Weight No Longer: Addressing Overweight/Obesity as an Integral Part of Type 2 Diabetes Management

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Disclosures

Learning Objective

Implement shared decision-making strategies to help patients with type 2 diabetes select and follow through with informed options for weight loss

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What Percentage of Patients With BMI ≥30 kg/m² Sought Help From HCP for Weight Loss?
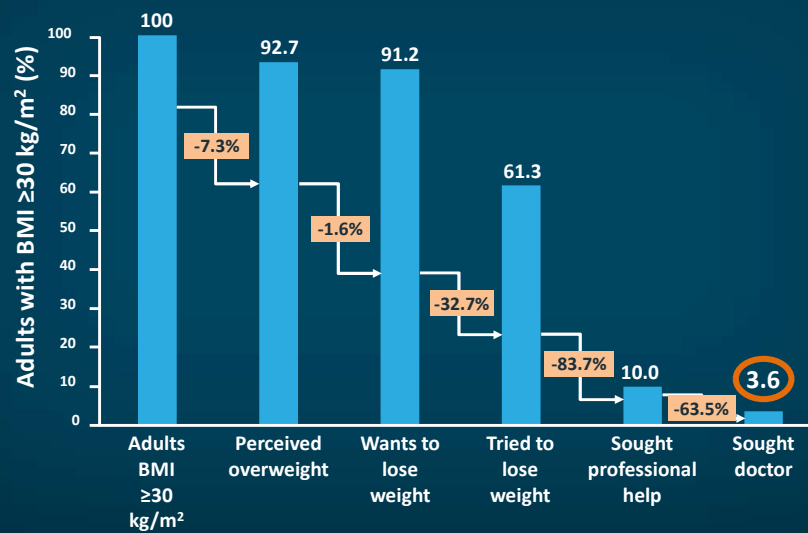
HCP = health care provider.
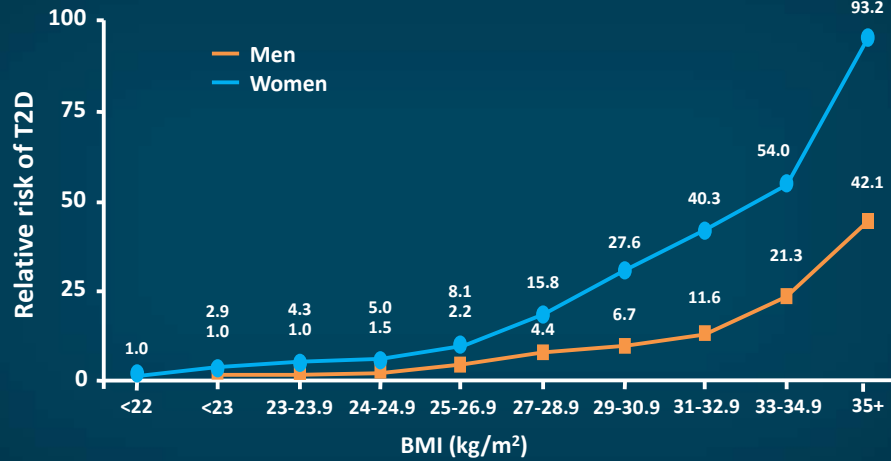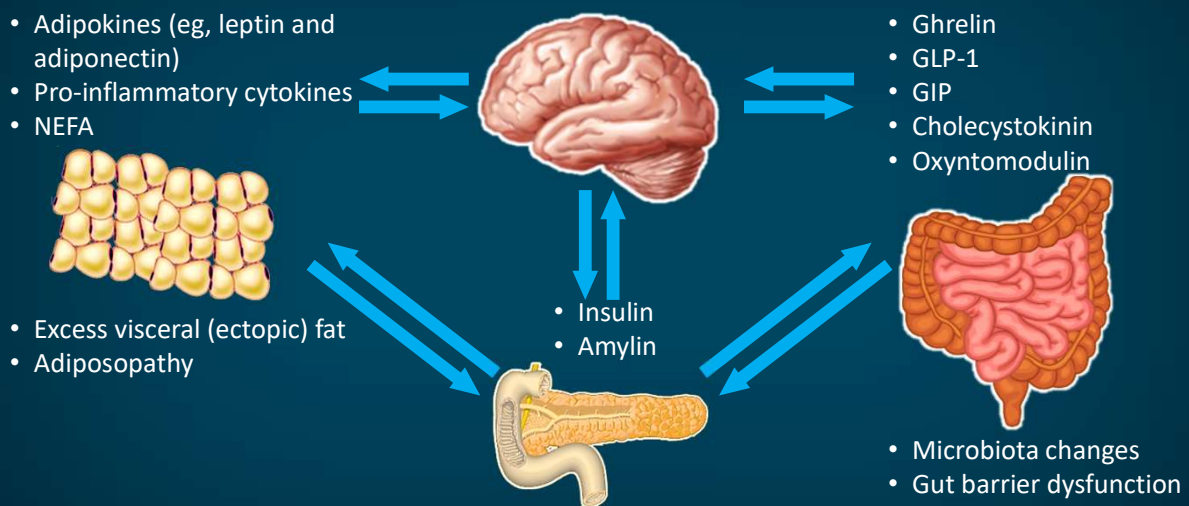Stokes A, et al. *Obesity (Silver Spring)*. 2018;26:814-818.

