anderson, et al. *J Am Coll Nutr* 2003 22:331

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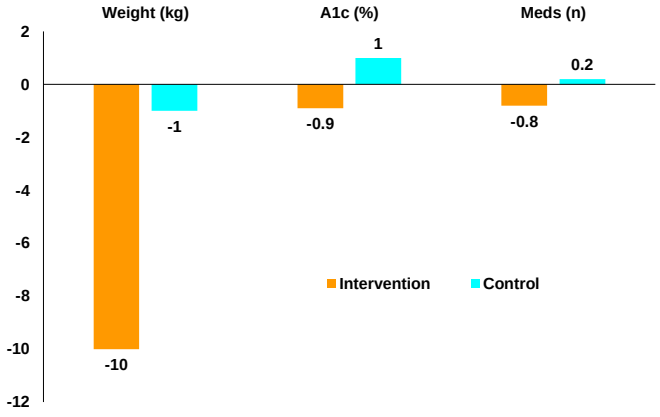
Beneficial Effects of a Very Low Calorie Diet for 1 Year on Diabetes



Lean, et al. *Lancet* 391:541-551, 2018.

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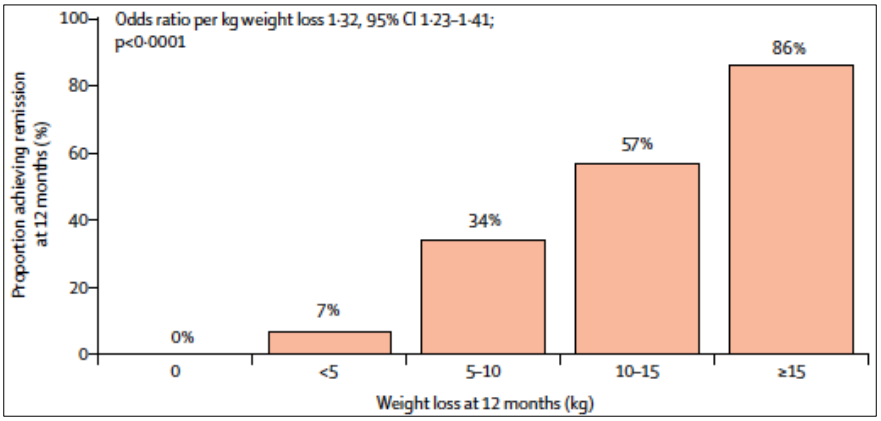
Percent Achieving Diabetes Remission by Degree of Weight Loss at 1 Year



Lean, et al. *Lancet* 391:541-551, 2018.

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What Should We Recommend to Our Patients?

- What are your goals?
- An "individualized" diet plan that results in:
  - Negative energy balance
  - Healthful eating
  - Sustainable weight loss
- In theory, a diet that is high in mono- and poly-unsaturated fats but low in saturated-fats may be ideal especially in the short-term…
- If referring for dietary counseling emphasize weight reduction as primary goal!

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What About Exercise and Type 2 Diabetes?

- Weight loss?
- Improves insulin sensitivity
- Improves cardiovascular risk factors
- Increased fitness is associated with reduced CVD, diabetes and mortality
- Reduce sedentary behavior
- More is better, but some is better than nothing!

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Guide to Selecting Treatment

	BMI					
Treatment	**<25**	**25-26.9**	**27-29.9**	**30-35**	**35-40**	**>40**
Diet Exercise		**+**	**+**	**+**	**+**	**+**
Pharmacology			**w/ co-morbidities**	**+**	**+**	**+**
Surgery					**w/ co-morbidities**	**+**

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Standards of Care in Diabetes 2025
Obesity Pharmacotherapy

- Minimize medications for comorbid conditions that are associated with weight gain.
- When choosing glucose-lowering medications for people with T2D and overweight or obesity, prioritize medications with beneficial effect on weight.
- Obesity medications should be considered for people with diabetes and overweight or obesity along with lifestyle changes. Potential benefits and risks must be considered.
- In people with diabetes and overweight or obesity, the preferred pharmacotherapy should be a GLP-1 or dual GIP/GLP-1 receptor agonist with greater weight loss efficacy, especially considering their added weight-independent benefits (e.g., glycemic and cardiometabolic).
- Obesity medications indicated for chronic therapy should be continued beyond reaching weight loss goals to maintain the health benefits.
- For those not reaching treatment goals, reevaluate weight management therapies and intensify treatment with additional approaches.
- Screen people with diabetes and obesity who have lost significant weight for malnutrition, especially those who have undergone metabolic surgery or treated with obesity medications.

