JACC
VOL. 86, NO. 7, 2025

PUBLISHED BY ELSEVIER

CONCISE CLINICAL GUIDANCE

2025 Concise Clinical Guidance: An ACC Expert Consensus Statement on Medical Weight Management for Optimization of Cardiovascular Health

A Report of the American College of Cardiology Solution Set Oversight Committee

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This document was approved by the American College of Cardiology Clinical Policy Approval Committee in May 2025.

The American College of Cardiology requests that this document be cited as follows: Gilbert O, Gulati, M, Gluckman TJ, Kittleson MM, Rikhi R, Saseen JJ, Tchang BG. 2025 concise clinical guidance: an ACC expert consensus statement on medical weight management for optimization of cardiovascular health: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2025;86(7):536-555.

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ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2025.05.024

PREFACE

The American College of Cardiology (ACC) has a long history of developing documents (eg, decision pathways, appropriate use criteria) to provide clinicians with guidance on both clinical and nonclinical topics relevant to cardiovascular care. In most circumstances, these documents have been created to complement clinical practice guidelines and to inform clinicians about areas where evidence is new and evolving or where sufficient data is more limited. Despite this, numerous gaps persist, highlighting the need for more streamlined and efficient processes to implement best practices in patient care.

Central to the ACC's strategic plan is the generation of actionable knowledge—a concept that places emphasis on making clinical information easier to consume, share, integrate, and update. To this end, the ACC has shifted from developing isolated documents to creating integrated "solution sets." These are groups of closely related activities, policy, mobile applications, decision-support tools, and other resources necessary to transform care and/or improve heart health. Solution sets address key questions facing care teams and offer practical guidance to be applied at the point of care. They use both established and emerging methods to disseminate information for cardiovascular conditions and their related management. The success of solution sets rests firmly on their ability to have a measurable impact on the delivery of care. Because solution sets reflect current evidence and ongoing gaps in care, the associated tools will be refined over time to match changing evidence and member needs.

Concise Clinical Guidance (CCG) documents are a key component of solution sets. Highly focused and limited in scope, CCGs provide recommendations where none currently exist and/or outline actions required for evidence to be implemented in practice for specific patient populations. Concise Clinical Guidance aim to illustrate clinical decision-making processes using tools (ie, figures, tables, and checklists) and are limited in scope, focusing on patient populations which share certain characteristics, such as conditions, subtypes, or lines of therapy. In some cases, covered topics will be addressed in subsequent expert consensus decision pathways, appropriate use criteria, clinical practice guidelines, and other related ACC clinical policy as the evidence base evolves. In other cases, these will serve as stand-alone policy and represent best standards.

Gurusher S. Panjrath, MBBS, FACC
Chair, ACC Solution Set Oversight Committee

1. INTRODUCTION

Affecting >1 billion adults worldwide, obesity is a debilitating, chronic disease with cardiovascular implications, including increased risk of heart failure, coronary artery disease, and stroke.[1,2] Across 3 decades, obesity rates in adults have doubled, and in children and adolescents, they have quadrupled internationally.[1] Within the United States, 40.3% of adults have obesity (body mass index [BMI] ≥30 kg/m^2), and 9.4% have severe obesity (BMI ≥40 kg/m^2).[3]

As severe obesity is associated with significant reduction in life expectancy of 9.1 years in men and 7.7 years in women, treatment is critical.[4] Whereas specific BMI cut points are recommended for different races, controversy still exists as to which diagnostic criteria for obesity are most accurate.

Obesity therapeutics vary in effectiveness regarding weight loss and cardiovascular disease (CVD) mitigation. In general, weight loss thresholds for risk reduction are 10% to 15% for CVD and >15% for cardiovascular mortality and adverse outcomes in heart failure with preserved ejection fraction (HFpEF).[5,6] Disappointingly, weight loss achieved with lifestyle interventions has not been associated with a reduction in adverse cardiovascular outcomes.[7] Although bariatric surgery is able to achieve substantial weight loss and reduced CVD events, it may be less desirable for some patients.[8]

More effective than lifestyle interventions and with less risk than procedure-based interventions, modern obesity medications are increasingly relevant to cardiologists for CVD modification. The intent of the current document is to provide the foundation for cardiologists to medically manage obesity using agents with proven CVD benefit.

In accordance with ACC's Relationships With Industry and Other Entities policy, relevant disclosures for the writing committee and comprehensive disclosures for external peer reviewers can be found in Appendices 1 and 2. A list of abbreviations relevant to this Concise Clinical Guidance can be found in Appendix 3. To ensure transparency, a comprehensive table of the writing committee's relationships with industry, including those not pertinent to this document, has been created. This can be found in the online Supplemental Appendix.

2. ASSUMPTIONS AND DEFINITIONS

2.1. Assumptions and Definitions

As the newest generation of obesity medications, nutrient-stimulated hormone (NuSH) therapies represent a broad treatment category that acts on metabolic pathways, while helping to control appetite. Current targets of U.S. Food and Drug Administration (FDA)-approved NuSH therapies include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (Section 4.3).[9] For the purposes of the current document, we utilize the term *NuSH therapies* to encompass the GLP-1 receptor agonists liraglutide and semaglutide, as well as the GLP-1/GIP receptor agonist tirzepatide.

2.2. Diagnosis

Overweight and obesity are defined as "abnormal or excessive fat accumulation that presents a risk to health."[10,11] Obesity is often diagnosed using BMI, which is calculated using an individual's weight and height. As classified by the Centers for Disease Control and Prevention, weight thresholds based on BMI are summarized in Table 1.[12-15]

TABLE 1 Obesity Threshold Classification

	Europoid	Asian
BMI category, kg/m²		
Healthy weight	18.5 to <25	
Overweight	25 to <30	23 to <25
Obesity	≥30	≥25
Class 1	30 to <35	25 to <30
Class 2	35 to <40	≥30
Class 3 (severe obesity)	≥40	
Additional anthropometric measures		
Waist circumference (in)	Women: ≥35 in Men: ≥40 in	Women: ≥31.5 in* Men: ≥35.5 in* Japanese women: ≥35.4 in Japanese men: ≥33.5 in
Waist-to-height ratio	≥0.50	

