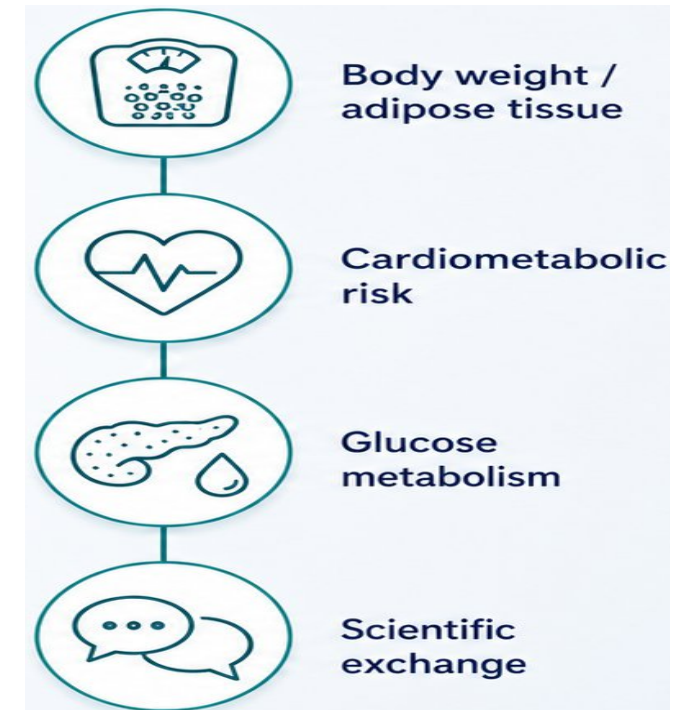


GLP-1/GIP Therapies in Obesity and Cardiometabolic Risk

Scientific background, clinical evidence, safety considerations, and non-promotional field medical exchange

[Portfolio sample | Prepared by: Minha Naseer]



This training supports balanced, evidence-based scientific exchange

Learning objectives

By the end of this training, MSLs should be able to:

- Describe obesity as a chronic cardiometabolic disease
- Explain the scientific rationale for GLP-1 and GIP receptor agonism
- Summarize key evidence from major obesity and cardiovascular outcome trials
- Discuss safety, tolerability, and practical clinical considerations
- Respond to common HCP questions using balanced, evidence-based language