Relationship Between BMI and Risk of T2DM

Relative risk of T2D vs BMI (kg/m²)

- Men
- Women

BMI (kg/m²)	<22	<23	23-23.9	24-24.9	25-26.9	27-28.9	29-30.9	31-32.9	33-34.9	35+
Women	1.0	2.9	4.3	5.0	8.1	15.8	27.6	40.3	54.0	93.2
Men		1.0	1.0	1.5	2.2	4.4	6.7	11.6	21.3	42.1

BMI = body mass index (weight in kilograms divided by height in meters squared, kg/m²); T2DM = type 2 diabetes.

Chan JM, et al. *Diabetes Care*. 1994;17:961-969. Colditz GA, et al. *Ann Intern Med*. 1995;122:481-486.

Complex Pathophysiology of Obesity and T2DM

- Adipokines (eg, leptin and adiponectin)
- Pro-inflammatory cytokines
- NEFA

- Excess visceral (ectopic) fat
- Adiposopathy

- Insulin
- Amylin

- Ghrelin
- GLP-1
- GIP
- Cholecystokinin
- Oxyntomodulin

- Microbiota changes
- Gut barrier dysfunction
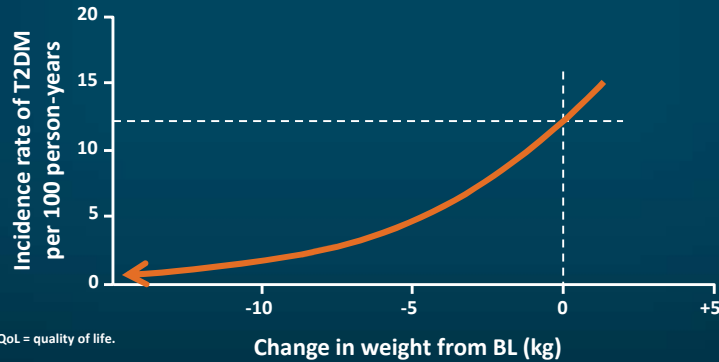
GIP = glucose-dependent insulinotropic polypeptide (gastric inhibitor polypeptide); GLP-1 RA = glucagon-like peptide-1 receptor agonist; NEFA = non-esterified fatty acid.

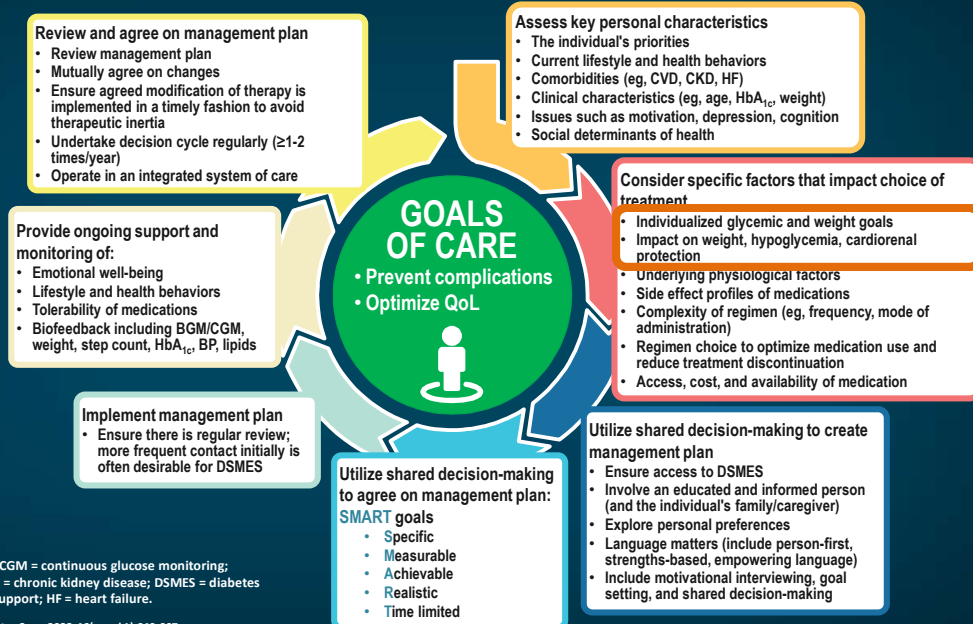Scheen AJ, Van Gaal LF. *Lancet Diabetes Endocrinol*. 2014;2:911-922.

How Much Weight Loss Is Needed to Provide Benefit?

- Modest weight loss (5%-10%) improves glycemia, BP, lipids, need for medications, mobility, and QoL

- In the Diabetes Prevention Program, weight loss averaged 5.5 kg and reduced the risk of conversion from impaired glucose tolerance to T2DM by 58%

BL = baseline; BP = blood pressure; QoL = quality of life.

Bray GA, Ryan DH. *Diabetes Obes Metab.* 2021;23(suppl 1):50-62.