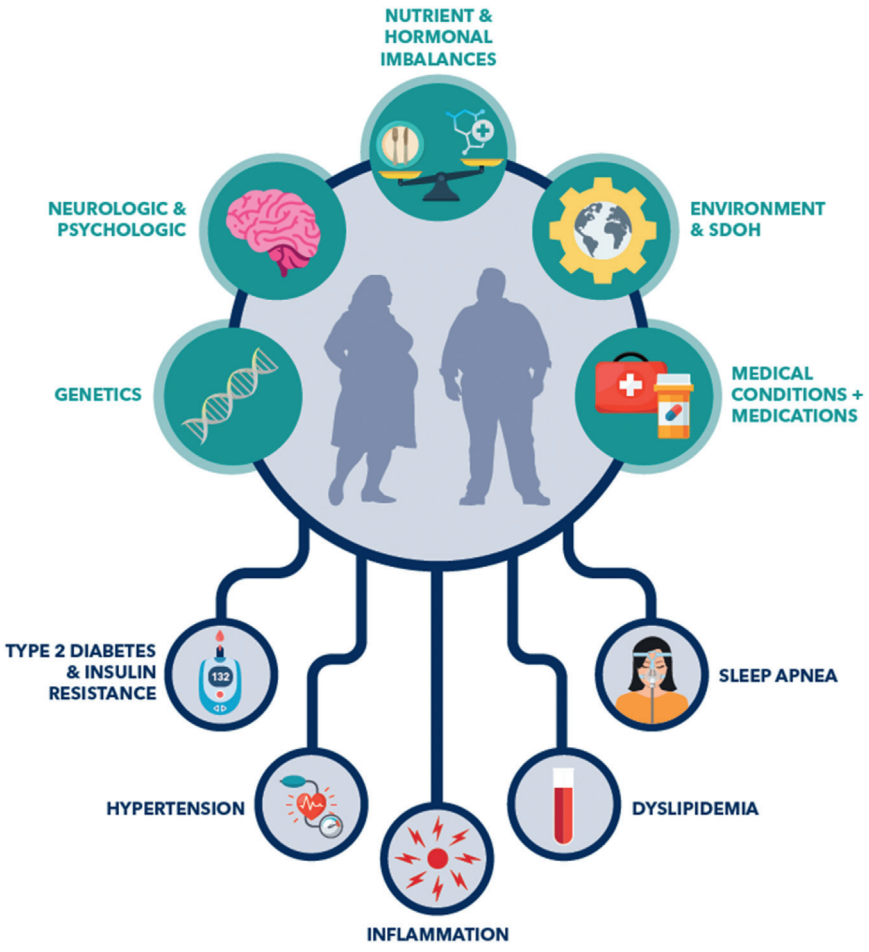
*South Asian, Chinese.
BMI = body mass index.

At a population level, BMI is a useful measure to assess excess weight; among individuals, however, BMI does not always correlate with adiposity. BMI cannot fully account for fat distribution or muscle mass in an individual. Additionally, it cannot account for sex or racial differences in adiposity distribution and health risks. Classifications may be inaccurate, particularly for South Asian and Chinese populations, where BMI cutoffs for overweight and obesity have been proposed to be ≥23 kg/m² and ≥25 kg/m², respectively.[16-21] Whereas other anthropometric measurements, such as waist circumference and waist-to-height ratio, may also be used to identify central adiposity and may better predict association with cardiovascular events, they require broader acceptance and definition of optimal thresholds across weight categories.[22] Combining these concepts, obesity is defined by excess adiposity in association with impaired organ and/or functional status where adiposity can be obtained by direct measurements of body fat (eg, dual-energy x-ray absorptiometry scan) or anthropometric measurements (Table 1) in addition to BMI.[11,23]

2.3. Etiology and Pathophysiology of Obesity

The etiology of obesity is complex.[24,25] Genetics,[26-29] neurological/psychological disorders,[30,31] nutrient and hormonal imbalances,[32] social determinants of health, the environment in which people live,[33,34] medications[35-38] and medical conditions[33] can all contribute to obesity (Figure 1). Its pathophysiology is defined by the

FIGURE 1 Causes of Obesity and its Association With Increased Cardiovascular Risk Factors



The causes of obesity are multiple and include genetics, neurological, psychological, nutrient and hormonal imbalances, and environmental, in addition to medical conditions and medications. The physiological consequences are multiple, with direct effects on cardiovascular risk factors. SDOH = social determinants of health.

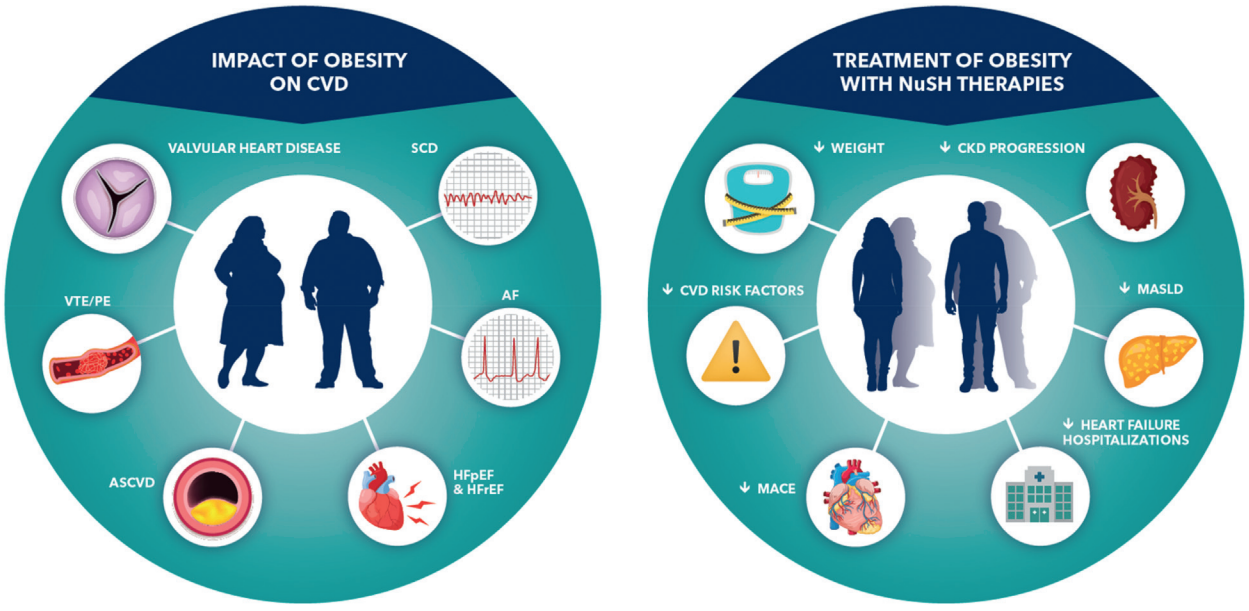
development and defense of an elevated lipostat that is accompanied by dysregulated appetitive hormone signaling and abnormal adipose tissue, which promotes inflammation characteristic of weight-related cardiometabolic and mechanical diseases.[39] Obesity has a strong impact on cardiovascular risk factors, including an increased risk of type 2 diabetes mellitus (T2DM), hypertension, hyperlipidemia, and obstructive sleep apnea,[40-42] along with other disabilities that can contribute to physical inactivity (Figure 1).[30,43] Obesity by itself is an independent risk factor for CVD.