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Rationale for Pharmacotherapy

- Overweight/obesity is a **chronic disease** associated with altered neurocircuitry, requiring long-term treatment and therapies
- Weight loss and long-term weight-loss maintenance are very difficult for many patients
- Obesity Medications should be considered as a long-term treatment and not as a “short-term” fix or “kick start”
- Obesity Medications should be considered as an “adjunct” therapy

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Summary of Obesity Medications*

	Mechanism of Action	Typical Maintenance Dose	Mean Weight Loss**	≥5% of Initial Weight**	≥10% of Initial Weight**	Key Points
Phentermine	Norepinephrine release	8-37.5mg daily	~5%	X	X	Approved for short-term use, lowest cost
Orlistat	Lipase inhibitor	60mg TID (OTC) 120 mg TID (Rx)	3-4%	~21%	~12%	Available over-the-counter, GI side effects
Naltrexone ER/ Bupropion ER	Opioid antagonist/ antidepressant (dopamine)	16 mg/180 mg BID	5-6%	35%	20%	Intermediate in effectiveness and side effects
Liraglutide	GLP-1 Receptor Agonist	3.0 mg daily	6-7%	36%	23%	Intermediate effectiveness and side effects, ?CVD benefit, high cost
Phentermine/ Topiramate ER	Sympathomimetic/ GABA	7.5-15mg/46-92 mg daily	8-11%	41-49%	30-41%	Effective, intermediate side effects
Semaglutide	GLP-1 Receptor Agonist	2.4 mg weekly	6-14%	40-55%	37-57%	Very effective, intermediate in side effects, high cost
Tirzepatide	GLP-1/GIB Receptor Agonist	15 mg weekly	10-20%	83-90%	65-85%	Most effective. Intermediate in side effects, high cost
Setmelanotide	MC4 receptor agonist	1-3 mg SC daily				For patients with genetically confirmed POMC, PCSK1, or LEPR deficiency

*Approved in the U.S.

**placebo subtracted

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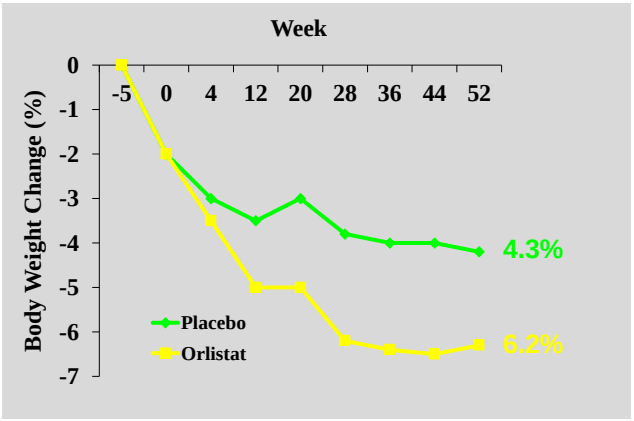
Orlistat Treatment of Obese Patients with Type 2 Diabetes



Hollander et al. *Diabetes Care* 1998 21:1288.

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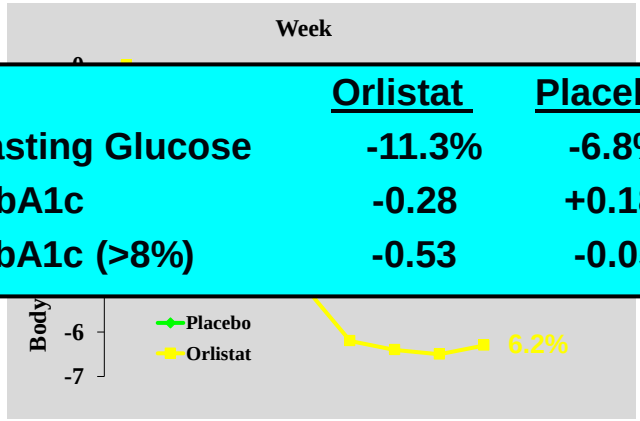
Orlistat Treatment of Obese Patients with Type 2 Diabetes



	Orlistat	Placebo
Fasting Glucose	-11.3%	-6.8%
HbA1c	-0.28	+0.18
HbA1c (>8%)	-0.53	-0.05

Hollander et al. *Diabetes Care* 1998 21:1288.