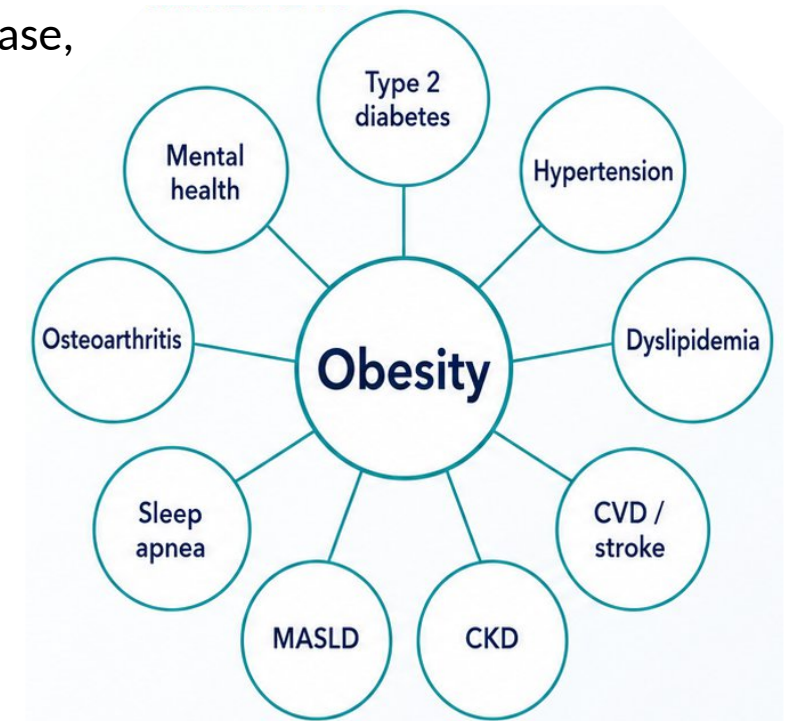
Portfolio disclaimer

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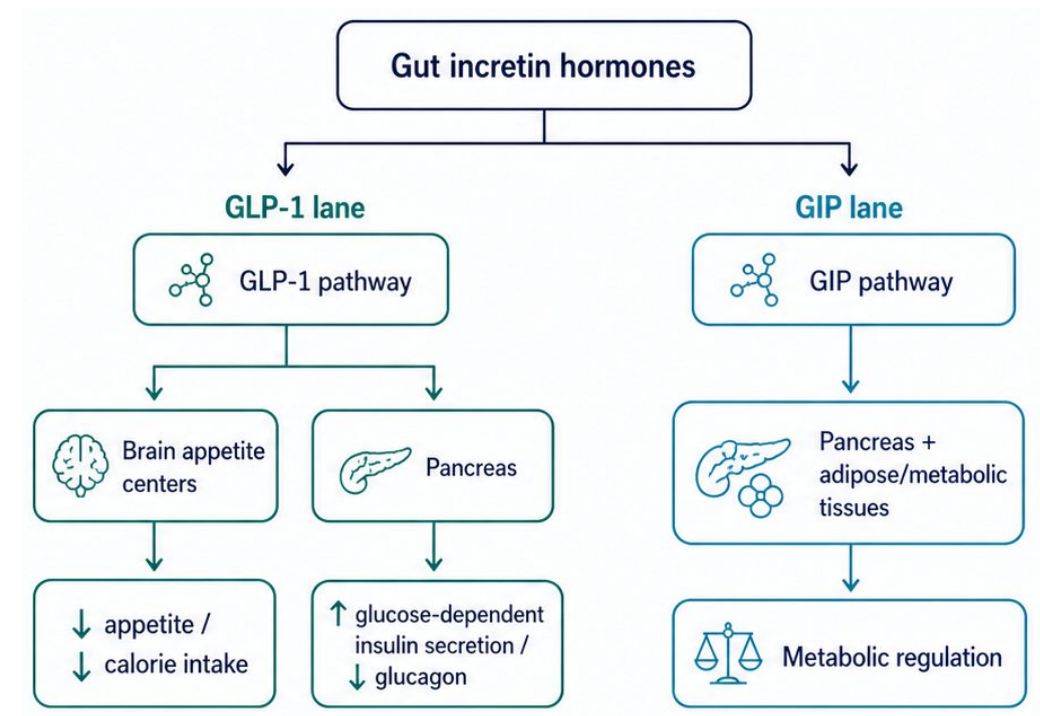
Obesity is a chronic disease with broad cardiometabolic consequences

- Obesity involves complex biological regulation of appetite, energy balance, metabolism, and adipose tissue function
- Excess adiposity can contribute to inflammation and long-lasting metabolic changes
- Obesity is associated with hypertension, dyslipidemia, type 2 diabetes, heart disease, stroke, CKD, MASLD, obstructive sleep apnea, and other complications
- Medical communication should use person-first, non-stigmatizing language