2.4. Risks Associated With Obesity

Obesity is associated with many different forms of CVD, including atherosclerotic CVD, heart failure (more commonly with HFpEF than reduced ejection fraction via inflammatory mechanisms), atrial fibrillation, sudden cardiac death, venous thromboembolism, and valvular heart disease (Figure 2).[28,43-45] Obesity-related mechanisms result in hemodynamic, functional, and structural changes to the cardiovascular system, which contribute to the development of these disparate forms of CVD.[41,43]

3. SUMMARY GRAPHIC

FIGURE 2 Obesity Management for Optimization of Cardiovascular Health



The presence of obesity is associated with multiple forms of CVD. The treatment of obesity with NuSH therapies has resulted in weight loss and proven beneficial in reducing CVD risk factors, cardiovascular endpoints, in addition to reduction in MASLD and CKD progression. AF = atrial fibrillation; ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; CKD = chronic kidney disease; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MACE = major adverse cardiovascular event; MASLD = metabolic dysfunction-associated steatotic liver disease; NuSH = nutrient-stimulated hormone; SCD = sudden cardiac death; VTE/PE = venous thromboembolism/pulmonary embolism.

4. DESCRIPTION, RATIONALE, AND IMPLICATIONS FOR MEDICAL THERAPIES

4.1. Rationale and Eligibility for NuSH Therapies

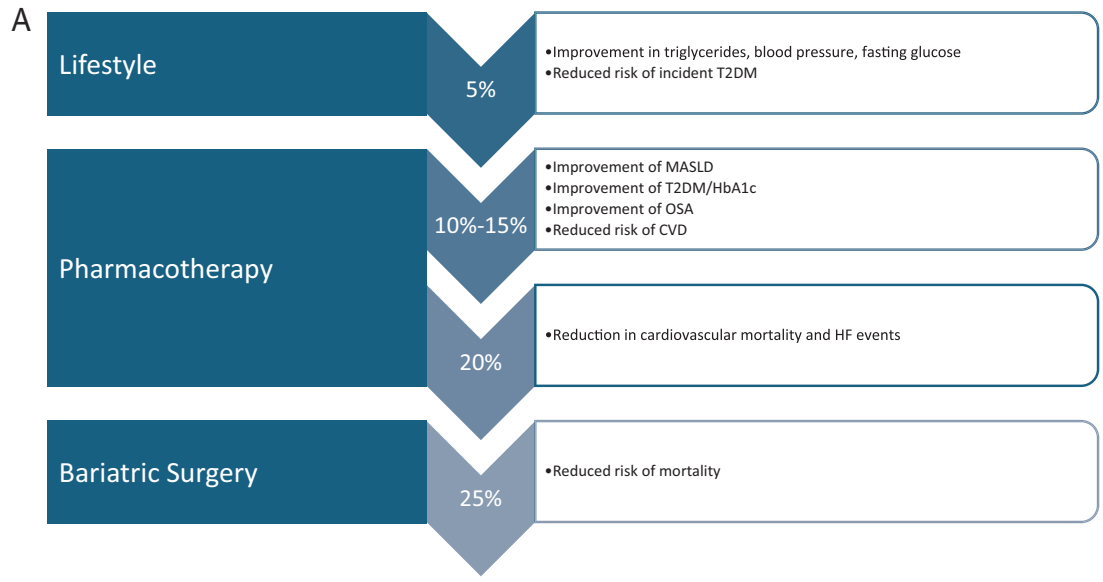
NuSH therapies are a crucial component of comprehensive obesity care for three reasons:

1. NuSH therapies fill the treatment gap between lifestyle therapy and bariatric surgery (**Figures 3A, 3B**). Unfortunately, lifestyle therapy achieves insufficient long-term weight loss to resolve complications and comorbidities for a majority of patients.[46] By contrast, bariatric surgery, while highly effective, is often undesired by patients. Pharmacotherapy strikes the balance between effectiveness and invasiveness.
2. NuSH therapies help to address the disease mechanisms of obesity by targeting the hormonal pathways that control appetite (eg, hunger, satiety, satiation, and cravings).
3. Because NuSH therapies are titratable, they allow dosing to minimize side effects and maximize weight loss, making them well suited to individualize care and address the obesity epidemic.

Eligibility for NuSH therapies may be determined by BMI thresholds, which other anthropometric data (**Table 1**) or direct measurement of excess adiposity, in combination with weight-related consequences. The BMI used to establish eligibility may be the patient's nonpregnant lifetime high, reflecting current understanding around the "weight set point"[49] and in concordance with managing obesity as a chronic disease.[23]

Whereas prior guidelines suggested a trial of lifestyle intervention prior to pharmacotherapy,[50] data from phase 3 trials evaluating semaglutide and tirzepatide show minimal additional weight loss when combined with intensive behavioral therapy/lifestyle intervention.[51,52] Patients should not be required to "try and fail" lifestyle

FIGURE 3A Weight Loss Thresholds Associated With Comorbidity Improvements



Sources for this figure: Rinella ME, et al.[47], Ryan DH, Yockey SR, et al.[5], and Younossi ZM, et al.[48] Weight loss with lifestyle changes results in approximately 5% weight reduction and is associated with a reduction in blood pressure, triglycerides, fasting glucose, and a reduction in incident T2DM. Current pharmacotherapy can result in 10% to 20% weight loss with a reduction in MASLD, T2DM, OSA, and cardiovascular events. Bariatric surgery can achieve approximately 25% weight loss with a demonstrated reduction in all-cause mortality, in addition to the reduction in other cardiovascular consequences of obesity. CVD = cardiovascular disease; HbA_{1c} = hemoglobin A1c; HF = heart failure; MASLD = metabolic dysfunction-associated steatotic liver disease; OSA = obstructive sleep apnea; T2DM = type 2 diabetes mellitus.