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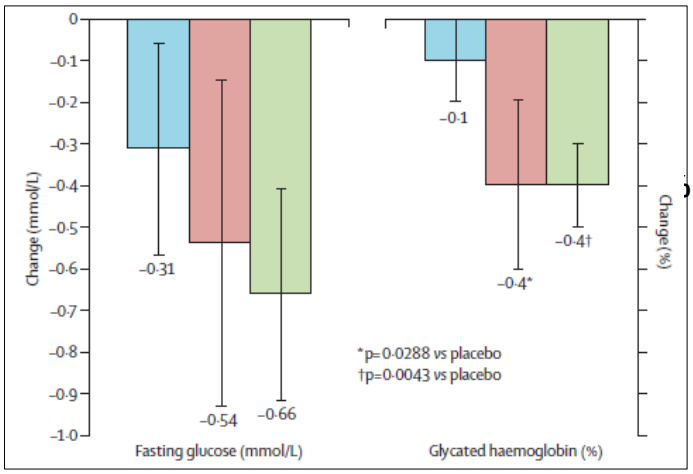
COUNTOUR Study: Effects of Phentermine/Topiramate on Glycemia



Gadde et al. *Lancet* 377:1341-1352, 2011.

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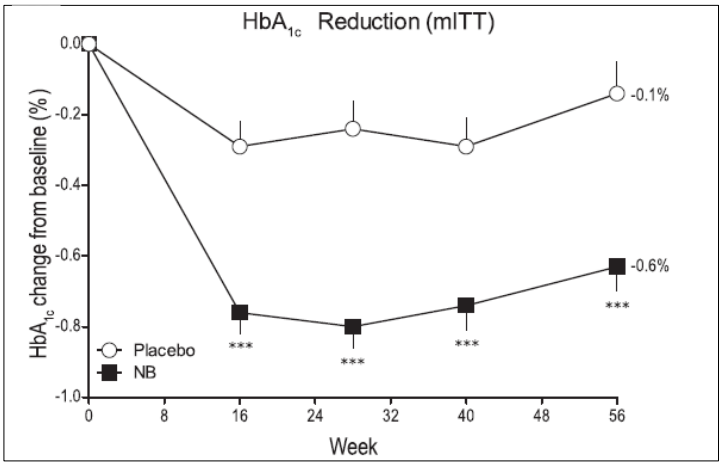
The Effects of Naltrexone/Bupropion on Glycemic Control



Hollander et al. *Diabetes Care*. 36:4022-4029, 2013.

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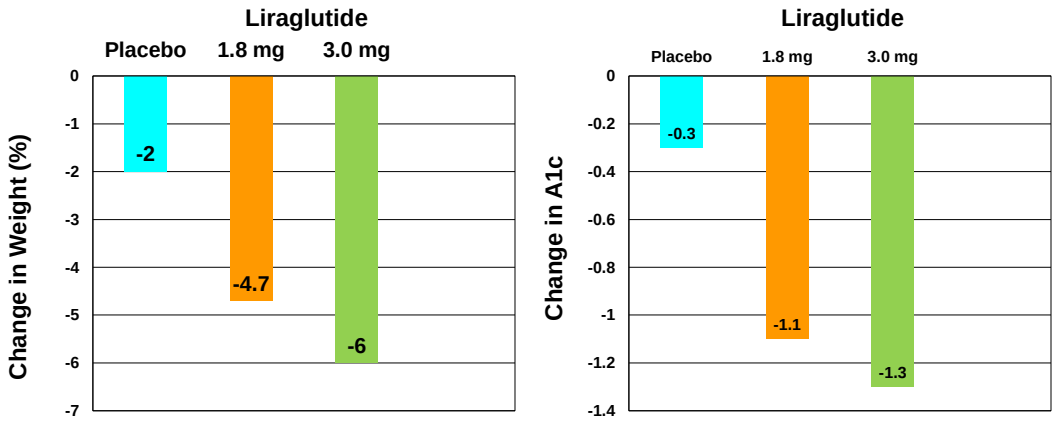
SCALE Diabetes RCT: Effects of Liraglutide 3.0 mg on Glycemic Parameters



Davies et al. *JAMA* 314:687, 2015.