Decision Cycle for Person-Centered Glycemic Management

Review and agree on management plan
- Review management plan
- Mutually agree on changes
- Ensure agreed modification of therapy is implemented in a timely fashion to avoid therapeutic inertia
- Undertake decision cycle regularly (≥1-2 times/year)
- Operate in an integrated system of care

Assess key personal characteristics
- The individual's priorities
- Current lifestyle and health behaviors
- Comorbidities (eg, CVD, CKD, HF)
- Clinical characteristics (eg, age, HbA$_{1c}$, weight)
- Issues such as motivation, depression, cognition
- Social determinants of health

Consider specific factors that impact choice of treatment
- Individualized glycemic and weight goals
- Impact on weight, hypoglycemia, cardiorenal protection
- Underlying physiological factors
- Side effect profiles of medications
- Complexity of regimen (eg, frequency, mode of administration)
- Regimen choice to optimize medication use and reduce treatment discontinuation
- Access, cost, and availability of medication

Provide ongoing support and monitoring of:
- Emotional well-being
- Lifestyle and health behaviors
- Tolerability of medications
- Biofeedback including BGM/CGM, weight, step count, HbA$_{1c}$, BP, lipids

GOALS OF CARE
- Prevent complications
- Optimize QoL

Implement management plan
- Ensure there is regular review; more frequent contact initially is often desirable for DSMES

Utilize shared decision-making to agree on management plan: SMART goals
- **S**pecific
- **M**easurable
- **A**chievable
- **R**ealistic
- **T**ime limited

Utilize shared decision-making to create management plan
- Ensure access to DSMES
- Involve an educated and informed person (and the individual's family/caregiver)
- Explore personal preferences
- Language matters (include person-first, strengths-based, empowering language)
- Include motivational interviewing, goal setting, and shared decision-making

BGM = blood glucose monitoring; CGM = continuous glucose monitoring; CVD = cardiovascular disease; CKD = chronic kidney disease; DSMES = diabetes self-management education and support; HF = heart failure.

Modified from ElSayed NA, et al. *Diabetes Care.* 2023;46(suppl 1):S49-S67.

How Is Obesity Defined in Adults?

Weight status category	BMI (kg/m^2)
Underweight	<18.5
Normal weight	18.5-24.9
Overweight	25.0-29.9
Class 1 obesity	30.0-34.9
Class 2 obesity	35.0-39.9
Class 3 obesity	≥40

CDC. Defining adult overweight & obesity, 6/3/2022 (https://www.cdc.gov/obesity/basics/adult-defining.html). Accessed 12/19/2022.

ADA Standards of Care: Obesity Treatment

| Treatment options for overweight and obesity in T2DM			
	BMI category (kg/m^2)		
	25.0-26.9 (or 23.0-24.9*)	27.0-29.9 (or 25.0-27.4*)	≥30.0 (or ≥27.5*)
Diet, physical activity, and behavioral counseling	†	†	†
Pharmacotherapy		†	†
Metabolic surgery			†

Assessment (ADA Standards of Care)

8.1 Use patient-centered, nonjudgmental language that fosters collaboration between patients and providers, including people-first language (eg, "person with obesity" rather than "obese person"). **E**

8.2 Measure height and weight and calculate BMI at annual visits or more frequently. Assess weight trajectory to inform treatment considerations. **E**

8.3 Based on clinical considerations, such as the presence of comorbid heart failure or significant unexplained weight gain or loss, weight may need to be monitored and evaluated more frequently. **B** If deterioration of medical status is associated with significant weight gain or loss, inpatient evaluation should be considered, especially focused on associations between medication use, food intake, and glycemic status. **E**

Diabetes Care Remains Highly Glucose-Centric
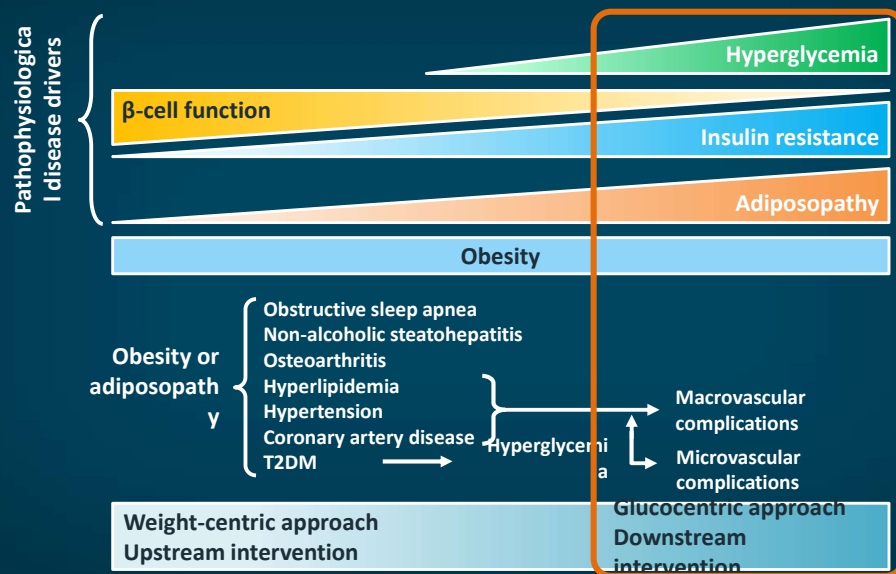
Assessment (ADA Standards of Care) (cont'd)

8.4   Accommodations should be made to provide privacy during weighing. **E**

8.5   Individuals with diabetes and overweight or obesity may benefit from modest or larger magnitudes of weight loss. Relatively small weight loss (approximately 3%-7% of baseline weight) improves glycemia and other intermediate cardiovascular risk factors. **A** Larger, sustained weight losses (>10%) usually confer greater benefits, including disease-modifying effects and possible remission of T2DM, and may improve long-term cardiovascular outcomes and mortality. **B**