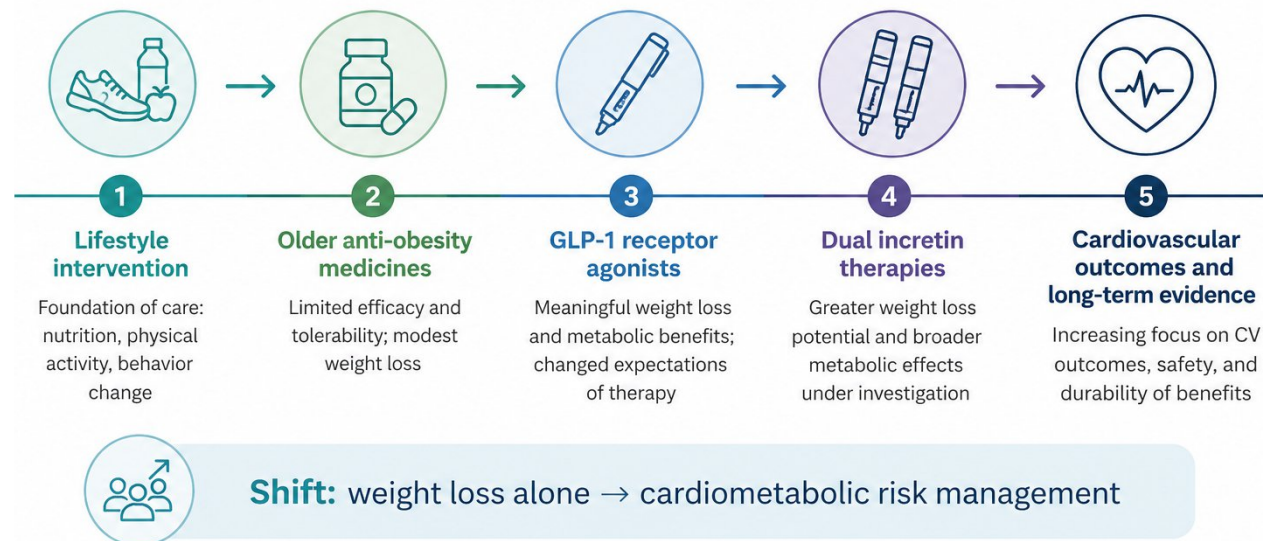
GLP-1 and GIP pathways connect appetite, glycemia, and metabolic regulation

- GLP-1 is a physiological regulator of appetite and caloric intake
- Semaglutide is a GLP-1 receptor agonist that activates GLP-1 receptors involved in appetite regulation
- Tirzepatide activates both GIP and GLP-1 receptors
- FDA labeling states that tirzepatide decreases calorie intake, with effects likely mediated by appetite regulation
- These mechanisms are relevant to obesity, type 2 diabetes, and broader cardiometabolic care



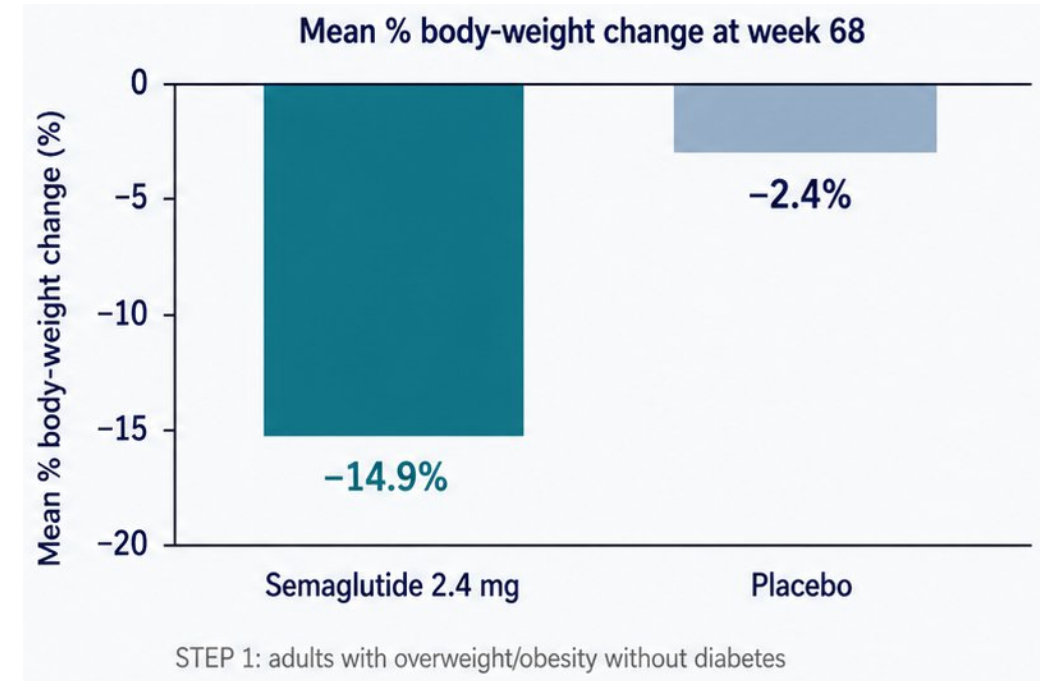
The treatment landscape is shifting toward long-term cardiometabolic risk management