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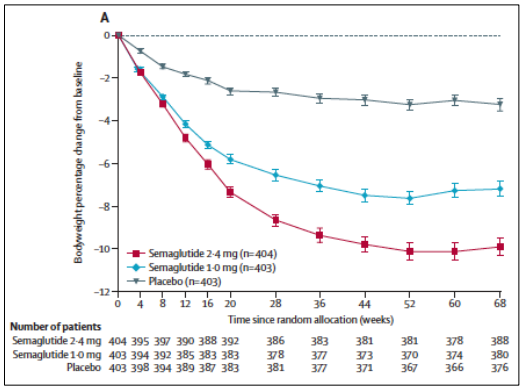
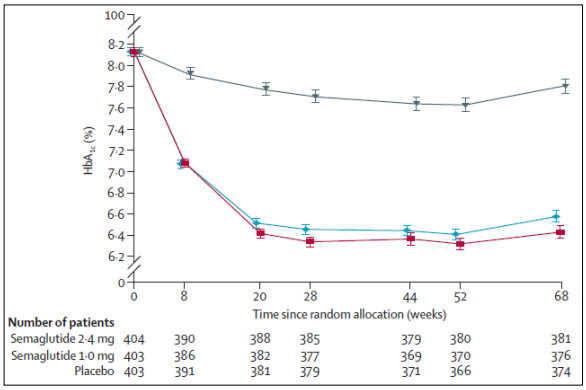
STEP 2: Weight Loss and A1c with Semaglutide 2.4 mg in Patients with Type 2 Diabetes and Obesity





Davies et al, *Lancet* 2021.

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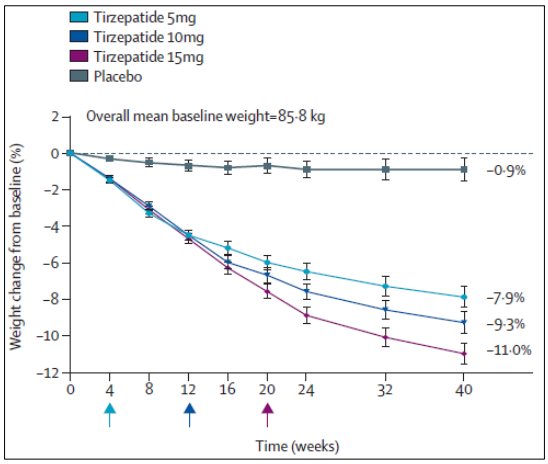
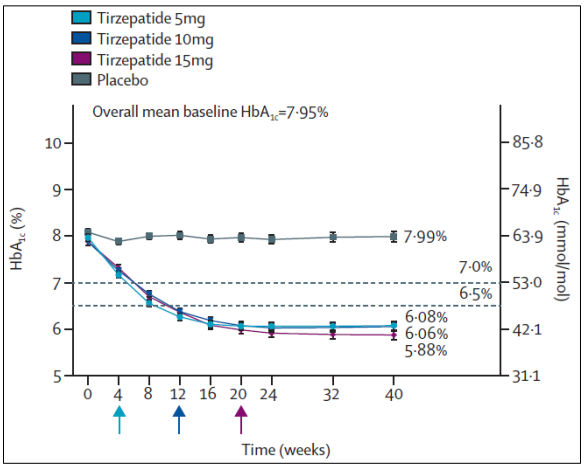
SURPASS-1: Tirzepatide for the Treatment of Diabetes





Rosenstock et al. *Lancet*. 2017.

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Medications Approved for Other Indications

- Diabetes Medications:
  - GLP-1 receptor analogs
  - GLP-1/GIP receptor analog
  - SGLT2 inhibitors
  - Metformin
- Others:
  - Topiramate
  - Bupropion
  - Fluoxetine

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Weight Loss with GLP-1 and GLP-1/GIP Receptor Agonists for Diabetes

Drug	Dosing	Weight Change in T2DM Trials (kg)
Exenatide	5-10 mcg BID	-1.4 to -4.0
Exenatide (weekly)	2 mg weekly	-1.6 to -3.7
Liraglutide	1.2-1.8 mg daily	-2 to -5.0
Dulaglutide	0.75-4.5 mg weekly	-0.8 to -5.0
Semaglutide	0.5-2 mg weekly	-3.5 to 6.5
Tirzepatide*	2.5-15 mg weekly	-7.0 to -10.1

*GLP-1/GIP dual agonist

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Do Weight Loss Medications Work in Patients with Diabetes?