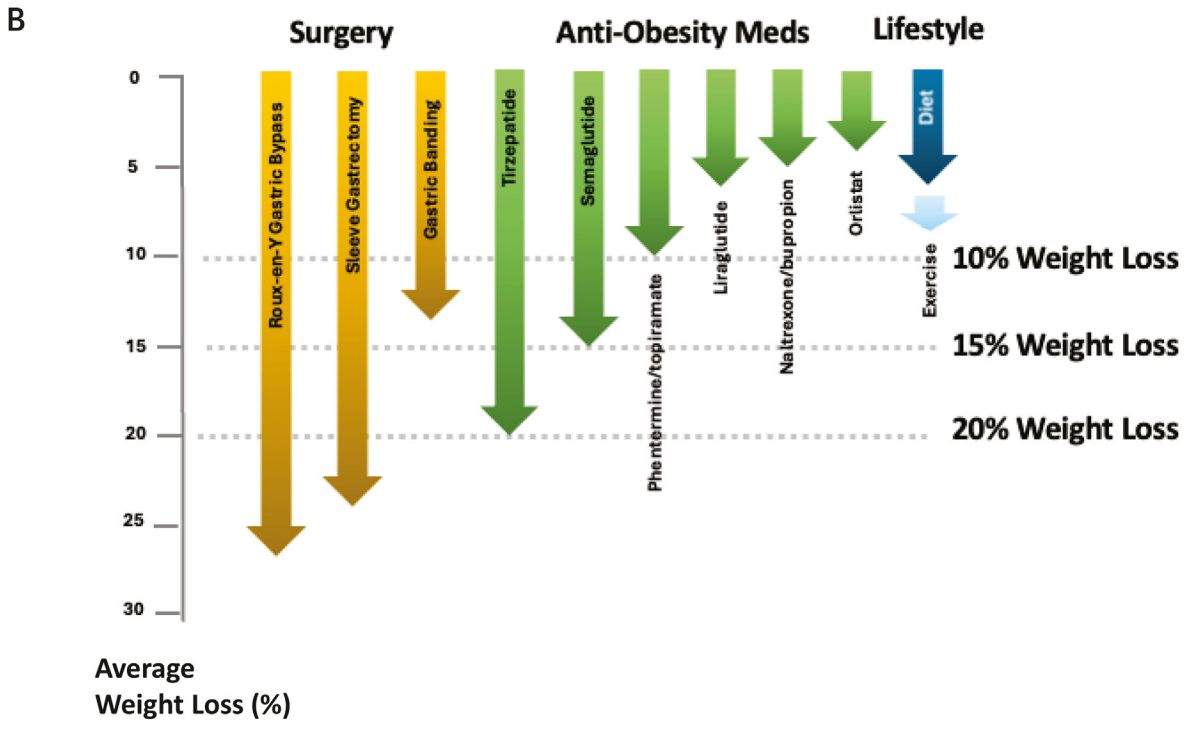
changes prior to initiating pharmacotherapy; nonetheless, lifestyle interventions should always be offered in conjunction with NuSH therapies.

4.2. Evolution and Current Landscape of Obesity Medications

Obesity medications have a long history dating back to the early 1900s.[53,54] First-generation medications included thyroid hormone, dinitrophenol, and amphetamines. Thyroid hormone stimulated metabolic rate but was accompanied by harmful cardiovascular side effects. Dinitrophenol, a mitochondrial uncoupler that increased metabolic rate, resulted in weight loss but increased hyperthermia, tachycardia, diaphoresis, tachypnea, nausea, and vomiting.[54] Ultimately, the FDA suspended use of dinitrophenol in 1938 due to the development of cataracts. Amphetamines, that are still available today and FDA-approved for short-term weight management (eg, phentermine, phendimetrazine, diethylpropion, benzphetamine), are effective appetite suppressants but lack data to support their long-term efficacy and safety with respect to cardiovascular and psychological effects.[53]

Second-generation medications were developed in accordance with the FDA clinical trial requirements seeking to prove long-term clinical efficacy and safety, and include oral therapies with novel mechanisms of action.[53,54] Some medications (ie, fenfluramine, dexfenfluramine, sibutramine, and lorcaserin) have been withdrawn from the market due to safety concerns.[53] Currently available second-generation agents approved for long-term weight management include orlistat,[55] phentermine/topiramate,[56] and naltrexone/bupropion.[57] Each of these is limited by modest weight loss

FIGURE 3B Achieving Clinically Significant Weight Reduction



Average weight loss with approved lifestyle, medical, and surgical treatments for obesity.

(5.9%-9.8%),[55-57] side effects, and a lack of outcome data related to CVD.

Third-generation weight loss medications that target NuSH have changed the landscape of obesity management with robust long-term (up to 4 years) efficacy and safety data for the management of obesity in those with and without CVD.[58] While all currently available medications (liraglutide, semaglutide, and tirzepatide) were initially approved by the FDA to treat T2DM, they are also approved for obesity. They share a similar side effect profile that includes primarily gastrointestinal side effects (eg, nausea, diarrhea, vomiting, abdominal pain, constipation) that can be mitigated with dose reductions or behavioral modifications (eg, hydration). Liraglutide, semaglutide, and tirzepatide have been shown to reduce body weight by an average of 8.0%, 14.9%, and 20.9% on maximal doses, respectively (Figures 3A and 3B).[59-61]

4.3. Pharmacological Options

Among FDA-approved obesity medications, NuSH therapies are most effective (Table 2). Liraglutide and semaglutide are GLP-1 receptor agonists. GLP-1 regulates blood glucose by stimulating glucose-dependent insulin secretion, slowing gastric emptying, and increasing satiety, collectively promoting weight loss. Tirzepatide is a dual-acting agent that is both a GLP-1 receptor and a GIP

TABLE 2 FDA-Approved NuSH Obesity Medications

Medication (Brand Name)	FDA-Approved Indication for Weight Management	Dosage/Titration/Storage	Clinical Efficacy for Weight Loss	Contraindications/Cautions	Most Common Side Effects
GLP-1 receptor agonists					
Liraglutide (Victoza,* Saxenda†)[65]	Adults with an initial BMI ≥30 kg/m^2 or ≥27 kg/m^2 with a weight-related comorbidity	■ Start 0.6 mg subcutaneously daily ■ Increase weekly up to a dose of 3 mg for adults ■ Can be stored for 30 days at controlled room temperature and longer with refrigeration‡	SCALE Obesity and Prediabetes[59] 56-week double-blind trial (n=3,731): ■ ↓ weight: 8.0% liraglutide, 2.6% placebo ■ ↓ weight ≥5%: 63.2% liraglutide, 27.1% placebo	Contraindicated if: ■ Personal/family history of medullary thyroid carcinoma, personal/family history of multiple endocrine neoplasia syndrome type 2 ■ Hypersensitivity to the medication or any excipients Cautions: Acute pancreatitis, acute gallbladder disease, hypoglycemia, renal impairment/acute kidney injury, hypersensitivity reaction, suicidal behavior/ideation	Nausea, diarrhea, constipation, vomiting, injection-site reactions
Semaglutide (Ozempic,* Wegovy†)[66]	Adults with obesity or overweight and a weight-related comorbidity	■ Start 0.25 mg subcutaneously weekly ■ Increase every 4 weeks up to a maintenance dose of 1.7 or 2.4 mg for adults ■ Ozempic can be stored for 56 days and Wegovy for 28 days at controlled room temperature and longer with refrigeration‡	STEP-1[60] 68-week double-blind trial (n=1,961): ■ ↓ weight: 14.9% semaglutide, 2.4% placebo ■ ↓ weight ≥5%: 86.4% semaglutide, 31.5% placebo		
Dual GLP-1 and GIP receptor agonist					
Tirzepatide (Mounjaro,*[67] Zepbound†)[68]	Adults with obesity or adults with overweight with a weight-related comorbidity	■ Start 2.5 mg subcutaneously once weekly ■ Increase the dose every 4 weeks up to a maintenance dose of 5, 10, or 15 mg ■ Can be stored for 21 days at controlled room temperature and longer with refrigeration‡	SURMOUNT-1[61] 72-week double-blind trial (n=2,539): ■ ↓ weight: 15.0% with tirzepatide 5 mg, 19.5% with tirzepatide 10 mg, 20.9% with tirzepatide 15 mg, 3.1% with placebo ■ ↓ weight ≥5%: 85% with tirzepatide 5 mg, 89% with tirzepatide 10 mg, 91% with tirzepatide 15 mg, 35% with placebo		