- Earlier obesity pharmacotherapy focused mainly on weight reduction
- Incretin-based therapies have changed expectations for clinically meaningful weight loss
- Cardiovascular outcomes are increasingly important in evaluating obesity therapies
- Treatment decisions depend on efficacy, safety, comorbidities, access, tolerability, and patient goals
- MSLs should distinguish approved indications from investigational or emerging evidence



STEP 1 showed clinically meaningful weight reduction with semaglutide 2.4 mg

- STEP 1 evaluated once-weekly semaglutide 2.4 mg plus lifestyle intervention in adults with overweight or obesity without diabetes
- Mean body-weight change at week 68 was **-14.9% with semaglutide vs -2.4% with placebo**
- More participants achieved $\geq 5\%$, $\geq 10\%$, and $\geq 15\%$ weight loss with semaglutide than placebo
- Gastrointestinal events were among the most commonly reported adverse events

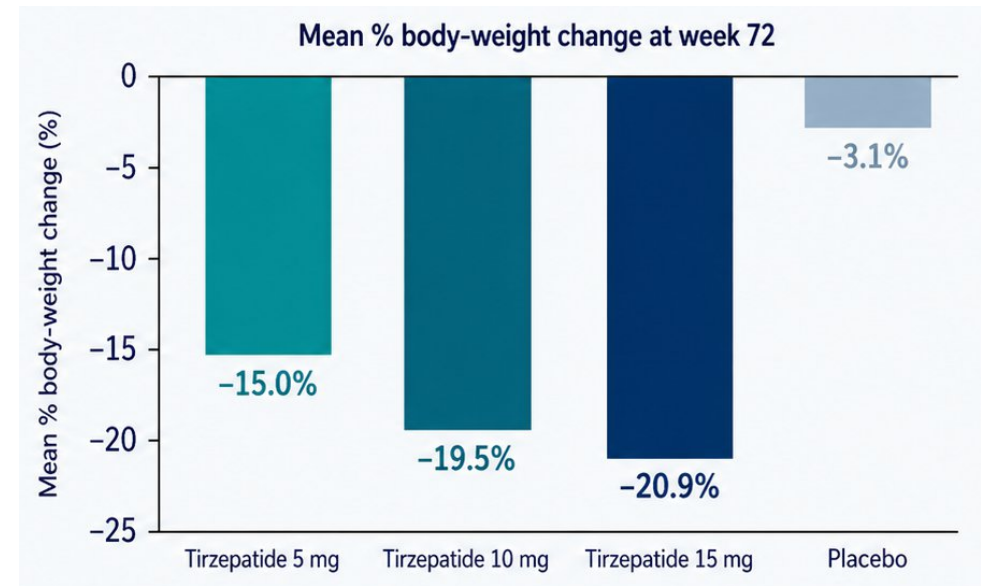


Wilding JPH et al. *N Engl J Med*. 2021;384:989–1002.

The STEP 1 result of -14.9% versus -2.4% is from the published NEJM trial abstract indexed in PubMed.

SURMOUNT-1 demonstrated dose-dependent weight reduction with tirzepatide

- SURMOUNT-1 evaluated once-weekly tirzepatide in adults with obesity or overweight without diabetes
- Mean body-weight change at week 72 was **-15.0%**, **-19.5%**, and **-20.9%** with tirzepatide 5 mg, 10 mg, and 15 mg, respectively
- Mean body-weight change with placebo was **-3.1%**
- Gastrointestinal adverse events were the most common adverse events and occurred mainly during dose escalation