- Yes, these agents are effective in producing clinically meaningful weight loss in patients with diabetes.
- In addition to weight loss these agents lead to improvements in glycemic control and other cardiac risk factors and cardiovascular outcomes.
- Does treatment need to be lifelong?
- One of the biggest barriers is that the costs are not usually covered by health care payers.
- Consider switching to diabetes agents that also promote weight loss
- These options should be discussed with our patients

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Guide to Selecting Treatment

	BMI					
Treatment	**<25**	**25-26.9**	**27-29.9**	**30-35**	**35-40**	**>40**
Diet Exercise		**+**	**+**	**+**	**+**	**+**
Pharmacology			**w/ co-morbidities**	**+**	**+**	**+**
Surgery					**w/ co-morbidities**	**+**

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Standards of Care in Diabetes 2025
Metabolic Surgery

- Consider metabolic surgery as a weight and glycemic management approach in people with diabetes with BMI ≥30.0 kg/m^2 (or ≥27.5 kg/m^2 in Asian individuals).
- Metabolic surgery should be performed in high-volume centers with interprofessional teams knowledgeable about and experienced in managing obesity, diabetes, and gastrointestinal surgery
- People being considered for metabolic surgery should be evaluated for comorbid psychological conditions and social and situational circumstances that have the potential to interfere with surgery outcomes.
- People who undergo metabolic surgery should receive long-term medical and behavioral support and routine micronutrient, nutritional, and metabolic monitoring.
- In people who undergo metabolic surgery, routinely screen for psychosocial and behavioral health changes and refer to a qualified professional as needed.

Diabetes Care, Suppl 1, 2025.

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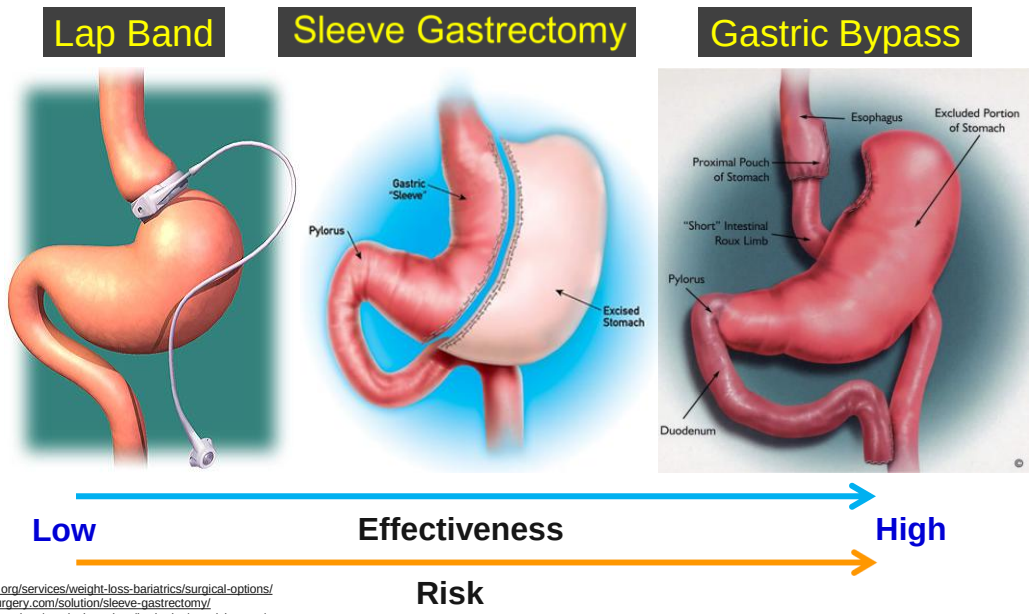
Bariatric/Metabolic Surgery



https://methodisthospitals.org/services/weight-loss-bariatrics/surgical-options/
https://michiganbariatricsurgery.com/solution/sleeve-gastrectomy/
https://christianacare.org/services/surgical-services/bariatrics/gastricbypass/