Pharmacotherapy (ADA Standards of Care)

8.14   When choosing glucose-lowering medications for patients with T2DM and overweight or obesity, consider a medication's effect on weight. **B**

8.15   Whenever possible, minimize medications for comorbid conditions that are associated with weight gain. **E**

8.16   Weight loss medications are effective as adjuncts to diet, physical activity, and behavioral counseling for selected people with T2DM and BMI ≥27 kg/m^2. Potential benefits and risks must be considered. **A**

8.17   If obesity pharmacotherapy is effective (typically defined as ≥5% weight loss after 3 months of use), further weight loss is likely with continued use. When early response is insufficient (typically <5% weight loss after 3 months of use) or if there are significant safety or tolerability issues, consider discontinuation of the medication and evaluate alternative medications or treatment approaches. **A**

Multiple, Complex Pathophysiological Abnormalities in T2DM

↓ Incretin effect

↓ Pancreatic insulin secretion

↑ Pancreatic glucagon secretion

?

Gut carbohydrate delivery and absorption

Hyperglycemia

−

+

↑ Hepatic glucose production

↑ Renal glucose excretion

↓ Peripheral glucose uptake

Modified from Inzucchi SE, Sherwin RS. Type 2 diabetes mellitus. In: Goldman L, Schafer AI, eds. *Goldman's Cecil Medicine*, 24th ed. WB Saunders; 2011.

Use of Glucose-Lowering Medications in Management of T2DM

Healthy lifestyle behaviors; DSMES; social determinants of health (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: cardiorenal risk reduction in high-risk patients with T2DM (in addition to comprehensive CV risk management)

+ASCVD
Defined differently across CVOTs but all including individuals with established CVD (eg, MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic CAD

+Indicators of high risk
While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF

+CKD
eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time, requiring repeat measure to document CKD.

+ASCVD/indicators of high risk
GLP-1 RA with proven CVD benefit — EITHER/OR — SGLT2i with proven CVD benefit

If HbA1c above target
- For patients on GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD

+HF
SGLT2i with proven HF benefits in this population

+CKD (on maximally tolerated dose of ACEi/ARB)
PREFERABLY
SGLT2i with primary evidence of reducing CKD progression
Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation
OR
GLP-1 RA with proven CVD if SGLT2i not tolerated or contraindicated

IF HbA1c above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: achievement and maintenance of glycemic and weight- management goals

Glycemic management: choose approaches that provide efficacy to achieve goals
Metformin OR agents(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals
Consider avoidance of hypoglycemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals
Efficacy for glucose lowering
Very high:
Dulaglutide (high dose); semaglutide; tirzepatide
Insulin
Combination oral, combination injectable (GLP-1 RA/insulin)
High:
GLP-1 RA (not listed above), metformin, SGLT2i, sulfonylurea, TZD
Intermediate:
DPP-4i

Achievement and maintenance of weight management goals:
Set individualized weight-management goals

General lifestyle advice: medical nutrition therapy/ eating patterns/ physical activity
Intensive evidence-based structured weigh-t management program
Consider medication for weight loss
Consider metabolic surgery

When choosing glucose-lowering therapies:
consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss
Very high:
Semaglutide, tirzepatide
High:
Dulaglutide, liraglutide
Intermediate:
GLP-1 RA (not listed above), SGLT2i
Neutral:
DPP-4i, metformin

If HbA1c above target

**Identify barriers to goals:**
- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (eg, diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

ACEi = angiotensin-converting enzyme inhibitor; ACR = albumin-to-creatinine ratio; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic CVD; CAD = coronary artery disease; CGM = continuous glucose monitoring; CV = cardiovascular; CVOT = CV outcomes trial; DPP-4i = dipeptidyl peptidase 4 inhibitor; eGFR = estimated glomerular filtration rate; GLP-1 RA = GLP-1 receptor agonist; HF = heart failure; HFpEF = HF with preserved ejection fraction; HFrEF = HF with reduced ejection fraction; HHF = hospitalization for heart failure; MACE = major adverse CV events; MI = myocardial infarction; SGLT2i = sodium-glucose cotransporter 2 inhibitor; TZD = thiazolidinedione.

ADA Professional Practice Committee. *Diabetes Care* 2023;46(suppl 1):S140-S157.

Weight Loss With Liraglutide

Trial	Participant characteristics	PBO-corrected weight loss	≥5% BW loss		≥10% BW loss	
			Liraglutide 3.0 mg	PBO	Liraglutide 3.0 mg	PBO
Astrup et al, 2009	76% women, stable body weight, BMI ≥30 kg/m² and ≤40 kg/m²	-4.4 kg	76.1%	29.6%	28.3%	2.0%
Astrup et al, 2012	76% women, stable body weight, BMI ≥30 kg/m² and ≤40 kg/m²	-5.8 kg	73%	28%	37%	10%
Wadden et al, 2013	81% women, stable body weight, BMI ≥30 kg/m² or ≥27 kg/m² with dyslipidemia or hypertension; lost ≥5% of initial body weight in low-calorie diet run-in period (4-12 weeks)	-5.9 kg	50.5%	21.8%	6.1%	6.3%
Pi-Sunyer et al, 2015	78% women, stable body weight, BMI ≥30 kg/m² or ≥27 kg/m² if with dyslipidemia or hypertension	-5.6 kg	63.2%	27.1%	33.1%	10.6%
Davies et al, 2015	50% women, stable body weight, BMI ≥27 kg/m²; T2D (HbA$_{1c}$ = 7.0%-10.0%) treated with diet and exercise alone or in combination with 1-3 oral hypoglycemic agents	-4.2 kg	54.3%	21.4%	25.2%	6.7%
Blackman et al, 2015	28% women, stable body weight, BMI ≥30 kg/m², moderate-to-severe obstructive sleep apnea, unwilling or unable to use CPAP	-4.9 kg	46.4%	18.1%	22.4%	1.5%