*Victoza, Ozempic, and Mounjaro are FDA-approved for T2DM regardless of weight status.
†Saxenda, Wegovy, and Zepbound are FDA-approved for weight loss with or without T2DM.
‡Refrigerator storage: 36 °F to 46 °F (2 °C to 8 °C), controlled room temperature: 59 °F to 86 °F (15 °C to 30 °C).

BMI = body mass index; FDA = U.S. Food and Drug Administration; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; NuSH = nutrient-stimulated hormone; SCALE = Satiety and Clinical Adiposity—Liraglutide Evidence; STEP-1 = Semaglutide Treatment Effect in People with Obesity-1; SURMOUNT-1 = Study of Tirzepatide in Participants With Obesity or Overweight-1; T2DM = type 2 diabetes mellitus.

receptor agonist. GIP is a potent gut-derived NuSH that stimulates glucose-dependent insulin secretion in response to food, contributing to endogenous postprandial insulin release. GIP regulates energy balance through cell-surface receptor signaling in the brain to suppress appetite and in adipose tissue to modify lipid metabolism.[62] This dual mechanism likely explains the greater weight loss achieved with tirzepatide compared with that of GLP-1 receptor agonists. Several novel agents with dual and triple mechanisms of action that target other NuSH therapies (eg, glucagon, amylin) are in development.

Among the NuSH therapies, semaglutide and tirzepatide have the highest efficacy and are the obesity medications of choice. Clinical trial and real-world observational data support slightly greater weight loss with tirzepatide.[58,63] Insurance coverage, availability, and affordability are likely to dictate agent selection.

Both GLP-1 and GIP receptor agonists are contraindicated in patients who have a personal or family history of medullary thyroid carcinoma, multiple endocrine neoplasia syndrome type 2, or known hypersensitivity to an individual product or any excipients (Table 2). In contrast with liraglutide, which is dosed

TABLE 3 Cardiovascular Outcomes of FDA-Approved NuSH Obesity Medications

Trial	Medication	Population	Size/Duration (Participants)/(Years)	Average Baseline BMI and Weight Change in Treatment Group	Effect on Primary Outcome (Composite of Cardiovascular Death, AMI, or CVA Unless Specified)	Effect on HF Hospitalization
Obesity with diabetes and high cardiovascular risk or CVD						
LEADER[69]	Liraglutide 1.8 mg	T2DM and high cardiovascular risk or disease (81.3% with CVD)	9,340 participants/ 3.8 years	32.5 kg/m^2 −2.3 kg	Reduction HR: 0.87; 95% CI, 0.78-0.97	No difference HR: 0.87; 95% CI, 0.73-1.05
SUSTAIN-6[77]	Semaglutide 1.0 mg	T2DM and high cardiovascular risk (83.0% with CVD)	3,297 participants/ 2.1 years	33.0 kg/m^2 −4.3 kg	Reduction HR: 0.74; 95% CI, 0.58-0.95	No difference HR: 1.11; 95% CI, 0.77-1.61)
SURPASS-CVOT[86] (NCT04255433)	Tirzepatide up to 15 mg vs dulaglutide 1.5 mg	CVD, T2DM, BMI ≥25 kg/m^2	13,299 participants enrolled	Trial fully recruited and ongoing	Estimated completion date 2025	Not available
Obesity without diabetes						
SELECT[79]	Semaglutide 2.4 mg	CVD and BMI >27 kg/m^2	17,604 participants/ 3.3 years	33.4 kg/m^2 −9.1 kg	Reduction HR: 0.80; 95% CI: 0.72-0.90	No difference HR: 0.79; 95% CI: 0.60-1.03
STEP-HFpEF[82]	Semaglutide 2.4 mg	HF with EF ≥45% and BMI ≥30 kg/m^2	529 participants/ 12 months	37.0 kg/m^2 −13.9 kg	Improvement in KCCQ	No difference (exploratory endpoint)
SUMMIT[85]	Tirzepatide 15 mg	HF with EF ≥50% and BMI ≥30 kg/m^2	731 participants/ 2.3 years	38.2 kg/m^2 weight change of −13.9%	Reduction in cardiovascular death, worsening HF HR: 0.62; 95% CI: 0.41−0.95	Reduction HR: 0.44; 95% CI: 0.22−0.87
SURMOUNT-MMO (NCT05556512)	Tirzepatide 15 mg	CVD or risk, BMI ≥27 kg/m^2	15,374 participants enrolled	Trial fully recruited and ongoing	Estimated completion date 2027	Not available

Weight changes represent placebo-subtracted outcomes from intention-to-treat analyses. Shaded cells indicate that the trials are ongoing.

AMI = acute myocardial infarction; BMI = body mass index; CVA = cerebrovascular accident; CVD = cardiovascular disease; EF = ejection fraction; FDA = U.S. Food and Drug Administration; HF = heart failure; HR = hazard ratio; KCCQ = Kansas City Cardiomyopathy Questionnaire; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; NuSH = nutrient-stimulated hormone; SELECT = Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity; STEP-HFpEF = Semaglutide Treatment Effect in People with Obesity and Heart Failure with Preserved Ejection Fraction; SUMMIT = Study Comparing the Efficacy and Safety of Tirzepatide Versus Placebo in Patients With Heart Failure With Preserved Ejection Fraction and Obesity; SURMOUNT-MMO (NCT05556512) = Study of Tirzepatide in Participants With Obesity or Overweight Metabolic and Mobility Outcomes; SURPASS-CVOT = Effect of Tirzepatide Versus Dulaglutide on Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes; SUSTAIN-6 = Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes-6; T2DM = type 2 diabetes mellitus.

daily, both semaglutide and tirzepatide are dosed once weekly. All agents require dose titration to minimize adverse effects, which are largely gastrointestinal. Slow titration (Table 2) mitigates intolerance. For patients with adverse effects, decreasing the dose to a previously tolerated dose is recommended.[64] In clinical trials, 4.3% to 7.1% of participants discontinued therapy due to adverse events.[59-61]

Among published clinical trials, the longest duration of treatment with a NuSH (liraglutide) was 3.8 years.[69] Observational data across 5 years, however, suggest that GLP-1 receptor agonists are safe and effective.[70] This is an important issue, given that obesity is a chronic disease, and weight regain after discontinuation of therapy is expected.[71] Nonetheless, this highlights the importance of long-term medication persistence and maintaining lifestyle modifications if pharmacotherapy is discontinued.