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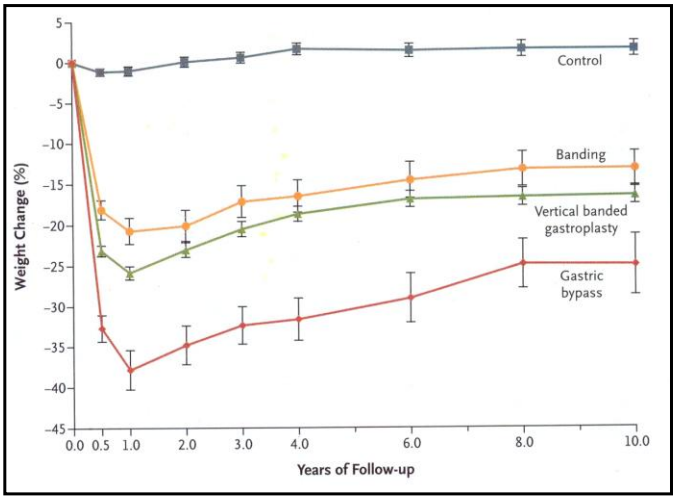
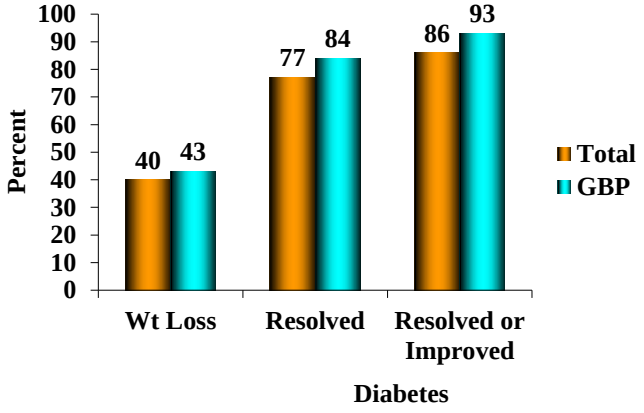
Weight Loss and Maintenance after Bariatric Surgery



Sjöström et al. *N Engl J Med* 351:26, 2004.

55

Bariatric Surgery: A Systematic Review and Meta-analysis

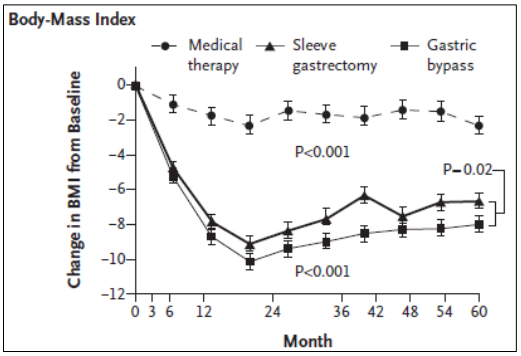


Buchwald et al. *JAMA* 292:1724, 2004.

56

Stampede Trial: 5-year Outcomes

N Engl J Med 2017;376:641-651



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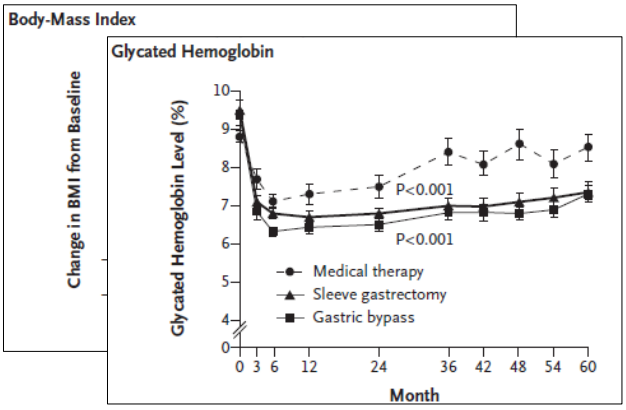
Stampede Trial: 5-year Outcomes