CPAP = continuous positive airway pressure (machine); PBO = placebo.

Mehta A, et al. *Obes Sci Pract*. 2017;3:3-14. (Complete references for the studies cited can be found in Mehta et al.)
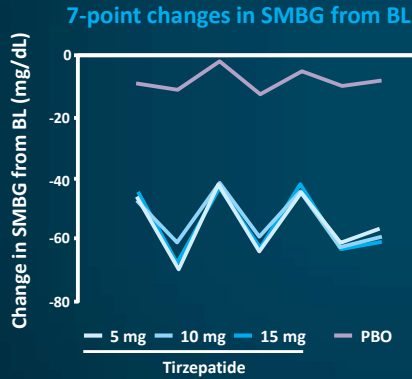
## The STEP Trials: Higher-Dose Semaglutide in Obesity
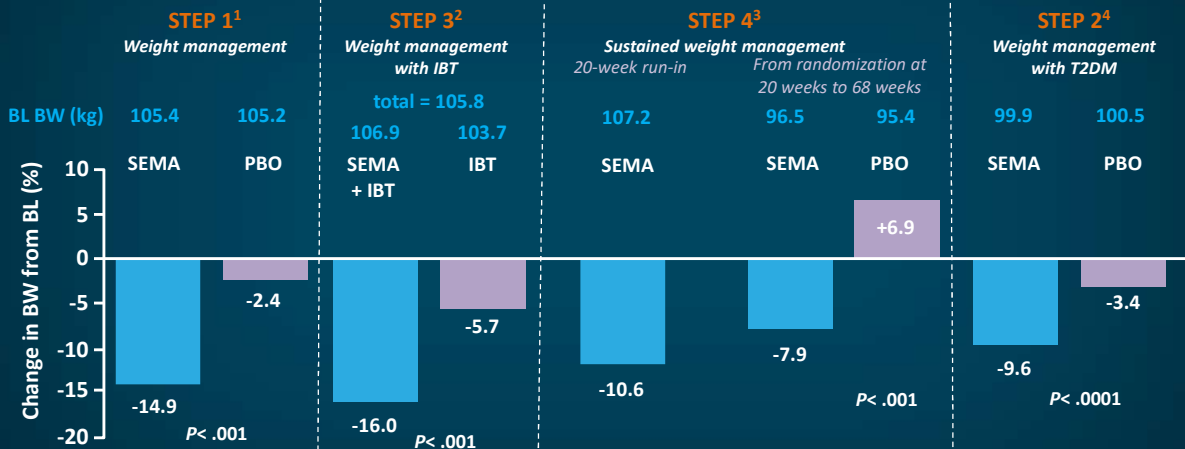
IBT = intensive behavioral therapy; SEMA = semaglutide.

1. Wilding JPH, et al. *N Engl J Med*. 2021;384:989-1002. 2. Wadden TA, et al. *JAMA*. 2021;325:1403-1413. 3. Rubino D, et al. *JAMA*. 2021;325:1414-1425. 4. Davies M, et al. *Lancet*. 2021;397:971-984.

Tirzepatide: Results From SURPASS Clinical Trials

7-point changes in SMBG from BL

SMBG = self-monitored blood glucose.