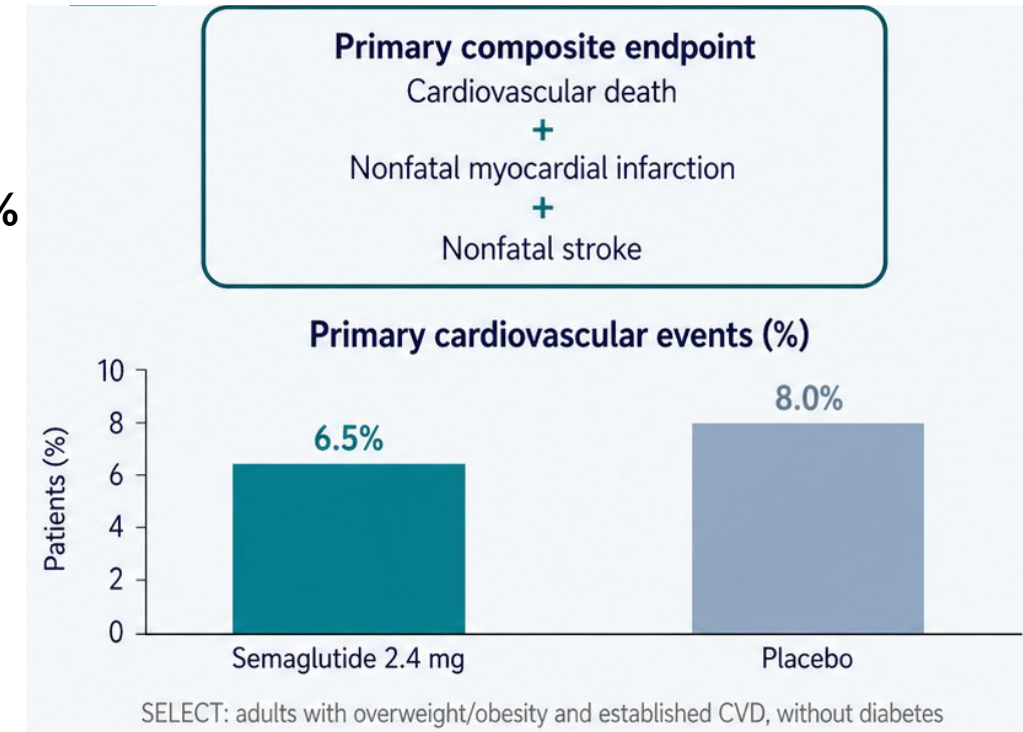


Jastreboff AM et al. *N Engl J Med.* 2022;387:205–216.

SURMOUNT-1 enrolled 2,539 adults with BMI ≥ 30 , or BMI ≥ 27 plus at least one weight-related complication, excluding diabetes; the published results report -15.0%, -19.5%, -20.9%, and -3.1% mean weight changes for tirzepatide 5/10/15 mg and placebo, respectively

SELECT expanded the discussion from weight loss to cardiovascular outcomes

- SELECT studied semaglutide 2.4 mg in adults with overweight or obesity and established cardiovascular disease, without diabetes
- The primary endpoint was cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke
- Primary cardiovascular events occurred in **6.5% with semaglutide vs 8.0% with placebo**
- These findings support discussion of obesity treatment in a broader cardiometabolic context



Lincoff AM et al. N Engl J Med. 2023;389:2221–2232.

SELECT reported primary cardiovascular endpoint events in 569 of 8,803 patients receiving semaglutide and 701 of 8,801 receiving placebo, corresponding to 6.5% and 8.0%.

Safety discussions should balance efficacy, tolerability, and individual risk

- Gastrointestinal adverse events are commonly reported with incretin-based therapies
- Dose escalation may influence tolerability
- Clinical assessment should consider comorbidities, contraindications, concomitant medicines, and treatment goals
- MSLs should not provide patient-specific treatment advice
- Patient-specific decisions should be referred to the treating clinician



GI tolerability



Dose escalation



Contraindications / warnings



Comorbidities and concomitant medicines



Patient goals and clinical context



MSL role: discuss evidence, not individual treatment decisions

FDA Wegovy Prescribing Information. 2026; FDA Zepbound Prescribing Information. 2026.