In addition to tolerance, major challenges with contemporary obesity medications, especially semaglutide and tirzepatide, include limited access (related to payer denial and supply shortages) and affordability. Should a patient miss dosages due to lack of access, published strategies to address this exist and also guide therapeutic interchanges.[72] For example, if ≥3 missed dosages of once-weekly semaglutide or tirzepatide occur, a dose reduction may be considered. Semaglutide and

TABLE 4 Multidisciplinary Considerations for Patients on NuSH Therapies

Specialty Topic	Obesity-Related Condition	Medication	Procedure
Cardiology	■ ASCVD ■ Atrial fibrillation ■ Heart failure ■ Hypertension ■ Hypertriglyceridemia/ dyslipidemia	■ De-escalate antihypertensives to avoid low blood pressure ■ De-escalate diuretics in heart failure to avoid intravascular depletion	
Endocrinology	■ T2DM	■ Consider repeat TSH at 10% weight loss as levothyroxine dose may be weight-based[95] ■ Reduce medications for T2DM to avoid hypoglycemia[96-99]	■ Screening thyroid ultrasound is not required prior to NuSH therapy initiation
Nephrology	■ Chronic kidney disease	■ AKI may occur in the setting of gastrointestinal side effects[68]	■ Adjust hemodialysis protocol for weight or body surface area[100] ■ Adjust dry weight in hemodialysis in patients undergoing active obesity treatment[101]
Gastroenterology/ hepatology	■ MASLD ■ GERD ■ Gallbladder disorders	■ Because NuSH therapies are associated with a higher risk of gallbladder disorders, there could be a low threshold to consider ursodiol in patients with cholelithiasis[64,102] ■ Adjust antireflux medications, given known improvement with weight loss[103] but common side effects of NuSH therapies[66,68]	■ There are no data to support stopping a GLP-1 receptor agonist prior to elective upper endoscopy[104,105] ■ Consider adjusting bowel preparation regimen for patients on NuSH therapy[106]
Obstetrics/gynecology	■ PCOS ■ Infertility	■ Tirzepatide may reduce the efficacy of some contraceptive agents[68] ■ Weekly NuSH therapies should be discontinued ≥2 months prior to conception[107]	
Psychiatry	■ Eating disorders ■ Depression ■ Anxiety ■ Severe mental illness	■ Consider re-evaluating medication dosages after significant weight loss, as the therapeutic window of some psychotropic medications may depend on body weight[108]	
Hematology/oncology	■ Some cancers ■ Venous thromboembolism	■ Consider re-evaluating medication dosages after significant weight loss, as chemotherapy or anticoagulant dosing may be weight-based[109]	
Surgery/ anesthesiology			■ GLP-1 receptor agonist therapy may be preoperatively continued in patients without elevated risk of delayed gastric emptying and aspiration. If the decision to hold semaglutide or tirzepatide is made, there is a lack of evidence to inform duration, but 1 week may be considered[110,111]
Pulmonary/critical care	■ OSA		■ Adjust CPAP settings or repeat OSA assessment after significant weight loss (≥7%)[88]
Geriatrics		■ Caution with excess weight loss and higher risk of sarcopenia and frailty in this age group ■ Re-evaluate medications and dosages after significant weight loss to reduce the risk of polypharmacy[112]	

AKI = acute kidney injury; ASCVD = atherosclerotic cardiovascular disease; CPAP = continuous positive airway pressure; GERD = gastroesophageal reflux disease; GLP-1 = glucagon-like peptide-1; MASLD = metabolic dysfunction-associated steatotic liver disease; NuSH = nutrient-stimulated hormone therapy; OSA = obstructive sleep apnea; PCOS = polycystic ovarian syndrome; T2DM = type 2 diabetes mellitus; TSH = thyroid-stimulating hormone.

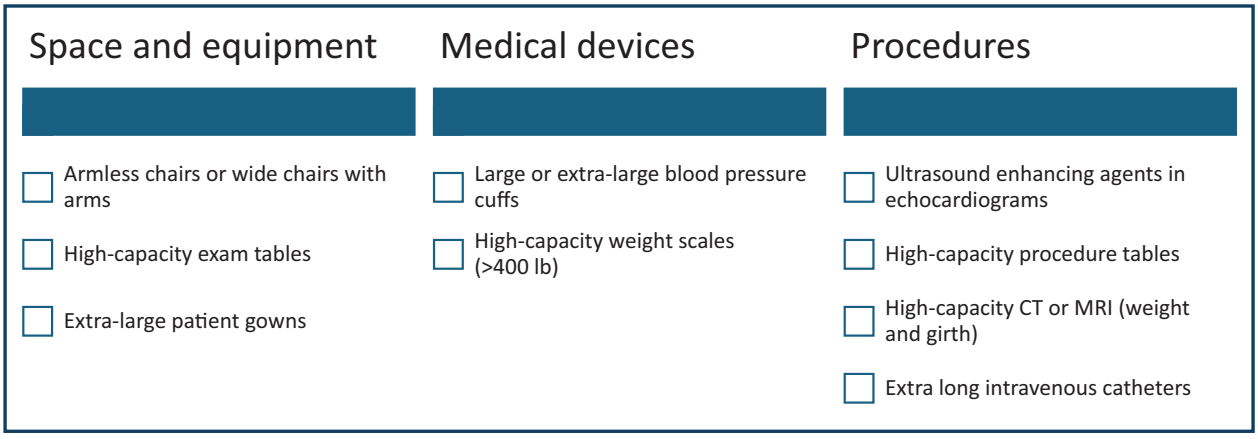
tirzepatide can also be interchanged based on clinical judgment. Use of compounded NuSH therapies is discouraged due to the potential for dosing errors and concern regarding counterfeit agents, which may contain impurities.[73-75]

4.4. Implications on Comorbidities

A summary of the effects of NuSH therapies on cardiovascular outcomes is shown in **Table 3**. NuSH therapies have been shown to reduce weight along with the risk of cardiovascular death, myocardial infarction, or stroke in patients with T2DM[76] at increased cardiovascular risk or with established CVD.[69,77,78]

The benefits of NuSH therapies extend beyond T2DM. In patients without T2DM but with atherosclerotic CVD and a BMI >27 kg/m^2, semaglutide resulted in significant weight loss as well as a reduction in a composite of cardiovascular death, myocardial infarction, and stroke.[79] Whether this benefit is also observed with tirzepatide is being tested in a similar population (NCT05556512)[80] as

FIGURE 4 Examples of Ways to Reduce Weight Stigma and More Optimally Deliver Care in Clinic and Hospital Settings