Kaneko S. *touchREV Endocrinol*. 2022;18:10-19. Rosenstock J, et al. *Lancet*. 2021;398:143-155. Frías JP, et al. *N Engl J Med*. 2021;385:503-515. Ludvik B, et al. *Lancet*. 2021;398:583-598.
Del Prato S, et al. *Lancet*. 2021;398:1811-1824. Dahl D, et al. *JAMA*. 2022;327:534-545.
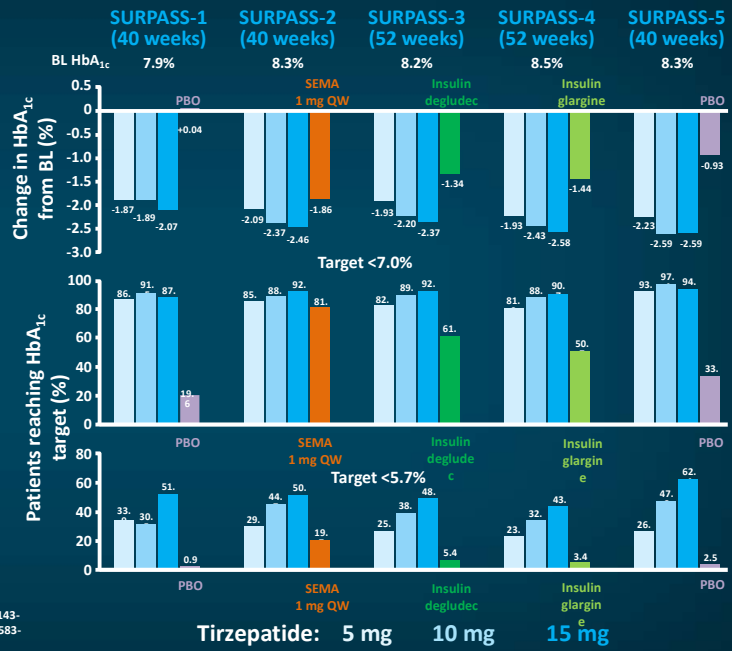
Tirzepatide: Change From Baseline in Body Weight in SURPASS
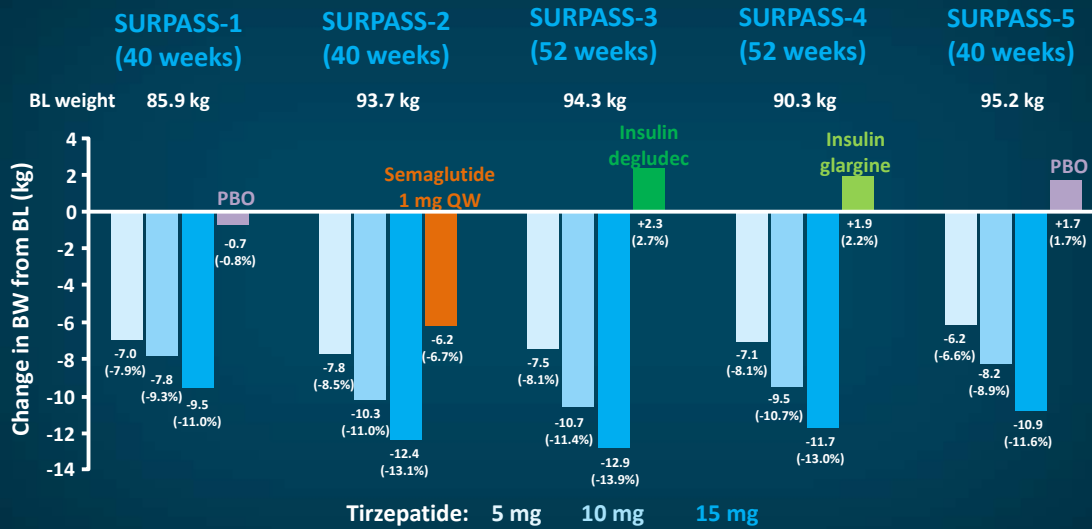
Kaneko S. *touchREV Endocrinol*. 2022;18:10-19. Rosenstock J, et al. *Lancet*. 2021;398:143-155. Frías JP, et al. *N Engl J Med*. 2021;385:503-515. Ludvik B, et al. *Lancet*. 2021;398:583-598. Del Prato S, et al. *Lancet*. 2021;398:1811-1824. Dahl D, et al. *JAMA*. 2022;327:534-545.

Efficacy of Tirzepatide vs Semaglutide in RCT Meta-Analysis

Study Scope: Network Meta-Analysis of 22 RCTs, totaling 18,472 Participants
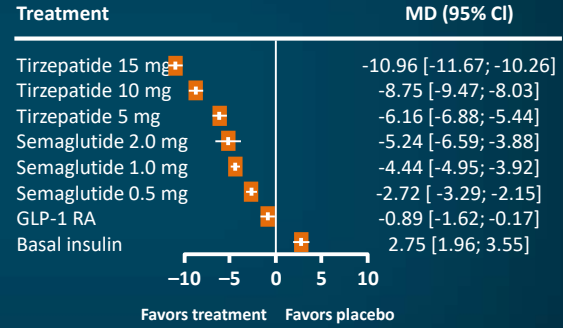
HbA1c Reduction: (Mean Difference)

- Tirzepatide 15 mg: Most efficacious vs placebo -2.00% (95% CI, -2.16 to -1.84)
- Tirzepatide 10 mg: -1.86% (95% CI, -2.02 to -1.84)
- Semaglutide 2.0 mg: -1.62% (95% CI, -1.96 to -1.28)

Weight Reduction:

- Tirzepatide vs Placebo: More efficacious in reducing body weight
- Tirzepatide 10 mg and 15 mg: Superior to semaglutide 1.0 mg and 2.0 mg
- Tirzepatide 5 mg: Superior to semaglutide 0.5 mg and 1.0 mg

Network meta-analysis results for the effect on change in body weight (kg) versus placebo

Treatment	MD (95% CI)
Tirzepatide 15 mg	-10.96 [-11.67; -10.26]
Tirzepatide 10 mg	-8.75 [-9.47; -8.03]
Tirzepatide 5 mg	-6.16 [-6.88; -5.44]
Semaglutide 2.0 mg	-5.24 [-6.59; -3.88]
Semaglutide 1.0 mg	-4.44 [-4.95; -3.92]
Semaglutide 0.5 mg	-2.72 [-3.29; -2.15]
GLP-1 RA	-0.89 [-1.62; -0.17]
Basal insulin	2.75 [1.96; 3.55]

−10 −5 0 5 10

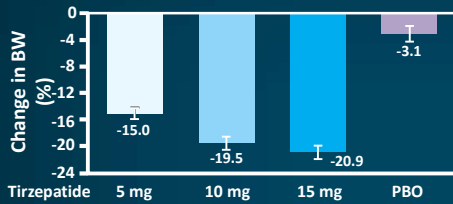Favors treatment   Favors placebo

MD, mean difference; GLP-1 RA, glucagon-like peptide 1 receptor agonist.