FDA labeling supports appetite-related mechanisms and includes safety/tolerability information for semaglutide and tirzepatide; use the label for exact safety language if you expand this slide

Patient selection depends on clinical profile and treatment goals

Different patient profiles may have different treatment priorities and expected benefits

	 Obesity alone (without T2D or CVD)	 Obesity with type 2 diabetes (T2D)	 Obesity with established CVD
 Clinical profile	BMI ≥ 30 kg/m ² or ≥ 27 kg/m ² with weight-related comorbidities; no diagnosis of T2D or established CVD	BMI ≥ 30 kg/m ² or ≥ 27 kg/m ² with inadequate glycemic control despite standard care	BMI ≥ 27 kg/m ² with established cardiovascular disease (e.g., prior MI, stroke, or peripheral arterial disease)
 Potential treatment goals	• Weight reduction • Improve obesity-related comorbidities • Enhance quality of life	• Weight reduction • Improve glycemic control • Reduce cardiometabolic risk • Enhance quality of life	• Weight reduction • Reduce major adverse cardiovascular events • Improve quality of life
 Key considerations	• Degree of obesity and comorbidities • Motivation and readiness • Access and affordability	• Glycemic status and treatment regimen • Risk of hypoglycemia • Comorbidities (e.g., CKD, NAFLD) • Access, coverage, and cost	• Cardiovascular history and risk factors • Evidence for CV benefit • Concomitant cardioprotective therapies • Access, coverage, and cost
 Approach	 Shared decision-making focused on weight and health priorities	 Shared decision-making focused on glycemic, weight, and cardiometabolic priorities	 Shared decision-making focused on cardiovascular risk reduction, weight, and overall health



Long-term adherence and persistence influence real-world use



Tolerability and safety influence sustained treatment



Access, affordability, and coverage are important factors



Shared decision-making remains essential across all patient profiles

Cross-trial comparisons should be interpreted cautiously

- Trial populations, inclusion criteria, background interventions, endpoints, and follow-up durations differ
- Direct comparisons between therapies require head-to-head evidence
- MSLs should avoid saying one therapy is “better” unless supported by appropriate comparative data
- Balanced communication should describe evidence strengths and limitations clearly

Medical Affairs best practice; MAPS External Scientific Engagement Guidance. 2025.

Field Medical teams are expected to provide non-biased, fact-based scientific information and support compliant scientific engagement

Common HCP questions require balanced, evidence-based responses

HCP question

How do GLP-1 and GIP mechanisms differ?

Can we compare semaglutide and tirzepatide directly?

What are the main tolerability issues?

Is obesity treatment only about weight loss?

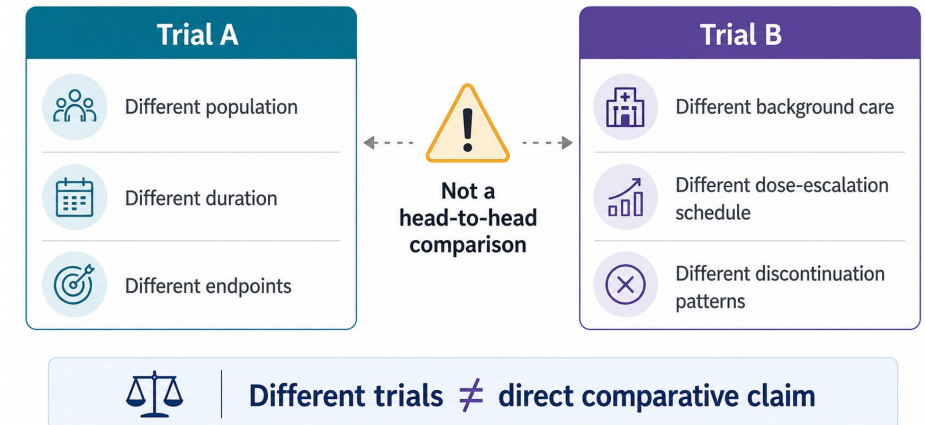
Balanced MSL response

GLP-1 and GIP are incretin pathways with overlapping but distinct metabolic roles. Tirzepatide activates both GIP and GLP-1 receptors.

Cross-trial comparisons are limited because study designs, populations, endpoints, and follow-up differ.

GI adverse events are commonly reported and should be discussed alongside efficacy, dose escalation, and patient factors.

Current evidence supports a broader cardiometabolic discussion, including metabolic and cardiovascular outcomes.