Sources for this figure: Beavers and Bagai[115]; Bianchettin et al[116]; Gerstein et al[117]; Madder et al[118]; Plourde et al[119]; Powell-Wiley et al[43]; Refahiyat et al[120]; Singh et al.[121]
Reducing weight stigma should be built into clinics and hospitals, improving the care of patients with excess weight. Some examples are listed in this figure. CT = computed tomography; MRI = magnetic resonance imaging.

well as in patients with CVD and T2DM with a lower BMI threshold of 25 kg/m^2 (NCT04255433).[81]

In patients with HFpEF, semaglutide resulted in improvement in symptoms, physical limitation, and exercise function.[82] Whereas the magnitude of benefit was directly related to the extent of weight loss,[83] there may be weight-independent mechanisms of benefit.[84] In a separate study that evaluated tirzepatide in patients with obesity and HFpEF, a significant reduction in the composite outcome of cardiovascular death and worsening heart failure was observed,[85] which may further extend the role of these agents to patients with HFpEF.[85]

4.5. General Treatment Considerations

4.5.1. General Principles That Apply to the Medical Management of Obesity

Comprehensive treatment of obesity is multimodal. Lifestyle interventions support overall weight management,[50,60,61] and their utility alongside highly effective obesity medications is evolving.[51,52,87]

Obesity treatment is multidisciplinary. The use of NuSH therapies may necessitate adjustments in the management of obesity-related comorbidities; as such, these patients benefit from coordination of care (**Table 4**).[5,88-90] Patients should be guided toward evidence-based interventions whenever possible and be educated regarding nonevidence-based options (eg, compounded peptides, over-the-counter supplements) that may pose potential harm.[91,92]

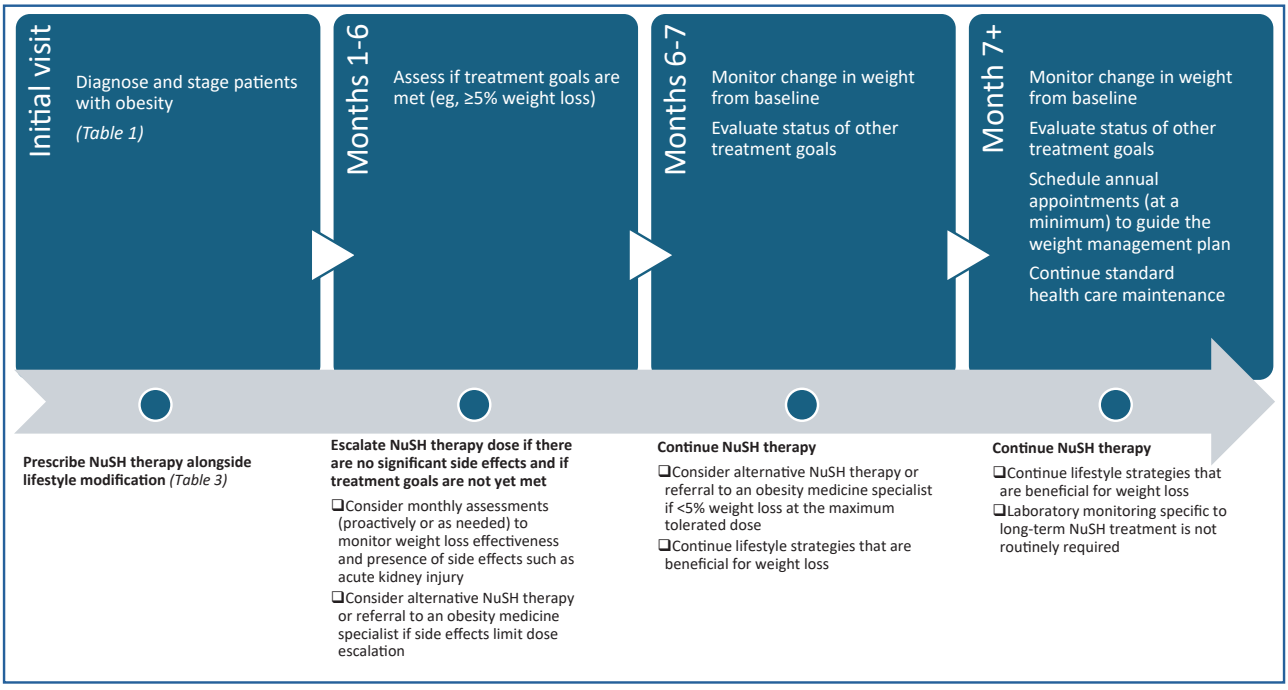
Clinicians should incorporate shared decision-making into their treatment approach to best balance risks and benefits. Off-label, but evidence-based, strategies may be considered to mitigate potential harms and optimize health outcomes (eg, lowest therapeutic dose for weight loss maintenance,[93] combination therapies).[88,94]

4.5.2. The Patient Experience

Obesity care should include attention to reducing weight bias and stigma. Person-first language should be used. In addition, the clinical space should be designed to appropriately welcome and treat patients (**Figure 4**).[113,114] Clinicians should make every effort to validate the lifelong journey that patients experience with this chronic disease.

The initial encounter should elicit potential contributors to and consequences of obesity, identify contraindications to obesity medications, and obtain anthropometric and clinical data to aid in the diagnosis and staging of obesity.[23] Blood work is unlikely to change the decision to pursue NuSH therapies, given that these medications' contraindications cannot be detected by laboratory results, but may be helpful for insurance coverage, however, if T2DM is diagnosed.[122] Published resources

FIGURE 5 General Overview of Patient's Weight Management Journey With NuSH Therapies



An overview of a patient's journey when undergoing treatment with NuSH therapies. Source for this figure: Rubino et al.[113] NuSH = nutrient-stimulated hormone.

may guide clinicians in establishing an obesity care practice.[50,114,123]

Frequency of follow-up depends on the stage of the patient's journey and the practice's capabilities (**Figure 5**). More frequent interactions with a weight management team have been associated with greater weight loss and weight loss maintenance success.[7,71,124] Given a paucity of data, practitioners should use their clinical judgment to best manage situations that might be concerning for unintentional or rapid weight loss, signs or symptoms of vitamin/mineral deficiencies, signs or symptoms of disordered eating behaviors, or excess weight loss associated with frailty.[71]

The goals of obesity treatment should be tailored to the individual. A reasonable initial goal is achievement of clinically significant weight loss, defined as ≥5% from baseline, which is associated with improvement in triglycerides, fasting blood glucose, and systolic blood pressure as well as the prevention of incident disease.[50,125] Individuals who seek to resolve weight-related comorbidities (eg, CVD, sleep apnea, metabolic dysfunction-associated steatotic liver disease) should aim for ≥10% weight loss.[5] Patient quality of life, functional status, and psychosocial health should also be considered as part of one's treatment goals, supporting a holistic approach to obesity care.