Karagiannis T, et al. Tirzepatide compared to subcutaneous semaglutide for type 2 diabetes: a network meta-analysis. Presented at the European Association for the Study of Diabetes. October 2023.
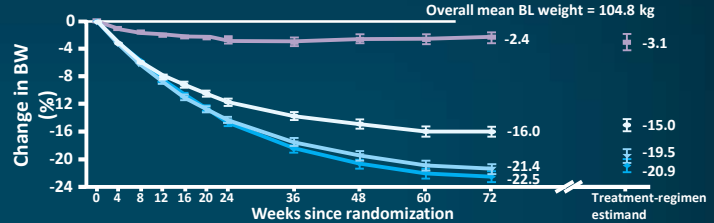Lingqo, E et al. *Diabetologia*. 2023;66(suppl 1):S3-S6.

Effect of Once-Weekly Tirzepatide vs PBO on Body Weight

■ Tirzepatide 5 mg　■ Tirzepatide 10 mg　■ Tirzepatide 15 mg　■ PBO

Change in BW from BL (treatment-regimen estimand)

Change in BW (%)

Tirzepatide 5 mg: -15.0
Tirzepatide 10 mg: -19.5
Tirzepatide 15 mg: -20.9
PBO: -3.1

Change in BW by week (efficacy estimand)

Overall mean BL weight = 104.8 kg

Change in BW (%)

-2.4 / -3.1
-16.0 / -15.0
-21.4 / -19.5
-22.5 / -20.9

Weeks since randomization: 0 4 8 12 16 20 24 36 48 60 72

Treatment-regimen estimand

Participants meeting weight-reduction targets (treatment-regimen estimand)

Participants (%)

BW-reduction target (%)	5 mg	10 mg	15 mg	PBO
≥5	85.1	88.9	90.9	34.5
≥10	68.5	78.1	83.5	18.8
≥15	48.0	66.6	70.6	8.8
≥20	30.0	50.1	56.7	3.1
≥25	15.3	32.3	36.2	1.5
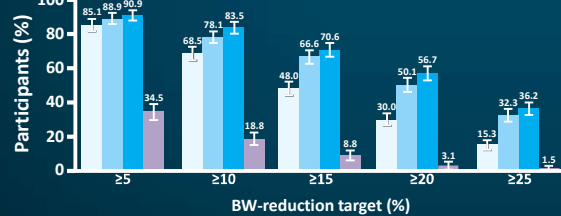
Participants meeting weight-reduction targets (efficacy estimand)

Participants (%)

BW-reduction target (%)	5 mg	10 mg	15 mg	PBO
≥5	89.4	96.2	96.3	27.9
≥10	73.4	85.9	90.1	13.5
≥15	50.2	73.6	78.2	6.0
≥20	31.6	55.5	62.9	1.3
≥25	16.5	35.0	39.7	0.3
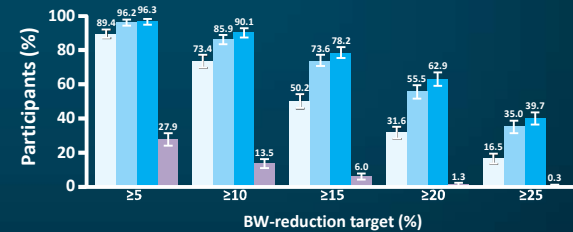
I bars indicate 95% CIs

Jastreboff AM, et al. *N Engl J Med*. 2022;387:205-216.

Suggested Script for Initiating Discussion of Obesity

Pre-screen: BMI and weight trajectory; 24-hour dietary recall; personal weight history; medications; physical activity; existing comorbidities or risk factors (eg, stress, sleep, QoL, depression)