Scientific exchange should remain balanced, accurate, and non-promotional

- Use evidence-based, referenced responses
- Distinguish approved indications from investigational or emerging evidence
- Avoid overstating efficacy or minimizing safety
- Do not make unsupported comparative claims
- Escalate off-label, safety, or patient-specific questions according to company policy

Do

Use referenced evidence

Discuss study design and limitations

Use balanced safety language

Clarify approved vs investigational data

Follow company policy

Do not

Make promotional claims

Overstate efficacy

Minimize adverse events

Provide patient-specific treatment advice

Improvise off-label responses

MAPS. External Scientific Engagement Field Medical Standards & Guidance. 2025.

MAPS describes Field Medical as providing expert, non-biased, fact-based information through scientific exchange with external stakeholders and internal decision-makers.

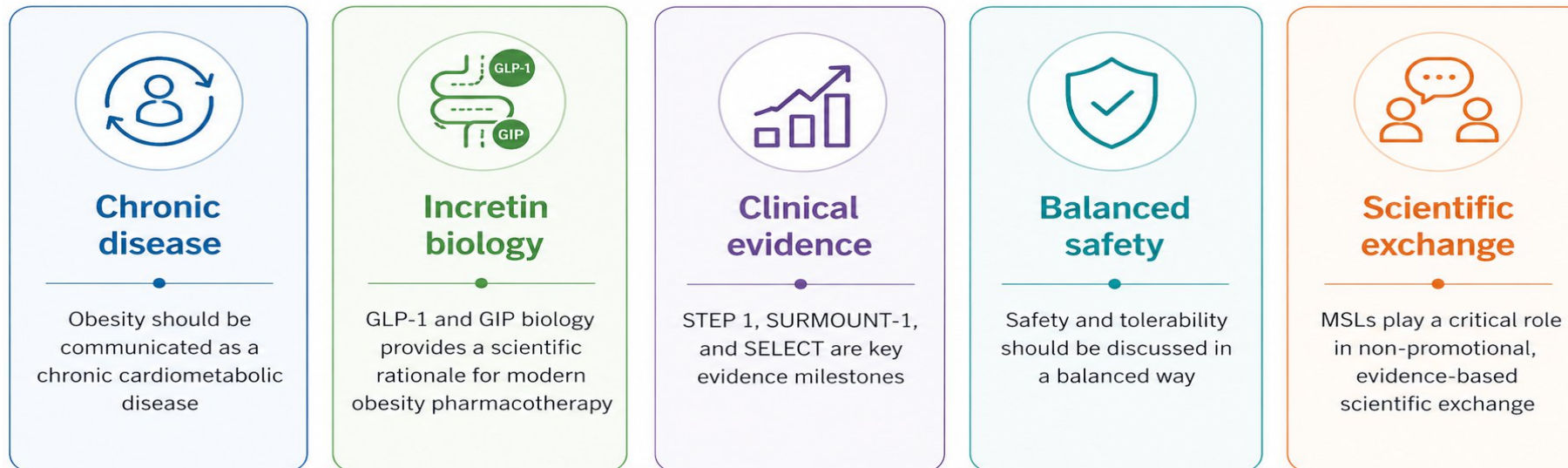
Evidence gaps remain despite rapid progress

- Long-term durability of weight loss
- Real-world persistence and discontinuation patterns
- Outcomes across diverse populations
- Comparative effectiveness and sequencing strategies
- Access, affordability, and health-equity considerations
- Broader cardiometabolic, renal, liver, and sleep-related outcomes



Key takeaways for MSL scientific exchange

- Obesity should be communicated as a chronic cardiometabolic disease
- GLP-1 and GIP biology provides a scientific rationale for modern obesity pharmacotherapy
- STEP 1, SURMOUNT-1, and SELECT are key evidence milestones
- Safety and tolerability should be discussed in a balanced way
- MSLs play a critical role in non-promotional, evidence-based scientific exchange



References

1. Centers for Disease Control and Prevention. Consequences of Obesity. Updated 2025.
2. FDA. Wegovy Prescribing Information. 2026.
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4. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384:989–1002.
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6. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389:2221–2232.
7. Medical Affairs Professional Society. External Scientific Engagement Field Medical Standards & Guidance. 2025.
8. The Obesity Society. Person-first language guidance.