N Engl J Med 2017;376:641-651



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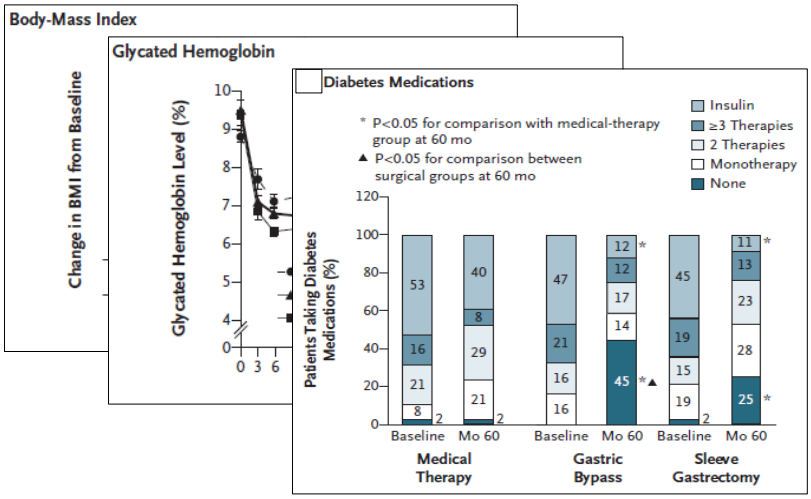
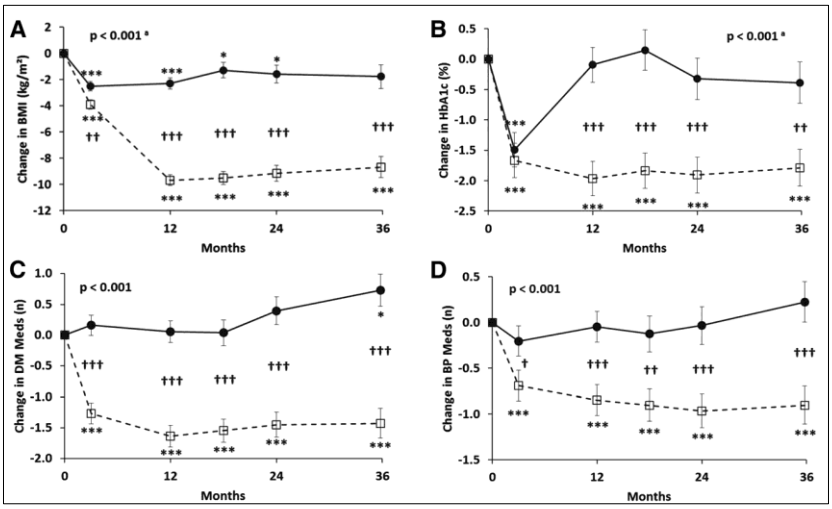
Stampede Trial: 5-year Outcomes

N Engl J Med 2017;376:641-651



59

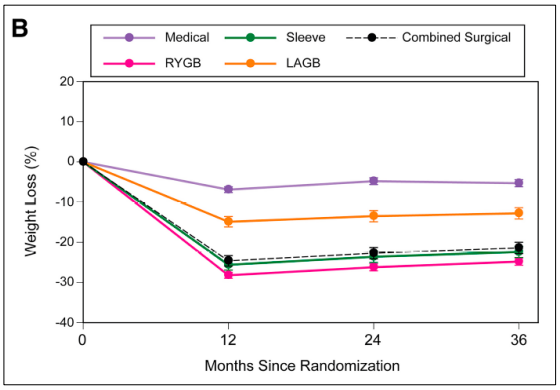
Outcomes in Obese T2D 3 Years After Randomization to Gastric Bypass Surgery Versus Intensive Lifestyle Management: *The SLIMM-T2D Study*

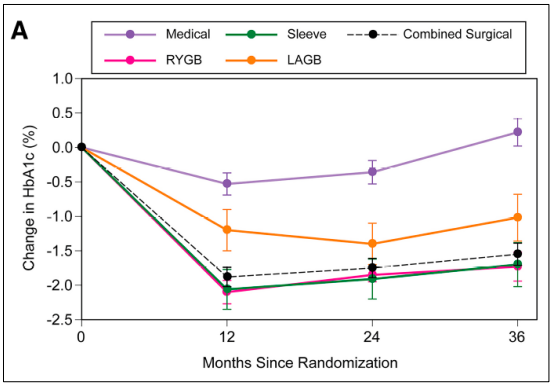


Simonson et al. *Diabetes Care*. Feb 6, 2018.