"Is now a good time for us to discuss how your weight and health may be affecting each other and how we can work together on it?"
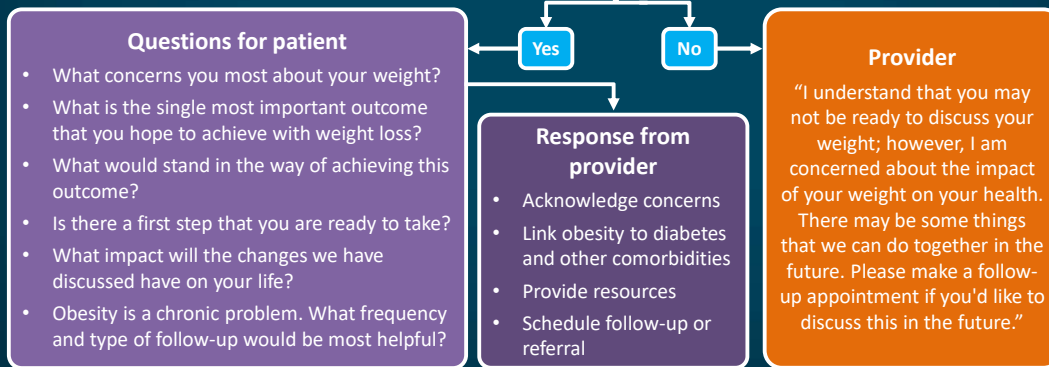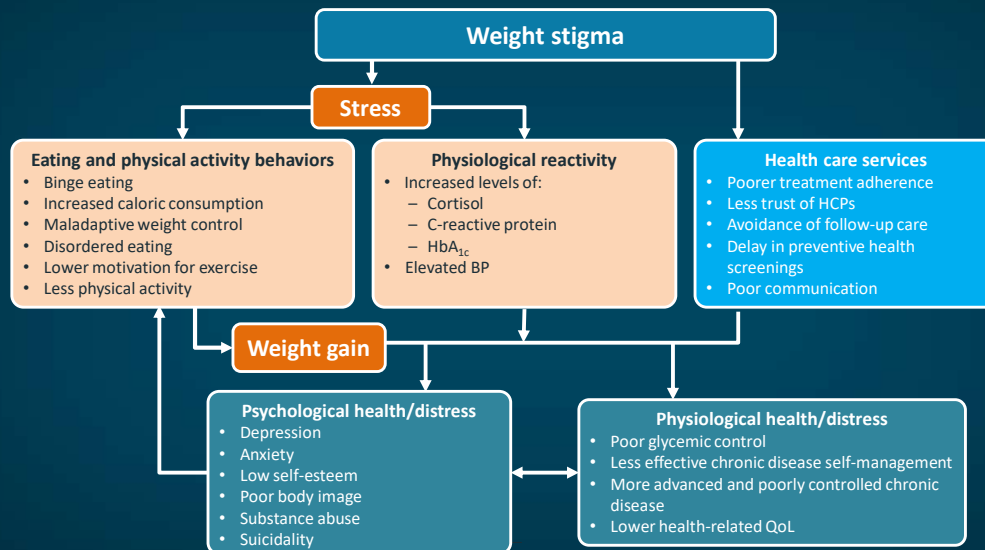
Yes **No**

Questions for patient
- What concerns you most about your weight?
- What is the single most important outcome that you hope to achieve with weight loss?
- What would stand in the way of achieving this outcome?
- Is there a first step that you are ready to take?
- What impact will the changes we have discussed have on your life?
- Obesity is a chronic problem. What frequency and type of follow-up would be most helpful?

Response from provider
- Acknowledge concerns
- Link obesity to diabetes and other comorbidities
- Provide resources
- Schedule follow-up or referral

Provider
"I understand that you may not be ready to discuss your weight; however, I am concerned about the impact of your weight on your health. There may be some things that we can do together in the future. Please make a follow-up appointment if you'd like to discuss this in the future."

Modified from Gallagher C, et al. *Obesity (Silver Spring)*. 2021;29:821-824.

Overcoming Weight Stigma in the Treatment of Obesity

Weight stigma

Stress

Eating and physical activity behaviors
- Binge eating
- Increased caloric consumption
- Maladaptive weight control
- Disordered eating
- Lower motivation for exercise
- Less physical activity

Physiological reactivity
- Increased levels of:
  - Cortisol
  - C-reactive protein
  - HbA_{1c}
- Elevated BP

Health care services
- Poorer treatment adherence
- Less trust of HCPs
- Avoidance of follow-up care
- Delay in preventive health screenings
- Poor communication

Weight gain

Psychological health/distress
- Depression
- Anxiety
- Low self-esteem
- Poor body image
- Substance abuse
- Suicidality

Physiological health/distress
- Poor glycemic control
- Less effective chronic disease self-management
- More advanced and poorly controlled chronic disease
- Lower health-related QoL

Puhl RM, et al. *Clin Diabetes*. 2016;34:44-50.

Core Components of Shared Decision-Making

	Meaning	Objective
Justify	Recognize when best current evidence shows there is no clear best choice for a particular decision	Create a conversation and partnership
Share information (both ways)	Inform patient of available options and benefits and harms of each of them; listen to patient's concerns and opinions about options and evidence	2-way exchange of high-quality information
Elicit values and preferences (both ways)	Listen and elicit patient's preferences about outcomes, goals, concerns, and priorities for treatment	Understand what patient values most, given the circumstances
Shared decision talk	Reach a decision after integrating all information (including possibilities of no treatment or deferral of the decision)	Reach a decision that fits unique patient's values, preferences, and context

Modified from Rodriguez-Gutierrez R, et al. *Lancet Diabetes Endocrinol*. 2016;4:706-716.

Approach: The 5As

ASK	**Ask the patient's permission** "Would you be willing to discuss your weight and the treatment options?"
ASSESS	Usual PMH/PSH including weight history, family history of obesity, obesogenic medications; review food intake, current activity, sleep duration, and stressors
ADVISE	Advise on treatment options
AGREE	Utilize motivational interviewing and shared decision-making to develop a plan of treatment from the options discussed
ASSIST	During follow-up visits, assist the patient in staying on track and reassess for needed changes in treatment; provide referrals and resources

PMH = prior medical history; PSH = prior social history.

O'Shea D, et al. *Adv Ther*. 2021;38:4138-4150. Schlair S, et al. *JCOM*. 2012;19:221-229. Jay M, et al. *BMC Health Serv Res*. 2010;10:159.