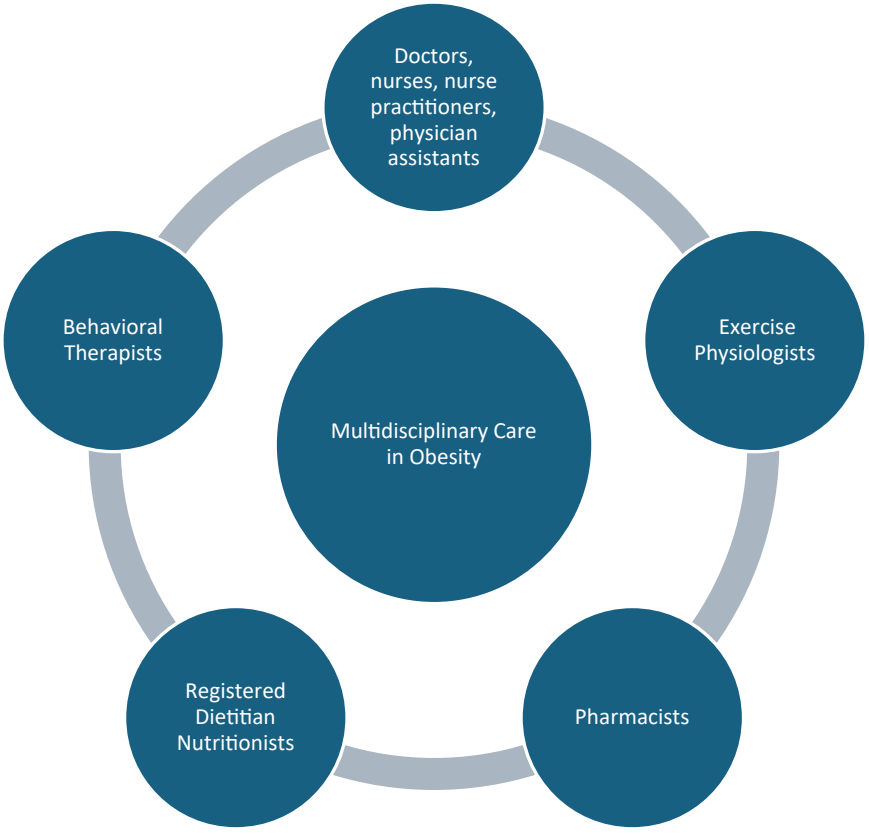
Therapies for weight-related comorbidities and weight-based medications should be de-escalated as needed (**Table 4**). As a patient achieves their weight management goals, actively reduce or discontinue interventions to avoid harm from overtreatment, mitigate polypharmacy, and reinforce progress.[96-99,126,127]

Long-term treatment should be the default plan. As such, obesity medications should not be discontinued unless determined by the patient and/or treating clinician, as this commonly results in weight regain.[71,124]

4.6. Multidisciplinary Care Approaches

Weight management is best optimized using a team-based approach to create personalized health assessments and identify contributing factors, modifiable risk factors, and comorbid conditions (**Figure 6**).[128] Early involvement with behavioral therapists can be beneficial to recognize individual stressors, encourage social support systems,

FIGURE 6 Multidisciplinary Team Approach for Weight Management



A multidisciplinary team-based approach to weight management is recommended, creating a personalized approach for individual patients. This integrated model will allow for comprehensive and tailored weight management.

identify long-term patient goals, and set reasonable expectations.[129] Additionally, health coaching with registered dietitians and exercise physiologists has been shown to improve weight loss, physical activity, and metabolic markers.[130,131] Finally, a team of clinicians with pharmacy support is integral for monitoring medication side effects, therapeutic goals, and improving access to care.[132] Thus, a multidisciplinary team approach allows for comprehensive and tailored weight management.[128]

4.7. Access Considerations

Despite profound cardiovascular and weight loss benefits with NuSH therapies, medication coverage serves as a major barrier for patients.[133] Whereas the average yearly cost for semaglutide, liraglutide, and tirzepatide in the United States is $14,080, $15,738, and $8,126, respectively, cost is significantly lower in other countries (eg, $2,066 for liraglutide, Switzerland).[133] NuSH therapies are covered by Medicare Part D for patients with obesity and other comorbid conditions, including T2DM and specific CVD diagnoses; however, these medications are not covered for obesity alone.[134] Initial strategies to improve access to NuSH therapies include identifying individuals most likely to benefit, close monitoring of treatment outcomes, and price negotiations.[133] There is ongoing need to improve access to NuSH therapies in the United States, acknowledging that this may be delayed by current price points limiting its cost-effectiveness.[133] It should also be noted that until prices are further adjusted, individuals may seek unregulated routes to access, such as compounding, which can be associated with increased risk of complications.[135,136] Advocacy efforts on behalf of

patients and health care professionals are ongoing with a focus on increasing access to comprehensive obesity care.[137]

4.8. Conclusions/Future Directions

In this new era of obesity management, there exists an ever-expanding set of tools to assist patients in diagnosis, weight reduction, and CVD risk mitigation. With more precise ways of identifying adipose tissue on the horizon, care will be further personalized. Beyond improvement of CVD risk factors, third-generation obesity medications (NuSH therapies) have been shown to reduce adverse cardiovascular events among those with obesity and established atherosclerotic CVD and/or HFpEF. In addition, a growing number of therapies are in development. Obesity management by the cardiovascular community needs to be embraced, given both the prevalence of obesity and the impact it has on many forms of CVD. Several questions remain that will need to be resolved to effectively assist our patients with initiation and continuation of these therapies in the treatment of this chronic disease.

PRESIDENT AND STAFF

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KEY WORDS GIP, GLP-1, NuSH, obesity, weight management

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2025 CONCISE CLINICAL GUIDANCE: AN ACC EXPERT CONSENSUS STATEMENT ON MEDICAL WEIGHT MANAGEMENT FOR OPTIMIZATION OF CARDIOVASCULAR HEALTH

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*Significant relationship.

ACC = American College of Cardiology; DSMB = Data Safety Monitoring Board.

APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—2025 CONCISE CLINICAL GUIDANCE: AN ACC EXPERT CONSENSUS STATEMENT ON WEIGHT MANAGEMENT FOR OPTIMIZATION OF CARDIOVASCULAR HEALTH

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ACC = American College of Cardiology.

APPENDIX 3. ABBREVIATIONS

ACC = American College of Cardiology
BMI = body mass index
CVD = cardiovascular disease
FDA = U.S. Food and Drug Administration
GIP = glucose-dependent insulinotropic polypeptide
GLP-1 = glucagon-like peptide-1
HFpEF= heart failure with preserved ejection fraction
NuSH = nutrient-stimulated hormone
T2DM = type 2 diabetes mellitus