60

Outcomes in Obese T2D 3 Years After Randomization to Metabolic Surgery Versus Intensive Medical/Lifestyle Management: *The ARMMS-T2D Study*

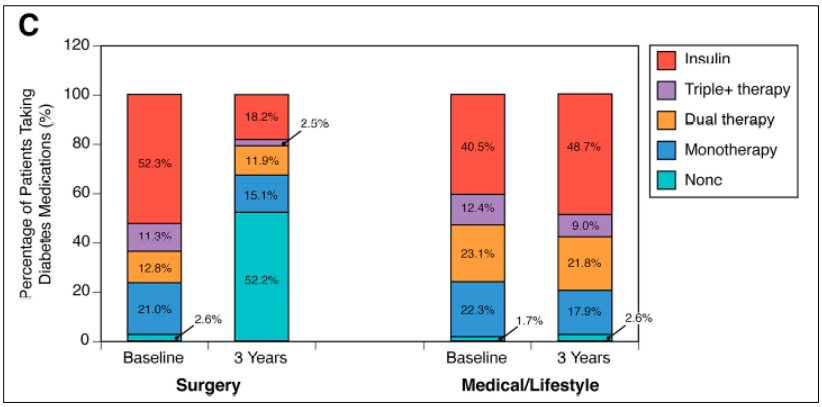




Kirwan et al. *Diabetes Care*. 45:1574-1583, 2022.

61

Outcomes in Obese T2D 3 Years After Randomization to Metabolic Surgery Versus Intensive Medical/Lifestyle Management: The ARMMS-T2D Study



Kirwan et al. *Diabetes Care*. 45:1574-1583, 2022.

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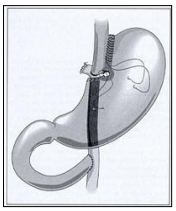
Bariatric Surgery in Type 2 Diabetes

- 20-40% weight loss
- Very effective in improving and even normalizing glycemia in patients with diabetes
- Best summarized by Dr Walter Pories*

  "Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus"



Many of our patients meet the requirements for bariatric surgery, so should we discuss this with them?

Why wouldn't we?

*Pories et al. *Ann Surg* 222:339. 1995.

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Case

- JM is a 45-year-old man recently diagnosed with type 2 diabetes. He is s/p kidney transplant 3 years ago doing well on immunotherapy, including tacrolimus, mycophenolate, and prednisone 5 mg. He had been on NPH insulin twice a day plus aspart sliding scale. At some point the NPH was changed to glargine. He reports more weight gain over the previous year or two especially during the COVID pandemic and is now wanting to lose weight.
- He is currently on glargine 28 units daily + aspart scale (does not use often)
- His current A1c is 8.4%
- His home monitoring shows mild to moderately elevated fasting blood glucose levels but no other data to review
- His BMI is currently up to 35.6 kg/m^2
- Labs are notable for a creatinine of 1.6 and eGFR of 45

Which of the Following Are True Regarding His Obesity and Diabetes?

A. His excess adiposity is not likely associated with his worsening glycemia
B. Weight gain and obesity are not only associated with insulin resistance but are also associated with worsening cardiovascular risk and mortality
C. Weight loss through lifestyle change is not likely to be sustainable and is not associated with clinical benefits such as better glycemic control or improvements in cardiovascular risk
D. Obesity medications are unsafe and not associated with long-term weight benefits or improvements in cardiometabolic risk
E. Bariatric/metabolic surgery is associated with significant improvements in diabetes-related outcomes but is also associated in increased cardiovascular disease and mortality

Which of the Following Would You Recommend as the Best Next Treatment Option for This Patient?

A. Counsel on lifestyle changes and behavior modification with a goal of 5-10% weight loss
B. Start true prandial insulin plus a correction factor
C. Counsel on lifestyle changes and initiate a GLP-1 receptor analog
D. Refer for bariatric/metabolic surgery
E. None of the above

Conclusions

- Obesity is a significant risk factor for developing type 2 diabetes and has a significant negative impact on the progression and treatment of diabetes.
- Weight loss is an effective therapy for diabetes management and prevention - the more the better.
- Although dietary therapy is the cornerstone to weight loss therapy the best dietary intervention is still unclear.
- Pharmacotherapy for weight loss is an effective yet under utilized treatment option in patients with diabetes.
- Bariatric/Metabolic surgery is the most effective weight loss treatment in patients with diabetes and should be considered in those with moderate to severe obesity.
- Be aggressive, individualize, and use all the appropriate tools!